How and when to use an alternative site in self-monitoring of blood glucose

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SUMMARY
Taking care of diabetic patients has considerably been improved for approximately fifty years both in the therapeutic field and in the glycaemia monitoring field. Prospective studies conducted on large cohorts have clearly shown the importance of taking optimal care of such patients in order to prevent the occurrence or aggravation of chronic diabetes-associated complications. However, despite the simplification of self-monitoring of blood glucose through technological developments, drawbacks, some of which are linked to the sampling site, the fingertip, still slow down the patients’ compliance. The use of an alternative site seems to be one of the solutions to offer in order to improve their monitoring and hence, their metabolic control. The development of such a monitoring mode has been slowed down after revealing, in some studies, a probably physiological delay in the detection of glycaemia variations, at the level of the alternative sites. Despite such conflicting observations, interest of using such alternative sites is to be defined in self-monitoring. Beside fast glycaemia variations, it proved to be reliable.

Key-words: Diabetes · Self-monitoring of blood glucose · Alternate site testing.

RéSUMÉ
La prise en charge des patients diabétiques s’est considérablement améliorée depuis une cinquantaine d’années tant sur le plan thérapeutique que sur le plan surveillance glycémique. Les études prospectives menées sur de larges cohortes ont clairement montrer l’importance d’une prise en charge optimale de ces patients afin d’éviter l’apparition ou l’aggravation des complications chroniques liées au diabète. Cependant, malgré la simplification de l’autosurveillance glycémique grâce aux évolutions technologiques, des inconvénients dont certains sont liés au site de prélèvement : le bout du doigt, freinent encore la compliance des patients. L’autosurveillance glycémique sur site alternatif apparaît comme une des solutions à apporter à certains patients pour améliorer leur surveillance et par là leur équilibre métabolique. L’essor de ce mode de surveillance a été freiné après la mise en évidence dans certaines études d’un retard de détection des variations glycémiques, probablement physiologique, au niveau des sites alternatifs. Malgré ces constatations discordantes, il convient de définir la place du prélèvement sur site alternatif dans l’autosurveillance. En dehors des variations rapides de la glycémie il a fait preuve de sa fiabilité.

Mots-clés : Diabète · Autosurveillance glycémique · Mesure sur site alternatif.

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Self-monitoring of blood glucose (SMBG) has recently become more widely used by virtue of the progress of technologies that started 50 years ago. Indeed, since 1956, the year when the Glucotest stripe was developed by Boehringer laboratory, the patient suffering from diabetes can monitor his/her capillary glycaemia several times a day and thereby better adapt his/her anti-diabetes therapy. The sampling and measuring difficulties, the measuring duration and the inaccuracy in the extreme values of the obtained results were able to be considerably improved by virtue of the joint developments of better measuring techniques, less painful blood drop obtaining methods and easier to handle and more reliable glycaemia reading devices.

The technological speeding-up took place in the 80s; a few tens of glycaemia meters are developed, their size, their weight and primarily their measuring time are considerably reduced. Thus, the evolution in taking care of diabetic patients is major and assisting the metabolic monitoring by a glycaemia measurement many times a day remains at the very centre of medical and scientific concerns. The DCCT [1] results during the last decade clearly showed the importance of a repeated SMBG in preventing the diabetes complications and SMBG is presently the subject of recommendations from medical societies, ALFEDIAM [2] and ADA [3, 4]. Unfortunately, compliance of diabetic patients too often remains unsatisfactory.

In fact, despite all those advances, there still remain several obstacles limiting the frequency of the daily measurements. Voluntarily, we will omit the obstacles linked to the psychological actual experience of the patient towards his disease and we will only focus on the physical obstacles.

The drawbacks of the self-monitoring of blood glucose

The first clearly established and well documented obstacle [5, 6] is the pain being induced by the cutaneous lancing at the fingertip required for the capillary sampling. This fact is due on the one hand to the innervation at the fingertip, being rich in sensitive fibres [7], and on the other hand to the extent of the cutaneous lancing required for obtaining a blood drop sufficient for dosing glycaemia, and finally to the repeated samplings.

The repeated samplings at the fingertip, except for the induced pain, could also be at the origin of a poor fine sensitivity of sore ends. More or less unpleasant side-effects depending on the patient’s activities and we can more precisely think of musicians, manual jobs, blind people using the Braille alphabet... The sampling at the fingertip is also not very practical for garage mechanics, bricklayers, and various people working in building and civil engineering.

Finally, despite the improvement of the technology and the constantly improved handiness of the glycaemia readers, some people encounter considerable difficulties to perform themselves and for various reasons, their SMBG. Partially sighted people and blind people, all people with skill problems (whether they are old, they suffer from a neuropathy of the pectoral limbs or a handicap of one pectoral limb...) cannot autonomously perform the SMBG.

This is the reason why, because of some difficulties remaining when performing the SMBG at the fingertip (despite strong efforts made on size and length of the lancets, the miniaturization of the blood volume required for the measurements...), other sampling sites were studied and various types of meters developed.

The various candidate sampling sites were first to meet two criteria: to be less painful than the fingertip and to be easily available allowing for a full autonomy of the SMBG. Although less painful, the earlobe [8, 9] was given up because it required a third party for sampling. Thus, since a few years, glycaemia readers have developed on alternative sites.

The alternative site testing

Using alternative sites (AS) for measuring glycaemia was developed with a view to alleviating the pain during the capillary sampling in order to improve the SMBG compliance. The results of the various studies comparing the secondary pain to the cutaneous lancing on AS to that at the fingertip, all show a large alleviation of the pain on AS for approximately 80% of the patients [5, 10, 12].

However, the “less pain, better compliance” relationship is controversial. Bennion et al. [12] in their study conducted on 121 patients with relatively well balanced type 1 and type 2 diabetes (average HbA1c: 7.4%) do not find any increase of the frequency of the daily self-monitoring tests despite a preference amongst 76% patients for the monitoring on alternative site compared to the fingertip. However, the patients in this study were relatively compliant at the start, as they performed on average 2.4 tests every day.

Improving the comfort and the compliance for the SMBG lies centrally amongst the medical interests. Comfort seems to be for a great part improved through the use of AS’s and even if improving the compliance is still questionable, the AS seems to be a precious help for some of the diabetic patients.

Capillary sampling at the fingertip was the only method used for a long time because:
— the blood drop required for measuring glycaemia is easy to obtain,
— measurement results of capillary glycaemia at the fingertip are comparable to those on venous blood,
— glycaemia meters with capillary sampling at the fingertip improved for their reliability.
Nowadays, by virtue of the technological progress, the blood amount required is minor (One Touch Ultra 1 ml, Papillon 0.3 ml) and sampling on a less vascularized site does not seem to be an obstacle any more.

The alternative sites are as follows:
- the arm
- the forearm
- the abdomen
- the thigh
- the calf.

Such locations for capillary samplings have the following anatomic advantages:
- to be less innervated [7] than the fingertip and therefore, the cutaneous lancing seems likely to be less painful,
- to have a sufficient subcutaneous tissue thickness for sampling, and
- to not require the help from a third party for sampling.

The thenar is also used, however it is different from the other alternative sites, because the innervation and the blood network in such a region are almost similar to those at the fingertip [13].

The drawbacks of the alternative sites (excluding the thenar) are mainly represented by the smaller vascularization of the subcutaneous tissue compared to the fingertip, which is likely to modify the sampling and its results.

Thus, is capillary glycaemia obtained on an alternative site the almost exact reflection of vein glycaemia?

A. Upon a study conducted in the unit [14], we evaluated the accuracy and comfort of the Sof-Tact™ Medisense® glycaemia reader from Abbott, using alternative sites of sampling. Sixty-nine patients (37 women and 32 men), aged from 21 to 71 (mean 41.6 ± 19.0 years old), equally affected by type 1 or 2 diabetes were included in the study and divided into two groups so as to determine the accuracy of the device (forearm, internal port Sof-Tact™ versus reference method as carried out in laboratory, Hitachi 917 automate, capillary samples through finger pricking) and the reliability thereof (forearm, internal port Sof-Tact™ versus finger, external port Sof-Tact™) by means of the Shuirmann test (IC 95%).

The patients gave their general impression about the device (very good - good - mean - poor) and evaluated the experienced pain upon brachial samplings compared to their usual sampling system. The experienced pain with both systems was compared using the Kruskal-Wallis test.

Thus, the results obtained with 31 patients from group 1 and 27 patients from group 2 (after excluding the 9 failures upon the use of the device on the forearm (13% patients) and 2 failures associated with an unsatisfactory blood amount being sampled for a laboratory analysis (1 failure) or through external port Sof-Tact™ (1 failure) show that:

\[ y = 0.8929x \]
\[ R^2 = 0.9025 \]
\[ \rho_{x,y} = 0.9536 \]

**Figure 1**
Relationship between the glycaemia values obtained with Sof-Tact™ on the forearm and the reference method.
— the glycaemia values as obtained with Sof-Tact™ through sampling on the forearm (181.5 ± 75.8) do not differ significantly from those given by the reference test (200.6 ± 87.4) (Fig 1),
— such an equivalence involves 3 patients with blood glucose values lower than 70 mg/dl, as shown in Figure 1,
— the glycaemia values as obtained with Sof-Tact™ through sampling on the forearm (181.4 ± 80.7) are statistically equivalent to those obtained by Sof-Tact™ through fingertip pricking (185.1 ± 84.9). Such measurements remain comparable with a 10% more stringent equivalence gap (Fig 2),
— such an equivalence involves two patients with low blood glucose values, lower than 70 mg/dl, as shown in Figure 2, and
— the pain experienced with Sof-Tact™ through brachial sampling is significantly lower than that experienced upon the usual capillary samplings through finger pricking (Fig 3).

The glycaemia results obtained on AS using the Sof-Tact™ automated device are comparable in our study to those obtained through fingertip pricking even in the low values. Being used on the forearm, such a meter makes it possible to significantly alleviate the pain experienced during capillary samplings. Comparable results were found by Lock et al. in a study conducted on 50 non fasting type 1 and 2 diabetic patients [15].

B. Are the fast glycaemic variations well appreciated on AS? Indeed, Jungheim and Kochinsky slow down the enthusiasm offered by the AS. In a study on 17 type 1 diabetic patients [16, 17] they show an approximate 30 minutes delay in displaying the glycaemia variations on AS both at the occasion of an hypoglycaemia (insulin hypoglycaemia) or an hyperglycaemia (after absorption of 75 g of carbohydrates). The same delays were observed whatever the meter being used (SOF Tact, Free Style or One Touch Ultra) and raise the hypothesis of a physiological delay in the glycaemia variations that could be explained by an anatomically different vascular network from that at the fingertip, more particularly a poorer vascularization and less capillarovenous anastomoses. Such differences between the compartments (interstitial fluid and blood) have been, since the use of continuous glucose monitoring, with a sampling on AS very concerning from a medical point of view. For the Kulcu et al. [18] who evaluated the relationship between glycaemia and the glucose concentration of the interstitial fluid by means of the GlucoWatch sensor (Cygnus, Redwood City, CA) in type 1 diabetic patients, such differences between the interstitial fluid and blood would be the physiological reflection of variations in glucose capture, use and removal between both compartments. This phenomenon seems nowadays to be recognised and individualised in the literature under the expression “The alternative site testing phenomenon”. However, if
those results question the reliability of the results as obtained on AS and the routine implementation of SMBG on AS, the results of the various clinical studies conducted on the subject are questionable and conflicting.

Indeed, in the small study by Jungheim and Koschinsky [18], the glycaemia variations between AS and fingertip were analysed using several glycaemia meters but not with reference glycaemia measurement methods of Hemo Cue type. This was done in an other study [16] on 50 type 1 and 2 diabetic patients. The results on such non fasting patients do not show any intra-individual difference between glycaemia measurements achieved with the Hemo-Cue whether the blood is sampled at the fingertip or on alternative sites. Consequently, before coming to a conclusion regarding the existence of physiological variations between the interstitial fluid and total and capillary blood, it is important to compare the various sampling sites with reference measurement methods in conditions of high physiological variations of glycaemia, and then to check the reliability of the readers being available on the market.

Finally, in any event, in the clinical practice, there seems to be some delays of detection for glycaemia variations with the currently marketed readers. Ellison et al. [20] confirm the delays of detection for glycaemia variations on AS with 42 type 1 and 2 diabetic patients during the 2 postprandial hours of a control meal involving 110 to 140 g of carbohydrates. In another study [20], the difference only occurs 60 minutes after the meal and the glycaemias at 90 and 120 minutes are identical whatever the sampling site with 87 type 2 diabetic patients.

Insulin induced hypoglycaemia in normal subjects led to conflicting results. Van Der Valk et al. [21] show 10 to 18% lower abdominal blood glucose value after the glycaemia nadir compared to those obtained at the fingertip. On the contrary, Nonaka et al. [22] do not find any significant difference between the various sites.

At the light of those various studies, it seems likely that the glycaemia variations should be detected with some delay at the AS level compared to the fingertip. However, “the alternative site testing phenomenon” did not question the development of the various continuous measurement types of glycaemia.

The alternative site testing in clinical practice

The risks of a delay in displaying glycaemia variations are mainly those associated to the possible delay in detecting hypoglycaemia. The glycaemia variations observed between AS and fingertip in a postprandial state have poorer immediate consequences, even if the postprandial glycaemia monitoring is more or less admitted as a criterion for improving the HbA1c. So, care should be currently taken regarding the use of AS’s in the SMBG, even if there does not exist any recommendation from the scientific societies on the subject.

Recommendations could however be suggested for training and using the alternative site testing in clinical practice
— Recommending a meter allowing for the measurement on AS should be preceded by some training clearly informing the patients about the risks from the lack of knowledge of hypoglycaemia.
— The meter should allow for the common use of AS and fingertip sampling.
— Using AS’s should be restricted to:
   — glycæmia at the fasting state,
   — glycæmia at least at one hour from a meal, and
   — glycæmia at least at one hour from the injection of an insulin fast analogue.
— Using AS’s should be forbidden:
   — for checking a hypoglycaemia symptomatology, and
   — with patients having hypoglycaemia perception disorders.

Which meter should be recommended and according to which criteria?

Schematically, there are nowadays 3 types of marketed glycæmia meters with a measurement ability on AS:
— Sof Tact from MediSense Abbott: combines self prick-
ing, vacuum drawing with immediate and automatic deposi-
tion of blood on the electrode and electrochemistry meter of the anperometry type,
— Free Style Papillon from MediSense Abbott: electro-
chemistry meter of the coulometric type only requiring a tiny blood drop: 0.3 μl,
— the meters One touch Ultra from LifeScan and Accu
Check Active and Go from Roche Diagnostic, allowing, due
to the little blood volume being required (1 to 2 μl), the measure-
ment on AS.

Recommending a meter allowing for the measurement of glycæmia on AS means:
— giving the opportunity to the patient to improve the SMBG comfort,
— customizing the patients’ care and better adapting it to their way of living,
— trying for some of them to improve the compliance in the SMBG, and
— improving the autonomy for some of them more partic-
ularly through the use of an all-in-one meter.

Conclusion

The technological advances during the last 20 years considerably modified the diabetic patients care and the place of the SMBG in the metabolic monitoring. Recently, the venous and interstitial glycæmia continuous measurement and the use of alternative sites were developed. The reliability of such various measurements types is still under evaluation. However, it should be also reminded that the glycæmia readers in the 90’s did not meet the criteria defined nowadays by learned societies and the authorities although their daily use was not dis-
appointing [23, 24]. Today, at the light of publications and clinical experience, a careful behaviour should be adopted in the absence of recommendations from learned societies and wider studies. Using AS’s should be part of an overall and customized training approach for the dia-
abetic patient.

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