Effective and optimized pharmaceutical care of patients with diabetes provided by community pharmacists

INAUGURAL-DISSERTATION

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultät
der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Maira Anna Deters

aus Oberhausen, Deutschland

Düsseldorf im Juni 2022

Die vorliegende Arbeit wurde über den Zeitraum vom 01.10.2015 bis 14.06.2022 verfasst und wurde im an der mathematisch-naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität am Institut für Klinische Pharmazie und Pharmakologie, durchgeführt. Betreut wurde sie von Prof. Dr. Stephanie Läer und Prof. Dr. Holger Schwender.

Gedruckt mit der Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität Düsseldorf

Berichterstatter:

1. Prof. Dr. Stephanie Läer
   Institut für Klinische Pharmazie und Pharmakotherapie, Universität Düsseldorf

2. Prof. Dr. Thilo Bertsche
   Zentrum für Arzneimittelsicherheit Klinische Pharmazie, Universität Leipzig

Tag der mündlichen Prüfung: 27.07.2023

"Probleme kann man niemals mit derselben Denkweise lösen, durch die sie entstanden sind."

Albert Einstein

I Selbstständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Promotionsarbeit mit dem Titel:

“Effective and optimized pharmaceutical care of patients with diabetes provided by community pharmacists”

selbstständig und ohne fremde Hilfe verfasst und keine anderen Hilfsmittel als angegeben verwendet habe. Insbesondere versichere ich, dass ich alle wörtlichen und sinngemäßen Übernahmen aus anderen Werken als solche kenntlich gemacht habe.

Ort: _____ Datum: _____

Unterschrift: _____

II Summary

Type 1 diabetes mellitus is one of the most common chronic endocrine diseases in children and adolescents worldwide. Both the prevalence and incidence of type 1 and 2 diabetes mellitus have increased in recent decades. There are a wide variety of therapeutic strategies including several types of insulin, oral antidiabetic agents and therapy schemes, as well as training courses for diabetes patients. Nevertheless, many patients find it difficult to achieve optimal diabetes control and to maintain it in the long term. Poor diabetes control can lead to serious short-term complications and life-shortening long-term consequences. Consequently, this study identifies relevant and effective pharmaceutical care for adolescent and adult patients with type 1 and 2 diabetes mellitus, in order to optimize pharmaceutical care in community pharmacies.

In the first chapter of this thesis, insulin therapy adjustments or lifestyle changes that were adopted by adolescents with type 1 diabetes mellitus in the DIADEMA study leading to improved glycemic control are examined. Analysis of the study data showed for example a benefit of both more frequent blood sugar measurements (allowing for better calculation of the insulin dose) and the existence of a nutrition plan. In addition, the relevant pharmaceutical care elements of the DIADEMA study are worked out in this section on the basis of a patient case.

In order to obtain a precise overview of current published studies and to identify relevant and effective pharmaceutical care components, the results of a systematic literature search and subsequent meta-analysis of randomized controlled trials on the pharmaceutical care of diabetes patients are presented in the second chapter of this thesis. In addition to identifying particularly effective pharmaceutical care content, the elements of the previous training conducted with the study pharmacists were examined and evaluated in a descriptive manner.

Thirdly, as part of a qualitative study (case series), the feasibility of the previously identified four effective pharmaceutical components was successfully tested. It was possible to formulate a hypothesis on the positive effect of these pharmaceutical components on fasting blood glucose level, medication appropriateness index, WHO-5 wellbeing index and the number of drug related problems. In addition, recommendations are given for conducting further hypothesis-testing studies.

Finally, based on two patient cases, a mobile health application for diabetes patients was tested. To evaluate how well the current functions of a diabetes mobile health application can support the provision of pharmaceutical care for diabetes patients, the Diabetes: M application was selected. The Diabetes: M application provides some features that can assist pharmacists to

implement the four effective pharmaceutical care components previously identified. However, in terms of performing a medication analysis or working as part of an interdisciplinary team, the application needs further improvement.

III Zusammenfassung

Diabetes mellitus Typ 1 ist weltweit eine der häufigsten chronischen Erkrankungen im Kindes- und Jugendalter. In den letzten Jahrzehnten ist die Inzidenz sowie Prävalenz des Diabetes mellitus Typ 1 und 2 gestiegen. Obwohl es unterschiedliche Insuline, orale Antidiabetika und Therapieschemata sowie spezielle Schulungen für Diabetespatienten gibt, fällt es vielen Patienten, jugendlichen wie erwachsenen, dennoch schwer, eine optimale Diabeteseinstellung zu erzielen und auch langfristig zu erhalten. Eine schlechte Diabeteseinstellung kann zu teilweise schwerwiegenden und lebensverkürzenden Kurzzeitkomplikationen und/oder Langzeitfolgen führen. Folglich beschäftigt sich diese Arbeit mit der Identifizierung von relevanten sowie effektiven pharmazeutischen Betreuungsinhalten für jugendliche sowie erwachsene Patienten mit Diabetes mellitus Typ 1 und 2 zur Optimierung der Diabetesbetreuung durch öffentliche Apotheker.

Im ersten Abschnitt der Arbeit wird die Fragestellung untersucht, welche Anpassungen der Insulintherapie oder Änderungen des Lebensstils von jugendlichen Patienten mit Diabetes mellitus Typ 1 in der DIADEMA-Studie übernommen wurden, um ihre Diabeteseinstellung zu verbessern. Die Analyse der Studiendaten ergab, dass insbesondere häufigere Blutzuckermessungen und damit zusammenhängend eine bessere Berechnung der Insulinmenge sowie das Vorhandensein eines Ernährungsplans zielführend waren. Zusätzlich werden in diesem Abschnitt anhand eines Patientenfalls die relevanten pharmazeutischen Betreuungselemente der DIADEMA-Studie herausgearbeitet.

Um einen genauen Überblick über die aktuelle Studienlage zu erhalten und um relevante und effektive pharmazeutische Betreuungsinhalte valide zu identifizieren, werden im zweiten Abschnitt der Arbeit die Ergebnisse einer systematischen Literaturrecherche sowie einer anschließenden Meta-Analyse von randomisierten kontrollierten Studien zur pharmazeutischen Betreuung von Diabetespatienten vorgestellt. Zusätzlich zur Identifizierung der besonders effektiven pharmazeutischen Betreuungsinhalte wurden die Elemente des zuvor durchgeführten Trainings der Studienapotheker untersucht und deskriptiv ausgewertet.

Drittens wurde im Rahmen einer qualitativen Studie (Fallserie) die Umsetzbarkeit der zuvor identifizierten vier effektiven pharmazeutischen Betreuungsinhalte erfolgreich sowie praxisnah getestet. Es konnte eine Hypothese zum positiven Effekt dieser pharmazeutischen Betreuungsinhalte auf insbesondere den Nüchternblutzuckerwert, den Medication-Appropriateness-Index, den WHO-5 well-being Index sowie die Anzahl an arzneimittelbezogenen Problemen formuliert werden. Zudem werden Empfehlungen gegeben für die Durchführung von weiterführenden, hypothesenprüfenden Studien.

Viertens wurde anhand von zwei Patientenfällen untersucht, inwieweit die aktuelle Version der Diabetes:M Application die Apotheker bei der Umsetzung der vier effektiven pharmazeutischen Betreuungsinhalte unterstützt. Die Diabetes:M Application bietet zwar einige Funktionen, welche den Apotheker bei der Durchführung der pharmazeutischen Betreuung unterstützen können. Jedoch fehlt es der aktuellen Version dieser Application gerade im Hinblick auf die Durchführung einer Medikationsanalyse oder bei der interprofessionellen Zusammenarbeit an unterstützenden Funktionen.

IV Aims and rationale of this thesis

There is a lack of knowledge regarding the effectiveness of pharmaceutical care for patients with type 1 and 2 diabetes mellitus provided by community pharmacists. Furthermore, there is a lack of knowledge as to which of the various pharmaceutical care components are effective at improving the glycemic control of diabetes patients, measured by glycated hemoglobin values. Therefore, this dissertation aims to identify relevant pharmaceutical care components for patients with diabetes mellitus and to enable deeper insights into how effective and optimized pharmaceutical care can be provided by community pharmacists. In addition, the knowledge gained from these findings were tested in practice.

Chapter 1: Optimized pharmaceutical care interventions for adolescent type 1 diabetes patients

The aim of the first chapter of this thesis was to quantitatively analyze the implementation of pharmaceutical care for adolescent type 1 diabetes mellitus provided by community pharmacists. Moreover, further information was generated about pharmaceutical care for patients with diabetes mellitus type 1 in general and special challenges for adolescent patients with diabetes mellitus type 1. The effects of pharmaceutical care on the following parameters were analyzed:

- Insulin therapy adjustments
- Acute diabetes complications
- Lifestyle changes

In addition, a representative patient case was chosen and described in detail, to illustrate pharmaceutical care for adolescent patients with diabetes mellitus type 1.

Chapter 2: Systematic literature review and meta-analysis of effective pharmaceutical care interventions provided by community pharmacists for patients with type 1 or 2 diabetes

The findings and results from the DIADEMA study led to the question: which pharmaceutical care components for diabetes mellitus patients are particularly effective? To date there has been no investigation of which pharmaceutical care components provided by community pharmacists for patients with diabetes mellitus type 1 and 2 are the most effective. In order to identify particularly effective pharmaceutical care components a systematic review and subsequent meta-analysis of the identified components for patients with diabetes mellitus type 1 and 2 provided by community pharmacists was conducted. The primary aim of this chapter was to identify effective pharmaceutical care components for patients with type 1 and 2 diabetes mellitus. The secondary aim was to identify and descriptively analyze elements of the training received by the study pharmacists.

Chapter 3: Proof of concept study to demonstrate the practicability of the four most effective pharmaceutical care interventions during a patient consult

After identification of particularly effective pharmaceutical care components for patients with diabetes mellitus in the second chapter, four of the most effective pharmaceutical care components were implemented in a realistic community pharmacy setting. A case series was designed and conducted to test the feasibility of these four components in practice. The secondary aim of this case series was to formulate hypotheses on the effect of this optimized pharmaceutical care on diabetes patients' glycemic control and to gain opportunities for improvement of this concept. One of the identified opportunities for improvement is the use of electronic health such as a diabetes mobile application for e.g., the documentation of patients' blood glucose values.

Chapter 4: Mobile health support for diabetes type 1 and 2 patients to support pharmaceutical care components in practice

The primary aim of this fourth chapter is to qualitatively test the option of using mobile health support for diabetes mellitus type 1 and 2 patients to support the implementation of pharmaceutical care components in practice. The mobile application Diabetes:M was used to evaluate mobile health support for the identified four pharmaceutical care components. It is intended that the results of this chapter will be used to formulate reasonable hypotheses and determine relevant parameters for future hypothesis-testing studies. To get a realistic insight and assessment, data from real patients was used.

V Table of contents

1 General introduction of type 1 and 2 diabetes mellitus

1.1 Definition, classification, and diagnosis of type 1 and 2 diabetes mellitus

Diabetes mellitus type 1

Type 1 diabetes mellitus (T1DM) is defined as absolute insulin deficiency due to autoimmune and/or idiopathic progressive beta cell destruction. Patients with diabetes, especially at onset, typically have symptoms of polyuria, polydipsia, and weight loss, and approximately one-third of patients have diabetic ketoacidosis (DKA). Often, the onset and diagnosis of T1DM is in childhood. (ADA 2019a, DiMeglio et al. 2018b, Mayer-Davis et al. 2018) In adulthood the symptoms of diabetes can greatly vary, and the classic symptoms may not be present. T1DM can occur at any age, and up to 50% of cases are diagnosed in adulthood. (DiMeglio et al. 2018b)

Islet autoimmunity and beta cell dysfunction begins months to years before the diagnosis of T1DM; during this time, insulin autoantibodies can be detected as markers of beta cell autoimmunity. The first stage and the onset of T1DM is defined by normoglycemia, the presence of autoimmunity (multiple islet antibodies), and pre-symptoms (see Figure 1). Only the presence of multiple autoantibodies can be used to diagnose diabetes at this stage. (Couper et al. 2018)

In addition to pre-symptoms and autoimmunity, the next stage is characterized by dysglycemia. Diagnostic methods at this stage test for impaired fasting blood glucose (IFG) and/or impaired glucose tolerance (IGT). Measurement of fasting plasma glucose levels, measurement of 2 hour plasma glucose levels after an oral glucose tolerance test (oGTT), and measurement of glycated hemoglobin (HbA1c) values can be done at this stage. Fasting blood glucose (FBG) is defined as blood glucose after no caloric intake for at least 8 hours. The thresholds and recommended ranges for FBG, 2-hour plasma glucose, and HbA1c according to the current American Diabetes Association (ADA) guideline are listed in Table 1. The final stage is defined by new-onset hyperglycemia and diabetes symptoms; thus, it can be diagnosed by clinical symptoms and the abovementioned tests. (ADA 2019a, Couper et al. 2018)

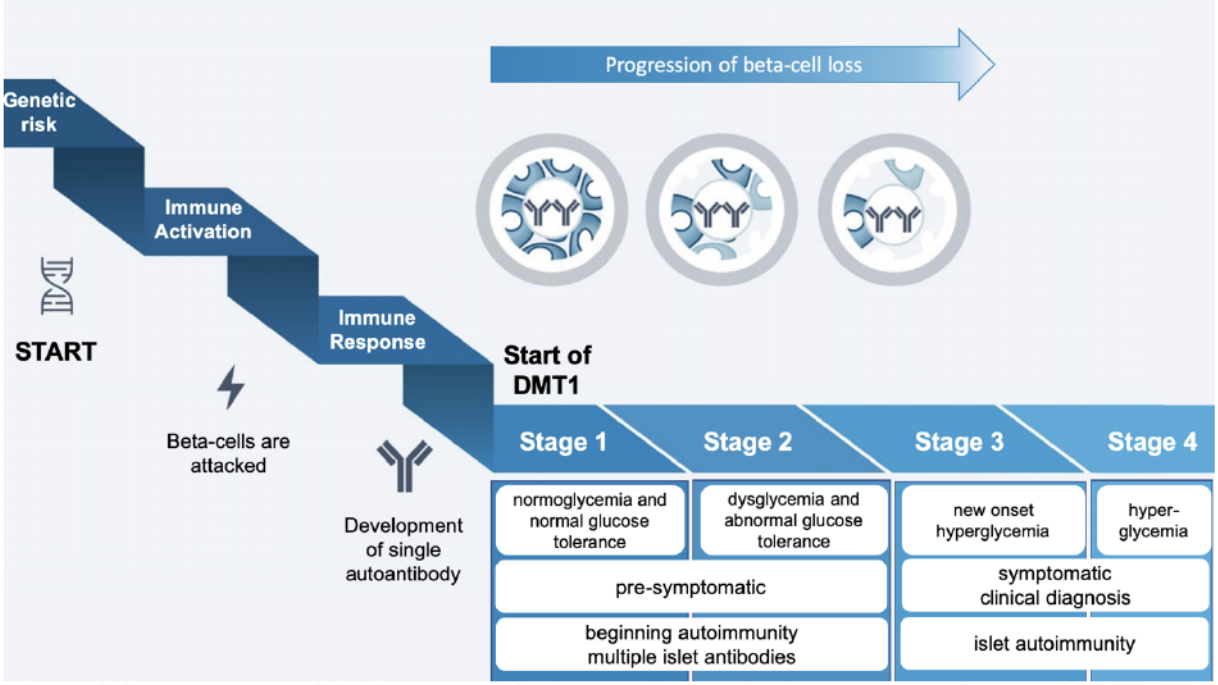


Figure 1 Stages to type 1 diabetes modified according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) Guidelines 2018 (Couper et al. 2018)

Table 1 Thresholds and recommended ranges for impaired fasting glucose and/or impaired glucose tolerance (ADA 2019a)

	Threshold	Recommended range
Fasting glucose levels [mg/dl]	>126	100–125
2-hour plasma glucose levels [mg/dl]	>200	140-199
Glycated hemoglobin values [%]	>6.5	5.7–6.4

Diabetes mellitus type 2

Patients with type 2 diabetes mellitus (T2DM) experience a progressive loss of beta cells, which leads to reduced insulin secretion. In many cases, the cause is insulin resistance. In contrast to T1DM, this loss of beta cells is not caused by autoimmunity.

Age brackets were often used in the past to classify or define the different types of diabetes, but these are no longer used because of the decreasing age of T2DM onset. (ADA 2019a, Kao et al. 2016) Various genetic and environmental factors can lead to a progressive loss of beta cells in the pancreas in both type 1 and 2 diabetes (see Table 2). (ADA 2019a)

Patients with T2DM have IFG and/or IGT similar to T1DM patients. Both IFG and IGT can be detected with an oGTT and the subsequent measurement of FBG or 2-hour plasma glucose levels. It is also recommended to measure the HbA1c value. The same threshold values are used for both T1DM and T2DM. (ADA 2019a)

Table 2 Overview of clinical characteristics of T1DM and T2DM in children and adolescents (Mayer-Davis et al. 2018, Tuomi et al. 2014)

Characteristic	T1DM Children and adolescents	T2DM Children and adolescents
Genetics	Polygenic	
Age of onset	>6–12 months	Pubertal (or later)
Clinical presentation	Acute, rapid	Variable: mild to severe
Symptoms	Polyuria, polydipsia, weight loss, tiredness	Often no diabetes symptoms at beginning
Insulin secretion	None or less	Subnormal to high
Insulin sensitivity	Normal	Subnormal
Associations		
Autoimmunity	Yes	No
Diabetes-associated antibodies	Yes	Rare
Ketosis	Common	Rare
Obesity	Population frequency	Increased frequency
Acanthosis nigricans	No	Yes
Incidence [%] in relation to all diabetes diseases	Approximately 90	<10
Parent with diabetes [%]	2–4	80

The ADA recommends an informal diabetes risk test for patients who have prediabetes. Patients who are older than 45 and have one or more risk factors should be screened for diabetes. The current guidelines contain no recommendation for the screening interval. However, patients with diagnosed prediabetes (HbA1c >5.7% and IGT or IFG) should be tested yearly, and women who had gestational diabetes mellitus should be tested throughout life approximately every 3 years. (ADA 2019a)

The risk factors for T2DM, modified according to the current ADA guidelines (ADA 2019a) are:

- First-degree relative with diabetes
- High-risk ethnicity, e.g., African American, Latino, Native American, Asian American, Pacific Islander
- History of cardiovascular disease (CVD)
- Hypertension (>140/90 mmHg or on therapy for hypertension)
- High-density lipoproteins (HDL), cholesterol level <35 mg/dl and/or a triglyceride (TG) level >250 mg/dl
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance

1.2 Epidemiology of type 1 and 2 diabetes mellitus

T1DM is one of the most common chronic endocrine diseases in childhood. Both the prevalence and incidence of T1DM and T2DM have increased in recent decades. (Demirel et al. 2013, Saeedi et al. 2019) Both the incidence and age-standardized incidence rate of diabetes mellitus increased significantly between 1990 and 2017 worldwide. (Liu et al. 2020) In 2019, 463 million people aged 20 to 79 years worldwide had diabetes, including 59 million people in Europe alone. It is predicted that there will be a 51% increase in the number of diabetes patients worldwide to approximately 700 million by 2045. In Europe, the predicted increase is smaller (15%), and it is predicted that in 2045 there will be 68 million diabetes patients. The prevalence of diabetes mellitus in adults aged 20 to 79 years was 9.3% in 2019, rising to 10.9% by 2045. The prevalence is higher in high-income countries and in urban areas (10.8%) than in rural areas (7.2%). (Saeedi et al. 2019)

An estimated 108,300 children under 15 years will be diagnosed T1DM in 2021. (Ogle et al. 2021) 2019, 1,110,100 children and adolescents worldwide had T1DM, and the prevalence has increased. (DiMeglio et al. 2018b, Saeedi et al. 2019) A 2009–2010 statistical analysis of the age-adjusted prevalence and incidence of T2DM in Germany showed that there was a steep increase in both prevalence and incidence from age 50 to 80. (Tamayo et al. 2016)

Many studies demonstrate the increasing global burden of diabetes (Khan et al. 2020, Lin et al. 2020, Liu et al. 2020) due to, among other things, demographic changes and their influence on health care. (Blüher et al. 2016) By 2050, the number of people over 65 in Germany will increase by 38% and the number over 80 by 156%. The incidence of age-related diseases such as T2DM will increase sharply by 2050 under the assumption of unchanged disease probabilities. (Peters et al. 2010) These increasing incidences, prevalences, and age-standardized incidence rates of diabetes mellitus and predictions regarding the future increase in the number of diabetes patients point to the growing need for effective antihyperglycemic drug treatments and other non-drug lifestyle measures for both T1DM and T2DM. Therefore, it is essential to provide, in addition to current standard care, optimized, targeted and individual pharmaceutical care (PhC) for patients with diabetes mellitus in community pharmacies.

1.3 Therapy for diabetes type 1 and 2

To be able to provide effective evidence-based individual PhC for patients with diabetes mellitus, pharmacists need expertise in current diabetes therapy and must know the guideline recommendations. This following chapter summarizes the pharmacological basics and most important aspects of the current guideline recommendations for diabetes therapy, including findings from recent studies, and explains the long- and short-term goals of diabetes therapy.

1.3.1 Insulin therapy for diabetes type 1 and 2

Insulin therapy for children and adolescents with type 1 diabetes mellitus

The treatment of T1DM is complex, especially in childhood and adolescence, and many aspects need to be considered. The required daily insulin dose depends on factors such as age, weight, stage of puberty, current phase of diabetes disease, and diabetes duration. Further factors that influence the required insulin dose include the state of injection sites, nutritional intake and distribution of meals, exercise, results of blood glucose monitoring and HbA1c levels, and intercurrent illness. These additional factors also need to be considered in other age groups. (Danne et al. 2018)

The insulin dose should be chosen to achieve the best attainable glycemic control and to avoid hypoglycemia or growth impairments. Prepubescent children need less insulin per kilogram body weight (0.7–1.0 IU/kg/day) than adolescents during puberty (>1.0 IU/kg/day and even up to 2.0 IU/kg/day). Patients need less insulin during the partial remission phase of the disease (<0.5 IU/kg/day). This phase is also called the honeymoon phase; during this phase of diabetes, insulin secretion in the pancreas increases temporarily until it stops completely. (Danne et al. 2018) Adult diabetes patients need 0.4–1.0 IU/kg/day of insulin. (ADA 2019a) The recommended calculations for the amount of carbohydrates covered by one insulin dose or the effect of each insulin dose on the reduction of blood glucose levels are listed in Appendix X 1. The total daily insulin dose should be adjusted if the target blood glucose level and/or HbA1c value is not achieved.

Insulin therapy for geriatric patients with type 1 and 2 diabetes mellitus

The insulin and HbA1c target levels depend on the geriatric patient's current health status and life expectancy. The individual recommended HbA1c target for geriatric patients is commonly 7.0–8.5%; the main aims are freedom from diabetes symptoms and to avoid hypoglycemia. In individual cases, if the patient is very old, has a short life-expectancy, or is cognitively impaired

but free of diabetes symptoms, the tolerable HbA1c value can be up to 9.0%. The initiation of insulin therapy is only recommended if lifestyle changes and other antidiabetic drugs cannot achieve the individual therapy goal or if other antidiabetic drugs are contraindicated. (Bahrmann et al. 2018)

Types of insulin therapy

Due to differences in patient lifestyles, such as eating habits and the amount of exercise, there are varying requirements for insulin therapy. Thus, there are currently several different types of insulin therapy available. Currently, intensified conventional insulin therapy (ICT) is the insulin therapy of choice for T1DM patients (see Table 3 and Appendix X 2). (Danne et al. 2018, DDG 2018) The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study cohort revealed that mortality was higher in the Conventional insulin therapy (CT) group, and the mortality increased significantly with increasing mean HbA1c, especially for HbA1c values >9%. (DCCT-/EDIC-Research-Group 2016) Other research (also a DCCT study cohort) indicated that ICT significantly reduced the long-term risk of clinical CVD and has long-term beneficial effects on the risk of CVD in patients with T1DM. (Cleary et al. 2006, Nathan et al. 2005)

CT is characterized by inflexible carbohydrate intake and a fixed insulin injection scheme. Supplementary insulin therapy (SIT) is only appropriate for the treatment of T2DM, and consists of bolus insulin injections at every main meal and the additional intake of oral antidiabetic drugs (OADs); e.g. metformin. (Landgraf 2014) Another type of insulin therapy that is only recommended for the treatment of T2DM is basal-supported oral therapy (BOT). (Landgraf 2014) Patients are treated with one or more antidiabetic drugs and also inject basal insulin in the late evening or right before they go to bed (see Appendix X 2). If a combination of two or three antidiabetic drugs is insufficient, then BOT is the next recommended insulin therapy in most cases. (Landgraf et al. 2019) One type of BOT is the combination of basal insulin with a glucagon-like peptide receptor agonist (GLP-1 RA) administered subcutaneously (SC) with or without an OAD. The advantage of this combination is that less insulin is needed, and the therapy is therefore weight neutral or associated with less weight gain. A disadvantage is the moderate gastrointestinal tolerance, especially at the beginning of therapy. (BÄK 2021)

Table 3 Overview different types of insulin therapy and their characteristics

	Intensified conventional insulin therapy (ICT)	Conventional insulin therapy (CT)	Supplementary insulin therapy (SIT)	Basal-supported oral therapy (BOT)	Continuous subcutaneous insulin infusion (CSII)
Characteristics	- Requires bolus insulin (coverage of carbohydrate intake) and basal insulin for the (basic insulin needs)[1,2] - More flexible with the amount of carbohydrate intake and timing of meals[1] - Possible restrictions for overweight T2DM patients: weight gain - Highest incidence of hypoglycemic episodes, especially patients with poor glycemic control	- Strict injection schedule with fixed insulin dose[1] - NPH- or mixed insulin is used[1] - Meal planning due to inflexible carbohydrate intake[1] - Dose adjustments and/or changes in food intake and/or physical exercise are needed if there are recurring blood glucose fluctuations or during acute illness[1]	- Advantages: adaptation to flexible and spontaneous eating habits, as well as the adaptation to shift work and strongly changing physical stress[1] - Relatively high risk of hypoglycemia compared to other insulin therapies, except ICT[1]	- Compared to ICT, BOT has lower hypoglycemic rates and typically results in positive body weight progress[9] - Advantages: Reduction of FBG levels, a meal-independent injection, and easy-to-perform monitoring[1]	- CSII therapy had a positive impact on CV morality[11] - Automatically injection of a fixed basal rate of (ultra)-rapid-acting analogs, or regular insulin and the patient calculates the adjusted insulin rate for each meal - Advantages: Insulin pump data can be downloaded and visualized on a computer to identify usage patterns[3,4]
Current guideline recommendations	- First choice for T1DM patients[3,4] - More frequent SMBG required: children and adolescents 6 to 10 times a day[3,5,6]; adults and geriatric patients 4 times a day[4,6,7-10] - More frequent SMBG required in special situations, such as before, during, or after exercise or after hypoglycemia[4,6,7,10] - Large amount of training required, because of the more difficult handling[1]	- Children and adolescents with T1DM: not recommended[3] - SMBG frequency depends on different factors such as current state of glycemic control[4,6]; at least twice a day[10] - Example geriatric T2DM patients: one measurement once a week before each injection[8] - Regular training on how to implement this therapy correctly is necessary[1]	- Recommended only for T2DM patients[1,2] - SMBG with four measurements per day is recommended[1]; only once per week four times a day for geriatric T2DM patients[8] - Increased training requirement[1]	- SMBG frequency: at least twice a day[10] and monthly four times a day; if the basal insulin dose needs to be adjusted then the FBG value is essential and should be measured by the patient[1,4] - Low training requirements[1]	- Preferable and widely used especially in children and adolescents who are not achieving their individual therapeutic goals or have reoccurring hypoglycemia[3] - Rarely indicated in patients with T2DM[1] - Optimal treatment is the combination of CSII with continuous glucose monitoring systems (CGMS)[1,3,4] - No valid meta-analytical difference: positive effect on the quality of life (QoL) of diabetes patients[12]

[1] Bundesärztekammer 2021; [2] Landgraf 2014; [3] Danne et al. 2018; [4] DDG 2018; [5] Abraham et al. 2018; [6] DiMeglio et al. 2018a; [7] Heinemann et al. 2019; [8] Bahrmann et al. 2018; [9] Landgraf et al. 2019; [10] Schlüter et al. 2021; [11] Steineck et al. 2015 (Steineck et al. 2015); [12] Barnard et al. 2007 (Barnard et al. 2007)

Abbreviations: CV: cardiovascular, CGMS: continuous glucose monitoring system, FBG: fasting blood glucose, NPH: Neutral Protamin Hagedorn, SMBG: self-measuremnt of blood glucose, T1DM: diabetes mellitus type 1, T2DM: diabetes mellitus type 2

The use of insulin pumps, also known as continuous subcutaneous insulin infusion (CSII), in conjunction with ICT is the recommended first-line therapy for children, adolescents, and adults with T1DM. (ADA 2019a, Danne et al. 2018, DDG 2018) In Germany, patients need a prescription and also specific order forms from their physician to apply for an insulin pump. If necessary, the Medical Service of Health Insurance (Medizinischer Dienst der Krankenversicherung; MDK) intervenes and contacts patients directly if further data is required. (Medtronic 2021)

A continuous glucose monitoring system (CGMS) continuously measures the blood glucose level at regular intervals. The measured blood glucose values are translated into dynamic data to show the direction and rate of change of blood glucose. Therefore, the CGMS can warn the patient if their blood glucose is trending towards hypoglycemia or hyperglycemia. (Danne et al. 2018, DiMeglio et al. 2018a) CGMS have been show to improve glycemic control measured by HbA1c (Battelino et al. 2012, Beck et al. 2017, Tumminia et al. 2015), reduce hypoglycemia (especially severe hypoglycemia); (Battelino et al. 2011, Little et al. 2014) and improve quality of life (QoL). (Polonsky et al. 2017)

Different insulin types

According to the onset and duration of action, the different insulin types are classified into bolus insulin, such as ultra-rapid-acting analogs, rapid-acting analogs, and regular insulin and basal insulin, such as Neutral Protamin Hagedorn (NPH)-insulin and basal long-acting insulin analogs. To date, there is only one ultra-rapid-acting insulin, insulin faster aspart. Due to the fast absorption Insulin faster aspart is beneficial for T1DM patients with high postprandial blood glucose levels, especially patients with insulin pumps (see Table 4). (Heise et al. 2015) The long-acting analogs such as insulin glargine, glargine U300 and degludec are injected SC once a day. They can be injected at any time of day but preferably at the same time each day. (ADA 2019b, Danne et al. 2018)

At present, three insulin biosimilars are approved for use in Germany, two insulin glargine biosimilars and one insulin lispro biosimilar. A biosimilar for insulin aspart is currently under evaluation for pharmaceutical registration. (Dingermann 2020) There are no significant differences in clinical efficacy and safety between the insulin biosimilars and the originator insulins. (Yamada et al. 2018) Additionally, the recommended injection frequency or timing of injection for biosimilars is not substantially different from that of the originator insulins.

Table 4 Different types of insulin modified according to the ISPAD guidelines 2018 (Danne et al. 2018)

Insulin	Onset of action [h]	Peak of action [h]	Duration of action [h]	Application and characteristics
Ultra-rapid-acting analogs (bolus insulin)				
Insulin faster aspart	0.1–0.2	1–3	3–5	- Injection immediately before or 20 minutes after the start of the meal - Rapid absorption - 50% higher insulin effect within 30 minutes after injection - Lower postprandial glucose levels
Rapid-acting analogs (bolus insulin)				
Insulin aspart Insulin glulisine Insulin lispro	0.15–0.35	1–3	3–5	- Injection immediately before meals
Regular (short acting – bolus insulin)				
	0.5–1.0	2–4	3–5	- Injection 20 to 30 minutes before the meal
NPH insulin (basal insulin)				
	2–4	4–12	12–24	- Fixed injection scheme - Commonly injected twice a day, due to the shorter duration of action - Need to be mixed thoroughly prior to injection because NPH insulins are in the form of a suspension and insufficient mixing will result in an altered insulin effect
Basal long-acting analogs				
Insulin detemir	1–2	4–7	20–24	- Injection once a day (late evening) or twice a day (morning and late evening); depending on the occurrence of nocturnal hypoglycemia - Less nocturnal hypoglycemia compared to NPH-insulin
Insulin glargine U 100	2–4	8–12	22–24	- Injection once a day (late evening) - Acid pH – burning effect at the injection site possible - Glycemic efficacy comparable to insulin glargine U 300
Insulin glargine U300	2–6	Minimal peak	30–36	- Injection once a day (late evening) - Full effect after 3 to 5 days of use - Flatter time-action profile and longer duration of action than insulin glargine U100 and less hypoglycemia (Lau et al. 2017, Ritzel et al. 2018) – preferable if patients have or are at risk for nocturnal hypoglycemia
Insulin degludec	0.5–1.5	Minimal peak	>42	- Injection once a day (late evening) - Stringent timing required - less positive impact with erratic dosing - DEVOT study results: insulin degludec is more cost-effective than insulin glargine U 100 for patients with diabetes type 2, intensified insulin therapy that have a high cardiovascular risk (Pollock et al. 2019)

1.3.2 Non-insulin therapy options for patients with type 1 diabetes in Germany

According to guidelines, patients with T2DM should first implement dietary and lifestyle changes before beginning pharmaceutical therapy. (ADA 2019b, BÄK 2021, Landgraf et al. 2019) If these changes are unsuccessful and the therapy target is not achieved, there are different therapy options depending on the patient's comorbidities and other factors, such as the need to minimize weight gain or hypoglycemia. Metformin is the first-choice therapy according to the ADA and Deutsche Diabetes Gesellschaft (DDG) guidelines if there are no contraindications, e.g., renal insufficiency with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 (see Figure 2). (ADA 2019b, Landgraf et al. 2019) However, if the current HbA1c value is above 10% or blood glucose levels are several times above 500 mg/dL, the current ADA guidelines recommend to immediately begin insulin therapy. (ADA 2019b) According to the partial publication of the current Nationale VersorgungsLeitlinie (NVL) T2DM guideline, patients with clinically relevant CVD should receive a combination of metformin and a sodium-dependent glucose co-transporter 2 (SGLT-2) inhibitor or a GLP-1 RA. (BÄK 2021)

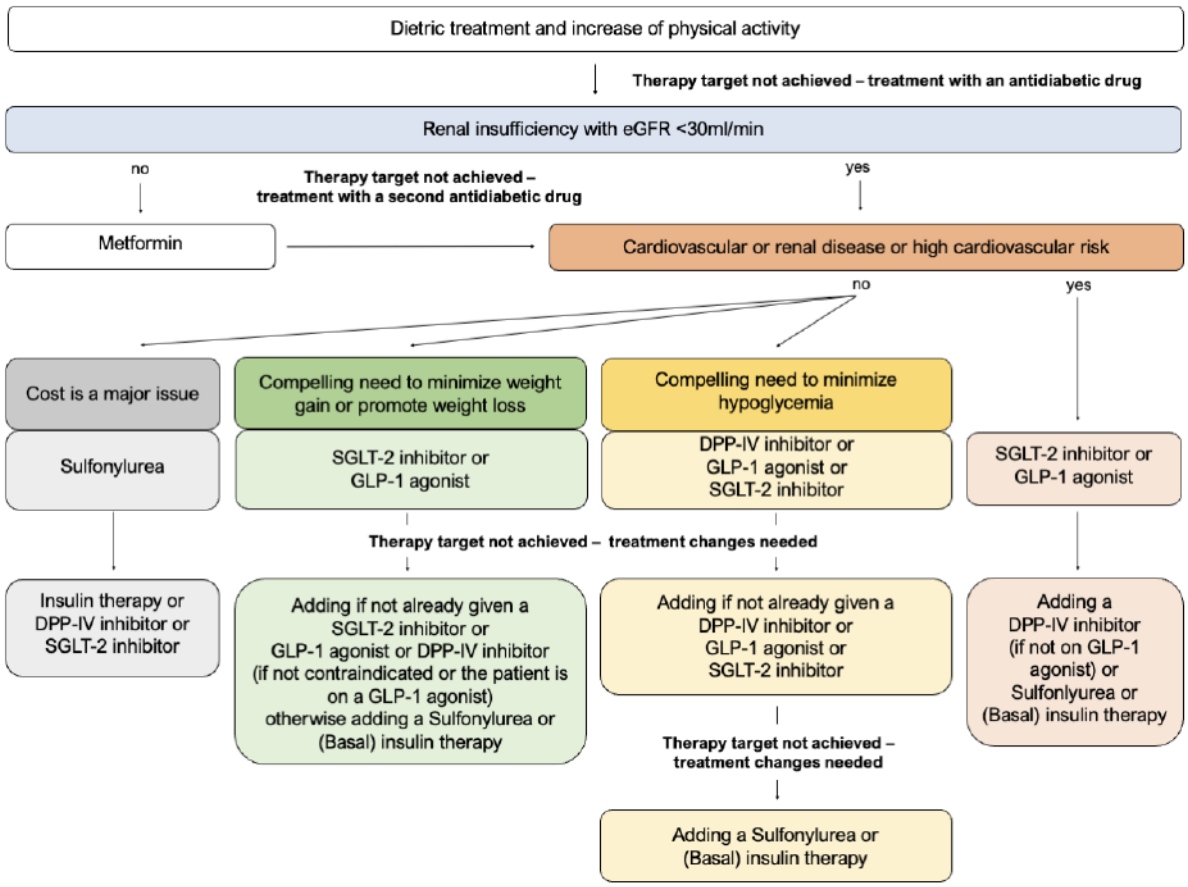


Figure 2 Therapy recommendations for patients with diabetes mellitus type 2 according to ADA and DDG practice guidelines (ADA 2019b, Landgraf et al. 2019)

Abbreviations: DDP-IV: dipeptidyl peptidase IV, eGFR: estimated glomerular filtration rate, GLP-1: glucagon like peptide 1, SGLT-2: sodium dependent glucose co-transporter 2

The current recommended therapy for T2DM patients is adapted to the patient's individual and current comorbidities and risk factors. Drugs are recommended, which have a beneficial effect proven by clinical studies on the patient's comorbidities and diabetes sequelae. Only focusing on improving glycemic control measured by the HbA1c value without considering the possible and actual individual risks of T2DM patients is obsolete. Further detailed information of the non-insulin diabetes therapy for children and adolescents is listed in the Appendix X 3. A meta-analysis by Palmer et al stated that the analyzed, currently used antidiabetic drugs were estimated to be effective when added to metformin, and the selection of the additional therapy or drug(s) should be based on patient-specific considerations. (Palmer et al. 2016)

In the UK Prospective Diabetes Study (UKPDS), metformin as a monotherapy was advantageous for diet-treated overweight T2DM patients; therefore, metformin is the first choice for the treatment of T2DM after implementing lifestyle changes. (UKPDS-Group 1998a) On metformin, there was no increased risk for hypoglycemic episodes (see Table 5), and the risk for developing lactic acidosis as a side-effect was increased in patients with eGFR less than 30 mL/min/1.73m^2. (Lazarus et al. 2018) It is uncertain whether metformin has a cardioprotective effect or reduces the risk of CVD in T2DM patients. (Griffin et al. 2017) Nevertheless, metformin is the recommended first-line therapy. Other antidiabetics and/or insulin therapy is recommended only if there are contraindications or if treatment with metformin is not successful in achieving individual therapy targets. (ADA 2019b, Landgraf et al. 2019, Maruthur et al. 2016) Further information about the mode of action of metformin and other non-insulin diabetes therapy options is listed in Appendix X 4.

A summary by Ceriello lists the advantages (e.g. cost-effectiveness) and disadvantages (e.g. side effects such as hypoglycemia) of sulfonylureas. (Ceriello 2020) A 2016 meta-analysis by Rados et al. concluded that the use of sulfonylureas was not associated with an increased risk of all-cause mortality, CV mortality, myocardial infarction, or stroke. (Rados et al. 2016) Other meta-analyses came to a different conclusion regarding the risk of major CVD-related events with sulfonylureas compared to other OADs. (Azoulay et al. 2017, Bain et al. 2017) Results of the CAROLINA trial revealed that glimepiride carries no greater CV risk than linagliptin. (Rosenstock et al. 2019a, Santamarina et al. 2019) Glinide therapy is not as common in Germany because the Gemeinsame Bundesausschuss der Krankenkassen und Ärzte (GBA) (the Federal Joint Committee of Insurance Companies and Physicians) has removed glinides from the list of OADs that are reimbursed by German health insurance organizations. There is one exception for repaglinide—when the eGFR is less than 25 mL/min/1.73m^2 and if other OADs or an insulin therapy is not applicable or is contraindicated. (GBA 2016)

Results of the LEADER study revealed that liraglutide, a GLP-1 RA, decreased CV mortality (Marso et al. 2016b) and major adverse CV events in patients with heart failure (Marso et al. 2020). In addition, liraglutide also protects against the development and progression of diabetic kidney disease (DKD). (Mann et al. 2017) In the SAVOR trial, treatment with saxagliptin resulted in improved renal outcomes such as an improved albumin/creatinine ratio in T2DM patients. (Mosenzon et al. 2017) The TECOS trial evaluated the efficacy and safety of sitagliptin for patients with T2DM and CVD and found that sitagliptin did not increase the risk of major adverse CV events or the risk of hospitalization for heart failure. Sitagliptin had no effect on CV events. (Bethel et al. 2017, Green et al. 2015) In the CARMELINA trial, adults with T2DM and high CV and renal risk received linagliptin in addition to standard care. Compared to placebo, linagliptin did not alter the risk of composite CV outcome. (Rosenstock et al. 2019b) A comparison between a combination of metformin and sulfonylureas and metformin and dipeptidyl peptidase IV inhibitors (DPP-IV inhibitors) showed that patients treated with DPP-IV inhibitors had a significantly lower relative risk of non-fatal CV events, as well as lower CVD mortality and all-cause mortality. (Wang et al. 2017) A meta-analysis by Kristensen et al. concluded that treatment with GLP-1 RAs has beneficial effects on CV endpoints and renal outcomes in patients with T2DM. 7 studies were included in this meta-analysis: the ELIXA trial with lixisenatide (Pfeffer et al. 2015), LEADER trial with liraglutide (Marso et al. 2016b), SUSTAIN-6 trial with semaglutide (Marso et al. 2016a), EXSCEL trial with exenatide (Holman et al. 2017), Harmony Outcomes trial with albiglutide (Hernandez et al. 2018), REWIND trial with dulaglutide (Gerstein et al. 2019), and PIONEER 6 trial with oral semaglutide (Husain et al. 2019). (Kristensen et al. 2019)

Renal SGLT-2 provides 90% of the glucose reabsorption; inhibition of SGLT-2 leads to increased glucose excretion in the urine (glucosuria). (Bakris et al. 2009, Mutschler 2020) Therefore, SGLT-2 inhibitors can be used regardless of pancreatic insulin secretion, and the risk of hypoglycemia is low (Grempler et al. 2012), especially if e.g. empagliflozin is administered alone or in combination with metformin, or metformin and a sulfonylurea. The use of combined insulin secretagogues or insulin combined with empagliflozin leads to an increased risk of hypoglycemia. (Ndefo et al. 2015) Studies have found that SGLT-2 inhibitors, in particular canagliflozin (CANVAS study) and empagliflozin (EMPA REG OUTCOME study), have nephroprotective and cardioprotective effects and reduce mortality in T2DM patients who have high CV risk. (Fitchett et al. 2016, Mahaffey et al. 2018, Neal et al. 2017, Perkovic et al. 2018, Wanner et al. 2016, Zelniker et al. 2019, Zinman et al. 2015) In the declare-timi-58 study, therapy with dapagliflozin resulted in a lower rate of CV death or hospitalization in patients with heart failure compared with placebo; however, there was no significant difference in all-cause

mortality. (Wiviott et al. 2019) Another study with dapagliflozin concluded that in patients with heart failure and reduced ejection fraction, the risk of worsening heart failure or death from CV causes was lower in those who received dapagliflozin than in those who received placebo, whether or not diabetes was present. (McMurray et al. 2019) An analysis of data from the US Food and Drug Administration (FDA) revealed that SGLT-2 inhibitor-associated DKA can occur with any duration of use. (Fadini et al. 2017) A retrospective cohort study by Douros et al. revealed that therapy with SGLT-2 inhibitors was associated with an almost 3-fold increased risk of DKA in some T2DM patients. (Douros et al. 2020) Absolute insulin deficiency leads to reduced glucose utilization and enhanced lipolysis. This causes an increased delivery of free fatty acids (FFAs) to the liver. Elevated glucagon levels promote the oxidation of FFAs and therefore the production of ketone bodies, leading to the development of DKA (see Chapter 1.4.1 for a further detailed explanation of the development, diagnosis, and treatment of DKA).

Table 5 Drug-specific and patient factors to consider when selecting antihyperglycemic treatment in adults with type 2 diabetes modified according to the ADA guideline 2019 and DDG guideline 2021 (ADA 2019b, BÄK 2021)

Drug	Metformin	SGLT-2 inhibitors	GLP-1 RAs	DPP-IV inhibitors	Sulfonylureas and glinide	Alpha-glucosidase inhibitors
Efficacy	High	Intermediate[1] or high[2]	High	Intermediate	High	Low
Hypoglycemia risk	No	No	No	No	Yes	No
Weight change	Neutral	Loss	Loss	Neutral	Gain	Neural
Application	Oral	Oral	Subcutaneous	Oral	Oral	Oral
Beneficial effects	- Macro-vascular risk reduction - CV effects: potential benefit	- Canagliflozin and Empagliflozin: beneficial against the progression of DKD and cardioprotective - Dapagliflozin[3]: reduced risk for CV death	- Liraglutide: Beneficial effect against the progression of DKD and CV	- Monotherapy: no increased risk for hypoglycemia	- Microvascular risk reduction	
Additional information	- First-line therapy - Contraindication: eGFR <30 ml/min - Risk of lactate acidosis - Pause in case of illness	- Contraindication: eGFR <45 ml/min - Risk of genital infection, atypical ketoacidosis and Fournier gangrene - Pause in case of illness	- Gastrointestinal side effects and gallstones as an adverse reaction	- Increased risk of urinary infections - Increased risk for hypoglycemia in combination with sulfonylureas and insulin - Risk of pancreatitis and inflammatory	- Not recommended for patients with renal insufficiency or liver diseases - Risk of prolonged hypoglycemia	- Contraindication chronic bowels disease - Not recommended for patients with severe renal insufficiency or liver diseases

[1] ADA 2019b [2] BÄK 2021 [3] Wiviott et al. 2019
CV: cardiovascular disease; DPP-IV inhibitors: dipeptidyl peptidase IV inhibitors; DKD: diabetic kidney disease; eGFR: estimated glomerular filtration rate, GLP-1 RAs: glucagon-like peptide receptor agonists; SGLT-2 inhibitors: sodium-dependent glucose co-transporter 2 inhibitors

1.3.3 Short- and long-term goals of diabetes therapy

Setting short- and long-term goals is recommended for effective care of patients with diabetes mellitus. Some short- and long-term goals are recommended for all T1DM and T2DM patients, as follows: (ADA 2020, Danne et al. 2018, DDG 2018, DiMeglio et al. 2018a, Landgraf et al. 2019)

Short-term goals:

- Increase the patient's diabetes therapy competence and their empowerment to self-manage their diabetes
- Achieve or maintain optimal glycemic control and avoid acute complications, such as DKA or severe hypoglycemia
- Low glycemic variability (normalization of glycemia while minimizing hypoglycemia)
- Optimal control of possible comorbidities
- Achieve or maintain the quality of life and therapy compliance or adherence
- Measure the HbA1c value at least quarterly
- Regularly review glucose values and adjust therapy as necessary
- Achieve and maintain target values (Table 6)

Long-term goals:

- Reduce the risk for and prevent diabetes complications, such as nephropathy or neuropathy
- Reduce mortality

Table 6 Target values for the diabetes therapy in children, adolescents, and adults with T1DM or T2DM

	ISPAD guidelines for children and adolescents with T1DM or T2DM (DiMeglio et al. 2018a)	ADA guidelines for adults with T1DM or T2DM (ADA 2020)	DDG guidelines for adults with T2DM (BÄK 2013, zuletzt geändert: April 2014)
HbA1c value [%]	< 7.0*	< 7.0*	< 7.0*
FBG level [mg/dl]	70–130	80–130	100–125
Postprandial blood glucose level [mg/dl]	90–180	<180	140–199
Blood glucose level before going to bed [mg/dl]	80–140	n.a.	n.a.

* individual exceptions possible, e.g. if lower HbA1c values have resulted in an increase of hypoglycemic episodes
Abbreviations: ADA: American Diabetes Association, DDG: Deutsche Diabetes Gesellschaft, FBG: fasting blood glucose, HbA1c: glycated hemoglobin, ISPAD: international society for Pediatric and Adolescent Diabetes, n.a.: not available

Recent research has revealed the limitations of the HbA1c value. The HbA1c value provides only the average blood glucose level over the previous past 2–3 months and does not indicate

the patient's current glucose variability (recurring hypoglycemia or hyperglycemia). Nevertheless, the HbA1c value is a validated indicator of glycation and helps to assess the current risk of complications. (Danne et al. 2017) A new additional predictor for glycemic control is the time in range (TIR), which assesses the percentage of time within the target (most used) or hypoglycemic range and therefore also takes the patient's glucose variability into account. (Danne et al. 2019) Glucose variability can identify the deterioration of glycemic control more accurately than the HbA1c test can, thereby reducing the risk for developing diabetes-related microvascular complications. (Sartore et al. 2012, Smith-Palmer et al. 2014, Šoupal et al. 2014)

Specific goals for children and adolescents with T1DM or T2DM

Targeted guidelines address the requirements and particularities of diabetes therapy for children and adolescents. One goal is to treat the patient in a multidisciplinary team that includes a pediatrician diabetologist, diabetes educator, dietitian, and (if required) a psychologist. There should be an optimized and smooth transition of the patient to a health care team for adults when required. (Cameron et al. 2018)

Additional goals for adolescent patients with T1DM are:

- Manage diabetes symptoms and avoid DKA as a potential life-threating acute diabetes complication
- Monitor glucose using CGM or self-measurement of blood glucose (SMBG) measurements up to 6–10 times per day

Additional goals to prevent future complications are:

- Reduce carbohydrate and calorie intake (weight loss if necessary)
- Increase physical activity and exercise capacity

Specific goals for adult and geriatric patients with T1DM and T2DM

Adult and geriatric diabetes patients often have several comorbidities. Therefore, one of the short-term goals is to avoid, if possible, polypharmacy and to increase medication adherence. Another aspect that is more relevant for adult and geriatric patients is the prevention of medication side effects because these patients generally take a larger amount of medications. The prevention of acute complications (particularly hypoglycemia) is also important for geriatric patients because these patients often cannot treat hypoglycemia autonomously. Geriatric patients are more likely to have cognitive or motor impairments; hence, the diabetes therapy goals and the therapy itself must be adapted to the capabilities of the patient. (Bahrmann et al. 2018)

1.4 Acute and long-term diabetes complications

One of the main short-term goals is to achieve or maintain optimal glycemic control and avoid acute complications, such as DKA or severe hypoglycemia and reduce the risk for long-term diabetes complications, such as nephropathy or neuropathy. Therefore, this topic is an essential part of effective and optimized PhC and it is very important for diabetes patients and pharmacists to acquire and, if necessary, refresh expertise in this area.

1.4.1 Acute diabetes complications

Hypoglycemia

Hypoglycemia is the most common acute diabetes complication in T1DM and T2DM patients treated with insulin or sulfonylureas. Blood glucose levels under 70 mg/dL (3.9 mmol/L) are defined in clinical practice as the threshold value for initiating hypoglycemia treatment. (Abraham et al. 2018) Hypoglycemia is one of the main causes of diabetes-related early mortality. An analysis of patient data revealed that severe hypoglycemia was associated with a significant increase in the adjusted risks of major macrovascular events, major microvascular events, death from a CV cause, and death from any cause. (Patterson et al. 2007, Zoungas et al. 2010) The ADA and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines classify blood glucose levels <70 and ≥54 mg/dL as level 1 hypoglycemia or hypoglycemia, respectively, with the need for initiation of patient self-treatment. Blood glucose levels <54 mg/dL are classified as level 2 hypoglycemia or clinically important or serious hypoglycemia, respectively (Abraham et al. 2018, ADA 2020) Severe hypoglycemia is defined in all three guidelines as a severe event and indicated by an altered mental and/or physical state requiring external assistance for treatment; there is no blood glucose threshold. (ADA 2020) Hypoglycemic episodes start with the activation of the autonomic nervous system; this adrenergic reaction causes symptoms such as sweating, tremor, and palpitation (see Table 7).

Many risk factors can promote the occurrence of hypoglycemic episodes: injection of too high an insulin dose, too little carbohydrate intake, increased insulin-dependent glucose utilization, e.g. during exercise, increased insulin sensitivity, e.g. after exercise, reduced gluconeogenesis, e.g. after alcohol intake, or reduced insulin clearance due to renal failure. (Jameson 2018) The physiological processes that cause hypoglycemia in diabetes patients are illustrated in Figure 3.

Table 7 Hypoglycemic symptoms according to the DDG 2018 guideline for T1DM patients (DDG 2018)

Autonomic symptoms	Neuroglycopenic symptoms	Unspecific symptoms	
Sweating	Flight of ideas	Nausea	
Tremor	Logorrhea	Headache	
Increased appetite	Amnestic aphasia		
Palpitation	Irritability		
	Impaired vision		
	Headache		
	Anxiety		
	Drowsiness		
	Coordination difficulties		
	Consciousness impairments		Serious and severe hypoglycemia
	Loss of consciousness		
	Cramps		

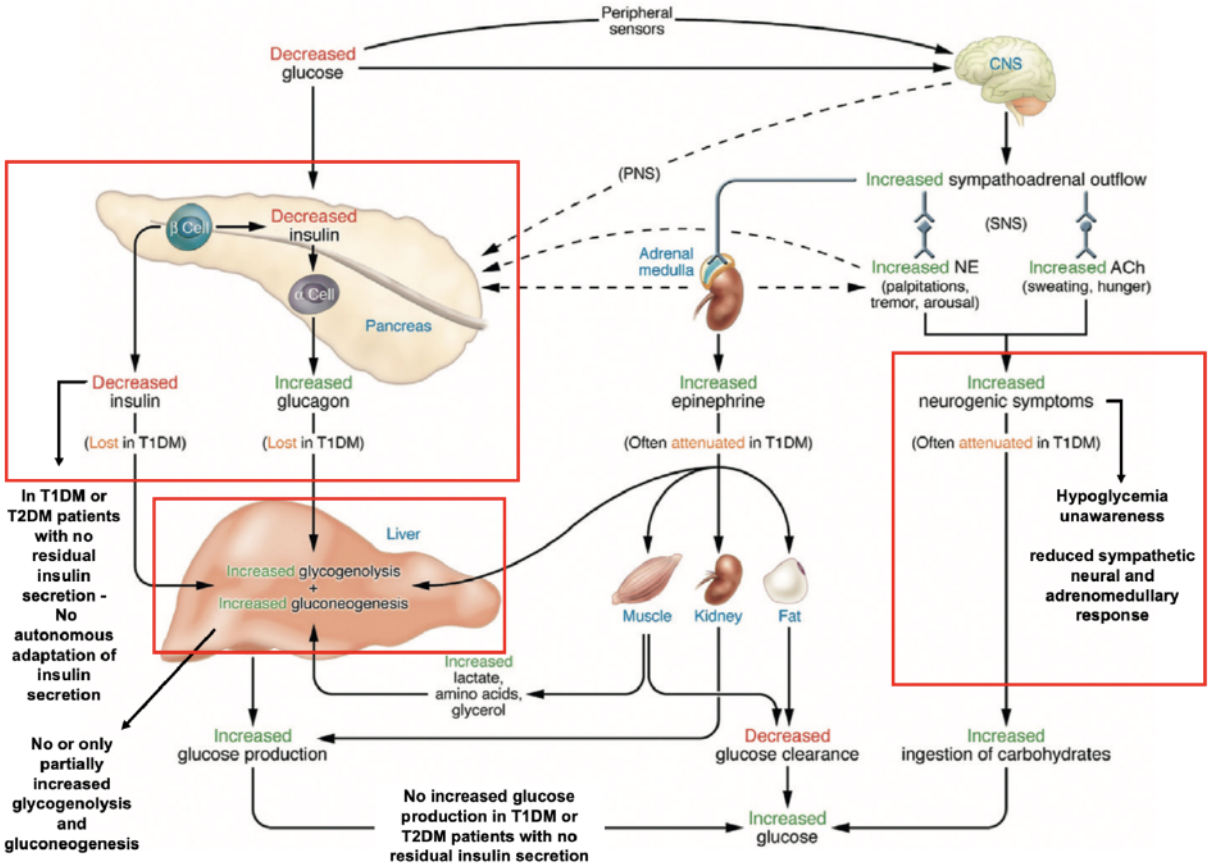


Figure 3 Physiology of glucose regulation including the mechanism for preventing and correcting hypoglycemic episodes and the relevant differences in T1DM and T2DM patients with no residual insulin secretion. Adapted from (Cryer et al. 2003).

Hypoglycemia is diagnosed according to the principle of Whipple's triad (Whipple 1938):

1) Signs and symptoms

2) Low plasma glucose concentration

3) Resolution of signs and symptoms after increase of plasma glucose concentration

Depending on the level of hypoglycemia, the currently recommended treatment for non-severe hypoglycemia is the administration of rapidly absorbed carbohydrates, such as a glucose solution or solid glucose. (ADA 2020) Adults should treat hypoglycemia with approximately 20 g of fast absorbing carbohydrates. (Brodows et al. 1984, Haak et al. 2018) The recommended amount of carbohydrates for children and adolescents is 0.3 g/kg bodyweight. (Abraham et al. 2018) After 15 minutes, the blood glucose level should be measured; if this is still <60 mg/dL then another 20 g of fast absorbing carbohydrates should be taken. If the blood glucose levels are very low and the patient is able to self-administer the glucose, the DDG recommends consuming 30 g of fast absorbing carbohydrates. Patients with severe hypoglycemia or who lose consciousness should be treated with 1 mg of glucagon intramuscularly (IM) or SC. Before the injection of glucagon, the unconscious patient should be brought into the rescue position because of the potential for vomiting. In the hospital, patients are treated with 50 mL of 40% glucose solution and 1 mg of glucagon. If the patient does not regain consciousness or the blood glucose levels are still too low, the whole procedure must be repeated. Glucagon is not effective if the patient has recently consumed alcohol. (Abraham et al. 2018, Haak et al. 2018)

Diabetic ketoacidosis

Risk factors for developing DKA include a high HbA1c value, longer diabetes duration, and adolescence. (Karges et al. 2015) The risk for developing DKA is high prior to T1DM diagnosis or at the beginning of insulin therapy in newly diagnosed T1DM patients, with frequencies varying widely from 12–80% between countries. (Usher-Smith et al. 2012) Other risk factors during insulin therapy are the omission of insulin or interrupted therapy. Patients using an insulin pump can develop DKA if an insulin pump failure occurs and is not recognized by the patient. (Wolfsdorf et al. 2018) For further information about the biochemical criteria, clinical signs and treatment of DKA, see Appendix X 5.

Hyperosmolar hyperglycemic state

The rate of hospital admission due to a hyperosmolar hyperglycemic state (HHS) is lower than for DKA. Less than 1% of all diabetes-related hospital admissions are related to HHS. (Fayfman et al. 2017) However, T2DM patients and (rarely) T1DM patients can develop HHS as an acute complication. (Wolfsdorf et al. 2018) HHS has higher mortality than DKA. (Cochran et al. 2006) Further information about the diagnosis and treatment of HHS are listed in Appendix X 5.

1.4.2 Long-term diabetes complications

To prevent the occurrence of micro- and macrovascular complications, diabetes patients should avoid repeated and lasting hyperglycemia. Risk factors for developing diabetes complications are a long diabetes duration e.g., more than 10 years, older age, and poor glycemic control during puberty. Further information about relevant screening methods, therapeutic aims and important additional information of long-term diabetes microvascular and macrovascular complications are listed in Appendix X 6. In the TODAY study of children and adolescents with T2DM, the prevalence of diabetes complications, such as hypertension and microalbuminuria, were assessed. Over the study period, the prevalence of hypertension and microalbuminuria increased. The risk for developing microalbuminuria was closely related to glycemic control. (TODAY-Studygroup 2013b) Screening for diabetic nephropathy, neuropathy, retinopathy, and diabetes-associated macrovascular diseases is recommended from the age of 11 years and after 2–5 years of diabetes duration for T1DM patients. (Donaghue et al. 2018) Patients with T2DM should be screened for diabetic neuropathy and retinopathy directly after diagnosis. (Hammes et al. 2019, Ziegler et al. 2019)

T1DM and T2DM patients with continuing, lasting hyperglycemia are at higher risk for the development of long-term diabetes complications, e.g., diabetic nephropathy as a result of microangiopathy. The so called “metabolic memory” phenomenon is based on the findings of the DCCT and EDIC study; poor metabolic control or continuing, lasting hyperglycemia is associated with changes in several cell types and a worsening ability of the endogenous vasoreparative system. The exact mechanism of metabolic memory is not known. (Berezin 2016, Misra et al. 2018) Oxidative stress is one of the key elements in the development and progression of diabetes-related complications. (Maritim et al. 2003, Rösen et al. 2001) There are several different oxidative stress pathways that influence the development and onset of diabetes disease and diabetes-related complications. One relevant pathway is the glucose oxidation (glycolysis) pathway. Due to hyperglycemia, glycolysis creates a precursor for advanced glycation end products (AGEs) and contributes to cellular oxidative stress. (Ighodaro 2018) Other complications such as arteriosclerosis and periphery circulatory disorders are a consequence of dyslipidemia (see Figure 4).

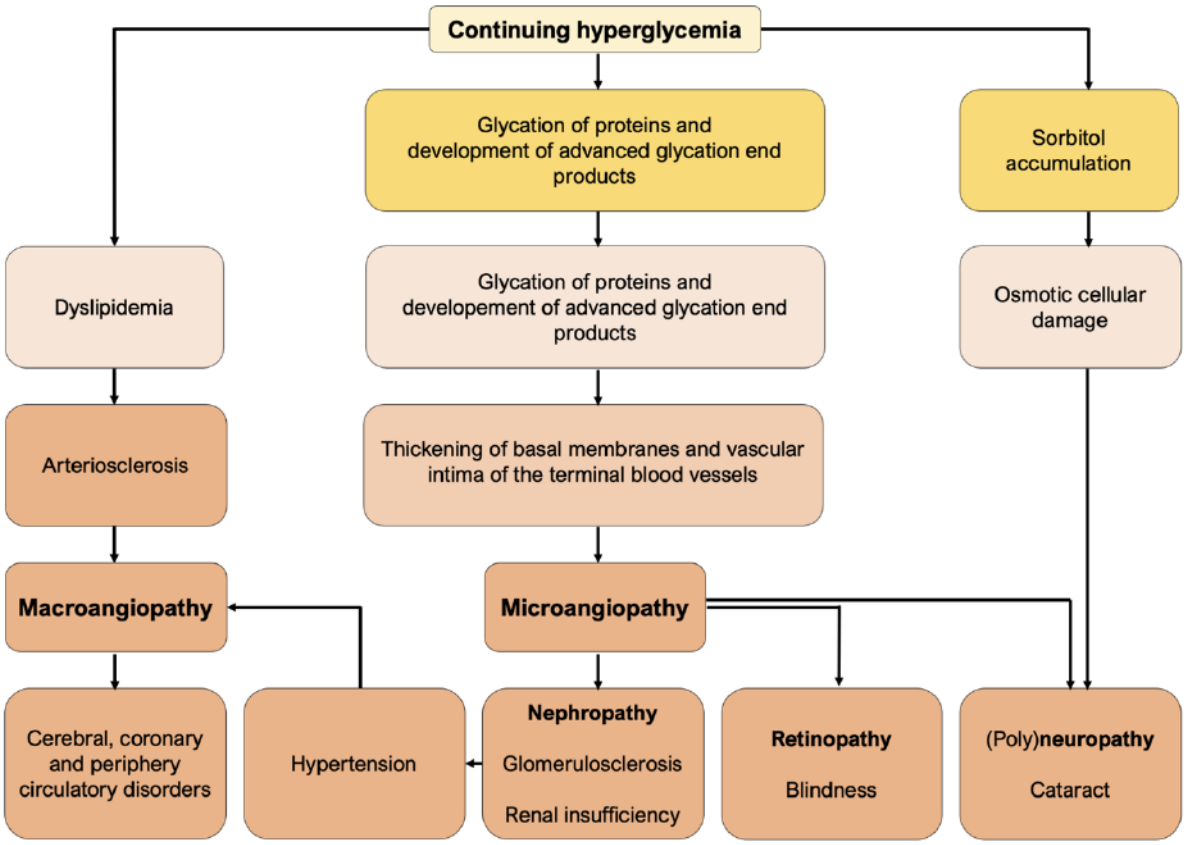


Figure 4 Development of long-term diabetes complications including micro- and macroangiopathy. Adapted from Deters et al. 2016

1.5 Current diabetes training and coaching content for diabetes mellitus type 1 and 2 patients

According to current guidelines, regular patient training should be used to help achieve or maintain optimal glycemic control and avoid acute complications such as DKA or severe hypoglycemia and reduce the risk of long-term diabetes complications. Depending on the patient's therapy regime, different diabetes training and coaching content is recommended for the patient (see Table 8). Patients with T1DM and T2DM should receive regular coaching from trained staff such as diabetologists, diabetes educators, or dietitians. (BÄK 2021, DDG 2018, Deutscher-Ärzteverlag 2022, Phelan et al. 2018) The German medical publisher "Deutsche Ärzteverlag" provides coaching content packages that contain important material and practical exercises for patients; the content of the training is DDG-recommended. (Deutscher-Ärzteverlag 2022)

Table 8 Training content for patients with diabetes mellitus according to current guidelines (BÄK 2021, DDG 2018, Deutscher-Ärzteverlag 2022, Phelan et al. 2018)

For all patients with diabetes mellitus	Only for patients with insulin therapy	Only for adolescent diabetes patients
Physiology basics (pathophysiology, epidemiology, classification, and metabolism)	Behavior in cases of sickness	Transition from adolescence to adulthood and sexual activity
Nutrition (e.g., explanation of how different food components affect the blood glucose levels)	Behavior while traveling or in other particular life circumstances	Exploration of the understanding of the training content
Monitoring of relevant parameters such as HbA1c, lipids, and albumin	Particular aspects for patients who attend kindergarten or school and for those who work	Exploration of the opportunities for peer and family support
Acute complications such as hypoglycemia (development, prevention, and treatment of hypoglycemia and DKA)	Practical skills of insulin therapy (insulin action and profile, adjustment of insulin, and (if applicable) diabetes technology)	
Sequelae of diabetes (development, prevention, and treatment of long-term diabetes complications)		
Problem-solving strategies such as coping with unexpected glucose fluctuations		
Physical activity (e.g., explanation of the effect of physical activity or exercise on blood glucose levels)		
Smoking, alcohol, and drug consumption		

Abbreviations: DKA: diabetic ketoacidosis, HbA1c: glycated hemoglobin

1.6 Pharmaceutical care for diabetes mellitus type 1 and 2 patients

One pertinent question is why we should provide PhC for patients with T1DM and T2DM. Non-communicable diseases such as diabetes mellitus (6th most common global cause of death) have replaced infectious diseases as the leading cause of death and chronic diseases such as diabetes mellitus cause increasing health costs due to acute and long-term complications. (WEF 2019) Poor adherence to medication regimens is a common problem and can contribute to substantial worsening of disease, death, and increased health care costs. (Osterberg et al. 2005) Based on the current literature and research, better adherence was found to be associated with improved glycemic control and decreased health care resource utilization. (Asche et al. 2011) A systematic review by Cramer et al. revealed that diabetes patients' adherence to their diabetes therapy ranged from 36–93%, and insulin therapy adherence among patients with T2DM was 62–64%. (Cramer 2004) Consideration of the increasing incidences, prevalences, and age-standardized incidence rates of diabetes mellitus (see Chapter 1.2) in combination with these adherence rates, leads to the conclusion that there is a growing need for effective and optimized PhC for patients with diabetes mellitus.

Definition of pharmaceutical care

There are different definitions of PhC; one of the most common and well-known definitions by Hepler et al., (1990) is: "Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve a patient's quality of life". (Hepler et al. 1990) The Pharmaceutical Care Network Europe (PCNE) updated the definition and defined PhC as "pharmacist's contribution to the care of individuals in order to optimize medicine use and improve health outcomes". (Allemann et al. 2014)

Provision of pharmaceutical care in general

Several studies have examined the provision of PhC in Europe and the effects of PhC and/or medication therapy management (MTM) on different outcomes. (Bulajeva et al. 2014, Costa et al. 2017) One study evaluated the effect of MTM provided by community pharmacists over a period of seven years. MTM was found to shift the primary education about patients' acute medication to also include chronic medications. In addition, MTM was associated with increased reimbursement and pharmacist-estimated cost-savings. (Barnett et al. 2009) A study of the provision of medication reviews in Europe found that in almost two-thirds of European countries, at least one type of medication review was provided. (Bulajeva et al. 2014) The provision of PhC has increased in Europe over the last decade; however, many barriers to the provision of PhC still remain. (Costa et al. 2017, Hughes et al. 2010) One of these barriers is that the current education of pharmacists in European countries does not focus on the skills

necessary to realize pharmaceutical services such as MTM in everyday work life. (Rose et al. 2018) Another limitation can be pharmacist–physician communication. To more effectively provide MTM, efficient and concise communication is needed, and reasons for the offered recommendations should be given. (Guthrie et al. 2017)

To implement and provide structured PhC, the way in which patient information is documented is crucial. One important and common method for health care providers to document patient data is the SOAP note. The idea of the SOAP note was developed by Lawrence L. Weed nearly 50 years ago. (Wright et al. 2014) The definitions of the components of the SOAP note are:

S (subjective):
Subjective patient information includes all experiences, personal views, feelings or patient lifestyle factors. It can also include the medical history, current medications, allergies, and symptoms. This section provides context for the assessment and plan.
O (objective):
Objective data includes vital signs, laboratory data, other diagnostic data or results, and the documentation of medication and medical history from clinicians or other health care providers.
A (assessment):
The assessment involves analyzing the subjective and objective data and evaluating the current drug therapy and any other therapy interventions. The pharmacist should identify relevant problems and evaluate them.
P (plan):
The plan of action is based on the information and assessment. This plan of action documents the suggested improvements in drug therapy and potential monitoring of the drug therapy. And can include therapy changes, patient education and counselling, and referrals to other health care providers.

A SOAP note provides all necessary subjective and objective information and provides an accurate assessment. The assessment and plan should be patient-specific and therefore include individual patient goals. (Podder et al. 2020) One way to methodically formulate (individual) goals is to use the SMART criteria:
S – specific
M – measurable
A – attainable
R – realistic
T – time-based

According to the SMART criteria, each formulated goal should include these five aspects to be effective and to support patient self-reliance in the realization of the goal. One study assessed the effect of implementing SMART criteria on the ability of medical students to set treatment goals with the patient. The students who used the SMART principle to formulate and set individual goals with the patient were able to better set treatment goals with the patient, and this was associated with improved treatment monitoring. (Tichelaar et al. 2016)

Provision of pharmaceutical care for patients with type 1 and 2 diabetes mellitus

Several studies and reviews have evaluated the effectiveness of PhC for diabetes patients. One study evaluated the feasibility of diabetes and CVD risk screening in community pharmacies. This screening was feasible to conduct during one pharmacy visit and lasted 27 minutes on average. (Alzubaidi et al. 2019) Randomized controlled trials (RCTs) have investigated whether PhC can improve the treatment adherence of diabetes patients (Erku et al. 2017, Kjeldsen et al. 2015, Mehuys et al. 2011, Obreli-Neto et al. 2011), but two systematic reviews came to the conclusion that further research is needed, particularly to clarify modifiable factors. (Antoine et al. 2014, Krass et al. 2015) A systematic review by Osterberg et al. stated that new technologies such as mobile health (mHealth) may be needed to help diabetes patients who have the most difficulty meeting therapy goals. (Osterberg et al. 2005) However, few studies have analyzed the impact of PhC on the QoL of T2DM patients. Differences in methods, such as the outcome measurement, make it difficult to compare these studies. (Krass et al. 2013)

Most of the relevant studies and reviews analyzed the impact of PhC on diabetes patients' glycemic control by measuring HbA1c values or FBG levels. In several studies (one pre–post cohort, one clinical trial, and five RCTs), additional PhC in a community pharmacy setting reduced HbA1c values and helped to improve glycemic control. (Clifford et al. 2005, Cranor et al. 2003, Krass et al. 2007, Mehuys et al. 2011, Mourao et al. 2013, Obarcanin et al. 2015, Wermeille et al. 2004) Other studies found no significant effect on the glycemic control of diabetes patients. (Castejon et al. 2013, Doucette et al. 2009, Sarkadi et al. 2004) To our knowledge, no study has evaluated the PhC components provided to T1DM and/or T2DM patients in a community pharmacy setting or systematically investigated which PhC content is particularly effective.

2 Chapter One – Optimized pharmaceutical care interventions for adolescent type 1 diabetes patients

Parts of this chapter have already been published. The author of this thesis, Maira Anna Deters, was first author and second author once each and made the following contributions to these publications:

*First publication: **Deters MA**, Läer S, Hasanbegović S, Nemitz V, Müller P, Krüger M, Schwender H, Obarcanin E. Diabetes Stewardship – Pharmaceutical care of adolescents with type 1 diabetes mellitus provided by community pharmacists. Med Monatsschr Pharm. 2016 Nov;39(11):477-82.*

(1) conceptualization with Dr. Emina Obarcanin and Prof. Dr. Stephanie Läer, (2) data extraction and evaluation of the DIADEMA case report forms (CRFs), (3) performing all statistical analyses with Prof. Dr. Holger Schwender (four eye principle) and (4) original draft preparation.

*Second publication: Obarcanin E, **Deters MA**, Nemitz V, Läer S. Pharmaceutical care of an adolescent with type 1 diabetes. Med Monatsschr Pharm. 2016 Nov;39(11):483-7.*

(1) conceptualization with Dr. Emina Obarcanin and Prof. Dr. Stephanie Läer, (2) data extraction, (3) original draft preparation with Dr. Emina Obarcanin and (4) review and editing with Verna Nemitz and Prof. Dr. Stephanie Läer.

2.1 Background

Why provide pharmaceutical care for adolescent patients with type 1 diabetes mellitus? Particularities and challenges of type 1 diabetes mellitus in adolescence

During adolescence many different factors influence glycemic control, such as hormonal changes, family dynamics and other social factors, and non-adherence to insulin therapy regimens. Another important factor that influences glycemic control and self-management is the type and structure of the transition of care from the pediatrician to the adult diabetologist. (Foster et al. 2016) Research on this topic has shown that adolescents who demonstrate higher levels of executive function, better diabetes self-management, reduced diabetes-related family conflict, and/or more frequent SMBG and better treatment adherence had a lower risk of developing diabetes-related complications in the future. (Rohan et al. 2014) The decline in parental monitoring with the increasing age of the child or adolescent is another reason for deterioration of adherence and often leads to worse glycemic control. (Helgeson et al. 2009)

To avoid worsening of diabetes self-management and a deterioration of glycemic control, the transition of adolescents to adult health care teams should be smooth and accompanied by continuous mentoring and self-empowerment guidance by health care professionals. (Ullrich

2014) Community pharmacists, who regularly dispense insulin and other diabetes devices, are well positioned to monitor adolescent diabetes patient self-management during the transition of care.

To my knowledge, the DIADEMA (Diabetes in ADolescents Engagement and Monitoring in phArmacies) study was the first to implement PhC interventions during this transition of care process for adolescents with T1DM. (Obarcanin et al. 2015)

Study design and implementation of the DIADEMA study

The 2014 DIADEMA study was an RCT that assessed the effect of PhC in adolescent T1DM patients. In total, 69 adolescent diabetes patients were randomized by the coin-toss method; 40 in the intervention group and 29 in the control group. Over a period of 6 months, the patients in the intervention group had monthly consultations with a community pharmacist (in Germany) or a clinical pharmacist (in Bosnia-Herzegovina). All 69 patients had T1DM, were between 12 and 18 years old at the start of the study, had HbA1c values above 7.5%, and had a diabetes duration of at least of 6 months. The primary study endpoint was the difference in HbA1c values after 3 and 6 months. Secondary endpoints were the number of severe hypoglycemic episodes each month and the well-being of the patients, measured by the World Health Organization (WHO)-5 well-being index (see Appendix X7). (Obarcanin et al. 2015)

The clinical pharmacist in Bosnia-Herzegovina for all cases was Dr. Emina Obarcanin; in Germany the enrolled patients individually chose their pharmacist. These pharmacists were coached before the study on the following topics:

- Implementation of PhC for adolescents with T1DM according to the current ISPAD guidelines
- DIADEMA study protocol, including the objective and setting of the study
- Documentation of the intervention and the usage of DIADEMA CRFs (see Appendix X 8)
- Insulin and relevant insulin dosage adjustments
- Preparation of an insulin plan
- Good clinical practice (GCP), implementation of an RCT, and the required documentation

The included patients visited the pharmacy monthly. Each visit had an average face-to-face time of 60–90 minutes. Where required, the pharmacist made additional phone calls. Every second month the physicians and pharmacists met for an interdisciplinary exchange. The written PhC plans of the pharmacists were submitted to the physicians at visits three and six and were discussed at team meetings. Quarterly, the physicians performed regular medical check-ups that included HbA1c measurement.

The mean HbA1c values of the intervention and control groups were both 9.4% at baseline. In the intervention group, the HbA1c values were significantly reduced to 8.3% (reduction of 1.09 percentage points) after 3 months and to 8.9% (reduction of 0.54%) after 6 months of intervention. After 3 and 6 months, the mean and median HbA1c values of the intervention group were classified as suboptimal according to the 2014 ISPAD guidelines. The baseline HbA1c value was classified as high-risk, which required immediate action (see Figure 5). (Rewers et al. 2014) After 3 months, the average HbA1c value in the control group increased to 9.7% (increase of 0.23%) and to 9.9% after 6 months. This improved glycemic control in the intervention group did not result in an increase of severe hypoglycemic episodes. (Obarcanin et al. 2015)

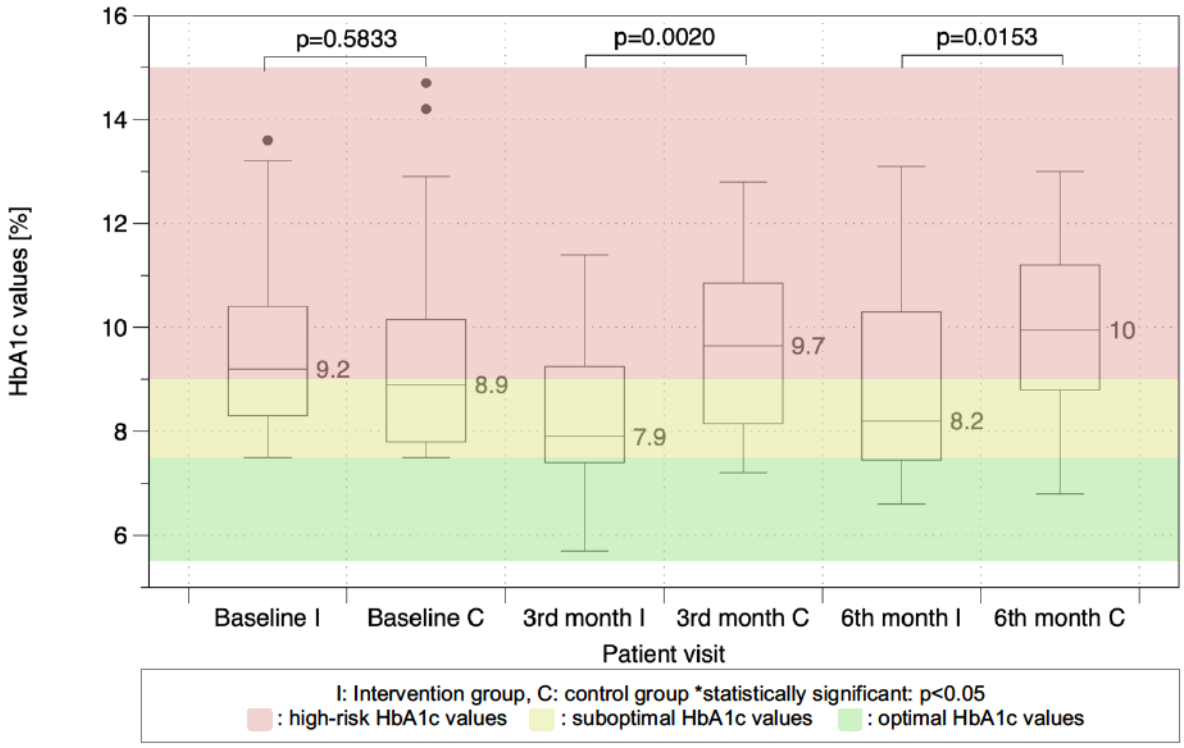


Figure 5 Boxplot with classification of HbA1c values of all DIADEMA study patients according to the 2014 ISPAD guidelines (Rewers et al. 2014)

The achievements and improvements that were identified in the DIADEMA study due to optimized PhC delivered in addition to usual care led us to further explore the question of which insulin therapy adjustments or lifestyle changes were adopted by the patients to improve their glycemic control. Further statistical analysis of DIADEMA patient data, as documented in the CRFs, could potentially reveal changes in insulin therapy and/or patient lifestyle and the occurrence of acute diabetes complications, such as DKA or severe hypoglycemia, over the study period.

2.2 Methods

2.2.1 Objectives of DIADEMA subanalysis

The statistical analysis of DIADEMA patient data (DIADEMA subanalysis) had two main objectives:

1. Review and analyze the whole DIADEMA CRF data of the intervention group to qualitatively identify relevant PhC components. In addition, describe one patient case in detail as an example of the implementation of the optimized PhC for adolescent T1DM patients in the DIADEMA study and to gain a better understanding of PhC in practice. This patient case is representative of the patients in the DIADEMA study, and it reflects the various topics and content of the implemented PhC interventions, especially for adolescent T1DM patients.

2. Quantitively assess the effect of the optimized PhC on the following, in adolescent T1DM patients:

(1) Glycemic control, measured by FBG levels
(2) Monitoring measurements recorded by the daily frequency of SMBG
(3) Insulin therapy adherence and insulin therapy adjustments measured by daily insulin injection frequency and insulin dose
(4) Occurrence of acute diabetes complications measured by the number of patients with light and severe hypoglycemia
(5) Patient lifestyle as recorded by compliance with the nutrition plan and recommend physical activity

2.2.2 Statistical analysis

Data extraction

To assess the effect of PhC on adolescent T1DM patients, relevant data from the monthly CRFs of the 39 patients were extracted. For each patient, there were a total of six CRFs (one from each visit) which were analyzed in detail. Missing values were marked as not available (n.a.), and if minimum and maximum values were given, the average value was calculated and used for statistical analysis. Datasets were transferred from the CRFs (paper-based) into Excel spreadsheets and were doubled-checked by a coworker for typing mistakes. All statistical analyses were conducted by me, using R-Studio version 0.99.484 and were verified by Prof. Holger Schwender.

Wilcoxon signed-rank test

The Wilcoxon signed–rank test was used to assess differences between study visits for non-normally distributed values. The test was paired because the values for each patient were compared to their data from their first (i.e., baseline) visit. For all measurements, one hypothesis was tested, for example, whether the FBG levels decreased compared to the previous visit; these tests were one-sided. This test is applicable even when the sample size is small. A significance level of α=0.05 was chosen a priori. The Wilcoxon signed–rank test was used for the statistical analysis of the following parameters:

(1) FBG level (alternative hypothesis: greater)
(2) Frequency of SMBG (alternative hypothesis: less)
(3) Daily insulin dose (alternative hypothesis: less)
(4) Frequency of daily insulin injection (alternative hypothesis: less)

Fisher's exact test

Fisher's exact test is a test for independence in contingency tables. This test is an alternative to the chi-squared test when the sample size is quite small such as n=5. The applied contingency tables were 2x2. The test was one-sided and a significance level of α=0.05 was chosen a priori. Fisher's exact test was used to analyze the following parameters:

(1) Medication adherence (alternative hypothesis: greater)
(2) Hypoglycemia (alternative hypothesis: less)
(3) Compliance with the nutrition plan (alternative hypothesis: greater)
(4) Physical activity (alternative hypothesis: greater)

2.3 Results

Design and implementation of optimized pharmaceutical care for adolescent type 1 diabetes patients

In the DIADEMA study, at each patient visit, the community pharmacists discussed aspects of the insulin therapy or other topics, e.g., lifestyle changes according to the current ISPAD guidelines (2014). At every patient visit the pharmacist assessed the patient's current diabetes therapy, adherence or lifestyle problems, and developed the PhC plan. The PhC plan included an assessment of current problems on the basis of the laboratory and self-measured values, the corresponding problem-solving interventions, and individually set goals for the next visit. The fulfilment of these individual goals was checked by the pharmacist at the next patient visit.

Pharmacists also coached the patients on a variety of topics. Each topic was to be addressed at least twice during the 6-month study period. In accordance with the actual patient situation, the pharmacists individually decided at which visit and how often each topic was discussed.

The topics discussed with the patients were:

(1) Currently recommended therapeutic goals as per the guidelines
(2) Principles of insulin therapy and practical skills
(3) Skills to individually adjust the insulin therapy
(4) Documentation and interpretation of self-measurements
(5) Prevention, identification, and treatment of diabetes acute complications
(6) Theoretical and practical skills concerning the effect of physical activity on blood glucose regulation
(7) Insulin therapy-related problem-solving strategies
(8) Relevant aspects of sexuality, especially the prevention of sexually transmitted disease
(9) Tobacco and alcohol use
(10) Relevant information about monitoring or control check-ups

The pharmacist intervention also included a review and assessment of SMBG values and any other relevant patient parameters, such as the current frequency of insulin injections, the occurrence and frequency of hypoglycemia, adherence to insulin therapy, or the patient's QoL. Some values, such as the HbA1c value, were only measured at the study beginning and at visits three and six. Other values, such as pre-prandial blood glucose levels and the number of daily insulin injections, were recorded at each PhC visit (see DIADEMA CRF Appendix X 8).

In order to better understand the various steps and content of PhC for adolescent patients with T1DM, the exact process will now be illustrated with a description of a patient case.

Detailed description of a patient case from the DIADEMA study

The adolescent T1DM patient chosen for the case presentation was 17 years old, had diabetes for 3 years, and also had asthma. In addition to ICT with NPH-insulin and insulin aspart, if required he used salbutamol once or twice daily to treat asthma attacks. At the beginning of the DIADEMA study, his HbA1c value was 9.3% (see Table 9). According to the ISPAD guidelines, this patient was at high risk for complications, and action was required. (Rewers et al. 2014)

Table 9 Laboratory data and relevant measurements of the patient

	Baseline	2nd visit	3rd visit	4th visit	5th visit	6th visit	Recommended value
Glycemic control and SMBG							
HbA1c value [%]	9.3		7.9			7.6	< 7.5[1]
FBG level [mg/dl]	269	270	182	136	106	324	90-145[1]
Blood glucose level at intervention [mg/dl]	218	220	88	115	89	74	
Number of daily SMBGs	4	4	4	4	3	4	4-6[1]
Insulin therapy adjustment							
Number of daily insulin injections	4.5	4.5	4.5	4.5	4.5	4.5	
Daily insulin dose [IU]	65	80	70	80	80	75	
Acute complications							
Number of hypoglycemic episodes	0	8	7	25	12	15	

[1] acoording to Rewers et al. 2014

By reviewing the SMBG values and other relevant patient data, the pharmacist identified the following drug-related problems (DRPs):

(1) Hyperglycemia in the morning

(2) Frequent hypoglycemia

(3) Potential interaction between insulin and salbutamol

Potential causes for frequent hyperglycemia in the morning:

(1) Underestimated insulin dose

(2) Dawn phenomenon

(3) Late meal the day before

(4) Nocturnal hypoglycemia (glucose counter-regulation)

(5) Infection not yet recognized and diagnosed

To identify the cause of the frequent morning hyperglycemia, it was recommended to measure the nocturnal blood glucose for a few nights (four nights) at approximately 3 AM. If the nocturnal blood glucose levels were low, then several possible causes could be considered: counter-regulation of hypoglycemia, over-adjusted basal insulin, physical exercise in the afternoon or evening, or the NPH insulin peak of action. High nocturnal blood glucose levels could indicate that the patient had a late evening meal, the needed short-acting insulin dose was too low, or the NPH dose was not adjusted correctly. The dawn phenomenon or infections (such as a cold) could also be a potential cause of hyperglycemic episodes in the morning.

Additionally, there was an increase of hypoglycemic episodes during the study period. At the beginning of the study, the patient had no hypoglycemic episodes, but at the last patient visit 15 hypoglycemic episodes had occurred within 1 month. Common reasons for hypoglycemia are:

(1) The insulin dose is too high
(2) Skipping meals
(3) Overestimated carbohydrate intake
(4) Incorrect insulin therapy adjustment before, during, and after physical activity

The pharmacist should review the patient's carbohydrate intake over the whole day and the exact composition of the meals. To evaluate whether the patient is able to correctly estimate the carbohydrate intake and, hence, the required bolus insulin, the pharmacist and patient should examine whether the timing of insulin injection is reasonable and whether the insulin peaks of the bolus insulin aspart match the glycemia peaks of each meal. If the patient (as in this case) participates in regular exercise, the importance of pre- and post-exercise snacks (15 to 30 g carbohydrates) should be addressed. In addition, the insulin peak of action should be considered; at the insulin peak of action, more carbohydrates are needed, particularly during exercise. Furthermore, the possibility of developing delayed hypoglycemia after exercise (e.g., during the night) should be considered. Patients should regularly measure their blood glucose levels before, during, and after exercise (1 or 2 hours after exercise, and if required, even at 3:00 AM) to identify low blood glucose levels and then eat carbohydrate snacks and/or reduce the amount of bolus or basal insulin. (Abraham et al. 2018)

Diabetes patients with frequent hypoglycemia often suffer from hypoglycemia unawareness. The increased neurogenic symptoms during hypoglycemia are often attenuated in T1DM patients. The sympathetic neuronal and adrenomedullary response is reduced in patients with hypoglycemia unawareness, and therefore the required glucose counter-regulation is missing.

(Cryer et al. 2003, Obarcanin 2013) However, there are several ways to manage hypoglycemia unawareness. Pharmacists can adjust the patient's glucose target upwards to avoid (frequent) reoccurrence of hypoglycemic episodes and empower the patient to increase the frequency of SMBG. For adolescent T1DM patients, ICT or CSII is the currently recommended first-line insulin therapy; other therapeutic strategies should be changed, if possible, to these two, especially when the patient suffers from frequent hypoglycemia. In addition, current guidelines recommend that patients with reoccurring hypoglycemic episodes or hypoglycemia unawareness use a CGMS. (Danne et al. 2018, DiMeglio et al. 2018a, Haak et al. 2018) The CGM-measured blood glucose values are translated to show the glucose direction and can warn the patient if the values are trending towards hypoglycemia or hyperglycemia. (Danne et al. 2018) Another option to treat hypoglycemia unawareness is blood glucose awareness training (BGAT), which has positive effects on the accuracy of patients' blood glucose estimations and hence reduces hypoglycemic unawareness. (Broers et al. 2005) Some co-morbidities (e.g., renal failure) can be a reason for recurrent hypoglycemia. Screening for these co-morbidities and for diabetes-related complications such as DKD is also recommended by the current ISPAD guidelines. (Abraham et al. 2018)

In this patient case, the insulin dose was increased over the study period. However, the pharmacist found that the reason for the increased hypoglycemic episodes was that some insulin doses were too high in combination with low carbohydrate intake (see Table 10). Additionally, the pharmacist explained to the patient that alcohol consumption suppresses gluconeogenesis and therefore increases the risk of hypoglycemia.

The pharmacist also documented a potential interaction between insulin and salbutamol. Salbutamol in higher doses can reduce the effectiveness of oral antidiabetics and insulin. However, the patient used salbutamol once or twice daily, as necessary; therefore, this potential interaction was not clinically relevant. Further steps such as providing information to the prescriber or informing the patient about this potential DRP were not taken in this case.

Table 10 Overview of discussed topics, assessment, and goal setting of the pharmaceutical care intervention modified according to Obarcanin et al. (Obarcanin et al. 2016)

Discussed topics	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit
Discussion of current guideline-recommended therapeutic goals	X	X	X	X	X	X
Principles of insulin therapy and practical skills	X	X	X	X		X
Skills to individually adjust the insulin therapy		X		X		
Documentation and interpretation of self-measurements		X		X	X	
Prevention, identification, and treatment of diabetes acute complications	X		X		X	X
Theoretical and practical skills concerning the effect of physical activity on blood glucose regulation	X		X			
Insulin therapy-related problem-solving strategies	X	X	X		X	
Discussion of relevant aspects of sexuality, especially the prevention of sexually transmitted diseases			X	X		X
Tobacco and alcohol use		X				X
Relevant information about monitoring or control check-ups		X	X	X		X

Assessment and individually set goals	
1st visit	***Pharmacist's assessment:*** • Insulin therapy self-management present • Secure handling of insulin pens and blood glucose measurement system • Stress • No nutrition plan available ***Individual goals:*** • Meeting the deadlines and adhering to the expectations of pharmaceutical care
2nd visit	***Pharmacist's assessment:*** • Hairline crack in the insulin cartridge → high blood glucose levels • Improved assessment of blood glucose fluctuations ***Individual goals:*** • Clarify the current situation in the family • Discuss relevant topics of sexuality and contraception
3rd visit	***Pharmacist's assessment:*** • Insufficient adjustment of insulin injection and SMBG frequency, especially before, during, and after physical activity ***Individual goals:*** • Reduce/prevent blood glucose fluctuations and hypoglycemia • Develop a problem-solving strategy to prevent and treat hypoglycemic episodes correctly
4th visit	***Pharmacist's assessment:*** • Insufficient adjustment of insulin injection to current blood glucose levels • Insufficient SMBG frequency ***Individual goals:*** • More frequent SMBG and adjust the insulin dose to the current blood glucose level
5th visit	***Pharmacist's assessment:*** • Insufficient SMBG frequency • Increased number of hypoglycemic episodes at noon and after physical activity ***Individual goals:*** • More consistent SMBG • Reduce the insulin dose in the morning and at lunchtime
6th visit	***Pharmacist's assessment:*** • Insufficient SMBG frequency ***Individual goals:*** • Continue the pharmaceutical care intervention

Abbreviations:
SMBG: self-measurement of blood glucose

As described earlier, the adolescents in the intervention group had significantly lower HbA1c values at the end of the DIADEMA study. This raises the question of whether this optimized PhC for adolescents with T1DM also has a positive effect on the following diabetes parameters:

(1) Glycemic control measured by FBG levels.
(2) Monitoring measurements recorded by the daily frequency of SMBG.
(3) Insulin therapy adherence and insulin therapy adjustments measured by daily insulin injection frequency and insulin dose.
(4) Occurrence of acute diabetes complications measured by the number of patients with mild and severe hypoglycemia.
(5) Patient lifestyle as recorded by compliance with the nutrition plan and recommended physical activity.

Effect of optimized PhC for adolescent patients with type 1 diabetes mellitus on the frequency of SMBG and the FBG levels

Pharmacists encouraged the adolescent T1DM patients to measure their blood glucose levels more often, and the frequency of SMBG increased over the study period. It is recommended to measure 6–10 times a day to adjust the insulin therapy to the current blood glucose levels. (DiMeglio et al. 2018a) At baseline, the patients measured their blood glucose levels 4.1 ± 1.3 times per day, which increased to 4.8 ± 1.5 times per day by the end of the study (see Table 11). This increase in SMBG frequency over the study duration was statistically significant (see Figure 6).

At baseline, only one adolescent had an FBG level that was within the recommended target range; the 2018 ISPAD guideline recommends a target FBG level of 70–130 mg/dL. (DiMeglio et al. 2018a) During the DIADEMA study period, the patients' FBG levels decreased from 218 ± 67 mg/dL at the beginning to 199 ± 69 mg/dL at the end of the study. The median FBG level also decreased, from 204 mg/dL to 178 mg/dL at the last patient visit. Most patients were within the recommended FBG target range at the fourth patient visit, which occurred four months into the study (see Figure 7).

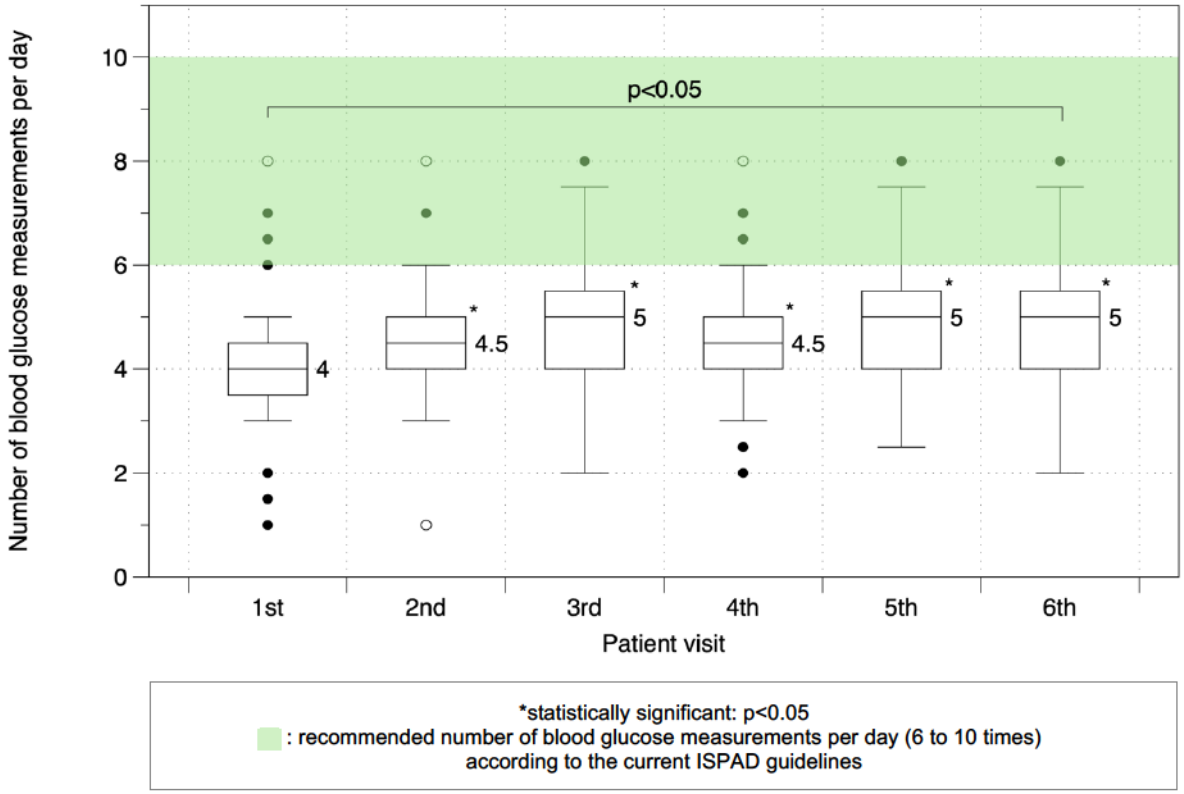


Figure 6 Boxplots frequencies of self-measurement of blood glucose per day in the intervention group

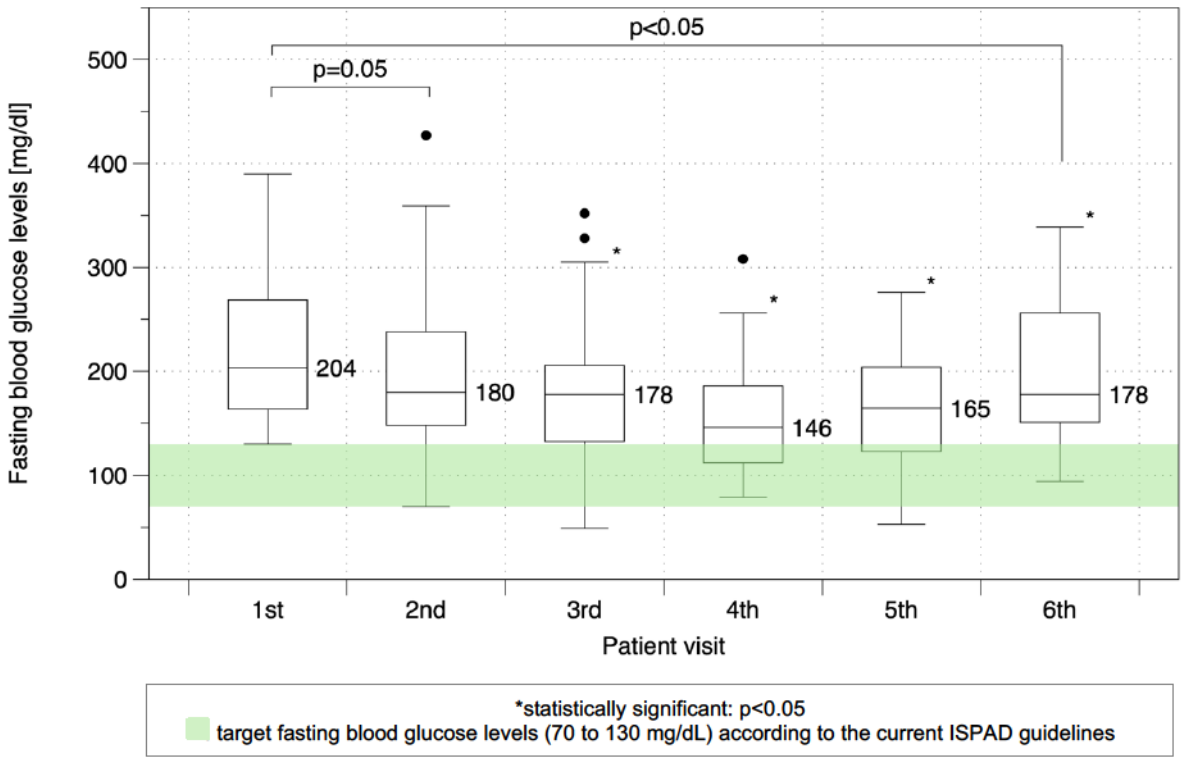


Figure 7 Boxplots showing changes in the fasting blood glucose levels in the intervention group

Table 11 Results of the analyzed CRFs of all 40 adolescent type 1 diabetes patients in the DIADEMA study intervention group (Deters et al. 2016)

	1st visit	2nd visit	3rd visit	4th visit	5th visit	6th visit
Blood glucose self-measurements						
Fasting blood glucose [mg/dL][1]	218 ± 67 n= 32	197 ± 82 n= 34	181 ± 70* n= 35	156 ± 54* n= 33	166 ± 51* n= 34	199 ± 69* n= 34
Number of daily blood glucose measurements[1]	4.1 ± 1.3 n= 39	4.6 ± 1.2* n= 38	4.9 ± 1.3* n= 39	4.6 ± 1.3* n= 37	4.9 ± 1.5 * n=37	4.8 ± 1.5* n= 37
Insulin therapy adjustments						
Daily insulin dose [IU][1]	56 ± 18 n= 35	59 ± 19* n= 34	58 ± 15* n= 36	56 ± 15 n = 35	57 ± 13 n= 34	57 ± 14 n= 35
Number of daily insulin injections[1,2] and given insulin dose[1,3]	6.9 ± 4.0 n = 31	6.5 ± 3.3 n= 27	7.3 ± 3.7 n= 33	6.9 ± 3.3* n= 29	7.1 ± 3.4* n= 32	6.9 ± 3.7* n= 32
Insulin therapy adherence[4]	15 (39) n= 38	25 (66)* n=38	30 (79)* n=39	25 (69)* n=36	23 (66)* n=36	22 (59) n=37
Acute complications						
Number of patients with hypoglycemia[4]	16 (42) n=38	14 (40) n=34	20 (51) n=39	13 (38) n=34	14 (44) n=32	16 (44) n=36
Lifestyle adjustments						
Compliance with the nutrition plan[4]	7 (22) n=32	20 (56)* n=36	23 (68)* n=35	17 (50)* n= 34	18 (50)* n= 36	14 (38) n=37
Number of patients who are doing exercise[4]	29 (74) n=39	33 (87) n=38	36 (92)* n=39	33 (89) n=37	32 (86) n=38	32 (86) n=37

[1]Average values ± standard deviation, p-values calculated with one-sided, paired Wilcoxon signed rank test
[2] Patients with insulin pens and ICT (basal and bolus insulin injections)
[3] Patients with insulin pumps
[4] Number of patients (proportion in %), p-values calculated with one-sided Fisher's exact test
n= Number of analyzed patients
* significant p-values ($p < 0.05$)

Effect of optimized pharmaceutical care for adolescent type 1 diabetes patients on insulin therapy adjustments, adherence and the occurrence of hypoglycemia

Over the study period, the number of patients who adhered to their insulin therapy increased significantly after the second visit. However, the difference between the first and last patient visit was not significantly different. At the third patient visit, 79% of the patients were adherent and complied with their individual insulin therapy recommendations. This also led to higher rates of daily insulin injection (see Figure 8). Higher rates of insulin injection and more frequent SMBG resulted in better adjustments of each insulin dose and lower FBG levels. The daily insulin dose increased significantly; however, the effect was temporary (see Figure 9).

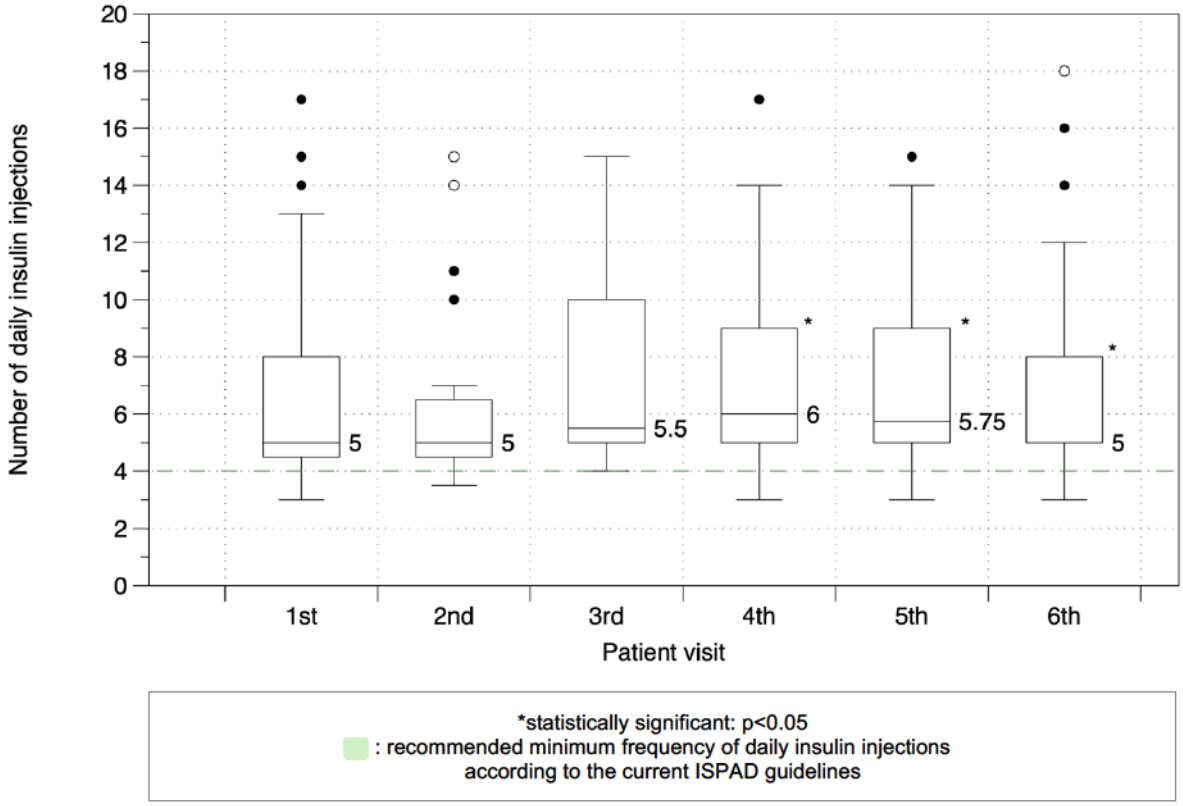


Figure 8 Boxplots frequencies of daily insulin injections in the intervention group

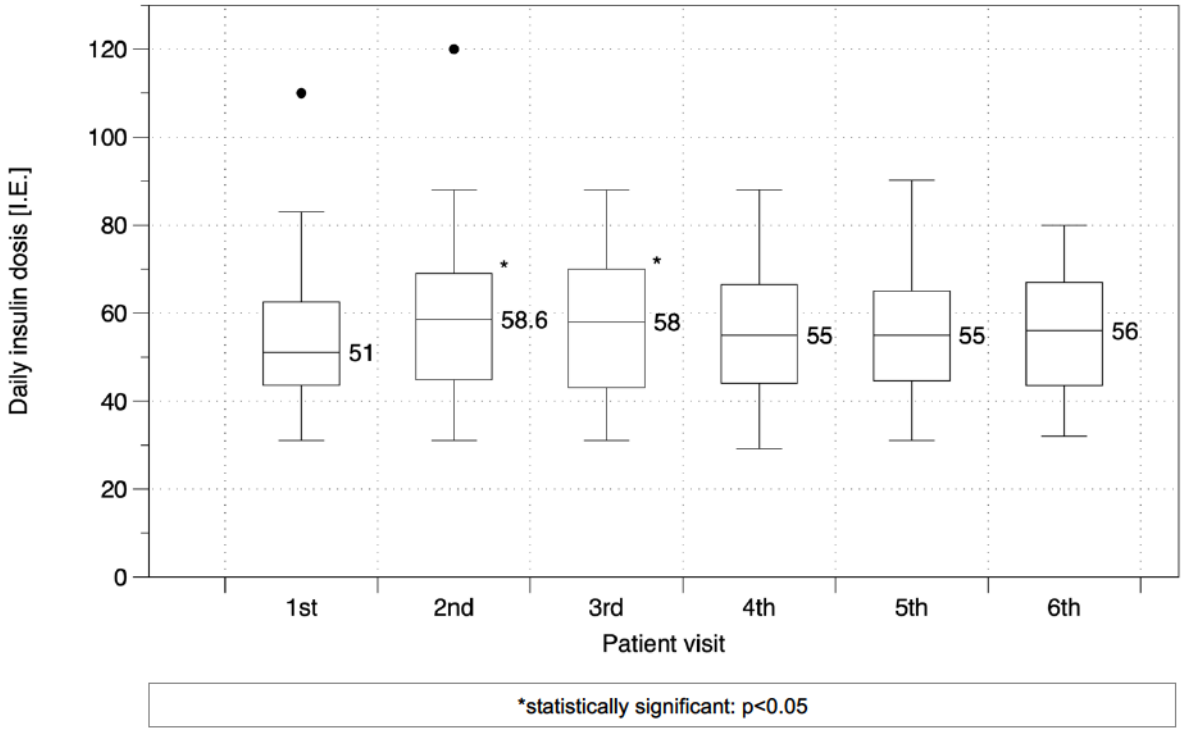


Figure 9 Boxplots of the daily insulin doses in the intervention group

The adjusted insulin therapy, particularly the higher insulin injection rates and the lower FBG levels, did not result in higher hypoglycemia rates. The number of patients with mild or severe hypoglycemia did not significantly increase over the study period (see Table 11). This is important, because reduced blood glucose levels that result in higher rates of hypoglycemia or increased fluctuations in blood glucose levels are not expedient.

Lifestyle adjustments – Nutrition plan and physical activity

Only 22% of patients complied with their individual nutrition plan at the beginning of the study. After the first patient visit, the PhC intervention significantly increased patient compliance with the nutrition plan to 56% ($p < 0.05$) at the second visit and to 68% ($p < 0.001$) at the third visit (see Table 11). If the adolescent patient did not have an individual nutrition plan then the pharmacist reminded them to make one. The current ISPAD guidelines recommend implementing an individual meal plan to improve prandial insulin adjustment and, therefore, glycemic control. A correctly calculated insulin dose that is in line with the actual blood glucose level and the carbohydrate intake prevents fluctuations in blood glucose. During the pharmacist intervention, the nutrition plan was discussed along with the importance of maintaining a healthy diet to avoid hyperglycemic episodes. If an individual nutrition plan was not available, the current guideline recommendations for intake of carbohydrates (45–55%), protein (15–20%), fiber (5 g per day), and fat (30–35%) were reviewed with the patient. (Smart et al. 2018)

Physical activity and the amount of exercise was not affected by the intervention. Overall, 74% of the patients performed exercise or were physically active at baseline. The difference between the first and third patient visit was statistically significant; at the third patient visit 92% of the patients were physically active. For diabetes patients, physical activity and exercise are relevant in two ways. On the one hand, exercise has a positive effect on the blood glucose level and increases non-insulin-mediated glucose transport. On the other hand, insulin therapy must be adapted to the duration and intensity of physical activity to avoid hyper- or hypoglycemia during or after exercise. (Adolfsson et al. 2018)

If not adapted to the duration and intensity of physical exercise, injected insulin can lead to a relative insulin excess, which inhibits glycolysis and gluconeogenesis in T1DM patients. During exercise, the blood glucose levels decrease due to increased blood flow to the muscles and elevated non-insulin-mediated glucose transport, thereby increasing glucose clearance (see Figure 10). (Esefeld et al. 2019) If the blood glucose levels before exercise are too low, T1DM patients need to decrease the bolus insulin dose (or if using an insulin pump, the temporary basal rate) to avoid hypoglycemia during or after exercise. The ISPAD guidelines recommend that if the blood glucose levels are below the target range before exercise, then the patient should decrease the bolus insulin dose by approximately 25–75% or consume 1.0 to 1.5 g of carbohydrates per kilogram of bodyweight per training hour. For example, patients should eat one banana or drink a sugar-containing drink such as juice. Occasionally, before or after endurance training, the patient will even need to reduce the basal insulin dose. Current guidelines also recommend measuring the blood glucose level before, during, and 1 to 2 hours after exercise; furthermore, to prevent late nocturnal hypoglycemia, they should measure the blood glucose level between 2:00–3:00 AM. (Adolfsson et al. 2018) It is also important to avoid the occurrence of DKA to ensure the required basal insulin supply during exercise. Without insulin, glucose uptake in the peripheral muscles is restricted, and, depending on the blood glucose level, hyperglycemia may result. Therefore, to prevent the occurrence of DKA, T1DM patients with blood glucose levels above 250 mg/dL should not start physical exercise. (Adolfsson et al. 2018, Esefeld et al. 2019) The pharmacists discussed the behavior before, during, and after physical activity and emphasized the importance of always having a blood glucose measuring device in their sports bag along with accessory devices, such as ketone urinary measuring stripes, a bolus insulin pen, glucose tables, fluids, and a glucagon hypo kit.

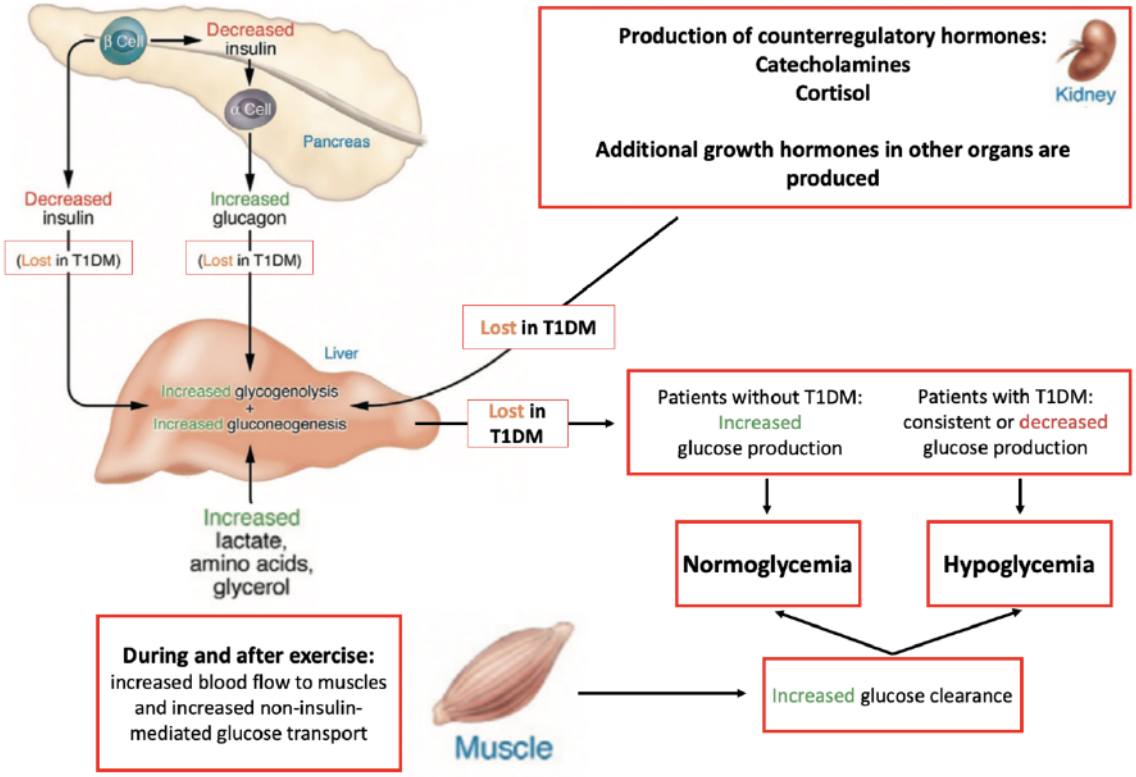


Figure 10 Glucose counter-regulation during and after exercise in patients with and without type 1 diabetes mellitus, adapted from (Cryer et al. 2003) and (Adolfsson et al. 2018)

2.4 Discussion

The glycemic control of the intervention group patients improved during the DIADEMA study. German community pharmacists and one clinical pharmacist in Bosnia-Herzegovina gave support and evidence-based recommendations to the adolescents with T1DM. More frequent SMBG and higher rates of adjusted insulin injections resulted in improved adjustments of the insulin dose. Increased adherence to individual insulin therapy targets and to the personal nutrition plans resulted in lower FBG levels without an increase in mild or severe hypoglycemic episodes.

Reductions in FBG levels, as seen in the intervention group, decrease the probability of the development of atherosclerotic CVD. (Park et al. 2013) According to Lee et al., even patients without diabetes who had temporarily impaired (100–125.9 mg/dL) or diabetic (≥126 mg/dL) FBG levels had an increased hazard ratio for the risk of myocardial infarction or stroke. In this retrospective cohort analysis, even the risk for all-cause mortality increased if the FBG levels were above the recommended range, after adjustment for age, lifestyle factors (such as smoking and alcohol consumption), body mass index (BMI), and blood pressure (BP). (Lee et al. 2018) A prospective cohort study by Yi et al. found that the association between hyperglycemia (indicated by an increased FBG level) and mortality was stronger at younger ages. (Yi et al. 2017)

Fluctuations in blood glucose are related to oxidative stress and therefore endothelial dysfunction and increased inflammatory factors. Some studies have revealed an association between the development of macrovascular disease and large blood glucose variability. (Škrha et al. 2016) In the DIADEMA study, pharmacists advised the adolescents to avoid and prevent extreme variations in blood glucose and thus hyper- and hypoglycemia. Over the study period the improved glycemic control did not result in an increase in mild or severe hypoglycemic episodes. Undetected and untreated, hypoglycemia can be life-threating. (Abraham et al. 2018) Recent research has identified a potential correlation between the repeated occurrence of hypoglycemia and an increased CV risk in T1DM and T2DM patients. (Yang et al. 2016)

Insulin therapy adherence is a common problem, and indeed the adherence to insulin therapy was low at the study beginning of the DIADEMA study, with only 22% of the adolescents adhering to their insulin therapy regimen. A literature review by Krass et al. that included 27 different studies of diabetes patients revealed that adherence varied widely between studies (38.5% to 93.1%). Several factors influence insulin therapy adherence, including depression or medication costs. (Krass et al. 2015) Goedken et al. evaluated the clinical records of 1566

patients with various diseases and detected a total of 8439 DRPs; 63% of these DRPs were related to non-adherence. (Goedken et al. 2018)

One of the key components of effective diabetes management and glycemic control is the type and amount of nutritional intake. (Hamdy et al. 2016) The right balance between carbohydrates, fats, and proteins, in combination with the correct calculation of the insulin dose, is important. (Smart et al. 2018) Implementing an individual nutrition plan and providing coaching by a registered dietitian or health care provider is the optimal solution according to current research and guidelines. (Hamdy et al. 2016, Smart et al. 2018) In the DIADEMA study, the individual nutrition plan was developed and optimized in collaboration with the patient and other health care providers as part of the pharmacist intervention. In addition, the adolescents received regular nutrition management training from the diabetologists and the diabetes educator.

In the intervention group, patients already participated in regular exercise and were physically active. One barrier to implementing physical activity guidelines as reported by Tully et al. is the fear of hypoglycemia during or after exercise. (Tully et al. 2016) Physical exercise has many beneficial outcomes, including increased glucose uptake, which leads to lower blood glucose levels. (Abraham et al. 2018) Regular exercise can improve the health and well-being of T1DM patients; it can help to achieve their target lipid profile or glycemia goals. Inadequate knowledge of the correct management of insulin therapy before, during, and after exercise is a frequent problem. (Riddell et al. 2017) Because of this, one of the mandatory PhC intervention topics addressed the theoretical and practical skills concerning the effect of physical activity on blood glucose regulation, the skills to individually adjust insulin therapy, and the correct documentation and interpretation of self-measurements.

Especially during adolescence, improved glycemic control can prevent the occurrence of acute and long-term diabetes complications such as severe hypoglycemia and microalbuminuria. (Cameron et al. 2018) Demirel et al. found that microalbuminuria was the most common microvascular complication in a group of adolescents with T1DM. (Demirel et al. 2013) In particular, long-term diabetes complications such as nephropathy and retinopathy can appear in young, middle, or advanced adulthood because patients with poor glycemic control develop these complications after 15–20 years of diabetes. (Nordwall et al. 2015) Viswanathan et al. studied 5,000 children with type 1 diabetes and found that that after 10 years, diabetic retinopathy was the most common microvascular diabetes complication, followed by nephropathy. (Viswanathan 2015) Worldwide, diabetic retinopathy is a prominent cause of visual impairment and even blindness. (Pascolini et al. 2012, Resnikoff et al. 2004)

One important aspect of the DIADEMA study was the interdisciplinary work between pharmacists, diabetologists, and diabetes educators. The interdisciplinary team met every 2 months to discuss the results and information about recent therapy changes. Physicians provided coded data from the regular medical check-ups to the pharmacists via telefax. Other studies have found that including a pharmacist in an interdisciplinary team significantly reduces the hospital and pharmacy costs. (Boyko et al. 1997, Haig et al. 1991) Team-based care including a clinical pharmacist was found to improve the overall quality of medication use and reduce the rates of readmission. (Makowsky et al. 2009)

2.5 Limitations

There are some limitations to this subanalysis and evaluation of patient data. A major limitation was the small number of patients (n=40) and the occurrence of missing values, which reduced the amount of analyzed data (n=27–39). A study duration of 6 months does not allow us to study long-term complications, although conclusions regarding the reduction and/or occurrence of acute complications could be made. Another potential limitation could be differences in the health care systems and differences in the education of the pharmacists in the two regions covered by the DIADEMA study. Regarding the reduction of HbA1c values, a comparative analysis found no statistically significant difference between the two regions.

2.6 Conclusion

The analysis of the DIADEMA study revealed that PhC can improve glycemic control in adolescents with T1DM. The reduced HbA1c values and improved glycemic control were particularly related to decreased FBG values and improved therapy adherence. Furthermore, patients increased their frequency of SMBG and daily insulin injections to better adjust their insulin therapy.

The interdisciplinary work between diabetologists, pharmacists, and diabetes educators conducted in the DIADEMA study was beneficial for the patients. Patient-tailored and target-oriented interdisciplinary work was shown to profoundly improve the patients' glycemic control.

The pharmacists in this study provided patient-centered PhC during the patient's transition of care. In this phase, adolescents need special additional support from health care professionals. Supporting and motivating the adolescents to take over self-management of their diabetes therapy and to transform current guideline recommendations into feasible and reasonable arrangements was one essential aim of this study.

A general objective should be to offer this optimized PhC to adolescent T1DM patients on a larger scale throughout Germany in community pharmacies. In particular, adolescents with poor glycemic control (HbA1c values above 9%) should have the opportunity to take part in a PhC intervention and to benefit from it. However, to be able to offer this structured and patient-centered PhC, pharmacists need to undergo specialized training, and they must receive the time and remuneration necessary to implement this service in everyday practice.

The results of this research led to further questions. For example, are there are other RCTs that have: (1) assessed the effectiveness of PhC interventions provided by community pharmacists for T1DM and T2DM patients in all age groups, (2) described in detail how the PhC interventions were provided, and (3) provided information about the content of training provided to the study pharmacists. In order to answer these questions, a literature search and meta-analysis of studies with PhC interventions provided by community pharmacists for T1DM and T2DM patients was conducted.

3 Chapter Two – Systematic literature review and meta-analysis of effective pharmaceutical care interventions provided by pharmacists for patients with diabetes type 1 and 2

Parts of this chapter have already been published. The author of this thesis, Maira Anna Deters, was first author of this publication and made the following contributions to the publication:

***Deters MA**, Laven A, Castejon A, Doucette WR, Ev LS, Krass I, Mehuys E, Obarcanin E, Schwender H, Laeer S. Effective Interventions for Diabetes Patients by Community Pharmacists: A Meta-analysis of Pharmaceutical Care Components. Ann Pharmacother. 2018 Feb;52(2):198-211. doi: 10.1177/1060028017733272. Epub 2017 Sep 26.*

Contributions: (1) conceptualization with Dr. Anna Laven and Prof. Dr. Stephanie Läer, (2) literature research as first reviewer with Dr. Anna Laven as second reviewer (four eye principle), (3) creation of the survey and cover letter to the coauthors, (4) meta-analysis and residual statistical analyses with Prof. Dr. Holger Schwender (four eye principle), and (5) original draft preparation.

3.1 Background

Many RCTs have assessed PhC generally (McLean et al. 2003, Park et al. 1996) and PhC for diabetes patients specifically (Grant et al. 2003, Hendrie et al. 2014, Kjeldsen et al. 2015). There is a wide variety of (systematic) reviews and meta-analyses that have assessed the effect of PhC in different pharmacy settings for diverse diseases and on various outcomes. Some reviews have shown that pharmacist interventions can have a positive impact on various outcomes for diabetes patients, such as HbA1c, FBG, and QoL. (Aguiar et al. 2014, Antoine et al. 2014, Blenkinsopp et al. 2005, Collins et al. 2011, Krass et al. 2015, Lindenmeyer et al. 2006, Machado et al. 2007, Omran et al. 2012, Santschi et al. 2012) A meta-analysis by Tricco et al. assessed the effectiveness of different quality improvement strategies regarding the reduction of HbA1c values. The authors found that the most effective quality improvement strategies were working interprofessionally, the facilitated relay of information to clinicians, and the promotion of self-management. (Tricco et al. 2012)

The aforementioned reviews and meta-analyses with diabetes patients included studies with varying study settings and/or designs, or did not include studies with community pharmacist interventions specifically, or the documented and analyzed primary outcomes varied widely.

To our knowledge, there are no systematic reviews or meta-analyses that have specifically evaluated the results of RCTs on the effect of PhC provided by community pharmacists to diabetes patients. Furthermore, the previously published systematic reviews and meta-analyses did not evaluate the effectiveness of the individual intervention components, nor did they describe, in detail, the training the study pharmacists received before the intervention.

3.2 Methods

3.2.1 Objective

The primary objective of this systematic literature research and meta-analysis was to evaluate the impact of PhC or MTM provided by community pharmacists on the glycemic control of T1DM and T2DM patients. Secondary objectives were the identification of effective PhC components and a description of the training that these pharmacists received as part of the study.

3.2.2 Data sources and search strategy

Data sources

PubMed (January 2000 to February 2016) and the Cochrane Central Register of Controlled Trials (January 2000 to April 2016) were searched by the reviewers (Anna Laven and the author of this dissertation, Maira Anna Deters) for RCTs that evaluated the impact of PhC provided by community pharmacists on T1DM and T2DM diabetes patients. RCTs have a strictly controlled study setting and methodology and therefore high internal validity; hence, RCTs are the gold standard of clinical trials. (Saturni et al. 2014) To ensure the quality of our meta-analysis results, we only included RCTs in our systematic review. Other study types were excluded to guarantee comparability of the study results. The time frame (2000 to 2016) was chosen to exclude studies that did not reflect the current conditions in community pharmacies, because the implementation of PhC has greatly developed in recent decades. (Bulajeva et al. 2014, Costa et al. 2017) An additional screening of the references of the included studies was carried out, and identified meta-analyses were also screened.

Search strategy

The following search strategies were developed a priori before the literature search was conducted. The keywords that were used for the formulation of the search strategy were selected due to their relevance and significance and/or frequency of being mentioned in other literature. For the PubMed search strategy, the keywords were searched in the published Title/Abstracts (TiAb) of the literature and MeSh terms were used. MeSh terms are assigned by PubMed and function as headings for thematic areas of research. In the Cochrane Central Register of Controlled Trials, one can only search for keywords and additional filters, such as publication date. Thus, these search strategies are quite different, and the PubMed search is more comprehensive.

The search strategy for PubMed was:
(((Community pharmacy services OR community pharmacists OR community pharmacy OR medication therapy management OR pharmaceutical care OR patient empowerment [MeSH terms]) AND (diabetes mellitus AND pharmacists [MeSH terms])) OR (((pharmaceutical care OR medication review OR pharmacist intervention OR pharmacist service OR community pharmacist OR MTM OR medication management OR medication therapy management [TiAb]) AND (diabetes OR glycaemic control OR glycemic control [TiAb])) AND randomized controlled trials [TiAb]). Filters: Publication date from January 1, 2000 to February 26, 2016.

The search strategy for the Cochrane Central Register of Controlled Trials:
(Community pharmacy services OR medication therapy management OR pharmaceutical care services) AND (diabetes mellitus AND pharmacists) [Keywords]. Filters: Publication date from January 1, 2000 to March 11, 2016.

3.2.3 Study selection and data extraction

Inclusion criteria

The inclusion criteria were:

- clinical and/or humanistic primary and secondary outcomes, such as HbA1c values or QoL parameters
- diabetes-related outcomes
- relevant components of the intervention were described
- description of the pertinent elements of the training received by the pharmacists

Exclusion criteria

Articles were excluded if:

- the primary clinical and humanistic outcomes were not diabetes-related, e.g., if BP or QoL was evaluated as the sole primary outcome
- the study indicated no pharmacist intervention outcomes; e.g., the intervention was conducted by pharmacists and life coaches and the results could not be evaluated separately

Procedure of the systematic literature search

The study inclusion and exclusion criteria were defined a priori. First, two reviewers reviewed the title and abstract of each article independently; discrepancies and uncertainties were discussed between these two reviewers afterward and were resolved. Subsequently, the reviewers independently screened the full text of all eligible articles. Again, all discrepancies or uncertainties were discussed and resolved. In the next step, the data of the included articles were extracted, and articles that did not have the HbA1c value as a primary outcome were excluded.

Data extraction

For all identified RCTs, the author name, publication title, year of publication, study design (such as sample size and study duration), intervention design (such as length and the implemented components), and the design of pharmacist training (such as the extent of training and the training elements used) were extracted. A table presenting this data is provided in Appendix X 9. Both review authors double-checked the entire extracted dataset of the eligible studies.

PRISMA and CONSORT statements

The documentation of the rationale, method, and results of the systematic literature search and meta-analysis was conducted according to the 2009 PRISMA statement, checklist, and flow diagram. (Liberati et al. 2009, Moher et al. 2015) To document the individual particularities of each included RCT, an Excel table was created that included relevant aspects such as participants, interventions, primary and secondary study outcomes, sample size, and statistical methods. This table was created according to the CONSORT statement for reporting RCTs to ensure that only high-quality RCTs were included. (Schulz et al. 2010)

Creation of the author survey

To obtain further information on the implementation of PhC and the training pharmacists received beforehand, a questionnaire was designed for the corresponding authors of the eligible RCTs. To identify the authors, their contact information (forenames, surname, telephone number, and e-mail address) was entered into the questionnaire. The first part of the questionnaire was designed according to the main contents of the PhC interventions reported in other systematic reviews or meta-analyses. (Aguiar et al. 2014, Antoine et al. 2014, Blenkinsopp et al. 2005, Collins et al. 2011, Krass et al. 2015, Lindenmeyer et al. 2006, Machado et al. 2007, Omran et al. 2012, Santschi et al. 2012) Pertinent elements of this questionnaire, including detailed information about the pharmacist interventions, were

extracted from these publications and classified into logical subtopics by the two reviewers. The first part of the questionnaire asked for detailed information about the pharmacist interventions, such as the intervention duration, interval, and the type and the content of patient education. In total, eight questions were formulated with the objective of clarifying the precise process of conducting the PhC in each RCT. The next part of the questionnaire asked questions about the training that the pharmacists received as part of the study. These questions were formulated according to the current DDG diabetes training for pharmacists. (DDG 2020) For example, this section of the questionnaire (13 questions) asked whether key aspects of the diabetes therapy or relevant soft skills were trained. To avoid missing any relevant aspects or content, the authors could enter free text as a comment in addition to selecting an answer from a set of provided options. In the last part of this questionnaire, the analyzed HbA1c values of their studies should be inserted (see Appendix X 10).

Conduction of the author survey

All corresponding authors were contacted first by email and subsequently, if required, by telephone. The authors were informed about the aim of this meta-analysis and the possibility of being included in the meta-analysis if they answered the whole questionnaire. In addition, the corresponding authors were informed about the content of the questionnaire (eight questions about the pharmacist intervention, 13 questions about the pharmacist training, and two questions about the analyzed HbA1c values). Additionally, the authors had to send their raw data, in particular the HbA1c values, to be included in this meta-analysis.

3.2.4 Statistical analysis

In this meta-analysis, the measure of impact was the HbA1c values. To identify the effectiveness of PhC provided by community pharmacists, a meta-analysis for continuous outcomes was first conducted using the random-effects model. Continuous outcomes are values that are measured on a numerical scale. The use of the random-effects model instead of the fixed-effect model was based on the assumption that the study effect estimates would show more variance if they were taken from a single population. To assess the effect of outliers, a sensitivity analysis was conducted using the leave-one-out method. A second meta-analysis was conducted to identify effective pharmacist interventions on glycemic control. Training components that had a significant positive impact on diabetes-related outcomes were identified. τ^2 and I^2 were calculated to evaluate the heterogeneity of the included studies. τ^2 is a measure of the between-study variance, and I^2 quantifies the inconsistency between the included and analyzed studies. All raw data were coded and divided into thematic subgroups.

In accordance with the published analyzed studies, missing data and incomplete data were excluded. A Spearman correlation analysis was conducted to identify the strength of possible correlations between differences in the HbA1c values and the study duration, intervention, and training elements. All statistical analyses were conducted by the author of this dissertation, Maira Anna Deters using R studio version 0.99.484 and were verified by Prof. Holger Schwender. (R-Foundation 2022)

3.3 Results

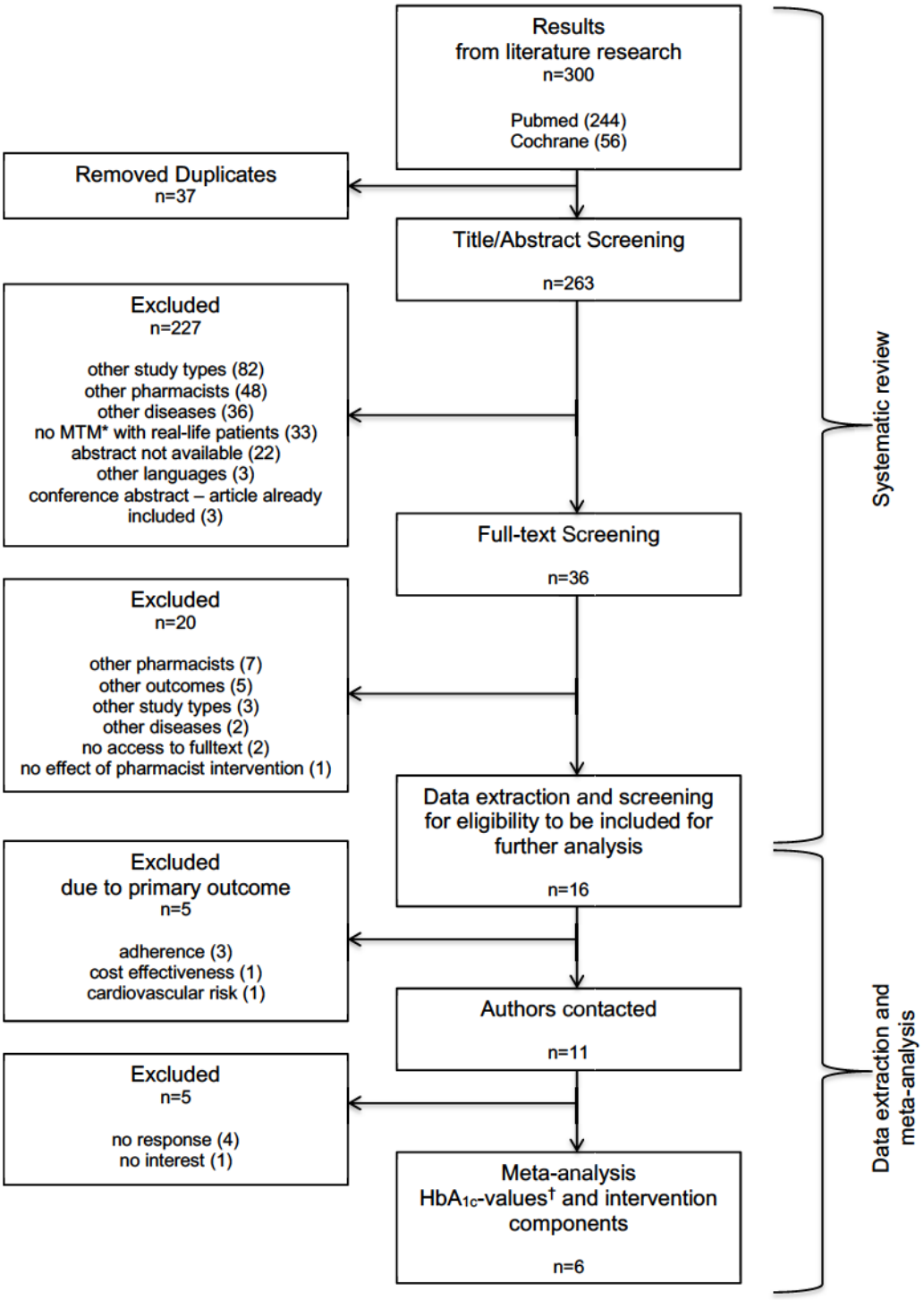
3.3.1 Systematic literature research

Systematic review results

The systematic literature search identified 244 articles from PubMed and 56 articles from Cochrane. After removing 37 duplicates, 263 articles remained for the title/abstract screening. From these 263 articles, only 36 were eligible for full-text screening. Most articles were excluded because they were not RCTs or because other pharmacists provided the pharmaceutical care (see Figure 11). The remaining 36 articles (representing 36 unique studies) underwent full-text screening, during which 20 studies were excluded by the two reviewers. In seven of these, other pharmacists provided the intervention, in five the primary outcomes were not eligible, in three the study design was not RCT, and in the remaining five studies, the study population included diseases other than diabetes, the effect of pharmaceutical care was not documented, or access to the full-text could not be obtained.

Further analysis procedures

The remaining 16 articles were included for further evaluation, and five of these were excluded because they had different primary outcomes. (Grant et al. 2003, Hendrie et al. 2014, Kjeldsen et al. 2015, Ladhani et al. 2012, Odegard et al. 2012) For these reasons, these articles were not directly comparable with the rest of the studies. The remaining 11 studies that had HbA1c values as a primary outcome were selected for inclusion in both meta-analyses. (Ali et al. 2012, Castejon et al. 2013, Doucette et al. 2009, Fornos et al. 2006, Jahangard-Rafsanjani et al. 2015, Jameson et al. 2010, Kraemer et al. 2012, Krass et al. 2007, Mehuys et al. 2011, Mourao et al. 2013, Obarcanin et al. 2015) The corresponding authors of these 11 studies received an online survey to provide further relevant information.



n= number of abstracts/articles; * medication therapy management; † glycated hemoglobin values

Figure 11 Flowchart of the systematic review and further data analysis (Deters et al. 2018)

3.3.2 Meta-analysis: effectiveness of pharmaceutical care for diabetes patients provided by community pharmacists

Of the 11 corresponding authors who received the survey, only six provided their raw data (HbA1c values) for inclusion in the meta-analysis and completed the entire questionnaire. The remaining five studies were excluded from further analysis due to differences in the description of the HbA1c values, such as missing standard deviation (SD) values. The absence of raw data made it impossible to calculate the exact meta-analytical effect of the intervention components of these five studies. (Ali et al. 2012, Fornos et al. 2006, Jahangard-Rafsanjani et al. 2015, Jameson et al. 2010, Kraemer et al. 2012) Another reason for excluding these five studies was inaccurate or incomplete descriptions of the PhC interventions, such as a list of intervention components and/or the type and duration of the pharmacist training.

Characteristics of the included studies

All PhC interventions were provided by community pharmacists (see Table 12). However, in one of the studies, one pharmacist was an external adviser in an ambulatory diabetes clinic in Bosnia-Herzegovina. (Obarcanin et al. 2015) The majority of studies included adult patients with T2DM, while only one study focused on adolescent patients with T1DM. The inclusion criteria of the studies were adapted to the research question. One RCT conducted in the USA investigated whether patients that already received two diabetes trainings within the last two years could benefit from PhC and therefore only included trained diabetes patients. (Doucette et al. 2009) One RCT only included Latino T2DM patients and excluded patients who were unable to watch the learning videos or participate in a focused discussion group due to hearing impairment. (Castejon et al. 2013) Two studies selected patients with insufficient glycemic control; for example, one of the inclusion criteria was an HbA1c value above 7%. (Krass et al. 2007) One RCT selected only obese patients who received oral antidiabetics (OADs) and who were aged between 45–75. (Mehuys et al. 2011)

Table 12 Design of the studies included in the meta-analysis

	Study setting	Study duration [months]	Inclusion criteria	Exclusion criteria	Analyzed (enrolled) patients	Age (diabetes duration [years][1]	Baseline HbA1c [%][1]
Castejon et al. 2013	Community-based setting	3	T2DM, Latinos with diabetes	Gestational diabetes, unable to watch a video or participate in a focused discussion group (hearing impairment)	I: 19 (NA) C: 24 (NA)	I: 54 ± 9 (NA) C: 55 ± 10 (NA)	I: 8.3 ± 0.4 C: 8.2 ± 0.4
Doucette et al. 2009	Community pharmacy	12	T2DM, HbA1c ≥7%, ≥18 years old, completed two diabetes courses within the past 2 years	Hepatic disorder, stage IV heart failure, severe ischemic/hemorrhagic stroke, legal blindness, diabetes-related amputation, gestational diabetes	I: 31 (36) C: 35 (42)	I: 61.2 ± 10.9 (NA) C: 58.7 ± 13.3 (NA)	I: 7.99 ± 1.45 C: 7.91 ± 1.91
Krass et al. 2007	Community pharmacy	6	T2DM, OADs (additionally insulin), HbA1c ≥7.5%, if ≥1 oral glucose-lowering medication or insulin, were used, A1C ≥7.0%, who were taking ≥1 oral glucose-lowering medication or insulin and who were on ≥1 antihypertensive, angina, or lipid-lowering drug	None	I: 149 (176) C: 140 (159)	I: 62 ± 11 (8.6[2]) C: 62 ± 11 (10.4[2])	I: 8.9 ± 1.4 C: 8.3 ± 1.3
Mehuys et al. 2011	Community pharmacy	6	T2DM, OADs intake ≥12 months, 45 to 75 years old, BMI ≥25 kg/m2, regular visitor of the pharmacy	Insulin therapy	I: 148 (153) C: 132 (135)	I: 63 [40-84] (NA) C: 62.3 [45-79] (NA)	I: 7.7 [5.7-12.9] C: 7.3 [5.6-1.1]
Mourao et al. 2013	Primary health care units	6	HbA1c >7%, OADs, ≥1 medication, ≥18 years old, ≥6 months medication intake, BG postprandial levels ≥180 mg/dL	Pregnant; nursing mothers; impaired physical mobility	I: 50 (65) C: 50 (64)	I: 60.0 ± 10.2 (NA) C: 61.3 ± 9.9 (NA)	I: 9.9 ± 2.1 C: 9.5 ± 1.8
Obarcanin et al. 2015	Community pharmacy and ambulatory setting	6	HbA1c ≥9%, T1DM, 12 to 18 years old, ≥0.5 IU insulin per day	None	I: 39 (NA) C: 26 (NA)	I: 14.5 [12-17] (5.9 [1-14]) C: 14.9 [12-18] (6.8 [1-14])	I: 9.4 C: 9.4

[1]Mean ± standard deviation or mean [min-max value]
[2]significant difference from baseline
Abbreviations: BG: blood glucose, BMI: body mass index, C: control group, HbA1c: glycated hemoglobin, I: intervention group, NA: not available, OADs: oral antidiabetics, T1DM: diabetes mellitus type 1, T2DM: diabetes mellitus type 2

There were large differences in the number of patients in the six included studies. The smallest study included only 43 patients, 24 in the control group and 19 in the intervention group. In contrast, the largest study enrolled 335 patients and analyzed 289 (140 in the control group and 149 in the intervention group). (Castejon et al. 2013, Krass et al. 2007) The median number of patients included in these RCTs was 83 patients per study. In contrast, the study duration was relatively consistent between studies. In four studies, the pharmacists provided PhC over a period of 6 months (median duration was 6 months), and in the other two the study durations were 3 and 12 months. Reflecting the inclusion criteria, the mean age in the majority of studies was over 60 years, while the study of adolescent T1DM patients had an average age of 15 years. Only two RCTs reported diabetes duration; in the other studies, this data was not available. (Krass et al. 2007, Obarcanin et al. 2015) There was a large variance in baseline HbA1c values between studies; to avoid bias or incorrect conclusions, a Spearman correlation analysis was planned a priori.

In all studies, the pharmacists provided face-to-face consultations, and in half of the studies the patients also received additional telephone calls. (Doucette et al. 2009, Krass et al. 2007, Obarcanin et al. 2015) All studies except one (Obarcanin et al. 2015) offered printed leaflets with further information. The median intervention duration was 45.5 minutes, with the longest taking 80 minutes and the shortest 30 minutes. Interventions were conducted monthly in most studies (n=5), although one RCT had an intervention interval of three months. (Doucette et al. 2009) The recorded, documented and analyzed clinical outcomes varied between the studies. All studies recorded HbA1c values and blood glucose levels. Other clinical outcome measurements were BP, lipid profile, weight, and number of hypoglycemic episodes. Five studies also recorded humanistic outcomes such as therapy adherence, health status, or the patients' diabetes knowledge (see Table 13).

Table 13 Intervention design of the studies included in the meta-analysis

	Average intervention duration [minutes]	Intervention interval	Types of interventions	Clinical outcome measurements	Humanistic outcome measurements
Castejon et al. 2013	45	Monthly	Personal visits, printed leaflets	HbA1c, BG, BP, lipid profile, weight, waist circumference	Adherence, diabetes knowledge, health status, patient satisfaction
Doucette et al. 2009	30	Every 3 months	Personal visits, telephone calls, printed leaflets	HbA1c, BG, BP, lipid profile, weight	Diabetes knowledge, patient satisfaction
Krass et al. 2007	approximately 46	Nearly monthly	Personal visits, telephone calls, printed leaflets	HbA1c, BG, BP, lipid profile, weight, checks for complications	Adherence, health status, patient satisfaction
Mehuys et al. 2011	approximately 30	Monthly	Personal visits, printed leaflets	HbA1c, BG	Adherence, diabetes knowledge
Mourao et al. 2013	30	Monthly	Personal visits, printed leaflets	HbA1c, BG, BP, lipid profile, weight	None
Obarcanin et al. 2015	60	Monthly	Personal visits, telephone calls	HbA1c, BG, BP, lipid profile, weight, number of hypoglycemic episodes	Adherence[1], diabetes knowledge, health status, patient satisfaction

[1]The pharmacists evaluated adherence, but not by recording the outcomes of methods such as the pill-count method or a valid questionnaire

Abbreviations: BG: blood glucose, BMI: body mass index, BP: blood pressure, HbA1c: glycated hemoglobin

Characteristics of studies excluded from the meta-analysis

The five excluded studies were also screened, and the relevant data was extracted. To prevent distortions in the conclusion of this meta-analysis, the six included and five excluded RCTs were compared qualitatively to identify whether they varied regarding the study setting and design. There were only a few minor differences between the included and excluded studies. The excluded studies had a longer mean study duration (10.8 months) compared to the included studies (6.5 months), and the five excluded RCTs had a smaller number of enrolled and analyzed patients (see Table 14). Additionally, the mean intervention duration of the included studies was longer (48.5 minutes) than that of the excluded studies (35 minutes) (see Table 16).

However, there were more commonalities than differences between the six included studies and the five excluded studies, such as the variation in inclusion and exclusion criteria between the studies. Some studies used HbA1c values as inclusion criteria to select patients who had poor glycemic control. Other studies included only adult patients or patients who were able to conduct SMBG. Another commonality was that most of the excluded RCTs (three of the five studies) only included patients with T2DM. Variation in the age of the included patients and in the baseline HbA1c values were the same between the included and excluded studies. The remaining aspects of the intervention design, such as intervention interval, types of intervention, and clinical and humanistic outcomes, were similar between the two groups of studies.

Table 14 Design of the studies excluded from the meta-analysis

	Study setting	Study duration [months]	Inclusion criteria	Exclusion criteria	Analyzed (enrolled) patients	Age (diabetes duration [years][1]	Baseline HbA1c [%][1]
Ali et al. 2012	Community-based setting	12	HbA1c ≥7%, OADs intake, ≥18, able to attend regular visits	Significant comorbidities, insulin use, involvement in other trials	I: 23 (25) C: 23 (23)	I: 66.4 ± 12.7 (7.5 ± 4.8) C: 66.8 ± 10.2 (6.8 ± 3.5)	I: 8.2 ± 1.65 C: 8.1 ± 0.97
Fornos et al. 2006	Community pharmacy	13	T2DM, OADs intake ≥2 months	Cognitively impaired or unable to look after themselves, involved in another PhC program or family members of patients who take part in a PhC program	I: 56 (58) C: 56 (56)	I: 62.9 ± 10.5 (NA) C: 64.9 ± 10.9 (NA)	I: 8.4 ± 1.8 C: 7.8 ± 1.7
Jahangard-Rafsanjani et al. 2015	Community pharmacy	5	HbA1c >7%, T2DM, OADs, ability to use a blood glucose self-monitoring advice	Stage IV heart failure, adjunct insulin therapy, fasted during Ramadan, received diabetes education within the past 6 months	I: 45 (51) C: 40 (50)	I: 57.3 ± 8.6 (4.6 ± 4.3) C: 55.9 ± 8.7 (5.7 ± 5.9)	I: 7.6 ± 1.6 C: 7.51 ± 1.9
Jameson et al. 2010	Primary health care site	12	A1C >9%, ≥18 years old, no office visits in the past 12 months	Endocrinologist was managing their diabetes or if participants were not expected to live for the duration of the study	I: 52 (52) C: 51 (52)	I: 49.3 ± 10.8 (NA) C: 49.7 ± 10.9 (NA)	I: 10.4 ± 1.2 C: 11.1 ± 1.6
Kraemer et al. 2012	Community pharmacy	12	≥18 years old, English speakers, employed by a participating employer, T1DM or T2DM	Gestational diabetes	I: 36 (37) C: 31 (32)	I: 55.6 ± 6.8 (9.9 ± 10.3) C: 52.6 ± 9.2 (8.0 ± 7.4)	I: 7.28 C: 7.38

[1]Mean ± standard deviation
Abbreviations: C: control group, HbA1c: glycated hemoglobin, I: intervention group, NA: not available, OADs: oral antidiabetics, PhC: pharmaceutical care, T1DM: diabetes mellitus type 1, T2DM: diabetes mellitus type 2

Table 15 Intervention design of the studies excluded from the meta-analysis

	Average intervention duration [months]	Intervention interval	Types of interventions	Clinical outcome measurements	Humanistic outcome measurements
Ali et al. 2012	30 with tests, 20 without tests	Monthly 2 months, then every 3 months	Personal visits	HbA1c, BG, BP, lipid profile, weight	Diabetes knowledge, health status, patient satisfaction, patient medication beliefs
Fornos et al. 2006	NA	Monthly	Personal visits	HbA1c, BG, BP, lipid profile, weight, identification of drug-related problems	Diabetes knowledge
Jahangard-Rafsanjani et al. 2015	30	Monthly	Personal visits, printed leaflets	HbA1c, BP, weight	Adherence, patient satisfaction
Jameson et al. 2010	30-60	Every 2 months	Personal visits, telephone calls	HbA1c, BG	Adherence
Kraemer et al. 2012	NA	Monthly (3 months), then every 1 -3 months	Personal visits, telephone calls, printed leaflets	HbA1c, BG, BP, lipid profile, weight	Adherence, diabetes knowledge

Abbreviations: BG: blood glucose, BP: blood pressure, HbA1c: glycated hemoglobin, NA: not available

Risk of bias

To assess the risk of bias, the CONSORT statements for reporting RCTs and the PRISMA statement for conducting meta-analyses were used. (Liberati et al. 2009, Moher et al. 2015, Schulz et al. 2010) The random sequence generation or allocation concealment was not described in detail or at all in three of the studies; therefore, the risk of bias was unspecified in these three studies. (Castejon et al. 2013, Doucette et al. 2009, Krass et al. 2007) For the remaining three studies that reported the generation of a random sequence and allocation concealment, the risk of bias was low. (Mehuys et al. 2011, Mourao et al. 2013, Obarcanin et al. 2015) None of the six studies blinded the participants or blinded the outcome assessments. The blinding of participants is not feasible when providing PhC due to the implementation of additional patient visits and the need for medication analysis. However, data completeness was addressed in all studies. In four of the six studies, a logical and detailed explanation was given for missing or incomplete data. (Doucette et al. 2009, Krass et al. 2007, Mourao et al. 2013, Obarcanin et al. 2015) The remaining two studies only briefly addressed missing data. (Castejon et al. 2013, Mehuys et al. 2011) All trials had a low risk of selective reporting because each measurement mentioned in the methods was reported in the results. Due to the limited number of included studies, the risk of publication bias could not be evaluated in a funnel plot. To meaningfully test for publication bias using funnel plot asymmetry, at least 10 studies are required. (Higgins et al. 2011)

Meta-analysis of HbA1c values

The meta-analytical effect of PhC provided by community pharmacists on the HbA1c values of the included 640 diabetes patients in this meta-analysis was an HbA1c difference of –0.66%, with a 95% confidence interval (CI) of [–0.86%, –0.45%] (see Figure 12). Hence, PhC reduced the HbA1c values of the intervention group compared to the control group. Although two RCTs reported results that were not statistically significant (Castejon et al. 2013, Doucette et al. 2009), the overall effect of the six studies was still positive. Figure 12 shows that the largest effect on HbA1c, –1.29% with a CI of [–2.02%, -0.56%], was obtained by Mourao et al. In that study, the HbA1c values of the control group patients increased and those of the intervention group decreased. (Mourao et al. 2013) The smallest (and non-significant) effect was in the study by Doucette et al.; the difference in HbA1c values was –0.29%, with a CI of [–0.96%, 0.38%]. (Doucette et al. 2009) The studies that had a stronger impact (i.e., weight) on the meta-analysis were those by Krass et al. and Mehuys et al., with 232 analyzed patients and a weight of 35.9% and 127 analyzed patients and a weight of 32.1%, respectively. (Krass et al. 2007, Mehuys et al. 2011)

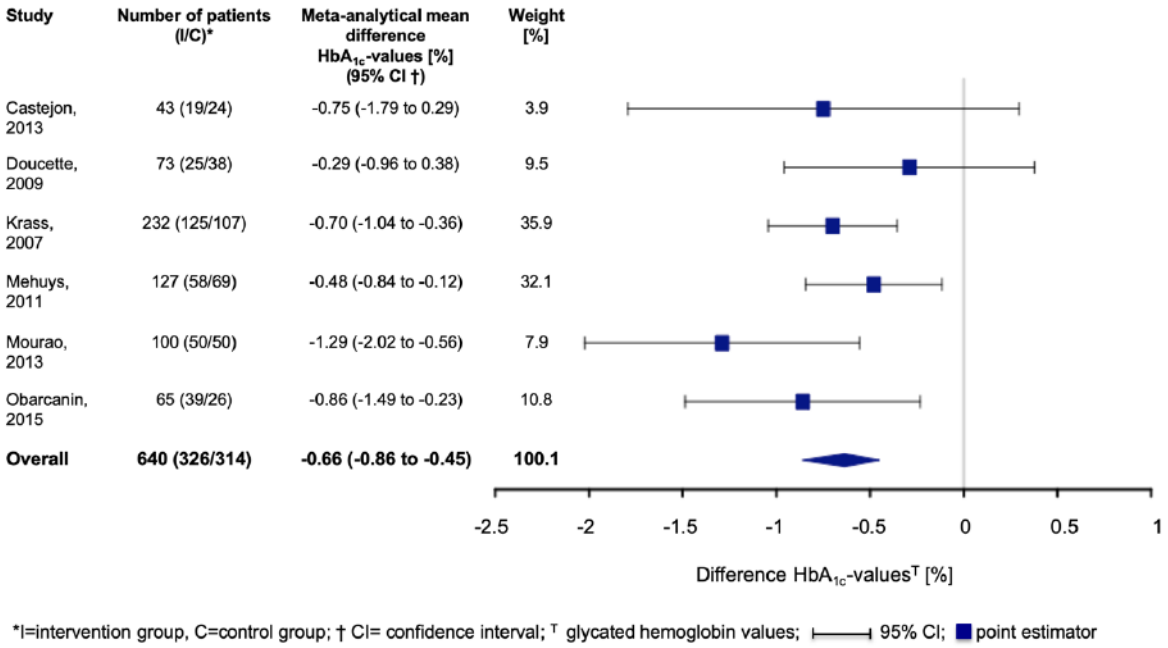


Figure 12 Forest-plot HbA1c-values meta-analysis according to Deters et al. (Deters et al. 2018)

Evaluation of heterogeneity and sensitivity analysis of the analyzed studies

To evaluate the inconsistency between the analyzed studies, τ^2 and I^2 were calculated. The Cochrane Handbook version 5.1 (Chapter 9.5.2) states that a value between 0% and 40% for I^2 indicates that the inconsistency across the analyzed studies might not be important. (Higgins et al. 2011) Here, the I^2 was 7.9%; this indicates that there was no inconsistency between the six included studies. This is supported by the τ^2, which was 0. The q value was calculated to assess the heterogeneity of the studies, and a significance test was conducted. The q value was 5.43 and the related p-value was 0.3659. Hence, we concluded that there was no significant heterogeneity between the six analyzed studies. A sensitivity test was also conducted to assess whether the meta-analytical effect changed when one of the studies was excluded. The results of this analysis varied between a meta-analytical HbA1c difference of –0.6018% when excluding Mourao et al. (the study with the highest effect) and –0.7393% when excluding Mehuys et al., which had a high weight (32.1%) and the smallest significant effect. (Mehuys et al. 2011, Mourao et al. 2013) The results of the sensitivity analysis indicate that the decisions made during the course of this meta-analysis, as well as potentially missing information, did not affect the overall meta-analysis results.

Meta-analysis of relevant intervention components

After conducting the meta-analysis of HbA1c values, 36 intervention components were analyzed. The corresponding authors of each study answered the aforementioned questionnaire about how the PhC was conducted and the training that the pharmacists received prior to the PhC intervention. Four components in the questionnaire asked about methods of patient education, such as personal visits or printed leaflets. Three questions dealt with medication examination, such as identifying DRPs during medication analysis. A large portion of the questionnaire (11 components) dealt with patient empowerment and disease management, such as setting individual goals with the patient and discussing diabetes-related complications. The remaining six components asked about interdisciplinary work, for example with the diabetologist or physician, or referrals to other health care professionals. The pharmacist gave feedback and recommendations for drug therapy changes to the physician in only a few studies (n=4), because in some studies the interdisciplinary collaboration between pharmacists and physicians was not mandatory in the study protocol.

The meta-analysis of the PhC intervention elements revealed that most of the analyzed elements had a significantly positive effect on HbA1c. The meta-analytical effect of the following five intervention components was not significant: (1) if recommended, skin examinations, (2) retinopathy screening, (3) nephropathy screening, (4) whether patients were referred to a specialist nurse for additional care if needed, and (5) watching an educational video. These components were likely not significant because they were included in only one RCT. (Castejon et al. 2013, Obarcanin et al. 2015) Table 16 shows that some components were more effective than others. The largest effect on the meta-analytic mean difference (–0.81% each) came from setting individual goals with the patient and sending recommendations to the diabetologist or physician. Hence, these two intervention components were the most effective. A medication review that identified patient DRPs was nearly as effective, with a meta-analytic mean difference of –0.79% with a CI of [–1.23%, –0.35%]. Assessing the patient's current health status with a questionnaire was the measurement/assessment with the largest effect on HbA1c; however, a similar effect was found by assessing and discussing the patient's health beliefs and medication knowledge and analyzing the patient's SMBG records. In most studies that evaluated the frequency of SMBG and/or the current blood glucose level, the patient's SMBG records were analyzed in any available form (e.g., handwritten). However, in the study by Krass et al., the SMBG measurements were downloaded in the form of graphs from the blood glucose meter using a software program. The pharmacists reviewed these records and the graphs with supportive explanations or statements and empowered the patients to improve their disease management. (Deters et al. 2018)

Table 16 Meta-analytic effect of the intervention outcomes according to Deters et al. (Deters et al. 2018)

Intervention component	Number of analyzed patients	Meta-analytic mean difference in HbA_{1c} values [%]	95% Confidence interval [%]
Analyzing the medication			
Medication review (including identification of drug-related problems)	281	–0.79	–1.23 to –0.35
Disease management			
Diabetes-related complications	540	–0.60	–0.82 to –0.39
Patient health beliefs and medication knowledge	513	–0.74	–0.99 to –0.49
Nutrition, exercise, and smoking recommendations	640	–0.66	–0.86 to –0.45
Review of diabetes record books	297	–0.74	–1.04 to –0.44
Individual goal setting	440	–0.81	–1.08 to –0.54
Measurements and assessments			
Blood glucose measurements	567	–0.70	–0.93 to –0.47
Adherence	402	–0.60	–0.85 to –0.36
Diabetes knowledge	308	–0.54	–0.81 to –0.26
Health status	340	–0.74	–1.03 to –0.45
Patient satisfaction with pharmacist intervention	413	–0.67	–0.93 to –0.40
Health care collaboration			
Sending feedback and recommendations to the physician	470	–0.81	–1.07 to –0.55

A correlation analysis was performed as part of this meta-analysis. There was a small correlation between the total number of intervention elements provided and the change in HbA1c. This correlation was small and negative, indicating that a larger number of intervention elements may lead to greater improvements in HbA1c and therefore glycemic control. Furthermore, there was a small, positive correlation between the study duration and the HbA1c change. This indicated that the effect decreased over the course of the study period; however, the correlation was quite small (0.10) and a valid conclusion cannot be drawn.

3.3.3 Description of pharmacist training prior to pharmaceutical care intervention

Before the studies began, the participating pharmacists received training on the relevant aspects of PhC and diabetes disease management. There was a large variability in training duration among the studies, with a minimum training duration of six hours and a maximum of 30 hours (mean training duration of 13.8 hours). Five of the six RCTs trained the pharmacists once before the study began; the study by Obarcanin et al. repeated the training every 2 months. (Obarcanin et al. 2015)

The education and profession of the trainers also varied widely among the six included studies. The largest number of professions of those who provided the training (e.g., community pharmacists, clinical pharmacists, physicians, and diabetes specialist nurses) was six in the study by Krass et al. and the lowest number was two in two studies (see Table 17). (Castejon et al. 2013, Krass et al. 2007, Mourao et al. 2013) A pharmacologist and a dietitian were trainers in only one study each. (Krass et al. 2007, Mourao et al. 2013) In one study the participating community pharmacists were trained together with postgraduate pharmacy students. (Castejon et al. 2013)

Table 17 Aspects of the pharmacist training of the included studies according to Deters et al. (Deters et al. 2018)

	Duration [hours]	Interval	Training provided by						
			Community pharmacists	Clinical pharmacists	Certified diabetes educators	Physicians	Diabetes specialist nurses	Dietitian	Pharmacologists
Castejon et al. 2013	12	None	X[1]		X				
Doucette et al. 2009	21[2]	None	X	X	X	X			
Krass et al. 2007	14	None	X	X	X	X	X	X	
Mehuys et al. 2011	6	None	X			X			
Mourao et al. 2013	20	None		X					X
Obarcanin et al. 2015	10	Every two months	X	X	X	X	X		

1Community pharmacists and pharmacists who can be counted among them

[2]15 hours of self-study and 6 hours of in-person training

Another aspect of the pharmacist training is the topics and content covered in the training. The questionnaire asked about the pharmacists' training before and during the study; in particular pertinent training contents that are recommended by the current DDG guidelines. (DDG 2020) These included the following topics: pathophysiology of diabetes, diagnosis and therapy for T1DM and T2DM patients, lifestyle and documentation advice, and practical aspects of diabetes self-management (see Table 18). In particular, pathophysiology included not just the physiological processes of insulin secretion and blood glucose regulation, it also included the effect of insulin deficiency in diabetes patients, the altered blood glucose counter-regulation, and the symptoms and impacts of hyper- and hypoglycemia. Theoretical and practical skills concerning the effect of physical activity on blood glucose regulation were also trained. Other relevant topics were discussed, such as high blood glucose levels, body weight, BP and lipid levels and their impact on diabetes therapy and management. The pharmacists also received a general introduction to recommended diagnosis and therapy options for diabetes patients according to the current ADA and ISPAD guidelines. This also covered general medication knowledge, including adverse events. Prevention, identification, and treatment of short-term and long-term diabetes complications were discussed. Practical skills such as SMBG and insulin injection techniques were also covered by the training so that the pharmacists would be able to assess and help develop the practical skills of the patients during the study. The lifestyle advice comprised different techniques to support patients' disease self-management and workable solutions to help the patient to correctly document various self-measurements such as SMBG. In addition, the pharmacists were trained in documentation methods for reporting patient adherence, diabetes knowledge, health status, and patient satisfaction with the provided PhC.

To avoid false inferences, correlations were calculated between parameters of the pharmacist training and the change in HbA1c values. There was no correlation between the number of pharmacist training components and the altered HbA1c values. However, because the number of analyzed studies was small and the total number of training elements was the same in half of the studies (i.e., six of the studies had three elements), it was difficult to assess the influence of the number of training components on the change in HbA1c values.

Table 18 Elements of the pharmacist training in the included studies according to Deters et al. (Deters et al. 2018)

	Pathophysiology		**Diagnosis and therapy**		
	Regulation of blood glucose and insulin secretion	Impact of high glucose levels	Impact of high blood pressure	General medication knowledge	Short- and long-term complications
Castejon et al. 2013					
Doucette et al. 2009	X	X	X	X	X
Krass et al. 2007	X	X	X	X	X
Mehuys et al. 2011	X	X		X	X
Mourao et al. 2013	X	X	X	X	X
Obarcanin et al. 2015	X	X	X	X	X

	Practical aspects			
	Self-measurement of blood glucose	Usage of insulin pens	Blood pressure measurement	Lipid level measurement
Castejon et al. 2013	X	X	X	X
Doucette et al. 2009	X	X	X	X
Krass et al. 2007	X	X	X	
Mehuys et al. 2011	X			
Mourao et al. 2013	X	X	X	
Obarcanin et al. 2015	X	X		

	Important (lifestyle) advice		
	Diet and exercise	Documentation of self-measurements	Methods to support self-management
Castejon et al. 2013	X	X	X
Doucette et al. 2009	X	X	X
Krass et al. 2007	X		X
Mehuys et al. 2011	X	X	
Mourao et al. 2013	X	X	X
Obarcanin et al. 2015	X	X	X

	Documentation			
	Adherence and/or compliance	Diabetes knowledge	Health status	Patient satisfaction
Castejon et al. 2013	X	X	X	X
Doucette et al. 2009	X	X		X
Krass et al. 2007	X		X	X
Mehuys et al. 2011	X	X		
Mourao et al. 2013	X			X
Obarcanin et al. 2015	X			X

	Communication techniques for practicing the pharmaceutical care intervention			
	Motivational interviewing	Role playing	Discussion of patient cases	Principles of pharmaceutical care
Castejon et al. 2013	X	X	X	
Doucette et al. 2009		X	X	X
Krass et al. 2007	X	X	X	X
Mehuys et al. 2011				
Mourao et al. 2013	X	X	X	X
Obarcanin et al. 2015	X		X	X

3.4 Discussion

Results of the meta-analysis: HbA1c values

The results of our systematic review and meta-analysis revealed that PhC provided by community pharmacists can have a significant and positive effect on the glycemic control of T1DM and T2DM patients, as indicated by their HbA1c value. This finding agrees with other studies of PhC interventions in diabetes patients. A meta-analysis by Machado et al. included 16 studies with hospital or community pharmacists of mixed trial design (RCTs, clinical trials, pre-post cohorts, and retrospective cohorts). The authors found an HbA1c difference of –0.62%, which is similar to our result. (Machado et al. 2007) The meta-analysis by Collins et al. included 14 RCTs that conducted PhC in community and hospital settings and found that the HbA1c values were reduced by –0.76%, which is also comparable to our findings. (Collins et al. 2011)

Improved glycemic control can lead to a reduced incidence of diabetes-related complications, such as CV complications. The UKPDS included patients with T2DM and evaluated, among other things, the effect of intensive glycemic control on the incidence of diabetes-related complications. In the intervention group, intensive glycemic control reduced the occurrence of microvascular complications by a quarter compared to the control group. The UKPDS also found that any improvement in glycemic control reduced diabetes-related complications. (King et al. 1999) The UKPDS also investigated whether intensive drug therapy and associated strict adjustment of glycemic control entails any risks or whether it provides only benefits. The treatment of T2DM patients with sulfonylureas or insulin to achieve intensive glycemic control substantially decreased the risk of microvascular complications in the intervention group, but the risk of hypoglycemia increased. (UKPDS-Group 1998b) Other studies, such as the study by Park et al., have investigated whether reduced FBG levels can decrease the probability of developing atherosclerotic CVD as a result of diabetes-related complications. (Park et al. 2013) Another study came to the same conclusion that impaired or diabetic FBG levels lead to an increased hazard ratio for the development of CV complications. (Lee et al. 2018)

Taken together, these findings indicate the positive effect of glycemic control on the risk of developing microvascular complications. Considering the results of our meta-analysis, community pharmacists should be a compulsory and vital part of the health care team to support the self-management of diabetes patients so that they achieve improved glycemic control. (Deters et al. 2018)

The studies that were excluded from our meta-analysis had a median study duration of 12 months, whereas the included studies had a median duration of 6 months. The calculated correlation between the study duration and the altered HbA1c values was positive but very small. Therefore, we assumed that a study duration longer than 6 months would not lead to either better or worse results. However, we found that 6 and 12 months were the most common study durations. Regarding the study populations, there was no difference in the median number of patients between the included and excluded studies. The studies that were excluded had a median of 85 patients per study. This was similar to the median number of patients in the six included studies (83 patients per study). Hence, the statistical effect size, based on the differences in HbA1c values of both groups, was similar.

Results of the meta-analysis: effect of the intervention component

The meta-analysis of the effect of each intervention element suggested that the most effective elements were patient-centered and interdisciplinary. The four most effective PhC elements were sending feedback to the physician, setting individual goals with the patient, analyzing blood glucose records, and analyzing the current medication to identify DRPs. We classified patient-centered interventions as interventions that assess or use individual patient information to provide personalized, necessary, and appropriate counseling. In addition to sending feedback to the physician, individual goal setting was one of the most effective intervention components (mean meta-analytical difference of HbA1c values –0.81%). We found that setting specific goals with diabetes patients leads to better performance. This finding is reinforced by previous studies on the effect and impact of setting goals. As stated in the goal setting theory by Latham et al., goals are regulators of behavior. There is a positive relationship between a specific high goal and task performance. (Latham et al. 2007, Latham et al. 1991) High goals lead to better performance, although there are various factors that should be taken into account, such as goal commitment, receiving feedback, and participation in decision-making. (Latham et al. 2011)

None of the aforementioned reviews and meta-analyses included a quantitative assessment of the effectiveness of individual intervention components. Hughes et al. described current insights and future directions of the role of the pharmacist in the management of T2DM patients. One qualitative analysis identified pertinent PhC components. (Hughes et al. 2017) There were many commonalities between our intervention components and those identified by Hughes et al., such as reviewing patient's medication and referring them to another health care professional. Therefore, we believe that we identified and analyzed many of the most relevant intervention and training components in our meta-analysis.

Results of the analysis: training design and content

Due to the small number of included studies and the large number of training elements, the precise effect of the different training components and content could not be statistically determined. Therefore, the specific content of the training implemented in the respective studies was described qualitatively. Further research is needed to more accurately assess the effect of the training that pharmacists received before and during the study. The pharmacists' training might influence and bias the effectiveness of the intervention components. Studies are also needed to evaluate the impact of different training methods and content.

Possible limitations and strengths of the included studies

One possible limitation of this meta-analysis was that the study by Castejon et al. had a small study population and broad inclusion criteria. This could be one reason for the non-significant difference in HbA1c values. Inclusion criteria such as a higher limit for the HbA1c value i.e., only including patients with HbA1c values above 8%, may have led to different results. One of the strengths of this study by Castejon et al. was the comprehensive data collection and evaluation. Additionally, in the included studies, many relevant tests were conducted on the diabetes patients, such as tests for kidney disease. (Castejon et al. 2013, Deters et al. 2018)

Doucette et al. focused more on patient education and motivation than on medication changes; this was one of the positive aspects of this RCT. The long study duration of 12 months was another strength of their study. If a study has a long duration then there is a higher probability that effects that occur only after a certain period of time will be detected. However, a longer intervention interval (i.e., every 3 months) could be a reason for the non-significant decrease in HbA1c values. (Deters et al. 2018, Doucette et al. 2009)

The largest study population of the six included studies was in Krass et al. This was one of the strengths of their study. Another positive aspect was the provision of the same blood glucose measurement system for all patients. This system offered the participating pharmacists the opportunity to download values and graphs of the patients' blood glucose levels at the community pharmacy. Hence, all pharmacists could review and discuss the blood glucose levels with the patient and give constructive recommendations on how to improve glycemic control. One of the limitations of this study was the small differences between baseline characteristics, such as the duration of diabetes, between the intervention and control group. (Deters et al. 2018, Krass et al. 2007)

There were two possible limitations of the study by Mehuys et al. The first limitation was the non-standardized physician-pharmacist collaboration; the cooperation between physicians and pharmacists was not precisely defined and therefore differences in the implementation could not be excluded. The second limitation was the assessment of the patients' medication adherence by the medication refill rate. Mehuys et al. reported that some patients had adherence rates over 100% due to the stockpiling of medication. One of the strengths of this study was the precisely defined inclusion and exclusion criteria to avoid inclusion of inappropriate patients. (Deters et al. 2018, Mehuys et al. 2011)

One limitation and influencing factor in the study by Mourao et al. was the ability of control group participants to access the laboratory results at baseline. This information about their current glycemic control could have had a positive influence on the final results of the control group patients. Positive factors of this RCT were the analyses of the impact of pharmacist interventions on the current drug therapy and the number of (unresolved) DRPs. (Deters et al. 2018, Mourao et al. 2013)

A larger number of measurements were conducted in the study by Obarcanin et al. than in the other studies. In addition to the HbA1c values, the FBG, blood glucose, and the number of hypoglycemic episodes were assessed and documented by the pharmacists. This is a positive factor because according to the current ISPAD or ADA guidelines, low glycemic variability is an important factor in the delay and prevention of short-term and long-term diabetes-related complications. Possible limitations of this study were the differences between the health care systems in Germany and Bosnia-Herzegovina and that secondary parameters such as FBG, blood glucose, and the number of light hypoglycemic episodes were recorded in the intervention group only. (Deters et al. 2018, Obarcanin et al. 2015)

3.5 Limitations

There were a few manageable limitations of this systematic review and meta-analysis. The meta-analysis included data from several countries including Germany, the United States, and Australia. Hence, there might be differences in the design of intervention or training programs as a result of the level of education of pharmacists in different countries. According to the corresponding authors of the included studies, the training was designed to ensure that the pharmacists could carry out the intervention according to the study protocol and as homogenously as possible. Thus, these differences should not have any marked influence on the analysis of the intervention content.

The realization and duration of the PhC interventions of the six individual studies might have varied because the PhC interventions included components such as individual goal setting and review of blood glucose levels that depend on the patient's personal situation and current lifestyle circumstances. However, the study protocols included some directives for the conduct of these components. Finally, the patient sample size in all studies was large; thus, the impact of the varying duration of PhC interventions was negligible. (Deters et al. 2018)

To account for differences in the design of the studies, correlations were calculated between different study design elements and the HbA1c values, for instance, the correlation between the study duration and the reduction or increase in HbA1c. It was difficult to assess the efficacy of each intervention separately. However, no general concordance was found, and therefore we believe that this meta-analysis was conducted correctly and successfully.

Another limitation was the response rate of the corresponding authors; only six of 11 authors answered the questionnaire and provided raw data. The other five studies had to be excluded due to missing or incomplete data.

3.6 Conclusion

The results of our systematic review and meta-analysis indicate that PhC provided by community pharmacists has a positive impact and improves the glycemic control of diabetes patients. From the six included RCTs, the meta-analytical mean difference in HbA1c values was –0.66%, with a 95% CI of [–0.86%, –0.45%]. Any improvement in glycemic control is beneficial for diabetes patients to avoid short- and long-term diabetes-related complications, such as microvascular disease. (King et al. 1999) Therefore, community pharmacists should offer PhC interventions for diabetes patients who have poor glycemic control. An interdisciplinary team is needed to optimally carry out PhC interventions, and pharmacists should become a compulsory part of the health care team of patients with diabetes.

The quantitative analysis of the intervention components revealed that components that were patient-centered and interdisciplinary were the most effective. Notably, the four most effective intervention components were sending feedback to the physician, setting individual goals with the patient, analyzing the patient's medication, and analyzing the patient's blood glucose records.

The results of this analysis revealed that in future the main focus of PhC activities and interventions for diabetes patients provided by community pharmacists should be patient-centered and interdisciplinary. Further research is needed to evaluate the precise effect of different training settings, components, and methods on the effectiveness of PhC interventions. In addition, the practicability and feasibility of the four most effective PhC components should be tested in practice, preferably in a standard community pharmacy setting. It would be reasonable to conduct a small-scale, preliminary, and qualitative pilot study to get a realistic estimate of the expected effect size and possible barriers to implementing the main interventions in practice. The results from this preliminary study should serve as a basis for further planning and calculations for larger hypothesis-testing studies.

4 Chapter Three – Proof of concept study to demonstrate the practicability of the four most effective pharmaceutical care interventions during a patient consult

Parts of this chapter have already been published. The author of this thesis, Maira Anna Deters, was first author of this publication and made the following contributions to the publication:

***Deters MA**, Obarcanin E, Schwender H, Laeer S. EMDIA Case Series – Effective Medication Therapy Management (MTM) for Diabetes Type 2 Patients – A Proof of Concept Study. Pharmacy 2021; 9(3):137. https://doi.org/10.3390/pharmacy9030137*

(1) conceptualization was done with Prof. Dr. Stephanie Läer, (2) methodology with Dr. Emina Obarcanin and Prof. Dr. Stephanie Läer, (3) formal analysis with Prof. Dr. Holger Schwender (four eye principle), (4) investigation with Dr. Emina Obarcanin, (5) original draft preparation and (6) project administration.

4.1 Background

The systematic review and meta-analysis suggested that PhC interventions provided by community pharmacists can have a significant positive effect on the glycemic control of patients with T1DM and T2DM. Quantitative analysis of the PhC intervention components revealed that some were more effective than others. To the best of our knowledge, no study has yet investigated whether the four components we identified (individual goal setting, sending feedback and recommendations to the physician, conducting a medication review including DRP identification, and reviewing the patient's current blood glucose measurements) are effective in combination. Most studies have combined many more than these four PhC components, and the included elements have varied widely. (Deters et al. 2018)

Many studies have investigated whether German pharmacists can perform medication reviews and identify DRPs in a community pharmacy setting. Bitter et al. examined the effect of a medication review program by community pharmacists in 12 German pharmacies. (Bitter et al. 2019) Rose et al. investigated whether pharmacists could identify and prioritize eligible patients for a medication review and whether they could identify evidence-based criteria for patient selection. The prescriber's implementation of the received recommendations and the factors influencing this were also evaluated. (Rose et al. 2016) Data from the ATHINA project in Germany (AKNR 2021) indicated that community pharmacists can, indeed, identify patients who require further medication information and who would benefit from a medication review

because they had potential or manifest DRPs. Pharmacist intervention reduced the occurrence of DRPs from 56.0 ± 22.7% to 28.9 ± 18.3%. (Seidling et al. 2017) However, there is still a lack of knowledge on whether the aforementioned four components in combination are effective in practice.

RCTs have a strictly controlled study setting and methodology and therefore high internal validity; however, the generalizability of their results is limited compared to results from real-world studies. (Saturni et al. 2014) Therefore, for a preliminary study that provides a realistic initial assessment of the expected effect, hurdles, and optimization requirements, the RCT is not appropriate as a study type. Other types of studies, such as case series, are better suited to this endeavor. The aim of this chapter was to get a realistic assessment of the effect and practicability of carrying out the four selected PhC components in a community pharmacy setting in practice, as a basis for further studies. This was accomplished by testing the feasibility of this structured additional PhC in a community pharmacy setting over a period of approximately 4 months.

4.2 Methods

4.2.1 Objective

The primary objective of this qualitative case series was to formulate a hypothesis about the feasibility of implementing the four PhC components. The case series included ten diabetes patients and was conducted in a community pharmacy setting. The practicability and feasibility of implementing the four PhC components identified in the meta-analysis should be verified. The implementation of these selected PhC components had to be conducted within a reasonable timeframe (60 minutes). The following four PhC components were implemented:

- medication review
- individual goal setting
- sending feedback to the physician
- reviewing blood glucose measurements

The secondary objective of this case series was to formulate a hypothesis about the effectiveness of implementing these four components in a community pharmacy setting within 60-minute patient visits on the following parameters:

- glycemic control measured by the HbA1c value and FBG level
- number of DRPs according to PCNE
- medication appropriateness index (MAI)
- well-being index measured by the WHO-5 questionnaire

4.2.2 Trial design and participants

The case series was a small-scale, preliminary, and qualitative pilot study with ten diabetes patients to formulate a realistic first estimation of the expected effect and possible hurdles of implementing the main intervention. The results from this case series will serve as a basis for further planning and calculations, such as case number analysis and later implementation of further hypothesis-testing studies. Therefore, there was no calculation of sample size for this case series. The number of patients to be recruited was set a priori at 10, so that the number of patients would be sufficient for statistical analyses. We included 10 patients who had a confirmed diagnosis of diabetes mellitus, were older than 12 years, signed the informed consent form, had an HbA1c value above 7.5%, had at least four chronic diseases, had to take medications at least 12 times daily, or had potential or manifest DRPs. The inclusion criteria were selected according to the current ADA guidelines and the German

Bundesapothekerkammer medication analysis guideline for quality assurance. (ADA 2020, BAK 2018) The patient data were analyzed per protocol; therefore, patients were excluded if they withdrew their informed consent or did not complete all four patient visits. Analyzing the data per protocol can confound the results. Per protocol analysis was undertaken anyway to ensure a sufficient amount of patient data. All patients were recruited and enrolled in one German community pharmacy in North Rhine Westphalia with face-to-face patient interviews.

The procedure for patient recruitment was as follows: a pharmaceutical technical assistant (PTA) or pharmacist approached the following patients:

- Patients who filled a prescription for insulin, OADs, or other supplies needed for diabetes therapy
- Patients who had a (pharmaceutical) question about an insulin, OAD, or other supplies needed for diabetes therapy
- Patients with T1DM or T2DM as a diagnosis who voiced acute DRPs during the consultation in the pharmacy

As a next step, patients were asked if they had a confirmed diagnosis of diabetes mellitus and were older than 12 years, if they had a current HbA1c value above 7.5%, had at least four chronic diseases, had to intake medications at least 12 times daily, or had potential or manifest DRPs. Only eligible patients received the informed consent form.

This study was approved by the ethics committee of Heinrich Heine University (ethical approval code: 2018-325-ProspDEuA, approval date: 25.03.2019) and was given the name EMDIA (**E**ffective **M**edication therapy management for **DIA**betes patients).

4.2.3 Intervention design

After signing the informed consent, I recorded the medication history, collected relevant patient data, such as HbA1c, FBG levels, and current medication, and reviewed the blood glucose recordings, where available, at baseline (see Figure 13). The patients brought their self-recorded data, blood glucose measurements, and medication history to each visit. The blood glucose data were recorded by SMBG. Afterward, 2 to 4 weeks after the first patient visit at baseline, the pharmacist informed the patients about potential DRPs related to their medication and set individual goals with the patient. If deemed necessary, the pharmacist sent feedback to the physician directly or indirectly (via the patient). Any conversations with the physicians or other health care professionals were documented in an additional form, and the dates were also saved in a checklist (see Appendix X 11 and 12). The pharmacist gave the

patient information about the current medication and checked the patient's medication knowledge if needed. The first and second follow-up visits were conducted approximately two and three months after baseline to check whether the individual goals were achieved. In those follow-up visits we collected all relevant data such as HbA1c, FBG levels, and current medication. The WHO-5 well-being index was completed at baseline and at the fourth visit. If deemed necessary, the pharmacist sent repeated feedback to the physician. All interviews, medication reviews, analysis of patient data, and correspondence with the physicians were provided by one pharmacist who was trained in the performance of medication reviews and MTM. For this case series, the definition of the German Pharmacy Operation Regulations (ApBetrO) for MTM and medication reviews was used. MTM is a pharmaceutical activity in which the patient's entire medication—including self-medication—is repeatedly analyzed to improve drug therapy safety and compliance by identifying and resolving DRPs. The PCNE for medication reviews defines the medication review as a structured evaluation of a patient's medicines to optimize medicine use and improve health outcomes. This entails detecting DRPs and recommending interventions. (Griese-Mammen et al. 2018) The medication review is a central component of MTM and, if provided separately from MTM, the medication is only analyzed once. Patient data were documented according to the SOAP (subjective patient information, objective data, assessment of the data, and plan) note. (Wright et al. 2014) The individual goals were mutually set with the patient according to the SMART criteria (**s**pecific, **m**easurable, **a**ttainable, **r**ealistic, and **t**ime-based).

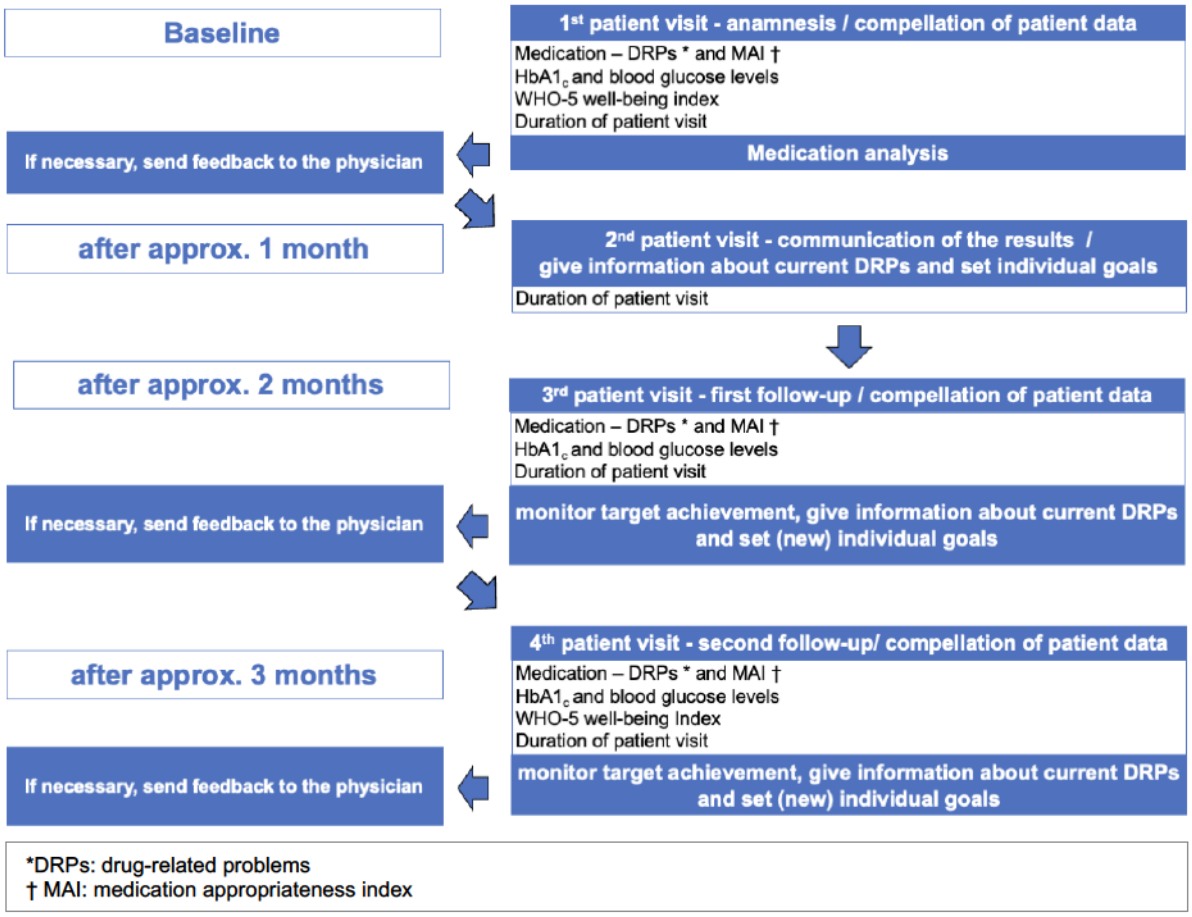


Figure 13 The design and chronological sequence of the EMDIA case series

4.2.4 Outcomes

The primary objective of the case series was to formulate a hypothesis on the feasibility of implementing the four PhC components mentioned above. Therefore, the duration of each patient visit was documented. A limit of 60 minutes per patient visit was set as realistic. In addition, the total time of each patient interview was recorded and documented. The secondary objective of the case series was to formulate a hypothesis on the effectiveness of implementing the four components in everyday practice. To develop a hypothesis about the effectiveness and successful implementation of the medication review, we identified and classified the current DRPs, according to the PCNE. (PCNE 2019a) The PCNE classification differentiates between existing (manifest) and potential DRPs. The outcomes of the interventions to solve DRPs are classified as: 1) unsolved—DRP is still completely existing, 2) partially solved—parts of the DRP are solved, 3) solved—the DRP no longer exists, or 4) DRPs with an unknown result, for example, if required laboratory values are not yet available. The MAI was determined according to Hanlon et al. and Samsa et al. (Hanlon et al. 1992, Samsa et al. 1994) If deemed necessary, the physician received the results of the medication reviews and relevant feedback. To evaluate the benefit of reviewing patients' blood glucose measurements, the patients'

current glycemic control, measured by HbA1c and FBG, was recorded by the pharmacist in the developed EMDIA-CRFs (see Appendix X 11). Mutually set individual goals can have a significant impact on the four PhC components and can influence patients' well-being. Hence, the well-being index was determined by using a German translation of the WHO-5 questionnaire (see Appendix X 7). (Petrak 2018) Patient data were analyzed by two pharmacists and the results of each medication review were discussed between them. The transmission of all data and the results were checked using the four-eye principle.

4.2.5 Statistical analysis

To formulate a hypothesis regarding the effect of this structured MTM on the different endpoints, average values and SDs of the data of all patient visits were compared before and after the intervention. Missing values were marked as not available (n.a.). To test whether the data was normally distributed, the Shapiro-Wilk test was used. The Wilcoxon signed-rank test was used to assess statistical significance between the different patient visits of these non-normally distributed values. This test is applicable even when the sample size is small. A significance level of α 0.05 was chosen a priori. All statistical analyses were performed using Microsoft Excel for Mac 2019 version 16.29.1 and RStudio for Mac version 1.4.1717. (R-Foundation 2022)

4.3 Results

4.3.1 Summary of relevant patient data

All of the included patients (four female and six male) had a confirmed diagnosis of T2DM. One patient was included in the case series because of an HbA1c value greater than 7.5%. Other patients had potential DRPs, such as strong daytime tiredness, hyperhidrosis, edema, or neuropathic pain. On average, patients were 70.70 ± 11.71 years old and, at baseline, had 6.0 ± 2.0 different disease states, including T2DM. The most common disease states at baseline were hypertension (n = 9), hyperlipidemia (n = 7), and chronic pain (n = 5). According to the patients' statements, two patients had neuropathy and diabetic foot syndrome, and one patient had diabetic retinopathy. The average HbA1c value decreased slightly from 7.04 ± 0.90% at baseline to 7.00 ± 0.61% at the end of the case series (see Table 19). A larger, non-significant reduction was observed in the FBG levels during the case series—from 141.86 ± 32.03 mg/dL to 119.63 ± 18.95 mg/dL—while the number of unsolved DRPs was reduced significantly from 6.90 ± 2.60 at baseline to 1.89 ± 1.90 at the second follow-up ($p < 0.003$). The patients' MAI values varied between 0 and 38 at baseline, with an average value of 19.1 ± 13.24. The index average decreased to 6.40 ± 8.88 by the end of the case series ($p = 0.007$). The average WHO-5 well-being index of all included patients increased from 17.10 ± 6.62 to 20.40 ± 5.83 points over the course of the study.

Table 19 Overview of relevant data and study endpoints (Deters et al. 2021)

Relevant data and study endpoints	1st Patient Visit: Anamnesis	2nd patient Visit: results of medication analysis	3rd Patient Visit: First Follow-up	4th Patient Visit: Second Follow-up
Medication				
Number of medications per patient	10.50 ± 3.75 n = 10	no measurement	11.00 ± 4.37 n = 10	10.90 ± 4.07 n = 10
Unsolved DRPs[1] per patient	6.90 ± 2.60 n = 10	no measurement	2.30 ± 2.11* p-value: <0.003 n = 10	1.89 ± 1.90* p-value: <0.003 n = 10
Solved DRPs[1]	none	no measurement	3.20 ± 1.99 n = 10	3.70 ± 2.45 n = 10
Partially solved DRPs[1]	none	no measurement	1.45 ± 2.16 n = 10	1.80 ± 2.30 n = 10
DRPs[1] with unknown result[1]	none	no measurement	0.90 ± 1.28 n = 10	1.00 ± 1.41 n = 10
Average MAI[2]	19.10 ± 13.24 n = 10	no measurement	10.20 ± 9.80* p-value: 0.007 n = 10	6.40 ± 8.88* p-value: 0.007 n = 10
Glycemic control				
HbA1c value[3] [%]	7.04 ± 0.90 n = 9	no measurement	6.90 ± 0.56 p-value: 0.50 n = 9	7.00 ± 0.61 p-value: 0.78 n = 9
Fasting blood glucose [mg/dl]	141.86 ± 32.03 n = 7	no measurement	147.29 ± 31.76 p-value: 0.85 n = 7	119.63 ± 18.95 p-value: 0.05 n = 8
Other relevant measurements				
Average WHO-5 well-being index	17.10 ± 6.62 n = 10	no measurement	no measurement	20.40 ± 5.83* p-value: 0.02 n = 10
Duration of patient visit	48.70 ± 8.83 n = 10	23.80 ± 9.34 n = 10	30.50 ± 10.19 n = 10	27.90 ± 9.57 n = 10

Mean values ± standard deviation
n: number of analyzed patients
*significant p-values (p <0.05)
[1] DRP: drug-related problems classified according to the PCNE classification
[2] MAI: medication appropriateness index
[3] HbA1c value: glycated hemoglobin

4.3.2 Primary objective – feasibility of implementing four effective pharmaceutical care components

Time expenditure for implementing the four selected pharmaceutical care components in practice

The primary objective of this proof-of-concept case series was to evaluate whether the four PhC components could be implemented with a reasonable timeframe in practice. Each patient visit should not be longer than 60 minutes. The first, baseline, visit that included taking the patients' medication history was the longest, with a mean duration of 48.70 minutes. The duration of the visits varied from 14–60 minutes depending on the number of medications, the number of diseases, frequency of blood glucose measurements, and potential DRPs. The average durations of the first and second follow-up visits were 30.50 ± 10.19 minutes and 27.9 ± 9.57 minutes, respectively. The second patient visit had the shortest duration; this visit was used to inform the patient about the current status of (potential) DRPs and to set individual goals (see Table 19). All patients showed up for all four patient visits and no patients dropped out.

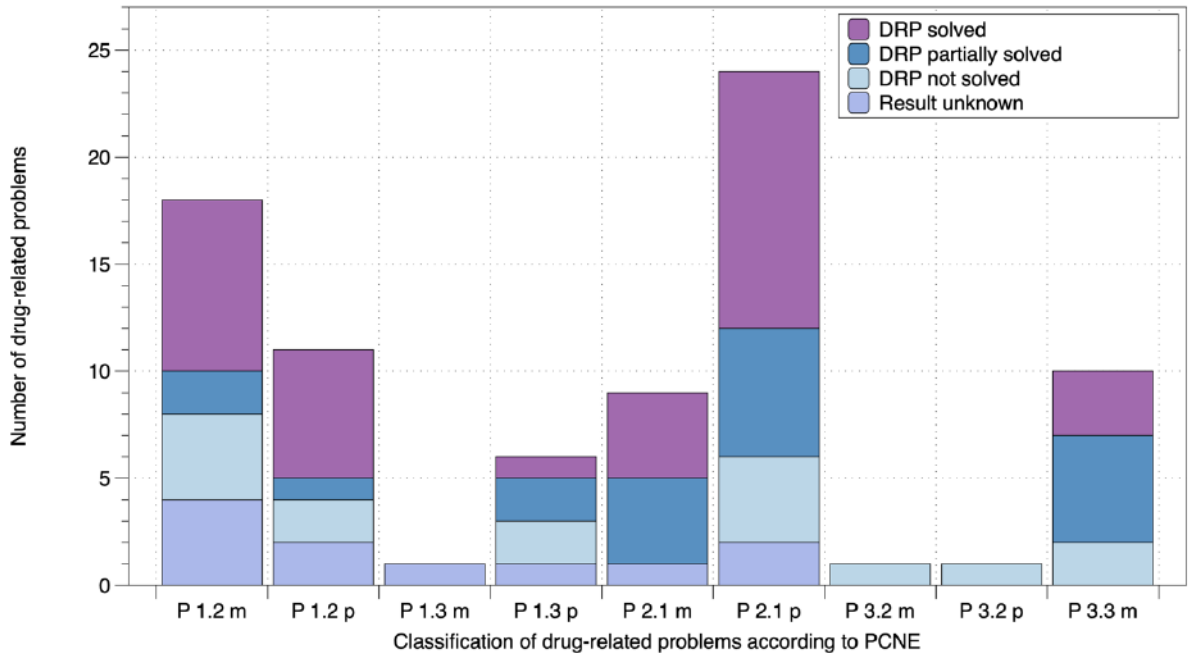
Implementation of the four selected pharmaceutical care components in practice

The pharmacists recorded each patient's medication history, collected all relevant patient data, and reviewed the blood glucose records in seven cases; three of the patients either had no diabetes record book or did not measure their blood glucose levels at the first patient visit. For nine patients, the medication analysis was a type 3 medication analysis; according to Bundesvereinigung deutscher Apothekerverbände e.V. (ABDA), a type 3 medication analysis includes a screening of the medication file or history, analysis of the current medication usage during the patient consultation, and a consideration of available clinical data such as laboratory data or the current diagnosis. Because of missing clinical and laboratory data, for one case the conducted medication analysis was type 2a according to the ABDA. A type 2a medication analysis includes a review of the medication file or history and an analysis of the current medication during the patient consultation. (ABDA 2014) At the second visit, the patients were informed about potential or manifest DRPs related to their current medication, and individual goals were set. If deemed necessary, the physician was directly contacted by the pharmacist, or the physician indirectly received feedback through the patient. In six cases the physician needed to be contacted directly, primarily via telefax and afterwards via a telephone call, in which all DRPs and relevant information were discussed. The pharmacist also gave the patients information about their current medication and checked, if deemed necessary, the patients' medication knowledge. Both of the follow-up visits (third and fourth visit) were used to check

whether the set goals were achieved and again, if necessary, the pharmacist sent feedback to the physician and analyzed the medication and blood glucose records.

4.3.3 Secondary objective – effects of the four effective pharmaceutical care components on relevant parameters

The secondary objective of this case series was to formulate a hypothesis about the effectiveness of implementing these four components in everyday practice. To formulate a hypothesis about the effectiveness and successful implementation of the medication review, the current DRPs were identified and classified, and the MAI was determined. At the beginning of the study, 6.90 ± 2.60 manifest or potential unsolved DRPs were identified per patient. The most common problems were adverse drug events (24 potential and 7 manifest) and a non-optimal effect of drug treatment (11 potential and 12 manifest). The distribution of all DRPs is shown in Figure 14. After the final patient visit, approximately 45% of all DRPs were solved and 20% were partially solved. For approximately 10% of DRPs, information on their resolution was not yet available.



DRPs: drug-related problems
PCNE: pharmaceutical care network Europe
m: manifest
p: potential
P 1.2 Effect of drug treatment not optimal
P 1.3 Untreated symptoms or indication
P 2.1 Adverse drug event (possibly) occurring
P 3.2 Unnecessary drug treatment
P 3.3 Unclear problem/complaint. Further clarification necessary

Figure 14 Drug-related problems of the EMDIA-patients classified according to the pharmaceutical care network Europe (Deters et al. 2021)

Over the whole study period, each patient had an average of 8.2 ± 3.4 DRPs; at the end of the case series, approximately half of all potential and manifest DRPs were solved. Only 10% of all insulin-related DRPs were solved at the second follow-up visit; most of the insulin-related DRPs were only partially solved (see Table 20). 10% of insulin-related DRPs remained unsolved at the end of the study. Due to pharmacist intervention, a high proportion of DRPs related to oral antidiabetics were solved (62.5%). The highest rate of unsolved DRPs was associated with residual medication, such as antihypertensives, with just 48.4% of these DRPs solved.

Table 20 Number of drug-related problems of the EMDIA-patients sorted by type of medication

	Solved DRPs	Partially solved DRPs	Unsolved DRPs	DRPs with unknown result
OADs	0.5 ± 0.7 (62.5.0%)	0.1 ± 0.3 (12.5%)	0.1 ± 0.3 (12.5%)	0.1 ± 0.3 (12.5%)
Insulin	0.1 ± 0.3 (10%)	0.6 ± 1.1 (60%)	0.1 ± 0.3 (10%)	0.2 ± 0.6 (20%)
Residual medication	3.1 ± 1.9 (48.4%)	1.1 ± 1.7 (17.2%)	1.5 ± 2.0 (23.4%)	0.7 ± 1.1 (10.9%)

Mean values ± standard deviation
DRPs = drug-related problems classified according to PCNE
OADs = (oral) antidiabetics

In many cases, the patient had issues with suboptimal effects of OADs and/or insulin; mainly, patients had elevated or fluctuating blood glucose levels. The most common DRP involving non-antidiabetic medication was the (possible) occurrence of adverse drug events. Hypoglycemia was the most frequent adverse drug event for OADs and insulin. The patients' MAI values varied between 0 and 38 at baseline, with an average value of 19.1 ± 13.24. The index average decreased significantly to 6.40 ± 8.88 ($p = 0.007$) by the end of the case series. Thus, the MAI of most patients was relatively low, which indicated that the medication was appropriate.

To formulate a hypothesis about the benefit of reviewing patients' blood glucose measurements, the patients' current glycemic control, measured by HbA1c and FBG, was recorded. Neither the HbA1c nor the FBG values changed significantly during the study. The average HbA1c at baseline was 7.04 ± 0.90%, and at the end of the case series was 7.00 ± 0.61%. Only one patient had an HbA1c value that was above the recommended range of the current guidelines (see Figure 15). There were no statistically significant changes to the average HbA1c values over the study duration: 7.04% at baseline, 6.90% at the third patient visit, and 7.00% at the fourth visit. Over the whole study period, only one patient did not have

any HbA1c measurements. The FBG levels decreased more steeply than the HbA1c values—from 141.86 ± 32.03 mg/dL to 119.63 ± 18.95 mg/dL during the case series.

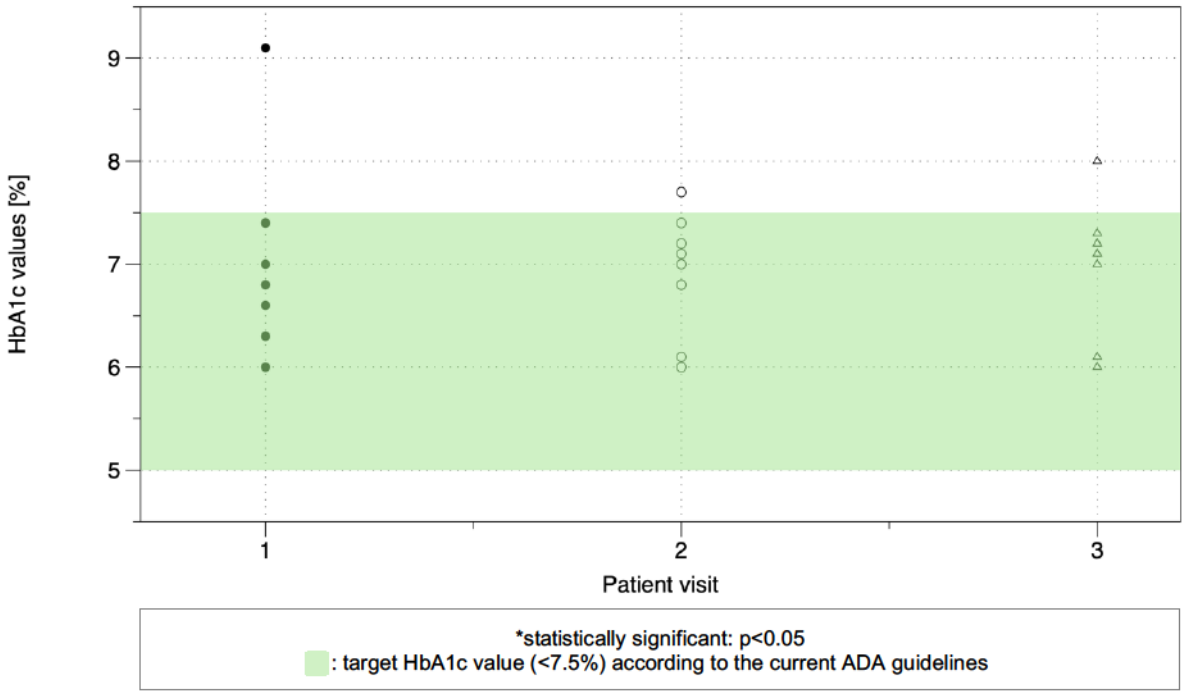


Figure 15 HbA1c values of the EMDIA patients

Although the HbA1c values of most patients were in the recommended target range at baseline and during the study, many patients had FBG levels that were above the recommended range of 100–125 mg/dL (at baseline: n=4). The average FBG level was 141 mg/dL at baseline and and 120 mg/dL at the final follow-up visit. At the final follow-up visit, half of the patients had FBG levels within the recommended target range (see Figure 16). This decrease in FBG levels was induced by reviewing the patients' blood glucose records. The review of patients SMBG data revealed that three patients experienced recurrent non-severe hypoglycemic and hyperglycemic episodes; one of these patients also had nocturnal hypoglycemia at baseline. One patient was identified to have poorly controlled diabetes with constant hyperglycemia. The pharmacist analyzed the patients' blood glucose records and discussed potential problems and current causes for fluctuation or hyperglycemia with the patient. Additionally, the patient and pharmacist discussed individual optimization options that were achievable, appropriate, and expedient for the patient.

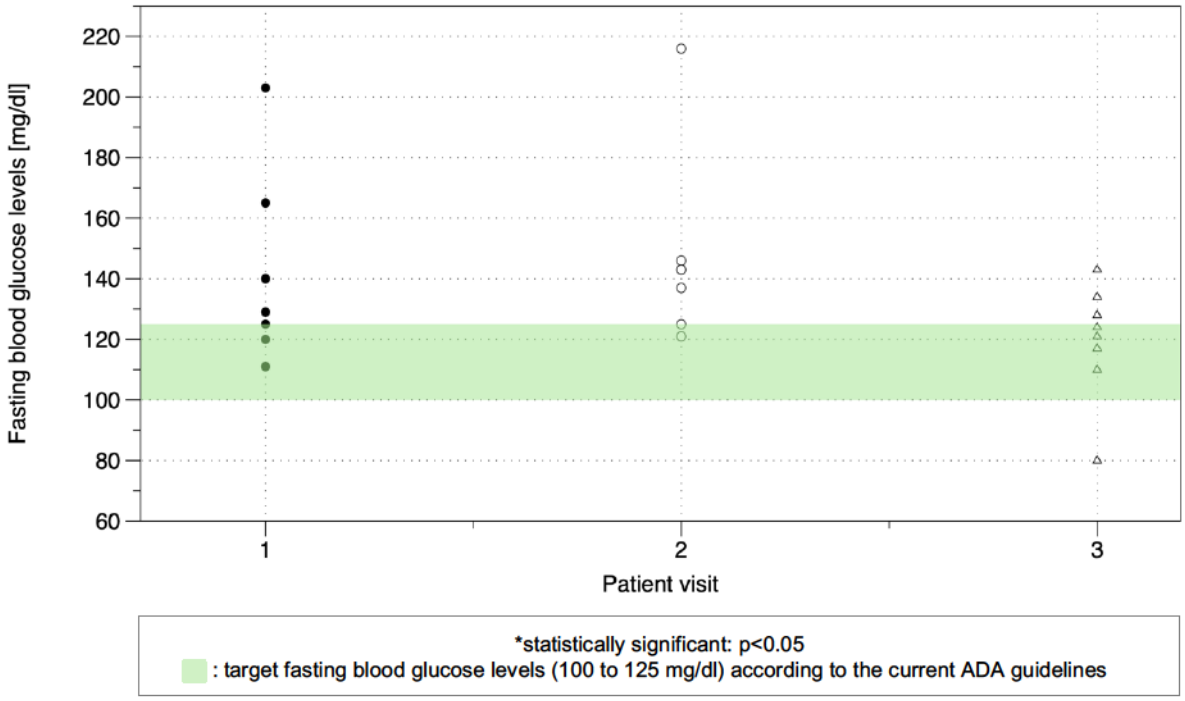


Figure 16 Fasting blood glucose levels of the EMDIA patients

Setting individual goals, sending feedback to the physician, and solving DRPs can impact a patient's well-being index. Throughout the study, the average WHO-5 well-being index increased significantly from 17.10 ± 6.62 to 20.40 ± 5.83 points ($p = 0.02$). At baseline, only two patients had fewer than 13 points, indicating that these patients had untreated depression. (Halliday et al. 2017, Rauwerda et al. 2018) One of these patients underwent professional psychological treatment but had problems adhering to the prescribed antidepressant because of its side effects. After changing the antidepressant drug, the WHO-5 well-being index for this patient increased to 18. The other patient had a low well-being index score due to substantial physical restrictions. The antihypertensive medication used by this patient caused deterioration in their diagnosed sleep apnea and resulted in daytime sleepiness. Unfortunately, a change in the antihypertensive medication had no positive effect on this patient's sleep apnea and daytime sleepiness; therefore, their WHO-5 well-being index score remained less than 13.

4.4 Discussion

4.4.1 Primary objective – feasibility of implementing four effective pharmaceutical care components

Our case series provides a proof of concept that the four most effective PhC components identified in a 2016 meta-analysis (Deters et al. 2018) are feasible for implementation in everyday pharmacy practice. The pharmacist in this study was able to: 1) conduct a medication review including the identification of DRPs and determination of the MAI based on scientific evidence (Hanlon et al. 1992, PCNE 2019a, Samsa et al. 1994), 2) set individual goals with the patient according to the SMART criteria (Tichelaar et al. 2016), 3) send feedback to the physician according to the SOAP note (Podder et al. 2020, Wright et al. 2014) using a structured form, and 4) review blood glucose measurements, all within 60 minutes. Of course, this hypothesis that it is feasible to conduct these four PhC components within 60 minute patient visits could also be tested as part of a hypothesis-testing study.

The diagnosis of T2DM was confirmed for all of the included patients. According to the Deutsche Diabetes Hilfe (DDH), 8.5 million people in Germany live with diabetes mellitus, 95% of whom have T2DM; only 341,000 have a confirmed diagnosis of T1DM. (DDH 2022) The surprising distribution of patients included in the EMDIA study may be due to the recruitment process. Because only patients who filled a prescription for insulin, OADs, or other supplies needed for diabetes therapy, or who had a (pharmaceutical) question about an insulin, OAD, or other supplies needed for diabetes therapy, or who expressed acute DRPs during the pharmacy consultation were asked to be included into the study and sign the informed consent form. Therefore, only older, multimorbid T2DM patients with a greater number of medication intakes were asked to participate.

Other qualitative studies (case reports or analysis of pharmacist's interviews) have evaluated the use of a special tool for implementation or the general process of implementation of PhC in practice (Feletto et al. 2012, Moullin et al. 2016, Silva et al. 2020) A study by Feletto et al. investigated the use of a research-based change management tool in practice and its impact on the implementation of PhC. Different influencing factors (external, internal, and individual) and barriers to implementation were identified. External influencing external factors were, for example, the need for professional support or the remuneration for providing the service. Individual factors, such as motivation to implement this research-based management tool, were also identified. (Feletto et al. 2012) In the German health care system, the provision of a medication review or continuous MTM is not covered by health insurance. Therefore, remuneration is a limiting factor, and the duration of all visits is a relevant influencing factor for the implementation of PhC, especially medication reviews and MTM.

The primary objective of the analysis by Moullin et al. was to investigate the process of implementing PhC in Australian pharmacies in practice and assess relevant influencing factors. This study identified five influences in the implementation process: direction and impetus, internal communication, community fit, staffing, and support. Each of these can positively or negatively influence several stages and activities (e.g., increased staff capacity has a positive influence on the implementation). (Moullin et al. 2016) Staff capacity was a major influencing factor: high capacity allowed the pharmacist to not be disturbed during the patient visits, and both study pharmacists (one pharmacist had a PharmD) were trained in the provision of MTM. Other influencing factors were also identified, such as the impetus of both pharmacists, which had a positive impact on the implementation due to high personal interest in the topic and research field.

Silva et al. identified principles and theories that drove the implementation of PhC in the Brazilian public health system. (Silva et al. 2020) This study revealed the importance of educational processes and suggested that we must pay attention to the current reality and needs of the situation in each health system. This coincides with the influencing factors and limitations that we identified, such as remuneration for PhC and training and education of the study pharmacists.

The intervention design of this case series was chosen based on the findings of the systematic literature research. (Deters et al. 2018) Previous RCTs implemented a variety of PhC components and combinations thereof. (Jahangard-Rafsanjani et al. 2015, Krass et al. 2007, Mourao et al. 2013, Obarcanin et al. 2015, Odegard et al. 2005). The pharmacist interventions in these studies were performed monthly or every second month to explore the impact of PhC on glycemic control in patients with diabetes mellitus. (Deters et al. 2018) Therefore, we chose a time interval of monthly pharmacist interventions. A 1-month intervention interval is useful for exploring the measurable impacts of PhC on glycemic control in diabetes patients. Finally, our study's average duration of patient visits was similar to that reported in other studies. (Kraemer et al. 2012, Krass et al. 2007)

4.4.2 Secondary objective – effects of the four effective pharmaceutical care components on drug-related problems, medication-appropriateness index, glycemic control, and WHO-5 well-being index

Effect on the number of unsolved DRPs and MAI

In our case series, 6.90 ± 2.60 DRPs were identified per patient at baseline. The WestGem study was a German RCT that evaluated the effect of interprofessional MTM in an ambulatory setting on different outcomes (including DRPs) and included 142 patients with other chronic diseases. In that study, the average MAI was 29.21, and the number of identified DRPs per patient was 6.98 at baseline, similar to our findings. (Koberlein-Neu et al. 2016) The RCT conducted by Fornos et al., which included only patients with diabetes mellitus, identified 2.7 DRPs per patient at baseline, of which nearly 60% were solved (1.7 unsolved DRPs at study end per patient). (Fornos et al. 2006) In our study, approximately 45% of all DRPs were solved, and 20% were partially solved by the final patient visit; the number of unsolved DRPs was reduced from 6.90 ± 2.60 at baseline to 1.89 ± 1.90 at the second follow-up. Interestingly, in our case series, insulin-related DRPs had the lowest rate of solution. This suggests that the adjustment of insulin therapy is particularly challenging for health care providers and patients. There are many possible reasons for this low rate of solved insulin-related DRPs in T2DM patients. Therefore, future studies should measure the percentage of resolved insulin-related DRPs and possible interactions, such as lack of adequate practical training beforehand, over a more extended period.

Many other studies that examined the effect of PhC on glycemic control for patients with diabetes mellitus included a medication review. However, none of these used the PCNE classification system for DRPs. (Jahangard-Rafsanjani et al. 2015, Krass et al. 2007, Mourao et al. 2013, Obarcanin et al. 2015, Odegard et al. 2005) In our study, DRPs were classified according to the current PCNE classification (version 8.03). (PCNE 2019a) This is a hierarchical DRP classification system, and was chosen because it is based on clear definitions according to van Mil et al. (van Mil et al. 2004). The validation of the DRP classification system has been published. In addition, pharmacist interventions were classified, which is not the case with many other classifications. The identified DRPs and the determined MAI depend on characteristics of the patient population such as the number of diseases and the types of medications used, as well as the DRP classification system. Therefore, it is difficult to compare our results regarding the number of solved and unsolved DRPs to those from other studies.

Effect of the four pharmaceutical care components on HbA1c and FBG values

The low HbA1c values at baseline (average 7.04%) and the short study duration (4 months) made it challenging to generate a hypothesis as to whether these four components, especially review of patient blood glucose measurements, can improve glycemic control, as measured by a reduction in HbA1c values and/or FBG levels. Previous RCTs of T2DM patients with higher baseline values have detected considerable reductions in HbA1c by the end of the study, for example, Krass et al. reported a reduction of −1.0% (95% CI: [−0.8%, 1.3%]) and Doucette et al. a reduction of −0.27 ± 1.11%. (Doucette et al. 2009, Krass et al. 2007) In the current study, the FBG levels decreased from an average of 141.86 ± 32.03 mg/dL at baseline to 119.63 ± 18.95 mg/dL at the end of the study. In the DIADEMA study (RCT with adolescent T1DM patients), the HbA1c values decreased from 9.4% to 8.9%, and the FBG levels decreased from 218 ± 67 mg/dL to 200 ± 69 mg/dL in the intervention group. (Deters et al. 2016, Obarcanin et al. 2015) A lower FBG level reduces the risk of developing atherosclerotic CVD, even in non-diabetic patients. On the other hand, impaired or diabetic FBG levels increase the risk for CVD and associated complications. (Lee et al. 2018, Park et al. 2013)

The ADA recommends that nonpregnant adults have an HbA1c value < 7.0%. (ADA 2020) In our case series, 50% of the patients were already within this target range at baseline. However, nearly all patients had problems with their diabetes medication and/or fluctuating blood glucose levels. Recent research has pointed out the limitation of the HbA1c value in that it only provides the average blood glucose level over the past 2–3 months, but does not indicate the patient's glucose variability (reoccurring hypoglycemia or hyperglycemia). (Danne et al. 2017) A new additional measure of glycemic control is the TIR which assesses in most cases the percentage of time within the target or less frequently used the hypoglycemic range and, therefore, provides a measure of the patient's glucose variability. (Danne et al. 2019) Glucose variability can identify the deterioration of glycemic control more accurately than the HbA1c test can, thereby reducing the risk for developing diabetes-related microvascular complications. (Sartore et al. 2012, Smith-Palmer et al. 2014, Šoupal et al. 2014) TIR is usually applied in continuous CGMS, indicated in Germany only for patients with T1DM or T2DM on ICT or CSII at risk of severe hypoglycemia. (Heinemann et al. 2020) Hence, none of our study patients used a CGMS. Therefore, we only used HbA1c to assess blood glucose control. However, we are aware that if the assessment of HbA1c values is used in combination with CGMS data, a more accurate depiction of both acute and chronic glycemic control can be obtained. (Wright et al. 2020) Consequently, further research is warranted to document and evaluate patient glucose variability by measuring the TIR. However, our case series suggests that even patients with an "optimal glycemic control" measured by HbA1c values can benefit from additional PhC provided by a community pharmacist. Therefore, we suggest examining this concept in a larger

study (RCT, cohort, or case-control study) with a longer study duration of 6 or 12 months, including TIR as measured value. The inclusion criteria should also be adjusted: patients with HbA1c values above 7.5% and/or fluctuating blood glucose levels or at risk for severe hypoglycemia should be included in the study.

Effect of the four pharmaceutical care components on the well-being index

Our case series showed that the WHO-5 well-being index could easily be used within the timeframe of 60 min due to the short amount of time required to answer the five questions. In this case series, the index was used as a tool to assess the emotional well-being of the included patients. This brief questionnaire can be used as a quick, first-pass screening for depressive symptoms. The Diabetes MILES study supported a cutoff of <13 points to identify depression in patients with diabetes mellitus regardless of the diabetes type or treatment. (Halliday et al. 2017, Rauwerda et al. 2018) Of course, other questionnaires, such as the Short Form 36 (SF-36), that assess the current health status of the patient might be more sensitive, but these more extensive questionnaires require more time to answer. Hence, we decided to use the WHO-5 well-being index to allow the collection and documentation of patient data in everyday pharmacy practice.

4.5 Limitations

There are limitations to this case series, including the low patient number, low HbA1c values at baseline (average 7.04%), and the short study duration (4 months). Although it is common for case series to have a small study population, the low HbA1c values at baseline made it difficult to generate conclusions regarding the effect of this structured PhC on the HbA1c or FBG values in this patient population. Other conclusions could be made because of the large effects, such the number of unresolved DRPs at study end and the decreased MAI. For consistency in patient recruitment, all patients were recruited at a single pharmacy. This pharmacy was located in Oberhausen (Germany), and all included patients were regular customers of this pharmacy. The pharmacy personnel asked patients with potential DRPs whether they wanted to participate in the study.

The PCNE classification chosen to determine DRPs has limitations. It is difficult to objectively assess whether the DRP is totally resolved, partially resolved, or remains unresolved. Many DRPs are subjective and difficult to measure objectively, such as daytime tiredness and discomfort. The decision as to whether these DRPs were resolved or not was solely influenced by the patient's report. Nevertheless, the PCNE classification is better than other DRP classification systems in many ways; for example, it has a hierarchical classification, the validation of its components has been published, and the pharmacist interventions are classified. Another limitation is that during this study a new, optimized version (9.0) of the PCNE classification was published. (PCNE 2019b) Therefore, to avoid inconsistency, the former version was used. (PCNE 2019a) The updated version of the PCNE classification added new causes for DRPs, such as the patient being unable to understand instructions.

Personnel costs and time constraints on more extended patient care visits can be factors that limit the implementation of MTM in regular community pharmacies. Regarding remuneration, the duration of all visits is relevant, as the patient or health insurance should be able to reimburse every minute of MTM or the total cost of the patient visit. Our results support the hypothesis that the four PhC components that we identified can likely be implemented in everyday pharmacy practice. This hypothesis might be challenged by an RCT in the future. The professional qualifications of the pharmacist and the training they receive beforehand could be important for the successful implementation of the four intervention components within a 60-minute visit. Before and during the EMDIA case series, I attended the ATHINA seminar on providing medication analysis and MTM in community pharmacies in February 2019 and received the ATHINA certificate. Some pharmacists have already taken part in

training to provide medication analysis and MTM, such as the ATHINA project or the AMTS project in North Rheine-Westphalia (Germany). Therefore, the qualification of the pharmacist needs to be documented and considered in future research projects.

4.6 Conclusion

As a preliminary proof-of-concept study of the four effective PhC components, this case series allows us to formulate the hypothesis that these structured MTM elements can be implemented in everyday pharmacy practice for T2DM patients. Our data suggest that they were feasible in practice and can be implemented in patient consultations that last a maximum of 60 minutes.

We also hypothesize that the implementation of these four PhC components can improve T2DM patients' number of unsolved DRPs, MAI, and WHO-5 well-being index scores. Further research should be conducted to clarify the effect of these four components on HbA1c values and TIR in diabetes patients in everyday pharmacy practice. Preferably, a study design should be selected that can test our hypothesis.

Since the EMDIA case series served as a preliminary small-scale study for the planning of later larger hypothesis-testing studies, it would be advisable to include devices such as mobile diabetes applications, as a current state of the art. In recent decades, the use of digital health products such as smartphone applications has rapidly developed. (Trawley et al. 2016) The benefits of this digital revolution for human development are obvious and during the Covid-19 pandemic digital technology has proved indispensable for work, education, health care and staying connected. (UNDP 2013, UNDP 2020) The WHO has recognized the increasing importance of mHealth and published the guideline “recommendations on the implementation of digital interventions for health systems”. (WHO 2019) Therefore, future research should include whether mHealth applications (e.g., diabetes mobile applications) would support the implementation of the four PhC components in practice and whether this technology would improve the outcomes of patients with T1DM and T2DM.

5 Chapter Four – Mobile health support for diabetes mellitus type 1 and 2 patients to support pharmaceutical care components in practice

5.1 Background

The EMDIA case series described in Chapter three was a small, preliminary, qualitative scale pilot study with ten diabetes patients that provided a realistic initial assessment of the expected impact and potential barriers to implementing the four effective PhC components in a realistic setting. Results from the EMDIA case series will serve as a basis for planning of further hypothesis-testing studies. (Deters et al. 2021) When planning this hypothesis-testing studies, it should be considered that the use of digital health products such as smartphone applications has evolved tremendously over the last decades. Health care providers and patients are already using emerging technologies such as sensors (CGMS), insulin pumps, telemedicine and mHealth applications to support both clinical and operational decisions. Combined with human capacity, these technologies could ultimately make it possible for everyone to access high-quality, consistent, affordable, timely and convenient care. (WEF 2019) The costs for the use of such mHealth applications are covered by the German statutory health insurance for approved products; since Germany was the first country to enact a law called “Digitale-Gesundheits-anwendungen-Verordnung” (DiGAV), which regulates the criteria that mHealth applications must meet in order to be covered by statutory health insurance. The German government has adopted the “Hightech-Strategie 2025”, which focuses the funding of research and innovation on people's needs such as in the area of "health and care". This strategy paper states that digitization is one of the top priorities for preventive and personalized medicine, which permeates all fields of medical research and health care. (BMBF 2021)

Looking at current research, many articles have described the development of digital diabetes therapy and its potential to provide solutions to multiple unmet needs in the field of diabetes disease prevention and for monitoring and preventing complications. (Cahn et al. 2018) A recent literature review concluded that mHealth technology with added support from health care professionals can result in improved outcomes in patients with T2DM. (Muralidharan et al. 2017) Another review and meta-analysis of studies involving T1DM patients revealed that the use of mHealth led to reductions in HbA1c. (Wang et al. 2019) Many different opportunities are offered by electronic health (eHealth) services, such as booking physician appointments online, consultations with a health care professional (including pharmacists), support for decision-making such as calculating bolus insulin, reminders for medication, and monitoring of health data such as blood glucose levels. Some of these eHealth opportunities have stronger

evidence than others owing to more robust research; one of those for which there is strong evidence is support for decision-making. Further research in the other fields of eHealth is urgently needed. (Car et al. 2017) The review by Kebede et al. analyzed the most popular mHealth applications for diabetes patients. They found that most used diabetes mobile applications were MySugr, Dexcom, One Drop Diabetes Management, Diabetes Connect, and Diabetes:M. (Kebede et al. 2019)

Considering all these recent developments, it is of utmost to conduct a preliminary evaluation of the use of mHealth diabetes applications from a community pharmacist's perspective for the use in pharmacy practice. This final chapter provides a descriptive assessment of the benefits and limitations of using mHealth diabetes applications in implementing effective, optimized PhC for diabetes patients in a community pharmacy setting.

5.2 Methods

5.2.1 Objective

We aimed to investigate whether the mHealth application Diabetes:M can support the four effective PhC components identified previously and therefore help to improve the outcomes of optimized PhC interventions. In particular, we aimed to address the strengths and limitations of the Diabetes:M application for PhC provided by community pharmacists and to make recommendations for improving this application for practical use within the framework of future studies or in daily community pharmacy practice.

5.2.2 Rationale for selection of the Diabetes:M as mobileHealth diabetes application

The review by Kebede et al. analyzed the most popular mHealth applications for diabetes patients. They found that the most commonly-used diabetes mobile applications were MySugr, Dexcom, One Drop Diabetes Management, Diabetes Connect, and Diabetes:M. (Kebede et al. 2019) Of these, MySugr, One Drop Diabetes Management, Diabetes Connect, and Diabetes:M offer a variety of useful features, including a diabetes diary to document insulin doses, blood glucose values, and other diabetes-related values, an insulin bolus calculator, a nutrition database, and various ways in which the documented values can be evaluated.

The main rationale for selecting the Diabetes:M application is that it has clinician access in addition to the common diabetes application features, and the bolus calculator includes active insulin in the calculation. (SirmaMedicalSystems 2021) Active insulin is defined as insulin that has been previously injected and is still active. And furthermore, the selection of Diabetes:M as an application was also based on an earlier unpublished evaluation by Dr. Emina Obarcanin. Dr. Emina Obarcanin evaluated the usefulness of the Diabetes:M application and patient satisfaction by providing PhC using Diabetes:M for three patients with T1DM, aged 4 years, 14 years and 27 years over a period of one month. The Diabetes:M application provided good and comprehensive PhC support for the patients, resulted in increased patient satisfaction and improved diabetes management. All these aspects led to the selection of the Diabetes:M application for this evaluation.

5.2.3 Selection of patients and procedure for entering and evaluating the data

To test the applicability and usability of the Diabetes:M application, clinical data of patients from the EMDIA case series were used, such as HbA1c and blood glucose levels, insulin dose

and medication intake, were retrospectively entered into the Diabetes:M application by the author Maira Anna Deters. Patients were eligible if they received insulin therapy (n = 6) and those who received OADs only were excluded directly (n=4). This inclusion criterion was chosen because a larger number of SMBG data is needed to evaluate this application to its full extent. Looking at current practice recommendations and guidelines for non-insulin dependent patients with T2DM, these patients should only conduct SMBG if needed. It is recommended that if the patient is taking medications that increase the risk of hypoglycemia, SMBG should be performed at least twice a week. (Schlüter et al. 2021) Nevertheless, two measurements per week would not provide enough data for full-scale evaluation. Currently, the main function of all available mHealth diabetes applications is to provide a diabetes book in which data entered manually or transferred from a glucometer or CGMS are entered, as well as insulin and medication tracking. Other features include the ability to import and export data, and communication functions. (Goyal et al. 2013) Of the six eligible patients, two were randomly selected by coin toss for this evaluation. For the evaluation, all patient data (e.g., blood glucose values for the last four months) were imported into the diabetes book of the Diabetes:M application by the author of this dissertation, Maira Anna Deters. Missing information and data were not imputed. None of our EMDIA patients used this Diabetes:M application in daily life.

The criteria for evaluating the usefulness of the Diabetes:M application for PhC, in practice, were developed based on an extensive literature review (Castensøe-Seidenfaden et al. 2018, Fredrick Debong 2019, Husted et al. 2018, Izahar et al. 2017, Oppong et al. 2021, Trawley et al. 2016) and important aspects from the earlier unpublished evaluation by Dr. Emina Obarcanin (Dr. Emina Obarcanin evaluated the usefulness of the Diabetes:M application and patient satisfaction by providing PhC using Diabetes:M for three patients with T1DM, aged 4 years, 14 years and 27 years over a period of one month) and elective practical WS2019/20 "PharMobileDM Study - "smart" coaching by the pharmacist" (Supervisors: Dr. Emina Obarcanin and Maira Anna Deters), which examined the various benefits and functions of the Diabetes:M application in relation to the PhC of T1DM and T2DM patients. The following criteria for evaluating the use of the Diabetes:M application were established:

- Time saving
- Data quality and clarity
- Data accessibility
- Online consultation possible. This is important nowadays due to the current pandemic situation

5.3 Results

5.3.1 Using Diabetes:M to document and analyze self-measurement of blood glucose levels

Before the patients' data can be imported from the blood glucose measurement system or manually entered into the digital diabetes record book, the application requires patient information such as body weight and current diabetes therapy (See Appendix X 14).

Comparing the functions of the digital diabetes diary with those of the classic analog diary, there are several advantages in terms of reviewing and analyzing patients' SMBG data. The main advantage of the Diabetes:M application over the other mHealth diabetes applications is the clinician access, which allows the pharmacist to view the current available SMBG data of the diabetes patients online in a time-saving way. The patient's data can also be easily downloaded in the form of a PDF or Excel spreadsheet; this saves a lot of work. This clinician access is only included in the premium version of Diabetes:M, for which a fee (ongoing subscription: 8.99€ for three months) is charged.

The Diabetes:M application provides pie charts that show the proportion of the different blood glucose values over a selected period of time (see Figure 17). These graphs make it easier for the pharmacist to evaluate the daily, weekly or monthly blood glucose values and allow one to identify specific problems in the diabetes management e.g. the occurrence of nocturnal hypoglycemia or hyperglycemia after eating. Further graphics and diagrams from the Diabetes:M application are listed in Appendix X 15. The ability to annotate and comment on patient data directly in Diabetes:M is currently not available.

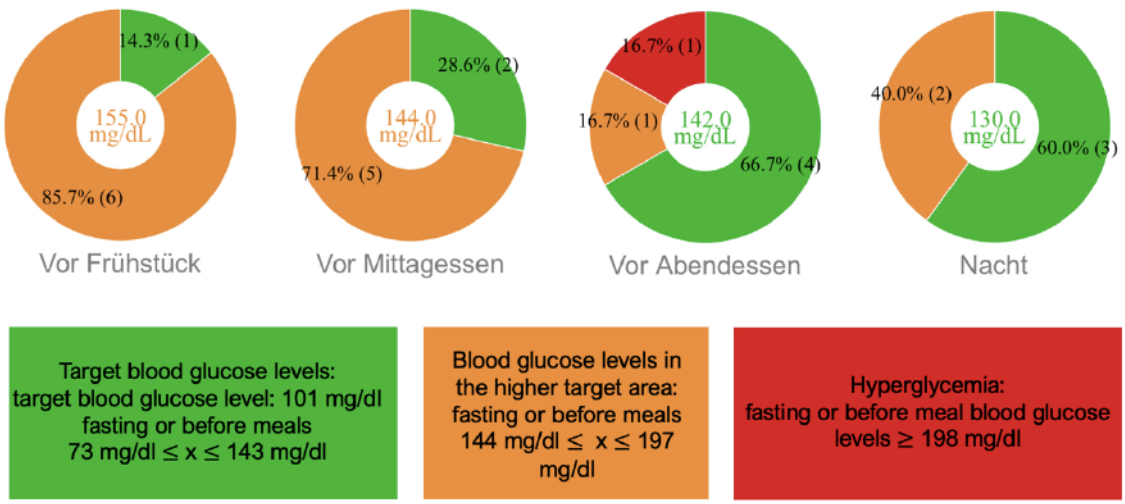


Figure 17 Diagram (exported from Diabetes:M) of blood glucose levels of the female patient case with T2DM – overview of previously recorded 7 days classified into before breakfast, lunch, and dinner, and nocturnal blood glucose levels

Another time-saving feature is the ability to create a graph showing the glucose variability of the patient's entered values for a selected time period (See Figure 18). This directly accessible graphical overview of patient glucose variability is a feature that no analog diabetes record book can provide. Among other things, this graph allows the pharmacist to directly identify blood glucose fluctuations.

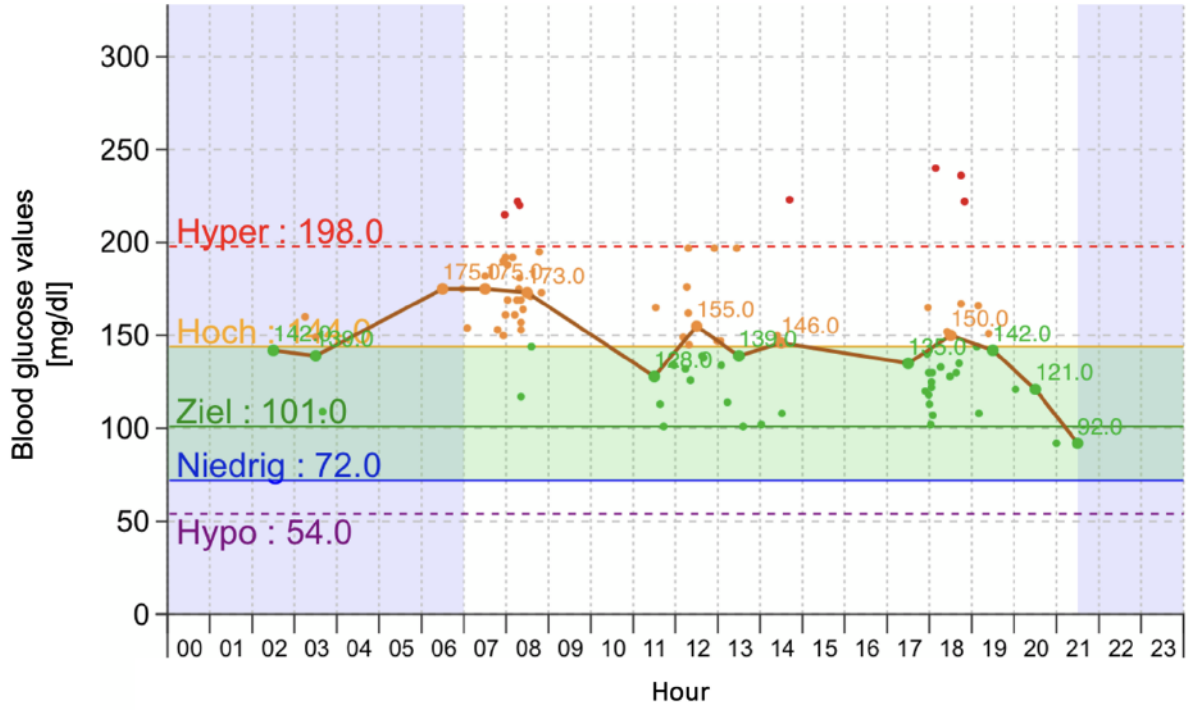


Figure 18 Graph exported from Diabetes:M of blood glucose levels of the female patient case with T2DM – overview of blood glucose variability of all self-measured blood glucose values of the previous month

5.3.2 Using Diabetes:M to support individual goal setting

The clinician access allows pharmacists to evaluate more easliy the current blood glucose values and other relevant health data entered by the patient, such as important laboratory values or lifestyle data. Thus, the Diabetes:M application is helpful in setting individual goals, in monitoring compliance with these goals, and in the subsequent personal evaluation of the goals.

Another useful feature is the activation of automatic repetitive or one-time reminders. These reminders can help the patient to achieve the set goals, as they can be set individually for each patient and can support the patient in implementing the therapy recommendations in everyday life. Two examples of functional and useful reminders are shown in Figure 19.

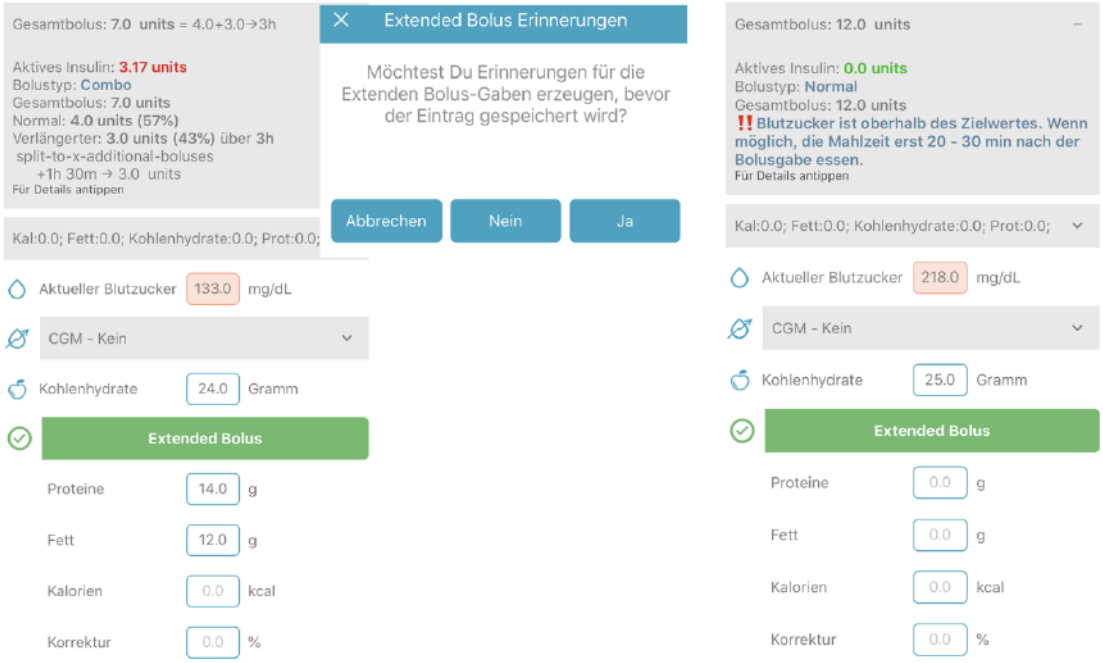


Figure 19 Screenshots of two different automatic reminders: 1) when the extended bolus calculation is activated, and 2) warning when the current blood glucose level is above the target value and the planned meal should be taken 20–30 minutes after insulin injection

5.3.3 Using Diabetes:M to support working in an interdisciplinary team

Another important question is whether using the Diabetes:M application supports the pharmacist to work in an interdisciplinary team (e.g., with diabetologists). The Diabetes:M application offers some useful advantages for collaboration with other health care professionals. Firstly, the clinician access can also be used by other health care professionals allowing information about the patient to be accessed by all who require it. Secondly, the option to export patient data in the form of a PDF, Excel file or as HTML code helps to provide data in a clear and appealing form. An option to establish direct contact with other health care professional or the patient, for example in the form of a chat function, is currently not available.

5.3.4 Diabetes:M limitations

The digital diabetes diary in the Diabetes:M application can also be used to enter the amount of insulin injected and the medications taken, including details of the individual and daily doses. However, there is functionality lacking that could support a medication analysis. Currently, it is not possible to enter the indication of the medication, the exact time at which the medication was taken, or the trade name and name of the active ingredient at the same time. A reminder for taking medication is also not automatically created, which would be helpful and desirable to support compliance and adherence. The overview of the drugs is currently still unclear, and the listed drugs can neither be sorted by indication nor by time of intake. In addition, there is no interaction check or medication analysis tool to analyze the medication in advance in a targeted and time-effective manner. It is also not possible to read in the data of the so-called national standardized medication plan “Bundeseinheitlicher Medikationsplan” via QR code or to export the medication listed in the application in the correct form for this medication plan. Therefore, the Diabetes:M application currently lacks functions that would support the time-effective implementation of a medication analysis in practice. Another limitation of Diabetes:M is the lack of a commentary or chat function to provide personalized feedback online in a time-effective manner.

5.4 Discussion

Many studies have revealed that mHealth can improve the glycemic control and adherence of patients with diabetes mellitus. (Bonoto et al. 2017, Goyal et al. 2017, Hou et al. 2016, Kumar et al. 2018, Yasmin et al. 2020) However, there are no studies which analyze the benefits of using mHealth for the provision of PhC for diabetes patients. There is also, to our knowledge, no published assessment or evaluation of the effort required when using a mobile diabetes application collaboratively in an interdisciplinary team.

One pertinent problem identified by Goyal et al. is that many of the currently available mHealth applications are not evidence-based and do not differentiate between the demands of T1DM and T2DM patients. (Goyal et al. 2013) Many T2DM patients and multimorbid T1DM patients would benefit from a periodic, iterated medication analysis. Hence, the comprehensive features of diabetes mHealth applications should, in future, include essential features to support medication analysis, such as an import function for the patient's medication plans or a drug-drug or drug-food interaction database. Greenwood et al. identified feedback as one of the four key elements of mHealth for improved glycemic control; other key elements were communication, patient-generated health data and education. (Greenwood et al. 2017) The beforementioned lack of personalized feedback was also identified as a limitation in a study by El-Gayar et al. (El-Gayar et al. 2013)

5.5 Limitations

There are some limitations of this descriptive evaluation. One is that it was based on only two T2DM patient cases to analyze the practicability and potential benefits of this mHealth application. However, this does not diminish the relevance and importance of these results. A larger number of patient cases or a hypothesis-testing study design is needed to analyze in detail the disadvantages and advantages of this Diabetes:M application in community pharmacy practice.

One limitation is that my prior knowledge of the functions of this application may have given rise to subjective perceptions and therefore subjective judgements of the advantages and disadvantages of this application. Therefore, although the results and conclusion of this evaluation are based on facts, they could be biased by my prior knowledge. Other pharmacists, especially those who are older, who do not use smart phone applications in everyday life, may have difficulties using this application and all its tools in a time-saving manner to provide PhC. It would therefore be useful to make this evaluation on a larger scale including a larger number of both diabetes patients and pharmacists.

Another limitation is that the criteria for evaluating the Diabetes:M application in terms of its benefits and usefulness for implementing effective, optimized PhC for patients with T1DM and T2DM, were made by me alone. For future studies, it would be useful to create a checklist for this purpose using a Delphi process in which several experts and community pharmacists participate.

To our knowledge, there are no systematic assessments of the Diabetes:M application (in its current version) regarding its usability or its strengths and weaknesses for the four effective PhC components: (1) individual goal setting, (2) sending feedback and recommendations to the physician, (3) conducting a medication review including identification of DRPs, and (4) reviewing blood glucose measurements.

5.6 Conclusion

The features of the Diabetes:M application are particularly useful for analyzing blood glucose values, individual goal setting with the patient, and interdisciplinary collaboration (clinician access and graphical evaluation tools). However, there are also weaknesses from the pharmacist's perspective, currently the application lacks supporting functions to perform medication analysis, especially for patients with multiple medications and has no direct comment or chat function.

According to my analysis of the patient data and the current features of the Diabetes:M application, it offers some supportive functions for the PhC of insulin-dependent patients with T1DM or T2DM. The application is also suitable for insulin-dependent patients with T1DM or T2DM to determine the correct insulin dose or gain a good overview of their current blood glucose control.

Since the use of mHealth applications reimbursed by the healthcare system is already established in Germany, but not yet widely used in daily practice, it is of great importance to include mHealth in the planning of further hypothesis-testing studies and to expand research in this area. In summary, these further studies should investigate whether mHealth can support the implementation of the four PhC components in practice and whether its use would improve patient outcomes. Therefore, a study with two arms (mHealth vs. analog diabetes record books) would be useful.

6 Summary overview of all chapters

6.1 Discussion

The DIADEMA study found that optimized PhC for adolescent T1DM patients was effective. Several aspects of insulin therapy such as therapy self-management and acute diabetes complications were addressed in patient consultations. More frequent SMBG and higher rates of adjusted insulin injections resulted from the monthly pharmacist interventions. These changes resulted in better adjusted insulin doses and improved glycemic control. Better adherence to individual insulin therapy targets and the personalized nutrition plan led to lower FBG levels without an increase in mild and severe hypoglycemic episodes. (Abraham et al. 2018) Reduced FBG levels, as seen in the DIADEMA intervention group, decreases the probability of developing atherosclerotic CVD. (Park et al. 2013)

The evaluation of the DIADEMA study and the results of our systematic review and meta-analysis came to the same conclusion — that PhC can improve diabetes patients' glycemic control. Some commonalities were found when comparing our results to previous studies, especially regarding the meta-analytical difference in HbA1c values. (Collins et al. 2011, Machado et al. 2007) Improved glycemic control can reduce the incidence of diabetes-related complications, such as CV complications. The findings of the DIADEMA study and the meta-analysis indicate that community pharmacists should become a compulsory part of the health care team for diabetes patients. (Deters et al. 2016, Deters et al. 2018)

One important aspect of the DIADEMA study was the interdisciplinary work between pharmacists, diabetologists, and diabetes educators. Other studies have found that including a pharmacist in an interdisciplinary team significantly reduced hospital and pharmacy costs. (Boyko et al. 1997, Haig et al. 1991) In the DIADEMA study, the pharmacist interventions were patient-centered and interdisciplinary; the meta-analysis of the intervention components revealed that the four most effective PhC elements were also patient-centered or interdisciplinary: (1) sending feedback to the physician, (2) setting individual goals with the patient, (3) analyzing blood glucose records, and (4) assessing the patient's current medication and identifying DRPs. None of the aforementioned reviews and meta-analyses included a quantitative assessment of the effectiveness of each intervention component. Hughes et al. described current insights into and future directions for the role of pharmacists in the management of T2DM patients. A qualitative analysis was conducted to identify pertinent PhC

components, such as medication review and working in an interdisciplinary team. (Hughes et al. 2017)

Due to the small number of included studies and the large number of training elements, the effect of the individual training components and content could not be statistically analyzed in our meta-analysis. Further research is needed to assess the effect of different training elements because the training of pharmacists and their level of education and professional knowledge can influence and bias the effectiveness of pharmacist interventions.

The EMDIA case series was a small, preliminary, qualitative pilot study with ten diabetes patients that provided a realistic initial assessment of the expected impact and potential barriers to implementing the four effective PhC components in a realistic setting. Results from the EMDIA case series will serve as a basis for planning of further hypothesis-testing studies. (Deters et al. 2021) Previous RCTs have implemented a variety of PhC components and combinations thereof. (Jahangard-Rafsanjani et al. 2015, Krass et al. 2007, Mourao et al. 2013, Obarcanin et al. 2015, Odegard et al. 2005) Other qualitative studies (case reports or analysis of pharmacist's interviews) have evaluated the use of a special tool such as a computer program for implementation or the general process of implementation of PhC in practice. (Feletto et al. 2012, Moullin et al. 2016, Silva et al. 2020) However, to date there is no study which evaluated the effect of these four components in pharmacy practice.

Our findings from the EMDIA case series led to the conclusion that future studies should measure the percentage of resolved insulin-related DRPs and possible interactions, such as lack of adequate practical training beforehand, include TIR as a measured value, and run over a more extended period. We also suggest examining this effective and optimized PhC in a larger study (RCT, cohort, or case-control study) with an inclusion criteria of HbA1c values above 7.5% and/or fluctuating blood glucose levels or risk for severe hypoglycemia. Furthermore, the qualifications and prior knowledge or training of the pharmacist needs to be documented and considered in further research projects, as well as the remuneration for pharmacist interventions.

Recently, the use of digital health products such as smartphone applications has developed tremendously, especially for diabetics. Many studies revealed that mHealth can improve the glycemic control and adherence of patients with diabetes mellitus. (Bonoto et al. 2017, Goyal et al. 2017, Hou et al. 2016, Kumar et al. 2018, Yasmin et al. 2020) However, there are no studies which analyze the benefit of using mHealth for the provision of PhC for diabetes

patients. There is also, to our knowledge, no published assessment or evaluation of the effort required to use a mobile diabetes application in an interdisciplinary team. Many T2DM patients and multimorbid T1DM patients would benefit from a periodic, iterated medication analysis. Hence, diabetes mHealth applications should, in future, include features to support medication analysis such as an import function for patient medication plans or a drug-drug or drug-food interaction database. One of the limitations of Diabetes:M is the lack of a commentary or chat function to provide personalized feedback online in a time-effective manner; the lack of personalized feedback was also identified as a limitation in a study by El-Gayar et al. (El-Gayar et al. 2013)

6.2 Conclusion

Detailed analysis of the DIADEMA study revealed that PhC can improve the glycemic control of adolescents with T1DM. The reduced HbA1c values and improved glycemic control were particularly related to decreased FBG values and improved adherence to diabetes therapy. Furthermore, patients increased their frequency of SMBG and daily insulin injections to better adjust their insulin therapy. Interdisciplinary work between diabetologists, pharmacists, and diabetes educators was beneficial for the patients. Pharmacists can support and motivate adolescents to take over self-management of their diabetes therapy and to transform current guideline recommendations into feasible and reasonable actions.

The findings of our systematic review and meta-analysis indicate that community pharmacists are able to improve the glycemic control of diabetes patients by conducting PhC. The meta-analytical mean difference in HbA1c values was –0.66%, with a 95% CI of [–0.86%, –0.45%]. Quantitative analysis of the implemented intervention components revealed that the following components were most effective: (1) sending feedback to the physician, (2) setting individual goals with the patient, (3) analyzing the patient's medication, and (4) analyzing the patient's blood glucose records. Evaluating the training that pharmacists received prior to the intervention revealed that further research is needed to determine the precise effects of different training elements.

As a preliminary, small-scale proof-of-concept study of the four effective PhC components, our case series allows us to formulate the hypothesis that these structured MTM elements can be implemented in everyday pharmacy practice for T2DM patients. We hypothesized that these four PhC components were feasible in practice and can be implemented in patient consultations that last a maximum of 60 minutes. We also hypothesized that the implementation of these four PhC components can improve T2DM patients' number of unsolved DRPs, MAI, and WHO-5 well-being index scores. Further research is required to clarify the effect of these four components on glycemic control, especially on HbA1c values and TIR, in diabetes patients in everyday pharmacy practice.

The descriptive evaluation of the Diabetes:M application revealed that it can help with the analysis of patients' SMBG values, setting individual goals with the patient, and interdisciplinary collaboration. The current version of Diabetes:M is does not have sufficient capability to support the conduction and documentation of medication reviews that include the identification of DRPs. In conclusion, pharmacists who provide PhC to diabetes patients requiring insulin can benefit significantly from the Diabetes:M application.

Further research and hypothesis-testing studies are needed. These should implement mHealth diabetes applications such as Diabetes:M and include their functions to improve the implementation of effective and optimized PhC in practice. One pertinent goal is to assess whether mHealth can support the implementation of the four PhC components and whether it would improve patient outcomes. Therefore, a study with two arms (mHealth vs. analog diabetes record books) would be preferable.

6.3 Outlook

Many studies have demonstrated the increasing global burden of diabetes and the growing need for effective antihyperglycemic drug treatments and non-drug lifestyle changes for both T1DM and T2DM. Poor adherence to medication regimens is a common problem and can contribute to the substantial worsening of diabetes. Poor glycemic control can lead to severe acute and long-term diabetes complications and therefore it is essential to provide, in addition to the current standard care, effective and optimized PhC for diabetes patients in community pharmacies. The results of this thesis indicate that optimized, effective PhC provided by community pharmacists can improve the glycemic control and diabetes self-management of T1DM and T2DM patients. The main goal in future should be to provide the effective PhC components described in this thesis, especially to patients with poor glycemic control (HbA1c values >9% or those already suffering from diabetes complications). Further research is required, especially hypothesis-testing studies, to test the in chapter three and four mentioned intervention and trial design. A case–control, cohort, CT, or RCT would be suitable for this aim.

It is also important that pharmacists who want to provide this effective, optimized PhC should be properly trained to effectively support diabetes self-management. In Germany, the availability of certified courses for MTM and PhC for diabetes patients needs to be increased. Training content should include the use of mHealth applications and modern, practical training methods such as simulation training or objective structured clinical examinations (OSCEs). These training methods are useful for learning the implementation of PhC in practice with real or simulated patients in a realistic setting, because diabetes self-management includes many practical aspects such as insulin injection techniques, calculation of carbohydrates, coping with acute complications or conducting SMBG. In addition, further research is required to evaluate the effect of different training components on the effectiveness and outcomes of pharmacist interventions for diabetes patients. If possible, a study that includes pharmacists with and without training should be undertaken.

These future studies should also test the capabilities and benefits of diabetes mHealth applications. These offer many opportunities for implementing effective, optimized PhC for diabetes patients with many diseases or medications. In addition, the development of different versions of the Diabetes:M application that are especially adapted to the needs of diabetes patients with and without insulin therapy would be beneficial for health care providers and patients. It is also important that the use of mHealth is implemented promptly in every community pharmacy that provides PhC for diabetes patients, as both pharmacists and

patients benefit from the use of an mHealth diabetes application. Further research is needed to identify the most useful and practical mHealth diabetes application.

VI Bibliography

ABDA. (2014, 24.06.2014). "Grundsatzpapier zur Medikationsanalyse und zum Medikationsmanagement." Retrieved 11. June, 2022, from https://www.abda.de/themen/arzneimitteltherapiesicherheit/foerderinitiative-pharmazeutische-betreuung/medikationsmanagement/.

Abraham, M. B., T. W. Jones, D. Naranjo, B. Karges, A. Oduwole, M. Tauschmann and D. M. Maahs (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Assessment and management of hypoglycemia in children and adolescents with diabetes." Pediatr Diabetes 19 Suppl 27: 178-192. doi: 10.1111/pedi.12698

ADA (2019a). "2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019." Diabetes Care 42(Suppl 1): S13-s28. doi: 10.2337/dc19-S002

ADA (2019b). "9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2019." Diabetes Care 42(Supplement 1): S90-S102. doi: 10.2337/dc19-S009

ADA (2020). "6. Glycemic Targets: Standards of Medical Care in Diabetes—2020." Diabetes Care 43(Supplement 1): S66-S76. doi: 10.2337/dc20-S006

Adolfsson, P., M. C. Riddell, C. E. Taplin, E. A. Davis, P. A. Fournier, F. Annan, A. E. Scaramuzza, D. Hasnani and S. E. Hofer (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes." Pediatr Diabetes 19 Suppl 27: 205-226. doi: 10.1111/pedi.12755

Aguiar, P. M., G. D. Brito, C. J. Correr, D. P. Lyra Júnior and S. Storpirtis (2014). "Exploring the Quality of Systematic Reviews on Pharmacist Interventions in Patients With Diabetes: An Overview." Ann Pharmacother 48(7): 887-896. doi: 10.1177/1060028014529411

AKNR. (2021). "Mit ATHINA in die Zukunft." Retrieved 11. June, 2022, from https://www.aknr.de/apotheker/inhalt.php?id=153.

Ali, M., F. Schifano, P. Robinson, G. Phillips, L. Doherty, P. Melnick, L. Laming, A. Sinclair and S. Dhillon (2012). "Impact of community pharmacy diabetes monitoring and education programme on diabetes management: a randomized controlled study." Diabet Med 29(9): e326-333. doi: 10.1111/j.1464-5491.2012.03725.x

Allemann, S. S., J. W. van Mil, L. Botermann, K. Berger, N. Griese and K. E. Hersberger (2014). "Pharmaceutical care: the PCNE definition 2013." Int J Clin Pharm 36(3): 544-555. doi: 10.1007/s11096-014-9933-x

Alzubaidi, H. T., S. Chandir, S. Hasan, K. McNamara, R. Cox and I. Krass (2019). "Diabetes and cardiovascular disease risk screening model in community pharmacies in a developing primary healthcare system: a feasibility study." BMJ Open 9(11): e031246. doi: 10.1136/bmjopen-2019-031246

Antoine, S. L., D. Pieper, T. Mathes and M. Eikermann (2014). "Improving the adherence of type 2 diabetes mellitus patients with pharmacy care: a systematic review of randomized controlled trials." BMC Endocr Disord 14: 53. doi: 10.1186/1472-6823-14-53

Asche, C., J. LaFleur and C. Conner (2011). "A Review of Diabetes Treatment Adherence and the Association with Clinical and Economic Outcomes." Clinical Therapeutics 33(1): 74-109. doi: 10.1016/j.clinthera.2011.01.019

Azoulay, L. and S. Suissa (2017). "Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies." Diabetes Care 40(5): 706-714. doi: 10.2337/dc16-1943

Bahrmann, A., P. Bahrmann, J. Baumann, J. Bauer, E. Brückel, M. Dreyer, M. Freitag, A. Friedl, S. Gölz, S. Grundke, S. Hiddemann, K. Hodeck, W. Kern, U. Kintscher, T. Kubiak, B. Kulzer, Y. H. Lee-Barkey, R. Lobmann, N. Marx, F. Schröder, A. Tombek, T. Uebel, J. Wernecke and A. Zeyfang (2018). "S2k-Leitlinie Diagnostik, Therapie und Verlaufskontrolle des Diabetes mellitus im Alter." Diabetologie und Stoffwechsel 13(05): 423-489. doi: 10.1055/a-0666-0820

Bain, S., E. Druyts, C. Balijepalli, C. A. Baxter, C. J. Currie, R. Das, R. Donnelly, K. Khunti, H. Langerman, P. Leigh, G. Siliman, K. Thorlund, K. Toor, J. Vora and E. J. Mills (2017). "Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: A Bayesian meta-analysis of survival data." Diabetes Obes Metab 19(3): 329-335. doi: 10.1111/dom.12821

BAK. (2018). "Leitlinie der Bundesapothekerkammer zur Qualitätssicherung Medikationsanalyse." Retrieved 11. June, 2022, from https://www.abda.de/fileadmin/user_upload/assets/Praktische_Hilfen/Leitlinien/Medikationsanalyse/LL_MedAnalyse.pdf.

BÄK (2013, zuletzt geändert: April 2014). "Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes – Langfassung." doi: 10.6101/AZQ/000203

BÄK (2021). "Nationale VersorgungsLeitlinie Typ-2-Diabetes – Teilpublikation der Langfassung." 1. Version. doi: 10.6101/AZQ/000475

Bakris, G. L., V. A. Fonseca, K. Sharma and E. M. Wright (2009). "Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications." Kidney Int 75(12): 1272-1277. doi: 10.1038/ki.2009.87

Barnard, K. D., C. E. Lloyd and T. C. Skinner (2007). "Systematic literature review: quality of life associated with insulin pump use in Type 1 diabetes." Diabet Med 24(6): 607-617. doi: 10.1111/j.1464-5491.2007.02120.x

Barnett, M. J., J. Frank, H. Wehring, B. Newland, S. VonMuenster, P. Kumbera, T. Halterman and P. J. Perry (2009). "Analysis of pharmacist-provided medication therapy management (MTM) services in community pharmacies over 7 years." J Manag Care Pharm 15(1): 18-31. doi: 10.18553/jmcp.2009.15.1.18

Battelino, T., I. Conget, B. Olsen, I. Schütz-Fuhrmann, E. Hommel, R. Hoogma, U. Schierloh, N. Sulli and J. Bolinder (2012). "The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial." Diabetologia 55(12): 3155-3162. doi: 10.1007/s00125-012-2708-9

Battelino, T., M. Phillip, N. Bratina, R. Nimri, P. Oskarsson and J. Bolinder (2011). "Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes." Diabetes Care 34(4): 795-800. doi: 10.2337/dc10-1989

Beck, R. W., T. Riddlesworth, K. Ruedy, A. Ahmann, R. Bergenstal, S. Haller, C. Kollman, D. Kruger, J. B. McGill, W. Polonsky, E. Toschi, H. Wolpert and D. Price (2017). "Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial." Jama 317(4): 371-378. doi: 10.1001/jama.2016.19975

Berezin, A. (2016). "Metabolic memory phenomenon in diabetes mellitus: Achieving and perspectives." Diabetes Metab Syndr 10(2 Suppl 1): S176-183. doi: 10.1016/j.dsx.2016.03.016

Bethel, M. A., S. S. Engel, J. B. Green, Z. Huang, R. G. Josse, K. D. Kaufman, E. Standl, S. Suryawanshi, F. Van de Werf, D. K. McGuire, E. D. Peterson and R. R. Holman (2017). "Assessing the Safety of Sitagliptin in Older Participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)." Diabetes Care 40(4): 494-501. doi: 10.2337/dc16-1135

Bitter, K., C. Pehe, M. Krüger, G. Heuer, R. Quinke and U. Jaehde (2019). "Pharmacist-led medication reviews for geriatric residents in German long-term care facilities." BMC geriatrics 19(1): 39-39. doi: 10.1186/s12877-019-1052-z

Blenkinsopp, A. and A. Hassey (2005). "Effectiveness and acceptability of community pharmacy-based interventions in type 2 diabetes: a critical review of intervention design, pharmacist and patient perspectives." International Journal of Pharmacy Practice 13(4): 231-240. doi: 10.1211/ijpp.13.4.0001

Blüher, S. and A. Kuhlmey (2016). Demographischer Wandel, Altern und Gesundheit. Soziologie von Gesundheit und Krankheit. M. Richter and K. Hurrelmann. Wiesbaden, Springer Fachmedien Wiesbaden: 313-324.

BMBF. (2021). "Hightech-Strategie 2025." Retrieved 11. June, 2022, from https://www.hightech-strategie.de/de/hightech-strategie-2025-1726.html.

Bonoto, B. C., V. E. de Araújo, I. P. Godói, L. L. de Lemos, B. Godman, M. Bennie, L. M. Diniz and A. A. Junior (2017). "Efficacy of Mobile Apps to Support the Care of Patients With Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." JMIR Mhealth Uhealth 5(3): e4. doi: 10.2196/mhealth.6309

Boyko, W. L., Jr., P. J. Yurkowski, M. F. Ivey, J. A. Armitstead and B. L. Roberts (1997). "Pharmacist influence on economic and morbidity outcomes in a tertiary care teaching hospital." American Journal of Health-System Pharmacy 54(14): 1591-1595. doi: 10.1093/ajhp/54.14.1591

Brodows, R. G., C. Williams and J. M. Amatruda (1984). "Treatment of insulin reactions in diabetics." Jama 252(24): 3378-3381. doi: 10.1001/jama.1984.03350240024032

Broers, S., K. P. van Vliet, S. le Cessie, P. Spinhoven, N. C. van der Ven and J. K. Radder (2005). "Blood glucose awareness training in Dutch type 1 diabetes patients: one-year follow-up." Neth J Med 63(5): 164-169. doi: 10.1046/j.1464-5491.2002.00682.x

Bulajeva, A., L. Labberton, S. Leikola, M. Pohjanoksa-Mäntylä, M. M. Geurts, J. J. de Gier and M. Airaksinen (2014). "Medication review practices in European countries." Res Social Adm Pharm 10(5): 731-740. doi: 10.1016/j.sapharm.2014.02.005

Cahn, A., A. Akirov and I. Raz (2018). "Digital health technology and diabetes management." J Diabetes 10(1): 10-17. doi: 10.1111/1753-0407.12606

Cameron, F. J., K. Garvey, K. K. Hood, C. L. Acerini and E. Codner (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes in adolescence." Pediatr Diabetes 19 Suppl 27: 250-261. doi: 10.1111/pedi.12702

Car, J., W. S. Tan, Z. Huang, P. Sloot and B. D. Franklin (2017). "eHealth in the future of medications management: personalisation, monitoring and adherence." BMC Med 15(1): 73. doi: 10.1186/s12916-017-0838-0

Castejon, A. M., J. L. Calderon, A. Perez, C. Millar, J. McLaughlin-Middlekauff, N. Sangasubana, G. Alvarez, L. Arce, P. Hardigan and S. E. Rabionet (2013). "A community-based pilot study of a diabetes pharmacist intervention in Latinos: impact on weight and hemoglobin A1c." J Health Care Poor Underserved 24(4 Suppl): 48-60. doi: 10.1353/hpu.2014.0003

Castensøe-Seidenfaden, P., G. R. Husted, A. K. Jensen, E. Hommel, B. Olsen, U. Pedersen-Bjergaard, F. Kensing and G. Teilmann (2018). "Testing a Smartphone App (Young with Diabetes) to Improve Self-Management of Diabetes Over 12 Months: Randomized Controlled Trial." JMIR Mhealth Uhealth 6(6): e141. doi: 10.2196/mhealth.9487

Ceriello, A. (2020). "Is it time to ban sulfonylureas?" J Diabetes 12(11): 848-850. doi: 10.1111/1753-0407.13095

Cleary, P. A., T. J. Orchard, S. Genuth, N. D. Wong, R. Detrano, J. Y. Backlund, B. Zinman, A. Jacobson, W. Sun, J. M. Lachin and D. M. Nathan (2006). "The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study." Diabetes 55(12): 3556-3565. doi: 10.2337/db06-0653

Clifford, R. M., W. A. Davis, K. T. Batty and T. M. Davis (2005). "Effect of a pharmaceutical care program on vascular risk factors in type 2 diabetes: the Fremantle Diabetes Study." Diabetes Care 28(4): 771-776. doi: 10.2337/diacare.28.4.771

Cochran, J. B., S. Walters and J. D. Losek (2006). "Pediatric hyperglycemic hyperosmolar syndrome: diagnostic difficulties and high mortality rate." Am J Emerg Med 24(3): 297-301. doi: 10.1016/j.ajem.2005.10.007

Collins, C., B. L. Limone, J. M. Scholle and C. I. Coleman (2011). "Effect of pharmacist intervention on glycemic control in diabetes." Diabetes Res Clin Pract 92(2): 145-152. doi: 10.1016/j.diabres.2010.09.023

Costa, F. A., C. Scullin, G. Al-Taani, A. F. Hawwa, C. Anderson, Z. Bezverhni, Z. Binakaj, M. Cordina, V. Foulon, B. Garcia de Bikuna, H. de Gier, A. G. Granas, O. Grinstova, N. Griese-Mammen, J. Grincevicius, S. Grinceviciene, S. Kaae, L. Kubiliene, E. L. Marino, S. Martins, P. Modamio, G. Nadin, L. S. Norgaard, E. Obarcanin, I. Tadic, L. Tasic, J. C. McElnay, K. E. Hersberger and T. Westerlund (2017). "Provision of pharmaceutical care by community pharmacists across Europe: Is it developing and spreading?" J Eval Clin Pract 23(6): 1336-1347. doi: 10.1111/jep.12783

Couper, J. J., M. J. Haller, C. J. Greenbaum, A. G. Ziegler, D. K. Wherrett, M. Knip and M. E. Craig (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents." Pediatr Diabetes 19 Suppl 27: 20-27. doi: 10.1111/pedi.12734

Cramer, J. A. (2004). "A Systematic Review of Adherence With Medications for Diabetes." Diabetes Care 27(5): 1218-1224. doi: 10.2337/diacare.27.5.1218

Cranor, C. W., B. A. Bunting and D. B. Christensen (2003). "The Asheville Project: long-term clinical and economic outcomes of a community pharmacy diabetes care program." J Am Pharm Assoc (Wash) 43(2): 173-184. doi: 10.1331/108658003321480713

Cryer, P. E., S. N. Davis and H. Shamoon (2003). "Hypoglycemia in diabetes." Diabetes Care 26(6): 1902-1912. doi: 10.2337/diacare.26.6.1902

Danne, T., O. Kordonouri, T. Biester, T. Siegmund, J. Krˆger, P. Bramlage and T. Haak (2019). "Time in Range: Ein neuer Parameter ñ komplement‰r zum HbA 1c." Dtsch Arztebl International 116(43): -4-. doi: 10.3238/PersDia.2019.10.25.01

Danne, T., R. Nimri, T. Battelino, R. M. Bergenstal, K. L. Close, J. H. DeVries, S. Garg, L. Heinemann, I. Hirsch, S. A. Amiel, R. Beck, E. Bosi, B. Buckingham, C. Cobelli, E. Dassau, F. J. Doyle, 3rd, S. Heller, R. Hovorka, W. Jia, T. Jones, O. Kordonouri, B. Kovatchev, A. Kowalski, L. Laffel, D. Maahs, H. R. Murphy, K. Nørgaard, C. G. Parkin, E. Renard, B. Saboo, M. Scharf, W. V. Tamborlane, S. A. Weinzimer and M. Phillip (2017). "International Consensus on Use of Continuous Glucose Monitoring." Diabetes care 40(12): 1631-1640. doi: 10.2337/dc17-1600

Danne, T., M. Phillip, B. A. Buckingham, P. Jarosz-Chobot, B. Saboo, T. Urakami, T. Battelino, R. Hanas and E. Codner (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Insulin treatment in children and adolescents with diabetes." Pediatr Diabetes 19 Suppl 27: 115-135. doi: 10.1111/pedi.12718

DCCT-/EDIC-Research-Group (2016). "Mortality in Type 1 Diabetes in the DCCT/EDIC Versus the General Population." Diabetes Care 39(8): 1378-1383. doi: 10.2337/dc15-2399

DDG. (2018, 28.03.2018). "Langfassung der S3-Leitlinie "Therapie des Typ-1-Diabetes"." 2. Retrieved 11. June, 2022, from https://www.awmf.org/leitlinien/detail/ll/057-013.html.

DDG. (2020). "Diabetes Schulungen und Kurse für Apotheker." Retrieved 30. July, 2020, from https://www.deutsche-diabetes-gesellschaft.de/weiterbildung/apotheker.html.

DDH. (2022). "Diabetes in Zahlen." Retrieved 11. June, 2022, from https://www.diabetesde.org/ueber_diabetes/was_ist_diabetes_/diabetes_in_zahlen.

Demirel, F., D. Tepe, O. Kara and I. Esen (2013). "Microvascular complications in adolescents with type 1 diabetes mellitus." J Clin Res Pediatr Endocrinol 5(3): 145-149. doi: 10.4274/Jcrpe.994

Deters, M. A., S. Laer, S. Hasanbegovic, V. Nemitz, P. Muller, M. Kruger, H. Schwender and E. Obarcanin (2016). "Diabetes Stewardship - Pharmaceutical care of adolescents with type 1 diabetes mellitus provided by community pharmacists." Med Monatsschr Pharm 39(11): 477-482. doi: not available

Deters, M. A., A. Laven, A. Castejon, W. R. Doucette, L. S. Ev, I. Krass, E. Mehuys, E. Obarcanin, H. Schwender and S. Laeer (2018). "Effective Interventions for Diabetes Patients by Community Pharmacists: A Meta-analysis of Pharmaceutical Care Components." Ann Pharmacother 52(2): 198-211. doi: 10.1177/1060028017733272

Deters, M. A., E. Obarcanin, H. Schwender and S. Läer (2021). "EMDIA Case Series—Effective Medication Therapy Management (MTM) for Diabetes Type 2 Patients—A Proof of Concept Study." Pharmacy 9(3): 137. doi: 10.3390/pharmacy9030137

Deutscher-Ärzteverlag. (2022). "Patientenschulungsprogramme für Diabetespatienten." Retrieved 11. June, 2022, from https://www.patientenschulungsprogramme.de/#Diabetes.

DiMeglio, L. A., C. L. Acerini, E. Codner, M. E. Craig, S. E. Hofer, K. Pillay and D. M. Maahs (2018a). "ISPAD Clinical Practice Consensus Guidelines 2018: Glycemic control targets and glucose monitoring for children, adolescents, and young adults with diabetes." Pediatr Diabetes 19 Suppl 27: 105-114. doi: 10.1111/pedi.12737

DiMeglio, L. A., C. Evans-Molina and R. A. Oram (2018b). "Type 1 diabetes." Lancet 391(10138): 2449-2462. doi: 10.1016/s0140-6736(18)31320-5

Dingermann, T. (2020, 05.05.2020). "Grünes Licht für erstes Biosimilar von Insulin aspart." Retrieved 11. June, 2022, from https://www.pharmazeutische-zeitung.de/gruenes-licht-fuer-erstes-biosimilar-von-insulin-aspart-117373/.

Donaghue, K. C., M. L. Marcovecchio, R. P. Wadwa, E. Y. Chew, T. Y. Wong, L. E. Calliari, B. Zabeen, M. A. Salem and M. E. Craig (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents." Pediatr Diabetes 19 Suppl 27: 262-274. doi: 10.1111/pedi.12742

Doucette, W. R., M. J. Witry, K. B. Farris and R. P. McDonough (2009). "Community pharmacist-provided extended diabetes care." Ann Pharmacother 43(5): 882-889. doi: 10.1345/aph.1L605

Douros, A., L. M. Lix, M. Fralick, S. Dell'Aniello, B. R. Shah, P. E. Ronksley, É. Tremblay, N. Hu, S. Alessi-Severini, A. Fisher, S. C. Bugden, P. Ernst and K. B. Filion (2020). "Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis: A Multicenter Cohort Study." Ann Intern Med. doi: 10.7326/m20-0289

El-Gayar, O., P. Timsina, N. Nawar and W. Eid (2013). "Mobile applications for diabetes self-management: status and potential." J Diabetes Sci Technol 7(1): 247-262. doi: 10.1177/193229681300700130

Erku, D. A., A. A. Ayele, A. B. Mekuria, S. A. Belachew, B. Hailemeskel and H. G. Tegegn (2017). "The impact of pharmacist-led medication therapy management on medication adherence in patients with type 2 diabetes mellitus: a randomized controlled study." Pharm Pract (Granada) 15(3): 1026. doi: 10.18549/PharmPract.2017.03.1026

Esefeld, K., S. Kress, P. Zimmer, M. Stumvoll, C. Brinkmann and M. Halle (2019). "Diabetes, sport and exercise." Der Diabetologe. doi: 10.1007/s11428-019-00529-2

Fadini, G. P., B. M. Bonora and A. Avogaro (2017). "SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System." Diabetologia 60(8): 1385-1389. doi: 10.1007/s00125-017-4301-8

Fayfman, M., F. J. Pasquel and G. E. Umpierrez (2017). "Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State." The Medical clinics of North America 101(3): 587-606. doi: 10.1016/j.mcna.2016.12.011

Feletto, E., G. W. Y. Lui, C. Armour and B. Saini (2012). "Practice change in community pharmacy: using change-management principles when implementing a pharmacy asthma management service in NSW, Australia." International Journal of Pharmacy Practice 21(1): 28-37. doi: 10.1111/j.2042-7174.2012.00225.x

Fitchett, D., B. Zinman, C. Wanner, J. M. Lachin, S. Hantel, A. Salsali, O. E. Johansen, H. J. Woerle, U. C. Broedl and S. E. Inzucchi (2016). "Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial." Eur Heart J 37(19): 1526-1534. doi: 10.1093/eurheartj/ehv728

Fornos, J. A., N. F. Andres, J. C. Andres, M. M. Guerra and B. Egea (2006). "A pharmacotherapy follow-up program in patients with type-2 diabetes in community pharmacies in Spain." Pharm World Sci 28(2): 65-72. doi: 10.1007/s11096-006-9003-0

Foster, C., J. Bellando and Y. C. Wang (2016). "Diabetes Control and Adherence in Adolescence." Pediatr Ann 45(9): e327-331. doi: 10.3928/19382359-20160817-01

Fredrick Debong, H. M., Johanna Kober (2019). "Real-World Assessments of mySugr Mobile Health App." Diabetes Technology & Therapeutics 21(S2): S2-35-S32-40. doi: 10.1089/dia.2019.0019

GBA. (2016, 04.03.2016). "Beschluss Arzneimittel-Richtlinie/ Anlage III und IV: Glinide zur Behandlung des Diabetes mellitus Typ 2 und Aufhebung eines Therapiehinweises zu Repaglinid." Retrieved 11. June, 2022, from https://www.g-ba.de/downloads/39-261-1142/2010-06-17_AM-RL-III_Glinide-2016-02-18_BAnz.pdf.

Gerstein, H. C., H. M. Colhoun, G. R. Dagenais, R. Diaz, M. Lakshmanan, P. Pais, J. Probstfield, J. S. Riesmeyer, M. C. Riddle, L. Rydén, D. Xavier, C. M. Atisso, L. Dyal, S. Hall, P. Rao-Melacini, G. Wong, A. Avezum, J. Basile, N. Chung, I. Conget, W. C. Cushman, E. Franek, N. Hancu, M. Hanefeld, S. Holt, P. Jansky, M. Keltai, F. Lanas, L. A. Leiter, P. Lopez-Jaramillo, E. G. Cardona Munoz, V. Pirags, N. Pogosova, P. J. Raubenheimer, J. E. Shaw, W. H. Sheu and T. Temelkova-Kurktschiev (2019). "Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial." Lancet 394(10193): 121-130. doi: 10.1016/s0140-6736(19)31149-3

Goedken, A. M., S. Huang, R. P. McDonough, M. J. Deninger and W. R. Doucette (2018). "Medication-Related Problems Identified Through Continuous Medication Monitoring." Pharmacy (Basel) 6(3). doi: 10.3390/pharmacy6030086

Goyal, S. and J. A. Cafazzo (2013). "Mobile phone health apps for diabetes management: current evidence and future developments." Qjm 106(12): 1067-1069. doi: 10.1093/qjmed/hct203

Goyal, S., C. A. Nunn, M. Rotondi, A. B. Couperthwaite, S. Reiser, A. Simone, D. K. Katzman, J. A. Cafazzo and M. R. Palmert (2017). "A Mobile App for the Self-Management of Type 1 Diabetes Among Adolescents: A Randomized Controlled Trial." JMIR Mhealth Uhealth 5(6): e82. doi: 10.2196/mhealth.7336

Grant, R. W., N. G. Devita, D. E. Singer and J. B. Meigs (2003). "Improving adherence and reducing medication discrepancies in patients with diabetes." Ann Pharmacother 37(7-8): 962-969. doi: 10.1345/aph.1C452

Green, J. B., M. A. Bethel, P. W. Armstrong, J. B. Buse, S. S. Engel, J. Garg, R. Josse, K. D. Kaufman, J. Koglin, S. Korn, J. M. Lachin, D. K. McGuire, M. J. Pencina, E. Standl, P. P. Stein, S. Suryawanshi, F. Van de Werf, E. D. Peterson and R. R. Holman (2015). "Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med 373(3): 232-242. doi: 10.1056/NEJMoa1501352

Greenwood, D. A., P. M. Gee, K. J. Fatkin and M. Peeples (2017). "A Systematic Review of Reviews Evaluating Technology-Enabled Diabetes Self-Management Education and Support." J Diabetes Sci Technol 11(5): 1015-1027. doi: 10.1177/1932296817713506

Grempler, R., L. Thomas, M. Eckhardt, F. Himmelsbach, A. Sauer, D. E. Sharp, R. A. Bakker, M. Mark, T. Klein and P. Eickelmann (2012). "Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors." Diabetes Obes Metab 14(1): 83-90. doi: 10.1111/j.1463-1326.2011.01517.x

Griese-Mammen, N., K. E. Hersberger, M. Messerli, S. Leikola, N. Horvat, J. W. F. van Mil and M. Kos (2018). "PCNE definition of medication review: reaching agreement." International Journal of Clinical Pharmacy 40(5): 1199-1208. doi: 10.1007/s11096-018-0696-7

Griffin, S. J., J. K. Leaver and G. J. Irving (2017). "Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes." Diabetologia 60(9): 1620-1629. doi: 10.1007/s00125-017-4337-9

Guthrie, K. D., S. C. Stoner, D. M. Hartwig, J. R. May, S. E. Nicolaus, A. M. Schramm and K. L. DiDonato (2017). "Physicians' Preferences for Communication of Pharmacist-Provided Medication Therapy Management in Community Pharmacy." J Pharm Pract 30(1): 17-24. doi: 10.1177/0897190015585764

Haak, T., S. Gölz, A. Fritsche, M. Füchtenbusch, T. Siegmund, E. Schnellbächer, H. H. Klein, T. Uebel and D. Droßel (2018). "Therapie des Typ-1-Diabetes." Diabetologie und Stoffwechsel 13(S 02): S120-S130. doi: 10.1055/a-0598-6528

Haig, G. M. and L. A. Kiser (1991). "Effect of pharmacist participation on a medical team on costs, charges, and length of stay." American Journal of Hospital Pharmacy 48(7): 1457-1462. doi: 10.1093/ajhp/48.7.1457

Halliday, J. A., C. Hendrieckx, L. Busija, J. L. Browne, G. Nefs, F. Pouwer and J. Speight (2017). "Validation of the WHO-5 as a first-step screening instrument for depression in adults with diabetes: Results from Diabetes MILES - Australia." Diabetes Res Clin Pract 132: 27-35. doi: 10.1016/j.diabres.2017.07.005

Hamdy, O. and M. Y. Barakatun-Nisak (2016). "Nutrition in Diabetes." Endocrinol Metab Clin North Am 45(4): 799-817. doi: 10.1016/j.ecl.2016.06.010

Hammes, H.-P., K. D. Lemmen and B. Bertram (2019). "Diabetische Retinopathie und Makulopathie." Diabetologie und Stoffwechsel 14(S 02): S240-S242. doi: 10.1055/a-0899-0033

Hanlon, J. T., K. E. Schmader, G. P. Samsa, M. Weinberger, K. M. Uttech, I. K. Lewis, H. J. Cohen and J. R. Feussner (1992). "A method for assessing drug therapy appropriateness." J Clin Epidemiol 45(10): 1045-1051. doi: 10.1016/0895-4356(92)90144-c

Heinemann, L., D. Deiss, T. Siegmund, S. Schlüter, M. Naudorf, S. von Sengbusch, K. Lange and G. Freckmann (2020). "Glukosemessung und -kontrolle bei Patienten mit Typ-1- oder Typ-2-Diabetes." Diabetologie und Stoffwechsel 15(S 01): S18-S39. doi: 10.1055/a-1179-2865

Heise, T., U. Hövelmann, L. Brøndsted, C. L. Adrian, L. Nosek and H. Haahr (2015). "Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart." Diabetes Obes Metab 17(7): 682-688. doi: 10.1111/dom.12468

Helgeson, V. S., L. Siminerio, O. Escobar and D. Becker (2009). "Predictors of metabolic control among adolescents with diabetes: a 4-year longitudinal study." J Pediatr Psychol 34(3): 254-270. doi: 10.1093/jpepsy/jsn079

Hendrie, D., T. R. Miller, R. J. Woodman, K. Hoti and J. Hughes (2014). "Cost-effectiveness of reducing glycaemic episodes through community pharmacy management of patients with type 2 diabetes mellitus." J Prim Prev 35(6): 439-449. doi: 10.1007/s10935-014-0368-x

Hepler, C. D. and L. M. Strand (1990). "Opportunities and responsibilities in pharmaceutical care." Am J Hosp Pharm 47(3): 533-543. doi: 10.1093/ajhp/47.3.533

Hernandez, A. F., J. B. Green, S. Janmohamed, R. B. D'Agostino, Sr., C. B. Granger, N. P. Jones, L. A. Leiter, A. E. Rosenberg, K. N. Sigmon, M. C. Somerville, K. M. Thorpe, J. J. V. McMurray and S. Del Prato (2018). "Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial." Lancet 392(10157): 1519-1529. doi: 10.1016/s0140-6736(18)32261-x

Higgins, J. P. T. and S. Green. (2011, March 2011). "Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0." Retrieved 11. June, 2022, from https://handbook-5-1.cochrane.org.

Holman, R. R., M. A. Bethel, R. J. Mentz, V. P. Thompson, Y. Lokhnygina, J. B. Buse, J. C. Chan, J. Choi, S. M. Gustavson, N. Iqbal, A. P. Maggioni, S. P. Marso, P. Öhman, N. J. Pagidipati, N. Poulter, A. Ramachandran, B. Zinman and A. F. Hernandez (2017). "Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med 377(13): 1228-1239. doi: 10.1056/NEJMoa1612917

Hou, C., B. Carter, J. Hewitt, T. Francisa and S. Mayor (2016). "Do Mobile Phone Applications Improve Glycemic Control (HbA_{1c}) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials." Diabetes Care 39(11): 2089-2095. doi: 10.2337/dc16-0346

Hughes, C. M., A. F. Hawwa, C. Scullin, C. Anderson, C. B. Bernsten, I. Bjornsdottir, M. A. Cordina, F. A. da Costa, I. De Wulf, P. Eichenberger, V. Foulon, M. C. Henman, K. E. Hersberger, M. A. Schaefer, B. Sondergaard, M. P. Tully, T. Westerlund and J. C. McElnay (2010). "Provision of pharmaceutical care by community pharmacists: a comparison across Europe." Pharm World Sci 32(4): 472-487. doi: 10.1007/s11096-010-9393-x

Hughes, J. D., Y. Wibowo, B. Sunderland and K. Hoti (2017). "The role of the pharmacist in the management of type 2 diabetes: current insights and future directions." Integr Pharm Res Pract 6: 15-27. doi: 10.2147/iprp.S103783

Husain, M., A. L. Birkenfeld, M. Donsmark, K. Dungan, F. G. Eliaschewitz, D. R. Franco, O. K. Jeppesen, I. Lingvay, O. Mosenzon, S. D. Pedersen, C. J. Tack, M. Thomsen, T. Vilsbøll, M. L. Warren and S. C. Bain (2019). "Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes." N Engl J Med 381(9): 841-851. doi: 10.1056/NEJMoa1901118

Husted, G. R., J. Weis, G. Teilmann and P. Castensøe-Seidenfaden (2018). "Exploring the Influence of a Smartphone App (Young with Diabetes) on Young People's Self-Management: Qualitative Study." JMIR Mhealth Uhealth 6(2): e43. doi: 10.2196/mhealth.8876

Ighodaro, O. M. (2018). "Molecular pathways associated with oxidative stress in diabetes mellitus." Biomedicine & Pharmacotherapy 108: 656-662. doi: 10.1016/j.biopha.2018.09.058

Izahar, S., Q. Y. Lean, M. A. Hameed, M. K. Murugiah, R. P. Patel, Y. M. Al-Worafi, T. W. Wong and L. C. Ming (2017). "Content Analysis of Mobile Health Applications on Diabetes Mellitus." Frontiers in Endocrinology 8(318). doi: 10.3389/fendo.2017.00318

Jahangard-Rafsanjani, Z., A. Sarayani, M. Nosrati, N. Saadat, A. Rashidian, M. Hadjibabaie, A. Ashouri, M. Radfar, M. Javadi and K. Gholami (2015). "Effect of a community pharmacist-delivered diabetes support program for patients receiving specialty medical care: a randomized controlled trial." Diabetes Educ 41(1): 127-135. doi: 10.1177/0145721714559132

Jameson, J. L. (2018). Harisson's Principles of Internal Medicine, McGraw-Hill Education.

Jameson, J. P. and P. J. Baty (2010). "Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial." Am J Manag Care 16(4): 250-255. doi: not available

Kao, K. T. and M. A. Sabin (2016). "Type 2 diabetes mellitus in children and adolescents." Aust Fam Physician 45(6): 401-406. doi: not available

Karges, B., J. Rosenbauer, P. M. Holterhus, P. Beyer, H. Seithe, C. Vogel, A. Böckmann, D. Peters, S. Müther, A. Neu and R. W. Holl (2015). "Hospital admission for diabetic ketoacidosis or severe hypoglycemia in 31,330 young patients with type 1 diabetes." Eur J Endocrinol 173(3): 341-350. doi: 10.1530/eje-15-0129

Kebede, M. M. and C. R. Pischke (2019). "Popular Diabetes Apps and the Impact of Diabetes App Use on Self-Care Behaviour: A Survey Among the Digital Community of Persons With Diabetes on Social Media." Front Endocrinol (Lausanne) 10: 135. doi: 10.3389/fendo.2019.00135

Khan, M. A. B., M. J. Hashim, J. K. King, R. D. Govender, H. Mustafa and J. Al Kaabi (2020). "Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends." Journal of epidemiology and global health 10(1): 107-111. doi: 10.2991/jegh.k.191028.001

King, P., I. Peacock and R. Donnelly (1999). "The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes." Br J Clin Pharmacol 48(5): 643-648. doi: 10.1046/j.1365-2125.1999.00092.x

Kjeldsen, L. J., L. Bjerrum, P. Dam, B. O. Larsen, C. Rossing, B. Sondergaard and H. Herborg (2015). "Safe and effective use of medicines for patients with type 2 diabetes - A randomized controlled trial of two interventions delivered by local pharmacies." Res Social Adm Pharm 11(1): 47-62. doi: 10.1016/j.sapharm.2014.03.003

Koberlein-Neu, J., H. Mennemann, S. Hamacher, I. Waltering, U. Jaehde, C. Schaffert and O. Rose (2016). "Interprofessional Medication Management in Patients With Multiple Morbidities." Dtsch Arztebl Int 113(44): 741-748. doi: 10.3238/arztebl.2016.0741

Kraemer, D. F., W. A. Kradjan, T. M. Bianco and J. A. Low (2012). "A randomized study to assess the impact of pharmacist counseling of employer-based health plan beneficiaries with diabetes: the EMPOWER study." J Pharm Pract 25(2): 169-179. doi: 10.1177/0897190011418513

Krass, I., C. L. Armour, B. Mitchell, M. Brillant, R. Dienaar, J. Hughes, P. Lau, G. Peterson, K. Stewart, S. Taylor and J. Wilkinson (2007). "The Pharmacy Diabetes Care Program: assessment of a community pharmacy diabetes service model in Australia." Diabet Med 24(6): 677-683. doi: 10.1111/j.1464-5491.2007.02143.x

Krass, I. and T. Dhippayom (2013). "Pharmaceutical care—Impact on quality of life in patients with type 2 diabetes: A review." Clinical Audit 5: 17-32. doi: 10.2147/CA.S30589

Krass, I., P. Schieback and T. Dhippayom (2015). "Adherence to diabetes medication: a systematic review." Diabet Med 32(6): 725-737. doi: 10.1111/dme.12651

Kristensen, S. L., R. Rørth, P. S. Jhund, K. F. Docherty, N. Sattar, D. Preiss, L. Køber, M. C. Petrie and J. J. V. McMurray (2019). "Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials." Lancet Diabetes Endocrinol 7(10): 776-785. doi: 10.1016/s2213-8587(19)30249-9

Kumar, S., H. Moseson, J. Uppal and J. L. Juusola (2018). "A Diabetes Mobile App With In-App Coaching From a Certified Diabetes Educator Reduces A1C for Individuals With Type 2 Diabetes." Diabetes Educ 44(3): 226-236. doi: 10.1177/0145721718765650

Ladhani, N. N., S. R. Majumdar, J. A. Johnson, R. T. Tsuyuki, R. Z. Lewanczuk, R. Spooner and S. H. Simpson (2012). "Adding pharmacists to primary care teams reduces predicted long-term risk of cardiovascular events in type 2 diabetic patients without established cardiovascular disease: results from a randomized trial." Diabet Med 29(11): 1433-1439. doi: 10.1111/j.1464-5491.2012.03673.x

Landgraf, R. (2014). "[National practice guideline therapy of type 2 diabetes]." MMW Fortschr Med 156 Spec No 1(1): 76-78. doi: 10.1055/s-0034-1384912 (Part 1) & 10.1055/s-0034-1384912 (Part 2)

Landgraf, R., M. Kellerer, J. Aberle, E.-M. Fach, B. Gallwitz, A. Hamann, H.-G. Joost, H. Klein, D. Müller-Wieland, M. A. Nauck, H.-M. Reuter, S. Schreiber and E. Siegel (2019). "Therapie des Typ-2-Diabetes." Der Diabetologe 15(2): 146-167. doi: 10.1007/s11428-019-0459-7

Latham, G., D. Ganegoda and E. Locke (2011). The Wiley-Blackwell Handbook of Individual Differences. Chapter: Goal setting: A state theory, but related to traits, Wiley-Blackwell.

Latham, G. and E. Locke (2007). "New Developments in and Directions for Goal-Setting Research." European Psychologist - EUR PSYCHOL 12: 290-300. doi: 10.1027/1016-9040.12.4.290

Latham, G. P. and E. A. Locke (1991). "Self-regulation through goal setting." Organizational Behavior and Human Decision Processes 50(2): 212-247. doi: 10.1016/0749-5978(91)90021-K

Lau, I. T., K. F. Lee, W. Y. So, K. Tan and V. T. F. Yeung (2017). "Insulin glargine 300 U/mL for basal insulin therapy in type 1 and type 2 diabetes mellitus." Diabetes Metab Syndr Obes 10: 273-284. doi: 10.2147/dmso.S131358

Lazarus, B., A. Wu, J.-I. Shin, Y. Sang, G. C. Alexander, A. Secora, L. A. Inker, J. Coresh, A. R. Chang and M. E. Grams (2018). "Association of Metformin Use With Risk of Lactic Acidosis Across the Range of Kidney Function: A Community-Based Cohort Study." JAMA internal medicine 178(7): 903-910. doi: 10.1001/jamainternmed.2018.0292

Lee, G., S. M. Kim, S. Choi, K. Kim, S. M. Jeong, J. S. Son, J. M. Yun and S. M. Park (2018). "The effect of change in fasting glucose on the risk of myocardial infarction, stroke, and all-cause mortality: a nationwide cohort study." Cardiovasc Diabetol 17(1): 51. doi: 10.1186/s12933-018-0694-z

Liberati, A., D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gøtzsche, J. P. Ioannidis, M. Clarke, P. J. Devereaux, J. Kleijnen and D. Moher (2009). "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration." PLoS Med 6(7): e1000100. doi: 10.1371/journal.pmed.1000100

Lin, X., Y. Xu, X. Pan, J. Xu, Y. Ding, X. Sun, X. Song, Y. Ren and P.-F. Shan (2020). "Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025." Scientific Reports 10(1): 14790. doi: 10.1038/s41598-020-71908-9

Lindenmeyer, A., H. Hearnshaw, E. Vermeire, P. Van Royen, J. Wens and Y. Biot (2006). "Interventions to improve adherence to medication in people with type 2 diabetes mellitus: a review of the literature on the role of pharmacists." J Clin Pharm Ther 31(5): 409-419. doi: 10.1111/j.1365-2710.2006.00759.x

Little, S. A., L. Leelarathna, E. Walkinshaw, H. K. Tan, O. Chapple, A. Lubina-Solomon, T. J. Chadwick, S. Barendse, D. D. Stocken, C. Brennand, S. M. Marshall, R. Wood, J. Speight, D. Kerr, D. Flanagan, S. R. Heller, M. L. Evans and J. A. Shaw (2014). "Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS)." Diabetes Care 37(8): 2114-2122. doi: 10.2337/dc14-0030

Liu, J., Z.-H. Ren, H. Qiang, J. Wu, M. Shen, L. Zhang and J. Lyu (2020). "Trends in the incidence of diabetes mellitus: results from the Global Burden of Disease Study 2017 and implications for diabetes mellitus prevention." BMC Public Health 20(1): 1415. doi: 10.1186/s12889-020-09502-x

Machado, M., J. Bajcar, G. C. Guzzo and T. R. Einarson (2007). "Sensitivity of patient outcomes to pharmacist interventions. Part I: systematic review and meta-analysis in diabetes management." Ann Pharmacother 41(10): 1569-1582. doi: 10.1345/aph.1K151

Mahaffey, K. W., B. Neal, V. Perkovic, D. de Zeeuw, G. Fulcher, N. Erondu, W. Shaw, E. Fabbrini, T. Sun, Q. Li, M. Desai and D. R. Matthews (2018). "Canagliflozin for Primary and Secondary Prevention of Cardiovascular Events: Results From the CANVAS Program

(Canagliflozin Cardiovascular Assessment Study)." Circulation 137(4): 323-334. doi: 10.1161/circulationaha.117.032038

Makowsky, M. J., S. L. Koshman, W. K. Midodzi and R. T. Tsuyuki (2009). "Capturing outcomes of clinical activities performed by a rounding pharmacist practicing in a team environment: the COLLABORATE study [NCT00351676]." Med Care 47(6): 642-650. doi: 10.1097/MLR.0b013e3181926032

Mann, J. F. E., D. D. Ørsted and J. B. Buse (2017). "Liraglutide and Renal Outcomes in Type 2 Diabetes." N Engl J Med 377(22): 2197-2198. doi: 10.1056/NEJMc1713042

Maritim, A. C., R. A. Sanders and J. B. Watkins, 3rd (2003). "Diabetes, oxidative stress, and antioxidants: a review." J Biochem Mol Toxicol 17(1): 24-38. doi: 10.1002/jbt.10058

Marso, S. P., F. M. M. Baeres, S. C. Bain, B. Goldman, M. Husain, M. A. Nauck, N. R. Poulter, R. E. Pratley, A. B. Thomsen and J. B. Buse (2020). "Effects of Liraglutide on Cardiovascular Outcomes in Patients With Diabetes With or Without Heart Failure." J Am Coll Cardiol 75(10): 1128-1141. doi: 10.1016/j.jacc.2019.12.063

Marso, S. P., S. C. Bain, A. Consoli, F. G. Eliaschewitz, E. Jódar, L. A. Leiter, I. Lingvay, J. Rosenstock, J. Seufert, M. L. Warren, V. Woo, O. Hansen, A. G. Holst, J. Pettersson and T. Vilsbøll (2016a). "Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes." N Engl J Med 375(19): 1834-1844. doi: 10.1056/NEJMoa1607141

Marso, S. P., G. H. Daniels, K. Brown-Frandsen, P. Kristensen, J. F. Mann, M. A. Nauck, S. E. Nissen, S. Pocock, N. R. Poulter, L. S. Ravn, W. M. Steinberg, M. Stockner, B. Zinman, R. M. Bergenstal and J. B. Buse (2016b). "Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med 375(4): 311-322. doi: 10.1056/NEJMoa1603827

Maruthur, N. M., E. Tseng, S. Hutfless, L. M. Wilson, C. Suarez-Cuervo, Z. Berger, Y. Chu, E. Iyoha, J. B. Segal and S. Bolen (2016). "Diabetes Medications as Monotherapy or Metformin-Based Combination Therapy for Type 2 Diabetes: A Systematic Review and Meta-analysis." Ann Intern Med 164(11): 740-751. doi: 10.7326/m15-2650

Mayer-Davis, E. J., A. R. Kahkoska, C. Jefferies, D. Dabelea, N. Balde, C. X. Gong, P. Aschner and M. E. Craig (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents." Pediatr Diabetes 19 Suppl 27: 7-19. doi: 10.1111/pedi.12773

McLean, W., J. Gillis and R. Waller (2003). "The BC Community Pharmacy Asthma Study: A study of clinical, economic and holistic outcomes influenced by an asthma care protocol provided by specially trained community pharmacists in British Columbia." Can Respir J 10(4): 195-202. doi: 10.1155/2003/736042

McMurray, J. J. V., S. D. Solomon, S. E. Inzucchi, L. Køber, M. N. Kosiborod, F. A. Martinez, P. Ponikowski, M. S. Sabatine, I. S. Anand, J. Bělohlávek, M. Böhm, C. E. Chiang, V. K. Chopra, R. A. de Boer, A. S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J. G. Howlett, T. Katova, M. Kitakaze, C. E. A. Ljungman, B. Merkely, J. C. Nicolau, E. O'Meara, M. C. Petrie, P. N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D. L. DeMets, K. F. Docherty, P. S. Jhund, O. Bengtsson, M. Sjöstrand and A. M. Langkilde (2019). "Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction." N Engl J Med 381(21): 1995-2008. doi: 10.1056/NEJMoa1911303

Medtronic. (2021). "Beantragung einer Insulinpumpe." Retrieved 11. June, 2022, from https://www.medtronic.com/de-de/diabetes/home/service/beantragung-einer-insulinpumpe/beantragung-insulinpumpe.html.

Mehuys, E., L. Van Bortel, L. De Bolle, I. Van Tongelen, L. Annemans, J. P. Remon and M. Giri (2011). "Effectiveness of a community pharmacist intervention in diabetes care: a randomized controlled trial." J Clin Pharm Ther 36(5): 602-613. doi: 10.1111/j.1365-2710.2010.01218.x

Merker, L., B.-W. Bautsch, T. Ebert, M. Guthoff and B. Isermann (2019). "Nephropathie bei Diabetes." Diabetologie und Stoffwechsel 14(S 02): S235-S239. doi: 10.1055/a-0898-9998

Misra, A. and Z. Bloomgarden (2018). "Metabolic memory: Evolving concepts." Journal of Diabetes 10(3): 186-187. doi: 10.1111/1753-0407.12622

Moher, D., L. Shamseer, M. Clarke, D. Ghersi, A. Liberati, M. Petticrew, P. Shekelle and L. A. Stewart (2015). "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement." Syst Rev 4: 1. doi: 10.1186/2046-4053-4-1

Mosenzon, O., G. Leibowitz, D. L. Bhatt, A. Cahn, B. Hirshberg, C. Wei, K. Im, A. Rozenberg, I. Yanuv, C. Stahre, K. K. Ray, N. Iqbal, E. Braunwald, B. M. Scirica and I. Raz (2017). "Effect of Saxagliptin on Renal Outcomes in the SAVOR-TIMI 53 Trial." Diabetes Care 40(1): 69-76. doi: 10.2337/dc16-0621

Moullin, J. C., D. Sabater-Hernández and S. I. Benrimoj (2016). "Qualitative study on the implementation of professional pharmacy services in Australian community pharmacies using framework analysis." BMC Health Services Research 16(1): 439. doi: 10.1186/s12913-016-1689-7

Mourao, A. O., W. R. Ferreira, M. A. Martins, A. M. Reis, M. R. Carrillo, A. G. Guimaraes and L. S. Ev (2013). "Pharmaceutical care program for type 2 diabetes patients in Brazil: a randomised controlled trial." Int J Clin Pharm 35(1): 79-86. doi: 10.1007/s11096-012-9710-7

Muralidharan, S., H. Ranjani, R. M. Anjana, S. Allender and V. Mohan (2017). "Mobile Health Technology in the Prevention and Management of Type 2 Diabetes." Indian journal of endocrinology and metabolism 21(2): 334-340. doi: 10.4103/ijem.IJEM_407_16

Mutschler, E. (2020). Mutschler Arzneimittelwirkungen : Lehrbuch der Pharmakologie, der klinischen Pharmakologie und Toxikologie, Wiss. Verlag-Ges.

Nathan, D. M., P. A. Cleary, J. Y. Backlund, S. M. Genuth, J. M. Lachin, T. J. Orchard, P. Raskin and B. Zinman (2005). "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes." N Engl J Med 353(25): 2643-2653. doi: 10.1056/NEJMoa052187

Ndefo, U. A., N. O. Anidiobi, E. Basheer and A. T. Eaton (2015). "Empagliflozin (Jardiance): A Novel SGLT2 Inhibitor for the Treatment of Type-2 Diabetes." P & T : a peer-reviewed journal for formulary management 40(6): 364-368. doi: not available

Neal, B., V. Perkovic and D. R. Matthews (2017). "Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes." N Engl J Med 377(21): 2099. doi: 10.1056/NEJMc1712572

Nordwall, M., M. Abrahamsson, M. Dhir, M. Fredrikson, J. Ludvigsson and H. J. Arnqvist (2015). "Impact of HbA1c, followed from onset of type 1 diabetes, on the development of severe retinopathy and nephropathy: the VISS Study (Vascular Diabetic Complications in Southeast Sweden)." Diabetes Care 38(2): 308-315. doi: 10.2337/dc14-1203

Obarcanin, E., M. A. Deters, V. Nemitz and S. Laer (2016). "Pharmaceutical care of an adolescent with type 1 diabetes." Med Monatsschr Pharm 39(11): 483-487. doi: not available

Obarcanin, E., M. Kruger, P. Muller, V. Nemitz, H. Schwender, S. Hasanbegovic, S. Kalajdzisalihovic and S. Laer (2015). "Pharmaceutical care of adolescents with diabetes mellitus type 1: the DIADEMA study, a randomized controlled trial." Int J Clin Pharm 37(5): 790-798. doi: 10.1007/s11096-015-0122-3

Obarcanin, E. R., O. (2013). "Hypoglykämie – die unterschätze Gefahr bei Diabetes mellitus." Retrieved 11. June, 2022, from https://www.deutsche-apotheker-zeitung.de/daz-az/2013/daz-30-2013/hypoglykaemie-die-unterschaetze-gefahr-bei-diabetes-mellitus.

Obreli-Neto, P. R., C. M. Guidoni, A. de Oliveira Baldoni, D. Pilger, J. M. Cruciol-Souza, W. P. Gaeti-Franco and R. K. Cuman (2011). "Effect of a 36-month pharmaceutical care program on pharmacotherapy adherence in elderly diabetic and hypertensive patients." Int J Clin Pharm 33(4): 642-649. doi: 10.1007/s11096-011-9518-x

Odegard, P. S. and D. B. Christensen (2012). "MAP study: RCT of a medication adherence program for patients with type 2 diabetes." J Am Pharm Assoc (2003) 52(6): 753-762. doi: 10.1331/JAPhA.2012.11001

Odegard, P. S., A. Goo, J. Hummel, K. L. Williams and S. L. Gray (2005). "Caring for Poorly Controlled Diabetes Mellitus: A Randomized Pharmacist Intervention." Annals of Pharmacotherapy 39(3): 433-440. doi: 10.1345/aph.1E438

Ogle, G. D., S. James, D. Dabelea, C. Pihoker, J. Svennson, J. Maniam, E. L. Klatman and C. C. Patterson (2021). "Global estimates of incidence of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Atlas, 10th edition." Diabetes Research and Clinical Practice: 109083. doi: 10.1016/j.diabres.2021.109083

Omran, D., L. M. Guirguis and S. H. Simpson (2012). "Systematic Review of Pharmacist Interventions to Improve Adherence to Oral Antidiabetic Medications in People with Type 2 Diabetes." Canadian Journal of Diabetes 36(5): 292-299. doi: 10.1016/j.jcjd.2012.07.002

Oppong, E., R. E. Hinson, O. Adeola, O. Muritala and J. P. Kosiba (2021). "The effect of mobile health service quality on user satisfaction and continual usage." Total Quality Management & Business Excellence 32(1-2): 177-198. doi: 10.1080/14783363.2018.1541734

Osterberg, L. and T. Blaschke (2005). "Adherence to Medication." New England Journal of Medicine 353(5): 487-497. doi: 10.1056/NEJMra050100

Palmer, S. C., D. Mavridis, A. Nicolucci, D. W. Johnson, M. Tonelli, J. C. Craig, J. Maggo, V. Gray, G. De Berardis, M. Ruospo, P. Natale, V. Saglimbene, S. V. Badve, Y. Cho, A. C. Nadeau-Fredette, M. Burke, L. Faruque, A. Lloyd, N. Ahmad, Y. Liu, S. Tiv, N. Wiebe and G. F. Strippoli (2016). "Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis." Jama 316(3): 313-324. doi: 10.1001/jama.2016.9400

Park, C., E. Guallar, J. A. Linton, D. C. Lee, Y. Jang, D. K. Son, E. J. Han, S. J. Baek, Y. D. Yun, S. H. Jee and J. M. Samet (2013). "Fasting glucose level and the risk of incident atherosclerotic cardiovascular diseases." Diabetes Care 36(7): 1988-1993. doi: 10.2337/dc12-1577

Park, J. J., P. Kelly, B. L. Carter and P. P. Burgess (1996). "Comprehensive pharmaceutical care in the chain setting." J Am Pharm Assoc (Wash) Ns36(7): 443-451. doi: 10.1016/s1086-5802(16)30099-7

Pascolini, D. and S. P. Mariotti (2012). "Global estimates of visual impairment: 2010." Br J Ophthalmol 96(5): 614-618. doi: 10.1136/bjophthalmol-2011-300539

Patterson, C. C., G. Dahlquist, V. Harjutsalo, G. Joner, R. G. Feltbower, J. Svensson, E. Schober, E. Gyürüs, C. Castell, B. Urbonaité, J. Rosenbauer, V. Iotova, A. V. Thorsson and G. Soltész (2007). "Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989." Diabetologia 50(12): 2439-2442. doi: 10.1007/s00125-007-0824-8

PCNE. (2019a). "PCNE classification of drug-related problems Version 8.03." V8.03. Retrieved 30.08., 2019.

PCNE. (2019b). "PCNE classification of drug-related problems Version 9.0." Retrieved 18.11., 2019.

Perkovic, V., D. de Zeeuw, K. W. Mahaffey, G. Fulcher, N. Erondu, W. Shaw, T. D. Barrett, M. Weidner-Wells, H. Deng, D. R. Matthews and B. Neal (2018). "Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials." Lancet Diabetes Endocrinol 6(9): 691-704. doi: 10.1016/s2213-8587(18)30141-4

Peters, E., R. Pritzkuleit, F. Beske and A. Katalinic (2010). "Demografischer Wandel und Krankheitshäufigkeiten." Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 53(5): 417-426. doi: 10.1007/s00103-010-1050-y

Petrak, F. (2018). "WHO-5 Wohlfühltest (WHO-Five Well-being index)." Retrieved 21. January, 2020, from https://www.cmc-gesundheitsmanagement.de/files/inhalte/cmc/downloads/WHO-5_Institut-Coaching-Prävention-Gesundheitsförderung.pdf.

Pfeffer, M. A., B. Claggett, R. Diaz, K. Dickstein, H. C. Gerstein, L. V. Køber, F. C. Lawson, L. Ping, X. Wei, E. F. Lewis, A. P. Maggioni, J. J. McMurray, J. L. Probstfield, M. C. Riddle, S. D. Solomon and J. C. Tardif (2015). "Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome." N Engl J Med 373(23): 2247-2257. doi: 10.1056/NEJMoa1509225

Phelan, H., K. Lange, E. Cengiz, P. Gallego, E. Majaliwa, J. Pelicand, C. Smart and S. E. Hofer (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes education in children and adolescents." Pediatr Diabetes 19 Suppl 27: 75-83. doi: 10.1111/pedi.12762

Podder, V., V. Lew and S. Ghassemzadeh (2020). SOAP Notes. StatPearls. Treasure Island (FL), StatPearls Publishing.

Pollock, R. F., W. J. Valentine, S. P. Marso, A. Andersen, J. Gundgaard, N. Hallén, D. Tutkunkardas, E. A. Magnuson and J. B. Buse (2019). "Long-term Cost-effectiveness of Insulin

Degludec Versus Insulin Glargine U100 in the UK: Evidence from the Basal-bolus Subgroup of the DEVOTE Trial (DEVOTE 16)." Appl Health Econ Health Policy 17(5): 615-627. doi: 10.1007/s40258-019-00494-3

Polonsky, W. H., D. Hessler, K. J. Ruedy and R. W. Beck (2017). "The Impact of Continuous Glucose Monitoring on Markers of Quality of Life in Adults With Type 1 Diabetes: Further Findings From the DIAMOND Randomized Clinical Trial." Diabetes Care 40(6): 736-741. doi: 10.2337/dc17-0133

R-Foundation. (2022). "A Language and Environment for Statistical Computing." Retrieved 11. June, 2022, from https://cran.r-project.org/mirrors.html.

Rados, D. V., L. C. Pinto, L. R. Remonti, C. B. Leitão and J. L. Gross (2016). "The Association between Sulfonylurea Use and All-Cause and Cardiovascular Mortality: A Meta-Analysis with Trial Sequential Analysis of Randomized Clinical Trials." PLOS Medicine 13(4): e1001992. doi: 10.1371/journal.pmed.1001992

Rauwerda, N. L., K. A. Tovote, A. Peeters, R. Sanderman, P. M. G. Emmelkamp, M. J. Schroevers and J. Fleer (2018). "WHO-5 and BDI-II are acceptable screening instruments for depression in people with diabetes." Diabet Med 35(12): 1678-1685. doi: 10.1111/dme.13779

Resnikoff, S., D. Pascolini, D. Etya'ale, I. Kocur, R. Pararajasegaram, G. P. Pokharel and S. P. Mariotti (2004). "Global data on visual impairment in the year 2002." Bull World Health Organ 82(11): 844-851. doi: /s0042-96862004001100009

Rewers, M. J., K. Pillay, C. de Beaufort, M. E. Craig, R. Hanas, C. L. Acerini and D. M. Maahs (2014). "ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and monitoring of glycemic control in children and adolescents with diabetes." Pediatr Diabetes 15 Suppl 20: 102-114. doi: 10.1111/pedi.12190

Riddell, M. C., I. W. Gallen, C. E. Smart, C. E. Taplin, P. Adolfsson, A. N. Lumb, A. Kowalski, R. Rabasa-Lhoret, R. J. McCrimmon, C. Hume, F. Annan, P. A. Fournier, C. Graham, B. Bode, P. Galassetti, T. W. Jones, I. S. Millán, T. Heise, A. L. Peters, A. Petz and L. M. Laffel (2017). "Exercise management in type 1 diabetes: a consensus statement." Lancet Diabetes Endocrinol 5(5): 377-390. doi: 10.1016/s2213-8587(17)30014-1

Ritzel, R., R. Roussel, A. Giaccari, J. Vora, C. Brulle-Wohlhueter and H. Yki-Järvinen (2018). "Better glycaemic control and less hypoglycaemia with insulin glargine 300 U/mL vs glargine 100 U/mL: 1-year patient-level meta-analysis of the EDITION clinical studies in people with type 2 diabetes." Diabetes Obes Metab 20(3): 541-548. doi: 10.1111/dom.13105

Rohan, J. M., J. R. Rausch, J. S. Pendley, A. M. Delamater, L. Dolan, G. Reeves and D. Drotar (2014). "Identification and prediction of group-based glycemic control trajectories during the transition to adolescence." Health Psychol 33(10): 1143-1152. doi: 10.1037/hea0000025

Rose, O., H. Derendorf, S. Erzkamp, K. Fujita, A. Hartl, K. Hoti, I. Krass, E. Obarcanin, J. Saevels, P. Srimongkon, M. Teichert and R. T. Tsuyuki (2018). "Development of clinical pharmacy services in Australia, Austria, Belgium, Bosnia-Herzegovina, Canada, Germany, Japan, Kosovo, Switzerland, the Netherlands, Thailand, USA and correlation with educational standards, level of research, and implemen." Int J Clin Pharmacol Ther 56(11): 518-530. doi: 10.5414/cp203264

Rose, O., H. Mennemann, C. John, M. Lautenschlager, D. Mertens-Keller, K. Richling, I. Waltering, S. Hamacher, M. Felsch, L. Herich, K. Czarnecki, C. Schaffert, U. Jaehde and J. Koberlein-Neu (2016). "Priority Setting and Influential Factors on Acceptance of Pharmaceutical Recommendations in Collaborative Medication Reviews in an Ambulatory Care Setting - Analysis of a Cluster Randomized Controlled Trial (WestGem-Study)." PLoS One 11(6): e0156304. doi: 10.1371/journal.pone.0156304

Rösen, P., P. P. Nawroth, G. King, W. Möller, H. J. Tritschler and L. Packer (2001). "The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society." Diabetes Metab Res Rev 17(3): 189-212. doi: 10.1002/dmrr.196

Rosenstock, J., S. E. Kahn, O. E. Johansen, B. Zinman, M. A. Espeland, H. J. Woerle, E. Pfarr, A. Keller, M. Mattheus, D. Baanstra, T. Meinicke, J. T. George, M. von Eynatten, D. K. McGuire and N. Marx (2019a). "Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial." Jama 322(12): 1155-1166. doi: 10.1001/jama.2019.13772

Rosenstock, J., V. Perkovic, O. E. Johansen, M. E. Cooper, S. E. Kahn, N. Marx, J. H. Alexander, M. Pencina, R. D. Toto, C. Wanner, B. Zinman, H. J. Woerle, D. Baanstra, E. Pfarr, S. Schnaidt, T. Meinicke, J. T. George, M. von Eynatten and D. K. McGuire (2019b). "Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial." Jama 321(1): 69-79. doi: 10.1001/jama.2018.18269

Saeedi, P., I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A. A. Motala, K. Ogurtsova, J. E. Shaw, D. Bright and R. Williams (2019). "Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition." Diabetes Res Clin Pract 157: 107843. doi: 10.1016/j.diabres.2019.107843

Samsa, G. P., J. T. Hanlon, K. E. Schmader, M. Weinberger, E. C. Clipp, K. M. Uttech, I. K. Lewis, P. B. Landsman and H. J. Cohen (1994). "A summated score for the medication appropriateness index: development and assessment of clinimetric properties including content validity." J Clin Epidemiol 47(8): 891-896. doi: 10.1016/0895-4356(94)90192-9

Santamarina, M. and C. J. Carlson (2019). "Review of the cardiovascular safety of dipeptidyl peptidase-4 inhibitors and the clinical relevance of the CAROLINA trial." BMC cardiovascular disorders 19(1): 60-60. doi: 10.1186/s12872-019-1036-0

Santschi, V., A. Chiolero, G. Paradis, A. L. Colosimo and B. Burnand (2012). "Pharmacist interventions to improve cardiovascular disease risk factors in diabetes: a systematic review and meta-analysis of randomized controlled trials." Diabetes Care 35(12): 2706-2717. doi: 10.2337/dc12-0369

Sarkadi, A. and U. Rosenqvist (2004). "Experience-based group education in Type 2 diabetes: a randomised controlled trial." Patient Educ Couns 53(3): 291-298. doi: 10.1016/j.pec.2003.10.009

Sartore, G., N. C. Chilelli, S. Burlina, P. Di Stefano, F. Piarulli, D. Fedele, A. Mosca and A. Lapolla (2012). "The importance of HbA1c and glucose variability in patients with type 1 and

type 2 diabetes: outcome of continuous glucose monitoring (CGM)." Acta Diabetol 49 Suppl 1: S153-160. doi: 10.1007/s00592-012-0391-4

Saturni, S., F. Bellini, F. Braido, P. Paggiaro, A. Sanduzzi, N. Scichilone, P. A. Santus, L. Morandi and A. Papi (2014). "Randomized Controlled Trials and real life studies. Approaches and methodologies: a clinical point of view." Pulm Pharmacol Ther 27(2): 129-138. doi: 10.1016/j.pupt.2014.01.005

Schlüter, S., D. Deiss, B. Gehr, K. Lange, S. von Sengbusch, A. Thomas, R. Ziegler and G. Freckmann (2021). "Glukosemessung und -kontrolle bei Patienten mit Typ-1- oder Typ-2-Diabetes." Diabetologie und Stoffwechsel 16(S 02): S119-1141. doi: 10.1055/a-1515-8660

Schulz, K. F., D. G. Altman and D. Moher (2010). "CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials." BMC Med 8: 18. doi: 10.1186/1741-7015-8-18

Seidling, H. M., A. F. J. Send, J. Bittmann, K. Renner, B. Dewald, D. Lange, T. Bruckner and W. E. Haefeli (2017). "Medication review in German community pharmacies - Post-hoc analysis of documented drug-related problems and subsequent interventions in the ATHINA-project." Res Social Adm Pharm 13(6): 1127-1134. doi: 10.1016/j.sapharm.2016.10.016

Silva, B. B. and C. Fegadolli (2020). "Implementation of pharmaceutical care for older adults in the brazilian public health system: a case study and realistic evaluation." BMC Health Services Research 20(1): 37. doi: 10.1186/s12913-020-4898-z

SirmaMedicalSystems. (2021). "Features of the Diabetes:M application." Retrieved 11. June, 2022, from https://www.diabetes-m.com/features/.

Škrha, J., J. Šoupal, J. Škrha, Jr. and M. Prázný (2016). "Glucose variability, HbA1c and microvascular complications." Rev Endocr Metab Disord 17(1): 103-110. doi: 10.1007/s11154-016-9347-2

Smart, C. E., F. Annan, L. A. Higgins, E. Jelleryd, M. Lopez and C. L. Acerini (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Nutritional management in children and adolescents with diabetes." Pediatr Diabetes 19 Suppl 27: 136-154. doi: 10.1111/pedi.12738

Smith-Palmer, J., M. Brändle, R. Trevisan, M. Orsini Federici, S. Liabat and W. Valentine (2014). "Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes." Diabetes Res Clin Pract 105(3): 273-284. doi: 10.1016/j.diabres.2014.06.007

Šoupal, J., J. Škrha, Jr., M. Fajmon, E. Horová, M. Mráz, J. Škrha and M. Prázný (2014). "Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control." Diabetes Technol Ther 16(4): 198-203. doi: 10.1089/dia.2013.0205

Steineck, I., J. Cederholm, B. Eliasson, A. Rawshani, K. Eeg-Olofsson, A. M. Svensson, B. Zethelius, T. Avdic, M. Landin-Olsson, J. Jendle and S. Gudbjörnsdóttir (2015). "Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18,168 people with type 1 diabetes: observational study." Bmj 350: h3234. doi: 10.1136/bmj.h3234

Tamayo, T., R. Brinks, A. Hoyer, O. S. Kuss and W. Rathmann (2016). "The Prevalence and Incidence of Diabetes in Germany." Dtsch Arztebl Int 113(11): 177-182. doi: 10.3238/arztebl.2016.0177

Tichelaar, J., S. H. Uil den, N. F. Antonini, M. A. van Agtmael, T. P. G. M. de Vries and M. C. Richir (2016). "A 'SMART' way to determine treatment goals in pharmacotherapy education." British journal of clinical pharmacology 82(1): 280-284. doi: 10.1111/bcp.12919

TODAY-Studygroup (2013a). "Effects of Metformin, Metformin Plus Rosiglitazone, and Metformin Plus Lifestyle on Insulin Sensitivity and β-Cell Function in TODAY." Diabetes Care 36(6): 1749-1757. doi: 10.2337/dc12-2393

TODAY-Studygroup (2013b). "Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial." Diabetes Care 36(6): 1735-1741. doi: 10.2337/dc12-2420

Trawley, S., J. Browne, V. Hagger, C. Hendrieckx, H.-T. Elizabeth, F. Pouwer, T. C. Skinner and S. Jane (2016). "The Use of Mobile Applications Among Adolescents with Type 1 Diabetes: Results from Diabetes MILES Youth—Australia." Diabetes Technology & Therapeutics 18(12): 813-819. doi: 10.1089/dia.2016.0233

Tricco, A. C., N. M. Ivers, J. M. Grimshaw, D. Moher, L. Turner, J. Galipeau, I. Halperin, B. Vachon, T. Ramsay, B. Manns, M. Tonelli and K. Shojania (2012). "Effectiveness of quality improvement strategies on the management of diabetes: a systematic review and meta-analysis." Lancet 379(9833): 2252-2261. doi: 10.1016/s0140-6736(12)60480-2

Tully, C., L. Aronow, E. Mackey and R. Streisand (2016). "Physical Activity in Youth With Type 1 Diabetes: a Review." Curr Diab Rep 16(9): 85. doi: 10.1007/s11892-016-0779-6

Tumminia, A., S. Crimi, L. Sciacca, M. Buscema, L. Frittitta, S. Squatrito, R. Vigneri and L. Tomaselli (2015). "Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial." Diabetes Metab Res Rev 31(1): 61-68. doi: 10.1002/dmrr.2557

Tuomi, T., N. Santoro, S. Caprio, M. Cai, J. Weng and L. Groop (2014). "The many faces of diabetes: a disease with increasing heterogeneity." Lancet 383(9922): 1084-1094. doi: 10.1016/s0140-6736(13)62219-9

UKPDS-Group (1998a). "Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34)." The Lancet 352(9131): 854-865. doi: 10.1016/S0140-6736(98)07037-8

UKPDS-Group (1998b). "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)." The Lancet 352(9131): 837-853. doi: 10.1016/S0140-6736(98)07019-6

Ullrich, G. (2014). "Transition: Mehr als ein „Transfer“." Dtsch Arztebl 111(37). doi: not available

UNDP. (2013). "Human Developement Report 2013." Retrieved 11. June, 2022, from https://www.undp.org/publications/human-development-report-2013.

UNDP. (2020). "Human Development Report 2020 " Retrieved 11. June, 2022, from https://hdr.undp.org/content/human-development-report-2020.

Usher-Smith, J. A., M. Thompson, A. Ercole and F. M. Walter (2012). "Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review." Diabetologia 55(11): 2878-2894. doi: 10.1007/s00125-012-2690-2

van Mil, J. F., L. T. Westerlund, K. E. Hersberger and M. A. Schaefer (2004). "Drug-Related Problem Classification Systems." Annals of Pharmacotherapy 38(5): 859-867. doi: 10.1345/aph.1D182

Viswanathan, V. (2015). "Preventing microvascular complications in type 1 diabetes mellitus." Indian J Endocrinol Metab 19(Suppl 1): S36-38. doi: 10.4103/2230-8210.155382

Wang, F., Y. He, R. Zhang, Q. Zeng and X. Zhao (2017). "Combination therapy of metformin plus dipeptidyl peptidase-4 inhibitor versus metformin plus sulfonylurea and their association with a decreased risk of cardiovascular disease in type 2 diabetes mellitus patients." Medicine (Baltimore) 96(36): e7638. doi: 10.1097/md.0000000000007638

Wang, X., W. Shu, J. Du, M. Du, P. Wang, M. Xue, H. Zheng, Y. Jiang, S. Yin, D. Liang, R. Wang and L. Hou (2019). "Mobile health in the management of type 1 diabetes: a systematic review and meta-analysis." BMC Endocrine Disorders 19(1): 21. doi: 10.1186/s12902-019-0347-6

Wanner, C., S. E. Inzucchi and B. Zinman (2016). "Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes." N Engl J Med 375(18): 1801-1802. doi: 10.1056/NEJMc1611290

WEF. (2019). "The Global Competitiveness Report." Retrieved 11. June, 2022, from https://www3.weforum.org/docs/WEF_Global_Risk_Report_2020.pdf.

Wermeille, J., M. Bennie, I. Brown and J. McKnight (2004). "Pharmaceutical care model for patients with type 2 diabetes: integration of the community pharmacist into the diabetes team--a pilot study." Pharm World Sci 26(1): 18-25. doi: 10.1023/b:phar.0000013465.24857.a8

Whipple, A. (1938). "The surgical therapy of hyperinsulinism." J Int Chir. 3: 237–276. doi: not available

WHO. (2019). "Recommendations on digital interventions for health system strengthening." Retrieved 11. June, 2022, from https://apps.who.int/iris/bitstream/handle/10665/311941/9789241550505-eng.pdf?ua=1.

Wiviott, S. D., I. Raz, M. P. Bonaca, O. Mosenzon, E. T. Kato, A. Cahn, M. G. Silverman, T. A. Zelniker, J. F. Kuder, S. A. Murphy, D. L. Bhatt, L. A. Leiter, D. K. McGuire, J. P. H. Wilding, C. T. Ruff, I. A. M. Gause-Nilsson, M. Fredriksson, P. A. Johansson, A. M. Langkilde and M. S. Sabatine (2019). "Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes." N Engl J Med 380(4): 347-357. doi: 10.1056/NEJMoa1812389

Wolfsdorf, J., N. Glaser and M. Sperling (2006). "Diabetic Ketoacidosis in Infants, Children, and Adolescents A consensus statement from the American Diabetes Association." Diabetes care 29: 1150-1159. doi: 10.2337/dc06-9099

Wolfsdorf, J. I., N. Glaser, M. Agus, M. Fritsch, R. Hanas, A. Rewers, M. A. Sperling and E. Codner (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state." Pediatr Diabetes 19 Suppl 27: 155-177. doi: 10.1111/pedi.12701

Wright, A., D. F. Sittig, J. McGowan, J. S. Ash and L. L. Weed (2014). "Bringing science to medicine: an interview with Larry Weed, inventor of the problem-oriented medical record." J Am Med Inform Assoc 21(6): 964-968. doi: 10.1136/amiajnl-2014-002776

Wright, E. E., K. Morgan, D. K. Fu, N. Wilkins and W. J. Guffey (2020). "Time in Range: How to Measure It, How to Report It, and Its Practical Application in Clinical Decision-Making." Clinical Diabetes 38(5): 439-448. doi: 10.2337/cd20-0042

Yamada, T., R. Kamata, K. Ishinohachi, N. Shojima, S. Ananiadou, H. Nom, T. Yamauchi and T. Kadowaki (2018). "Biosimilar vs originator insulins: Systematic review and meta-analysis." Diabetes Obes Metab 20(7): 1787-1792. doi: 10.1111/dom.13291

Yang, S. W., K. H. Park and Y. J. Zhou (2016). "The Impact of Hypoglycemia on the Cardiovascular System: Physiology and Pathophysiology." Angiology 67(9): 802-809. doi: 10.1177/0003319715623400

Yasmin, F., N. Nahar, B. Banu, L. Ali, R. Sauerborn and A. Souares (2020). "The influence of mobile phone-based health reminders on patient adherence to medications and healthy lifestyle recommendations for effective management of diabetes type 2: a randomized control trial in Dhaka, Bangladesh." BMC Health Serv Res 20(1): 520. doi: 10.1186/s12913-020-05387-z

Yi, S. W., S. Park, Y. H. Lee, H. J. Park, B. Balkau and J. J. Yi (2017). "Association between fasting glucose and all-cause mortality according to sex and age: a prospective cohort study." Sci Rep 7(1): 8194. doi: 10.1038/s41598-017-08498-6

Zeitler, P., S. Arslanian, J. Fu, O. Pinhas-Hamiel, T. Reinehr, N. Tandon, T. Urakami, J. Wong and D. M. Maahs (2018). "ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth." Pediatr Diabetes 19 Suppl 27: 28-46. doi: 10.1111/pedi.12719

Zelniker, T. A., S. D. Wiviott, I. Raz, K. Im, E. L. Goodrich, M. P. Bonaca, O. Mosenzon, E. T. Kato, A. Cahn, R. H. M. Furtado, D. L. Bhatt, L. A. Leiter, D. K. McGuire, J. P. H. Wilding and M. S. Sabatine (2019). "SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials." Lancet 393(10166): 31-39. doi: 10.1016/s0140-6736(18)32590-x

Ziegler, D., J. Keller, C. Maier and J. Pannek (2019). "Diabetische Neuropathie." Diabetologie und Stoffwechsel 14(S 02): S243-S257. doi: 10.1055/a-0899-0129

Zinman, B., C. Wanner, J. M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, M. Mattheus, T. Devins, O. E. Johansen, H. J. Woerle, U. C. Broedl and S. E. Inzucchi (2015). "Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes." N Engl J Med 373(22): 2117-2128. doi: 10.1056/NEJMoa1504720

Zoungas, S., A. Patel, J. Chalmers, B. E. de Galan, Q. Li, L. Billot, M. Woodward, T. Ninomiya, B. Neal, S. MacMahon, D. E. Grobbee, A. P. Kengne, M. Marre and S. Heller (2010). "Severe Hypoglycemia and Risks of Vascular Events and Death." New England Journal of Medicine 363(15): 1410-1418. doi: 10.1056/NEJMoa1003795

VII Abbreviations

ABDA: Bundesvereinigung Deutscher Apothekerverbände e. V

ApBetrO: Apothekenbetriebsordnung

ADA: American Diabetes Association

AGEs: advanced glycation endproducts

ATP: adenosine triphosphate

BAK: Bundesapothekerkammer

BÄK: Bundesärztekammer

BGAT: blood glucose awareness training

BMBF: Bundesministerium für Bildung und Forschung

BMI: body mass index

BOT: basal supported oral therapy

BP: blood pressure

CGM(S): continuous glucose monitoring (system)

CI: confidence interval

CRF(s): case report form(s)

CSII: continuous subcutaneous insulin infusion

CT: conventional insulin therapy

CV: cardiovascular

CVD: cardiovascular disease

DAV: Deutscher Apothekerverband

DCCT: Diabetes Control and Complications Trial

DDG: Deutsche Diabetes Gesellschaft

DDH: Deutsche Diabetes Hilfe

DIADEMA: DIabetes in ADolescents Engagement and Monitoring in phArmacies

DiGAV: Digitale-Gesundheits-anwendungen-Verordnung

DKA: diabetic ketoacidosis

DKD: diabetic kidney disease

DPP-IV inhibitors: dipeptidyl peptidase IV inhibitors

DRP(s): drug-related problem(s)

EDIC: Epidemiology of Diabetes Interventions and Complications

eGFR: estimated glomerular filtration rate

eHealth: electronic health

EMDIA: Effective Medication therapy management for DIAbetes patients

FBG: fasting blood glucose

FDA: US Food and Drug Administration

FFAs: free fatty acids

GBA: Gemeinsamer Bundesausschluss der Krankenkassen

GCP: good clinical practice

GLP-1 RAs: glucagon like peptide receptor agonists

HbA1c: glycated hemoglobin

HDL: high-density lipoproteins

HHS: hyperosmolar hyperglycemic state

HRQoL: health-related quality of life

ICT: intensive conventional insulin therapy

IFG: impaired fasting blood glucose

IGT: impaired glucose tolerance

IM: intramuscular

ISPAD: International Society for Pediatric and Adolescent Diabetes

IV: intravenous

MAI: medication appropriateness index

MDK: Medizinischer Dienst der Krankenversicherung

mHealth: mobile Health

MTM: medication therapy management

n: number of analyzed patients

n.a.: not available

NPH: neutral protamine Hagedorn

NVL: Nationale Versorgungsleitlinie

OAD(s): oral antidiabetic drug(s)

oGTT: oral glucose tolerance test

OSCEs: Objective structured clinical examinations

PCNE: pharmaceutical care network Europe

PhC: pharmaceutical care

PTA: pharmaceutical technical assistant

QoL: quality of life

RCT(s): randomized controlled trial(s)

SC: subcutaneous or subcutaneously

SD: standard deviation

SF-36: Short Form 36

SGLT-2: sodium dependent glucose co-transporter 2

SIT: supplementary insulin therapy

SMBG: self-measurement of blood glucose

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

TiAb: Title/Abstracts

TG: triglyceride

TIR: time in range

UKPDS: UK Prospective Diabetes Study

UNDP: united nations development programme

WEF: world economic forum

WHO: world health organization

VIII Figures

IX Tables

X Attachment

(1) Calculation of the insulin doses and guideline recommendations

Calculation of the amount of carbohydrates covered by one insulin dose – "500-rule" (Danne et al. 2018):

$$\frac{500}{daily\ insulin\ doses\ (basal + bolus)\ [IU]} = amount\ of\ carbohydrates\ [g]\ covered\ by\ 1\ IU\ insulin$$

Calculation of correction doses for patients, which use rapid-acting insulin and measure blood glucose levels in mg/dl – "1800-rule" (Danne et al. 2018):

$$\frac{1800}{daily\ insulin\ doses\ (basal + bolus)\ [IU]} = reduction\ of\ blood\ glucose\ levels\ \left[\frac{mg}{dL}\right] per\ 1\ IU\ of\ rapid-acting\ insulin$$

Calculation of correction doses for patients, which use rapid-acting insulin and measure blood glucose levels in mol/l – "100-rule" (Danne et al. 2018):

$$\frac{100}{daily\ insulin\ doses\ (basal + bolus)\ [IU]} = reduction\ of\ blood\ glucose\ levels\ \left[\frac{mol}{L}\right] per\ 1\ IU\ of\ rapid-acting\ insulin$$

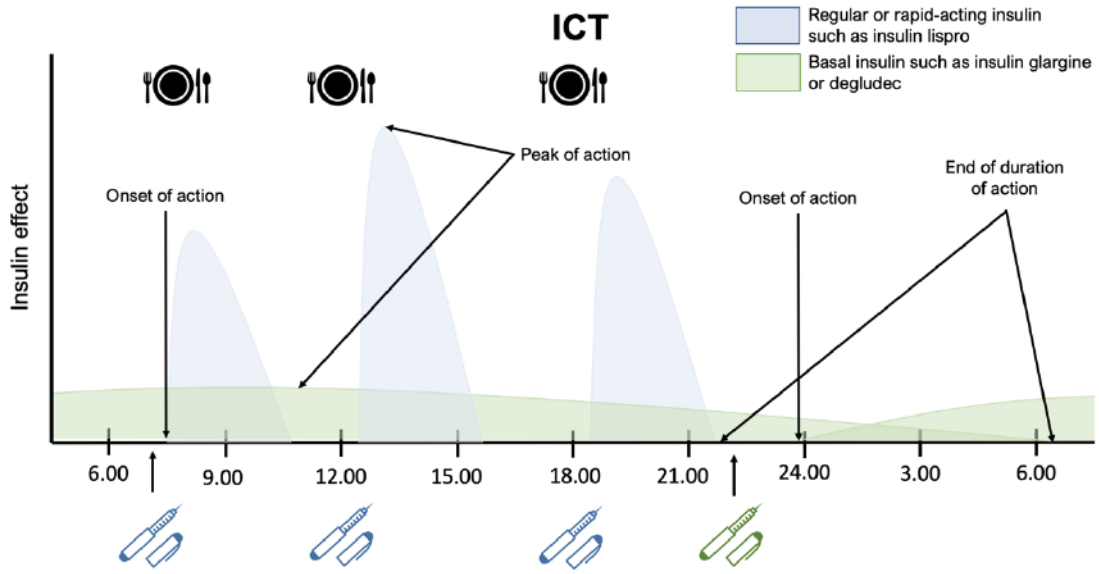
Calculation of correction doses for patients, which use regular insulin and measure blood glucose levels in mg/dl – "1500-rule" (Danne et al. 2018):

$$\frac{1500}{daily\ insulin\ doses\ (basal + bolus)\ [IU]} = reduction\ of\ blood\ glucose\ levels\ \left[\frac{mg}{dL}\right] per\ 1\ IU\ of\ regular\ insulin$$

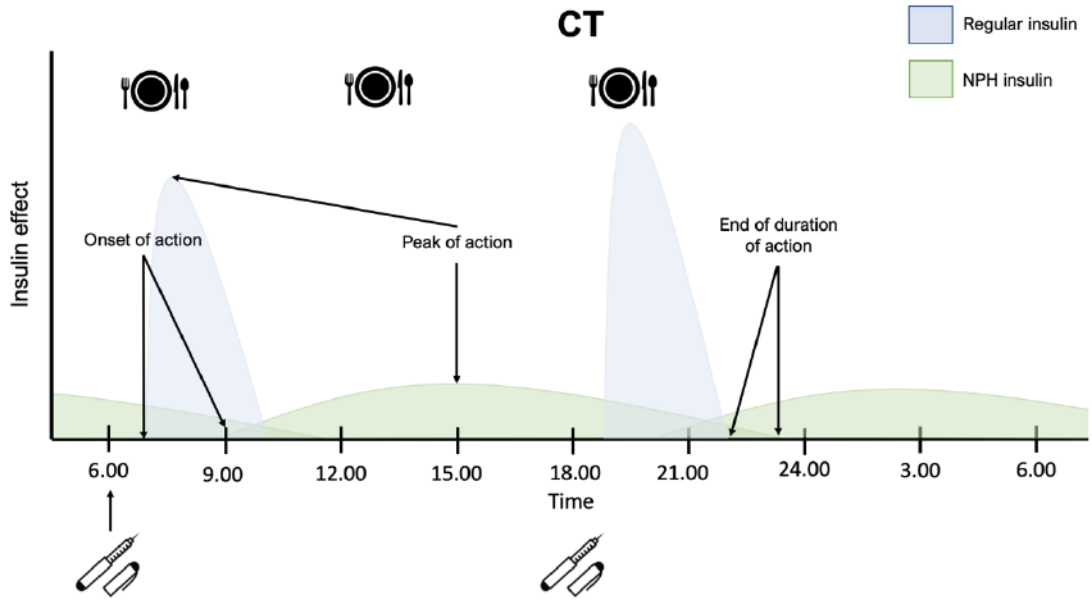
Calculation of correction doses for patients, which use regular insulin and measure blood glucose levels in mol/l – "83-rule" (Danne et al. 2018):

$$\frac{83}{daily\ insulin\ doses\ (basal + bolus)\ [IU]} = reduction\ of\ blood\ glucose\ levels\ \left[\frac{mol}{L}\right] per\ 1\ IU\ of\ regular\ insulin$$

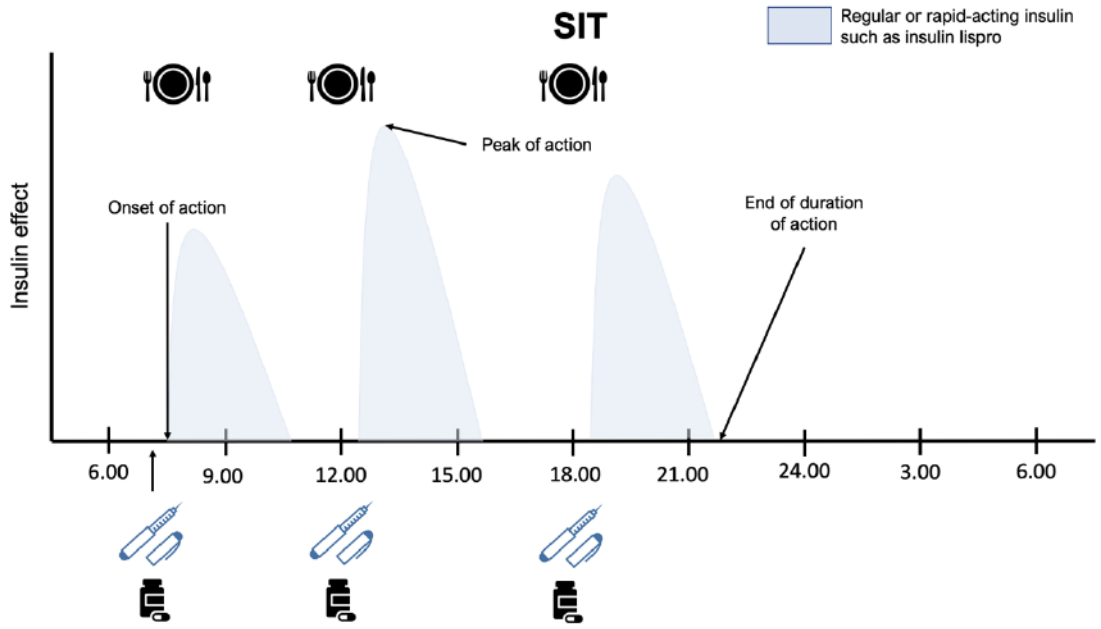
(2) Figures: Different types of insulin therapy



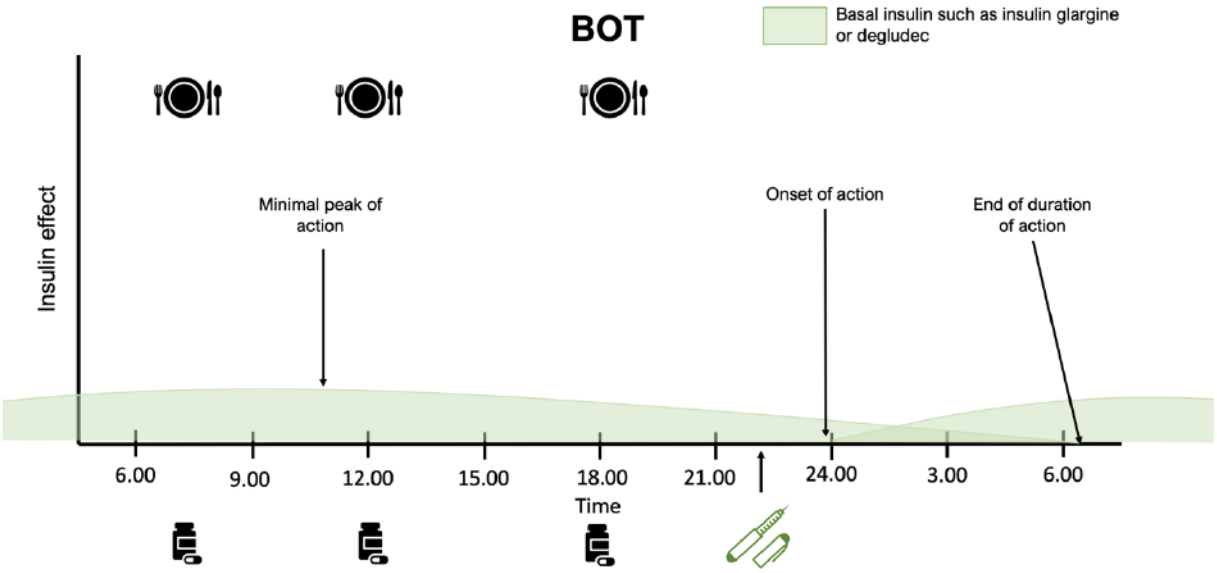
Intensified conventional insulin therapy with bolus and basal insulin



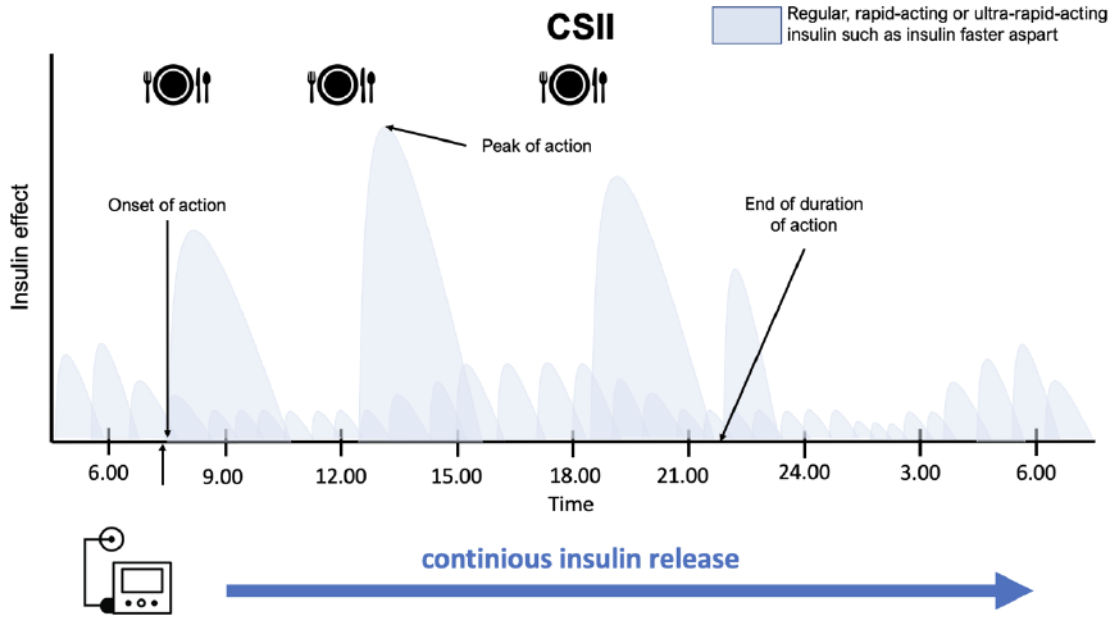
Conventional therapy with premixed insulin



Supplementary insulin therapy with bolus insulin and oral antihyperglycemic treatment



Basal-supported oral therapy with basal insulin and oral antihyperglycemic treatment



Continuous subcutaneous insulin infusion – insulin pump therapy

(3) Diabetes therapy for adolescents with type 2 diabetes mellitus

Few studies have examined the management of T2DM in the pediatric age group. The largest clinical trial, Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY study), showed that oral agent monotherapy does not maintain lasting glycemic control in approximately 50% of patients with adolescent-onset T2DM, and that an HbA1c value >6.3% in females and >5.6% in males after implementing initial metformin monotherapy predicts glycemic deterioration. (TODAY-Studygroup 2013a) Thus, it is important to optimize treatment using a combination of pharmacologic and non-pharmacologic interventions, with close monitoring and follow-up. One important factor for effectively treating adolescents with T2DM is that both the family and child should understand the medical implications of obesity and T2DM. The health beliefs and behaviors of the child's or adolescent's family and community are relevant to the design and implementation of an effective behavioral plan and to promote long-term changes in eating behavior and physical activity. Support and counseling are need from a multidisciplinary team that includes an endocrinologist, nurse educator, dietitian (especially for obese patients), mental health professional, and sometimes an exercise physiologist. Patients should receive detailed information regarding the durability of glycemic control and the early emergence of complications. Smoking cessation and the negative effect of alcohol on glycemic control should also be discussed with adolescent patients. (Zeitler et al. 2018)

Despite the results of the TODAY study, the initial drug treatment for children and adolescents with T2DM according to the current ISPAD guidelines is metformin and/or insulin, alone or in combination. Metformin in addition to lifestyle changes is selected if the patient has no symptoms of diabetes and the HbA1c value is <8.5%. Insulin therapy is required if the patient has symptoms such as ketoacidosis or an HbA1c value >8.5%; initially, most of these patients are treated with basal insulin only. Treatment goals are, for example, to avoid diabetes complications and to achieve or maintain glycemic control. The ISPAD guidelines recommend that if glycemic control (HbA1c value <7.0%) cannot be achieved within 4 months of treatment with metformin and basal insulin, prandial insulin should be added. (Zeitler et al. 2018)

(4) Mode of action of non-insulin therapy options for patients with type 2 diabetes mellitus

Mode of action of metformin (biguanide derivate)

Metformin inhibits mitochondrial complex 1 (NADH-ubiquinone oxidoreductase) of the respiratory chain in the liver, leading to a reduced energy supply in favor of an increase in anaerobic glycolysis due to a reduction in adenosine triphosphate (ATP) synthesis. In addition, hepatic glucose release and liver gluconeogenesis are decreased. These changes lead to increased glucose uptake in peripheral tissues, e.g., skeletal muscles and fat. (Mutschler 2020)

Mode of action of alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors are not absorbed by the intestinal tract; in the upper parts of the intestinal tract they inhibit the metabolism and absorption of carbohydrates from ingested food. Hence, the blood glucose levels increase more slowly, and peak at a lower level. (Mutschler 2020) Today, therapy with alpha-glucosidase inhibitors (such as acarbose) is obsolete and not recommended in the current American or German guidelines (see Figure 7).

Mode of action of sulfonylureas and glinides

Sulfonylureas and glinides are calcium channel blockers; by inhibiting these channels in the beta cells of the pancreas, the cytosolic calcium concentration is increased. A higher cytosolic calcium concentration in pancreatic beta cells leads to insulin secretion. Sulfonylureas and glinides bind at different subunits of the calcium channel; hence, they differ in their onset of action and efficacy. All glinides have a short duration of action and therefore a lower risk for hypoglycemia compared to sulfonylureas. Sulfonylureas and glinides are only effective if the T2DM patient has enough beta cells in the pancreas left to secrete sufficient insulin. (Mutschler 2020)

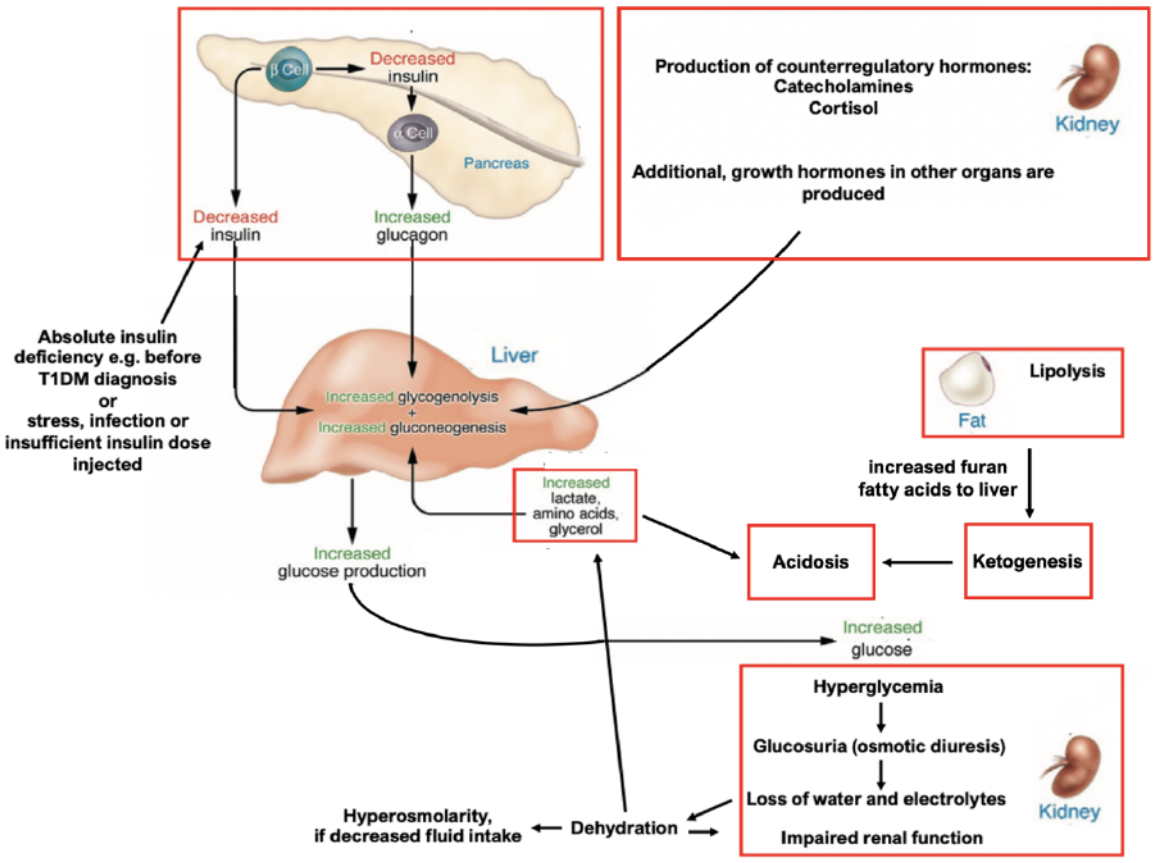
Mode of action of glucagon like peptide receptor agonists and dipeptidyl peptidase IV inhibitors

GLP-1 RAs stimulate insulin secretion and inhibit glucagon distribution by binding to the GLP-1 receptor in the intestinal tract. This leads to many positive effects for diabetes patients, such as delayed emptying of the stomach and therefore a more rapid feeling of satiation. DPP-IV inhibitors can inhibit cleavage of GLP-1 by DPP-IV. GLP-1 stimulates insulin secretion after eating, and the activity of this hormone leads to a reduction of glucagon secretion in the pancreatic alpha cells and increases insulin secretion in the beta cells. (Mutschler 2020)

(5) Diagnosis and therapy of DKA and HHS

Biochemical criteria and clinical signs are used for DKA diagnosis. The biochemical criteria are blood glucose levels above 200 mg/dL (hyperglycemia), venous pH <7.3, serum bicarbonate <15 mmol/L, and ketones in the urine (ketonuria). Diabetes patients have the following clinical signs during DKA: abdominal pain, acetone smell, blurred vision, confusion, deep sighing respiration, dehydration, drowsiness, tachycardia, tachypnea, nausea, and occasionally vomiting and decreased consciousness. In severe cases the patient can fall into coma.

DKA treatment depends on the symptoms; patients who are minimally dehydrated and who can drink autonomously are given oral fluids and SC insulin injection. If this has no effect then intravenous (IV) therapy is recommended, which is also used for patients with dehydration, hyperventilation, and vomiting. At the beginning of treatment, 10 mL/kg body weight of 0.9% saline is given IV over 1 hour, an electrocardiogram (ECG) is recommended and, if required, potassium chloride is given. After 1 hour of fluid infusion, infusion doses of 0.05 to 0.1 insulin units per kg bodyweight per hour are recommended, and hourly blood glucose readings are taken. The neurological status of the patient and their fluid input and output are observed, and ECG monitoring is implemented. Depending on the blood glucose levels, glucose is added into the given fluids; to obtain the desired serum sodium concentration, additional sodium can also be added to the 0.45% or 0.9% saline solution. If the patient's status improves, the IV insulin therapy is changed to SC injections of insulin at appropriate intervals. Patients who are in shock, have reduced conscious, or are in coma need an airway tube and 100% oxygen for breathing and 0.9% saline infusion (10 to 20 mL/kg bodyweight) for an additional 1–2 hours. If there is no improvement or the patient (with milder symptoms initially) shows neurological warning signs during treatment, then mannitol (0.5–1.0 g/kg bodyweight) and fluids are given IV to maintain normal blood pressure (BP). Cranial imaging should also be considered. (Wolfsdorf et al. 2018) The pathophysiological process of DKA development is shown in the following figure.



The development of DKA due to absolute insulin deficiency or insufficient insulin dose injected during insulin therapy in T1DM patients modified according to Cryer et al (Cryer et al. 2003) and Wolfsdorf et al (Wolfsdorf et al. 2006)

The current criteria for HHS diagnosis according to the ISPAD guidelines (Wolfsdorf et al. 2018) include the following symptoms and signs:

- Plasma glucose concentration >600 mg/dL
- Arterial pH >7.30 and venous pH >7.25
- Serum bicarbonate >15 mmol/L
- Low ketonuria
- Effective serum osmolality >320 mOsm/kg
- In some cases, approximately 50% obtundation, combativeness, or seizures

Similar to the treatment of DKA, if the patient has HHS then fluid intake (oral or IV) and eventually potassium hydrochloride substitution is required. The insulin sensitivity is an important aspect that should be considered by giving insulin SC or IV; therefore, the guidelines recommend less insulin (0.05 U/kg bodyweight per hour) compared to the treatment of DKA in T1DM patients. (Haak et al. 2018, Wolfsdorf et al. 2018)

(6) Recommended, relevant screening methods, therapeutic aims and important additional information of long-term diabetes microvascular and macrovascular complications modified according to ISPAD guidelines and DDG guidelines (Donaghue et al. 2018, Hammes et al. 2019, Merker et al. 2019, Ziegler et al. 2019):

	Screening methods	Risk factors	Important additional information
Nephropathy	- Screen for albuminuria by measuring urinary albumin/ creatinine ratio - Determine eGFR at least once per year or, depending on the current eGFR, every 3 to 6 months	- Poor glycemic control - High BP or hypertension - Smoking - Urarthritis - Extremely elevated protein intake - Lipid abnormalities	- Increased risk for hypoglycemia (reduced renal elimination of insulin or oral antidiabetic drugs – increased half-life period) - Dosage adjustments of antidiabetic drugs or other medications pursuant to the patients' renal clearance
Neuropathy and diabetic foot	- Patient medical or medication history - Specific tests include assessment of sensation, vibration, and reflexes in the feet for peripheral neuropathy - Measurement of heart rate variability to screen for cardiac autonomic neuropathy	- Poor glycemic control - Long diabetes duration - Hypertension - Peripheral vascular disease - Diabetic retinopathy and nephropathy - Dyslipidemia - Higher body mass index (BMI) - Genetics	- Non-steroidal anti-inflammatory drugs are not indicated to treat neuropathic pain due to long-term substance-related renal and CV risks - Hypoglycemia, unawareness, or extreme, unexplainable plasma glucose fluctuations can indicate autonomic neuropathy
Retinopathy	- Screening for diabetic retinopathy includes an examination through dilated pupils via mydriatic ophthalmoscopy or fundal photography	- Poor glycemic control - Long diabetes duration - Hypertension - (Diabetic) Nephropathy - Hormonal changes, e.g., puberty or pregnancy - Smoking (T1DM) - Higher BMI - Lipid abnormalities - Male sex	- Early ophthalmic therapy - Laser treatment and intravitreal injections of anti-VEGF agents reduce the rate of visual loss for individuals with vision-threatening stages of retinopathy - Management of hypertension - Therapy intensification with insulin (CSII, ICT) and with GLP-1ras should be accompanied by careful consideration of a deterioration in retinopathy

BMI: body mass index, BP: blood pressure, CSII: continuous subcutaneous insulin infusion, CV: cardiovascular, GLP-1 Ras: glucagon-like-peptide-1 receptor agonists, eGFR: estimated glomerular filtration rate, ICT: intensified conventional insulin therapy, T1DM: type 1 diabetes mellitus

(7) WHO-5 well-being index questionnaire:

INSTITUT für Coaching • Prävention Gesundheitsförderung
Prof. Dr. Frank Petrak

Name _____ **Datum:**_____

WHO-5 Wohlfühltest (WHO-Five Well-being index)

Wählen Sie zu jeder Aussage jeweils eine Antwort, die Ihrer Meinung nach am besten beschreibt, wie Sie sich *in den letzten 2 Wochen* gefühlt haben.

In den letzten zwei Wochen	Die ganze Zeit	Meistens	Etwas mehr als die Hälfte der Zeit	Etwas weniger als die Hälfte der Zeit	Ab und zu	Zu keinem Zeitpunkt
... war ich froh und guter Laune	5	4	3	2	1	0
... habe ich mich ruhig und entspannt gefühlt	5	4	3	2	1	0
... habe ich mich energisch und aktiv gefühlt	5	4	3	2	1	0
... habe ich mich beim Aufwachen frisch und ausgeruht gefühlt	5	4	3	2	1	0
... war mein Alltag voller Dinge, die mich interessieren	5	4	3	2	1	0

Erläuterung: Summenwert: 0 bezeichnet das schlechteste Befinden, 25 das beste.
Prozentwert (= Summenwert x 4): 0 bezeichnet das schlechteste Befinden, 100 das beste.

Ihr Summenwert: _____

Ihr Prozentwert : _____

Summenwert 25-13: Dieses Ergebnis spricht für ein gutes Wohlbefinden. Ihre Lebensqualität ist momentan nicht beeinträchtigt.

Summenwert < 13 Punkte: Eine behandlungsbedürftige Überlastung, ein Burnout oder eine Depression können nicht sicher ausgeschlossen werden. Geringe Wohlfühlwerte rechtfertigen noch keine Diagnose. Sie sind jedoch ein ausreichender Grund, eine gezielte Diagnostik durchführen zu lassen.

Hintergrund: Der WHO-5 Fragebogen zum Wohlbefinden wurde von der Weltgesundheitsorganisation (WHO) entwickelt und hat seine Eigenschaften als hervorragendes Depressions-Screening weltweit in einer Vielzahl wissenschaftlicher Studien belegt.

Quelle: Psychiatric Research Unit, WHO Collaborating Center for Mental Health, Frederiksborg General Hospital, DK-3400 Hillerød.

(8) DIADEMA CRF

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

DATUM: ___ ___ / ___ ___ /___ ___ (TT.MM.JJ) **BESUCH NR.**_____

TEILNEHMERNUMMER : _____

1.PERSONENDATEN

PATIENT
Vorname _____
Nachname _____
Strasse _____ Nr. _____
PLZ Ort _____
Geburtsdatum: ___ ___ / ___ ___ /___ ___ (TT.MM.JJ)
E-Mail _____
Telefon:_____

ARZT
Vorname _____
Nachname _____
Strasse _____ Nr. _____
PLZ Ort _____
E-Mail _____
Telefon:_____

APOTHEKE
Name der Apotheke_____
Name des Apothekers _____
Strasse _____ Nr. _____
PLZ Ort _____
E-Mail _____
Telefon:_____
Ort des Interviews: _____
Anwesende Personen:_____

Einwilligungserklärung unterzeichnet am: ___ ___ / ___ ___ /___ ___ (TT.MM.JJ)

1

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

2. KLINISCHE INFORMATION

Geburtsdatum: ___ ___ / ___ ___ /___ ___ (TT.MM.JJ)

Geschlecht: weiblich ☐ **männlich** ☐

Diagnose Diabetes : **Typ** 1 ☐ **Typ 2** ☐ **Anderer Typ** ☐ _____

Datum der ersten Diagnose : ___ ___ / ___ ___ /___ ___

Größe: ____ **cm** **Quartal, Jahr:** _____

Gewicht: ____ **kg** **Quartal, Jahr:** _____

BMI ___ **kg / m²** **Quartal, Jahr:** _____

Letzter HbA1c _____ **Prozent** **Quartal, Jahr:**_____

Blutdruck: ___/___ **mmHg** **Quartal, Jahr:** _____

Blutzuckerselbstmessung: ja ☐ **nein** ☐

Blutzuckertagebuch (schriftlich oder elektronisch): ja ☐ **nein** ☐

Häufigkeit der Blutzuckermessung ____ **mal/Tag**

Zeit der Blutzuckermessung: nüchtern ☐ vor dem Essen ☐ 2 Stunden nach dem Essen ☐ Vor dem Schlafen ☐ in der Nacht ☐

Nüchternglukose: ____ **mg/dl** **Quartal, Jahr**_____

Bluglukose am Tag der Intervention _____**mg/dl oder** _____**mmol/l**

Hypoglykämien im Letzten Monat: ja ☐ **nein** ☐

Anzahl der Hypoglykämien* im letzten Monat: _____ **(Blutzuckertagebuch, Memory-Speicher des Blutzuckermessgerätes)**

***Ein BZ von 50mg/dl oder 2.8 mmol/l mit Hinweisen auf Hypoglykämische Anzeichen**

Anzahl der schweren Hypoglykämien mit Fremdhilfe im letzten Monat: _____

2

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

DKA im letzten Monat: **ja** ☐ **nein** ☐

Ketonmessung im Blut oder Urin wenn BG>250mg/dl: ja ☐ **nein** ☐

Letzter Ketonwert: _____ **Datum:_____**

Gesamtcholesterol/HDL/LDL____/____/____/mg/dl **Quartal, Jahr: _____**

Triglyceride _____mg/dl **Quartal, Jahr: _____**

Albumin:____ mg/l oder ____mg/24h **Quartal, Jahr: _____**

Albumin:Kreatinin ____mg/g **Quartal, Jahr: _____**

Gibt es Hinweise auf eine Nierenfunktionsstörung? ☐ **ja** ☐ **nein**

Erhöhte oder erniedrigte Labordaten in den letzten 3 Monaten (Quartal, Jahr):

_____

_____

_____

Bekannte Arzneimittelallergien oder unerwünschte Arzneimittelwirkungen:

_____

_____

_____

Andere Diagnosen:

_____

_____

_____

Andere Arzneimitteleinnahme:_____

_____

3

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

3.INSULIN ANWENDUNG:

Pumpe □ Pen □ Andere Methode □

Gesamttagesdosis Insulin: _____ I.E.

Gesamtdosis Langwirksames Insulin (Basal): _____ I.E.

Gesamtdosis Schnellwirksames Insulin (Bolus): _____I.E.

Insulinspritzen pro Tag: _____

Bolusdosen (Pumpe) pro Tag: _____

Verwendetes Insulin: NPH □ Levemir□ Lantus □ Novolog □ Humalog □ Novorapid □ Regular □ Anderes_____

Adhärenz mit Insulintherapie: □ ja □ nein

Probleme: _____

_____

_____

Gründe für die Non-Compliance :_____

_____

_____

Korrekte Applikation : □ ja □ nein
Nebenwirkungen der Insulintherapie: □ ja □ nein
Wenn ja bitte angeben:_____
_____
Wechselwirkungen mit anderen Arzneimitteln: □ ja □ nein

Wenn ja bitte angeben: _____

4

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

4. LIFESTYLE / ERNÄHRUNG

Regelmäßige Bewegung/Sport : Ja☐ Nein☐

Anpassung des Insulins an die sportliche Aktivität : Ja☐ Nein☐

Probleme: _____

_____

_____

Einhaltung der Ernährungplans: **: Ja☐ Nein☐**

Probleme: _____

_____

_____

5

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

5. EINSCHÄTZUNG DES APOTHEKERS / INDIVIDUELLE ZIELE
1.
2.
3.
4.
5.
6.
7.
8.

6. PLAN BIS ZUM NÄCHSTEN BESUCH IN DER APOTHEKE
1.
2.
3.
4.
5.
6.
7.
8.
9.

Plan weitergeleitet an den zuständigen Arzt: Ja☐ Nein☐ **Datum : ___ ___ / ___ ___ /___ ___ (TT.MM.JJ)**

Unterschrift: _____

6

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

7.EINHALTUNG DER DIABETISCHEN RICHTLINIEN (ISPAD)

1.Ein individueller Plan zu Haufigkeit und Interventionsgrenzen derBlutzuckermessung, Insulingaben (Modus, Zeit, Dosisberechnung), Mahlzeitenfestlegung, Symptomen und Management bei Hypo- und Hyperglykamie soll fur die Einrichtung (z. B. Schule) erstellt werden.
☐Ja ☐Nein Quartal, Jahr: _____

2.Blutglukosemessung soll mindestens 4x täglich erfolgen
☐Ja ☐Nein

3.Der angestrebte HbA1c soll < 7.5% ohne, daß schwerwiegende Hypoglykämien auftreten.Blutzuckerschwankungen sollten möglichst gering gehalten werden.
☐Ja ☐Nein

4.Eine Bestimmung des HbA1c-Wertes zur Kontrolle der Stoffwechseleinstellung soll mindestens all drei Monate erfolgen.
☐Ja ☐Nein Quartal, Jahr: _____

5.Ophtalmologische Kontrolle soll einmal im Jahr erfolgen
☐Ja ☐Nein Quartal, Jahr: _____

6.Screeining auf Nephropathie soll einmal im Jahr erfolgen
☐Ja ☐Nein Quartal, Jahr: _____

7.Blutdruck soll alle 3 Monate, mindestens aber einmal im Jahr gemessen werden.
☐Ja ☐Nein Quartal, Jahr: _____

8.Ein Lipidscreening soll alle 2 Jahre erfolgen
☐Ja ☐Nein Quartal, Jahr: _____

9.Neuropathiescreening soll jährlich erfolgen
☐Ja ☐Nein Quartal, Jahr: _____

10.Impfungen nach STIKO insbesondere Grippe und Pneumokokken Impfung für Kinder mit Typ 1 Diabetes
☐Ja ☐Nein Quartal, Jahr: _____

11.Krankentage Mangement (Sick Day Management) Protokoll soll erstellt werden
☐Ja ☐Nein Quartal, Jahr: _____

12.Urin oder Blutketone sollen bestimmt werden während der Episoden von unkotrollierter Hyperglykämie, Insulinmangel, Krankheit oder drohender Ketoazidose
☐Ja ☐Nein Quartal, Jahr: _____

7

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

INHALTE DIE IN DER PHARMAZEUTISCHEN BETREUUNG VERMITTELT WERDEN SOLLEN

Bewertung von individuellen Therapiezielen orientiert an den Therapie-Leitlinien
Erfolgt: ☐Ja ☐Nein **Datum _____**

Vermittlung der Grundlagen der Insulintherapie sowie praktischer Fertigkeiten zur Durchführung der Insulintherapie
Erfolgt: ☐Ja ☐Nein **Datum _____**

Vermittlung von Fertigkeiten zur eigenständigen Insulinanpassung
Erfolgt: ☐Ja ☐Nein **Datum _____**

Erlernen von Selbstkontrollmaßnahmen sowie deren Dokumentation und Interpretation
Erfolgt: ☐Ja ☐Nein **Datum _____**

Erkennung, Behandlung und Prävention von Akutkomplikationen (Hypoglykämien, Hyperglykämien, Infekte etc.)
Erfolgt: ☐Ja ☐Nein **Datum _____**

Vermittlung von Kenntnissen und praktischen Fertigkeiten bezüglich der Auswirkung von körperlicher Aktivität auf die Blutglukoseregulation
Erfolgt: ☐Ja ☐Nein **Datum _____**

Training von Problemlösestrategien für besondere Situationen
Erfolgt: ☐Ja ☐Nein **Datum _____**

Vermittlung von Kenntnissen zur Sexualität, Kontrazeption, Menstruation, Familienplanung
Erfolgt: ☐Ja ☐Nein **Datum _____**

Umgang mit möglichem Tabak-, Alkohol- und/oder Drogenkonsum;
Erfolgt: ☐Ja ☐Nein **Datum _____**

Informationen über Kontrolluntersuchungen
Erfolgt: ☐Ja ☐Nein **Datum _____**

8

DOKUMENTATIONSBOGEN: Pharmazeutische Betreuung von Jugendlichen mit Diabetes Mellitus Typ 1

9. SONSTIGE ANMERKUNGEN:

9

(9) Tabular list of the entire data and information extracted for the meta-analysis

General			
Citation			
Objective			
Method			
Study design	***Outcomes***	***Inclusion criteria***	***Exclusion criteria***
Blinding [yes/no] Cluster-Randomization [yes/no] Study duration [months] Study setting - place Study setting - country Analysis type (intention to treat or per protocol) Patient recruiting type Patient recruiting time [months]	Primary outcomes Secondary outcomes	HbA1c value [%] Diabetes type Medication type Amount of medication Age [years] Language Other relevant inclusion criteria	Other diseases Diabetes complications Other relevant exclusion criteria
Training design	***Intervention design***	***Intervention contents – Patient consultation***	***Intervention contents – Medication analysis***
Training includes the following topics… Training was provided by… Training duration [hours]	Intervention was provided by… Mean intervention duration [minutes] Intervention period [months] Intervention type face to face [yes/no] Intervention type skype or facetime [yes/no] Intervention type telephone follow-up [yes/no] Intervention type printed leaflets [yes/no] Intervention type education video [yes/no]	Health beliefs [yes/no] Lifestyle changes: diet, [yes/no] Lifestyle changes: exercise [yes/no] Lifestyle changes: smoking cessation [yes/no] General medication knowledge [yes/no] Side-effects of medicines/DRPs [yes/no] Goal setting [yes/no]	Medication review [yes/no] Implementation of medication plan [yes/no]
Intervention contents – Monitoring	***Intervention contents – Tests, examinations and physical assessment***	***Intervention contents – Patient education***	***Intervention contents – Interdisciplinary work***
Assessment of adherence (questionnaire) [yes/no] Review and analysis of blood glucose meter measurements/ diabetes record book [yes/no]	Blood pressure [yes/no] Lipid levels [yes/no] Boys weight [yes/no] Diabetic feet screening [yes/no] Skin /Neuropathy screening [yes/no] Eyes /Retinopathy screening [yes/no] Kidney /Nephropathy screening [yes/no] HbA1c-measurements [yes/no]	Usage of blood glucose meters [yes/no] Medication knowledge [yes/no] Diabetes complications [yes/no]	Partnership with other health care professionals [yes/no] Sending feedback to physicians [yes/no] Sending medication recommendations to physicians [yes/no] Referral to other health care professionals [yes/no] Physician referral for patient education [yes/no] Referral to specialist nurse or diabetes educator [yes/no] Physician referral for medical advice [yes/no]
Definition of usage care (control group)			

Baseline data

General information about study population (intervention and control group)	*Relevant clinical outcomes (intervention and control group)*	*Relevant humanistic outcomes (intervention and control group)*	*Relevant economic outcomes (intervention and control group)*
Mean age [years] Mean diabetes duration [years] Females [%] Smoker [%]	Mean HbA1c-value [%] Mean blood glucose levels [mg/dL] Mean systolic blood pressure [mmHg] Mean diastolic blood pressure [mmHg] Mean total cholesterol [mg/dl] Mean HDL [mg/dL] Mean LDL [mg/dL] Mean TG [mg/dL] Mean BMI [kg/m^2] Cardiovascular risk score (UKPDS risk score) Hypoglycemic episodes per months Hyperglycemic episodes per months	Diabetes knowledge test Assessment of health status - Short Form 36 Adherence score [%] Diabetes-related quality of life Health-related quality of life Beliefs about medicines questionnaire Satisfaction with information received about medicines Amount of identified drug-related problems	

Results

Number of participants (intervention and control group)	*Amount of health care professionals (intervention and control group)*	*Clinical outcomes (intervention and control group)*	*Humanistic outcomes (intervention and control group)*
Number of enrolled patients Number of analyzed patients Drop-out rate [%]	Number of pharmacists Number of enrolled pharmacies Number of enrolled physicians	Mean HbA1c value [%] Mean blood glucose levels [mg/dL] Mean systolic blood pressure [mmHg] Mean diastolic blood pressure [mmHg] Mean total cholesterol [mg/dl] Mean HDL [mg/dL] Mean LDL [mg/dL] Mean TG [mg/dL] Mean BMI [kg/m^2] Cardiovascular risk score (UKPDS risk score) Hypoglycemic episodes per months Hyperglycemic episodes per months	Diabetes knowledge test Assessment of health status - Short Form 36 Adherence score [%] Diabetes-related quality of life Health-related quality of life Beliefs about medicines questionnaire Satisfaction with information received about medicines Amount of identified drug-related problems

Economic outcomes (intervention and control group)	*Additionally results (intervention and control group)*		
	Emergency or hospital visits Other (validated) questionnaires used		

Conclusion

Limitations
Intern validation
Extern validation
Interpretation of results

(10) Questionnaire meta-analysis

Intervention & Training Design of Pharmaceutical Care Provided by Community Pharmacists

Welcome

Thank you very much for participating in our survey. Your feedback is important to evaluate, which intervention component is essential to achieve a positive impact on the HbA1c values of the enrolled participants.
Besides we want to assess the effect of training community pharmacists at the beginning of your randomized controlled trial.

* 1. Contact information

Name	
University/Pharmacy	
Email Address	
Phone Number	

Intervention & Training Design of Pharmaceutical Care Provided by Community Pharmacists

Part 2 - Intervention design

The subsequent questions are dealing with details about the pharmacists' intervention design.

* 2. Mean intervention duration [minutes]

* 3. Mean intervention interval [months]

* 4. Pharmaceutical care included the following intervention types:

	Yes	No	Not documented
Face-to-face visits	○	○	○
(additional) telephone calls	○	○	○
Printed leaflets	○	○	○
Educational video	○	○	○

Other (please specify)

* 5. Pharmaceutical care included the following advice for lifestyle changes:

	Yes	No	Not documented
Diet/Nutrition	○	○	○
Exercise	○	○	○
Smoking cessation	○	○	○
Alcohol consumption	○	○	○

Other (please specify)

* 6. Pharmacists investigated the following key aspects:

	Yes	No	Not documented
Patients' general medication knowledge	○	○	○
Side-effects of the current medication	○	○	○
Drug related problems (DRPs)	○	○	○
Patients health beliefs	○	○	○
(individual) goal setting	○	○	○

Other (please specify)

* 7. Pharmacists and/or other health care personal conducted the following examinations/tests:

	Yes	No	Not documented
Medication review	○	○	○
HbA1c values measurements	○	○	○
Blood glucose measurements	○	○	○
Blood pressure measurements	○	○	○
Lipid profile measurements	○	○	○
Weight measurements	○	○	○
Feet and/or skin examinations	○	○	○
Retinopathy screening	○	○	○
Nephropathy screening	○	○	○
Assessment of patients' adherence by using pill-count method or questionnaire	○	○	○
Assessment of health status e.g. short-form-36	○	○	○
Assessment of patients' diabetes knowledge e.g. questionnaire	○	○	○
Evaluation of patients' satisfaction with pharmacist intervention	○	○	○

Other (please specify)

* 8. Pharmacists' patient education included the following aspects:

	Yes	No	Not documented
Blood glucose meter usage	○	○	○
Medication application	○	○	○
Diabetes associated short-term complications	○	○	○
Diabetes associated long-term complications	○	○	○
Review and evaluation of the diabetes record books	○	○	○

Other (please specify)

* 9. Pharmacist-physician collaboration included the following aspects, if necessary:

	Yes	No	Not documented
Pharmacists send recommendations to the physician e.g. required medication changes	○	○	○
Pharmacists send feedback to the physician e.g. patients progress	○	○	○
Pharmacists referred patients to the physician for patient education	○	○	○
Pharmacists referred patients to the physician for medical advice	○	○	○
Pharmacists referred patients to a specialist nurse	○	○	○
Pharmacists referred patients to other health care professionals	○	○	○

Other (please specify)

Intervention & Training Design of Pharmaceutical Care Provided by Community Pharmacists

Part 3 - Design of Pharmacists' Training

The subsequent questions are dealing with details about the training of pharmacists before or during the study.

* 10. Pharmacists received training before the beginning of the study:

- ◯ Yes
- ◯ No
- ◯ Not documented

* 11. Mean training duration [hours]

* 12. Mean training repetition interval [months]

* 13. Training was provided by:

	Yes	No	Not documented
Community pharmacists	◯	◯	◯
Clinical pharmacists	◯	◯	◯
Certified diabetes educators (pharmacists)	◯	◯	◯
Physicians	◯	◯	◯
Diabetes specialist nurses	◯	◯	◯

Other (please specify)

* 14. Training was given to:

	Yes	No	Not documented
Community pharmacists	○	○	○
Certified diabetes educators (pharmacists)	○	○	○

Other (please specify)

* 15. The training of pharmacists included the following key aspects of the pathophysiology of diabetes type 1 and/or 2:

	Yes	No	Not documented
Regulation of blood glucose and insulin secretion	○	○	○
Physiology and pathophysiology of intermediary metabolism (e.g. carbohydrate-metabolism)	○	○	○
Insulin effect and effect of insulin deficiency	○	○	○

Other (please specify)

* 16. The training of pharmacists included the following key aspects of the diagnosis and therapy of diabetes type 1 and/or 2:

	Yes	No	Not documented
Type 1 diabetes: cause, development and therapy strategies	○	○	○
Type 2 diabetes: cause, development and therapy strategies	○	○	○
Glucose levels in blood and/or urine, HbA1c values and lipid profile	○	○	○
Impact and regulation of body weight	○	○	○
Impact of high blood pressure	○	○	○
Detection and treatment of hypoglycemia and/or diabetic ketoacidosis	○	○	○
General diabetes medication knowledge	○	○	○
Effect, side-effects and interactions of insulin and/or OADs	○	○	○
Short- and long-term diabetes complications e.g. macroangiopathy	○	○	○

Other (please specify)

* 17. The training of pharmacists included conduction of the following "practical" key aspects:

	Yes	No	Not documented
Instructions on self-monitoring of blood glucose/usage of blood glucose meters	○	○	○
Methods to measure urine glucose levels	○	○	○
Methods to (self-)measure blood pressure	○	○	○
Methods to determine the lipid profile	○	○	○
Methods to measure ketones in urine and/or blood	○	○	○
Methods to measure albuminuria	○	○	○
Usage of insulin syringes and/or pens or other insulin injection methods	○	○	○

Other (please specify)

* 18. The training of pharmacists included the following aspects of lifestyle advice:

	Yes	No	Not documented
Diet/Nutrition recommendations for diabetes type 1 and/or 2 patients	○	○	○
Documentation of self-measurements and/or medication intake	○	○	○
Methods to support patients' self-management	○	○	○
Importance of physical activity, weight control, foot care, self-observation and diabetes complications	○	○	○
Medication and diabetes interactions	○	○	○

Other (please specify)

* 19. The training of pharmacists included the explanation and/or documentation of the following humanistic outcomes:

	Yes	No	Not documented
Adherence and/or compliance	○	○	○
QoL and/or DQoL and/or HRQoL	○	○	○
Diabetes knowledge questionnaire/score	○	○	○
Health status e.g. short-form-36	○	○	○
Satisfaction with pharmacist intervention	○	○	○

Other (please specify)

* 20. The training of pharmacists included the following soft skills:

	Yes	No	Not documented
Motivational interviewing	○	○	○
Role plays	○	○	○
Discussion of patient cases	○	○	○

Other (please specify)

* 21. Additional information about the content of the given training to the pharmacists:

	Yes	No	Not documented
Instructions on counseling at first prescription	○	○	○
Information about the study protocol	○	○	○
Principles of pharmaceutical care	○	○	○

Other (please specify)

* 22. The training of pharmacists was based on the following guidelines (e.g. ISPAD guideline 2014):

Intervention & Training Design of Pharmaceutical Care Provided by Community Pharmacists

Part 4 - HbA1c values

Please fill in the subsequent boxes the correct HbA1c values of all analysed participants, if available.

23. HbA1c values of the analysed control participants

Mean baseline HbA1c values ± SD	
Mean final HbA1c values ± SD	
Mean difference HbA1c values ± SD	
Minimum difference HbA1c values	
Maximum difference HbA1c values	

24. HbA1c values of the analysed intervention participants

Mean baseline HbA1c values ± SD	
Mean final HbA1c values ± SD	
Mean difference HbA1c values ± SD	
Minimum difference HbA1c values	
Maximum difference HbA1c values	

(11) EMDIA-CRF

KLINISCHE PHARMAZIE & PHARMAKOTHERAPIE

Medikationsanalyse CRF

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

PATIENTENDATEN

Patienten-ID*: Geburtsdatum: Geschlecht ☐ w ☐ m Datum der Analyse:

Name des durchführenden Apothekers: Einwilligungserklärung unterschrieben am:

Fertigstellung der Analyse mitteilen: ☐ telefonisch ☐ postalisch ☐ per E-Mail

Name und Kontaktdaten des Hausarztes: Name und Kontaktdaten des Diabetologen:

*wird von den Verantwortlichen zur Durchführung der Studie ausgefüllt

PATIENTENANAMANESE

Bekannte Diagnosen/Erkrankungen:

Vorliegende Unterlagen des Patienten:
☐ Medikationsplan ☐ Arztbrief ☐ Laborwerte ☐ Entlassbrief des Krankenhauses
Sonstiges:

Blutzuckertagebuch:
☐ vorhanden ☐ nicht vorhanden

Letzter Nüchternblutzuckerwert:
[mg/dl] am Datum:

Letzter HbA1c-Wert:
[%] am Datum:

Größe: Gewicht:

Tgl. Anzahl der Blutzuckermessungen: Ketonkörpermessungen im Urin:

Mtl. Anzahl leichter Hypoglykämien: Mtl. Anzahl schwerer Hypoglykämien:

Diabeteskomplikationen:

Anzahl der Mahlzeiten pro Tag:

Ernährungsplan:
☐ vorhanden ☐ nicht vorhanden

☐ kein Nikotinkonsum ☐ kein Alkoholkonsum ☐ gelegentlich körperlich aktiv
☐ Raucher ☐ Alkoholkonsum ☐ regelmäßig körperlich aktiv
☐ ehemaliger Raucher ☐ früherer Alkoholkonsum Sportart:

Allergien & Unverträglichkeiten:

Sonstige relevante Informationen z.B. Beruf, geplante Operationen oder Schwangerschaft:

KLINISCHE PHARMAZIE & PHARMAKOTHERAPIE

Medikationsanalyse CRF

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

ARZNEIMITTEL (außer Insulin)

Name des Arzneimittels: Wirkstoffname:

Stärke und Darreichungsform des Wirkstoffs: Grund der Einnahme:

Art der Medikation:
☐ Selbstmedikation ☐ Bedarfsmedikation ☐ Dauermedikation wird eingenommen seit:

Dosierung morgens mittags abends nachts ☐ zum ☐ während ☐ nach dem Essen

Besondere Einnahmehinweise oder sonstige Angaben:

AUSWERTUNG DES APOTHEKERS

Beratungsbedarf des Patienten:
☐ kein Bedarf ☐ Handhabung/Anwendung ☐ Grund der Anwendung ☐ Dosierung
☐ Compliance/Adhärenz ☐ Sonstiges:

Arzneimittelbezogene Probleme:
☐ keine ☐ Nebenwirkungen vorhanden ☐ Interaktion liegt vor ☐ Kontraindikation ☐ fehlerhafte Indikation
☐ Doppelverordnung ☐ fehlerhafte Dosierung ☐ Priscus-AM ☐ Sonstiges:

Name des Arzneimittels: Wirkstoffname:

Stärke und Darreichungsform des Wirkstoffs: Grund der Einnahme:

Art der Medikation:
☐ Selbstmedikation ☐ Bedarfsmedikation ☐ Dauermedikation wird eingenommen seit:

Dosierung morgens mittags abends nachts ☐ zum ☐ während ☐ nach dem Essen

Besondere Einnahmehinweise oder sonstige Angaben:

AUSWERTUNG DES APOTHEKERS

Beratungsbedarf des Patienten:
☐ kein Bedarf ☐ Handhabung/Anwendung ☐ Grund der Anwendung ☐ Dosierung
☐ Compliance/Adhärenz ☐ Sonstiges:

Arzneimittelbezogene Probleme:
☐ keine ☐ Nebenwirkungen vorhanden ☐ Interaktion liegt vor ☐ Kontraindikation ☐ fehlerhafte Indikation
☐ Doppelverordnung ☐ fehlerhafte Dosierung ☐ Priscus-AM ☐ Sonstiges:

Name des Arzneimittels: Wirkstoffname:

Stärke und Darreichungsform des Wirkstoffs: Grund der Einnahme:

Art der Medikation:
☐ Selbstmedikation ☐ Bedarfsmedikation ☐ Dauermedikation wird eingenommen seit:

Dosierung morgens mittags abends nachts ☐ zum ☐ während ☐ nach dem Essen

Besondere Einnahmehinweise oder sonstige Angaben:

AUSWERTUNG DES APOTHEKERS

Beratungsbedarf des Patienten:
☐ kein Bedarf ☐ Handhabung/Anwendung ☐ Grund der Anwendung ☐ Dosierung
☐ Compliance/Adhärenz ☐ Sonstiges:

Arzneimittelbezogene Probleme:
☐ keine ☐ Nebenwirkungen vorhanden ☐ Interaktion liegt vor ☐ Kontraindikation ☐ fehlerhafte Indikation
☐ Doppelverordnung ☐ fehlerhafte Dosierung ☐ Priscus-AM ☐ Sonstiges:

KLINISCHE PHARMAZIE & PHARMAKOTHERAPIE

Medikationsanalyse CRF

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

INSULIN

Name des Insulins:	Wirkstoffname:
Angabe zu Einheiten pro ml:	☐ Bolusinsulin ☐ Basalinsulin
Durchschnittlicher tgl. Insulinverbrauch [I.E.]:	☐ Insulinpen ☐ Insulinpumpe
Dosierung [I.E.] morgens mittags abends nachts	Anzahl tgl. Insulininjektionen:
AUSWERTUNG DES APOTHEKERS	
Beratungsbedarf des Patienten: ☐ kein Bedarf ☐ Handhabung/Anwendung ☐ Grund der Anwendung ☐ Dosierung ☐ Compliance/Adhärenz ☐ Sonstiges:	
Arzneimittelbezogene Probleme: ☐ keine ☐ Nebenwirkungen vorhanden ☐ Interaktion liegt vor ☐ Kontraindikation ☐ fehlerhafte Indikation ☐ Doppelverordnung ☐ fehlerhafte Dosierung ☐ Priscus-AM ☐ Sonstiges:	
Name des Insulins:	Wirkstoffname:
Angabe zu Einheiten pro ml:	☐ Bolusinsulin ☐ Basalinsulin
Durchschnittlicher tgl. Insulinverbrauch [I.E.]:	☐ Insulinpen ☐ Insulinpumpe
Dosierung [I.E.] morgens mittags abends nachts	Anzahl tgl. Insulininjektionen:
AUSWERTUNG DES APOTHEKERS	
Beratungsbedarf des Patienten: ☐ kein Bedarf ☐ Handhabung/Anwendung ☐ Grund der Anwendung ☐ Dosierung ☐ Compliance/Adhärenz ☐ Sonstiges:	
Arzneimittelbezogene Probleme: ☐ keine ☐ Nebenwirkungen vorhanden ☐ Interaktion liegt vor ☐ Kontraindikation ☐ fehlerhafte Indikation ☐ Doppelverordnung ☐ fehlerhafte Dosierung ☐ Priscus-AM ☐ Sonstiges:	

(12) EMDIA form for documenting the correspondence with the physician or diabetologist

KLINISCHE PHARMAZIE & PHARMAKOTHERAPIE

Formblatt Ergebnis Medikationsanalyse Arzt

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Sehr geehrte/r Frau/Herr Dr. med. ,

anbei senden wir Ihnen die Ergebnisse der Medikationsanalyse mit der Bitte um Kenntnisnahme.

PATIENTENDATEN

Patienten-ID*:	Ansprechpartner in der Apotheke:	Datum der Analyse:

Vorliegende Unterlagen des Patienten:

☐ Medikationsplan vom ☐ Arztbrief von vom

☐ Laborwerte vom ☐ Entlassbrief des Krankenhauses vom

Sonstiges:

*wird von den Verantwortlichen zur Durchführung der Studie ausgefüllt

ERGEBNIS DER MEDIKATIONSANALYSE

Potenzielle arzneimittelbezogene Probleme:	Mögliche Ursache sowie Folgen für den Patienten:	Unsere Empfehlung:

Folgende Zielvereinbarungen wurden mit dem Patienten getroffen:

Sehr gerne möchte ich mit Ihnen über das Ergebnis der Medikationsanalyse sprechen. Hierfür möchte ich mit Ihnen einen Termin vereinbaren für ein Telefonat/persönliches Gespräch.

Vielen lieben Dank für Ihre Unterstützung.

Mit freundlichen Grüßen,

Ihr Ansprechpartner:
Apothekerin Maira Anna Deters
Universitätsstr. 1 Gebäude 26.22.02 Raum 21
40225 Düsseldorf
Telefon: 0211 81 13840
Fax: 0211 81 10741
E-Mail: maira.deters@hhu.de

(13) EMDIA checklist

KLINISCHE PHARMAZIE & PHARMAKOTHERAPIE

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

CHECKLISTE ZUR DURCHFÜHRUNG DER MEDIKATIONSANALYSE

Allgemeine Angaben zum Patienten:

Patienten-ID*: Geburtsdatum: ☐ Patientenkartei vorhanden

Patienteninformation und Einwilligungserklärung mitgegeben am:
Erstgespräch ist geplant am:

Erstgespräch durchgeführt am: Name des Apothekers:

Fertigstellung der Analyse mitgeteilt am: Abschlussgespräch Medikationsanalyse am:

Kontakt zum Hausarzt:
am via

Kontakt zum Diabetologen:
am via

1. Kontrolltermin:	Kontakt zum Hausarzt:	Kontakt zum Diabetologen:
am	am via	am via
2. Kontrolltermin:	Kontakt zum Hausarzt:	Kontakt zum Diabetologen:
am	am via	am via

*wird von den Verantwortlichen zur Durchführung der Studie ausgefüllt

1. Gewinnung des Patienten

- ☐ Überprüfung des potenziellen Nutzens der Medikationsanalyse für den Patienten - Multimorbidität und/oder Polymedikation
- ☐ Ansprache des Patienten - Nutzen und Vorteile für den Patienten darstellen
- ☐ Einwilligungserkärung erhalten
- ☐ Vereinbarung eines Gesprächstermins für die Medikationsanalyse

2. Datenerhebung und Datenerfassung

Daten aus der Patientenkartei

- ☐ Aktuelle Medikation
- ☐ Diagnosen, Laborwerte, Arztbriefe, Allergien und Unverträglichkeiten etc.
- ☐ sonstige gesundheitsrelevanten Informationen

Gespräch mit dem Patienten

- ☐ aktuelle Medikation und weitere relevante Informationen erfassen mittels Medikationsanalyse CRF
- ☐ Diagnosen, Laborwerte, Arztbriefe, Allergien und Unverträglichkeiten etc.
- ☐ Sozialanamnese (Lebensgewohnheiten etc.)
- ☐ WHO-5 well-being Index Fragebogen ausfüllen
- ☐ sonstige gesundheitsrelevanten Informationen

3. Pharmazeutische Überprüfung der Medikation

- ☐ Überprüfung der Wirkung der Medikation (z.B. wirkungslos, teilweise wirksam, Auftritt von Nebenwirkungen)
- ☐ Überprüfung der Indikation (z.B. Arzneimittel ohne Indikation, falsche Indikation, Kontraindikation liegt vor)
- ☐ Überprüfung von Interaktionen (z.B. AM-AM oder AM-NM oder AM-NEM)
- ☐ Überprüfung der Compliance oder Adhärenz des Patienten
- ☐ Überprüfung der Lagerung und des Anbruchsverfalls der Medikamente

Zusätzliche Überprüfung der Medikation bei speziellen Patientengruppen:

- ☐ bei Patienten ≥60 Jahren Verwendung der Priscus-Liste
- ☐ bei eingeschränkter Nierenfunktion Verwendung von www.dosing.de
- ☐ bei Schwangeren und Stillenden Verwendung von www.embryotox.de

KLINISCHE PHARMAZIE & PHARMAKOTHERAPIE

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

4. Erarbeitung von Vorschlägen zur Lösung der arzneimittelbezogenen Probleme

Patient
- ☐ medikamentöse Lösungsansätze
- ☐ nicht medikamentöse Lösungsansätze
- ☐ Monitoringmaßnahmen

Arzt
- ☐ medikamentöse Lösungsansätze
- ☐ nicht medikamentöse Lösungsansätze
- ☐ Monitoringmaßnahmen

5. Abschlussgespräch
- ☐ Erläuterung aller Lösungsansätze
- ☐ Erläuterung aller Monitoringmaßnahmen
- ☐ Ausgabe des aktuellen Medikationsplans

6. Dokumentation
- ☐ Gespräch mit dem Patienten – Arzneimittelanamanese (Nutzung des Medikationsanalyse CRF)
- ☐ Arzneimittelanalyse ggf. Auschnitt der Leitlinie oder Fachinformation markieren sowie speichern
- ☐ Information für den behandelnden Arzt (Nutzung der Vorlage)
- ☐ Abschlussgespräch mit dem Patienten (Nutzung der Vorlage)

7. ggf. Vereinbarung eines Folgetermins zur Kontrolle
- ☐ Nach ca. einem Monat – Kontrolle der Medikation sowie Werte und der Einhaltung der gemeinsam vereinbarten Ziele
- ☐ Nach ca. drei Monaten – Kontrolle der Medikation sowie Werte und der Einhaltung der gemeinsam vereinbarten Ziele

(14) Required entries and settings for the effective use of the diabetes record book

To simplify the input of the required, personal health data, the Diabetes:M application offers a configuration wizard (see red box).

To effectively use the diabetes record book, the patient must select the measurement units they currently use.

To calculate the bolus doses or BMI correctly, the application needs the weight and height of the patient.

In order to enable the activation of relevant functions directly and to facilitate the documentation of the therapy, the current diabetes therapy should be entered next.

If insulin therapy is selected in the previous section, you can now choose a bolus and/or basal insulin from an up-to-date list. If other medications are taken, you can now enter them. A list of oral antidiabetics is also available.

After the initial configuration is complete, other features such as the reminder functions and user interface adjustments can be set in the settings. Additionally, you can select our blood glucose measurement system and import all your values.

(15) Pie chart from the Diabetes:M application - overview blood glucose levels different timeframes

XI Lebenslauf

Persönliche Daten und Lebenslauf

Nachname: Deters

Vorname: Maira Anna

Geburtsjahr: 1989

Kontaktdaten

Adresse des Lehrstuhls/Instituts:

Institut für Klinische Pharmazie und Pharmakotherapie

Universitätsstraße 1

40225 Düsseldorf

Geb. 26.22.02.21

Tel.: 0211/81-12531

E-Mail: maira.deters@uni-duesseldorf.de

Beruflicher Werdegang

Berufsabschluss: Apothekerin

September 2015	Praktikum am Institut für Klinische Pharmazie und Pharmakotherapie der Heinrich-Heine-Universität Düsseldorf - Arbeitsgruppe Univ.-Prof. Dr. med. Läer
Oktober 2015 bis Juli 2017	Wissenschaftliche Mitarbeiterin am Institut für Klinische Pharmazie und Pharmakotherapie der Heinrich-Heine-Universität Düsseldorf & Apothekerin in der ABC-Apotheke Oberhausen
Juli 2017 bis August 2018	Mutterschutz und anschließende Eltern-/Erziehungszeit
September 2018 bis August 2020	Wissenschaftliche Mitarbeiterin am Institut für Klinische Pharmazie und Pharmakotherapie der Heinrich-Heine-Universität Düsseldorf & Apothekerin in der ABC-Apotheke Oberhausen
seit September 2020	Mutterschutz und anschließende Eltern-/Erziehungszeit

Hochschulausbildung	
August 2015	Approbation als Apothekerin
Juli 2015	Dritter Abschnitt des Staatsexamens
Praktisches Jahr	
Juli bis August 2014	Pharmaziepraktikantin in der ABC-Apotheke in Oberhausen
September 2014 bis Februar 2015	Pharmaziepraktikantin am Institut für Klinische Pharmazie und Pharmakotherapie der Heinrich-Heine-Universität Düsseldorf - Arbeitsgruppe Univ.-Prof. Dr. med. Läer
März bis Juni 2015	Pharmaziepraktikantin in der ABC-Apotheke in Oberhausen
Studium	
2009 bis 2014	Pharmaziestudium an der Heinrich-Heine-Universität Düsseldorf
August bis Oktober 2010	Famulatur in der ABC-Apotheke in Oberhausen
Herbst 2011	Erster Abschnitt des Staatsexamens
Frühjahr 2014	Zweiter Abschnitt des Staatsexamens
Schulausbildung	
bis 2009	BMV-Schule in Essen Abschluss: Abitur

XII Publikationen, Vorträge, Posterpräsentationen und Kongressbesuche

Publikationen

- November 2016 — Publikation - Erstautor:
  Deters MA, Läer S, Hasanbegović S, Nemitz V, Müller P, Krüger M, Schwender H, Obarcanin E. Diabetes Stewardship – Pharmaceutical care of adolescents with type 1 diabetes mellitus provided by community pharmacists. Med Monatsschr Pharm. 2016 Nov;39(11):477-82.
- November 2016 — Publikation - Zweitautor:
  Obarcanin E, Deters MA, Nemitz V, Läer S. Pharmaceutical care of an adolescent with type 1 diabetes. Med Monatsschr Pharm. 2016 Nov;39(11):483-7.
- Februar 2018 — Publikation - Erstautor:
  Deters MA, Laven A, Castejon A, Doucette WR, Ev LS, Krass I, Mehuys E, Obarcanin E, Schwender H, Laeer S. Effective Interventions for Diabetes Patients by Community Pharmacists: A Meta-analysis of Pharmaceutical Care Components. Ann Pharmacother. 2018 Feb;52(2):198-211. doi: 10.1177/1060028017733272. Epub 2017 Sep 26.
- Oktober 2018 — Publikation - Zweitautor:
  Laven A, Deters MA, Rose O, Schwender H, Smaranda A, Waltering I, Laeer S. PharmAdhere: training German community pharmacists with Objective Structured Clinical Examinations. Int J Clin Pharm. 2018 Oct;40(5):1317-1327. doi: 10.1007/s11096-018-0710-0. Epub 2018 Aug 11.
- November 2020 — Publikation - Drittautor:
  Farahani I, Farahani S, Deters MA, Schwender H, Laeer S. Efficacy of an Objective Structured Clinical Examination Training Approach for Training Pharmacy Students in Diabetes Mellitus Counseling: A Randomized

Controlled Trial. Pharmacy (Basel). 2020 Nov 26;8(4):229. doi: 10.3390/pharmacy8040229.

- Mai 2021 — Publikation - Drittautor:
  Farahani I, Farahani S, Deters MA, Schwender H, Laeer S. Training Pharmacy Students in Self-Medication Counseling Using an Objective Structured Clinical Examination-Based Approach. J Med Educ Curric Dev. 2021 May 31;8:23821205211016484. doi: 10.1177/23821205211016484.
- Juni 2021 — Publikation - Drittautor:
  Farahani S, Farahani I, Deters MA, Schwender H, Burckhardt BB, Laeer S. Blended Learning on Blood Pressure Measurement: Investigating Two In-Class Strategies in a Flipped Classroom-Like Setting to Teach Pharmacy Students Blood Pressure Measurement Skills. *Healthcare (Basel)*. 2021;9(7):822. 2021 Jun 28. doi:10.3390/healthcare9070822.
- August 2021 — Publikation - Erstautor:
  Deters MA, Obarcanin E, Schwender H, Läer S. EMDIA Case Series-Effective Medication Therapy Management (MTM) for Diabetes Type 2 Patients-A Proof of Concept Study. Pharmacy (Basel). 2021 Aug 9;9(3):137. doi: 10.3390/pharmacy9030137.

Vorträge

- 25.03.2017 — Vortrag mit dem Thema „Vorstellung der DIADEMA Studie“ bei der Mitgliederversammlung des LAV Rheinland-Pfalz
- 22.11.2019 bis 23.11.2019 — DGKPh-Kongress in Aachen (DGKPh Stipendium)
  Kurzvortrag mit dem Schwerpunkt praktische Umsetzung des effektiven Medikations-managements:
  „Proof of concept Studie „EMDIA” – effektives Medikationsmanagement für Patienten mit Diabetes mellitus Typ 2”

- 28.11.2020 DGKPh-Mitgliederversammlung (online)
  Kurzvortrag mit dem Schwerpunkt der Darstellung und Auswertung der entdeckten ABPs:
  „Proof of concept Studie „EMDIA" – effektives Medikationsmanagement für Patienten mit Diabetes mellitus Typ 2"
- 12.05.2021 bis 15.05.2021 DDG-Kongress (online)
  Workshop (90 Minuten) zum Thema: Medikamentöse Fallstricke bei polypharmazie-geplagten Menschen mit Diabetes (Darstellung von Fallbeispielen aus der EMDIA-Studie)

Posterpräsentationen

- 04.10.2016 bis 07.10.2016 DPhG Kongress in München
  Posterpräsentation:
  „Pharmaceutical Care Provided by Community Pharmacists für Adolescents with Type 1 Diabetes Mellitus – Follow up of DIADEMA"
- 21.06.2017 bis 23.06.2017 ESDPPP Kongress in Leuven
  Posterpräsentation:
  „Transition instead of transfer for drug treatment in adolescent diabetes type 1"
- 08.10.2017 bis 11.10.2017 ESCP Kongress in Heidelberg
  Posterpräsentation:
  "Effective interventions for diabetes pa-tients by community pharmacists – a me-ta analysis of pharmaceutical care com-ponents."
- 29.05.2019 bis 01.06.2019 DDG-Kongress in Berlin (DDG-Nachwuchsstipendium)
  Posterpräsentation:
  „A Meta-analysis of pharmaceutical care components for diabetes patients"
- 23.10.2019 bis 25.10.2019 ESCP Kongress in Ljubljana (Slowenien)
  Posterpräsentation:
  „Assessment of selected pharmaceutical care components for coaching community pharmacists in Medication Therapy Management (MTM) for patients with diabetes

- 22.11.2019 bis 23.11.2019 DGKPh-Kongress in Aachen (DGKPh Stipendium)
  Posterpräsentation mit dem Schwerpunkt praktische Umsetzung des effektiven Medikations-managements: „Proof of concept Studie „EMDIA" – effektives Medikationsmanagement für Patienten mit Diabetes mellitus Typ 2"

Kongresse auf nationaler Ebene

- 23.09.2015 bis 25.09.2015 DPhG Kongress in Düsseldorf
- 04.10.2016 bis 07.10.2016 DPhG Kongress in München

XIII Danksagung

Ganz besonders möchte ich mich bei Frau Prof. Stephanie Läer für Ihre sehr umfangreiche Betreuung sowie die stetige Unterstützung in den letzten Jahren bedanken. Ihre hilfreichen und konstruktiven Anmerkungen haben meine wissenschaftlichen Arbeiten maßgeblich verbessert. Ich bin sehr dankbar, dass ich die Möglichkeit erhalten habe, an solch einem interessanten sowie zukunftsrelevanten Thema zu arbeiten. Mein Interesse an der pharmazeutischen Betreuung von Diabetespatienten ist insbesondere durch den von Frau Dr. Emina Obarcanin im Jahr 2014 gehaltenen Vortrag zur DIADEMA-Studie geweckt worden.

Ich möchte mich bei Frau Dr. Obarcanin ganz herzlich für die wertvolle, produktive und auf viele Arten bereichernde Zusammenarbeit in den letzten Jahren bedanken. Wir haben zusammen die DIADEMA-Subanalyse, EMDIA-Fallserie und die Bewertung der Diabetes:M App durchgeführt und ich möchte ihr für den damit verbunden hohen Arbeitseinsatz, die unzähligen Skype-Gespräche sowie die tolle Betreuung danken.

Bei Frau Dr. Anna Laven möchte ich mich insbesondere für die umfangreiche Unterstützung gerade zu Beginn meiner Promotion bei der Themenfindung sowie bei der Planung und Durchführung der Meta-Analyse bedanken. Selbstverständlich gilt mein Dank auch den vielen anderen Coautoren der Meta-Analyse, welche alle einen bedeutsamen Beitrag zu meiner wissenschaftlichen Arbeit geleistet haben.

Prof. Dr. Holger Schwender hat mich kontinuierlich während meiner Promotion wissenschaftlich begleitet und mein Fachwissen im Bereich der Statistik wesentlich erweitert.

Ganz besonders möchte ich mich bei Herrn Prof. Thilo Bertsche für die Übernahme des Koreferats bedanken.

Ich möchte mich auch bei den vielen Wahlpflichtstudentinnen bedanken, welche mich mit ihrem Engagement und ihrem Feedback insbesondere bei der Durchführung der EMDIA-Fallserie sowie der Bewertung der Diabetes:M unterstützt und weitergebracht haben.

Mein Dank gilt auch dem gesamten Team der ABC-Apotheke sowie den Patientinnen und Patienten der EMDIA-Fallserie, da diese die Durchführung der Fallserie erst möglich gemacht haben.

Ich möchte mich ganz herzlich bei allen aktuellen und ehemaligen Kolleginnen und Kollegen des Arbeitskreises, für die schöne und auf viele Arten bereichernde Zeit bedanken. Einen besonderen Dank gilt meinen Freunden Dr. Björn Burckhardt und Dr. Benjamin Ehlers für viele gute Denkanstöße und emotionale Unterstützung. Und bei Dr. Fabian Süßenbach möchte ich mich zudem ganz herzlich für die vielen schönen, lustigen und lebensbereichernde Momente bedanken.

Zuletzt möchte ich mich von ganzem Herzen bei meinem Mann Herbert, der mich intensiv unterstützt und motiviert hat, den zwei Wirbelwinden Paul Josef und Theo Benedict (dafür, dass ihr Mama in „Ruhe“ habt schreiben lassen), meiner gesamten Familie, insbesondere Mama, Papa, David und Jörg, sowie meinen Freunden bedanken, dass diese auf ihre Art und Weise meine wissenschaftlichen Arbeiten unterstützt und teilweise kritisch hinterfragt, gegengelesen sowie deren Inhalte mit mir diskutiert haben.