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Evaluation of the relationship between capillary and venous plasma glucose concentrations obtained by the HemoCue Glucose 201+ system during an oral glucose tolerance test

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**Abstract**

In 55 women with previous gestational diabetes mellitus, simultaneous capillary and venous plasma glucose concentrations were measured at 0, 30 and 120 min during a 75 g oral glucose tolerance test (OGTT). The aims of the study were to examine the relationship between capillary and venous glucose measurements, and to establish equations for the conversion of capillary and venous glucose concentrations using the HemoCue Glucose 201+ system. Additionally, the correlation between the capillary and venous glucose concentrations with the diagnostic cut-off limits proposed by the WHO 1999 was evaluated. Capillary glucose concentrations were consistently higher than venous glucose concentrations at all time points of the OGTT ( $p < 0.001$ ), and the correlations between the measurements were statistically highly significant ( $p < 0.001$ ). The differences between the samples were greatest in the non-fasting state as revealed by the 95% prediction intervals (mmol/L) in Bland-Altman plots;  $\pm 0.54$  at 0 min,  $\pm 2.01$  at 30 min, and  $\pm 1.35$  at 120 min. Equivalence values for capillary plasma glucose concentrations derived from this study tended to be higher than those proposed by the WHO as diagnostic cut-off limits. Stratifying subjects by glucose tolerance status according to the WHO criteria revealed disagreements related to glucose values close to the diagnostic cut-off points. The study findings highlight the uncertainty associated with derived equivalence values. However, capillary plasma glucose measurements could be suitable for diagnostic purposes in epidemiological studies and when translating results on a group basis.

**Key Words:** Agreement, Bland-Altman plot, comparison method, conversion algorithm, correlation

## Introduction

An oral glucose tolerance test (OGTT) is the standard of choice to diagnose diabetes mellitus or impaired glucose tolerance (IGT) in population studies [1]. While the American Diabetes Association recommend venous plasma to be used for diagnostic purposes [2], the World Health Organization (WHO) provides cut-off limits for both venous and capillary glucose concentrations [1]. However, they give no evidence for their statements. Several reports have evaluated differences between capillary and venous glucose measurements in whole blood and plasma [3-6]. Most studies [3-5] indicate no difference in the fasting state, but after a glucose load the levels are consistently higher in capillary than in venous samples. Several factors affect the results of the glucose measurements, including the kind of sample material used [7-9]. Since capillary blood samples are easier to obtain and require less skill, it would be desirable, both from a scientific and a clinical point of view, if capillary and venous glucose values could be used interchangeably along the concentration scale by the use of conversion algorithms. However, this may not be applicable to all analytical systems and there is a need for more data from the manufacturers to provide reliable information on the different sample procedures.

Women with gestational diabetes mellitus are at increased risk for the development of diabetes after pregnancy and should therefore be screened for diabetes postpartum [1, 10]. In southern Sweden women with gestational diabetes mellitus are offered a 75 g OGTT one year after delivery to detect those with abnormal glucose tolerance postpartum. Capillary samples are analyzed using the HemoCue Glucose 201+ system, converting blood glucose to equivalent plasma glucose concentrations [11, 12]. The aims of the present study were to examine the relationship between capillary and venous glucose measurements obtained by the

HemoCue device during the OGTT and to establish equations for the conversion of capillary and venous glucose concentrations. An additional aim was to evaluate the correspondence between the capillary and venous glucose concentrations obtained in this study with the diagnostic cut-off limits proposed by the WHO 1999 [1].

## **Material and methods**

### *Study population*

Subjects were recruited from an on-going study in southern Sweden evaluating the effects of different categories of glucose tolerance during pregnancy on the development of diabetes mellitus and IGT postpartum [13]. For the present study 55 consecutive non-smoking women undergoing an OGTT five years after the index pregnancy were included; median (range) age 37 (29--48) years, and BMI 24.4 (18.3--36.2) kg/m<sup>2</sup>. Participants were predominantly Scandinavians, with 31% non-European representation and 9% representing other countries in Europe. During pregnancy 44 women were classified as having abnormal glucose tolerance and 11 as having normal glucose tolerance.

### *Measurements*

Glucose tolerance was defined according to the WHO 1999 criteria [1] and was measured by a standard 75 g OGTT, which was performed by one specially trained laboratory assistant. The test procedure followed the following sequence: after an overnight fast, a Venflon catheter (Becton Dickinson, Helsingborg, Sweden) was inserted into an antecubital vein. Duplicate samples of 5 µl blood were collected in HemoCue Glucose cuvettes and immediately analyzed in a HemoCue Glucose 201+ Analyzer (HemoCue, Ängelholm,

Sweden), which converts blood glucose concentrations to equivalent plasma glucose concentrations by multiplying by an adjustment factor of 1.11 [11, 12]. Immediately thereafter, glucose concentration was measured in duplicate samples of capillary blood from the third or fourth fingertip of the non-dominant hand according to the same procedure. Subsequently, 75 g anhydrous glucose dissolved in 300 mL water was given. The sampling and measurement procedures were then repeated after 30 and 120 min. All calculations were performed on mean values from the duplicates.

The study was carried out in accordance with the World Medical Association Declaration of Helsinki and the Ethics Committee, Lund University, approved the study protocol (LU 259-00).

### *Statistical methods*

Statistical analysis was performed by SPSS 19.0.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean  $\pm$  standard deviation (SD). A two-sided p-value of less than 0.05 was considered significant. The statistical significance of difference between mean capillary and venous glucose concentrations at each time interval was evaluated by Student's paired t-test. Correlations were performed by Pearson's test. Results obtained for venous and capillary plasma glucose measurements were compared using the method of Bland and Altman, in which differences between paired measurements are plotted against the mean of each pair [14]. Conversion equations were derived according to the method described for not constant differences [15]. To study the agreement between categories of glucose tolerance obtained by either capillary or venous glucose measurements a cross table was made. The overall indicator kappa ( $\kappa$ ) was calculated. A value of 0 indicates that agreement is no better

than chance, while values larger than 0.80 indicate very good agreement. Values between 0.61--0.80 may be taken to represent good agreement [16].

## Results

Mean imprecision (coefficient of variation) of the duplicate capillary analyses performed in this study was 1.8%, and of the venous analyses 1.6%.

Mean capillary and venous glucose concentrations obtained during the OGTT are shown in Table I. For two women venous samples were missing in the fasting state and for three women at 120 min post load. Capillary plasma glucose values were significantly higher than venous plasma glucose values at all the time points. However, the deviation between the samples was greatest in the non-fasting state.

The relation between the capillary and venous plasma glucose concentrations at the different time points of the OGTT are shown in Figure 1, panel a--c. A high correlation was found during fasting ( $r = 0.93$ ;  $p < 0.001$ ), at 120 min post load ( $r = 0.94$ ;  $p < 0.001$ ), and to a lesser extent at 30 min post load ( $r = 0.81$ ;  $p < 0.001$ ).

The Bland-Altman difference plots are shown in Figure 2, panel a--c. Capillary glucose concentrations were consistently higher than venous. Best agreement was found in the fasting state with data points clustered near the regression line, resulting in a narrow 95% prediction interval (p.i.). The 30 min glucose values showed the widest p.i., reflecting a greater variation of differences between capillary and venous samples. Furthermore, the difference increased



with increasing glucose concentrations. In contrast, the regression line for the fasting and 120 min glucose values showed a negative slope with smaller differences between the methods with increasing glucose values.

According to Carstensen [15], equations were calculated for conversions between the two measurement methods. The equations, conversion lines and 95% p.i. are shown in Figure 1. We tested the formulae to compare the equivalence values obtained in this study for venous and capillary plasma glucose with the corresponding equivalence values published by the WHO for diagnostic levels of IGT and diabetes [1]. In the fasting state, the capillary plasma glucose value equivalent to a venous plasma glucose of 7.0 mmol/L derived from this study was 7.2 mmol/L, compared with the WHO value of 7.0 mmol/L. Similarly, for the venous 2-h post load values of 7.8 mmol/L and 11.1 mmol/L, the capillary equivalence values were 9.3 mmol/L and 12.4 mmol/L respectively, compared with the WHO values of 8.9 mmol/L and 12.1 mmol/L. The differences were within the 95% p.i.

The women with complete data ( $n = 50$ ) were stratified by glucose tolerance status as diabetes mellitus, IGT, or normal glucose tolerance (NGT) according to the WHO 1999 criteria [1] using either venous (v) or capillary (c) plasma glucose concentrations (Table II). The consistency in classifying between capillary and venous glucose measurements was 82% (41/50) and  $\kappa$  was 0.70, indicating good agreement. All women classified as having diabetes based on venous samples were also classified as having diabetes based on capillary samples. In the NGT category five out of 26 women were classified as IGT by capillary glucose criteria. Their capillary 2-h glucose concentrations were in the range 9.0--10.0 mmol/L vs. 7.0--7.7 mmol/L for venous samples. Of the women classified as IGT by venous criteria, capillary concentrations indicated NGT in three women (2-h venous glucose concentrations in

the range 8.0--8.5 mmol/L vs. 7.8--8.8 for capillary samples), and diabetes in one woman (2-h venous glucose concentration 10.6 mmol/L vs. 12.4 mmol/L for capillary sample).

## Discussion

The HemoCue device is widely used in Sweden for diagnostic purposes. In 2004 glucose measurements in Sweden switched from blood to plasma glucose and a transformation factor of 1.11 was agreed on [12]. The HemoCue Glucose 201+ Analyzer was introduced to comply with the IFCC's recommendation of reporting plasma glucose. The instrument, which converts blood glucose concentrations to equivalent plasma glucose concentrations by multiplying by an adjustment factor of 1.11, has been shown to satisfy the requirements for diagnostic determination of plasma glucose [11].

The present study found capillary plasma glucose levels to be consistently higher than the venous levels at all the time points of the OGTT. This finding is in contrast to other published results that did not find any difference between capillary and venous measurements in the fasting state [3-5]. However, a more recent study based on a considerably larger number of subjects ( $n = 350$ ) reported results similar to ours [6]. In agreement with previous reports [3-6], the differences were of a greater magnitude after glucose ingestion and were most pronounced at 30 min post load, coincident with the peak of the glucose curve. Additionally, as shown by the Bland-Altman plot, the differences at 30 min post load increased with increasing glucose concentrations. In contrast, glucose concentrations in the fasting state and at 120 min post load were negatively associated with the differences between the measurements and the p.i. were not as wide as for the 30 min glucose differences, indicating

less variation. The observed differences may be explained by individual and physiological variations [17], in part related to glucose uptake and elimination, the capillary samples primarily reflecting the uptake while the venous values more reflect the elimination.

Equivalence values for capillary plasma glucose concentrations derived from this study tended to be higher than those proposed by the WHO as diagnostic cut-off limits [1], especially the 2-h measurements. These results are in agreement with the findings by Colagiuri et al. [18]. Contrary results were reported by Carstensen et al. [8], who also demonstrated a greater variability in measurements based on capillary blood compared with other specimens.

When comparing the classification of glucose tolerance status according to the WHO 1999 criteria [1] for capillary and venous plasma glucose concentrations best agreement was found among subjects with NGT and diabetes. Scrutinizing measurements of all individuals revealed discrepancies close to the cut-off limits for either glucose category. Similar results were obtained in the study by Kruijschoop et al [6], who argued that the lesser agreement in the IGT category could be due to an artefact, caused by the narrow range of defined cut-off points for 2-h glucose concentrations in IGT. The results are supported by previous studies of the reproducibility of the OGTT, showing a high intra-individual variation in the 2-h plasma glucose concentrations, resulting in low reproducibility of the IGT category in particular [19-21]. As glucose levels increase, the diagnostic impact of the variation in 2-hour glucose concentrations decreases [19].

A limitation of the study is the rather low number of participants, especially when considering the number of measurements in the upper glucose range. Furthermore, the study was restricted

to the female gender. Due to these circumstances we are unable to draw any generalized conclusions from our results. However, our main concern was to focus on differences in a subsample of women with previous gestational diabetes mellitus as a guide for further evaluations and decisions.

In conclusion, the study findings highlight the uncertainty associated with derived equivalence values, which may lead to misclassification when used for diagnostic purposes on an individual basis. However, capillary plasma glucose measurements could be suitable for diagnostic purposes in epidemiological studies and when translating results on a group basis. The results underline the need for more conclusive data from the manufacturers of the different measuring systems regarding sample impact and correlation.

Table I. Capillary and venous plasma glucose concentrations during the oral glucose tolerance tests.

Time interval (min)	0	30	120
n	53	55	52
Capillary <sup>a</sup>	6.0 (0.7)	10.5 (1.7)	9.2 (1.9)
Venous <sup>a</sup>	5.8 (0.7)	8.7 (1.6)	7.7 (2.0)
Capillary-venous difference <sup>a</sup>	0.2 (0.3)	1.8 (1.0)	1.5 (0.7)
<i>p</i>	< 0.001	< 0.001	< 0.001

<sup>a</sup>Plasma glucose concentration (mmol/L). Data shows mean (SD). Differences between means were tested by Student's paired t-test.

Table II. Classification of glucose tolerance status according to the WHO 1999 criteria for capillary (c) and venous (v) plasma glucose concentrations.

	NGT	IGT	Diabetes	Total
	(v)	(v)	(v)	(c)
NGT (c)	21	3	0	24
IGT (c)	5	14	0	19
Diabetes (c)	0	1	6	7
Total (v)	26	18	6	50

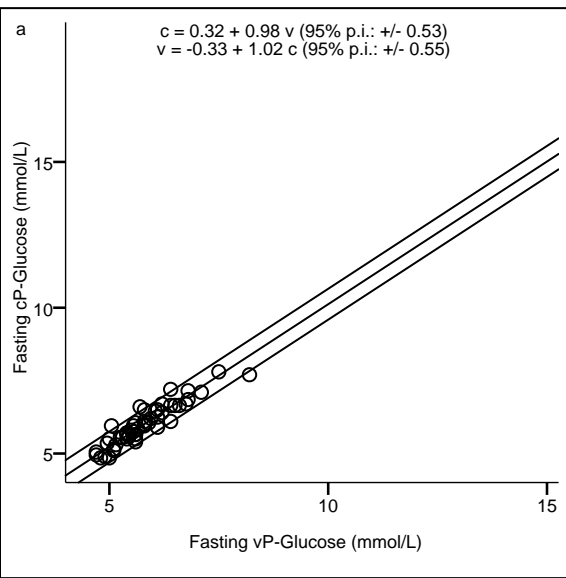
Data show numbers. Complete data were available for 50 women.

NGT, normal glucose tolerance; IGT, impaired glucose tolerance

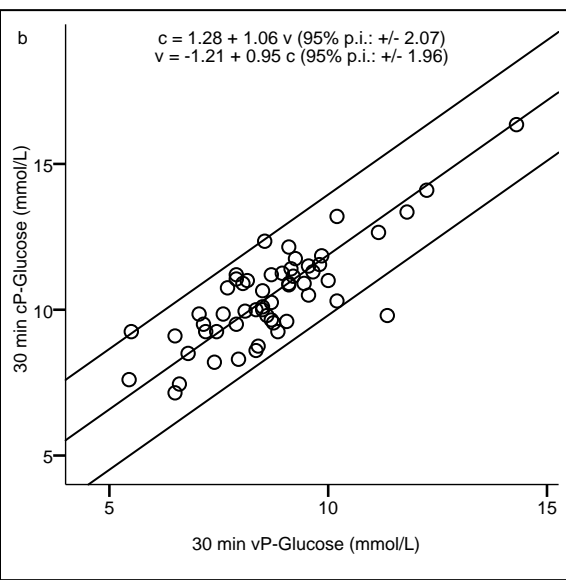
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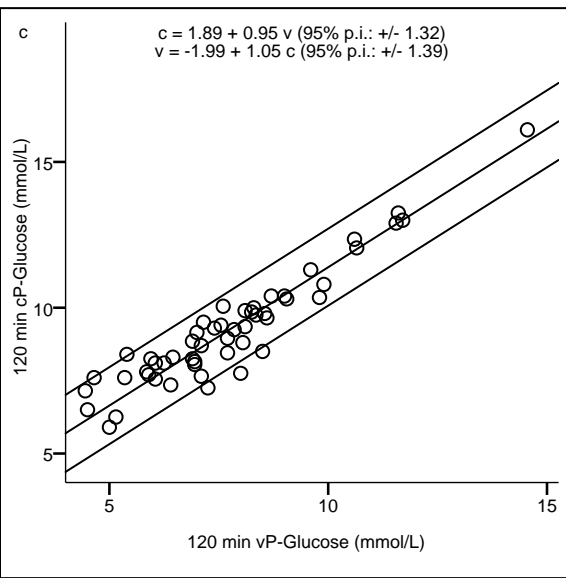
Figure 1. Scatter plots of capillary (c) and venous (v) plasma glucose concentrations during oral glucose tolerance test; panel a fasting ( $n = 53$ ), panel b 30 min ( $n = 55$ ), panel c 120 min ( $n = 52$ ). Equations for the conversions are given. Conversion lines and 95% prediction intervals (p.i.) are drawn.

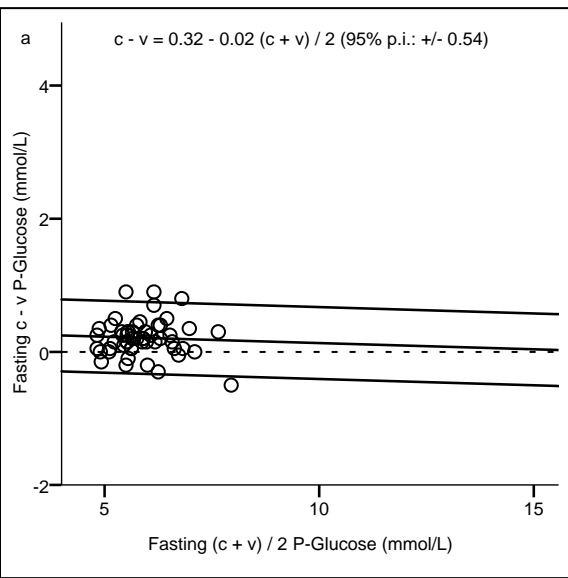
Figure 2. Bland-Altman plots of capillary and venous differences ( $c - v$ ) versus capillary (c) and venous (v) mean  $((c + v) / 2)$  of plasma glucose concentrations during oral glucose tolerance test; panel a fasting ( $n = 53$ ), panel b 30 min ( $n = 55$ ), panel c 120 min ( $n = 52$ ). Lines for the regressions and 95% prediction intervals (p.i.) are drawn. Equations for the regressions are given.

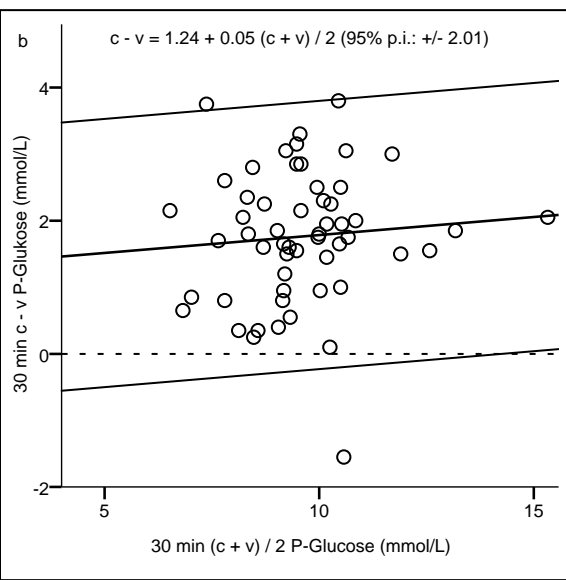


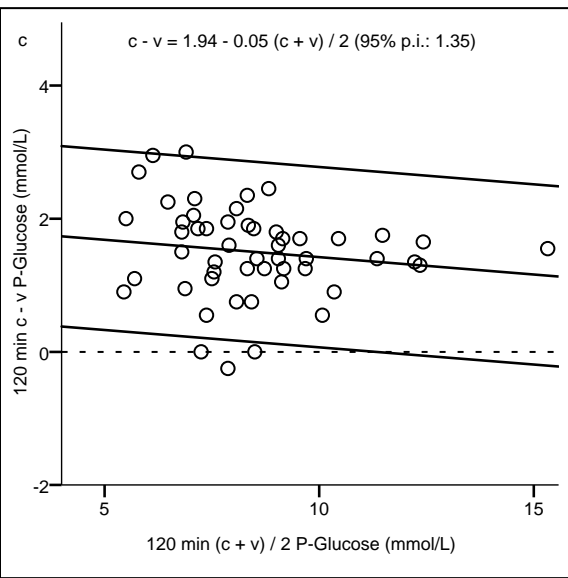












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