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Kinetik der kapillären Blutglukose-Konzentration an alternativen Kapillarblut-Entnahmestellen

– Einfluss von schnellen Änderungen der systemischen Blutglukose-Konzentration –

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
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Kinetics of Capillary Blood Glucose Concentration at Alternative Capillary Blood Sampling Sites

– Effects of Rapid Changes in Systemic Blood Glucose Concentration –

Dissertation

for the Degree of a Doctor of Medicine
of the Faculty of Medicine of the Heinrich-Heine-University Düsseldorf

submitted by

Karsten Jungheim

2004

This cumulative dissertation is based on the following published peer-reviewed original studies:

- Jungheim, K., Koschinsky, T.
  Risky delay of hypoglycemia detection by glucose monitoring at the arm.
  Diabetes Care 24: 1303-1304, 2001

- Jungheim, K., Koschinsky, T.
  Glucose monitoring at the arm: Risky delays of hypoglycemia and hyperglycemia detection.
  Diabetes Care 25: 956-960, 2002

- Jungheim, K., Koschinsky, T.
  Glucose monitoring at the thenar: evaluation of upper dermal blood glucose kinetics during rapid systemic blood glucose changes.
  Horm Metab Res 34: 325-329, 2002

These studies have been officially discussed within the following publications:

- McGarraugh, G.
  Response to Jungheim and Koschinsky.
  Diabetes Care 24: 1304-1306, 2001

- Pfützner, A., Forst, T.
  Response to Jungheim and Koschinsky.
  Diabetes Care 25: 638-639, 2002

- Jungheim, K., Koschinsky, T.
  Response to letter by Pfützner and Forst.
  Diabetes Care 25: 639-640, 2002

TABLE OF CONTENTS

1 ABBREVIATIONS

AST ..... alternative (or alternate) site blood glucose testing

AV ..... arteriovenous

BG ..... blood glucose

SD ..... standard deviation

vs. ..... versus

2 ABSTRACT

Introduction: Capillary blood glucose (BG) testing at sites other than the fingertip, so called “alternative site glucose testing” (AST), is associated with markedly reduced pain. Devices for AST have been recently approved under the assumption that capillary BG measurements in samples derived at these sites (e.g., forearm or thumb) do not differ systematically from results obtained by sampling at the fingertip. Unexpectedly, patients reported to us discrepancies between clinical symptoms of hypoglycaemia with hypoglycaemic values at the finger and normoglycaemic blood glucose values measured at the forearm. These discrepancies occurred particularly during periods with rapidly changing BG concentration. Therefore, a possibility of so far unknown regional differences in blood glucose concentration kinetics during rapid BG changes could not be ruled out. Thus, the aim of the thesis was (a) to describe capillary BG kinetics at the forearm and palm during rapid BG change, (b) to study the effect of local skin manipulation by rubbing, (c) to develop a model explaining the observations and finally (d) to establish adequate guidelines for the use of BG monitoring at AST sites.

Methods: In different studies, capillary BG measurements at the forearm or thenar eminence were compared to capillary BG measurements at the fingertip. Therefore, a standardised rapid BG change (>2.0 $mg \cdot dL^{-1} \cdot min^{-1}$) was induced in patients with diabetes mellitus. In a subgroup of patients, a local rubbing procedure was performed at the forearm before additional capillary samples were taken.

Results: Metabolic steady-state BG concentrations at the forearm and fingertip were similar. But during rapid systemic BG increase or decrease large BG differences [on average up to 84-91 mg/dL (4.7-5.0 mmol/L)] occurred due to the fact that BG concentration in capillary blood from the forearm was lagging behind the fingertip by on average about 30 minutes. Timely hypoglycaemia detection was seriously impaired as up to 80% of forearm BG measurements were higher than 90 mg/dL (up to 169 mg/dL (9.4 mmol/L)] at the moment when BG concentration at the fingertip dropped into hypoglycaemic range. The rubbing procedure diminished the BG concentration difference between forearm and fingertip during rapid BG change on average by about 50%. But there was a distinguished intraindividual and interindividual heterogeneity in the rubbing effect on forearm-fingertip BG concentration difference. At the thenar eminence relevant BG concentration

differences occurred neither at metabolic steady-state nor during blood glucose concentration changes which were rapid enough to induce relevant blood glucose differences between fingertip and forearm.

Discussion: So far unknown, clinically highly relevant differences in capillary BG kinetics exist between forearm and fingertip, but not between fingertip and palm. These observations can be explained by a physiological model, the PLEXUS EXCHANGE MODEL, which is based on the hypothesis that subepidermal plexus blood, from which “capillary” blood is derived, is exchanged rapidly at glabrous skin areas (e.g. fingertip and palm) but only slowly at non-glabrous skin areas (e.g., forearm). As a consequence, it should be recommended that BG testing at AST-sites is performed only when rapid BG change (e.g., < 2 hours postprandially, during physical exercise) or hypoglycaemia can be excluded.

3 INTRODUCTION

Capillary blood glucose self-monitoring is the cornerstone of intensified insulin therapy in diabetes mellitus [1]. In general, the required capillary blood sample is obtained by puncturing the fingertip. This procedure, which a patient on intensified insulin therapy should perform more than 1500 times per year, is painful enough to warrant a search for alternatives.

Recently, new blood glucose self-monitoring devices received approval from the United States Food and Drug Administration for so called alternative (or alternate) capillary blood sampling sites (e.g., arm, leg, palm). The sensible innervation of the dermis at these sites is less dense [2]. Skin puncture is therefore less painful at alternative sites as shown for the forearm [3-8], thigh [8], abdomen [9;10] and palm [3;4;8]. As a result, sampling at alternative sites has an important potential of improving the quality of life of patients with diabetes and of improving patients' compliance to blood glucose self-monitoring.

Nevertheless, blood glucose monitoring at alternative sampling sites has to be effective with regard to the functions of blood glucose self-monitoring. For insulin-treated patients, the major functions of blood glucose self-monitoring are (a) to guide insulin dose adjustments and (b) to detect hypoglycaemia, especially for those patients with impaired awareness of hypoglycaemia. In order to detect hypoglycaemia early enough to prevent severe deterioration of brain function, any blood glucose self-measurement must indicate a hypoglycaemic event before brain glucose concentration is critically lowered. As brain glucose concentration is rapidly equilibrating with arterial (i.e., systemic) blood glucose concentration [11], it is required that glucose concentration measurements at whatever site or compartment reflect systemic blood glucose concentration without relevant delay. Glucose concentrations in capillary blood derived from the fingertip closely follow systemic blood glucose concentration and therefore fulfil this requirement. Previously it had been assumed that blood glucose levels in capillary blood obtained by puncturing the skin are identical at any skin site throughout the body. Therefore, for alternative sampling sites, comparative data was gathered during metabolic steady-state, but virtually no data existed on glucose concentration kinetics during rapid blood glucose concentration changes.

Unexpectedly, patients reported discrepancies between clinical symptoms of hypoglycaemia with hypoglycaemic values at the finger and normoglycaemic blood glucose values measured at the forearm [e.g., 50 vs. 101 mg/dL (2.8 vs. 5.6 mmol/L)]. These discrepancies could neither be explained by technical meter performance [6;12] nor inadequate device handling . Therefore, there existed a possibility of unexplained regional differences in blood glucose concentration kinetics.

Local skin manipulation by rubbing has been recommended by some manufacturers of glucose meters in order to increase the blood volume obtainable by skin puncture at alternative sampling sites. But the effect of this procedure on the blood glucose concentration kinetics had not been examined in detail.

4 AIM OF THE THESIS

The aim this thesis was to examine whether regional differences in capillary blood glucose concentration kinetics exist during rapid systemic blood glucose changes.

In particular:

► to describe capillary blood glucose concentration kinetics
  - at the forearm
  - at the palm (thenar eminence)

► to study the effect of local skin manipulation by rubbing

► to develop a model explaining the observations

► to establish adequate guidelines for the use of BG monitoring at alternative sites

5 METHODS

5.1. Patients

Insulin-treated patients with diabetes mellitus were recruited among the in-patients of the German Diabetes Research Institute (Duesseldorf, Germany) undergoing routine hypoglycaemia awareness testing. Decision for hypoglycaemia awareness testing was independently made by the responsible physicians. Characteristics of the participating patients are shown in TABLE 1.

		Study/Article		
		Diabetes Care (2001) 24:1303	Diabetes Care (2002) 25:956	Horm Metab Res (2002) 34: 325
Participants [male/female]	[n]	6 [6/0]	17 [15/2]	16 [13/3]
Age	[years]	38 ± 9	38 ± 10	37 ± 11
Diabetes type 1/ Diabetes type 2	[n]	5 / 1	13 / 4	13 / 3
Diabetes duration	[years]	12.3 ± 10.0	12.9 ± 8.9	11.6 ± 9.2
Participants with mild microvascular diabetic complications	[n]	2	5	3
Participants with impaired awareness of hypoglycaemia	[n]	2	5	2
HbA_{1c}	[%]	8.7 ± 1.5	9.8 ± 3.1	9.3 ± 2.9

TABLE 1: Characteristics of participating patients.
Either number or mean ± SD is given.

5.2. Devices for blood glucose concentration measurements

Capillary blood glucose concentration was determined by self-monitoring devices approved for the fingertip as well as for alternative capillary sampling sites [FreeStyle™ (TheraSense, Alameda, CA, USA); Soft-Sense™ (Abbott, Bedford, MA, USA); One Touch® *Ultra* (LifeScan, Milpitas, CA, USA)].

For control purposes, additional capillary blood samples from the fingertip were analysed (hexokinase-based method) in the clinical chemistry laboratory of the German Diabetes Research Institute.

5.3. Procedures

5.3.1 Induction of rapid changes in blood glucose concentration

After an overnight fast and on their individual basal insulin, the patients' pre-breakfast rapid-acting insulin was omitted and the breakfast was replaced by an oral glucose load (75 g) in order to achieve blood glucose values of 300-400 mg/dL. Subsequently, short acting insulin was injected intravenously at an individual dose in order to induce a fast blood glucose decline >2.0 $mg \cdot dL^{-1} \cdot min^{-1}$ down to hypoglycaemic values (≤ 60 mg/dL).

5.3.2 Blood glucose concentration measurements

Every 15 min, capillary blood samples were taken in parallel from the fingertip (lateral pulps of fingertip 2-4) and from alternative sampling sites (TABLE 2). In each patient, the same blood glucose monitor was used for measurements of capillary blood glucose samples from all sites. If not stated otherwise, the forearm skin was not rubbed prior to blood glucose sampling (contrary to the recommendations of some manufacturers) in order to avoid any disturbance of the normal regional blood flow. In a subset of patients, additional forearm blood samples were collected from after a rubbing procedure (in accordance to manufacturers' recommendations) was performed.

	Study/Article		
	Diabetes Care (2001)	Diabetes Care (2002)	Horm Metab Res (2002)
Reference sampling site			
Fingertip	All patients	All patients	All patients
Alternative sampling sites			
Forearm (without rubbing procedure)	All patients	All patients	Subset of patients
Forearm after rubbing procedure	-	Subset of patients	-
Thenar eminence	-	-	All patients

TABLE 2: Sampling sites used.
Fingertip: lateral pulps of fingertips 2nd-4th finger; *forearm:* ventral and dorso-radial surface; *thenar eminence:* palmar skin above the m. abductor pollicis brevis & m. flexor pollicis brevis

5.4. Data analysis

Glucose profiles were analysed separately for the increase part, i.e. from the ingestion of the glucose load to the blood glucose concentration maximum measured at the fingertip, and the decrease part, i.e. from insulin injection to the blood glucose concentration minimum measured at the fingertip. For each patient, the average of blood glucose concentration differences between different sampling sites (intraindividual average blood glucose-difference) was calculated.

Data was compared by parametric or non-parametric tests for matched pairs. P-values were up-rounded with two-decimal-precision and a P-value ≤ 0.05 was considered statistically significant. If appropriate, P-values were adapted according to the Bonferroni-procedure.

6 RESULTS

6.1. Capillary blood glucose kinetics at the forearm

At metabolic steady-state (baseline), blood glucose concentration was not significantly different between forearm and fingertip. But during rapid blood glucose increase [2.3 ± 0.5 mg·dL^{-1}·min^{-1} (0.13 ± 0.03 mmol·L^{-1}·min^{-1})] or rapid blood glucose decrease [3.1 ± 1.1 mg·dL^{-1}·min^{-1} (0.17 ± 0.06 mmol·L^{-1}·min^{-1})] blood glucose kinetics at the forearm were lagging behind kinetics at the fingertip by on average about 30 minutes (FIGURE 1).

There was no difference between the different blood glucose meters used.

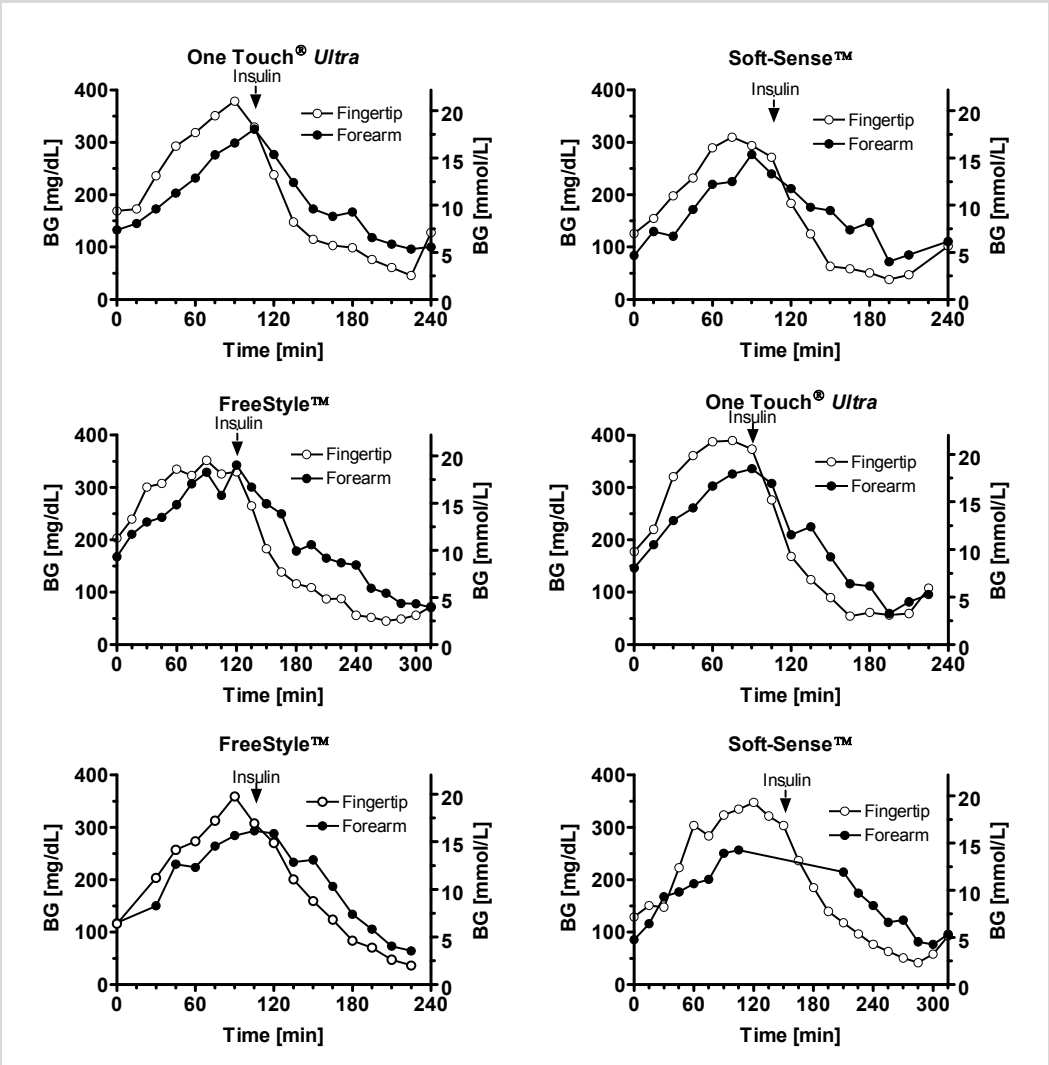

FIGURE 1: Blood glucose kinetics at the forearm.
Representative blood glucose profiles derived from the forearm and the fingertip of six patients with diabetes.

As a consequence, clinically relevant differences occurred between blood glucose concentrations measured at the forearm and the fingertip (TABLE 3). The maximal difference observed per single patient was 84 ± 22 mg/dL (4.7 ± 1.2 mmol/L) during blood glucose increase (forearm blood glucose lower than fingertip blood glucose), and 91 ± 18 mg/dL (5.0 ± 1.0 mmol/L) during blood glucose decrease (forearm blood glucose higher than fingertip blood glucose).

	Fingertip	Forearm
Baseline-BG	141 ± 43 mg/dL (7.8 ± 2.4 mmol/L)	130 ± 42 mg/dL (7.2 ± 2.3 mmol/L) (P=0.06)
BG-increase amplitude	199 ± 43 mg/dL (11.0 ± 2.4 mmol/L)	149 ± 38 mg/dL (8.3 ± 2.1 mmol/L) (P<0.001)
BG-decrease amplitude	259 ± 45mg/dL (14.4 ± 2.5 mmol/L)	206 ± 47 mg/dL (11.4 ± 2.6 mmol/L) (P<0.001)

TABLE 3: Blood glucose (BG) difference between forearm and fingertip occurring during rapid blood glucose concentration-change.
P-value for difference of forearm and fingertip is shown.

Hypoglycaemia detection by blood glucose measurement was severely impaired if blood was obtained from the forearm. At the onset of hypoglycaemia [≤ 60 mg/dL (3.3 mmol/L) at the fingertip], 80 % of blood glucose values at the forearm were ≥ 90 mg/dL (5.0 mmol/L) (TABLE 4).

Forearm-BG	Fingertip-BG	Clinical symptoms of hypoglycaemia
169 mg/dL (9.4 mmol/L) [S]	63 mg/dL (3.5 mmol/L) [S]	Drowsiness
162 mg/dL (9.0 mmol/L) [S]	59 mg/dL (3.3 mmol/L) [S]	None
159 mg/dL (8.8 mmol/L) [F]	52 mg/dL (2.9 mmol/L) [F]	None †
151 mg/dL (8.4 mmol/L) [F]	56 mg/dL (3.1 mmol/L) [F]	None †
142 mg/dL (7.9 mmol/L) [F]	50 mg/dL (2.8 mmol/L) [F]	None †
119 mg/dL (6.6 mmol/L) [S]	63 mg/dL (3.5 mmol/L) [S]	Visual Disturbance, Warmth
115 mg/dL (6.4 mmol/L) [U]	54 mg/dL (3.0 mmol/L) [U]	None †
112 mg/dL (6.2 mmol/L) [F]	56 mg/dL (3.1 mmol/L) [F]	Hunger, Drowsiness,
106 mg/dL (5.9 mmol/L) [U]	61 mg/dL (3.4 mmol/L) [U]	Sweating, Tremor
106 mg/dL (5.9 mmol/L) [F]	43 mg/dL (2.4 mmol/L) [F]	Hunger, Drowsiness, Dizziness
105 mg/dL (5.8 mmol/L) [F]	59 mg/dL (3.3 mmol/L) [F]	Drowsiness
90 mg/dL (5.0 mmol/L) [F]	40 mg/dL (2.2 mmol/L) [F]	Sweating, Nausea
81 mg/dL (4.5 mmol/L) [F]	47 mg/dL (2.6 mmol/L) [F]	None
74 mg/dL (4.1 mmol/L) [F]	47 mg/dL (2.6 mmol/L) [F]	None †
70 mg/dL (3.9 mmol/L) [S]	56 mg/dL (3.1 mmol/L) [S]	None

TABLE 4: Capillary forearm-blood glucose concentration (BG) compared to the first hypoglycaemic value at the fingertip.
Hypoglycaemia [≤ 63 mg/dL (3.5 mmol/L)] was not reached in 2 patients (data not displayed). BG-monitor: S= Soft-Sense™; F= FreeStyle™; U= One Touch® Ultra
† Known history of impaired awareness of hypoglycaemia

6.2. Capillary blood glucose kinetics at the thenar eminence

At the thenar, capillary blood glucose concentration did not differ from the fingertip even during rapid blood glucose changes, rapid enough to induce significant blood glucose concentration differences at the forearm (FIGURE 2, TABLE 5).

At the onset of hypoglycaemia [≤ 60 mg/dL (3.3 mmol/L) at the fingertip], blood glucose concentrations at the thenar and at the fingertip were not significantly different [50 ± 6 vs. 53 ± 10 mg/dL (2.8 ± 0.3 vs. 2.9 ± 0.6 mmol/L), p=0.20].

There were no obvious device specific differences.

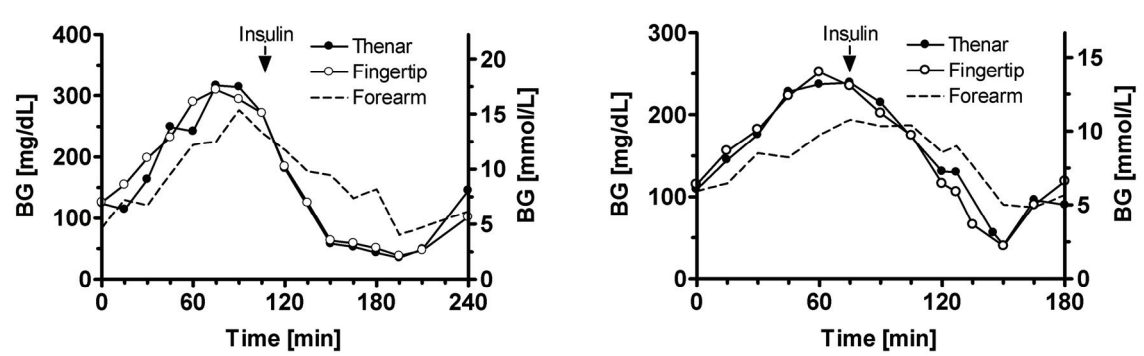

FIGURE 2: Blood glucose kinetics at the thenar.
Representative study blood glucose profiles from the thenar, the forearm and fingertip of two patients with diabetes.

	Fingertip	Thenar		Forearm	
All patients (n=16)					
Baseline-BG	135±34 mg/dL (7.5±1.9 mmol/L)	136±41mg/dL (7.5±2.3 mmol/L)	P=0.86	ND	
BG-increase amplitude	190±35 mg/dL (10.5±1.9 mmol/L)	188±41 mg/dL (10.4±2.3 mmol/L)	P=0.65	ND	
BG-decrease amplitude	255±32 mg/dL (14.1±1.8 mmol/L)	257±47 mg/dL (14.3±2.6 mmol/L)	P=0.83	ND	
Subgroup with "Forearm-control" (n=10)					
Baseline-BG	143±39 mg/dL (7.9±2.2 mmol/L)	145±47 mg/dL (8.0±2.6 mmol/L)	P=1.00	126±38 mg/dL (7.0 mmol/L)	P=0.04
BG-increase amplitude	194±33 mg/dL (10.8±1.8 mmol/L)	196±43 mg/dL (10.9±2.4 mmol/L)	P=1.00	153±36 mg/dL (8.5±2.0 mmol/L)	P<0.01
BG-decrease amplitude	276±26 mg/dL (15.3±1.4 mmol/L)	280±54 mg/dL (15.5±3.0 mmol/L)	P=1.00	226±31 mg/dL (12.5±1.7 mmol/L)	P<0.01

TABLE 5: Capillary blood glucose (BG) during rapid systemic BG-changes.
Blood samples were taken in parallel from the fingertip and the thenar. In a subgroup additional samples were taken from the forearm in order to demonstrate that BG-change was sufficiently rapid.
Mean ± SD are shown. ND denotes "not done".
P-values in comparison to the fingertip-BG are given.

6.3. Effect of rubbing on capillary blood glucose kinetics at the forearm

There was a large intraindividual and interindividual variation of the rubbing effect on the finger-forearm blood glucose difference in the subset of patients (n=8) on which a rubbing procedure was performed. In these patients, the effect ranged from virtually no change of forearm blood glucose to the establishment of full equilibrium with the fingertip blood glucose (FIGURE 3). On average, the individual maximal difference between forearm and finger was reduced during the increase part from 81 ± 13 to 56 ± 20 mg/dL (4.5 ± 0.7 to 3.1 ± 1.1 mmol/L) ($p<0.05$) and during the decrease part from 86 ± 20 to 54 ± 16 mg/dL (4.8 ± 1.1 to 3.0 ± 0.9 mmol/L) ($p<0.01$). Again, no device specific differences were observable

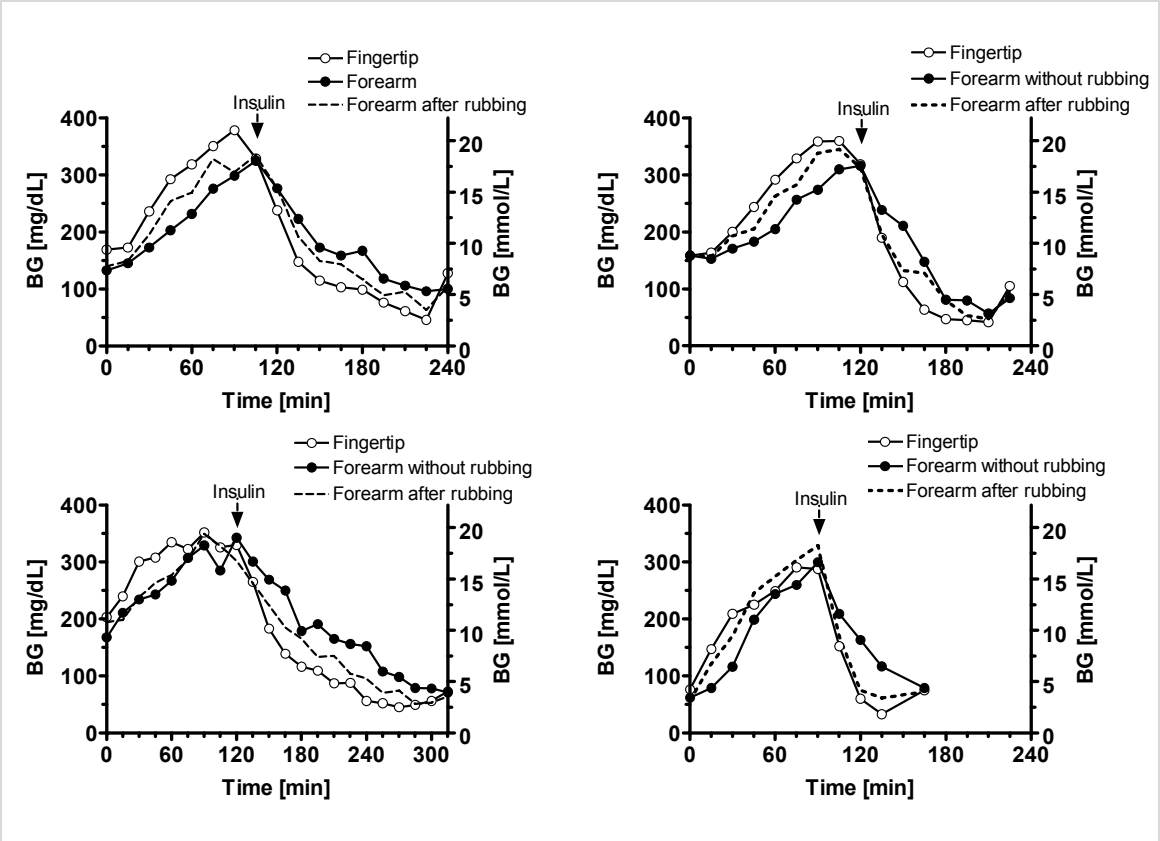

FIGURE 3: Effect of rubbing on forearm blood glucose (BG) kinetics.
Representative study BG profiles from four patients with diabetes.

7 SUMMARY AND DISCUSSION

It could be shown for the first time that capillary blood glucose kinetics within the upper dermal compartment (≤ 2 mm) are markedly site-specific. The assumption of a permanent blood glucose concentration equality within capillary blood from different body sites is proved false.

None of the observations was device-specific. Therefore, the observations should be due to site-specific physiological differences.

7.1. Capillary blood glucose kinetics at the forearm

Capillary blood glucose concentration is virtually equal between forearm and fingertip at metabolic steady-state. Unfortunately and unexpectedly, transient but clinically important blood concentration differences occur during rapid changes in systemic blood glucose concentration.

The rate of change in forearm blood glucose concentration is decelerated compared to the rate of change in capillary blood from the fingertip. Therefore, absolute blood glucose concentration at the forearm lags behind the blood glucose concentration at the fingertip by 30 minutes on average. As a result, systemic blood glucose concentration is underestimated during rapid systemic blood glucose concentration increase and overestimated during blood glucose concentration decrease if capillary blood is derived from the forearm site.

The detection of hyperglycaemia as well as hypoglycaemia can be delayed. Clinical relevance is obvious as even a few delays in hypoglycaemia detection may cause serious harm to patients with diabetes mellitus, especially in those with impaired awareness of hypoglycaemia.

This pattern (decelerated blood glucose concentration change at alternative blood glucose sampling sites resulting in blood glucose concentration-under- and overestimation) is further on called ALTERNATIVE-SITE-TESTING PHENOMENON (AST-PHENOMENON).

7.2. Capillary blood glucose kinetics at the thenar eminence

At the thenar, blood glucose concentration does not differ from the fingertip even during blood glucose changes sufficiently rapid to induce large blood glucose differences between the forearm and fingertip. In contrast to the fingertip, hypoglycaemia detection is not impaired if blood samples are obtained from the thenar.

Clinical observation and studies done during slower blood glucose changes [3;4;10;13-18] point to the critical role of a sufficient rapid blood glucose change in order to unmask the differences in glucose concentration in dermal blood compartments at different body sites, e.g., forearm and fingertip. Therefore, observing the similarity between thenar and fingertip as such gives only limited information. It is the observation of clinically identical glucose kinetics between thenar and fingertip in the face of diverging kinetics at the forearm that is the major finding in this study.

7.3. Influence of local skin manipulation (rubbing) on capillary blood glucose kinetics

Rubbing of the forearm skin can reduce blood glucose concentration differences during rapid blood glucose changes. However, due to the considerable intraindividual and interindividual variability the effect of rubbing on the forearm blood glucose concentration value is unpredictable. Therefore, rubbing of forearm skin can not be regarded as a reliable compensatory action.

7.4. Underlying Mechanisms (PLEXUS EXCHANGE MODEL)

Two anatomical and physiological facts have to be taken into account in order to explain the observed AST-PHENOMENON.

First, the observed slower glucose kinetics at the forearm are most likely related to physiologically occurring skin-type specific differences in dermal circulation. In healthy individuals as well as in type 1 and type 2 diabetics, upper-dermal blood flow is 5 to 20-times higher at glabrous skin-areas (also called: non-hairy skin type) (e.g., fingertip) than at non-glabrous skin areas (also called: hairy skin type) (e.g., forearm) [19-21]. This is mainly based on the fact that at the glabrous skin-areas many arteriovenous anastomoses are found within the upper dermis whereas in non-glabrous skin areas very few arteriovenous anastomoses exist [19;22]. In addition, capillary density is higher at glabrous skin areas (50-70/mm²) than at non-glabrous skin areas (20-40/mm²) [2;19].

Secondly, one has to consider that the main part of “capillary blood” obtained by puncturing the skin (typical penetration depth $\leq$ 2 mm) is derived from subepidermal venous plexus and only just a small fraction from capillaries [2;23].

As a consequence, at the glabrous skin-areas (e.g., fingertip) the numerous arteriovenous anastomoses can directly drain into the venous plexus. Thus, exchange of blood within the subepidermal plexus will be fast. In contrast, in non-glabrous skin areas (e.g., forearm) inflow of blood in the subepidermal plexus should be solely derived from capillaries. So it seems reasonable to postulate that blood exchange within the plexus takes longer at the non-glabrous skin areas than at glabrous skin areas. This hypothesis, further on named *PLEXUS EXCHANGE MODEL* is illustrated in FIGURE 4.

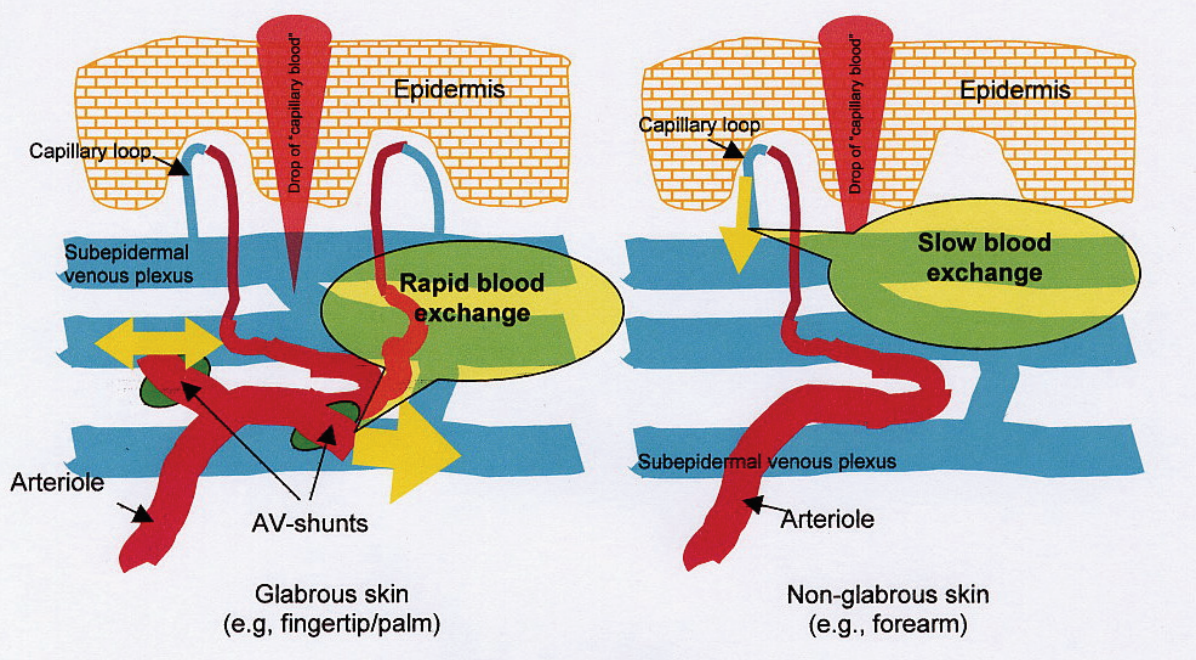

FIGURE 4: **PLEXUS EXCHANGE MODEL (schematically).**
Capillary blood obtained by puncturing the skin (red shaded cone) (typical penetration depth ≤ 2 mm) is derived from subepidermal venous plexus and just a small part from capillaries.
At glabrous skin areas (e.g., fingertip, palm) these venous plexus get blood inflow from arteriovenous (AV) shunts. Therefore, exchange of plexus blood is rapid so that a clinical apparent glucose concentration differences between capillary blood and systemic (arterial) blood is not developing even when arterial glucose concentration is changing rapidly.
At non-glabrous skin areas (e.g., forearm) blood inflow in the subepidermal plexus is derived from capillaries only. Thus, exchange of plexus blood is very slow. As a consequence, rapid systemic blood glucose concentration change can induce a considerable glucose concentration gradient between capillary and arterial blood.

As blood exchange in subepidermal plexus is not easily examinable in humans the PLEXUS EXCHANGE MODEL has not be proven directly so far. Nevertheless, there is a considerable indirect evidence of its validity as the following major experimental and clinical observations can be consistently explained by the PLEXUS EXCHANGE MODEL [24]:

- *Blood glucose kinetics at the thenar eminence* – No differences in blood glucose kinetics are found in comparison to the fingertip if capillary blood is obtained from the palm [3;4;8;25]. The thenar-eminence as well as the remaining palm belong to the glabrous skin area which possess multiple arteriovenous shunts [19].

- *Blood glucose kinetics at the thigh and abdomen* – In principle, a blood glucose kinetic phenomenon similar to the one demonstrated for the forearm has been observed if capillary blood was sampled at the thigh [8;17] and abdomen [26]. Both areas belong to the non-glabrous skin area like the forearm.
- *Influence of blood flow: Effect of pharmaceutically induced hyperaemia* – It could be shown that if blood flow at the forearm is artificially increased by the hyperaemic cream Finalgon® (nonivamide + nicoboxil) no differences in blood glucose concentration kinetics between forearm and fingertip are found [27]. Finalgon®, a remedy routinely used for inducing hyperaemia in order to sample arterialised capillary blood for blood gas analysis, induces a fivefold increase in skin blood flow [28]. Interestingly, natural forearm blood flow is about 4-6-times lower than fingertip blood flow [29]. According to the PLEXUS EXCHANGE MODEL blood glucose concentration kinetics have to be equal if blood flow is equal. Thus, the observation that artificially induced hyperaemia eliminates the AST-PHENOMENON at the forearm site further supports the PLEXUS EXCHANGE MODEL.
- *Influence of blood flow: Effect of Rubbing* – Rubbing of forearm skin prior to skin puncture reduced blood glucose concentration differences on average. If one looks at individual experiments it is obvious that sometimes any blood glucose concentration differences disappeared when the rubbing procedure was applied, while (even in the same patient) in the next moment the rubbing procedure did not have any effect at all. To understand this putative contradiction, the effect of rubbing on upper dermal circulation was examined by scanning laser Doppler flowmetry [29]. It could be shown, that at the forearm skin manipulation by rubbing increases dermal blood flow on average. But remarkable spatial heterogeneity in the hyperaemic effect of rubbing was observed as spots with no blood flow increase were found in close proximity to areas where forearm blood flow reached values comparable to the fingertip. Thus, the heterogeneity of the effect of rubbing on the blood glucose concentration can be fully explained by the spatial heterogeneity of the hyperaemic effect of rubbing.
- *Influence of blood glucose change velocity* – Blood glucose change velocity and the magnitude of occurring blood glucose difference are directly related [17;18]. The faster the systemic blood glucose change, the larger is the observed blood glucose difference. If systemic blood glucose concentration does not change

faster than 2 $mg \cdot dL^{-1} \cdot min^{-1}$ the AST-PHENOMENON is masked by the inherent imprecision of blood glucose self-measurement. Can this be explained by the PLEXUS EXCHANGE MODEL? According to the model it takes a relevant time period to exchange blood within the subepidermal venous plexus of non-glabrous skin area. From this follows that the capillary blood sample derived by skin puncture represents a time-averaged mean of the blood glucose concentrations within the time period that is needed to exchange the plexus blood. If systemic blood glucose concentration (i.e. blood glucose concentration in plexus inflow) changes only irrelevantly during the exchange period then the capillary blood glucose concentration will be close to systemic blood glucose concentration at the sampling moment. But if systemic blood glucose concentration changes quickly in the given period, the difference between time-averaged glucose concentration (i.e., plexus blood glucose concentration at the sampling moment) and systemic blood glucose concentration at the sampling moment will be large.

All observations in the field of alternative site monitoring, as discussed above, can be consistently explained by the PLEXUS EXCHANGE MODEL. This certainly is not a formal proof of the model, but nevertheless is a strong evidence in favour of the model. At present, a direct experimental proof of the model is not yet available due to technical difficulties, especially as skin physiology must remain unchanged by the measuring technique itself. Therefore, the PLEXUS EXCHANGE MODEL is momentarily the best explanation of the AST-PHENOMENON and may thereby be a valuable guide to the further understanding of dermal glucose concentration kinetics.

7.5. Clinical recommendations for capillary blood glucose testing at alternative sites

Despite the described problems, it has to be acknowledged that puncture-associated pain is markedly reduced by alternative site blood glucose testing [3-10;30;31]. Therefore, alternative site blood glucose testing can be a valuable and attractive additional option for patients performing blood glucose self-monitoring if recommendations for a differentiated use are followed (TABLE 6).

DIFFERENTIATED RECOMMENDATIONS	
At hairy skin areas (i.e., arm, leg, abdomen)	
✓	Metabolic steady-states (e.g., preprandially)
⚠	Rapid blood glucose-changes (e.g., <2hrs. postprandially)
✗	Exclusion of hypoglycaemia
At hairless skin areas (i.e., palm)	
✓	Metabolic steady-states & during rapid blood glucose change

TABLE 6: Clinical recommendations for the differentiated use of alternative site blood glucose Testing.

At non-glabrous skin areas (e.g., arm, leg, abdomen), blood glucose monitoring is safe in metabolic steady-states (e.g., fasting state, preprandially). But during rapid blood glucose changes, e.g., postprandially, during exercise or induced by insulin administration, glabrous skin areas should not be used for blood glucose testing due to risky delays in hypo- and hyperglycaemia detection. In particular, we would not recommend to rely on blood glucose values from the these sites if there is any concern about hypoglycaemia (e.g., when driving a car).

At glabrous skin areas (e.g., thenar eminence, palm), blood glucose monitoring is safe in metabolic steady-states as well as in periods of rapid blood glucose concentration change.

7.6. Consequences for other glucose monitoring techniques

As our observations are based on physiological differences in local dermal blood flow they presumably affect any glucose test system which relies on glucose values from the upper skin layer of non-glabrous skin areas [32;33]. Test systems measuring glucose concentration within dermal interstitial fluid should theoretically detect rapid blood glucose concentration changes only with significant delay. As glucose diffusion into the interstitial space will need additional time the observable time delay might be even greater than in alternative site blood glucose testing.

The correctness of the assumption that other devices measuring within the upper dermal compartment are prone to the AST-PHENOMENON has just recently been supported by Kulcu *et al.*. They analysed data gathered with the GlucoWatch® (Cygnus, USA), which measures glucose concentration within upper dermal interstitial fluid by a reverse iontophoretic approach, and demonstrated glucose kinetics nearly identical to the AST-PHENOMENON, i.e., a blunted blood glucose change velocity during rapid blood glucose increase and decrease [34].

Other devices measuring within the upper dermal compartment like the non-invasive optical devices Diasensor® 1000 (Biocontrol Technology, USA) or Pendra™ (Pendragon, Switzerland) have so far not been studied with concern to the AST-phenomenon.

Another set of systems measure glucose within deep-dermal or subcutaneous interstitial fluid, e.g., CGMS™ (Medtronic MiniMed, USA), GlucoDay™ (Menarini, Italy), GlucOnline (Disetronic, Switzerland) or FreeStyle Navigator™ (Therasense, USA). Microcirculation in the deep-dermal or subcutaneous compartment is different to the upper dermal (subepidermal) compartment [2;35] and therefore results obtained in the upper dermal compartment cannot directly be transferred to this compartment. The data on the time delay in glucose concentration published so far is diverse [33;34;36]. Nevertheless, glucose kinetics in the deep dermal/ subcutaneous compartment have to be studied in further detail during rapid blood glucose concentration change.

On the other hand, there are also possibilities that a potential delay is diminished by “side-effects” of the measuring techniques themselves. For example, local blood flow

could be increased by the subclinical skin inflammation induced by the measuring techniques [37].

Therefore, it is difficult to predict wither a certain device is prone to the AST-PHENOMENON. Any of these devices should, thus, be tested vigorously during rapid blood glucose concentration changes before being launched to the market.

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9 CURRICULUM VITAE

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11 REPRINTS OF ORIGINAL STUDIES AND PUBLISHED DISCUSSIONS

Reprints of original studies

Study 1

Jungheim, K., Koschinsky, T.

Risky delay of hypoglycemia detection by glucose monitoring at the arm.

Diabetes Care 25: 1303-1304, 2001

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High Incidence of Maternal Transmission of Diabetes in Obese Uruguayan Children

Metabolic experiences in utero, as reflected by a high amniotic fluid insulin concentration, may condition diabetes-associated risk factors such as high BMI (1).

As part of our survey (performed between June and September 2000) of overweight and obese Uruguayan children (age 9–12 years) and the contributing factors of their condition, we evaluated the incidence of maternal transmission of diabetes.

The cross-sectional survey comprised 886 children (452 boys and 434 girls), living in Montevideo, Uruguay, and other cities in Uruguay with >10,000 inhabitants, who were interviewed at home in the presence of at least one parent. The sample was stratified, aleatory, polyetapic, and systematic according to the last national survey (2) and represented an urban population (total 3,200,000: 91% living in urban zone, 88% Caucasian, 8% crossbred, and 4% black). The children were weighed and measured in light clothes and without shoes using equal balances and scales. BMI was calculated according to tables (3) for age and sex. Three subgroups were established: normal weight (NW) (BMI ≤ 85th percentile), overweight (OW) (BMI 85th to 94.9th percentiles), and obese (OB) (BMI ≥ 95th percentile). Incidence of antecedent diabetes was inquired and recorded for both the mother and father.

A total of 17% of the children were classified as OW and 9% as OB. No differences in BMI were found between sexes at the age interval studied. All of the mothers in the OB group had type 2 diabetes, 1% of the mothers in the NW and OW groups had type 1 diabetes, and no differences were found between diabetic and nondiabetic fathers. This maternal transmission of type 2 diabetes was addressed in a recent study (4).

These are the first data regarding Uruguayan children that emphasize the significance of intrauterine environment with respect to exceeding transmission obesity and insulin resistance (a prediabetic condition). Recent reports have suggested that early consequences of an adverse in utero environment do not seem to be attenuating with time (5). Considering the vertiginous increase in type 2 diabetes among adolescents (6) and the pivotal role that obesity plays in the disease (7), we feel these data are very important for the prevention of type 2 diabetes in our clinical practice.

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Risky Delay of Hypoglycemia Detection by Glucose Monitoring at the Arm

Several devices for self-monitoring of blood glucose (SMBG) (e.g., AtLast, Amira; OneTouch Ultra, LifeScan; FreeStyle, TheraSense, Alameda, CA; Glucometer-Elite XL+Microlet-Vaculance, Bayer; and Sof-Tact, Abbott) recently received Food and Drug Administration approval for alternative site monitoring of capillary blood glucose. These alternatives are marketed with considerable efforts under the assumption that capillary blood glucose measurements, e.g., those taken at the forearm, do not differ from the results obtained by classic finger pricking. Diabetic patients using different devices for SMBG reported

Letters

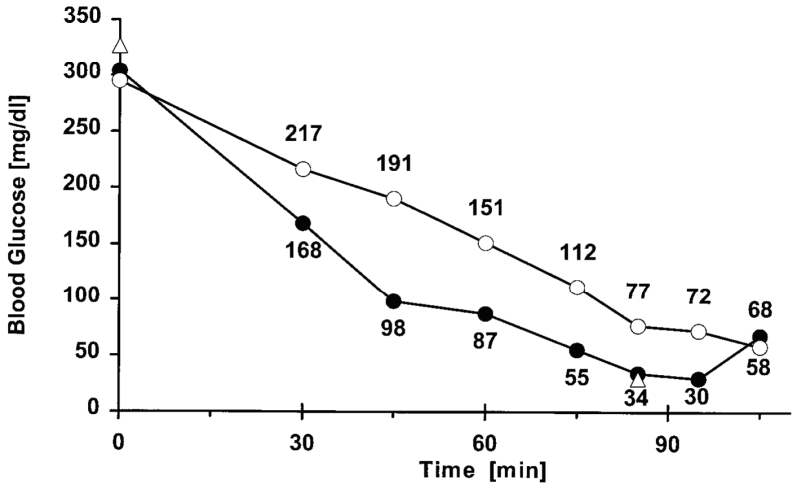

Figure 1—*Effect of a fast blood glucose decrease (3 mg · dl^{-1} · min) on capillary blood glucose values at the fingertip (●) and at the forearm (○) using the FreeStyle system in a type 1 diabetic patient. Control blood glucose values from the fingertip measured at the laboratory are indicated (△).*

discrepancies between clinical symptoms of hypoglycemia and normoglycemic SMBG values at the forearm. Neither standardized quality control assessments of technical performance of such SMBG devices (1,2) nor patient device handling resulted in any obvious explanation of the reported discrepancies. Because of this, we examined whether or not fast blood glucose changes over a larger range of blood glucose concentrations could result in clinically relevant blood glucose differences between forearm and fingertip.

Capillary blood glucose samples were taken from the fingertip and the forearm of six male type 1 diabetic patients on intensified insulin treatment (age 26–54 years, diabetes duration 0.1–25 years) using the FreeStyle system (TheraSense) because it required the smallest blood glucose amount: 0.3 μl/sample. To avoid any disturbance of the normal regional blood flow, the forearm skin was not rubbed before blood glucose sampling, as recommended by the manufacturer. The following protocol was applied: after an overnight fast the usual prebreakfast insulin was omitted and the breakfast was replaced by oral Dextro O.G.T. (Roche, Mannheim, Germany), equivalent to 75 g glucose, in order to achieve blood glucose values of 300–400 mg/dl. Then the patient's usual short-acting insulin was given intravenously at an individual dose (6–15 U/injection). The blood glucose decrease was followed every 5–15 min until either steady state or hypoglycemia (<60 mg/dl) was reached. Hypoglycemia was compensated by oral glucose. For control purposes, additional blood glucose samples from the fingertip were analyzed by the Gluco-quant method (Roche, Mannheim, Germany).

The capillary blood glucose decrease (mean ± SD) at the forearm (208 ± 38 mg/dl) was significantly smaller than at the fingertip (295 ± 16 mg/dl) (Student's paired *t* test: $P < 0.01$) within 111 ± 26 min for all patients. An example is shown in Fig. 1. For the two patients with hypoglycemic unawareness, the first asymptomatic hypoglycemic values at the fingertip (51 and 53 mg/dl) were accompanied by normoglycemic values at the forearm (142 and 159 mg/dl). Compared with the fingertip, it took an additional 27–34 min until the capillary blood glucose levels at the forearm reached hypoglycemic values.

Despite the preliminary state of our investigation, the consistency of clinically relevant delays of blood glucose changes at the forearm prompted us to draw attention to a potentially very dangerous situation. Our results raise the possibility that the delayed glucose concentration changes at the forearm occur physiologically. To our knowledge, this has not been fully recognized as a potential problem by the certifying administrations in the U.S. or Europe.

Even a few delays of hypoglycemia detection could unnecessarily endanger the life of diabetic patients. Because of this, we strongly recommend providing sufficient evidence that the suggested use of SMBG at the forearm and other alternative sites does not result in a risky delay of hypoglycemia detection. Meanwhile, SMBG at the forearm should only be used when ongoing fast blood glucose changes can be excluded.

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COMMENTS AND RESPONSES

Response to Jungheim and Koschinsky

Glucose monitoring at the arm

In this issue of *Diabetes* Care, we read with interest the letter of Jungheim and Koschinsky (1) comparing glucose measurements using blood extracted from the finger versus blood extracted from the forearm. The phenomenon they discuss is not a simple function of measurement technology, but a complex function of circulatory physiology. Our cognizance and study of the phenomenon resulted in the explicit instruction to the users of the TheraSense FreeStyle blood

Reprints of original studies

Study 2

Jungheim, K., Koschinsky, T.
Glucose monitoring at the arm: risky delays of hypoglycemia and hyperglycemia detection.
Diabetes Care 25: 956-960, 2002

Clinical Care/Education/Nutrition
ORIGINAL ARTICLE

Glucose Monitoring at the Arm

Risky delays of hypoglycemia and hyperglycemia detection

KARSTEN JUNGHEIM, MD
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OBJECTIVE — We have examined whether rapid changes in blood glucose (BG) result in clinically relevant differences between capillary BG values measured at the forearm and the fingertip and whether local rubbing of the skin before blood sampling can diminish such differences.

RESEARCH DESIGN AND METHODS — Capillary BG samples were collected every 15 min for 3–5 h from the fingertip and the forearm of 17 insulin-treated diabetic patients and analyzed with different glucose monitors (FreeStyle, One Touch Ultra, and Soft-Sense). In a subgroup of patients (n = 8), local rubbing of the forearm skin was performed before blood sampling. A rapid increase in BG was induced by oral administration of glucose, and subsequently, a rapid decrease in glucose was induced by intravenous administration of insulin.

RESULTS — In the fasting state, the BG values at the fingertip and at the forearm were similar (7.8 ± 2.4 vs. 7.2 ± 2.3 mmol/l, P = 0.06). However, during rapid increase in glucose, BG values at the fingertip were consistently higher than at the forearm (maximal difference 4.6 ± 1.2 mmol/l, $P < 0.001$). During rapid decrease in glucose, lower BG values were recorded at the fingertip (maximal difference to forearm 5.0 ± 1.0 mmol/l, $P < 0.001$). At the forearm, BG was delayed by a median of 35 min ($P < 0.01$) in relation to the fingertip. Rubbing of forearm skin decreased the observed differences but with a large intraindividual and interindividual variability. There were no obvious device-specific differences.

CONCLUSIONS — To avoid risky delays of hyperglycemia and hypoglycemia detection, BG monitoring at the arm should be limited to situations in which ongoing rapid changes in BG can be excluded.

Diabetes Care 25:956–960, 2002

Alternate site testing of capillary blood glucose (BG), i.e., at sites other than the fingertip, has been requested by individuals with diabetes to reduce the pain associated with finger-pricking and by their physicians to increase compliance with self-monitoring of blood glucose (SMBG). SMBG is an essential part of diabetes management, e.g., for insulin adjustments, and plays an important role in the detection of impending hypoglycemia. Blood samples for SMBG are usually obtained by pricking the fingertip, where BG closely follows arterial BG concentrations. However, pricking the fingertip is painful and uncomfortable, even with modern lancing devices.

Sampling at sites less densely innervated than the fingertip is associated with significantly reduced pain (1–3) and is consequently an attractive alternative. So far, this has been hindered by the minute blood volume (≤3 μl) obtainable from these sites. Recently, several new SMBG devices (Accu-Check Active, Roche Diagnostics, Indianapolis, IN; AtLast, Amira, Scotts Valley, CA; FreeStyle, TheraSense, Alameda, CA; Glucometer Elite XL in combination with Microlet Vaculance, Bayer, Tarrytown, NY; One Touch Ultra, LifeScan, Milpitas, CA; Soft-Sense, Abbott, Bedford, MA) with sample volumes between 0.3 and 2.6 μl received approval from the U.S. Food and Drug Administration for alternate site testing at the forearm, upper arm, abdomen, thigh, and calf. They have been marketed with considerable efforts in Europe and America under the assumption that capillary BG measurements at alternate sites do not differ from the usual measurements at the fingertip.

We were alerted by patients with diabetes who reported discrepancies between clinical symptoms of hypoglycemia with hypoglycemic values at the finger and normoglycemic SMBG values measured at the forearm (e.g., 2.8 vs. 5.6 mmol/l) (4). Neither standardized quality control assessments of technical performance (2,5) nor patient device handling resulted in any obvious explanation of the reported discrepancies. Because the clinical circumstances pointed to the critical role of rapid BG changes, we studied *1*) whether rapid BG changes result in clinically relevant BG differences between the forearm and the fingertip, and *2*) whether local rubbing of the forearm skin (recommended by some manufacturers to increase blood volume) diminishes such differences.

RESEARCH DESIGN AND METHODS

Participants

Insulin-treated patients with diabetes were consecutively recruited between December 2000 and April 2001 among inpatients from the German Diabetes Research Institute (Duesseldorf, Germany) who were undergoing routine hypoglycemia awareness testing (n = 20). Decision for hypoglycemia awareness testing was independently made by the caring physicians. Three patients refused to participate due to the required additional BG sampling. A total of 17 patients participated in the study: 2 women, 15 men; age range 20–59 years (median 38);

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Abbreviations: BG, blood glucose; SMBG, self-monitoring of blood glucose.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

13 patients with type 1 diabetes, 4 patients with type 2 diabetes; duration of diabetes 2 weeks to 28 years (median 13). Diabetes-specific complications were absent in 12 patients, whereas mild microvascular complications were observed in 5 patients (retinopathy in 5, sensorimotor neuropathy in 2, microalbuminuria in 2). Five patients reported impaired awareness of hypoglycemia.

BG measurements

Capillary BG samples were analyzed with SMBG devices approved for quantitative glucose measurements in capillary blood taken from the fingertip as well as the forearm. For BG measurements, the following SMBG devices were used: FreeStyle (TheraSense, Alameda, CA) requiring a sample volume of 0.3 μl (10 patients), MediSense Soft-Sense (Abbott, Bedford, MA) requiring a sample volume of 2.6 μl (4 patients), and One Touch Ultra (LifeScan, Milpitas, CA) requiring a sample volume of 1.0 μl (3 patients).

In all patients, additional capillary whole blood samples (20 μl) from the fingertip were collected in parallel to the SMBG device samples and analyzed in our clinical chemistry laboratory by a hexokinase-based method (Gluco-quant; Roche Diagnostics, Mannheim, Germany). These laboratory values matched the respective fingertip values measured with the examined SMBG devices (Figs. 1 and 2; Table 1). The technical performance of all BG monitors within the study was evaluated (6) and was within the limits expected for SMBG devices [median (quartiles) of relative glucose deviation (i.e., capillary BG from the fingertip: SMBG monitor value divided by clinical chemistry lab value) was 0.9% (−1.9; 5.8) for Free Style, 2.9% (−3.6; 7.6) for Soft-Sense, and 3.7% (−0.8; 8.9) for One Touch Ultra].

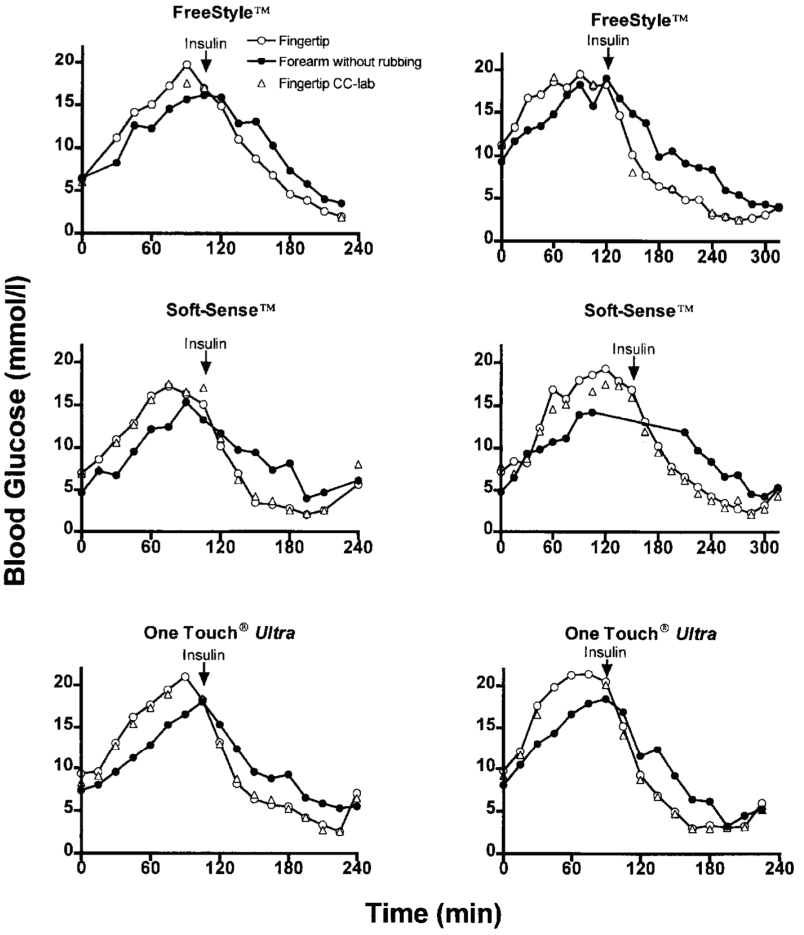

Figure 1—*Representative study BG profiles from the forearm and the fingertip of six patients with diabetes. Changes in BG were induced with 75 g oral glucose (t = 0) and by intravenous insulin injection. BG was analyzed using three different BG monitors as well as a clinical chemistry laboratory (CC-lab) method.*

Procedures

After an overnight fast and on their individual basal insulin, the patients' prebreakfast rapid-acting insulin was omitted, and the breakfast was replaced by an oral glucose load (Dextro O.G-T.; Hoffmann-LaRoche, Grenzach-Wyhlen, Germany), equivalent to 75 g glucose, to achieve BG values of 16–22 mmol/l. The glucose load was reduced to half in those patients with a baseline fingertip BG >10 mmol/l to reach comparable BG values of 16–22 mmol/l. Then, the patient's usual short-acting insulin was injected intravenously at an individual dose (6–40 units) to induce a fast decrease in BG (>0.1 mmol · l^{-1} · min^{-1}) down to hypoglycemic values (≤3.5 mmol/l). Hypoglycemia was treated by oral administration of glucose.

Capillary blood samples were collected by a trained research nurse in parallel (within 3 min) from the fingertip (lateral pulps of fingers 2–4) and the forearm (ventral and dorsoradial surface) every 15 min. In each patient, the same BG monitor was used for capillary BG measurements at both sites. The forearm skin was not rubbed before BG sampling, as recommended by some manufacturers, to avoid any disturbance of the normal regional blood flow. In a subset of patients (n = 8), additional blood samples were collected from the other forearm after a research nurse rubbed the forearm skin area (≈20 cm^2), which was subsequently used for lancing. The rubbing required 5–10 s and aimed to result in marked warming and redness of the skin area.

All procedures were followed in accordance with the standards of the Ethical committee at the Heinrich-Heine University (Duesseldorf, Germany), and written informed consent was obtained from each participant before the study.

Data analysis

Glucose profiles were analyzed separately for the increase part, i.e., from the ingestion

Glucose monitoring at the arm

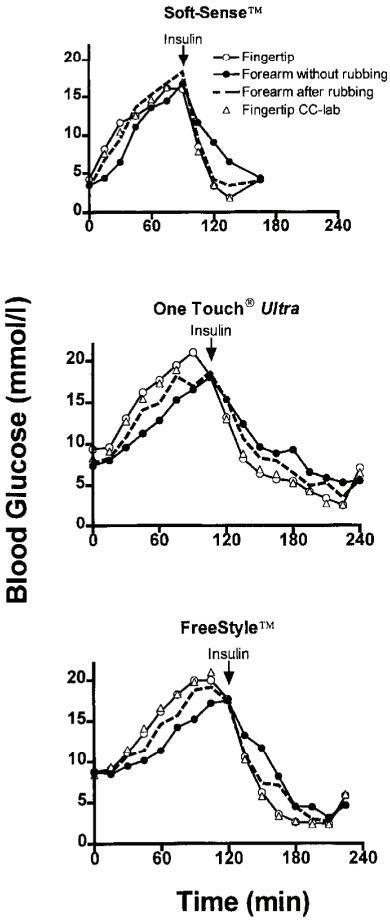

Figure 2—*Effect of rubbing on forearm BG values: representative study BG profiles from three patients with diabetes. BG changes were induced and measured as described in Fig. 1.*

of the glucose load to the BG maximum measured at the fingertip, and the decrease part, i.e., from insulin injection to the BG minimum measured at the fingertip.

Data were compared by a two-sided Wilcoxon's matched-pairs signed-rank test. If appropriate, *P* values were adapted according to the Bonferroni procedure. A *P* value <0.05 was considered statistically significant. Time delays in forearm BG increase and decrease were determined at a BG level of 3.5, 5.5, and 14 mmol/l, respectively. Unless otherwise stated, data are expressed as median (interquartile range).

RESULTS — With all three BG monitors, we observed similar capillary BG differences between the forearm and the fingertip during the increase part as well as the decrease part. Representative examples of all BG monitors are shown in Fig. 1. For further analysis, results of all BG monitors were combined.

At baseline, no relevant differences between BG values at the finger and forearm [7.7 (2.9) vs. 6.5 (2.4) mmol/l, $P = 0.06$] were observed. The increase in BG at the fingertip was consistently larger than that at the forearm [11.5 (2.4) vs. 8.4 (1.9) mmol/l, $P < 0.001$]. The rate of increase in BG measured at the fingertip was 0.13 ± 0.03 mmol $\cdot$ l^{-1} $\cdot$ min^{-1}. An individual maximal difference in BG between forearm and finger of 4.7 mmol/l (1.3) (range 2.6–7.6) was observed 30–90 min after the ingestion of glucose. The decrease in BG at the fingertip was also consistently larger than that at the forearm [15.0 (1.6) vs. 12.1 (2.4) mmol/l, $P < 0.001$]. The rate of decrease in BG measured at the fingertip was 0.17 ± 0.06 mmol $\cdot$ l^{-1} $\cdot$ min^{-1}. An individual maximal difference in BG between forearm and finger of 5.4 mmol/l (1.6) (range 3.4–6.6) was observed 15–75 min after administration of insulin. At the first hypoglycemic fingertip BG value (≤3.5 mmol/l), 80% of forearm BG values were ≥5.0 mmol/l (Table 1).

During the increase and decrease parts, BG at the forearm was lagging behind BG at the fingertip by a median of 27 min (6–91, $P < 0.001$), of 35 min (22–67, $P < 0.001$), and of 34 min (27–35, $P < 0.05$) at 14.0, 5.5, and 3.5 mmol/l, respectively.

There was a large intraindividual and interindividual variation of the rubbing effect on the finger-forearm BG difference in the subset of patients ($n = 8$) on which a rubbing procedure was performed. In these patients, the effect ranged from virtually no change of forearm BG to the establishment of full equilibration with the fingertip BG (Fig. 2). On average, the individual maximal difference between forearm and finger was reduced during the increase part from 4.5 ± 0.7 to 3.1 ± 1.1 mmol/l ($P < 0.05$) and during the decrease part from 4.8 ± 1.1 to 3.0 ± 0.9 mmol/l ($P < 0.01$).

CONCLUSIONS — Glucose monitoring at the arm is an attractive, nearly painless alternative to the more painful fingertip site. BG values from both sites are virtually equal at metabolic steady state. Unfortunately, due to rapid BG changes, transient but clinically relevant differences between forearm BG and the fingertip BG occur. During rapid BG changes, the forearm BG is lagging behind the fingertip BG by >30 min on average. As a result, the detection of hyperglycemia as well as hypoglycemia can be delayed. Clinical relevance is obvious, as even few delays of hypoglycemia detection could cause serious adverse events in diabetic patients, especially in those with impaired awareness of hypoglycemia.

Several systems for BG testing at alternate sites have been recently approved according to the provided evidence that BG values from these sites do not differ from values measured in blood samples collected at the fingertip. These results are related to the general design of standard study protocols for the technical and clinical evaluation of SMBG devices (7). They do not specify whether BG values must be taken during periods of slow or rapid BG changes. Actually, the BG measurements used for evaluation are normally taken for insulin dose adjustments and therefore focus on fasting and preprandial values, i.e., times usually not characterized by rapid BG changes. Therefore, it is not surprising that the observed differences during rapid BG changes were overlooked. Similarly, studies comparing glucose values measured in dermal interstitial fluid with those measured in blood were either done in the fasting state or during slow or moderate BG changes (8–12) and might therefore not have found significant differences.

The observed slower glucose kinetics at the forearm are most likely related to physiologically occurring site-specific differences in dermal circulation. In healthy individuals as well as those with type 1 and type 2 diabetes, dermal blood flow is 5–20 times higher at the fingertip than at the forearm (13–15). This is due to the fact that arteriovenous anastomoses within the dermis are numerous in glabrous (hairless) skin (e.g., fingertip) but nearly absent in nonglabrous (hairy) skin (e.g., forearm) (13,16). Therefore, the total exchange of blood within cutaneous venous plexus, from which blood obtained by skin-pricking is mainly derived (17), will take more time at the forearm than at the fingertip. This interpretation is supported by the ameliorating effect of local rubbing of the skin, which increases local blood flow.

Because our observations are based

Table 1—*Capillary forearm BG compared with the first hypoglycemic value (BG ≤3.5 mmol/l) at the fingertip*

Blood glucose (mmol/l)			
Forearm	Fingertip		
BG monitor	BG monitor	CC-lab	Clinical symptoms of hypoglycemia
9.4^{S}	3.5^{S}	4.2	Drowsiness
9.0^{S}	3.3^{S}	3.4	None
8.8^{F}	2.9^{F}	ND	None†
8.4^{F}	3.1^{F}	3.4	None†
7.9^{F}	2.8^{F}	ND	None†
6.6^{S}	3.5^{S}	ND	Visual disturbance, warmth
6.4^{U}	3.0^{U}	2.9	None†
6.2^{F}	3.1^{F}	ND	Hunger, drowsiness
5.9^{U}	3.4^{U}	2.8	Sweating, tremor
5.9^{F}	2.4^{F}	2.2	Hunger, drowsiness, dizziness
5.8^{F}	3.3^{F}	ND	Drowsiness
5.0^{F}	2.2^{F}	1.8	Sweating, nausea
4.5^{F}	2.6^{F}	2.7	None
4.1^{F}	2.6^{F}	ND	None†
3.9^{S}	3.1^{S}	3.2	None

Additional capillary blood samples from the fingertip were analyzed using a clinical chemistry laboratory method. Clinical symptoms of hypoglycemia are given according to patients' perception. Hypoglycemia was not reached in two patients (data not displayed). CC-lab, clinical chemistry laboratory; ND, not done; S, Soft-Sense; F, FreeStyle, U, One Touch Ultra; †known history of impaired awareness of hypoglycemia.

on physiological differences in local dermal blood flow, they presumably affect any glucose test system that relies on glucose values from the upper skin layer of the arm (18). This is in accordance with our observations in all three examined BG monitors and supported by findings of their manufacturers (19–21). Test systems that measure glucose concentration within dermal interstitial fluid, such as the recently approved GlucoWatch (Cygnus, Redwood City, CA) or noninvasive optical devices such as the Diasensor 1,000 (Biocontrol Technology, Indiana, PA) might possibly detect rapid changes in BG with that significant delay. Due to the similarity of dermal blood flow, BG samples taken at other nonglabrous skin areas (e.g., upper arm, abdomen, thigh, or calf) could be affected in a similar way.

Rubbing of the forearm skin can reduce differences in BG during rapid changes in BG. However, due to the considerable intra- and interindividual variability the effect of rubbing on the forearm BG value is unpredictable. Therefore, rubbing of forearm skin cannot be regarded as a reliable compensatory action.

We conclude that BG testing at the forearm under metabolic steady-state conditions (e.g., fasting state, preprandially) can be a reliable and valuable alternative to BG testing at the usual finger site. However, during rapid changes in BG, e.g., postprandially or insulin-induced, the forearm should not be used for BG testing due to risky delays in detection of hypoglycemia and hyperglycemia. In addition, we would not recommend relying on BG values from the forearm if there is any concern about hypoglycemia (e.g., when driving a car). Diabetic patients and their health care providers should be informed and trained specifically in the proper use of alternate site testing at the arm. Before recommending other alternate sites for BG testing, site-specific information about the reliability of BG results during rapid BG changes should be provided. Evaluation protocols should be extended appropriately to ensure that BG is tested during periods of sufficiently rapid change in BG. There is a need for more studies covering various aspects of daily life (e.g., physical exercise or vasoactive drugs) that might change the BG equilibration process at alternate sites.

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Reprints of original studies

Study 3

Jungheim, K., Koschinsky, T.

Glucose monitoring at the thenar: Evaluation of upper dermal blood glucose kinetics during rapid systemic blood glucose changes.

Horm Metab Res 34: 325-329, 2002

K. Jungheim
T. Koschinsky

Glucose Monitoring at the Thenar: Evaluation of Upper Dermal Blood Glucose Kinetics During Rapid Systemic Blood Glucose Changes

Abstract

Objective: We compared blood glucose measurements at the thenar with those at the fingertip during glucose increase and decrease that was rapid enough to induce glucose differences between the forearm and the fingertip. **Methods:** A rapid glucose increase was induced by oral glucose; subsequently, a rapid glucose decrease was induced by intravenous insulin in 16 insulin-treated patients with diabetes. Capillary samples were taken in parallel from the thenar and fingertip. Different glucose monitors (FreeStyle™, OneTouch®Ultra, Soft-Sense™) were used. Additional samples were taken from the forearm (n = 10 patients) in order to demonstrate that the blood glucose change achieved was rapid enough to principally induce glucose differences at alternative sites. **Results:** Neither blood glucose at baseline (135 ± 34 *vs.* 136 ± 41 mg/dl, p = 0.86) nor glucose amplitude during increase (190 ± 35 *vs.* 188 ± 41 mg/dl, p = 0.65) or decrease (255 ± 32 *vs.* 257 ± 45 mg/dl, p = 0.83) differed significantly between the fingertip and the thenar. Intra-individual average thenar-fingertip glucose difference was – 2 ± 12 (p = 1.00) and + 5 ± 9 mg/dl (p = 0.11). In the subgroup, intra-individual average forearm-finger difference was – 50 ± 19 (p < 0.01) and + 45 ± 11 mg/dl (p < 0.01) during glucose-increase and decrease, respectively. There were no obvious device-specific differences. **Conclusions:** Blood glucose measurements at the thenar are a safe alternative to measurements at the fingertip at steady state as well as during blood glucose change that is sufficiently rapid to induce clinically relevant differences between forearm and fingertip.

Key words
Alternative-Site Blood-Glucose Testing · Self-Monitoring of Blood Glucose · Fingertip · Dermal Blood Flow · Hypoglycaemia

Introduction

Several new devices for self-monitoring of blood glucose (SMBG) (Accu-Chek Active™/Roche Diagnostics; AtLast®/Amira; FreeStyle™/TheraSense; One Touch®*Ultra*/LifeScan; Soft-Sense™/Abbott) have recently been approved for alternative site testing, that is, SMBG at sites other than the fingertip. Currently, the majority of patients with diabetes obtain capillary blood glucose (BG) samples by lancing the fingertip, a procedure which is particularly associated with pain. In contrast to the fingertip, sensible innervation at alternative sites such as the palm, arm and leg is less dense. Skin puncture should therefore be less painful at these sites, and so far, this has been confirmed for the forearm [1 – 4], abdomen [5] and palm [1]. Consequently, alternative site BG testing presents an important potential for improving the quality of life of patients with diabetes. In addition, it may improve metabolic control by improving patients' compliance to SMBG [6].

Glucose concentration in capillary blood obtained from the fingertip closely follows the arterial glucose concentration without any significant delay as well as hypoglycaemic symptoms correlate to it. For these reasons, clinical equivalency to the fingertip should be demanded for any body site used for alternative glucose testing. For the forearm, this has been unequivocally shown during metabolic steady-state [1 – 4, 7 – 10, 16]. But during rapid BG changes, clinically relevant differences (up to 200 mg/dl) have been observed [7 – 12] as BG concentration at the forearm

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Table **1** Characteristics of participating diabetic patients (N = 16)

		Mean ± SD	*(Range)*
Age	(years)	37 ± 11	(18 – 62)
Gender			
Female	(n)	3/16	
Male	(n)	13/16	
Body-Mass-Index	(kg/m^2)	26 ± 4	(20 – 37)
DM-type			
Type 1	(n)	13/16	
Type 2	(n)	3/16	
DM-duration	(years)	11.6 ± 9.2	(0.06 – 28)
Microvascular complications			
None	(n)	13/16	
Non-proliferative retinopathy	(n)	2/16	
Sensomotoric neuropathy	(n)	2/16	
Microalbuminuria	(n)	1/16	
Hypoglycaemia unawareness	(n)	2/16	
HbA1c	(%)	9.3 ± 2.9	(5.4 – 15.3)

DM denotes diabetes mellitus; SD denotes standard-deviation.

lags by up to 60 minutes behind BG concentration at the fingertip. This lag phenomenon results in lower forearm BG than in the corresponding fingertip BG during BG increase, and higher forearm BG during BG decrease. The possibility of risky delays in detection of hyper- and hypoglycaemia have consequently led to the inconvenient recommendation of restricting SMBG at alternative sites to situations of presumed metabolic steady state [1,8 – 10,12].

The lag phenomenon observed may be due to differences in upper dermal blood flow since, physiologically, flow is considerably higher in glabrous (non-hairy) skin areas such as the fingertip and palm than non-glabrous (hairy) skin areas such as the forearm [13 – 15]. If this causal link is accurate, the only approved alternative testing site belonging to a glabrous skin area – the palm – may not present the observed delays. This would be particularly attractive since it would offer patients the advantages of alternative-site testing without subjecting them to any additional risk.

Therefore, we compared BG measurements at the thenar eminence (as part of the palm) and the forearm with that at the fingertip during BG increase and decrease sufficiently rapid to induce BG differences between the forearm and the fingertip.

Methods

Participants

Insulin-treated patients with diabetes mellitus were consecutively recruited within 3 months from among the inpatients of the German Diabetes Research Institute in Düsseldorf, Germany, who were undergoing routine hypoglycaemia awareness testing. Decision for hypoglycaemia awareness testing was independently made by the physicians directly involved. The characteristics of participating patients (n = 16) are summarised in Table **1**.

Blood glucose measurements

Capillary BG samples were analysed using SMBG devices approved for quantitative glucose measurement in capillary blood taken from the fingertip as well as from alternative sites. For BG measurements, the following SMBG devices were used: FreeStyle™ (TheraSense, Alameda, CA, USA) requiring a sample volume of 0.3 µl (10 patients), MediSense® Soft-Sense™ (Abbott, Bedford, MA, USA) requiring a sample volume of 2.6 µl (3 patients) and One Touch® *Ultra* (LifeScan, Milpitas, CA, USA) requiring a sample volume of 1.0 µl (3 patients).

From all patients, additional capillary whole-blood samples (20 µl) from the fingertip were taken in parallel to the SMBG device samples and analysed in our clinical chemistry laboratory by a hexokinase-based method (Gluco-quant®, Roche Diagnostics, Mannheim, Germany). The technical performance of all SMBG monitors within the study was evaluated [19] in order to ensure an adequate comparability between glucose measurements performed by the SMBG monitors and glucose measurements performed by the clinical chemistry laboratory method (mean ± SD of relative glucose deviation – that is, capillary BG from the fingertip: SMBG monitor value minus clinical chemistry value, divided by clinical chemistry lab value – FreeStyle™: 1.4 ± 9.8 %; Soft-Sense™: 1.9 ± 9.9 %; One Touch® *Ultra*: 3.9 ± 7.3 %).

Procedures

After an overnight fast and on their individual basal insulin, the patients' pre-breakfast rapid-acting insulin was omitted and the breakfast was replaced by an oral glucose load (Dextro® O.G-T.; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) equivalent to 75 g glucose in order to achieve BG values of 300 – 400 mg/dl. Glucose load was cut by half in those patients with a baseline fingertip BG >180 mg/dl in order to reach comparable BG values of 300 – 400 mg/dl. Then each patient's usual short-acting insulin was injected intravenously at an individual dose (6 – 40 U) in order to induce a fast BG decline >2.0 mg/dl/min down to hypoglycaemic values (≤ 60 mg/dl). Hypoglycaemia was treated by oral administration of glucose.

Capillary blood samples were taken by a trained research nurse in parallel from the fingertip (lateral pulps of fingertip 2 – 4) and the thenar eminence (palmar skin area above the m. abductor pollicis brevis & m. flexor pollicis brevis) every 15 min. In a control subgroup (n = 10 patients), additional samples were taken in parallel from the forearm (ventral and dorsoradial surface) in order to demonstrate that achieved BG change was sufficiently rapid to unmask BG differences at an alternative site with established lag phenomenon. In each patient, the same BG monitor was used for measurements of capillary BG samples from all sites. The forearm skin was not rubbed prior to BG sampling as recommended by some manufacturers so as to avoid any disturbance of the normal regional blood flow.

All procedures were followed in accordance with the standards of the Ethical committee at the Heinrich Heine University, Düsseldorf, Germany, and written informed consent was obtained from each participant before the study.

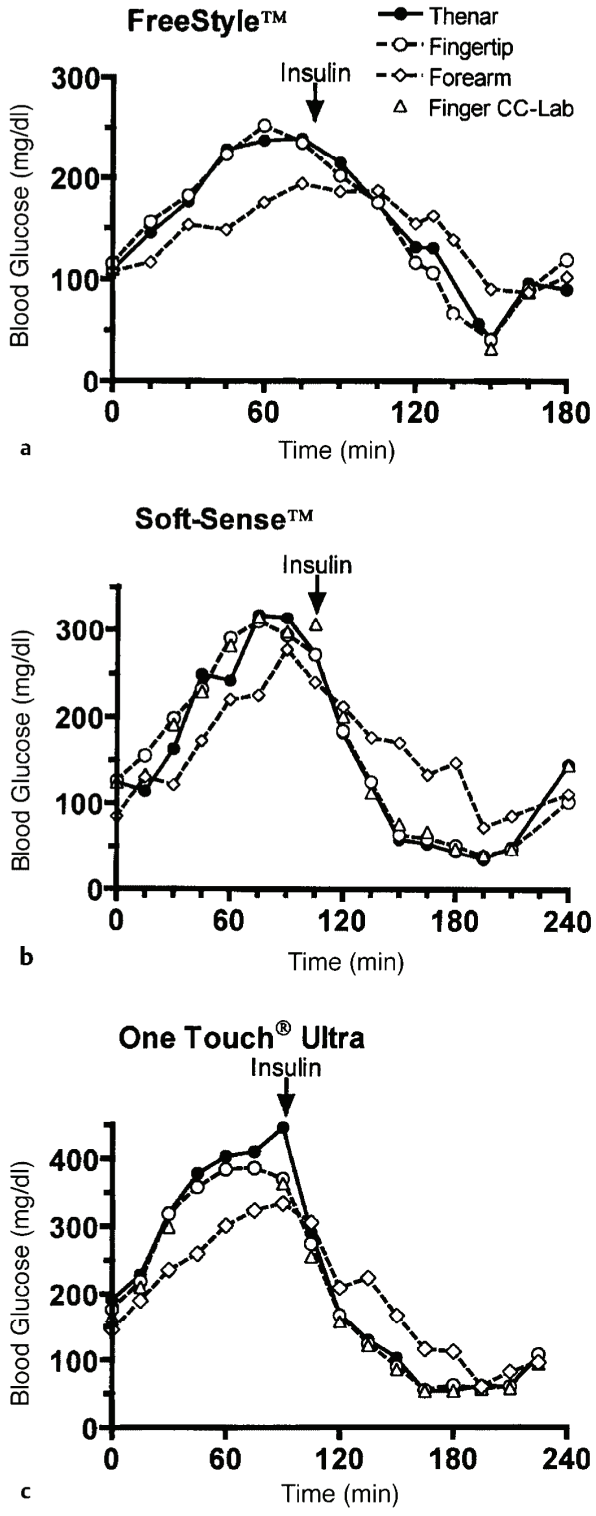

Fig. **1** Representative study BG profiles from the thenar, the forearm and the fingertip of three patients with diabetes. BG changes were induced with 75 g oral glucose (t = 0) and by intravenous insulin injection. BG was analysed using three different BG monitors: FreeStyle™ (**a**), Soft-Sense™ (**b**), One Touch® *Ultra* (**c**). For control purposes additional samples from the fingertip were analysed by a clinical chemistry lab (CC-Lab) based hexokinase-method.

Data analysis

Glucose profiles were analysed separately for the increase part, that is, from the ingestion of the glucose load to the BG maximum measured at the fingertip, and the decrease part, that is, from insulin injection to the BG minimum measured at the fingertip. For each patient, the average BG difference between different sampling sites (intra-individual average BG difference) was calculated. As BG concentration is known to be approximately normally distributed, BG data were compared by a two-sided paired *t*-test. Mean individual BG differences were analysed for deviation from zero by a two-sided one-sample *t*-test. Where appropriate, p-values were adapted according to the Bonferroni procedure; p-values were rounded up to two decimal places, and a p-value ≤ 0.05 was considered statistically significant. Unless otherwise stated, data are expressed as the mean ± SD.

Results

With all three BG monitors, we observed similar capillary BG differences between the thenar, the forearm and the fingertip during the increase part as well as the decrease part. Representative examples of all three BG monitors are shown in Fig. **1**. Thus, results of all BG monitors were combined for further analysis.

The rate of the induced BG change at the fingertip was 2.3 ± 0.5 mg/dl/min during BG increase and 3.0 ± 0.7 mg/dl/min during BG decrease.

Within all patients (n = 16), neither BG at baseline nor BG amplitude during increase and decrease differed significantly between the thenar and the fingertip (Table **2**). The intra-individual average BG difference between thenar and fingertip was not significantly different during BG increase (– 2 ± 12 mg/dl [p = 1.00]) or during BG decrease (+ 5 ± 9 mg/dl [p = 0.11]). At the first hypoglycaemic (≤ 60 mg/dl) fingertip BG value, BG at the thenar and at the fingertip were not significantly different (50 ± 6 *vs.* 53 ± 10 mg/dl, p = 0.20).

Within the subgroup (n = 10), BG at the thenar and fingertip were similar, while a significant divergence between BG at the forearm and fingertip occurred in the same patients (Tables **2** and **3**). At the first hypoglycaemic (≤ 60 mg/dl) fingertip BG, the forearm BG was significantly higher than the thenar BG as well as higher than the fingertip BG (106 ± 27 *vs.* 55 ± 10 [p < 0.01] and 50 ± 7 mg/dl [p < 0.01]). At the same time, the BG at the thenar and fingertip were not significantly different (p = 0.82).

Discussion and Conclusions

Capillary BG concentration during rapid BG changes is obviously site-specific. At the thenar eminence, no significant differences could be found in comparison to the fingertip. In contrast, large differences occurred at the forearm that were similar to those described before [1, 7 – 10]. The detection of hypoglycaemia was also unimpaired by BG monitoring at the thenar, although it was critically impaired by monitoring at the forearm. Clinical observation and studies done during slower BG change velocity [1,7,11,12,16] point to the critical role of a sufficient rapid BG change in order to unmask the differences in glucose concentra-

Table **2** Capillary blood glucose (BG) during rapid systemic BG changes. Blood samples were parallelly taken from the fingertip and the thenar. In a subgroup additional samples were taken from the forearm. Mean ± SD are shown

All patients (n = 16)	**Fingertip**	**Thenar**	**Forearm**
Baseline BG (mg/dl)	135 ± 34	136 ± 41 (p = 0.86†)	ND
BG increase amplitude (mg/dl)	190 ± 35	188 ± 41 (p = 0.65†)	ND
BG decrease amplitude (mg/dl)	255 ± 32	257 ± 47 (p = 0.83†)	ND
Subgroup (n = 10)			
Baseline BG (mg/dl)	143 ± 39	145 ± 47 (p = 1.00†)	126 ± 38 (p = 0.04†)
BG increase amplitude (mg/dl)	194 ± 33	196 ± 43 (p = 1.00†)	153 ± 36 (p < 0.01†)
BG decrease amplitude (mg/dl)	276 ± 26	280 ± 54 (p = 1.00†)	226 ± 31 (p < 0.01†)

ND, Not done; †, p-value in comparison to the fingertip BG.

Table **3** Capillary blood glucose (BG) differences between thenar, fingertip and forearm during rapid systemic BG-change. Subgroup results (n = 10 patients) were analysed for divergence against zero by two-sided one-sample *t*-test. Mean ± SD are shown

	Intra-individual average BG-difference (mg/dl)		
	Thenar – Fingertip	***Thenar – Forearm***	***Forearm – Fingertip***
Baseline	2 ± 17 (p = 1.00)	19 ± 16 (p = 0.05)	– 17 ± 19 (p = 0.05)
BG increase	– 1 ± 14 (p = 1.00)	50 ± 19 (p < 0.01)	– 52 ± 15 (p < 0.01)
BG decrease	4 ± 10 (p = 0.66)	– 27 ± 39 (p < 0.01)	45 ± 11 (p < 0.01)

tion in dermal blood compartments at different body sites, such as the forearm and fingertip. Therefore, observing the similarity between thenar and fingertip is for itself of limited information. It is the observation of clinically identical glucose kinetics between thenar and fingertip in the face of diverging kinetics at the forearm that is the major finding in this study.

The findings support the supposed mechanisms [8,10] underlying the observed differences in glucose concentration between fingertip and forearm. These mechanisms are based on site-specific differences in upper-dermal blood flow, being 5 to 20 times higher at the fingertip than at the forearm [13 – 15]. According to the supposed mechanisms, the main part of "capillary blood" obtained by lancing the skin (typical penetration depth ≤ 2 mm) is derived from subpapillary dermal venous plexus and just a small part from capillaries [17]. At the glabrous skin areas (such as the fingertip), many arteriovenous anastomoses can be found that can directly drain into the venous plexus [13,18]. In contrast, very few arteriovenous anastomoses are found within the upper dermis in non-glabrous skin areas (such as the forearm). Thus, in-flow of blood in the subpapillary dermal plexus at non-glabrous skin areas should be derived from capillaries. In addition, the density of capillaries at the non-glabrous skin areas (~ 30/mm^2) is lower compared to that of glabrous skin areas (~ 60/mm^2) [13]. Taking these anatomical and physiological data together, it seems reasonable to us to postulate that blood exchange within these plexus takes longer at the non-glabrous skin areas than at glabrous skin areas. The palm, including the thenar, is part of the glabrous skin, and shares its skin circulation specifics. Therefore, the similarity in glucose concentration during rapid BG change between blood from the thenar and fingertip can be easily explained by the postulated mechanisms. In addition, at the thigh (another non-glabrous skin area), blood glucose differences similar to the forearm were found postprandially if compared to corresponding fingertip values [11]. This also implies that any glucose test system relying on the upper dermal compartment of non-glabrous skin areas, such as alternative site SMBG, minimally invasive interstitial or non-invasive iontophoretic and near-infrared spectroscopic approaches, should be carefully evaluated for site-specific glucose kinetics. Although experimental studies are fundamental in describing physiological phenomena, observational clinical studies should follow to demonstrate the validity of our findings in "daily life."

In conclusion, in contrast to the forearm site, there is no evidence of impaired safety of BG measurements at the thenar eminence at steady state or during rapid BG changes. Recommendations for alternative site glucose testing during rapid BG changes should distinguish carefully between these sites.

Acknowledgements

We thank Elisabeth Moll and Christa Riedel for excellent technical assistance.

Abbreviations

BG: blood glucose
SMBG: self-monitoring of blood glucose.

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Reprints of official discussions

Discussion of Study 1

McGarraugh, G.

Response to Jungheim and Koschinsky.

Diabetes Care 24: 1304-1306, 2001

Letters

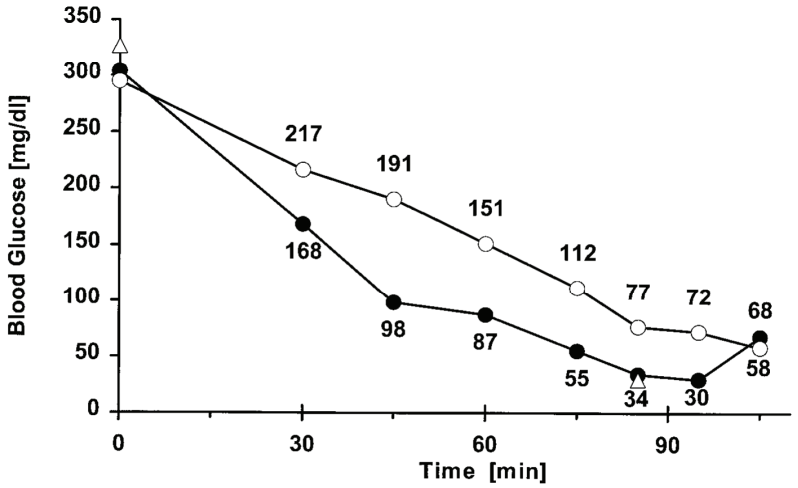

Figure 1—*Effect of a fast blood glucose decrease (3 mg · dl^{-1} · min) on capillary blood glucose values at the fingertip (●) and at the forearm (○) using the FreeStyle system in a type 1 diabetic patient. Control blood glucose values from the fingertip measured at the laboratory are indicated (△).*

discrepancies between clinical symptoms of hypoglycemia and normoglycemic SMBG values at the forearm. Neither standardized quality control assessments of technical performance of such SMBG devices (1,2) nor patient device handling resulted in any obvious explanation of the reported discrepancies. Because of this, we examined whether or not fast blood glucose changes over a larger range of blood glucose concentrations could result in clinically relevant blood glucose differences between forearm and fingertip.

Capillary blood glucose samples were taken from the fingertip and the forearm of six male type 1 diabetic patients on intensified insulin treatment (age 26–54 years, diabetes duration 0.1–25 years) using the FreeStyle system (TheraSense) because it required the smallest blood glucose amount: 0.3 μl/sample. To avoid any disturbance of the normal regional blood flow, the forearm skin was not rubbed before blood glucose sampling, as recommended by the manufacturer. The following protocol was applied: after an overnight fast the usual prebreakfast insulin was omitted and the breakfast was replaced by oral Dextro O.G.T. (Roche, Mannheim, Germany), equivalent to 75 g glucose, in order to achieve blood glucose values of 300–400 mg/dl. Then the patient's usual short-acting insulin was given intravenously at an individual dose (6–15 U/injection). The blood glucose decrease was followed every 5–15 min until either steady state or hypoglycemia (<60 mg/dl) was reached. Hypoglycemia was compensated by oral glucose. For control purposes, additional blood glucose samples from the fingertip were analyzed by the Gluco-quant method (Roche, Mannheim, Germany).

The capillary blood glucose decrease (mean ± SD) at the forearm (208 ± 38 mg/dl) was significantly smaller than at the fingertip (295 ± 16 mg/dl) (Student's paired *t* test: $P < 0.01$) within 111 ± 26 min for all patients. An example is shown in Fig. 1. For the two patients with hypoglycemic unawareness, the first asymptomatic hypoglycemic values at the fingertip (51 and 53 mg/dl) were accompanied by normoglycemic values at the forearm (142 and 159 mg/dl). Compared with the fingertip, it took an additional 27–34 min until the capillary blood glucose levels at the forearm reached hypoglycemic values.

Despite the preliminary state of our investigation, the consistency of clinically relevant delays of blood glucose changes at the forearm prompted us to draw attention to a potentially very dangerous situation. Our results raise the possibility that the delayed glucose concentration changes at the forearm occur physiologically. To our knowledge, this has not been fully recognized as a potential problem by the certifying administrations in the U.S. or Europe.

Even a few delays of hypoglycemia detection could unnecessarily endanger the life of diabetic patients. Because of this, we strongly recommend providing sufficient evidence that the suggested use of SMBG at the forearm and other alternative sites does not result in a risky delay of hypoglycemia detection. Meanwhile, SMBG at the forearm should only be used when ongoing fast blood glucose changes can be excluded.

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COMMENTS AND RESPONSES

Response to Jungheim and Koschinsky

Glucose monitoring at the arm

In this issue of *Diabetes* Care, we read with interest the letter of Jungheim and Koschinsky (1) comparing glucose measurements using blood extracted from the finger versus blood extracted from the forearm. The phenomenon they discuss is not a simple function of measurement technology, but a complex function of circulatory physiology. Our cognizance and study of the phenomenon resulted in the explicit instruction to the users of the TheraSense FreeStyle blood

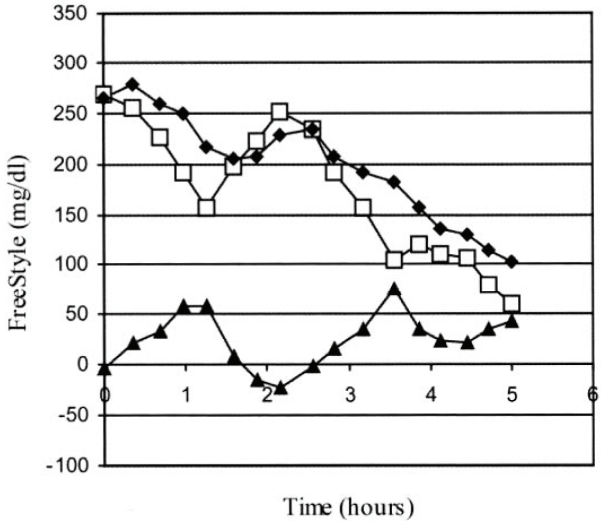

Figure 1—*Glucose profile of arm (no rubbing) and finger. —□—, average finger; —◆—, average arm; —▲—, difference. For average finger and average arm, the data points are the average of duplicate measurements.*

glucose monitoring system to rub the test site before drawing blood. The increased perfusion from rubbing significantly reduces the difference in fingertip and forearm blood glucose measurements (see discussion below). It is significant that Jungheim and Koschinsky did not rub the test site. In addition, their protocol, which involved a glucose tolerance test followed by intravenous insulin, created physiological extremes and influenced the observed differences in study subjects.

An initial TheraSense study involved 100 subjects with both type 1 and type 2 diabetes, in which blood glucose measurements from the arm versus the finger were taken at random times throughout the day. Blood from the forearm (obtained without rubbing) and blood from the fingertip was measured for glucose concentration with the FreeStyle meter. The elevated intercept and low slope were unexpected (Table 1). This was further examined in a study where finger and arm blood samples (obtained without rubbing) were measured over several hours in patients with type 1 diabetes. The study indicated that changes in blood glucose are first detected in finger blood and lag in forearm blood (Fig. 1). A similar study, which included blood from the forearm before and after rubbing, indicated that arm and finger differences are reduced by rubbing the test site (Fig. 2). This led to a final study of 120 subjects with type 1 and type 2 diabetes, in which blood obtained from the forearm (after rubbing) and blood obtained from the finger was measured for glucose concentration using the FreeStyle meter. The comparison yielded a correlation that was nearly ideal (Table 1). The final study also assessed the accuracy and clinical utility of the FreeStyle meter by comparing venous finger and arm (with rubbing) blood to YSI-plasma readings (Table 1).

The current state of our research indicates that there would be very little difference in therapeutic decisions when the arm (following rubbing) rather than the finger is used as the test site. However, when blood glucose concentration is falling rapidly, the lag in glucose change could cause a delay in the detection of hypoglycemia. Accordingly, when testing with the express purpose of detecting hypoglycemia (such as when symptoms of hypoglycemia are present or when a meal has been delayed after taking insulin), the finger may be the preferred test site. Our studies indicate that a delay in the detection of hypoglycemia is not a common occurrence in routine testing on the arm. However, this phenomenon must be seriously considered and thoroughly understood. TheraSense has undertaken additional studies under a variety of circumstances to better understand this complex question of circulatory physiology. These studies will be the subject of future publications.

We feel that the obvious benefits of new technologies should not be overshadowed by the manageable risks. The introduction of fingertip blood glucose testing enabled the aggressive management of glucose levels in people with diabetes, yet it also increased the frequency

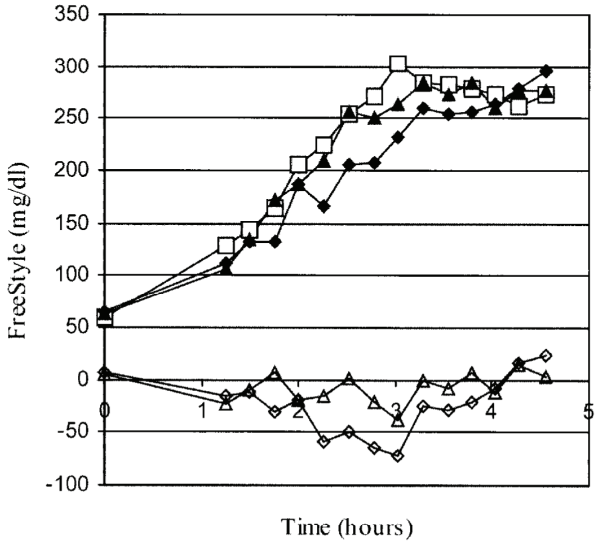

Figure 2—*Glucose profile of arm (no rubbing), arm (with rubbing), and finger. —□—, Average finger; —◆—, arm unrubbed; —▲—, arm rubbed; —◇—, difference unrubbed; —△—, difference rubbed. For average finger, the data points are the average of duplicate measurements.*

Letters

Table 1—*Linear regression statistics and Clarke Error Grid Analysis*

Comparison	Intercept (mg/dl)	Slope	*r*	Clarke Error Grid Zones (% of readings in the zone) A	B	C	D
Arm (no rubbing) vs. finger	19.4	0.913	0.956	NA	NA	NA	NA
Arm (rubbing) vs. finger	−0.5	1.027	0.971	NA	NA	NA	NA
Venous vs. venous YSI	7.1	0.923	0.992	99.6	0.4	0	0
Finger vs. finger YSI	6.6	0.934	0.982	98.3	1.7	0	0
Arm (rubbing) vs. finger YSI	9.0	0.945	0.967	87.7	11.4	0	0.8

NA, not applicable.

of hypoglycemic events. Clearly, the benefits of intensive insulin therapy outweighed the risks of hypoglycemia. Similarly, greatly reducing the pain associated with blood glucose testing by permitting testing on the forearm and other sites is likely to have a significant positive impact on compliance with monitoring regimens.

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G.M. is employed by and holds stock in TheraSense, which manufacturers and markets the FreeStyle blood glucose monitoring system.

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How Cost-Effective Is the Treatment of Dyslipidemia in Patients With Diabetes but Without Cardiovascular Disease?

A response to Grover et al.

In the January 2001 issue of *Diabetes Care*, Grover et al. (1) reported on the cost-effectiveness of dyslipidemia treatment in patients with diabetes but without cardiovascular disease. Although the article was interesting and relevant, further review of the assumptions of the study's Markov model raise several questions.

First, in the cost-effectiveness model, the choice of years of life saved (YOLS) rather than quality-adjusted life years (QALYs) is debatable. Diabetes is known to have a significant effect on morbidity, mortality, and quality of life. In addition, other aspects of diabetes (including cardiovascular disease) are known to influence the quality of life of people with diabetes. Therefore, the use of YOLS as a measure of effectiveness may be simplistic and insufficient as an outcome measure because it usually counts as less than one full QALY (2). What effect would the use of QALYs have had on the study results and conclusions?

Second, the assumptions that lipid levels and the effectiveness of simvastatin therapy were similar to that observed in the Scandinavian Simvastatin Survival Study trial appear problematic in light of current evidence. The assumptions include LDL cholesterol of 188 mg/dl (4.87 mmol/l) and HDL cholesterol of 46 mg/dl (1.18 mmol/l). Expected effects of simvastatin therapy based on a decrease in LDL cholesterol of 35% and an increase in HDL cholesterol of 8% would be 122 mmol/dl (3.15 mmol/l) and 50 mmol/dl (1.29 mmol/l), respectively. However, these targets run contrary to the American Diabetes Association (ADA) practice guidelines for 2001 (3). The goals of lipid therapy include LDL cholesterol of ≤100 mmol/dl (≤2.60 mmol/l) and HDL cholesterol of 45 mg/dl (1.15 mmol/l) and 55 mg/dl (1.40 mmol/l) in men and women, respectively.

Very few patients were likely to meet current standards of lipid treatment based on the assumptions of the study. Therefore, to achieve ADA goals, higher doses of simvastatin or longer duration of lipid treatment may be required. The implication is that the cost calculations are likely to yield higher figures, which may alter the cost-effectiveness ratios. What effect would varying the cost calculations to achieve ADA end points have had on the study results?

These questions and comments should not undermine the importance of the work of Grover et al. Rather, they are important clinical questions that may need consideration in future studies on cost-effectiveness, particularly on primary prevention of cardiovascular disease in people with diabetes.

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Response to Egede

We thank Dr. Egede (1) for his letter in this issue of *Diabetes Care* and for taking the time to read our study (2) and provide us with his thoughtful comments. He raises several important points.

The first point concerns the choice of

Reprints of official discussions

Discussion of Study 2

Pfützner, A., Forst, T.

Response to Jungheim and Koschinsky.

Diabetes Care 25: 638-639, 2002

Response

Jungheim, K., Koschinsky, T.

Response to letter by Pfützner and Forst.

Diabetes Care 25: 639-640, 2002

LETTERS

Table 1—*Comparison of characteristics at diagnosis with early and usual type 2 diabetes*

	Early onset	Usual onset	*P*
n	48	560	
BMI (kg/m^2)	32.0 ± 7.5	29.4 ± 5.0	<0.005
Sex (% female)	56.3	42.1	NS
HbA_{1c} (%)	8.2 ± 3.1	8.2 ± 2.5	NS
Total cholesterol (mg/dl)	244.0 ± 59.8	244.0 ± 54.6	NS
Triglycerides (mg/dl)	275.8 ± 172.7	275.8 ± 179.3	NS
Hypertension (%)	29.5	51.5	<0.005
Diet prescription (%)	97.7	97.8	NS
Biguanides (%)	30.0	30.0	NS
Sulfonylurea (%)	44.2	40.4	NS
Referral to diabetologist (%)	31.0	11.0	0.006

Data are means ± SD or %. Hypertension is defined as systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg. NS, not significant.

portant pressure points for optimal collaboration are lack of clearly defined tasks on the one hand and lack of refunding for dietary advice on the other (5). Although obesity is more frequent in the early-onset group, we found no differences in the prescription rate for metformin, the first choice for obese diabetic patients (6). We also found that young people with type 2 diabetes are significantly more referred to the diabetologist at the time of diagnosis than older patients.

The representativeness of both the sentinel physicians and sentinel population, with respect to the whole population, remains an important pressure point in this kind of epidemiological analysis. Although the registering physicians are representative of the whole Belgian population of physicians for age and sex, it is not possible to extrapolate the medical practice of family doctors in Belgium. Due to the voluntary nature of participation in the network, random selection of the participants is impossible because the physicians with the greatest motivation answer the call. Registration is done by the physician himself based on his medical file; therefore, the results could be presented rather euphemistically because the data on the follow-up questionnaire probably come closer to the expected guideline level rather than the actual data in the medical record. However, the voluntary nature of the registration and the anonymity of the registering physicians reduce this possible bias. So far, we consider that extrapolation from the sentinel population to the total population is possible.

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Response to Jungheim and Koschinsky

In a recent letter of observation, Jungheim and Koschinsky (1) reported on their findings about a risky delay of hypoglycemia detection by glucose monitoring at the arm. Given the possible significant implications of their findings, we repeated their experiment in our own clinical unit in an institutional review board (IRB)-approved study. We would hereby like to report on our results with 10 patients (4 women, 6 men, 6 type 1 diabetic, and 4 type 2 diabetic subjects; age [mean ± SD] 49 ± 14 years, mean disease duration: 50 ± 14 years). During an oral glucose tolerance test (OGTT) phase, results obtained from the arm with no rubbing (Soft-Sense; Abbott Medisense) were lower than the results obtained with our reference method (Super GL; Mueller Apparatebau) from the fingertip, but the differences were clinically acceptable. However, during an intravenous intervention phase, the results from the arm nicely tracked the results obtained from the fingertip. There was no potential risk for overlooking development of a hypo-

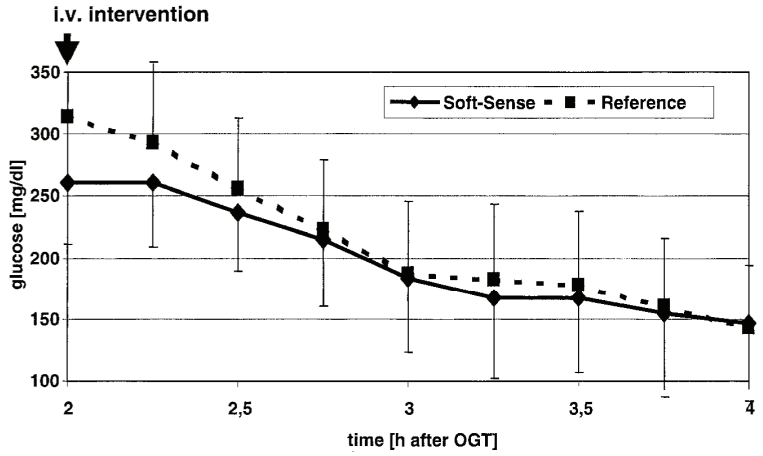

Figure 1—*Drop of blood glucose in 10 patients after intravenous insulin intervention during an OGTT experiment (reference: Super GL, glucose oxidase method).*

glycemic episode in any of the experiments, even in the two cases where we reached glucose levels <70 mg/dl (Fig. 1).

The differences between our data and the observations from Jungheim and Koschinsky may be due to differences in *1*) the experimental design, e.g., how extreme and artificial the experimental conditions were; *2*) the testing device; *3*) the patient populations; and *4*) the methodology, including how the skin was prepared and how the blood was collected.

It also has to be considered that the artificial design chosen by Jungheim and Koschinsky does not match with the daily treatment situation, and it is rather unlikely that such rapid glucose decreases occur when not induced by intravenous insulin treatment. Therefore, in another IRB-approved study using the same devices, we explored the performance of alternative site testing in a regular treatment situation with preprandial insulin treatment before a standardized test meal (66 g carbohydrate) in 10 patients with type 1 diabetes (6 women, 4 men, age 35 ± 11 years, mean disease duration 13 ± 13 years). In a randomized crossover setting, they either received an appropriately calculated dose of regular human insulin 20–30 min before the meal or only 25% of this dose on the other experimental day. The arm measurements were not different from the fingertip measurements in both treatment arms, even in the phase of glucose increase after an insufficient insulin dose (Fig. 2).

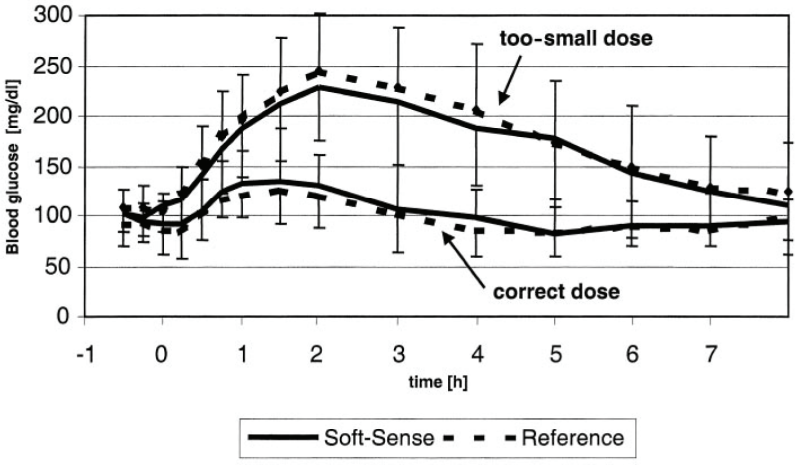

Figure 2—*Glucose excursions after a standardized meal (66 g carbohydrate content) in 10 patients with a correct insulin dose and a too-low insulin dose (25% of correct dose), respectively.*

Because our data and those of other studies (2) suggest good performance of the Soft-Sense meter regarding accuracy and precision in daily practice, we consider this device to be a suitable alternative option for virtually pain-free glucose monitoring in daily practice. If confirmation of an alternative site test is desired, the user can always simply perform a finger test with the same device. Furthermore, more practical studies will be required to establish whether patient groups or circumstances exist where alternative site testing should not be performed.

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Response to the Letter by Pfützner and Forst

Pfützner and Forst (1) report that they found no significant blood glucose (BG) differences between the arm and finger during *1*) BG decrease induced by intravenous insulin injection, and *2*) BG increase and decrease induced

Letters

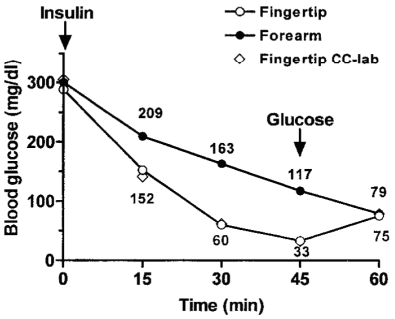

Figure 1—*BG profiles of a patient with diabetes. BG samples from the forearm and the fingertip were analyzed by the Soft-Sense glucose monitor. BG changes were induced with 75 g oral glucose and followed by intravenous insulin injection (t = 0). At hypoglycemia, oral glucose was administered. For validation, additional BG samples from the fingertip were analyzed by a clinical chemistry laboratory (CC-Lab) method.*

by a standardized meal in combination with subcutaneous insulin injection.

As previously suggested by Pfützner and Forst, the observed differences between our data and their observations are caused by differences in experimental design. Our study protocol aimed at rapid BG decreases and achieved a mean BG change at the finger (averaged over total decline) of 3 mg · dl^{-1} · min^{-1}. Hypoglycemic values at the finger were reached faster after insulin injection. This velocity has not been repeated by Pfützner and Forst, as their mean rate of BG decline did not exceed 2 mg · dl^{-1} · min^{-1} during the first hour after insulin injection and fell below 1 mg · dl^{-1} · min^{-1} during the second hour after insulin injection. Hypoglycemic values <60 mg/dl were not reached at all (Fig. 1 of Pfützner and Forst).

The same applies to the BG data in Pfützner and Forst's Fig. 2, as these BG values declined at a mean rate <0.5 mg · dl^{-1} · min^{-1} from the second until the eighth hour after subcutaneous insulin injection. These results are well in agreement with our own observations that the chance of observing clinically relevant BG differences are very low if mean BG change rates (averaged over at least 45–60 min) are <2 mg · dl^{-1} · min^{-1} (2). Applying our original study protocol, we have provided evidence that the described BG differences between the arm and finger can be observed with the Soft-Sense device (Fig. 1) (used by Pfützner and Forst), as well as with other BG devices approved for alternative-site testing. We conclude that the data provided by Pfützner and Forst do not sufficiently address the question of the effects of rapid BG changes on BG differences between the finger and alternate skin sites such as the arm. Therefore, their data do not support their unrestricted statement that Soft-Sense would be a suitable alternative option, as far as rapid BG changes are concerned, for glucose monitoring in daily practice.

Concerning the likelihood of rapid BG changes >2 mg · dl^{-1} · min^{-1} in daily life, it is well known from continuous glucose monitoring studies, particularly in insulin-treated patients with type 1 diabetes, that such rapid BG changes can occur and often go unrecognized by patients (3,4). Based on our studies with 17 diabetic patients on subcutaneous continuous glucose monitoring up to 72 h/patient (4), an average 7% of all BG changes have been >2 mg · dl^{-1} · min^{-1} (maximum 5.7). Therefore, our study design does match daily treatment situations and is so far realistic, not artificial.

Our study was designed to examine whether potential clinical risks can be associated with alternative-site monitoring at the forearm and, if such risks exist, to estimate the potential severity of the risks. A standardized experimental protocol was therefore used. Exact determination of the probability and severity of the described potential hazard is an important task originating from our findings. Keeping the probability of rapid BG changes in mind, we feel that experimental studies per se, even if they are designed to mimic daily life (as done by Pfützner and Forst), are an inadequate tool to exclude the relevance of our findings in daily life. We would suggest proving clinical significance under real daily life conditions in population-based field studies that include samples taken at times of presumed rapid BG change. Such a study has been performed and presented to the U.S. Federal Drug Administration (5). The results of this study support our concern that clinically relevant BG differences occur under daily life conditions, as BG differences between fingertip and forearm exceeding even 100 mg/dl were observed. Therefore, our preliminary clinical recommendations remain unchanged. This is supported by essentially identical recommendations of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee Panel to the U.S. Food and Drug Administration (6).

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12 APPENDIX

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Kinetik der kapillären Blutglukose-Konzentration an alternativen Kapillarblut-Entnahmestellen
– Einfluss von schnellen Änderungen der systemischen Blutglukose-Konzentration –

Karsten Jungheim

ZUSAMMENFASSUNG

Einleitung: Der mit kapillärer Blutglukose (BG)-Bestimmung verbundene Schmerz kann reduziert werden, wenn die Kapillarblutprobe nicht an der Fingerbeere, sondern an alternativen Körperarealen (z.B. Unterarm oder Daumenballen) entnommen wird [*engl.:* "Alternative Site Glucose Testing" (AST)]. AST-geeignete Messgeräte wurden jüngst unter der Annahme zugelassen, dass zwischen der Fingerbeere und alternativen Körperarealen keine systematischen Unterschiede in der kapillären BG-Konzentration bestehen. Jedoch berichteten Patienten über unerwartete Diskrepanzen zwischen erlebten Hypoglykämie-Symptomen, hypoglykämischen BG-Werten am Finger und normoglykämischen BG-Werten am Unterarm. Diese traten vor allem während schneller Änderungen der BG auf. Daher konnte nicht ausgeschlossen werden, dass während schneller BG-Änderung unbekannte regionale Unterschiede in der Kinetik der kapillären BG-Konzentration bestehen. Ziel der Dissertation war somit (a) die Kinetik der kapillären BG an Unterarm und Daumenballen während schneller BG-Änderung zu beschreiben, (b) den Effekt lokaler Hautmanipulation durch Reiben zu untersuchen, (c) ein Modell zu entwickeln, welches die Beobachtungen erklären kann, und schließlich (d) adäquate Empfehlungen zum Einsatz der BG-Bestimmung in AST-Arealen zu erstellen.

Methodik: In verschiedenen Studien wurden kapilläre BG Messungen am Unterarm oder Daumenballen mit Messungen an der Fingerbeere verglichen. Hierzu wurden Patienten mit Diabetes mellitus untersucht, bei denen in standardisierter Weise ein schneller BG-Anstieg und -Abfall (> 2.0 $mg \cdot dl^{-1} \cdot min^{-1}$) induziert wurde. In einer Untergruppe wurde zusätzlich, vor Entnahme kapillärer Proben am Unterarm, eine lokale Hautmanipulation mittels Reibens durchgeführt.

Ergebnisse: Im Ruhezustand waren die BG-Konzentrationen an Unterarm und Fingerbeere ähnlich. Im Gegensatz dazu traten während schnellem BG-Anstieg oder -Abfall große BG-Differenzen auf [durchschnittlich bis zu 84-91 mg/dl (4.7-5.0 mmol/l)]. Im Vergleich zum Finger änderte sich die BG-Konzentration am Unterarm mit einer Verzögerung von durchschnittlich 30 Minuten. Die zeitnahe Hypoglykämie-Entdeckung war schwer beeinträchtigt, da zum Zeitpunkt des ersten hypoglykämischen Finger-BG Wertes noch 80% der Unterarm Messungen > 90 mg/dl [bis zu 169 mg/dl (9.4 mmol/l)] waren. Lokales Reiben verringerte die, während schneller BG Änderung auftretende, BG Differenz zwischen Unterarm und Finger um durchschnittlich etwa 50%. Jedoch war bezüglich der Unterarm-Finger BG-Differenz eine beträchtliche intra- und interindividuelle Heterogenität des Reibe-Effektes zu beobachten. Dagegen traten am Daumenballen weder im Ruhezustand noch während schneller BG-Änderung relevante Differenzen auf.

Diskussion: Es existieren klinisch höchst relevante Differenzen zwischen der Kinetik der kapillären BG des Unterarms und der der Fingerbeere. Zwischen Daumenballen und Fingerbeere bestehen diese nicht. Diese Beobachtungen können durch ein physiologisches Modell, das PLEXUS EXCHANGE MODEL, erklärt werden. Dieses basiert auf der Hypothese, dass das Blut aus subepidermalen venösen Plexus, aus denen "kapilläres" Blut stammt, im Bereich der Leistenhaut (z.B. Fingerbeere, Handteller) schnell, im Bereich der Felderhaut (z.B. Unterarm) jedoch nur langsam ausgetauscht wird. Daher wird empfohlen, kapilläre BG Bestimmungen in AST-Arealen nur dann durchzuführen, wenn im betreffenden Moment eine schnelle BG-Änderung (z.B. < 2 Stunden postprandial, bei Sport) als auch eine Hypoglykämie ausgeschlossen werden kann.

20.5.04