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Review

Non-invasive glucose monitoring: Assessment of technologies and devices according to quantitative criteria

Andrea Tura [a,*], Alberto Maran [b], Giovanni Pacini [a]

[a] *Metabolic Unit, ISIB-CNR, Padua, Italy*
[b] *Department of Clinical and Experimental Medicine, University of Padua, Italy*

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Abstract

Aim of this review was to describe the main technologies for non-invasive glucose monitoring and the corresponding most relevant devices. The review tries to overcome the limitations of previous reviews on this topic, such as the lack of objective criteria for inclusion or exclusion of technologies or devices, and the poor organization of the information, which often does not allow easy comparison between technologies and devices. In this review, the information is concise and organized into specific categories, and hence it becomes easy to compare advantages and disadvantages of the different technologies and devices. For technologies, the categories of information considered are the technology name, the underlying physical principle, the technology limitations and the measurement sites on the human body. For devices, the categories of information are the device name, its approval condition (FDA Approval and/or CE Mark), the technology on which it is based, a device general description, the tests performed on the device, the corresponding results, safety information, aspects affecting usability, current status of the device and the manufacturer, an Internet reference for the device. A total of 14 technologies and 16 devices are included. Conclusions of the review were that, despite some interesting and promising technologies and devices, a satisfactory solution to the non-invasive glucose monitoring problem still requires further efforts.

Keywords: Non-invasive glucose meters; Needle-free; Blood-free; Painless glycaemia testing; Health technology assessment

Contents

* Corresponding author at: ISIB-CNR, Corso Stati Uniti 4, 35127 Padua, Italy. Tel.: +39 049 829 5786; fax: +39 049 829 5763.
E-mail address: tura@isib.cnr.it (A. Tura).

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1. Introduction

Pathologies like Type 2 diabetes and, especially, Type 1 diabetes require frequent self-monitoring of glycemia. In the last two decades, several studies were carried out to establish a non-invasive technique for evaluation of glycemia, i.e. a technique not requiring blood collection. However, it can be claimed that non-invasive glucose monitoring is still in its early phase of development. The aim of this review was to describe all the main technologies for non-invasive glucose monitoring and the most relevant devices derived from those technologies.

Some other reviews by consulting companies already dealt with this topic, such as refs. [1–4], but they have several limitations: (i) they miss important elements, especially in terms of technologies; (ii) they do not justify their inclusion and exclusion criteria; (iii) they are not freely available. There are also some reviews freely available,[1] but still with critical limitations. For instance, the reviews [5,6] are focused on technologies even in deep details, but not on devices derived from them. Furthermore, some technologies have not been presented. This may be due to the definition of ''non-invasive'' accepted by the authors, but it was not stated explicitly. Finally, these reviews do not make any effort to present the reviewed technologies in a comparable format, so that the reader can easily understand advantages and disadvantages. Regarding the reviews freely available on the Internet, it is worth mentioning one on the non-invasive devices (more precisely, on companies working in the field) [7]. The site provides interesting and updated information, but just little information is usually provided for each element and, again, with no attempt to make the information comparable.

The methodology adopted in this review is that of the Health Technology Assessment, HTA (see EUCOMED Position Paper [8]). According to HTA methodology, it is important to reduce the collected information to a clearly defined format for a straightforward and objective comparison: in this review, all the information is in fact reduced into precise information categories. However, also our review has some limitations and hypotheses: (i) only sources of information in English language were considered; (ii) at least one Internet reference had to be found for each device; (iii) we included only devices fully developed and ready for the market or, at least, in ''advanced'' status (as defined below); (iv) devices providing qualitative or semi-quantitative glucose measurements (e.g. in urine or saliva), as well as those only detecting hypoglycaemia,

[1] We consider ''free'' the information accessible over the Internet requiring not more than a free registration, and the information published in sources, such as journals or books that, although protected by copyright, can be accessed for consultation through a proper organism (such as a library).

were not considered. A project is considered in advanced status when it has led to a stand alone device (except, possibly, uncritical aspects, such as power supply): i.e., not laboratory equipment, but a device potentially ready to be used in a domestic environment. It was considered a proof of that the existence over the Internet of a photograph of the device. It must be acknowledge that this choice has some drawbacks: some devices were included though little information was available, while others were excluded as no photo was found, despite the presence of rich information. However, though it can be criticised this is an objective criterion for inclusion. Several other criteria for inclusion were considered, but any of them had even worse drawbacks. For instance, if we had considered only the devices with an official approval (FDA and/or CE Mark), it would have limited the review to a few devices, excluding some very promising ones.

As regards, the definition of ''non-invasive'', it must be noted that some authors consider ''non-invasive'' only the optical (or opto-acoustic) technologies (and derived devices), whereas technologies involving generation of electric currents in a body part, or causing creation of even microscopic holes in the skin, are considered ''minimally invasive''. Conversely, other authors consider as ''non-invasive'' everything that does not require blood collection. The definition of ''non-invasive'' considered in this review is in the middle: we considered ''non-invasive'' what is not leading to blood extraction and is not causing skin penetration through a solid object. Thus, we did not consider ''non-invasive'' the use of a needle implanted even superficially in the subcutaneous tissue. However, we accepted as ''non-invasive'' those technologies creating microscopic holes on the skin with weak laser lights or ultrasounds. We also accepted the use of weak electric currents.

2. Technologies for non-invasive glucose monitoring

The order of presentation is partially arbitrary: we tried to report first those technologies more known, used and described. Technologies with similarities were reported one next to the other.

2.1. Near infrared spectroscopy (NIR)

2.1.1. Principle

Near infrared (NIR) spectroscopy is based on focusing on the body a beam of light in the 750–2500 nm spectrum [9]. NIR spectroscopy allows glucose measurement in tissues in the range of 1–100 mm of depths, with a decrease in penetration depth for increasing wavelength values. The light focused on the body is partially absorbed and scattered, due to its interaction with the chemical components within the tissue. Attenuation of light in tissue is described, according to light transport theory, by the equation $I = I_0\, e^{-\mu_{eff} d}$, where I is the reflected light intensity, I_0 the incident light intensity, μ_{eff} the effective attenuation coefficient and d is the optical path length in tissue [5]. On the other hand, μ_{eff} can be expressed as a function $\mu_{eff} = f(\mu_a, \mu_s)$, where μ_a is the absorption coefficient and μ_s is the scattering coefficient. Changes in glucose concentration can influence μ_a of a tissue through changes of absorption corresponding to water displacement or changes in its intrinsic absorption. Changes in glucose concentration also affect the intensity of light scattered by the tissue, i.e. μ_s. This coefficient is a function of the density of scattering centers in the tissue observation volume, the mean diameter of scattering centers, their refractive index and the refractive index of the surrounding fluid. For the case of cutaneous tissue, connective tissue fibers are the scattering centers. Erythrocytes are the scattering centers for blood. In summary, glucose concentration could be estimated by variations of light intensity both transmitted through a glucose containing tissue and reflected by the tissue itself. Transmission or reflectance (localized or diffuse) of the light can be measured by proper detectors.

2.1.2. Limitations

The absorption coefficient of glucose in the NIR band is low and is much smaller than that of water by virtue of the large disparity in their respective concentrations. Thus, in the NIR the weak glucose spectral bands only overlap with the stronger bands of water, but also of hemoglobin, proteins and fats. As regards the scattering coefficient, the effect of a solute (like glucose) on the refractive index of a medium is non-specific, and hence it is common to other soluble analytes. Furthermore, physical and chemical parameters, such as variation in blood pressure, body temperature, skin hydration, triglyceride and albumin concentrations may interfere with glucose measurement [10]. Errors can also occur due to environmental variations, such as changes in temperature, humidity, carbon dioxide and atmospheric pressure. Changes in glucose by themselves can introduce other confounding factors: for instance, it has been proved that hyperglycemia, as well as hyperinsulinemia (often connected to the former in obese patients) can induce vasodilatation, which results in increased perfusion [11,12]. This

phenomenon increases light absorption, and hence it can lead to errors in the estimation of the blood glucose concentration if not taken into account. It has also been reported that hyperglycemia can have effects on skin structural properties. Diabetic subjects in fact can exhibit ''thick skin'' and ''yellow skin'', probably due to accelerated collagen aging and elastic fiber fraying [13,14]. Thus, light reflected from the skin of diabetic subjects may have different intensity than in healthy subjects at equal level of glycemia. Also thermal properties of the skin were found to be different in subjects with hyperglycemia, thus affecting the localized reflectance of light [15]. Hyperglycemia can also cause differences in the refractive index of red blood cells, thus leading to different light scattering [16,17]. Another confounding factor is due to the fact that NIR measurements often reflect glucose concentration in different body compartments, that is, not only blood but also the interstitial fluid in different body tissues can contribute to the measured signal.

2.1.3. Measurement sites

NIR light transmission or reflectance has been studied through an ear lobe, finger web and finger cuticle, skin of the forearm, lip mucosa, oral mucosa, tongue, nasal septum, cheek, arm. NIR diffuse reflectance measurements performed on the finger showed a correlation with blood glucose but predictions were often not sufficiently accurate to be clinically acceptable [10]. Diffuse reflectance studies of the inner lip also showed good correlation with blood glucose and indicated a time lag of some minutes between blood glucose and the measurement signal [18]. Salivary glucose levels (a component of lip measurements) did not reflect blood glucose levels. These locations were selected for some advantages, such as high vascularization, little fatty tissue, homogeneous composition, limited temperature variations. It must be noted that, depending on the considered site, some specific intervals in the NIR band have been considered and the choice of one specific site also influenced the type of studied light, i.e. transmitted, or reflected (localized or diffuse), or both.

2.1.4. Notes

Definitions of NIR band are not always in agreement: some authors define NIR in the 750–2500 nm band [9], others in 1000–2500 nm band, whereas they define the 700–1000 nm band as the infrared band [10]. However, wavelengths under 1000 nm are rarely used for glucose measurements: some studies have been performed, but with no good results [19].

2.2. Mid-infrared spectroscopy (Mid-IR)

2.2.1. Principle

Mid-infrared (Mid-IR) spectroscopy is based on light in the 2500–10,000 nm spectrum [5]. The physical principle is similar to that of NIR. When compared to NIR, however, due to the higher wavelengths, Mid-IR exhibits decreased scattering phenomena, and increased absorption. For this reason, the tissue penetration of light can reach a few micrometers [20]: in the case of human skin, that corresponds to the stratum corneum. As a consequence, only reflected, scattered light can be considered: there is no light transmitted through a body segment. On the other hand, a possible advantage of Mid-IR compared to NIR is that the Mid-IR bands produced by glucose, as well as other compounds, are sharper than those of NIR, which are often broad and weak.

2.2.2. Limitations

One strong limitation is the poor penetration. Furthermore, Mid-IR is affected by similar problems and confounding factors than NIR, despite glucose bands potentially improved. For instance, some studies have shown significant dependence of skin Mid-IR spectrum on its water content [20].

2.2.3. Measurement sites

Mid-IR is less studied technique compared to NIR for glucose measurement, probably due to the strong limitation in penetration. Studies are reported related to finger skin and oral mucosa [21].

2.2.4. Notes

Some authors provide a broader definition of the Mid-IR band than that reported above, considering it in the 2500–25,000 nm range [10].

2.3. Optical coherence tomography

2.3.1. Principle

The optical coherence tomography (OCT) is based on the use of a low coherence light, such as a superluminescent light, an interferometer with a reference arm and a sample arm, a moving mirror in the reference arm and a photodetector to measure the interferometric signal [22]. Light backscattered from tissues is combined with light returned from the reference arm of the interferometer, and the resulting interferometric signal is detected by the photodetector. What is measured is the delay correlation between the backscattered light in the sample arm and the reflected light in the reference arm [5]. A block diagram of the

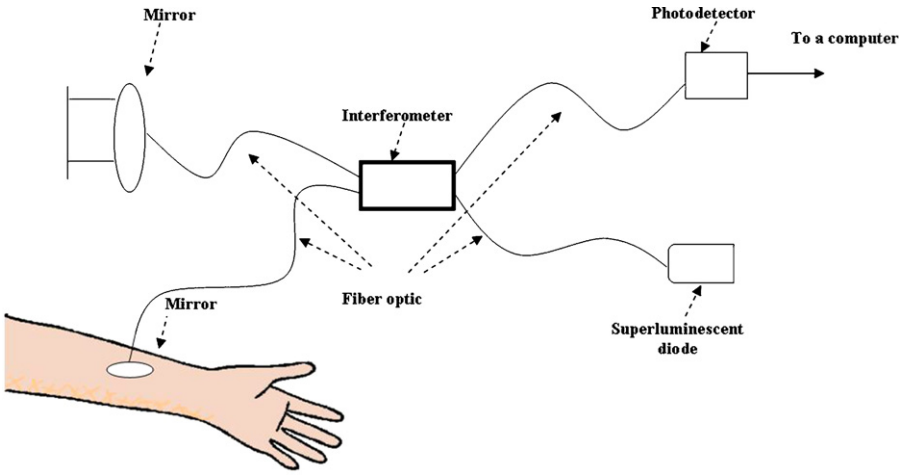

Fig. 1. Sketch of the optical coherence tomography system.

experimental system is reported in Fig. 1. Moving the mirror in the reference arm of the interferometer allows scanning the tissues up to a depth of about 1 mm. By moving the mirror into the sample arm scanning of the tissue surface is obtained. Therefore, this technique has unique capability of in-depth and lateral scanning to obtain two-dimensional images with high resolution. Tissue scattering properties are highly dependent on the ratio of the refractive index of scattering centers (cellular components, proteins, etc.) to the refractive index of the interstitial fluid. An increase of glucose concentration in the interstitial fluid causes an increase in its refractive index, thus determining a decrease in refractive index mismatch, and hence of the scattering coefficient. Therefore, from the OCT data, generated by the backscattered light, it is possible to get an estimation of glucose concentration in the interstitial fluid. It must be noted that OCT technique is similar to the light scatter technique described before, because both techniques exploit the scattering of light. However, in the light scatter technique (localized reflectance) the intensity of collected light is studied, while in OCT the delay of backscattered light compared to the light reflected by the reference arm mirror is considered. However, some studies demonstrated that the effect of glucose on the scattering coefficient values measured by OCT is similar to that measured by light scatter technique [23].

2.3.2. Limitations

OCT technique can be sensitive to motion artefacts. Moreover, although little changes in skin temperature have negligible effects, changes of several degrees have a significant influence on the signal [24]. Finally, as already mentioned there is currently no clear indication that this technique has advantages compared to other scattering based techniques [23].

2.3.3. Measurement sites

The body site for measurement is the skin, typically in the forearm. More specifically, glucose concentration in the interstitial fluid of the upper dermis of the skin is investigated.

2.4. Temperature-modulated localized reflectance

2.4.1. Principle

This is again in the field of light scatter-based technique. It is based on the observation that temperature changes causes variations in the tissues refractive index (which influences the light scattering), but on the other hand the entity of these changes depend upon glucose concentration [5]. More specifically, the temperature modulation of the localized reflected light due to scattering is analyzed. Glucose concentration is estimated with localized reflectance signals at 590 and 935 nm. In some studies, a probe was placed in contact with the skin and the probe temperature was varied between 22 and 38 °C. After each variation, skin was equilibrated for some minutes. During each of those intervals some light packets were collected, related to glucose concentration [24].

2.4.2. Limitations

Several parameters can affect this kind of measurements, both physiological and technical (such as the probe position). Also a peculiar health status, such as an inflammatory state with possible fever condition, can in fact affect the measurement.

2.4.3. Measurement sites

Measurements are usually performed on the skin of the forearm. In particular, glucose in the dermis layer is estimated.

2.5. Raman spectroscopy

2.5.1. Principle

The Raman spectroscopy is based on the use of a laser light to induce oscillation and rotation in molecules of one solution [5,10]. The consequent emission of scattered light is influenced by this molecules vibration, which depends on the concentration of the solutes in the solution. Therefore, it is possible to derive an estimation of glucose concentration in human fluids where glucose is present. The Raman spectrum usually considered is in the interval 200–1800 cm^{-1} [25,26]. In this band, Raman spectrum of glucose is quite clearly differentiable from that of other compounds. In fact, Raman spectroscopy usually provides sharper and less overlapped spectra compared, for instance, to NIR. Other advantages are the modest interference from luminescence and fluorescence phenomena [27]. Fixed wavelength lasers at relatively low cost can be used [28]. Recently, an improvement in traditional Raman spectroscopy has been proposed (surface-enhanced Raman spectroscopy), which may increase the sensitivity of the acquisition and/or decreasing the acquisition time [29].

2.5.2. Limitations

Main limitations are related to instability of the laser wavelength and intensity, and long spectral acquisition times. Moreover, similarly to other techniques described before, the problem of the interference related to other compounds remains.

2.5.3. Measurement sites

The eye is the most common site. The laser light is passed tangentially through the front of the eye. Another possible site is human skin, although more confounding compounds, such as lipids, are present [30].

2.6. Polarization changes

2.6.1. Principle

It is based on the phenomenon that occurs when polarized light transverses a solution containing optically active solutes (such as chiral molecules): the light, in fact, rotates its polarization plane by a certain angle, which is related to the concentration of the optically active solutes [5]. Glucose is a chiral molecule, and its light rotation properties have been known for a long time. Indeed, investigation of the polarization changes induced by glucose is reported to be the first proposed non-invasive technique for glucose measurement in humans [31]. One advantage of this technique is that it can make use of visible light, easily available. Moreover, the optical components can be easily miniaturized [32].

2.6.2. Limitations

This technique is sensitive to the scattering properties of the investigated tissue, since scattering depolarizes the light. As a consequence, skin cannot be investigated by polarimetry, since it shows high scattering due in particular to the stratum corneum [10]. Moreover, the specificity of this technique is poor, since several optically active compounds are present in human fluids containing glucose, such as ascorbate and albumin. However, specificity can be partially improved by using multiple light wavelengths. Other general sources of errors are variations in temperature and pH of the solution. Some error sources specific of the investigated site are reported below.

2.6.3. Measurement sites

The preferential site for this technique is the eye, and, more specifically, the aqueous humor beneath the cornea [33]. Cornea has in fact low scattering properties, since it does not have the stratum corneum. However, some sources of errors are due to eye movements and corneal rotations [34]. The corneal birefringence, due to its collagen structure, is another error source. Moreover, a time delay between glucose concentration in aqueous humor and blood has been observed, and hence it has to be taken into account [35].

2.7. Ultrasound technology

2.7.1. Principle

The most used technology based on ultrasound is the photoacoustic spectroscopy, which is based on the use of a laser light for the excitation of a fluid and consequent acoustic response [10]. The fluid is excited by a short laser pulse (from pico to nanoseconds), with a wavelength that is absorbed by a particular molecular species in the fluid. Light absorption causes microscopic localized heating in the medium, which generates an ultrasound pressure wave that is detectable by a microphone. In clear media (that is, optically thin), the photoacoustic signal is a function of the laser light energy, the volume thermal expansion coefficient, the speed of sound in the fluid, the specific heat and the light absorption coefficient [5]. In these media, the

signal is relatively unaffected by scattering. The photoacoustic spectrum as a function of the laser light wavelength mimics the absorption spectrum in clear media. However, this technique can provide higher sensitivity than traditional spectroscopy in the determination of glucose. This is also due to the relatively poor photoacoustic response of water, which makes easier the determination of compounds, such as hydrocarbons and glucose [36]. The laser light wavelengths that can be used vary in a wide interval (from ultraviolet to NIR).

One variation in photoacoustic spectroscopy is based on combining it with ultrasounds emission and detection [5]. A possible approach is the use of an ultrasound transducer to locate a bolus of blood in a vessel and then illuminate it with the laser pulse at a glucose absorption wavelength. The ultrasound transducer also detects the generated photoacoustic signal. Another approach is detecting ultrasound signal reflected from a blood vessel before and after photoacoustic excitation. Glucose is then determined from the difference in reflected ultrasound intensity. A third approach is exciting a blood bolus via photoacoustic effect: the change in the dimensions and speed of the excited bolus causes a Doppler shift in an ultrasound directed towards the blood vessel; glucose is determined from the magnitude and the delay of the Doppler-shifted ultrasound peak. Finally, a different approach is using ultrasound, possibly coupled with other techniques, but without any photoacoustic effect [37].

2.7.2. Limitations

The technique is sensitive to chemical interferences from some biological compounds and to physical interferences from temperature and pressure changes. Moreover, when the laser light transverses a dense media, its contribution to the photoacoustic signal is due not only to the absorption coefficient but also to the scattering coefficient, thus possibly resulting in a confounding factor if not taken into account. Indeed, the photoacoustic spectrum of a dense media is similar to the diffuse reflectance spectrum rather than the absorption spectrum. On the other hand, the scattering can enhance the signal, and hence it can provide an advantage if properly considered. A technological disadvantage is that the instrumentation is still custom made, expensive and sensitive to environmental parameters.

2.7.3. Measurement sites

A possible body site for measurement is the eye, and, especially, the eye sclera. Other sites are fingers, and forearm, with contribution in glucose determination by blood vessels, by skin and tissues or both [38].

2.8. Fluorescence technology

2.8.1. Principle

This technique is based on the generation of fluorescence by human tissues when excited by lights at specific frequencies. In the case of glucose, one study demonstrated that when a glucose solution is excited by an ultraviolet laser light at 308 nm, fluorescence can be detected at 340, 380, 400 nm, with maximum at 380 nm [5]. It was also proved that fluorescence intensity was dependent upon glucose concentration in the solution. Also light in the visible spectrum can be used, but this is more adequate for studying fluorescence of tissues rather than that of solutions.

2.8.2. Limitations

In tissues, the use of ultraviolet light could lead to strong scattering phenomena, in addition to fluorescence. Moreover, even when using different wavelengths, the fluorescence phenomenon can depend not only on glucose, but on several parameters, such as skin pigmentation, redness, epidermal thickness [39].

2.8.3. Measurement sites

In humans, estimations of glucose concentration have been attempted on skin with patented blue light fluorescence technology.

2.9. Thermal spectroscopy

2.9.1. Principle

This technology does in fact include different approaches. In thermal gradient spectroscopy, it is considered the absorptive effects of glucose on the body naturally emitted infrared (IR) radiation [5]. Such IR absorption effect of glucose is obviously related to its concentration. In some studies, the skin was cooled to approximately 10 °C to suppress its absorptive effects [15].

2.9.2. Limitations

Every variation of body or tissue temperature is a strong confounding effect. It must be noticed that several factors can induce temperature variations, both physiological (such as the circadian periodicity) and pathological (for instance, a fever status) [24].

2.9.3. Measurement sites

A traditional site for this technique is the skin of the forearm or the finger. However, a different possible site is the ear: a sensor can in fact be inserted in the ear canal to measure the IR radiation emitted by the tympanic membrane.

2.10. Ocular spectroscopy

2.10.1. Principle

This technique is based on the use of a special contact lens where a hydrogel has been added. In ref. [40], a hydrogel wafer with 7 μm of thickness based on boronic acid derivatives was bonded to the lens. The boronic acid derivative is able to create reversible covalent bonds with glucose, and the phenomenon is influenced by the glucose concentration in tears. When the lens is illuminated by a light source (such as a laser light), the reflected light changes its wavelength (i.e. its colour) depending on the entity of the binding phenomenon, which is related to tear glucose concentration. The light colour changes can be detected by a spectrometer.

2.10.2. Limitations

There is a delay between glucose in blood and in tears. Moreover, the use of contact lens, though it can be considered a non-invasive approach, may be uncomfortable to some subjects.

2.10.3. Measurement sites

The measurement site is the eye.

2.11. Impedance spectroscopy

2.11.1. Principle

The impedance of one tissue can be measured by a current flow of known intensity through it. If the experiment is repeated with alternating currents at different wavelengths, the impedance (dielectric) spectrum is determined. The dielectric spectrum is measured in the frequency range of 100 Hz to 100 MHz. Variations in plasma glucose concentration induce in red blood cells a decrease in sodium ion concentration, and an increase in potassium ion concentration [41]. These variations cause changes in the red blood cells membrane potential, which can be estimated by determining the permittivity and conductivity of the cell membrane through the dielectric spectrum [42,43].

2.11.2. Limitations

Some problems remain to be clarified, such as the effect of body water content and of dehydration [41]. Moreover, some diseases affecting the cell membranes can also have an influence that needs to be evaluated [5].

2.11.3. Measurement sites

The most known study was performed with a watch-like device, positioned on the wrist [44].

2.12. Electromagnetic sensing

2.12.1. Principle

Similarly to impedance spectroscopy, this technique detects the dielectric parameters of blood. However, in the former an electric current is used, while in the latter the electromagnetic coupling between two inductors is exploited [45]. The inductors are turned around the medium under study: in an in vitro context, the system can be described by the sketch reported in Fig. 2. The tubes, simulating the human veins, contain blood. To make the experiment more realistic, the tubes can be covered by gelatine, which simulates (although roughly) the tissues surrounding blood vessels in the in vivo context [46]. The electromagnetic coupling of the two inductors is modified by variations in the dielectric parameters of the solution, i.e. blood in this case. On the other hand, dielectric parameters of the solution are influenced by glucose, and hence an estimate of glucose concentration can be derived. More specifically, the method is based on the application of a

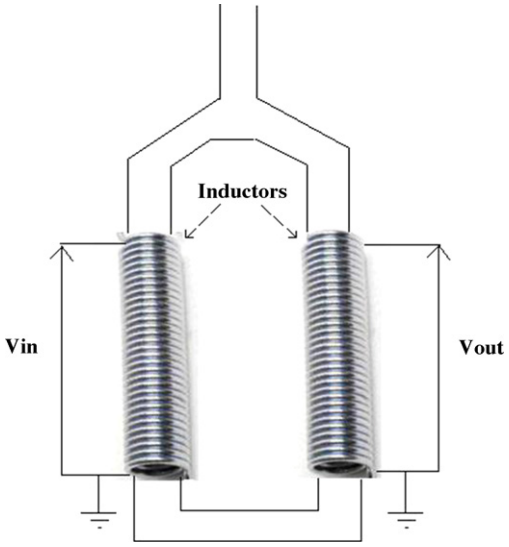

Fig. 2. Sketch of the electromagnetic sensing system.

voltage signal, Vin, with proper frequency, to the primary inductor. For electromagnetic coupling a signal, Vout, will be produced at the secondary inductor. The ratio $Vout_{RMS}/Vin_{RMS}$, where RMS indicates the effective value, depends in fact by the glucose concentration. The frequencies used in this technique are in the 2.4–2.9 MHz range. However, depending on the temperature of the investigated medium, there exists an optimal frequency, where the sensitivity to glucose changes reaches the maximum. For instance, at 24 °C optimal frequency is 2.664 MHz [45].

2.12.2. Limitations

The temperature has a strong effect on the measurement; since it also influences the optimal investigation frequency, temperature measurement has to be performed and the information properly considered. Furthermore, the blood dielectric parameters depend on several components other than glucose [47].

2.12.3. Measurement sites

At the moment, we have not found studies on humans with this technique, probably due to its recent introduction.

2.13. Fluid harvesting

2.13.1. Principle

This technique is based on the use of a laser light [48] or ultrasounds [49] to create an array of microscopic holes (micropores) on human skin. The interstitial fluid, containing glucose, tends to migrate through the micropores to a glucose sensor (of traditional type) placed in contact with the skin where the micropores have been created, and hence direct glucose measurement becomes possible. The technique based on laser light is called by some authors ‘‘biophotonic technique’’, whereas that based on ultrasound is also called ‘‘sonophoresis’’.

2.13.2. Limitations

No limitations or confounding factors have been explicitly described, except than the possible mismatch between glucose in the interstitial fluid and glucose in blood.

2.13.3. Measurement sites

The site for measurement is human skin in general. The arm is probably the most common application site.

2.13.4. Notes

Due to micropores generation, the technique is considered by some authors as minimally invasive.

2.14. Iontophoresis

2.14.1. Principle

Iontophoresis (or, more exactly, reverse iontophoresis) is based on the flow of a low electrical current through the skin, between an anode and cathode positioned on the skin surface. An electric potential is applied between the anode and cathode, thus causing the migration of sodium and chloride ions from beneath the skin towards the cathode and anode, respectively [50]. In particular, it is sodium ion migration that mainly generates the current [51]. Uncharged molecules, such as glucose, are carried along with the ions by convective flow (electroosmosis). This flow causes interstitial glucose to be transported across the skin, thus being collected at the cathode where a traditional glucose sensor is placed to get direct glucose concentration measurement. Over the typical range of iontophoretic current densities (<0.5 mA/cm^2), glucose extraction is approximately in linear relation with the density and duration of iontophoretic current.

2.14.2. Limitations

The main drawback of this technique is that it tends to cause skin irritation. This problem may be avoided by limiting the time interval of the electrical potential application. On the other hand, a minimum duration is required to get a sufficient amount of glucose for measurement. Furthermore, this approach cannot be used if the subject is sweating significantly. There is also discussion as to whether this technology can be able to detect rapid changes in blood glucose. This is, actually, a general problem of any measurement of glucose not in blood.

2.14.3. Measurement sites

The measurement can be obtained with a watch-like device placed on the wrist.

2.14.4. Notes

Similarly to the fluid harvesting technique, also iontophoresis is considered by some authors as minimally invasive. In fact, the glucose is again extracted from the skin and directly measured. The two techniques are sometimes defined as ‘‘transdermal’’.

3. Non-invasive glucose meters

The information categories *approvals, technology, Internet reference* are reported in Table 1 for all the devices. When no information is available for a device on a specific category, the category is not reported.

3.1. Meters approved and available

3.1.1. GlucoWatch®, Cygnus Inc.

3.1.1.1. Description. The meter has a wrist-watch format. It measures glucose through the skin using a disposable pad, which clips into the back of the meter. The pad uses an adhesive to stick to the skin allowing it to come in contact with a small electrical current, which causes the reverse iontophoresis. The electrical charges bring glucose to the skin surface where an enzyme reaction similar to that found in a standard meter occurs. Thus, glucose levels in the interstitial fluid can be estimated. Compared with finger-stick readings, the meter measurements have a 15-min lag time. The meter is intended for use to supplement, but not to replace, information obtained from a standard blood glucose meter. The meter has 2–3 h warm-up period. Afterwards, it measures glucose every 10 min (at least in the latest version, called GlucoWatch G2 Biographer): 3 min of electrical stimulation, then 7 min of glucose measurement. An alarm also occurs when a rapid change is seen in the blood sugar (more than a 35% change from any reading in the last hour), when you are sweating, and for any measurements above or below the patient's target levels. A trend indicator appears to show the direction of the blood sugar when the current measurement is more than 18 mg/dl (1 mmol/l) higher or lower than the previous measurements. Event markers can be recorded for activities like meals, insulin intake and exercise.

3.1.1.2. Tests

Several trials have been carried out on the meter, documented in peer-reviewed scientific journals. Of note, not only the meter performance were assessed in terms of accuracy, but also different aspects connected to the use of the meter were investigated, such as the long-term effect of using the meter on the glycated hemoglobin compared to traditional finger-stick testing. The most important studies are briefly reported in the following (divided into Cohort Studies and Randomized Controlled Trials, and ordered by publication date within each category):

3.1.1.2.1. Cohort studies.

(i) Twenty-eight different young adults with Type 1 diabetes were studied in a controlled outpatient clinic setting. Some subjects participated on multiple days. Subjects wore two GlucoWatch, each on the forearm. Comparisons were made to capillary blood glucose measurements (HemoCue analyzer). In addition, GlucoWatch (one each day for 3 consecutive days) was used by 12 diabetic subjects in a home setting. Comparisons were made to capillary blood glucose (One Touch Profile meter) [52].

(ii) Ninety-two subjects with Type 1 or 2 diabetes requiring treatment with insulin were studied. Participants wore up to two GlucoWatch during the 15-h study session and performed two finger-sticks per hour for comparative blood glucose measurements [53].

(iii) A clinical trial was performed to assess the effect of acetaminophen (a potential interference for traditional blood glucose meters) on the accuracy of the GlucoWatch in adult subjects with diabetes ($n = 18$). One thousand milligram doses of acetaminophen were administered to the subjects. The GlucoWatch readings were compared to serial finger-stick blood glucose measurements [54].

(iv) The performance of GlucoWatch was evaluated in two large clinical studies in a controlled clinical environment ($n = 231$), and home environment ($n = 124$). All the subjects were diabetic (Type 1 or 2). In the clinic, the test last 1 day with 2 meters, at home 5 days with 1 meter. Accuracy of the GlucoWatch was evaluated by comparing its readings to serial finger-stick blood glucose measurements [55].

(v) This study was done to evaluate the accuracy and safety of measuring glucose with the GlucoWatch in children and adolescents with diabetes. Sixty-six subjects each wore three GlucoWatch at sites including the forearm, upper arm, leg and torso. Accuracy was assessed by comparing GlucoWatch glucose measurements with hourly blood glucose measurements (HemoCue). Safety was evaluated by examining the GlucoWatch application sites immediately upon removal of the devices, and then at regular intervals [56].

(vi) This study was done to evaluate the ability of GlucoWatch to detect nocturnal hypoglycemia in a diabetes camp, a non-clinical environment with multiple activities. Forty-five campers (7–17 years old) wore a GlucoWatch. The meter was

Table 1
Some information categories of the devices included in the review (in the order as presented in the text)

	Approvals	Technology	Internet reference
GlucoWatch®, Cygnus Inc.	CE Mark in 1999. FDA Approval in 2001 for adults only, in 2002 for children aged 7–17 years	Iontophoresis	www.glucowatch.com (Last updated: 2005. Last checked: 15/03/2006)
Diasensor®, BICO Inc.	CE Mark in 2000 (for the latest device version)	Near infrared spectroscopy	http://www.americandiabetes.com/diasensor.htm (Last updated: 2004. Last checked: 15/03/2006)
Pendra®, Pendragon Medical Ltd.	CE Mark in 2003	Impedance spectroscopy	http://www.devicelink.com/emdm/archive/03/10/013.html (Last updated: 2003. Last checked: 15/03/2006)
Aprise™, Glucon Medical Ltd.	The Company is working to achieve FDA Approval. It also plans to achieve CE Mark	Ultrasound technology (photoacoustic spectroscopy)	http://www.glucon.com (Last updated: 2006. Last checked: 13/03/2006)
Glucoband®, Calisto Medical Inc.	The device already meets the requirements for FDA Approval: registration is in progress	Impedance spectroscopy	http://www.calistomedical.com (Last updated: 2006. Last checked: 16/03/2006)
GlucoTrack™, Integrity Applications Ltd.	CE Mark is expected within 2006, FDA Approval 1 year later	Ultrasound technology	http://www.integrity-app.com (Last updated: 2006. Last checked: 13/03/2006)
OrSense Ltd.	The Company has the rights over several patents, but approvals are not reached yet	Near infrared spectroscopy	http://www.orsense.com (Last updated: 2006. Last checked: 13/03/2006)
SpectRx Inc.	Not approved yet	Fluid harvesting	http://www.spectrx.com (Last updated: 2006. Last checked: 13/03/2006)
SugarTrac™, LifeTrac Systems Inc.	A multi-center study is planned to reach FDA approval	Near infrared spectroscopy	http://www.sugartrac.com/product_information.htm (Last updated: 2005. Last checked: 13/03/2006)
Symphony™, Sontra Medical Corporation	Sontra claims to start clinical studies for FDA Approval in 2006	Fluid harvesting	http://www.sontra.com (Last updated: 2006. Last checked: 14/03/2006)
Dream Beam, Futrex Medical Instrumentation Inc.	Not approved	Near infrared spectroscopy	http://www.childrenwithdiabetes.com/d_06_e20.htm (Last updated: 2002. Last checked: 13/03/2006)
GluCall, KMH Co. Ltd.	No information	Iontophoresis	http://www.glucall.net/english_html/main/index_english.jsp (Last updated: 2005. Last checked: 15/03/2006)
GluControl GC300®, ArithMed GmbH	In 2000, the meter was not approved yet. No recent information found	Near infrared spectroscopy	http://www.diabetesnet.com/diabetes_technology/arithmed.php (Last updated: 2005. Last checked: 13/03/2006)
Hitachi Ltd.	The Company is working to achieve regulatory approval under the Pharmaceutical Affairs Law in Japan and FDA Approval	Thermal spectroscopy	http://www.hitachi.com/New/cnews/040223.html (Last updated: 2004. Last checked: 13/03/2006)
Sysmex Corporation	No information	Unclear (probably iontophoresis)	http://www.sysmex.co.jp/en/news/press/2003/030417.html (Last updated: 2003. Last checked: 15/03/2006)
TouchTrak Pro 200, Samsung Fine Chemicals Co. Ltd.	In 1999 not approved yet	Unclear (probably near infrared spectroscopy)	http://www.diabetiker-mailbox.com/bz/a3_834b.html (Last updated: 1998. Last checked: 14/03/2006)

placed on the arm at 6:00 p.m., with the low alarm set to 85 mg/dl. Overnight glucose monitoring occurred per usual camp protocol. Blood glucose value was checked if the meter alarmed. The meters were worn for 154 nights by 45 campers [57].

(vii) The purpose of the investigation was to measure the effectiveness of GlucoWatch and determine the validity of its readings, during rest and exercise both indoors and outdoors. Four subjects with Type 1 diabetes and five subjects without diabetes participated in rest, mild, moderate and heavy exercise both indoors and outdoors. Subjects monitored blood glucose levels and readings were taken by the GlucoWatch during and following testing conditions [58].

(viii) GlucoWatch requires invasive daily calibration with a conventional finger-stick: aim of the study was to develop an ''internal standard'' to render the approach completely non-invasive. That was based on the use of both glucose and sodium data simultaneously extracted by iontophoresis. These data were used for each subject to calculate an extraction constant K. Fourteen non-diabetic subjects were studied for a total of 42 experiments of 5 h each. After 2.5 h, the subjects ingested 75 g of glucose dissolved in water [59].

(ix) The purpose of this study was to characterize the distribution of the rate of change of blood glucose for a diabetic population. The study population consisted of 124 adults with Type 1 or 2 diabetes requiring insulin. Study participants applied a GlucoWatch during the day at home for 5 consecutive days and took finger-prick blood glucose measurements hourly. Subjects kept a diary of meals. Rates of glucose change were calculated for both GlucoWatch and blood glucose measurements [60].

(x) The study was performed to assess the performance of GlucoWatch alarms: the hypoglycemia alarm is triggered when the current glucose measurement falls below the level set by the user, and the ''down alert'' alarm is triggered when extrapolation of the current glucose trend anticipates hypoglycemia to occur within the next 20 min. During a 24-h clinical research center stay, 89 children and adolescents with Type 1 diabetes mellitus wore 174 GlucoWatch meters and had frequent serum glucose determinations during the day and night [61].

(xi) The study aim was to evaluate usability, accuracy, and hypoglycemia detection of the GlucoWatch in children aged 1–17 years. Forty six children with Type 1 diabetes were enrolled for an extended-wear outcome study: two daytime and two nighttime 15-h wear periods each week and blood glucose monitoring four times daily for 3 months [62]; similar study was performed in ref. [63].

(xii) The study evaluated how children (4–17 years old) with Type 1 diabetes respond to alarms for hypo- and hyperglycemia during sleeping. Twenty subjects were admitted to a clinical research center for approximately 24 h. Each subject wore two GlucoWatch and was videotaped through infrared camera to check his response to the alarms [64].

3.1.1.2.2. Randomized controlled trials.

(i) Aim of the study was to determine whether use of the GlucoWatch improves glucose control in children and adolescents with Type 1 diabetes. Forty children in poor glucose control (glycohemoglobin, HbA1c, $>8\%$) were randomized to diabetes management with or without glucose monitoring using the GlucoWatch. Conventional glucose monitoring was performed four times daily in both groups. Those randomized to the GlucoWatch group were asked to wear the device four times per week for 3 months (intervention phase) and to perform blood glucose monitoring if the GlucoWatch alerted them that glucose was $\leq$70 or $\geq$300 mg/dl. After 3 months, all patients received GlucoWatch and were followed for 6 months (observation phase). HbA1c values were determined at baseline and after 1, 3, 6 and 9 months [65].

(ii) The study examined whether pre-application of corticosteroid preparations could reduce skin irritation from iontophoresis used by the GlucoWatch. Numerous corticosteroid preparations were screened to identify formulations that did not interfere with adhesion of the meter to the skin or glucose sensing. Triamcinolone acetonide and hydrocortisone sprays were finally selected and, in a double-masked, randomized, controlled trial, were applied to the forearms of 66 subjects with diabetes. GlucoWatch meters were applied and worn for 15 h, and home blood glucose measurements were taken every 30 min to assess accuracy. Irritation was assessed periodically by trained observers [66].

(iii) Aim of the study was the measurement of psychological parameters in a randomized trial of the GlucoWatch. A multi-center group of 200

youths with Type 1 diabetes was randomized to 6 months of usual care by conventional home glucose meter or improvement of usual care by GlucoWatch [67]. A similar study was developed by the same research group in ref. [68].

(iv) A group of 200 subjects (7–18 years) with Type 1 diabetes were randomly assigned to standard glucose monitoring or standard glucose monitoring plus GlucoWatch use for 6 months. Study outcomes included glycated hemoglobin values and occurrence of hypoglycaemic events [69].

3.1.1.3. Evidence

The main results of the mentioned studies are reported.

3.1.1.3.1. Cohort studies.

(i) GlucoWatch glucose values correlated well with capillary blood glucose values determined using the HemoCue analyzer in the clinic setting ($R = 0.90$, 1554 paired data points) and using the One Touch Profile meter in the home setting ($R = 0.85$, 204 paired data points).

(ii) An analysis of 2167 data pairs shows a linear relationship ($R = 0.88$) between GlucoWatch readings and serial glucose measurements. The mean absolute error between the two measurements was 15.6%, and 96.8% of the data fell in the therapeutically relevant regions of the Clarke error grid analysis (A + B regions) [70].

(iii) The mean difference between the two measurements is between 8 and 12 mg/dl. The mean absolute value of the relative difference is less than 20%, and more than 93% of the points were in the clinically acceptable (A + B) region of the Clarke error grid.

(iv) Mean difference between GlucoWatch and finger-stick measurements was −0.01 and 0.26 mmol/l for the clinical and home environments, respectively. The mean absolute value of the relative difference was 1.06 and 1.18 mmol/l for the same studies. Correlation coefficient (R) between GlucoWatch and finger-stick measurements was 0.85 and 0.80 for the two studies. In both studies, over 94% of the GlucoWatch readings were in the clinically acceptable A + B region of the Clarke error grid.

(v) For the forearm, the mean absolute relative difference between GlucoWatch readings and blood glucose was 21%. Ninety-five percent of GlucoWatch readings fell into the A or B regions of the Clarke error grid. Data from GlucoWatch worn at the alternative sites were similar. Two strong reactions to the adhesive pad of the GlucoWatch were observed. Most skin reactions were mild.

(vi) Thirty-four percent of readings were skipped because of: data errors (65%), sweat (20%) and temperature change (16%). Reported GlucoWatch values correlated with blood glucose values measured 11–20 min before ($R = 0.90$). Of 20 low-glucose alarms with corresponding meter values measured within 20 min, there were 10 true-positive alarms, 10 false-positive alarms and no false-negative alarms.

(vii) Significantly, more GlucoWatch readings were obtained during rest (55.6% outdoors, 66.7% indoors) than during moderate (11.1%) or heavy (0%) exercise. A similar number was obtained during mild outdoor exercise (46.6%), but not indoors (29.2%). Sweating rates corresponded to a reduced effectiveness during indoor exercise only ($P < 0.01$). A weak association between GlucoWatch and matched glucometer readings ($R = 0.81$) was found. The effectiveness of the GlucoWatch during any moderate to heavy exercise was extremely poor.

(viii) A constant value of K was established for two thirds of the study population. Of the 181 paired data points (GlucoWatch and blood glucose measurement) 78.5% were in region A of the Clarke error grid, 21.5% in B. Thus, the use of the sodium ion as an internal standard could refine the determination of glycemia without requiring calibration with a blood sample.

(ix) Mean (±S.D.) rates of change of glucose of -0.36 ± 0.95 and 0.36 ± 0.99 mg/(dl min) were found before and after lunch using blood glucose data, and -0.31 ± 1.23 and 0.43 ± 1.26 using GlucoWatch data. The GlucoWatch was found to be effective in tracking trends in glucose levels and yielded similar results as obtained by finger-prick blood samples.

(x) Sensitivity to detect hypoglycemia (reference glucose $\leq$60 mg/dl) during an insulin-induced hypoglycemia test was 24% with the hypoglycemia alarm alone and 88% when combined with the down alert alarm. Overnight sensitivity from 11 p.m. to 6 a.m. was 23% and 77%, respectively.

(xi) In ref. [62], a total of 531 paired readings were available for accuracy assessment. The correlation coefficient R was 0.58 and 0.74 (ages $<$7 and $\geq$7 years, respectively). There was no significant change in hemoglobin A1C or weight-adjusted

insulin dose at 3 months after GlucoWatch use. Forty-two episodes of hypoglycemia were detected by the GlucoWatch, 33 of which were confirmed by blood glucose meters. No significant side effects were reported.

(xii) A total of 240 alarms occurred during the night. Subjects awoke in the 29% of the alarms. However, in more than 50% of the alarm events no actual hypo- or hyperglycemia was found.

3.1.1.3.2. Randomized controlled trials.

(i) The median HbA1c was 8.6% and 8.9% (control versus GlucoWatch group) at baseline and was significantly lower in the GlucoWatch group after 3 months (8.4% versus 9%). More hypoglycemia was detected when subjects were wearing the GlucoWatch, especially at night. No severe hypoglycemia occurred. During the observation phase, HbA1c values at 6 months were 8.5% and 8.3% and at 9 months were 8.6% and 8.4% in the control and GlucoWatch groups, respectively. Only one child dropped out of the study because of skin irritation from using the device. Thus, the GlucoWatch was well tolerated by children and adolescents and significantly improved glucose control compared with standard therapy.

(ii) Skin irritation was reduced by both corticosteroid sprays; the fraction of subjects who experienced moderate irritation was reduced by 57% and 43% with triamcinolone acetonide and hydrocortisone sprays, respectively. The treatment effect persisted at the 1-week assessment. Pre-application of these preparations did not affect the clinical utility of interstitial glucose readings.

(iii) In ref. [67], no special effects were found at the end of the study on parameters, such as diabetes treatment adherence, diabetes-specific quality of life and diabetes-related anxiety.

(iv) The mean glycated hemoglobin at baseline was 8.0% in both groups, and remained not different at the end of the study (7.9% in the usual care group and 8.1% in the GlucoWatch group). Similarly, there was no significant difference in the occurrence of hypoglycemic events.

3.1.1.4. Usability. The use of the meter is made comfortable by its wrist-watch format. The data download to a PC and subsequent analysis through a proper tool also allows powerful use of the collected data. The meter has a memory that can store up to 8500 records. One limitation is that the meter requires calibration through a standard blood sugar meter. Moreover, the disposable pad must be replaced every 12–13 h of monitoring time to ensure continued accuracy; the meter must then go through the warm-up period and calibration again. In addition, it may take more than one try to calibrate the meter, thus requiring additional finger-stick tests. Occasionally, the meter will not calibrate at all. Some drawbacks have also been documented during the meter use. In fact, the measurements can fail, or be inaccurate, if the patient is sweating, or in the case of rapid temperature changes, excessive movement of the meter, strenuous exercise. Moreover, the user cannot shower, bathe or swim during the warm-up period. Finally, most users report that the electrical discharge is quite noticeable during the first use of the meter, although it becomes less noticeable on subsequent use.

3.1.1.5. Safety. As already mentioned, the meter causes skin irritation to some extent. Skin irritation in fact limits reuse of the same site to a week or two.

3.1.1.6. Status. After approvals, the meter has been sold in the United States (at a price around US$ 700, plus US$ 120 for a box of 16 disposable pads). However, in 2005 it was reported that the Company was going out of business, had stopped manufacturing its meters and was planning to sell all of its assets to another Company, Animas Corporation. In fact, Cygnus Internet site (www.cygn.com) has been shut down. However, the meter Internet site (see Table 1), that was not online for a period, is now online again (maintained by Animas Corporation). It is claimed that the meter is on sale both in the US and UK (though there are not price indications), and some telephone numbers for customers are reported.

3.2. Meters approved but withdrawn

3.2.1. Diasensor®, BICO Inc.

3.2.1.1. Description. Diasensor operates by placing the patient's forearm on the arm tray of the meter (see Internet reference in Table 1 for a photograph). The blood glucose test is obtained in less than 2 min. The dimensions of the meter are relevant compared to other meters, but it is still sufficiently compact to be used in a domiciliary environment. It is claimed that the Diasensor is not for everyone, but it is not clear what patient categories are allowed to use it. In any case, it is not intended as a replacement for the traditional invasive blood glucose meter: its aim is to promote greater compliance for self-monitoring by allowing

patients to perform the majority of their daily blood glucose monitoring with a non-invasive meter. The Diasensor is declared not to be adequate to detect hypoglycaemic events.

3.2.1.2. Tests. A trial was performed where a total of 100 testing sequences were evaluated over a period of more than 1 month. In each sequence, six measurements were performed: the first two with traditional glucose meters, the third with Diasensor and the following again with the 3 meters but in the opposite order. The trial seems to have occurred in late 2000. In another study, the effectiveness of the Diasensor for the management of long-term blood glucose control was evaluated in Type 1 and insulin-requiring Type 2 diabetic patients. Approximately, 200 men and women from nine US medical centers, at least 18 years of age, with Type 1 or insulin-requiring Type 2 diabetes for at least 1 year, participated in the study. The study lasted about 9 months. It was running in 2002.

3.2.1.3. Evidence. In the late 2000 trial, the average difference between Diasensor and the traditional meters was around 25%. No results were found on the second trial.

3.2.1.4. Usability. Due to the relatively large size, the device is not portable.

3.2.1.5. Status. The Diasensor was marketed in Europe at a price of US$ 9000 (starting between 1998 and 1999). It seems that the distributor was EuroSurgical Ltd., UK. However, the Web site of the Company does not currently mention Diasensor, and hence it could be concluded that it is not on sale anymore. That could be also connected to the problems of BICO. In fact, in September 2002, it was reported that BICO was in financial troubles. In October 2004, BICO was merging with another Company, cXc Services, Inc., in the attempt to solve their financial problems. At the moment, BICO seems not to have a website and to be out of business.

3.2.2. Pendra®, Pendragon Medical Ltd.

3.2.2.1. Description. The meter measures how changes in blood composition affect the impedance pattern of the skin and underlying tissue. In particular, the meter is optimized to detect the effects of glucose on the impedance pattern, so that blood glucose concentration is estimated. The meter has wrist-watch format (53 mm × 46 mm × 15 mm), and it has an open resonant circuit which lies in contact with the skin. This circuit generates small currents in a proper frequency range and performs the impedance measurement. Sensitivity was reported to be in the range of 20–60 mg/dl of glucose per Ohm [71]. The meter can provide up to four measurements per minute, but a new value every minute is displayed (averaged above the measurements in the last 5 min). Alerts are provided in the case of hypoglycemic events, and whether rapid changes of glucose concentration occur. Variations on impedance due to temperature changes are self-corrected. The meter can be used by both Types 1 and 2 diabetic subjects. However, in Type 1 subjects possible warning from the meter must be followed by a finger-stick test.

3.2.2.2. Tests. Some clinical tests were performed, as reported in ref. [71]: (i) 10 non-diabetic subjects used the meter while their blood glucose was raised from 100 to 300 mg/dl; (ii) 15 non-diabetic subjects used the meter while their blood glucose was clamped at high and normal levels. In another study, presented at ADA 2004 Congress, 12 Type 1 diabetic patients underwent a 75 g oral glucose tolerance test, with administration of insulin after 2 h. Moreover, one study was performed to evaluate the effects on the device of motion-induced blood flow variations due to different forearm postures. Fifteen volunteers without diabetes were included, and two devices were fixed at both upper extremities with different fixation techniques (bracelet and tape). Standardized position changes of the upper extremities to induce variations in microcirculation were performed and measured [72].

3.2.2.3. Evidence. Test results are the following: (i) 95% of the meter measurements, compared to a gold standard, were in region A + B of Clarke error grid (52% in A, 43% in B); (ii) 99% of the meter measurements, compared to a gold standard, were in region A + B of Clarke error grid (81% in A, 18% in B). In the study on the 12 Type 1 patients, no systematic differences were observed between the meter measurements and the reference values obtained from the fingertip. During slow glucose decrease the meter measurements were in region A of Clarke error grid by 85.1% (14% in B), whereas during rapid decrease 73.5% were in A and 23.3% in B. With regard to the study on motion effects, some changes in microcirculation were observed in some of the motion actions with consequent influence on the impedance signal. However, these effects were minimized when fixing the device by both bracelet and tape.

3.2.2.4. Usability. The wrist-watch size allows comfortable use. The battery has autonomy up to 24 h. The internal memory can store data for up to 24 h. The meter also has USB connection to a PC for downloading and easy display of glucose readings. A drawback is that, due to differences in the thickness of skin and underlying tissues among individuals, the meter requires a two-point calibration process. Furthermore, some information sources reports that the device does not perform equally in all the individuals.

3.2.2.5. Status. Commercialization should have started in September 2004, at a price around €2500. In fact, at that time the device was introduced in the Netherlands, but commercialization was stopped since there were still concerns about actual performances of the meter: a post-marketing study showed a correlation coefficient between Pendra measures and traditional glucometer measures equal to 35% only [73]. In February 2005, the Company files for bankruptcy. Recently, a new Swiss Company has appeared that seems to continue the previous experience, though the Pendra device is not mentioned anymore (Solianis Monitoring AG: www.solianis.com). One publication is in press [74], where this new Company presents new data on glucose monitoring of patients through impedance spectroscopy approach.

3.3. Meters not approved yet

3.3.1. Aprise™, Glucon Medical Ltd.

3.3.1.1. Description. The meter is claimed to be for real-time and continuous blood glucose monitoring, with alarms. It is based on the use of ultrasounds, generated by illuminating the tissue with laser pulses at several selected wavelengths (photoacoustics). Ultrasounds are also used for the localization of the measured volume inside a blood vessel, and for removing the influence of the outer layers of the skin. The Company claims that photoacoustics is superior to traditional optical technologies, as it attains blood glucose measurements directly from inside the blood vessels and allows improved specificity (identification) and sensitivity (detection of level changes) of the glucose measurement.

3.3.1.2. Tests. The Company has performed comparative tests on more than 60 volunteers and diabetic patients in various clinical settings. Blood glucose level was monitored by the Glucon meter continuously (every 10 s) during an OGTT (Oral Glucose Tolerance Test), and sampled every 10–15 min by a reference device. Hypo- and hyperglycemia cycles were also inducted, showing accuracy of the device to measure also in the extreme glucose ranges. In a recent note, it is reported that new tests have been performed over 30 diabetic subjects with different protocols to induce glycemic variations: in one protocol dextrose solution and insulin were injected by venous infusion; in the other protocols glucose was administered orally (through a solution or regular meal) followed by diabetic subject's medications.

3.3.1.3. Evidence. With regard to the comparative tests on the 60 volunteers, a correlation coefficient R of 0.94 was found. The mean absolute deviation was 20 mg/dl. In the more recent tests, a mean absolute relative deviation of 19% was found.

3.3.1.4. Usability. The meter is comfortable, since it is wearable like a watch.

3.3.1.5. Status. The Company is active on the project, but in the Internet site it is not declared when the meter will be available on the market. The Company itself declares that the current prototype will be further improved, especially the case. Other sources of information indicate the second half of 2007 as possible date for commercialization.

3.3.2. Glucoband®, Calisto Medical Inc.

3.3.2.1. Description. The meter has a wrist-watch shape. It is based on the detection of impedance variations in the human tissues due to the application of an electromagnetic field. For each glucose concentration in the body, there is a specific electromagnetic field (called the ''glucose signature'') able to produce a resonance phenomenon, which in turn determines the impedance variation. The meter has an internal database of several glucose signatures, each one related to a glucose concentration of a reference solution. Thus, the glucose in the body can be estimated from the specific glucose signature, which determines the resonance phenomenon. The Company calls this approach ''Bio-Electromagnetic Resonance (BEMR™) technology''. The meter is able to provide alarms for both hypo- and hyperglycaemic events, whose thresholds can be set properly for each individual. The measure needs 3–8 min at the most to take place. Measured data can be stored in the internal memory and downloaded to a PC through USB interface.

3.3.2.2. Tests. In a first trial conducted at the City of Angels Hospital in Los Angeles 44 subjects measured

their blood glucose level by the Glucoband® and by a traditional meter. No details about the studied subjects are provided. A new trial should have been started in mid 2005, which is probably not concluded: in the Internet site (see Table 1) it is claimed that it is still possible to take part in the clinical trials.

3.3.2.3. Evidence. In the first trial, the correlation coefficient between Glucoband® and traditional meter measures was 0.89. In the Clarke error grid 79% of the samples were in region A, and 21% in region B. The mean absolute deviation was 19 mg/dl.

3.3.2.4. Usability. The meter is comfortable to be worn. It is powered with batteries lasting 3–6 months. It does not use any disposable material. Calibration occurs automatically in a few seconds before each measurement.

3.3.2.5. Safety. The Company emphasizes that the device is absolutely painless and risk-free.

3.3.2.6. Status. The Company seems to actively work in the development of the final prototype and in the regulatory process aimed at reaching FDA Approval. The device is expected to be on the US market within 2006.

3.3.3. GlucoTrack™, Integrity Applications Ltd.

3.3.3.1. Description. It is a handheld meter based on ultrasonic measurements to get the glucose level in the blood. To achieve more accuracy and precision, the meter also measures tissue conductivity and heat capacity. The Company claims that, to the best of his knowledge, the approach of using three technologies is unique. The meter is made of two units: main unit, containing display, transmitter, receiver and processor, and ''Earring'' Unit, containing sensors and calibration electronics, to be attached (externally clipped) to the earlobe. The meter normally measures spot glucose level, but a continuous mode can be set to perform sequential measurements automatically, thus indicating trends. Extreme values, as set by each user, cause visual and audible alerts. The measured data can be downloaded for further analysis (through USB port or IR interface). The meter can be used by Type 1, Type 2, gestational diabetic subjects and by subjects with Impaired Glucose Tolerance. It is claimed that the accuracy of the measurements enable the diabetic patients to decide about the optimal timing to take their medicine. A specific application that is mentioned is related to pediatric incubators, to keep tracking of low glucose level of premature babies, providing alerts when a hypoglycemia episode occurs.

3.3.3.2. Tests. A validation test was performed on 69 subjects, on which 174 measurements were taken globally with the meter and compared to a gold standard. Calibration data of over 3 months old were used (up to 7 months old). The Company also claims that they are currently performing other clinical trials in Soroka Medical Center, Beer Sheba, and that they are looking for volunteers for clinical tests participation.

3.3.3.3. Evidence. With regard to the test on the 174 glucose measurements, a correlation coefficient R equal to 0.94 was found.

3.3.3.4. Usability. The meter is easy to use and allows easy reading thanks to the large LCD screen. Furthermore, the meter supports up to three users, thus making the device more convenient and comfortable in cases of multiple diabetic subjects in the family: the meter does in fact maintain each individual's data, while each individual has his calibrated earring unit, which can be distinguished thanks to different colours. The meter can work with batteries, and can be easily fastened to the patient's belt. A disadvantage is that, differently to other non-invasive meters, it requires disposable tapes. The meter requires calibration rarely (less than one per month) differently than many other non-invasive meters requiring calibration every few hours or days.

3.3.3.5. Safety. The Company put emphasis on the fact that the technology used is particularly safe for the patient, with no side effects.

3.3.3.6. Status. The Company claims that the next working steps will be final-stage development, miniaturization, completion of clinical trials and regulatory processes. Commercialization is estimated to begin already in 2006.

3.3.4. OrSense Ltd.

3.3.4.1. Description. In this meter, near infrared spectroscopy is complemented with the study of the red band, as well as with a special technique of occlusion and release of the blood vessels in one finger. The Company calls its unique technology red near infrared (RNIR) occlusion spectroscopy. With this technique a temporary cessation of the tissue's blood flow at the testing site (the finger) is obtained. The Company calls this condition ''artificial kinetics''. While projecting a multi-wavelength RNIR source, the occlusion and release action causes enhanced aggregation (rouleaux) of red blood cells, which in turn changes the detected RNIR optical signal in relation to the blood

glucose, the hemoglobin/hematocrit ratio and oxygen saturation concentration. The optical properties of blood are affected by the concentration of each constituent and the phenomenon is enhanced by occlusion. For each combination of concentrations, there is a specific optic profile (''fingerprint''). By matching the patient's data to a known ''fingerprint'' an algorithm deduces the concentration of glucose, as well as the other mentioned blood constituents. Occlusion spectroscopy overcomes the problem of the very low signal-to-noise ratio inherent in non-invasive blood measurement. The Company claims that the meter is adequate for both screening and diagnostic purposes, and, more specifically, to monitor post-prandial events, hyperglycemia and hypoglycemia. Measurements are available within 1 min.

3.3.4.2. Tests. The Company claims to have conducted multi-center clinical trials on hundreds of patients to determine the accuracy of its blood glucose meter. A first study was conducted on five men with Type 1 diabetes, which underwent a hyperinsulinemic hypoglycemic clamp: insulin was infused at a constant rate, and stepped hypoglycemia was achieved by varying glucose infusion. Glucose values ranged from 40 to 270 mg/dl. A second, wider study was performed: 41 subjects were studied (17 females and 24 males, aged 19–82 years, 7 with Type 1 diabetes, 28 with Type 2 diabetes and 6 healthy volunteers). Measurements were performed after a 4-h fasting period for 1 h and hence for other 3 h after a light lunch. Reference blood glucose levels were evaluated every 30 min concurrently with non-invasive readings. Measurements were performed on 10 consecutive workdays. Calibration algorithms were formulated for each subject based on data from the first 2 days of the 10-day trial.

3.3.4.3. Evidence. In the first study, high degree of correlation ($R = 0.91$) with a gold standard was found, with mean error less than 10%. In the second study, the meter glucose measurements showed again good correlation with the gold standard ($R = 0.71$); the relative absolute difference was 14% and the mean absolute error was 20 mg/dl (10–25 range). Furthermore, the trial indicated that the meter may be used to detect glycemic excursions. The Company claims that the accuracy level is similar to that of invasive meters used in home care, since they reach a 10% error rate due to handling errors, impure blood intake, etc.

3.3.4.4. Usability. The meter is portable, and the Company claims that it guarantees exceptional ease of use, also thanks to the infrequent calibration requirements. The meter has an easy-to-read display and an internal memory able to record over 500 entries (blood glucose values, daytime references, etc.). The meter also includes additional features for improved usability, such as trend analysis data and alarm warning on low or high glucose values. It is also claimed that the meter supports telemedicine applications, although this concept is not further explained.

3.3.4.5. Safety. The Company declares his meter safe, with no hazardous material handling and no risk of contamination for the patient or medical professionals.

3.3.4.6. Status. The Company seems to be active to reach the approvals, but no indication is provided about expected time for it and consequent commercialization.

3.3.5. SpectRx Inc.

3.3.5.1. Description. The meter is made mainly of two units: the first unit is a handheld laser, which creates micropores in the external, dead layer of the skin. The micropores have the size of a hair. The interstitial fluid, containing glucose, flows through the micropores and is collected by a patch. Then, it reaches a glucose sensor, which is the second unit. Since the sensor comes in direct contact with the interstitial fluid, a traditional sensor can be used. The meter also includes a transmitter that sends wirelessly the glucose measurements to a handheld display device. The Company calls his methodology ''biophotonic technology''.

3.3.5.2. Tests. The main Web site reports information on several clinical tests: (i) 64 adult subjects (29 Type 1 diabetic, 31 Type 2 diabetic, 4 non-diabetic) were studied to know how long the interstitial fluid can be acquired by the micropores; (ii) 30 children, ranging in age from 7 to 18 (19 Type 1 diabetic, 11 non-diabetic) were studied to evaluate interstitial fluid flow rates; (iii) 36 subjects (16 Type 1 diabetic, 9 Type 2 diabetic, 11 non-diabetic) were studied to investigate whether the amount of interstitial fluid harvested is the same for different sites on the body, such as arm or abdomen; (iv) in 20 subjects (all diabetic) the meter measurements were taken for 4–8 h, and compared to finger-stick blood measurements, in order to evaluate the correlation coefficient. A total of 280 paired measurements were taken; (v) in 27 subjects (all diabetic) the meter measurements were taken for 4–8 h, and compared to finger-stick blood measurements, in order to evaluate both correlation coefficient and mean delay time. A total of 738 paired measurements were taken; (vi) in 8 subjects (all diabetic) the meter

measurements were taken for overnight periods (8–48 h), and compared to finger-stick blood measurements, in order to evaluate the correlation coefficient. A total of 263 paired measurements were taken; (vii) in 56 subjects (all diabetic) the meter measurements were taken consecutively for 2 days and compared to finger-stick blood measurements, in order to evaluate the correlation coefficient. A total of 1167 evaluable paired measurements were obtained; (viii) in 252 (187 diabetic, 65 non-diabetic) subjects the meter measurements were taken consecutively for 2 days and compared to blood measurements through a commercial blood glucose system, in order to evaluate the correlation coefficient. A total of 4059 evaluable paired measurements were obtained. One study was also described in a peer-reviewed international journal [75]: four diabetic patients underwent an intravenous injection of sodium fluorescein. Then, the interstitial fluid was sampled with the Company proprietary fluid harvesting technique and fluorescence levels were measured by a fluorometer.

3.3.5.3. Evidence. Some information on results of the above-mentioned tests are reported: (i) interstitial fluid can be acquired for up to 96 h; (ii) interstitial fluid flow rates are slightly higher for children than for adults, and hence system may be adaptable for use in children; (iii) the amount of interstitial fluid harvested is nearly the same for the different body sites; (iv) the correlation coefficient R was 0.901; (v) the correlation coefficient R was 0.894, and the mean time delay between interstitial fluid and blood measurements was 11.5 min; (vi) the correlation coefficient R was 0.898; (vii) the correlation coefficient R was 0.875, with 97.7% of points within A + B regions of Clarke error grid; (viii) the correlation coefficient R was 0.946, with 99.1% of points within A + B regions of Clarke error grid.

In the study [75], the time delay in fluorescein concentration between blood and interstitial fluid was found to be in the 2–4 min range.

3.3.5.4. Usability. The Company claims that the system was designed to be comfortable to wear.

3.3.5.5. Status. The Company seems to be actively working on the project, and possible recruitment of new subjects for other clinical trials (both on adults and children) is indicated in the Internet site.

3.3.6. SugarTrac™, LifeTrac Systems Inc.

3.3.6.1. Description. The meter has the size of a mobile phone. A low energy beam of near IR light is transmitted through the earlobe thanks to an engaged earpiece, thus allowing measurement of glucose in the patient's blood. The earpiece has to remain on the ear for less than 1 min. The meter is not intended for continuous use, but it allows an unlimited number of readings. A 5 min wait between readings is recommended. The meter includes light sources having a wavelength of 940 nm to illuminate the tissue, and receptors for receiving light and generating a transmission signal. The light sources are LED pulsed at 1 kHz for a 1 ms pulse width. A signal analyzer, which includes a trained neural network, determines the glucose concentration in the blood of the subject. In the main Web site, the Company claims that a redesigned, even further miniaturized device will be produced.

3.3.6.2. Tests. A clinical trial at Brigham & Women's Hospital, Biddeford, ME, seems to have occurred, although in the Internet site (see Table 1) it is indicated as still on course. In other information sources a next study at Harvard is announced, which should be a double blind study using the meter for 40 patients.

3.3.6.3. Evidence. The Brigham study showed a correlation coefficient R of 0.88 with a reference glucose meter. No further details are provided.

3.3.6.4. Usability. Good usability is allowed by its compact size and by the comfortable power supply simply based on a standard 9 V battery.

3.3.6.5. Safety. The Company claims that the transmitting diode is only active for 5 s, and it is impossible to look directly into with an opening of only 0.531 of an inch. In any case, near infrared light is not damaging a human eye. Furthermore, there is no contact to the skin possible from the photo diode (transmitter) or the photo pickup (receptor), due to the fact that the transmitter and receptor are embedded into nylon plastic, prohibiting contact with any metal parts. The only part a user will come into contact with will be the glass domes of the transmitter and receptor, and the plastic surrounding them. In any case, the voltage to the earpiece is only 0.17 V. The Company also claims that the earpiece is not damaging the earlobe: the maximum opening of the earpiece is such that the pressure exerted is comparable to that of a clip-on earring.

3.3.6.6. Status. The Company seems to be working to reach the FDA Approval. Although some information sources had foreseen FDA Approval within 2003, in the Internet site it is clearly indicated that the approval is

not reached. There are no indications about commercialization phase.

3.3.7. Symphony™, Sontra Medical Corporation

3.3.7.1. Description. The meter is made essentially of two units: an ultrasonic device, coupled with the skin through an aqueous medium, which increases skin permeation, and a glucose biosensor, which measure glucose in the interstitial fluid reaching the sensor through the micropathways generated on the skin [76]. From the biosensor, some data are transmitted through wireless technology to a glucose meter that eventually provides and displays the glucose reading.

3.3.7.2. Tests. In the study [76], 10 patients with Type 1 or 2 diabetes where studied for a period of 8 h. Blood glucose measurements were taken every 20 min, whereas the glucose sensors placed over the treated skin sites (two per person) provided readings every 5 s. In the Internet site (see Table 1), the Company also claims to have finished a new study on humans at the Vanderbilt University in fall 2004.

3.3.7.3. Evidence. In the study [76], a correlation coefficient R of 0.84 is reported, with 95% of the glucose measurement pairs in the A + B region of the Clarke error grid. In the second study, a correlation coefficient R of 0.90 is indicated, but no further details are provided.

3.3.7.4. Usability. It is claimed that the application of the ultrasonic device for 15 s is enough to make the skin permeable for several hours. The technology is absolutely painless.

3.3.7.5. Safety. In the study [76], it is reported that no patient suffered pain or skin irritation during the study.

3.3.7.6. Status. The Company claims that the current activity is related to the improvement of the glucose biosensor, especially for the development of the wireless connection to the glucose meter. The Company expects to enter the market with its first glucose monitoring device within the end of 2006. The first application foreseen is the monitoring of patients in intensive care units.

3.4. Meters poorly described

In this section, we included some devices matching our inclusion criteria, but with very poor information on them. In particular, no results of tests on these devices were reported (information category *evidence* always missing).

3.4.1. Dream Beam, Futrex Medical Instrumentation Inc.

3.4.1.1. Description. The meter measures the blood glucose in a finger. In the Internet site (see Table 1), the device dimensions are reported (about 5.5 in. × 3 in. × 1.5 in.), and it is indicated an expected price (under US$ 2500).

3.4.1.2. Tests. Futrex claimed to have successfully tested the meter at Mount Sinai Medical Center in New York in May of 1991. However, the Company was asked to repeat the Mount Sinai study at hospitals in the Washington/Baltimore area in 1992, and it seems that these tests, which were analyzed by Eli Lilly, failed to show that Futrex's meter could correctly ascertain blood glucose levels. In 1998 new tests were performed in Chile, especially to study the glycemic oscillations in children with insulin-dependent diabetes, and to determine the meal order effects on post-prandial hyperglycemia.

3.4.1.3. Usability. Good usability is allowed by its compact dimensions, which make it portable, and by the use of batteries to power the meter. However, it requires individual calibration.

3.4.1.4. Status. The Internet site (see Table 1) reports that in 1996 research activity on the Dream Beam was stopped due to lack of funding, and field trials that had been planned at four eastern US hospitals were never done. This information, however, conflicts with that of a trial, at least initiated, in Chile in the 1998. Currently, Futrex Internet site is not advertising the meter any more.

3.4.2. GluCall, KMH Co. Ltd.

3.4.2.1. Description. The meter allows continuous glucose measurements in the interstitial fluid. It is worn like a wrist-watch and it is used with a single-use disposable sensor, which is attached to the backside of the meter case and is in contact with the skin. Each sensor provides up to three glucose measurements in 1 h for 6 h, giving up to 18 readings per use. To obtain the measurement a very low level of direct current is applied across the skin to get the interstitial fluid. Thanks to reverse iontophoresis the glucose in the interstitial fluid is extracted and collected into the two hydrogel disks in the sensor. Afterwards the extracted glucose reacts with the glucose oxidase (GOD) enzyme

immobilized in the hydrogel disks to form hydrogen peroxide (H_2O_2). Hydrogen peroxide is oxidized on a platinum electrode to produce electric currents. These signals are translated into an equivalent blood glucose level by a data conversion algorithm. The measuring range goes from 50 to 600 mg/dl. The meter has alarms for high and low glucose level, as well as for rapid changes.

3.4.2.2. Usability. The meter is comfortable to be used since it can be worn like a watch. It also has a large LCD display. Furthermore, the meter internal memory can store up to 8000 readings and special events can be marked. The readings can also be downloaded to a PC where a software tool allows easy data display and management. One drawback of the meter is that before performing the glucose measurements it needs about 1 h of warming period, and afterwards it has to be calibrated through a traditional blood glucose meter.

3.4.2.3. Status. No updated information can be found on the device. It is likely that the device has not reached any approval and is not on the market.

3.4.3. GluControl GC300®, ArithMed GmbH

3.4.3.1. Description. The meter monitors blood sugars in the 50–400 mg/dl range. Blood glucose values, time and date are automatically stored in the meter memory. It measures 17.6 cm × 11.6 cm × 6 cm, with a weight of 500 g.

3.4.3.2. Tests. It has been declared that clinical trials have been conducted in Germany, Japan and Korea, but no details are provided.

3.4.3.3. Usability. The meter does not require additional materials. It works with batteries.

3.4.3.4. Status. The meter was developed together with a Korean Company, Samsung Fine Chemicals Co. Ltd., but it is not clear the current meter status. A telephone and fax number is provided on the Internet site (see Table 1) for more information, but these references are not reported in the official Web site of Samsung Fine Chemicals. With regard to ArithMed, it seems that no Internet site is currently available.

3.4.4. Hitachi Ltd.

3.4.4.1. Description. Hitachi claims the development of a non-invasive blood sugar monitoring device based on the use of special sensors to detect physiological parameters related to human metabolism. In fact, extensive Company studies showed that thermal energy generated by metabolic reactions in the human body reflects a balance between blood sugar levels and local oxygen supply. Therefore, it is possible to determine the level of blood sugar by measuring the thermal energy generated by the metabolic reactions, together with other parameters, such as the level of oxygen saturation of hemoglobin and the blood flow. The meter uses sensors to measure various temperatures and light characteristics in the fingertip. The Company has in fact developed a complex sensor, which contains a contact thermometer, a radiation thermometer, and a multi-wavelength reflective photometer. To execute the test, the patient places a finger on the meter for 10 s and repeats the action 2 min later. The meter takes a further 2 min to display the results.

3.4.4.2. Usability. All the device units are integrated in a unique sensor, and hence the meter has a compact size that makes it easily portable and adequate for home use.

3.4.4.3. Status. The Company seems to be still working on the device and conducting clinical trials. However, in the original plans the market should have been reached already in 2005. No new dates are suggested.

3.4.5. Sysmex Corporation

3.4.5.1. Description. The meter has a wrist-watch format. The meter is based on a new fluid extraction technology developed by the Company, which is able to provide stable interstitial fluid samples, and on a glucose biosensor chip (developed by another Company, Toshiba) able to measure the little amounts of glucose in the interstitial fluid samples.

3.4.5.2. Usability. The compact format should allow a comfortable use.

3.4.5.3. Status. Commercialization was foreseen in 2005, but recent information is missing and the device seems to be still at prototype level.

3.4.6. TouchTrak Pro 200, Samsung Fine Chemicals Co. Ltd.

3.4.6.1. Description. The meter is a hand-held device, which measures blood glucose levels. Some sources of information indicate it as the first non-invasive glucose meter commercialized in the world (commercial production seems to have started in 1998, at a price around US$ 30,000). Another meter, cheaper (around

US$ 3000) and hence for personal, domiciliary use (TouchTrak HC 300) should have been developed and put on the market around the end of 1999. However, it was not possible to find further information on this second meter on the Internet.

3.4.6.2. Tests. It seems that in 1999 the Company was performing clinical trials both in Korea and in the US, but no further details were found.

3.4.6.3. Status. Due to the very little information, and provided that the Company Internet site, although existing, does not mention the meter, it has to be concluded that the project is currently abandoned, maybe also due to the fact that the Company has developed a different non-invasive glucose meter with ArithMed. Furthermore, since it seems that the device never reached approvals, there are doubts on its presence on the market even for a short period of time.

4. Conclusions

In this review, we presented a description of technologies and devices for non-invasive glucose monitoring. According to the indications of the HTA methodology, we carried out the analysis on the basis of clear and objective criteria. Some of the technologies have not been exploited in a device yet, while some others have led to a device at least in advanced prototype condition. It must be noted, however, that currently only three devices have reached a regulatory approval for commercialization in United States and/or Europe (apart from a couple of device whose approval condition is unclear, but it is probably not reached). Among these three, for different reasons two of them are not on the market anymore. The only available one (only in the US and in the UK) is the GlucoWatch, and in any case it cannot completely substitute a traditional meter. Furthermore, GlucoWatch is reported to possibly have some drawbacks: in fact, it sometimes causes skin irritation, and it may be uncomfortable to use in the daily life of the patients (it may be inaccurate in the case of changes in body or environmental temperature, in the presence of relevant movement, or if the patient is sweating). Sensitivity to those factors, often rapidly changing in the ordinary daily life, may be a limitation also for several other devices, especially for those designed to be wearable. In conclusion, the problem of non-invasive glucose monitoring is currently not solved, and further efforts are still necessary to reach the goal of having a reliable and inexpensive device for the benefit of the diabetic patient.

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