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Differences in venous, capillary and interstitial glucose concentrations in individuals without diabetes after glucose load

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Abstract

Objectives: Differences between capillary and venous glucose concentrations have been reported in the past. In continuous glucose monitoring (CGM) system performance studies, comparator measurements are often performed in venous samples, despite CGM systems typically aiming at providing capillary-like values. In this study, differences between venous, capillary and interstitial glucose concentrations, measured with a laboratory analyzer, a self-monitoring of blood glucose (SMBG) system and an intermittent-scanning CGM system were investigated in subjects without diabetes after glucose load.

Methods: During the study, an oral glucose tolerance test (oGTT) was performed with 41 participants who had no known history of diabetes (mean age 25.5 ± 9.7 years). Venous blood samples for measurement with a laboratory analyzer were collected before drinking the standardized 75 g glucose solution and after 60 and 120 min. In parallel, capillary blood was obtained for measurement with a laboratory analyzer and an SMBG system, and interstitial glucose values were measured with an intermittent-scanning CGM system.

Results: Glucose concentrations in the fasting state were slightly different for the three different compartments whereas considerable differences (some median differences exceeding 30 %) in glucose concentration were observed 60 and 120 min after the start of the oGTT.

Conclusions: Marked differences with a high inter-individual variability between venous, capillary, and interstitial fluid glucose concentrations were found especially after glucose load. These differences can affect perceived CGM accuracy in performance studies depending on the specific comparator method used, and they are potentially relevant in clinical practice, like diabetes diagnosis.

Keywords: blood glucose; capillary blood; continuous glucose monitoring; diabetes diagnosis; oral glucose tolerance test; venous blood.

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Introduction

Continuous glucose monitoring (CGM) systems are widely used in the treatment of diabetes mellitus. Their efficacy in people with type 1 diabetes has repeatedly been shown [1–3], and there may be cost-efficient benefit in people with type 2 diabetes as well [4].

To demonstrate that a CGM system is accurate and reliable, e.g., for regulatory approval, CGM performance studies are conducted. In such studies, values obtained with a CGM system are compared with measurement results from a comparator method. Many studies implement venous comparator measurements, which can be traced to a combination of reasons. First, some regulatory authorities, like the United States Food and Drug Administration, require the use of laboratory analyzers [5], which require a relatively large sample volume. And second, some protocols, like the Clinical and Laboratory Standard Institute's POCT05, require high-frequency measurements of up to one measurement per 15 min [6]. It may simply not be possible to obtain large enough volumes of capillary blood in such a study setting, whereas it is comparably easy to draw sufficiently large venous blood volumes.

Despite the widespread use of venous blood samples in CGM performance studies, CGM systems for at-home use by lay users are intended to either supplement traditional capillary blood glucose (BG) monitoring or even replace it in most situations.

The topic of differences in venous and capillary BG concentrations has been investigated before. However, some studies on this topic did not use the same analyzer for venous and capillary samples [7, 8], so that it may remain unclear to what degree these differences can be attributed to physiologic differences rather than bias of the analyzers. Furthermore, the physiologic differences can be expected to be dependent from the rates with which glucose concentrations change [9]. However, even the one identified study that used the same analyzer for venous and capillary samples does not provide sufficiently detailed results on any time- or rate-of-change-dependency [10]. In the case of CGM systems, another factor is the technical time lag introduced by signal processing [11]. In addition, different measuring systems may exhibit biases between each other and imprecision may vary [12, 13].

Outside of CGM performance studies, differences between glucose concentrations in different compartments are potentially relevant in clinical practice, like the diagnosis of diabetes.

In the present study, we measured venous, capillary and interstitial glucose concentrations during an oral glucose tolerance test (oGTT) with a laboratory analyzer, a system for self-monitoring of BG (SMBG) and an intermittent-scanning CGM (iscCGM) system in people without diabetes in order to assess differences depending on sample matrix and measurement method before the start of the oGTT as well as 60 and 120 min afterward.

Materials and methods

This open, mono-center study was performed between January and March 2018 at the Institut für Diabetes-Technologie, Forschungs-und Entwicklungsgesellschaft mbH an der Universität Ulm, Germany under consideration of the Declaration of Helsinki and in compliance with the Guideline for Good Clinical Practice and the national regulations and provisions. The study protocol was approved by the responsible Ethics Committee and the study was registered at clinicaltrials.gov (NCT03405415). This study's primary objective was the characterization of glucose concentrations in people without diabetes under daily-life conditions [14].

Participants

Adult subjects with no history of diabetes mellitus were eligible for the study. Informed consent was signed prior to any study procedures. After a screening visit, subjects were included if they fulfilled the eligibility criteria. Inclusion criteria were age ≥18 years, and the willingness to abstain from medications containing ascorbic acid or salicylic acid during the study period. Exclusion criteria were diabetes; acute or severe chronic illness (at the physician's discretion); pregnancy or lactation period; known severe allergy to medical grade adhesive; language or other barriers that might preclude sufficient understanding of the study procedures and blood donation in the previous two months. After screening, 41 subjects were included in the study.

Study devices and comparison measurements

Venous and capillary plasma glucose measurements were performed in duplicate on a Cobas Integra® 400 plus laboratory analyzer using a hexokinase-based method (Roche Diagnostics GmbH, Mannheim, Germany) with the GLUC2 Glucose HK application (Roche). Measurements were performed at three different time points (0 min, 60 and 120 min) during a 75 g oGTT (Accu-Chek Dextrose O.G-T., Roche Diabetes Care Deutschland GmbH, Mannheim, Germany). The oGTT was performed according to the recommendations of the German Diabetes Society at that time [15, 16], which were based on the WHO guideline [17]. The conformity to traceability requirements of the method to ISO 17511 was confirmed by the analyzer's manufacturer and verified using higher-order control material (Standard Reference Material 965b; National Institute for Standards and Technology, Gaithersburg, MD). With the four levels of this material, bias was ≤1.9 % and coefficient of variation (CV) was ≤1.2 %.

In parallel, capillary whole blood glucose duplicate measurements were performed using the glucose dehydrogenase-based CONTOUR®NEXT ONE (Ascensia Diabetes Care Holdings AG, Basel, Switzerland) BG monitoring system, which yields capillary plasma-equivalent values. This system was intended for use by lay persons and by healthcare professionals. As it was used by the participants themselves in this study, it is designated as an SMBG system for the purpose of this article.

The factory-calibrated FreeStyle® Libre (Abbott Diabetes Care, Alameda, CA) iscCGM system was used for glucose measurements in the interstitial fluid of the subcutaneous fatty tissue of the upper arm. This iscCGM system measured glucose levels every minute and stored one value every 15 min for up to 14 days. To obtain continuous glucose data, the iscCGM system needed to be actively scanned using a handheld reader device. Each participant wore two iscCGM sensors in parallel.

Study procedures

Study duration of the complete study was 15 calendar days for each participant. On day 1, subjects arrived for screening at the study site. After enrollment, participants were instructed in the use of the iscCGM and SMBG systems and two iscCGM sensors were placed on the subjects' upper arms (one sensor per arm). The iscCGM was allowed to stabilize, and participants returned on the morning of day 3 for the oGTT. According to the recommendations of the German Diabetes Society, participants were asked to abstain from food, nicotine and alcohol for the previous 10–12 h and to eat a high-carbohydrate diet on the preceding days (≥150 g carbohydrates per day) [15, 16]. Results of the complete study, including analysis of glucose profiles of people without diabetes have been published previously [14].

Statistical analysis and visual report of glucose data

For the venous and capillary duplicate glucose measurements on the hexokinase-based laboratory analyzer as well as the duplicate SMBG measurements, mean values were calculated. Laboratory analyzer data were excluded if CV of the duplicate exceeded 5 %. SMBG measurements

were excluded if the second value was outside ±10 mg/dL or ±10 % (whichever was larger) of the first value. For the iscCGM system, the iscCGM values, which were continuously stored every 15 min, were linearly interpolated on a 1-min time grid for each iscCGM sensor separately. Then, the linearly interpolated values from two sensors in the same participant that had the same timestamp were averaged (median difference of left arm vs. right arm −2.1 %, interquartile interval −6.5 % to +3.0 %). Scanned values were not used due to suspicion of increased variability related to differences between scanned values and continuously stored values [18].

Using venous plasma glucose mean values as reference values, relative differences were calculated for each participant and each time point separately for the capillary plasma glucose mean values (laboratory analyzer), the capillary plasma-equivalent glucose mean values (SMBG system) and the iscCGM mean values.

The results are given as median relative difference with 2.5 and 97.5 % quantiles (thus indicating the central 95 % of values) in parentheses, if not indicated otherwise.

Results

Population characteristics

Out of 41 participants, 17 were male and 24 were female with a mean (±standard deviation) age of 25.5 ± 9.7 years and a BMI of 24.2 ± 3.9 kg/m^2. HbA_{1c} was 5.2 ± 0.2 % (33.8 ± 2.1 mmol/mol) and ranged from 4.9 to 5.7 % (30–38 mmol/mol), suggesting the absence of diabetes [15, 16].

Glucose concentrations during oGTT

The median glucose profile from all participants, based on iscCGM as it was the only source of continuous glucose values, showed a baseline median glucose concentration at the start of the oGTT of approximately 95 mg/dl (5.3 mmol/L). It indicated a glucose peak approximately 35–40 min later and a median peak interstitial glucose concentration of approximately 160 mg/dl (8.9 mmol/L) (Figure 1A). Before participants left the study site approximately 180 min after the start of the oGTT, median interstitial glucose concentrations were at approximately 80 mg/dl (4.4 mmol/L) and thus lower than the fasting glucose concentrations.

Inter-individual glucose variability, as shown in Figure 1B and Table 1, in the fasting state was markedly higher for the interstitial glucose concentrations than for the other glucose concentrations. It was most pronounced 60 min after glucose intake for all comparison measurements. The maximum values, depicted as circles above the whiskers in Figure 1, were obtained from the same participant 60 and 120 min after the start of the oGTT, and from two different participants immediately before the start of the oGTT.

In the fasting state immediately before the start of the oGTT, the capillary glucose concentrations measured in plasma with the laboratory analyzer were nearest to those measured in venous plasma, followed by interstitial glucose concentrations and plasma-equivalent capillary SMBG glucose concentrations. After 60 and 120 min, the interstitial glucose concentrations exhibited the smallest median difference from venous plasma concentrations, followed by the capillary plasma concentrations and the capillary plasma-equivalent SMBG concentrations. The systematic difference between the capillary plasma-equivalent concentrations obtained from the SMBG system and the capillary plasma concentrations obtained from the laboratory analyzer was consistent between the three time points, as median SMBG values were approximately 5–7 % higher than median capillary laboratory analyzer values.

Detailed results are provided in Figure 2 and Table 2.

Across time points the smallest median differences were found in the fasting state, ranging from +3.1 to +8.5 %. After 60 min, the median relative differences were substantially larger as depicted in Figure 2 ranging from +23.6 to 37.3 %. This was most prominent for the capillary glucose concentration determined with the SMBG system (see Figure 2 and Table 2). Even 120 min after the start of the oGTT, median relative differences were still markedly higher than in the fasting state (+10.7 to +30.3 %).

Discussion

In this study, marked differences between venous, capillary and interstitial glucose concentrations, measured with a laboratory analyzer (venous and capillary concentrations), an SMBG system (capillary concentrations) and an iscCGM system (interstitial concentrations) were found in people without diabetes during an oGTT. These differences are caused both by physiologic processes and by technical aspects of the different measurement methods employed [7–9, 11].

In the fasting state, differences between glucose concentrations in the three compartments were small, but still potentially clinically relevant for diagnosis or therapy of diabetes. Considerable differences (some median differences exceeding 30 %) in glucose concentrations with high variability were observed 60 and 120 min after start of the oGTT using different measurement procedures, with SMBG measuring capillary glucose showing the largest median relative difference towards venous BG concentrations. This finding is consistent with the results of other studies published some time ago, which reported no differences in venous and capillary glucose concentrations in the fasting

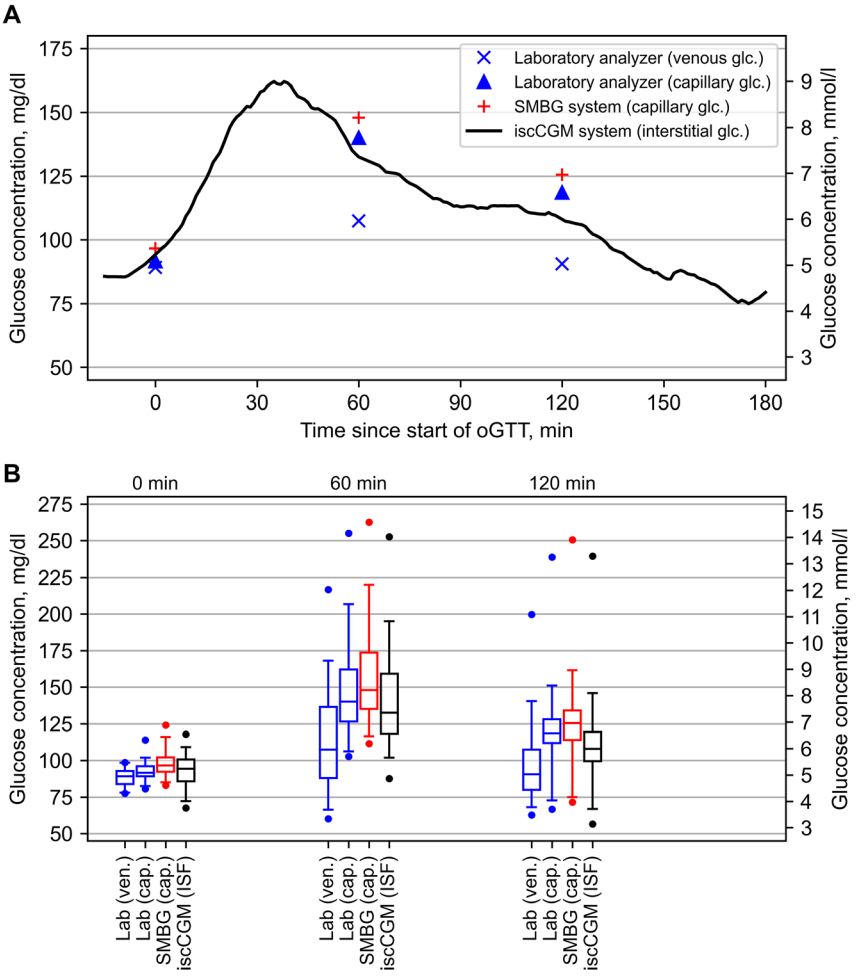

Figure 1: Glucose concentrations during the oral glucose tolerance test (oGTT). (A) Median venous, capillary and interstitial glucose concentrations during the oGTT (n=41) measured with a laboratory analyzer, an SMBG system or an iscCGM system. iscCGM values were linearly interpolated to a 1-min time grid before median values were calculated for each timestamp. (B) Box-Whisker plots for these glucose concentrations at the start of the oGTT, after 60 min, and after 120 min. Whiskers cover the central 95 % of values, circles indicate individual values outside of this interval. cap., capillary samples; glc., glucose concentrations; iscCGM, intermittent-scanning continuous glucose monitoring; ISF, interstitial fluid; Lab, laboratory analyzer; SMBG, self-monitoring of blood glucose; ven., venous sample.

Table 1: Median (2.5 and 97.5 % quantiles) of venous, capillary and interstitial glucose concentrations during an oral glucose tolerance test in 41 subjects. Laboratory analyzer measurements were performed on separated plasma; the SMBG system was used with whole blood but provided plasma-equivalent results.

Time	Laboratory analyzer (ven. glc.), mg/dL [mmol/L]	Laboratory analyzer (cap. glc.), mg/dL [mmol/L]	SMBG system (cap. glc.), mg/dL [mmol/L]	iscCGM system (interst. glc.), mg/dL [mmol/L]
0 min	89.2 (78.0; 98.5) [4.95 (4.33; 5.47)]	91.6 (82.5; 101.8) [5.09 (4.58; 5.65)]	96.6 (85.0; 116.2) [5.36 (4.71; 6.45)]	94.3 (72.1; 109.4) [5.23 (4.00; 6.07)]
60 min	107.3 (66.3; 168.1) [5.96 (3.68; 9.33)]	140.1 (106.2; 207.8) [7.78 (5.89; 11.53)]	148.0 (116.5; 220.0) [8.21 (6.47; 12.21)]	132.5 (101.8; 195.0) [7.35 (5.65; 10.82)]
120 min	90.6 (67.8; 143.3) [5.03 (3.76; 7.95)]	118.6 (72.6; 151.1) [6.58 (4.03; 8.39)]	125.5 (75.0; 161.5) [6.97 (4.16; 8.96)]	108.0 (66.8; 145.8) [5.99 (3.71; 8.09)]

cap., capillary; glc., glucose concentration; interst., interstitial; iscCGM, intermittent-scanning continuous glucose monitoring; SMBG, self-monitoring of blood glucose; ven., venous.

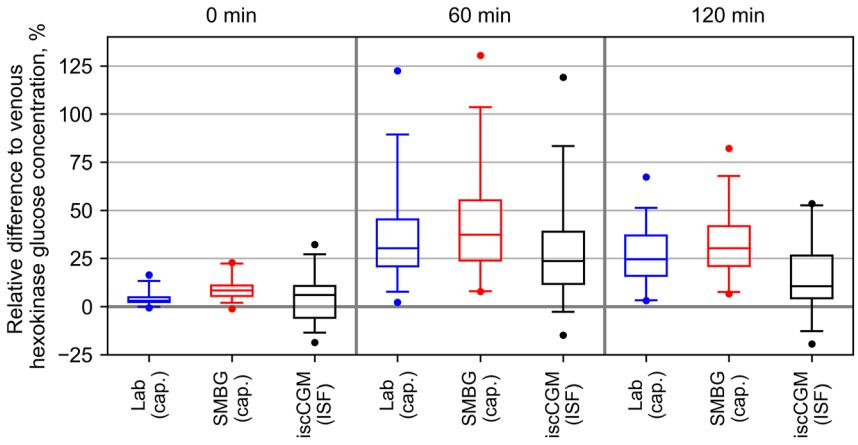

Figure 2: Box-Whisker plots for the relative difference in capillary and interstitial glucose concentration of subjects without diabetes (n=41) measured with a laboratory analyzer, an SMBG system or an iscCGM system compared to the venous glucose concentration measured with a laboratory analyzer at three different time points during an oral glucose tolerance test. Whiskers cover the central 95 % of values, circles indicate individual values outside of this interval. cap., capillary samples; iscCGM, intermittent-scanning continuous glucose monitoring; ISF, interstitial fluid; Lab, laboratory analyzer; SMBG, self-monitoring of blood glucose.

Table 2: Median (2.5 and 97.5 % quantiles) of relative paired differences in capillary and interstitial glucose concentration compared to the venous glucose concentration measured with a laboratory analyzer during an oral glucose tolerance test in 41 subjects.

Time	Laboratory analyzer, % (cap. glc.)	SMBG system, % (cap. glc.)	iscCGM system, % (cap. glc.)
0 min	+3.1 (−0.6; +13.7)	+8.5 (+1.6; +22.4)	+6.0 (−14.1; +27.7)
60 min	+30.3 (+7.6; +90.2)	+37.3 (+8.0; +103.6)	+23.6 (−2.7; +83.4)
120 min	+24.5 (+3.4; +52.1)	+30.3 (+7.7; +68.6)	+10.7 (−13.0; +52.6)

cap., capillary; glc., glucose concentration; interst., interstitial; iscCGM, intermittent-scanning continuous glucose monitoring; SMBG, self-monitoring of blood glucose.

state, but significantly higher post-load glucose levels in capillary blood than those in venous blood [19, 20]. More recent studies also confirm this outcome [21]. However, none of these studies assessed interstitial fluid glucose concentrations obtained with a CGM system in parallel to venous and capillary glucose concentrations. In this study, venous and capillary glucose concentrations were measured in plasma with the same laboratory analyzer, so that these differences can be attributed to physiologic processes. In addition, capillary plasma-equivalent BG concentrations were obtained with a high-quality SMBG system [22]. It has to be noted that the average relative difference between the SMBG results and capillary BG values obtained with the laboratory analyzer was consistent across all three time points, indicating a measurement bias. The glucose concentration ranges measured by all four methods were similarly wide for any specific time point as shown by 2.5 % quantile and 97.5 % quantile in Table 1. As the range of relative differences was similar among the capillary values from the laboratory analyzer and the SMBG system at any specific time point (Figure 2), the increase in variability can likely be attributed to physiologic differences rather than technical aspects. For the iscCGM system, it remains unclear to what degree the differences are caused by physiologic processes as opposed to technical aspects, because the variability of fasting differences between iscCGM values and venous laboratory analyzer values was larger than for the other two methods. No correlation between within-subject iscCGM differences and the differences between iscCGM and venous laboratory analyzer values was found.

Differences in venous, capillary and interstitial fluid glucose concentrations affect results from CGM performance studies. Since interstitial fluid cannot be sampled in sufficiently large volumes over sufficiently short time, comparator measurements have to be performed either on venous or on capillary blood (or plasma) samples. Venous samples benefit from the use of laboratory analyzers that are typically more accurate than SMBG systems. However, even in the absence of known physiologic differences [23, 24], the potential for pre-analytical and analytical errors exists. Due

to glycolysis, there is a need to either perform immediate measurements on whole blood or centrifuge the sample to separate plasma very quickly after a sample was drawn, or glycolysis inhibitors have to be used. With liquid additives, which require a conversion factor due to sample dilution, the sampling tubes have to be filled very carefully. SMBG systems, on the other hand, tend to show less accurate results than laboratory analyzers (i.e., potentially more analytical errors), although qualitative differences exist between different brands of SMBG systems [22]. Advantages of using SMBG systems lie in the comparably small blood volumes needed for measurement and the ability of applying the reagent system directly to the fingertip, like in traditional SMBG-based diabetes therapy, thus potentially being less affected by pre-analytical errors than laboratory analyzers.

Due to differences between venous and capillary glucose concentrations, the performance data of CGM systems obtained with venous comparator samples are thus not necessarily relevant for daily-life use. In performance studies, manually calibrated CGM systems could be calibrated with venous BG values, so that similar to daily-life use, the same compartment would be used for calibration and for comparison. However, this is not an option for factory-calibrated CGM systems.

There is a reasonable expectation that CGM systems for home use should indicate capillary-like glucose concentrations especially if they are intended to supplement traditional SMBG or if they are calibrated manually. Otherwise, users would have to have guidance when discrepant results are acceptable or not, which is currently not provided. Therefore, the results of this study question the use of comparator measurements in venous samples. Not only were there marked systematic differences between venous and capillary and interstitial values, but these differences also varied between subjects. Since in analytical performance studies, the comparator is often viewed as error-free and measurement error is thus mostly or even completely attributed to the test system, using venous comparator measurements will introduce sources of error that should not reasonably be attributed to the test system. Furthermore, comparison with venous BG concentrations could provide an incentive for manufacturers to adapt their calibration algorithms in order to reduce differences between CGM values and venous BG concentrations. This could ultimately lead to a CGM system that shows high levels of accuracy in analytical performance studies, but the values it provides may be non-optimal for diabetes therapy.

Outside of CGM performance studies, differences in glucose concentrations in various compartments play a role, for example, in the diagnosis of diabetes. If a diagnosis is based on glucose concentrations rather than HbA_{1c} alone, it is best practice to determine venous plasma concentrations from samples where all pre-analytical and analytical steps were conducted properly [25]. This study reinforces the importance of using venous samples when applying the established diagnostic thresholds. If capillary BG results or CGM values were used in the diagnosis of diabetes, a tendency towards higher numbers of non-normal glucose tolerance could be expected. For example, both the American and the German Diabetes Associations state that a random venous plasma glucose concentration ≥200 mg/dl (≥11.1 mmol/L) allows for diagnosing diabetes [25, 26]. The American Diabetes Association additionally requires that symptoms of hyperglycemia or hyperglycemic crisis are present. In the primary analysis of this study's data [14], random CGM values above 200 mg/dl (11.1 mmol/L) did not necessarily indicate presence of diabetes mellitus. Therefore, if capillary glucose concentrations, or CGM values were to be used for diagnosis of diabetes, new diagnostic thresholds or parameters would have to be defined [27].

A limitation of this study is the use of a first generation iscCGM which may not be as accurate as current generation devices. Sufficient accuracy of CGM systems at times of rapid changes in glucose concentration like during an oGTT is indispensable to reliably predict glycemic excursions; this needs to be taken into account when interpreting CGM values. As a consequence of the issues associated with sampling interstitial fluid, CGM systems have to be calibrated with either venous or capillary samples [28]. It is therefore likely, that any CGM system does not show the "true" interstitial glucose concentrations, but rather a hybrid glucose concentration that lies between venous or capillary BG and interstitial glucose concentrations. Future research may investigate the use of newer generation sensors. Furthermore, the sample size was relatively small and mostly young adult participants were included (mean age≈25 years), which is not representative for the general population.

Another potential limitation regarding the use of CGM values is that the displayed glucose value is not directly comparable to the corresponding capillary, venous or interstitial glucose concentration, because of signal processing and calibration occurring in the CGM system [28]. In particular after carbohydrate intake, physiological differences leading to a time lag between the three compartments (capillary, venous and interstitial fluid) need to be considered [23, 24], which can be compounded by technical time lag when CGM systems are used [11]. In addition, the SMBG system used for calibration can influence the accuracy of manually calibrated CGM systems [29]. As there is no traceability chain established for CGM systems for assessment of their analytical performance, there may be differences in measurement accuracy between different models of CGM systems [30].

Conclusions

In conclusion, there were clinically relevant differences in absolute values and relative differences between venous, capillary and interstitial glucose concentrations, measured with a laboratory analyzer, an SMBG system and a CGM system in subjects without diabetes during an oGTT. Especially 60 and 120 min after the start of the oGTT, relative differences exhibited a high inter-individual variability. These differences can impact the perceived accuracy of a CGM system in a performance study depending on the selected comparator method. In addition, they underscore the use of venous plasma samples when applying the established diagnostic thresholds.

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Competing interests: G.F. is general manager of the Institut für Diabetes-Technologie Forschungs- und Entwicklungsgesellschaft mbH an der Universität Ulm (IfDT, Ulm, Germany), which carries out clinical studies on the evaluation of BG meters and medical devices for diabetes therapy on its own initiative and on behalf of various companies. G.F./IfDT have received research support, speakers' honoraria or consulting fees in the last 3 years from Abbott, Ascensia, Berlin Chemie, Boydsense, Dexcom, Lilly, Metronom, Medtronic, Menarini, MySugr, Novo Nordisk, Pharamsens, Roche, Sanofi, Terumo. All other authors were employees of IfDT at the time.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by the authors' responsible Ethics Committee (Ethikkommission bei der Landesärztekammer Baden-Württemberg; application no. F-2017-095).

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