INTRODUCTION

The number of patients with diabetes mellitus constitutes approximately 7.8% of the general population, and this number is expected to rapidly grow with the aging of the Korean society [1–3]. Diabetes has also been shown to be the fifth major cause of death nationwide in 2005 [4, 5]. However, patients with diabetes can maintain a satisfactory quality of life by preventing the adverse effects of the disease, which can be achieved through appropriate disease management by ensuring proper diet, exercise, medication, and healthy living habits [6, 7]. To maintain their glucose levels within a desired range, patients are required to perform the blood glucose test (BGT) by themselves at home 3–4 times everyday [8].

Portable glucometers with good performances are widely
available in the market, and the standard technique for a self-test involves sampling the capillary blood from the finger by a disposable lancet so that the requisite amount of blood required by the device can be obtained. Although the fingertip possesses well-developed capillaries to provide enough blood for the test, pain receptors concentrated on the fingertip induce significant pain when the skin is punctured [9]. As a result, some patients avoid the self-test, which could lead to failure of glucose control. In a survey by Park et al. [10], 55% of the diabetes patients responded to the survey questions, and only 35% performed the self-test. These survey results show that only 20% of the patients may perform the routine self-test to control their blood glucose levels.

Despite the fact that BGT using skin puncture is a well-established technique [11], the pain during sampling not only makes the patient avoid the self-test, but also causes both physiological and psychological problems, particularly in infants [12, 13]. To minimize pain, new techniques involving sampling at alternative sites with fewer pain receptors, such as the forearm, have been developed [14]. We have recently developed a vacuum-assisted auto-lancing technique to facilitate nearly painless blood sampling [15]. The BGT results obtained for the forearm showed no significant differences to those for the finger in 50 non-fasting subjects [16]. However, a large-scale clinical study encompassing a wide range of glucose levels should precede the introduction of this new capillary blood sampling technique into clinical practice. Therefore, in the present study involving more than 500 subjects, BGT was first performed at the finger, which was immediately followed by BGT at the forearm, and then, within an hour, at the vein, and the results obtained from the 3 sites were compared to demonstrate the validity of the forearm blood-sampling technique.

**MATERIALS AND METHODS**

1. **Subjects**

The purpose and procedure of the study were explained to the subjects who visited the Health Enhancement Center of the Chungbuk National University Hospital for regular monitoring of fasting glucose levels. Informed consent was obtained from 530 subjects who participated in the study. The study design was approved by the institutional review board (IRB). Among the 530 subjects, only 36 (6.8%) had been previously diagnosed with diabetes. An additional 25 patients with diabetes were recruited and scheduled for regular morning visits under fasting conditions. Therefore, 494 normal subjects and 61 diabetes patients were included in the study, thereby making the total number of participants 555.

2. **Devices**

Blood samples were obtained from the finger and forearm using a disposable auto-lance (Autolet: Geosang Med, Co., Chungju, Korea) and a vacuum-assisted auto-lancing device (CareLance: CKInt, Co., Cheongju, Korea), respectively. Venous blood was sampled from the antecubital vein using a vacutainer needle. Glucose concentration in the blood was measured using a portable glucometer (CareSens: i-sens Co., Ltd., Seoul, Korea), which has been certified for use in Europe (EC-Certificate, No. V1 09 04 51072 013) and also allowed for sale in the United States by Food and Drug Administration (No. k080923). Venous glucose levels were measured using an automated chemical analyzer (747; Hitachi, Tokyo, Japan) using hexokinase (Climate GLU: DAIICHI, Tokyo, Japan), which is currently being used for patient samples in the Clinical Laboratory of the Chungbuk National University Hospital. Both glucose-measuring devices are known to have a good performance, and are widely available in the international market. In particular, the portable glucometer is capable of measuring glucose levels in less than 5 sec by using a very small amount of capillary blood (less than 1 μL). Its accuracy and precision has been previously studied in comparison with 4 other latest device models (Accu-Check Go and Accu-Check Advantage manufactured by Roche; Optimum, Abbott; and GlucoMan PC, Menarini), which confirmed its precision and accuracy with a mini-
3. Procedure

The general data about the physical characteristics of the subjects along with their medical history were recorded, followed by measurement of their height and weight to evaluate obesity. Capillary blood was sampled from the index finger of the subjects for glucose measurement (GF). Immediately after measuring the GF value, the frontal side of the forearm was rubbed by hand for 5 sec to enhance the capillary circulation underneath before collecting the blood sample for glucose measurement (GA). After completing the BGT at the finger and forearm, the subject was moved to the Clinical Laboratory, and glucose concentration in the venous serum (GV) was measured within an hour. Therefore, GA and GF measurements were considered to be “almost” simultaneous, while GV was measured 30–60 min after GA. Forty-one of the 555 subjects refused to undergo venous sampling; therefore, GV data were available for only 514 subjects.

4. Data analysis

1) Simple linear regression analysis

Since the number of the normal subjects (494) was much larger than that of patients with diabetes (61), the subjects were divided into normal and patient groups. The grouping also helped to evaluate any potential intergroup differences with regard to glucose measurement. Since our major interest was to compare GA with GF and since GF is a standard for glucose self-testing, simple linear regression analysis was performed using the SPSS/Win10.0 program by considering GF to be an independent variable. Although, GV measurement was performed 30–60 min after GA measurement, GA-GV regression analysis was performed under the reasonable assumption that blood glucose levels would not change significantly within an hour in overnight-fasted subjects (subjects fasted since the last supper of the previous day). In GA-GF and GA-GV regression analyses, slope, constant (or intercept), and Pearson correlation coefficient were evaluated and compared between normal and patient groups.

2) Intraclass correlation analysis

The WHO considers GF and GV as the standards for self and clinical tests, respectively [18]. Therefore, the Food and Drug Administration (FDA) of the US requires a simple linear regression analysis to be performed when evaluating a new glucose measurement technique for approval [19]. However, significant measurement error and/or environmental effect might interfere with the standard measurement technique to such a degree that the standard measurement cannot be considered independent. To test this possibility, the intraclass correlation analysis was performed to evaluate the extent of agreement between the forearm BGT data and the fingertip or the vein BGT data in the measurement of glucose concentration [20]. The intraclass correlation coefficients were obtained for both GA-GF and GA-GV data sets in the normal and the patient groups.

3) Passing-Bablok regression analysis

In the above analyses, both the Pearson and intraclass correlation coefficients were comparable in value and were statistically significant (see the RESULTS section). Moreover, since no significant intergroup differences were observed, Passing and Bablok regression analysis was performed by pooling all data together [21]. This regression analysis technique allows for non-uniform distribution, such as the one in our data where having more normal subjects than the diabetic patients was of major concern. With no special assumptions in the regression procedure, 95% confidence intervals for the slope and constant parameters could be obtained in a linear relationship, which helped demonstrate the valid glucose measurement range of the forearm BGT technique.
RESULTS

1. Subject characteristics

The general characteristics of the subjects are summarized in Table 1. Two hundred and two (36.4%) male and 353 (63.6%) female subjects were enrolled in the study. Approximately 92% of the subjects were over the age of 40 yr, which is an age category with high risk of diabetes. About 50% of the subjects were obese, and 23.4% had a history of diabetes and/or hypertension. A total of 555 subjects were divided into 2 groups: normal subjects (N=494) and patients with diabetes (N=61).

2. Overall data features

Intergroup GA-GF and GA-GV difference were calculated (Table 2). All mean differences were within ±10 mg/dL, but paired student’s t test showed statistically significant differences between all comparisons (P<0.001), which can be attributed to the large sample size with relatively small variance (described in the Discussion section). The mean relative errors (or bias) were also calculated to be within ±5–12%, which were well below the error limit of ±20% recommended by CLSI and ISO [22, 23].

The glucose levels of most subjects in the normal group ranged between 60–130 mg/dL, with a few patients, possibly those with diabetes, showing glucose levels of up to 200 mg/dL. However, these subjects were included in the normal group because the subjects in question had not been officially diagnosed with diabetes at the time of the study. At the end of the testing period, they were informed of them being at a high risk for diabetes and were recommended to visit a physician. The glucose levels in the patient group showed a very wide range (approximately 60–350 mg/dL), despite the small sample size, which was expected due to their decreased ability to regulate glucose levels even under fasting conditions.

3. Results of the correlation analysis

1) Results of simple linear regression analysis

The results of simple linear regression analysis of GA–GF plotted with both regression and identity lines for both groups have been shown in Fig. 1. GA–GF regression analysis revealed no significant correlation between the forearm and the finger glucose measurements in the normal (A) and the patient (B) groups.

Table 2. Mean (SD) values of the differences in glucose measurements in the normal and the patient groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normal</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>eAF (mg/dL)</td>
<td>9.7±8.46</td>
<td>8.3±12.11</td>
</tr>
<tr>
<td>%eAF = eAF x 100%</td>
<td>11.6±10.15</td>
<td>7.1±9.63</td>
</tr>
<tr>
<td>eAV (mg/dL)</td>
<td>5.4±9.86</td>
<td>-8.1±15.25</td>
</tr>
<tr>
<td>%eAV = eAV x 100%</td>
<td>6.3±10.99</td>
<td>-4.8±9.11</td>
</tr>
</tbody>
</table>

eAF and eAV represent the differences between the forearm and the finger measurements (G-F), and between the forearm and the vein measurements (G-V), respectively, and %eAF and %eAV are the corresponding bias relative to G-F and G-V, respectively.

Fig. 1. Simple linear regression results between the forearm (G-F) and the finger (G-F) glucose measurements in the normal (A) and the patient (B) groups. The solid and dotted lines represent the regression and the identity lines, respectively.
ysis results for both groups have been shown in Fig. 2. The parameter values are summarized in Table 3.

The Pearson correlation coefficients (r) of GA-GF and GA-GV relationships in the normal group were 0.86 and 0.79, respectively, while the patient group demonstrated an excellent r value of 0.97 in both GA-GF and GA-GV relationships. All r values were statistically highly significant (P<0.0001). Despite the intergroup difference in r values, the slope values of the 2 groups were very close to each other, such that a=0.95 (normal group) and 0.99 (patient group) in the GA-GF relationship. The same was true in the case of GA-GV relationship, although these groups showed slightly smaller slope values (a=0.91 and a=0.94 for the normal and patient groups, respectively). Similar slope values in the normal and the patient groups for both GA-GF and GA-GV relationships imply not only that the measurement sensitivity on the forearm did not signifi-
cantly differ from that on the finger or the vein but also that only a minor difference in measurement character-
istics seemed to exist between the normal and the patient groups. This becomes more obvious from the fact that the constant values of GA-GF relationship resulted in very similar values of b=13.54 mg/dL and b=10.40 mg/dL for the normal and patient groups, respectively. These values (which are less than 15 mg/dL) are well below 70 mg/ dL, which is the clinically acceptable limit recommended by FDA [19] for the hypoglycemic region in the error grid analysis [24]. Therefore, the regression lines of GA-GF data were very close to the identity line in both groups. The GA-GV relationship also showed similar features in both groups, except for the small constant value of b=1.67 mg/dL in the patient group.

Since there were no significant intergroup differences, all data were pooled before analysis: the results are pre-
sented in Table 3. In GA-GF analysis, all parameter values of the pooled data were in the range of the values obtained for the individual groups. However, the slope parameter of a=0.88 in GA-GV regression analysis of pooled data was lower than the individual values obtained for both groups. We noted that the constant value of the patient group in GA-GV regression (b=1.67 mg/dL) was much smaller than that of the normal group (b=13.29 mg/dL), despite similar slope values in both groups (a=0.91 [normal group], a=0.94 [patient group]), which means that the regression line of the patient group on the GA-GV plane lay lower

Fig. 2. Simple linear regression results between the forearm (Ga) and the vein (Gv) glucose measurements in the normal (A) and the patient (B) groups. The solid and dotted lines represent the regression and the identity lines, respectively.

Table 3. Parameter (slope, intercept, and Pearson correlation coefficient) values obtained from simple linear regression analysis presented with both the intraclass correlation coefficient and results of Passing-Bablok analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Simple linear regression</th>
<th>Passing-Bablok regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>Constant (mg/dL)</td>
</tr>
<tr>
<td>Ga-GF</td>
<td>Normal</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>0.97</td>
</tr>
<tr>
<td>Ga-GV</td>
<td>Normal</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Ga-GF and Ga-GV represent the forearm-fingertip and the forearm-vein regressions, respectively. All correlation coefficients were statistically significant (P<0.0001).
than that of the normal group. Considering this and know-
ing that the range of glucose levels in the patient group
was much wider and higher than that of the normal group,
we inferred that the slope value for the pooled data was
smaller than the individual slope values for both groups.
The fact that the constant value of the pooled data (15.98
mg/dL) was higher than the individual values obtained
for both normal (b=13.29 mg/dL) and patient (b=1.67 mg/
dL) groups also supports this statistical outcome.

2) Intraclass correlation coefficients

The intraclass correlation coefficient values were slightly
smaller than the Pearson correlation coefficients by mag-
nitudes of 0.01–0.14 (Table 3). Furthermore, the intraclass
correlation coefficient values were statistically highly sig-
nificant (P<0.0001), thereby indicating that Ga correlated
well with both Gf and Gv. Similar values between these
2 different types of correlation coefficient not only imply
insignificant difference in the measurement characteris-
tics between the groups but also reflect that no significant
error was introduced in our experiment, thereby satisfy-
ing the pre-requisite of the simple linear regression anal-
ysis usually performed in glucose measurement [14, 16] as
per the FDA recommendations for approval [19].

3) Results of Passing-Bablok analysis

The Passing–Bablok analysis results are plotted in Fig.
3 with the regression lines showing the 95% confidence
region (in between the dotted lines), and also with the
internationally accepted limit lines (slope=unity±20%)
[22, 23]. Since there were no significant intergroup differ-
ences with regard to the results of simple regression and
intraclass correlation analyses, the data were pooled into
Ga–Gf or Ga–Gv data sets. The slope of the Ga–Gf rela-
tionship (Fig. 3A) was 1.04–1.14; therefore, the 95% con-
fidence region was located inside the limit region (±20%).
Similarly, the slope of Ga–Gv relationship was 1.08–1.20,
thereby resulting in most of the 95% confidence region
falling inside the limit region. Some outliers in the limit
region in the hypoglycemic range can be attributed to non-
ideal constant values of -2.97~5.39 mg/dL and -16.57~
-3.00 mg/dL in the Ga–Gf and Ga–Gv relationships, res-
pectively, both of which were much lower than the clin-
ically acceptable limits [24].

When the analysis was performed separately for each
group, the slope parameter of the normal group was 1.30,
which was higher than the acceptable value of 1.20 (Table
3). This can be attributed to the large number of data in
the normal group falling within a narrow glucose range,
which can result in a statistically erroneous slope value.
However, the 95% confidence region of the pooled data
lies inside the acceptable region, as has been mentioned
before: therefore, we think that the overall Ga–Gv rela-
tionship was clinically relevant.

**DISCUSSION**

Self–BGT using capillary blood sampled from the finger
is a standard technique for the management of diabetes.
However, it induces pain and may force the patient to avoid
the test, thereby leading to a failure in maintaining the
appropriate glucose levels. Therefore, the pain experienced
during sampling is considered to be a significant problem,
and a few alternative methods have been suggested. Non-
invasive bloodless glucose measurement techniques have
been evaluated; however, their accuracy and consistency
have not been proven in clinical application, and the high-
er costs of commercialization of these techniques may
also have to be considered [25, 26]. Capillary blood sam-
pling from an alternative site, such as the forearm, could
minimize pain, and perhaps be a practical solution to this problem [14, 15]. While blood sampling from the forearm induces significantly less pain than that from the finger, only a small amount of blood, usually less than a few microliters, can be obtained due to the low degree of capillary distribution in the forearm. This small volume of blood is not sufficient for traditional glucometers. Fortunately, modern high-end but inexpensive glucometers, such as the one used in this study, can provide accurate glucose measurements within 5 sec by using less than 1 \( \mu \text{L} \) of blood. Therefore, to minimize the pain during glucose self-testing, blood sampling from the forearm is a feasible and practical option.

The difference between the whole-blood glucose levels obtained by capillary blood sampling from the forearm and from the finger was reported to be statistically insignificant, but that assessment was performed in a limited number of subjects [16]. However, clinical practice usually requires additional validation in a sufficiently large subject population as well as over a wide range of glucose concentrations, and these requirements served as the motivations for the present study. We performed BGT at the forearm and at the finger almost simultaneously, and followed the procedures with BGT at the vein within an hour in more than 500 subjects, which can be considered a sufficiently large population. Since most study subjects had only visited the hospital for regular health check-ups, approximately 80% of them were normal and free of chronic diseases. To overcome this concern, we recruited 25 diabetic patients in the study. Since the experimental procedure was identical for all subjects, all data were pooled and then divided into the normal and the patient groups before analysis. We consider that the study population was appropriate to satisfy the objectives of this study for the following reasons: First, when comparing 2 different techniques, the most important pre-requisite is the measurement range, and the glucose concentration in our study ranged up to 350 mg/dL, which was approximately 4 times the normal fasting glucose level and was probably wide enough for most applications. Secondly, there is no reason to believe that the technique abruptly fails beyond this range, since the principle for the measurement of glucose, more specifically amperometry with enzyme process, has long been established both in vitro and in vivo. Thirdly, the present study population included many obese (57%) and aged (>60 yr) subjects (Table 1) who may be considered to have a potential risk of diabetes. In fact, 23% of the subjects had diabetes and/or hypertension.

Although our study population was appropriate, the normal group was much larger (494 subjects) than the patient (61) group; therefore, data analysis was performed separately on each group. FDA requires the performance of a simple linear regression analysis between the tested and the reference measurement techniques, and an additional analysis on the error grid is also recommended [19]. The reference technique (or the independent variable) must be a standard technique, which should be BGT by finger sampling or BGT with venous serum according to the recommendations of WHO [18]. Therefore, we chose the simple linear regression analysis as the first statistical method for the forearm BGT evaluation.

Since self-BGT is usually performed at home using a portable glucometer, \( G_A - G_F \) comparison is of major interest. Fig. 1 clearly shows that the regression lines fell very close to the identity line for both the normal and the patient groups, with a slight deviation of the slope and the constant from the ideal values of unity and zero, respectively. When comparing \( G_A - G_F \) data between the normal (Fig. 1A) and the patient (Fig. 1B) groups, the normal group showed a relatively narrower \( G_F \) range with a larger \( G_A \) variance, probably because of a much larger sample size of subjects. Accordingly, the correlation coefficient of the normal group was somewhat lower than that of the patient group and showed slightly different slope and constant values from the theoretically ideal values of unity and zero, respectively. When compared by a paired t test, \( G_A \) was significantly different from \( G_F \), but this difference was within the clinically acceptable bias. The linear relationship (or the regression lines) cannot exactly coincide with the identity line; thus, we think that the paired comparison is not an appropriate statistical test when the data are distributed over a wide range, such as those in our
study. Instead, in such cases, the correlation analysis better describes the degree of agreement between the 2 measuring techniques. Nevertheless, the mean differences were <10 mg/dL, which corresponded to a mean relative error of <12% that was well below the international limit of 20% [22, 23]. Moreover, the fact that the regression lines between the normal and the patient groups were very much close to each other with statistically significant correlation coefficients shows that the forearm BGT provides values that are similar to the standard fingertip BGT with practically acceptable errors.

Although the essential goal of our study was to compare forearm BGT with the finger BGT in terms of pain reduction during glucose self-testing, we also measured the glucose concentration in venous serum to strengthen our experimental outcome. G_A was measured immediately after GF, after which the subject moved to the Clinical Laboratory for venous blood sampling, which led to a time lag of 30–60 min between the GA and GV measurement. Although GA and GV were measured with a 30–60 min time difference, we proceeded to perform GA–GV comparison under the assumption that the glucose level would not change significantly in overnight-fasted subjects (subjects who had fasted since the last supper of the previous day before visiting the hospital next morning). We think that this assumption is physiologically reasonable, and GA–GV data were also well-correlated as described in the following section.

Comparison of G_A with GV, a standard measurement performed in hospitals, showed that both values were only slightly different, i.e., the mean differences were <±10 mg/dL (Table 2). The G_A–GV plots for the 2 groups showed a similar degree of scattering around the regression line of the G_A–G_F relationship (Fig. 1, 2). Although the linear relationship was similar to the G_A–G_V relationship, the slope values of both the normal and the patient groups revealed small but inherent differences in the G_A–G_V nature. In Table 3, the slope values of G_A–GV relationships are lower than those of G_A–G_F relationships in both groups by the same magnitude (0.04–0.05), with comparable levels of the constant. Therefore, G_A was measured consistently lower than G_V by approximately 5%. Glucose in the whole blood is known to be lower than that in the plasma by 10–15% [18, 27], and the commercially available glucometers for self-testing also show a similar tendency with the hematocrit [28], a finding that is consistent with our results. The industrial process of calibrating glucometers usually includes this hematocrit compensation procedure, which seemed to have been not completed in the glucometer used in this study, leading to 5% difference in G_A–GV comparison. Furthermore, the time lag between G_A and G_V could also have affected this difference. However, the goodness-of-fit in regression analysis was satisfactory, similar to G_A–G_F relationship with the mean relative error of <±10% (Table 2). Thus, G_A could provide high-quality glucose measurements similar to those provided by the automated chemical analyzer in the Clinical Laboratory, with slight adjustments as required.

Although the above simple linear regression analysis is recommended by FDA [19], since G_F and G_V are considered as standard measurement variables recommended by WHO [18], the reference variables (G_F and G_V) may be assumed to be free of measurement error, an assumption that is not feasible under every practical situation. For further validation of our experimental results, we introduced the intraclass correlation coefficient [20] with a view that the forearm BGT and the finger (or the vein) BGT measure the same single variable (blood glucose) with no differences in technical properties. In such cases, the intraclass correlation analysis evaluates different types of correlation coefficients and shows the extent to which the 2 compared data sets agree with each other. As demonstrated in Table 3, the intraclass correlation coefficient values showed a tendency similar to the Pearson correlation coefficients except that the values were slightly lower. Therefore, we think that forearm BGT provides glucose measurements similar to those obtained from standard techniques widely applied at home as well as in hospitals.

Although both Pearson and intraclass correlation coefficients showed a good agreement of G_A with G_V or G_F in the normal and the patient groups, this finding does not necessarily prove that the forearm BGT is clinically accept-
able. This is because the variance of \( G_A \) could be large enough to exceed the allowable limit in any particular range. A new measurement technique, in general, should demonstrate that data measured over a full range resides in the acceptable region. One method to assess this property of the data is to evaluate the 95% confidence interval (or region) and test whether it is within the acceptable range. Therefore, we performed the Passing–Bablok regression analysis on both \( G_A - GF \) and \( G_A - GV \) data [21].

The normal and the patient group data were pooled because, firstly, both groups did not differ in the simple regression and the intraclass correlation analyses described above, and secondly, this regression technique does not require any \textit{a priori} assumptions such as uniform distribution. As shown in Fig. 3, the 95% confidence region (in between the dotted lines) was within the acceptable limit region (in between the solid lines with slope values of 0.8 and 1.2) [22, 23]. Therefore, forearm BGT can be considered to maintain a satisfactory accuracy over the entire range of blood glucose concentrations. However, a closer look at Fig. 3 shows us that the 95% confidence regions occupied an area above the identity line, which may indicate that \( G_A \) was consistently higher than \( GF \) or \( GV \). This may be true in regions where many data points are available (\( GF \) or \( GV \leq 200 \text{ mg/dL} \)), but this assumption does not hold true in the higher glucose region (\( GF \) or \( GV > 200 \text{ mg/dL} \)), where more data points were outside the 95% confidence region. In other words, even the Passing–Bablok regression analysis technique is affected to some degree in the presence of a sufficiently large degree of imbalance in data distribution, thereby indicating the inability of this method to accurately reveal the complete characteristics of our data. This was because our experiment included more normal subjects than diabetic patients. In other words, no single statistical analysis method can satisfactorily describe the highly non-uniform feature of the whole data set. Nevertheless, the fact that the 95% confidence regions are within the acceptable region implies that forearm BGT can be introduced into clinical practice with some cautions when necessary.

We think that the 3 kinds of statistical methods applied in this study are complementary for the following reasons: First of all, all the 3 methods showed a statistically significant correlation between \( G_F \) and \( G_A \) and between \( G_A \) and \( G_V \) in the normal and the patient groups. Secondly, the simple linear regression analysis evaluates the linear relationship between the tested (or dependent) technique (or \( G_A \)) and the reference (or independent) technique (or \( GF/GV \)), while the intraclass correlation analysis decides the extent to which the \( G_A \) data set agrees with \( GF \) or \( GV \) regardless of the variable assigned as the independent quantity. Finally, the Passing–Bablok regression analysis estimates the 95% confidence region over the entire range of measured variables without any \textit{a priori} assumptions about the overall data features. Our \( G_A - GF \) and \( G_A - GV \) data passed all these different statistical tests; therefore, one might conclude the validity of the forearm BGT technique, at least in the statistical sense. Since the statistical methods applied in this study were successful, more detailed discussion on experimental data properties are provided below.

Cunningham et al. [14] who first introduced the vacuum-assisted forearm blood sampling technique reported a value of 0.96 as the overall correlation coefficient between \( GF \) and \( G_A \). Lock et al. [16] compared \( GF \) and \( G_A \) in 50 non-fasting subjects and found no statistical significance. These reports strongly support the results of our analysis. However, Jungheim and Koschinsky [29] criticized glucose monitoring at the arm as being risky under rapidly changing conditions of glucose concentration since changes in \( G_A \) appeared with a delay of about 35 min, particularly in hypoglycemia detection [30]. However, they mentioned that \( G_A \) showed similar values to \( GF \) in the fasting state. Therefore, the time delay between \( G_A \) and \( GF \) did not play a role in our fasting subjects; thus, we concluded that \( G_A \) is a valid technique to monitor blood glucose, at least in the fasting state or “for routine self-monitoring before meals” as suggested by a previous study [31].

The ~35-min time delay between \( G_A \) and \( GF \) under rapidly changing glucose concentrations observed by Jungheim and Koschinsky [29] may have been caused by the higher capillary circulation on the fingertip, which is 5–20 times
higher than that at the forearm \([32-34]\), thereby leading to a slower glucose dynamics. On the other hand, McGarraugh \([35]\) compared \(G_A\) and \(G_F\) with and without rubbing the forearm, and found that when the forearm was rubbed, the comparison yielded a nearly ideal correlation between \(G_A\) and \(G_F\) in the rapidly changing hyperglycemia region. They noted a few shortcomings in the experimental protocol of Jungheim and Koschinsky \([29]\), e.g., they did not rub the test site; moreover, their protocol, which involved a glucose tolerance test followed by intravenous insulin administration, created physiological extremes. We particularly recommend caution in the detection of hypoglycemia, which is a frequent event in the diabetic patient’s routine self-testing regimen. We rubbed the forearm for 5 sec before blood sampling, similar to McGarraugh’s experimental protocol \([35]\); thus, the time delay factor should have been minimized. Further, it should be noted that our comparison between \(G_A\) and \(G_F\) was only intended to measure glucose in the steady state, such as under fasting conditions, and hence, our results can be considered valid from this viewpoint.

After carefully reviewing our measurement data in both the normal and the patient groups, we found that \(G_A\) was consistently higher than \(G_F\) by a small margin (Fig. 1), which is perhaps related to the slower dynamics at the forearm. Although the subjects were considered as being under steady state fasting conditions, the glucose levels might have been very slowly decreasing since the last meal; in such a scenario, slightly higher \(G_A\) could be observed. In addition, rubbing the forearm to enhance local circulation may also have been performed for different durations and with different intensities, thereby leading to possible differences in measurement. Nevertheless, the excellent correlation, particularly in the patient group, between \(G_A\) and \(G_F\) obtained at least 30 min after \(G_A-G_F\) measurements may exclude this possibility. Although the discrepancy in the experimental procedure as well as the physiological condition of the subject might have caused this difference, we believe that small differences in the high glucose range would not prevent the present sampling technique from being applied in a clinical setting, since a small degree of variability in hyperglycemia assessment would not lead to irrevocable decisions on the state of diabetes.

To further pursue the clinical applicability with a more reasonable approach, an evaluation tool called error grid analysis, different from statistical analysis, was introduced \([24]\). Correlation coefficients describe the linear relationship between 2 sets of data, as in this study. However, the correlation coefficients that evaluate the entire range of blood glucose values may misinterpret the true relationship between subsets of data, as explained in the report by Pohl et al. \([36]\). Error grid analysis is an efficient method that describes the accuracy over the entire range of blood glucose values and evaluates the clinical significance of the accuracy of a particular system. This analysis has been successfully applied in some studies \([37, 38]\). In this analysis, the test-reference (or \(G_A-G_F\) in our case) plane is divided into A, B, C, D, and E zones, all data points are plotted, and the data points in the A and B zones are considered as “clinically accepted”. These 5 zones were generated by the University of Virginia Medical School (Charlottesville, USA) on the basis of the clinical implications of blood glucose values obtained from patients \([24]\). Zone A represents “glucose values that devi-

![Fig. 4. Individual blood glucose data points obtained from the forearm (GA) and finger (GF) plotted in the GA-GF plane superimposed on the error grid. In addition, the figure shows clinically accepted zones (denoted by AU, and BU, respectively) in which 98% of the data are included (refer to text).](image-url)
ate from the reference by no more than 20% or are in the hypoglycemic range (<70 mg/dL) when the reference is also <70 mg/dL” (refer to [24] and our Fig. 4). These criteria are basically the same as the ones put forth by other international organizations [22, 23], and glucose values within this region are clinically accurate, thereby leading to clinically correct treatment decisions. Zone B represents “values that deviate from the reference by >20% but would lead to benign or no treatment” based on the clinical implications. Values in zones C, D, and E are “potentially dangerous and therefore are clinically significant errors”, while values in zones A and B are clinically acceptable. We plotted all individual data in the G\textsubscript{A}–Gr plane superimposed with the error grid as seen in Fig. 4. Fewer but higher-range glucose (>200 mg/dL) data points fell in the A (upper & lower) zone. Overall, 98% of the data points were included in the clinically acceptable (A & B) zones. Therefore, the error grid analysis of G\textsubscript{A}–Gr shown in Fig. 4 successfully visualizes the clinical validity of our experimental results.

The present study compared blood glucose measurements using samples taken from the forearm, samples obtained using standard finger skin puncture, and venous serum. Capillary blood sampling technique used on the forearm can minimize pain and enables glucose measurements as accurate as those obtained by the standard blood sampling techniques used for the finger or the vein and performed under fasting conditions. Therefore, capillary blood sampling technique from an alternative site, such as the forearm, could be introduced in clinical practice, particularly in self-BGT before meals, for the successful management of diabetes.

REFERENCES


