

*For debates***Non-invasive continuous glucose monitoring in Type I diabetic patients with optical glucose sensors****L. Heinemann<sup>1</sup>, G. Schmelzeisen-Redeker on behalf of the Non-invasive task force (NITF)**<sup>1</sup> Department of Metabolic Diseases and Nutrition, Heinrich-Heine-University Düsseldorf, Germany

Systematic self-monitoring of glycaemia represents a cornerstone in intensified insulin therapy. In fact, self-monitoring of blood glucose (SMBG) marks probably the most important advance in diabetes care since the discovery of insulin. However, at least two aspects make conventional SMBG difficult. Finger pricking to obtain the droplet of blood is regarded by many patients as even more daunting and painful than insulin injections [1]. On the other hand, spot measurements of blood glucose, even if performed several times daily, only provide an incomplete picture of the blood glucose changes occurring over the whole day. A continuous and reliable in-vivo glucose monitoring system would allow diabetic patients to check their metabolic control at their convenience. This would supply the diabetic patient with all information required to optimise insulin therapy and, possibly, to improve metabolic control. Furthermore acute metabolic deteriorations, such as hypoglycaemic episodes, should easily become detectable by a continuously working glucose sensor.

Several minimally invasive and non-invasive approaches have been studied to monitor blood glucose more or less continuously: 1) Implantable subcutaneous (s.c.) glucose sensors, 2) S.c. interstitial fluid sampling by microdialysis or open-tissue microperfusion, 3) Transdermal glucose monitoring systems, 4) Optical glucose sensors. The minimally invasive approaches (1 and 2) are based on the analysis of interstitial fluid. Insertion of electrodes into the s.c. tissue has not yet resulted in a glucose sensor that could be used reliably for longer periods of time in humans [2–5]. Lack of biocompatibility of the electrode surface results in drifts of the electrode signal, associated

with a loss of glucose sensitivity. The minimally invasive microdialysis technique and related techniques reduce such problems by pumping a perfusate through a dialysis fibre inserted in the subcutaneous tissue [6–10]. Glucose diffuses from the interstitial fluid into the perfusate and is measured *ex vivo*. In other approaches devices are attached to the skin to collect glucose containing fluid transdermally [11]. We will not review these minimally invasive approaches for glycaemic monitoring but will focus on non-invasive optical glucose sensors that avoid a number of the problems of former approaches. We will discuss the problems of reliable glucose monitoring using the spectrometric absorption technology and present a novel approach making use of the fact that the variation of blood glucose levels changes the light scattering properties of skin tissue.

**In-vivo glucose monitoring by light absorption measurement**

Some research groups are trying to develop non-invasive glucose monitoring systems based on absorption measurements [12–16]. Up to now, however, none has been converted into a reliable glucose monitoring system, although a number of companies have presented or announced glucose monitoring devices using similar approaches.

Spectrophotometry is an established method for the quantification of solutes in liquids. It is based on solute specific absorption bands in the visible (VIS), near infra-red (NIR) or mid infra-red (MIR) spectral range. Quantification of the solutes is possible by determination of light attenuation caused by absorption at a single wavelength when taking the light path length (i.e. the cuvette thickness) into account. The solution has to be clear, as light scattering would result in an additional attenuation of light.

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Quantification of a single solute in a complex mixture of substances is possible using various wavelengths and requires complex mathematical procedures like multivariate calibration. The more the spectra of the substances are different from each other, the better the reliability of such a quantification. Today the *ex vivo* quantification of glucose in complex matrices like plasma, serum or whole blood is feasible by using high performance spectroscopic equipment in combination with sophisticated mathematical calibration procedures [12, 14, 15, 17]. MIR radiation is particularly appropriate for such measurements because glucose specific absorption bands are prominent in this frequency range. Thus, it can be expected that it is also possible to use spectrophotometric approaches to measure glucose non-invasively in the skin.

Water, however, as the main tissue constituent and many other components of skin, absorb MIR radiation very effectively. Hence, the *in-vivo* penetration depth of MIR-light in skin is low [15]. In contrast, light in the NIR and VIS region penetrates to deeper blood perfused skin layers potentially allowing for glucose monitoring (“optical window”) and glucose exhibits no specific absorption properties in this frequency range. If tissue thickness is low, transmission spectra can be recorded. Otherwise only diffusely reflected light intensity has to be used.

The current status of blood glucose monitoring in human skin by near infra-red absorption measurements using different spectrophotometric methods has been reviewed recently [15]. Although non-invasive determination of blood glucose by some of these methods seems to be possible, none of them allows for a sufficient precision within the clinically relevant blood glucose range. The question arises, as to why none of these attempts has been successful so far.

Besides profound methodological problems with the calibration methods necessary for the analysis of absorption measurements, any spectrometric estimation of glucose in skin faces a number of problems [18]:

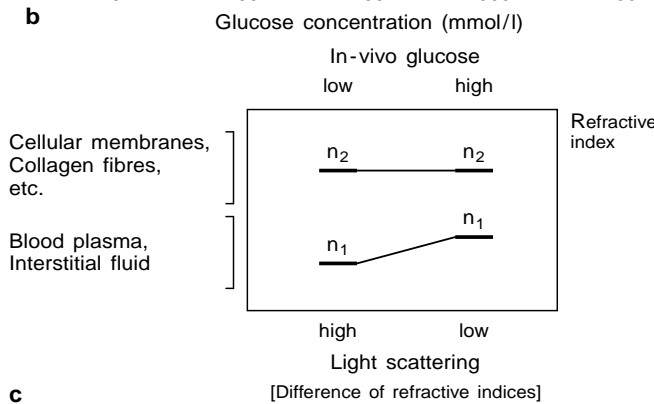
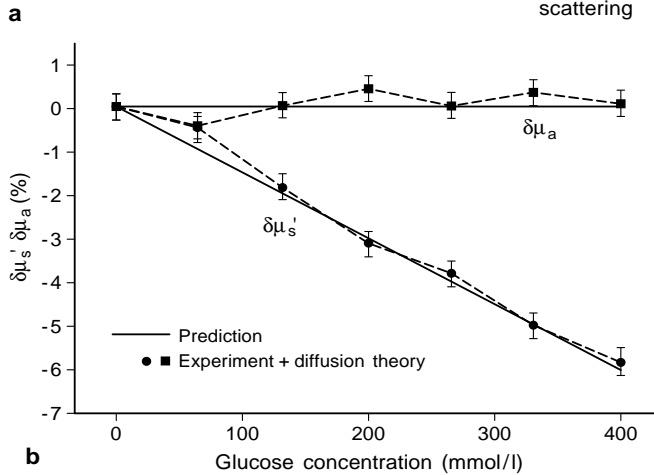
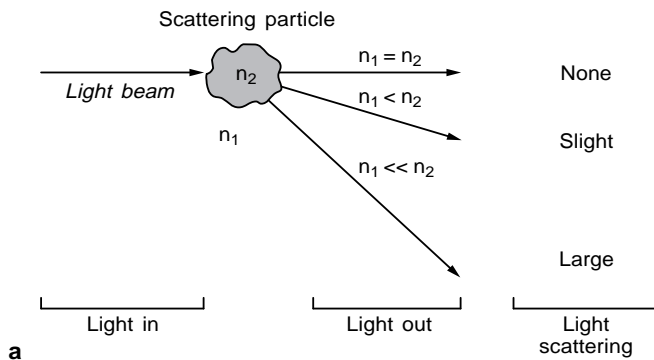
- significant scattering of light
- heterogeneous distribution of light absorbing and light scattering structures which additionally are variable over time (in part due to changes in blood supply and blood oxygenation)
- unknown path length of light in skin
- heterogeneous glucose distribution in skin (intracellular/interstitial/blood)
- presence of many other interfering light absorbers (like water) in much higher concentrations
- very similar absorption spectra of water and glucose
- pronounced temperature dependence of light absorption

The problems listed highlight the complexity of non-invasive blood glucose estimations based on spectrophotometric approaches. The small effect of blood glucose changes on light absorption in the NIR region has to take into account a number of interferences which hamper blood glucose monitoring by means of the light absorption technique. In search for alternatives, we evaluated the feasibility of light scattering the measurement as a new approach to glucose monitoring.

### **Glucose monitoring by light scattering measurement – *in-vitro* experiments**

Next to light absorption light scattering is the other major optical interaction mechanism in tissue. For the main part, light scattering in tissue is caused by the so-called Mie scattering that takes place when the size of the scattering particles and the wavelength of light are in the same order of magnitude. In tissue, Mie scattering mainly originates from the passage of light through the boundary between media with different refractive indices. This situation can be simulated *in-vitro* in suspensions of small scattering particles in aqueous solutions, e. g. a turbid suspension of fat droplets in water (that is the reason, why milk is white and not transparent). The scattering properties strongly depend on the ratio of the refractive indices of the scattering particles and the solute in a suspension (Fig. 1 a). If the ratio of the refractive indices decreases, the scattering properties are decreased as well. When there is a perfect match of both refractive indices the scattering suspension becomes transparent.

In a series of *in-vitro* experiments the effect of glucose concentration on scattering coefficient of aqueous turbid suspensions were studied [19, 20]. The main results were, an increase of the glucose concentration leads to a decrease in the scattering coefficient of the suspension (i. e. it becomes more transparent). The relative change of the scattering coefficient of the suspension upon a change of the glucose concentration depends on the refractive index of the scattering particles: the smaller the difference in the refractive index of the scattering particles and the solute the more pronounced is the effect of a glucose concentration change on scattering coefficient. Thus, the “glucose sensitivity” of the suspension depends on the refractive index of the scattering particles. For example, in a suspension of particles with an extreme high refractive index (polystyrene particles with a refractive index of 1.58) an increase in glucose of 100 mmol/l induces a decrease in the scattering coefficient of 1.5 % (Fig. 1 b). For the range of blood glucose concentrations common in diabetic patients, the effect on scattering coefficient is extremely small. Nevertheless, as the suspected scattering particles in tissue (e.g. membranes, subcellular structures, col-

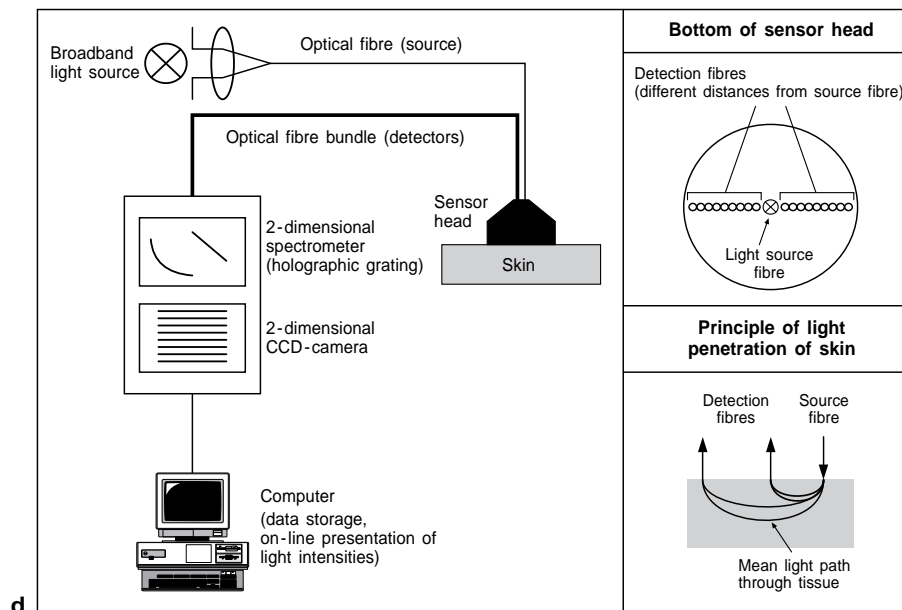


lagen fibres) have much lower refractive indices, the glucose effect on scattering coefficient is expected to be considerably higher (5–10 times [19, 20]).

### Glucose monitoring by scattering measurement – in-vivo situation

In tissue, the light scattering structures are surrounded by blood plasma, interstitial fluid and intracellular fluids, each having specific refractive indices. The refractive index of most of the scattering particles in tis-

**Fig. 1.** **a** Light scattering in turbid media depends on the ratio between the refractive index of the solvent ( $n_1$ ) and the scattering particles ( $n_2$ ). If the difference between the refractive indices is pronounced, light scattering is large. With identical refractive indices the media is transparent. **b** The scattering coefficient of an aqueous suspension of polystyrene particles decreases with increasing glucose concentration ( $\delta\mu_s$ ; relative change of scattering coefficient) at a wavelength of 804 nm (19). In contrast, variation of the glucose concentration does not cause a change in absorption coefficient ( $\delta\mu_a$ ). **c** An in-vivo increase in glucose raises the refractive index of blood and interstitial fluid ( $n_1$ ). In contrast, the refractive index of the scattering particles in the skin ( $n_2$ ) is not affected. Consequently, light scattering of the skin is lower, because the difference of the refractive indices is reduced. **d** Output from a broadband light source was directed down an optical fibre to the sensor head into the skin. The diffusely reflected light was transferred back via an optical fibre bundle with a number of detection fibres and was imaged through a two-dimensional spectrometer onto a two-dimensional CCD camera. This allows spectral information to be obtained for each detection fibre simultaneously. Data were stored in a computer and light intensity profiles were shown on-line on the computer monitor. The detection fibres were located at different distances from the source fibre to obtain spatially separated information, depending on the penetration depth of the light into the skin



sue is assumed to be constant over time. In contrast, composition of tissue liquids can vary rapidly, changing their refracting indices. Each variation in the difference of the refractive index between the scattering particles and the liquids leads to a variation in the 'transparency' of the tissue, since light scattering is changed (Fig. 1 c).

In dermis approximately 50% of the volume fraction consists of collagen and elastic fibres (assumed to be the prominent scattering structures) and interstitial fluid accounts for approximately 45%. Only a small fraction is constituted of cells and blood vessels. Due to the free exchange of glucose between blood and interstitial fluid, changes in glucose concentrations of these body fluids are closely correlated. Since the refractive index of interstitial fluid is lower than that of the scattering structures an increase in glucose concentration causes a reduction of the refractive index differences between fluid and scattering structures. In effect, the light scattering coefficient of skin is decreased due to an increase of blood glucose concentration. In contrast to the spectrometric approach, changes in the scattering properties of skin are not directly due to different glucose concentrations, but to the indirect effect of a refractive index change of body fluids. The glucose effect on scattering coefficient described is not due to the glucose molecule per se.

The in-vitro observations and theoretical considerations indicate that changes in blood glucose of 5.5 mmol/l result in changes of the light scattering coefficient in the order of 1% [19, 20]. Thus, it seems reasonable to assume that variations of blood glucose concentrations can be monitored continuously by measuring light scattering properties of skin tissue. The aim of our studies was to investigate whether this assumption can be confirmed by in-vivo studies. If this concept can be substantiated, this approach might be suitable for continuous non-invasive blood glucose monitoring.

## Material and methods

*Methodological approach to measure the light scattering coefficient of the skin.* To measure scattering coefficients a narrow beam of light was directed through the skin surface into skin tissue. As a result of the interaction of light and tissue a certain fraction of the light is diffusely reflected back to skin surface. The intensity of light returned from skin tissue depends on both the scattering coefficient and the absorption coefficient of skin. By measuring light intensity at different distances from the light entry point, a light intensity profile (intensity vs distance) was registered. The intensity of diffusely reflected light leaving the skin nearby the light entry point reflects mainly scattering properties of skin. At greater distances scattering and absorption have a comparable influence on light intensity. Appropriate algorithms allow for the differentiation of the effects of light scattering and light absorption on the light intensity profiles [20, 21]. The calculation of the scattering coefficient

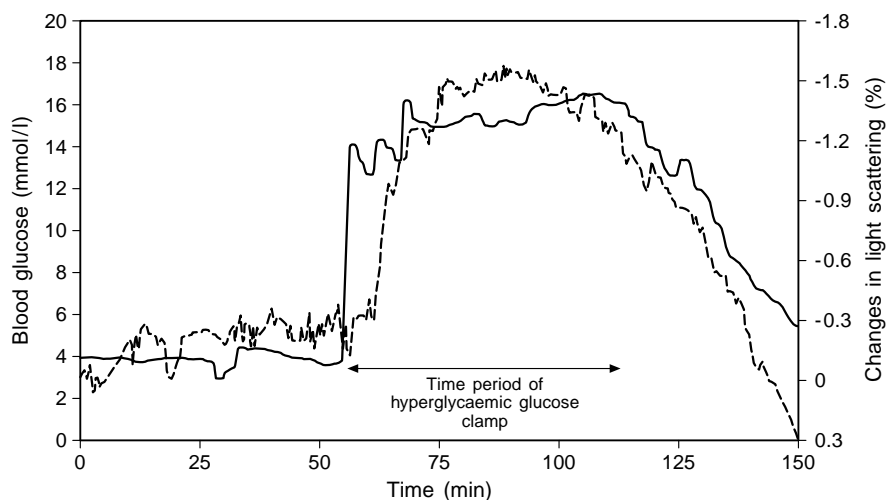
from the light intensity data was done off-line based on light diffusion theory [21]. Changes in the scattering coefficient are assumed to be glucose dependent.

We conducted several studies using two different experimental set-ups (laboratory models for research studies): 1) A fibre optic set-up of a large bedside system (consisting of light source, spectrograph, camera and fibre probes, for additional information see below) allowing variation of a number of technological parameters (wavelength, number and position of detectors etc.), 2) A small system with restricted options which could be worn by the volunteer. To measure tissue reflectance the sensor head (consisting of light source fibre and detection fibres) of the bedside system was attached directly to the abdominal skin by means of an adhesive tape (Fig. 1 d). In detail, the bedside system operates in the following way: Output from a broadband quartz-tungsten-halogen light source (source: photometric power supply model 68831 with a DC regulated broad band QHT source; housing: Series Q, convective lamp housing model 6000; both from L.O.T. Oriel, Darmstadt, Germany) was directed down the source fibre to the sensor head into the skin. The diffusely reflected light was transferred back via the 8 or 16 detection fibres (number depended on the design of the sensor head) and was imaged through a two-dimensional spectrometer (HS-f/2.2i-NIR, Kaiser Optical Systems Inc., Ann Arbor, USA) onto a thermoelectrically cooled CCD camera (TE/CCD 1242E; wavelength range recorded: 650–950 nm; with the camera controller ST 138S; both from Princeton Instruments, Trenton, USA). This allows spectral information of each detection fibre to be obtained simultaneously. Data were stored in a computer and light intensity profiles were shown on-line on the computer monitor. Skin temperature was monitored continuously throughout the experiments.

A first laboratory type version of a portable non-invasive glucose monitoring system was also studied. This device had two optical sensor heads, a small box containing the batteries and electronics for the measurement and an additional electronic memory (all components were self-constructions by Boehringer Mannheim, Mannheim, Germany). Each head had four light emitting diodes transmitting light of different wavelengths into the skin through the same light entry point. Six photodetectors were located at distances between 0.8 to 5.2 mm from the light entry point. Separation of the absorption coefficient and the scattering coefficient has not been possible with the portable device so far, but will be feasible in future versions.

## Preliminary results

*Separation of absorption coefficient and scattering coefficient.* The key factor for the success of our approach for glucose monitoring is the precision of the scattering coefficient measurement. Since variations of light absorption in tissue (e.g. caused by blood volume changes) affect the intensity of diffusely reflected light it is necessary that the measurement of scattering coefficient is independent of variations in absorption. In order to evaluate the separation of scattering coefficients from variations in absorption coefficients, indocyanin green was injected i.v. into healthy nearly motionless volunteers. Changes in light intensities upon passage of the dye through the cutaneous blood vessels were recorded. After indocyanin



**Fig. 2.** Blood glucose was increased in a Type I diabetic patients during a glucose clamp experiment from euglycaemic to hyperglycaemic values and back again (—). This leads to parallel changes in the light scattering coefficient of the skin (---). For better visualisation of the correlation between blood glucose and scattering coefficient, the calculated scattering coefficient is inverted

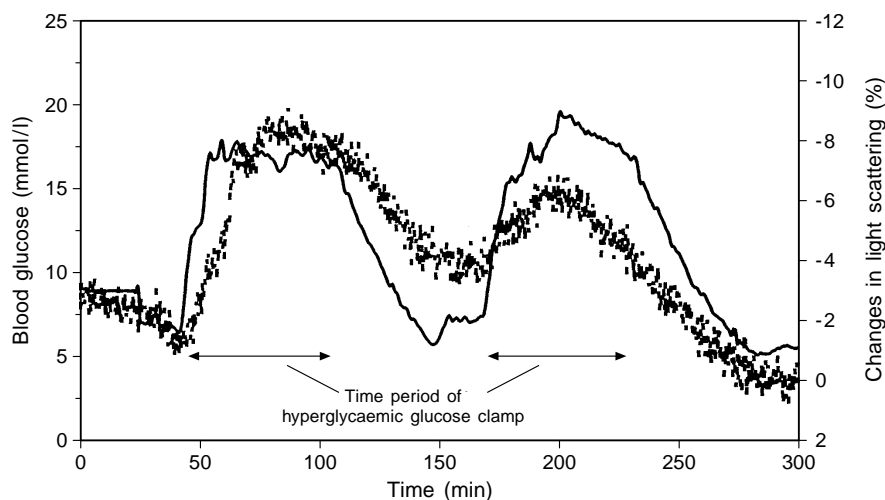
anin green injection the absorption coefficient at 800 nm (absorption maximum of this substance) increased considerably. Some minutes later the absorption coefficient returned to baseline level due to rapid hepatic clearance of the dye. Simultaneously, no significant variation in the scattering coefficient took place indicating a sufficient separation of the scattering measurement from the absorption measurement.

*Detection of glucose – glucose clamp experiments.* In a series of experiments with Type I diabetic patients blood glucose was kept constant at different levels during glucose clamp experiments with a Biostator (glucose-controlled insulin infusion system, Life Science Instruments, Elkhart, Indiana, USA). To investigate whether a change in blood glucose has an impact on the scattering coefficient of skin, glycaemia was kept constant at an euglycaemic level (5.5 mmol/l) for 60 min. Subsequently, glycaemia was increased rapidly to a hyperglycaemic level (15.0 mmol/l) and lowered again to the euglycaemic level (also 60 min at both levels). Parallel to the variation in blood glucose we observed a change in the scattering coefficient of the skin: the increase in glycaemia caused a decline in the light scattering coefficient of skin (Fig. 2) [22]. The calculated scattering coefficients were not subject to any calibration, however, they were adjusted in magnitude to fit graphically to the registered changes in glycaemia. The decline in the scattering coefficient observed in seven experiments (approximately 1.0% per 5.5 mmol/l increase of glucose) was in accordance with values predicted from

theoretical and in-vitro studies [19, 20, 23]. Changes in the scattering coefficient were more or less independent of the wavelength used. No glucose related changes of the absorption coefficient for the wavelengths studied were observed. Infusion of pure saline with infusion rates comparable to those in the glucose clamp experiments did not lead to relevant changes in the scattering coefficient.

Intra-individual reproducibility of the changes in the scattering coefficient was studied by increasing blood glucose rapidly to hyperglycaemic values and lowering it again to euglycaemic values repeatedly within one experiment. The time periods at the two different glycaemic levels (usually at least 60 min) and the number of hyperglycaemic episodes (2 or 3) during the clamps were varied in different sets of experiments. Again, the increases in glycaemia in this study resulted in a reproducible decline in the scattering coefficient (Fig. 3). The inter-individual responses varied considerably, i. e. the magnitude of the relative changes of the scattering coefficient differed. This can be seen in Figure 2 and 3. Moreover, as indicated in Figure 3, the intra-individual responses to similar glucose steps were different. This can be attributed to the drift phenomena described below. Such drifts also influenced the time relationships between changes in blood glucose and scattering coefficient (compare Fig. 2 and 3). Despite the differences in blood glucose response our experiments showed that its excursions correlated reproducibly with changes of the scattering properties of human skin.

The changes in light intensity measured during the glucose clamps with the portable device were in accordance with the changes recorded with the bedside set-up. Glucose related changes in light intensity measured at different areas of the abdominal skin suggest that at least in this area of the body the exact location of the sensor head on the skin is of minor importance. However, orientation of the sensor head on the skin has a profound influence on light intensity recorded.



**Fig. 3.** Repeated changes in blood glucose (—) during another experiment with a Type I diabetic patient reproducibly led to comparable changes in the light scattering coefficient (---) of the skin

*Glucose independent changes in scattering coefficient.* In order to assess the feasibility of a continuous glucose sensor it is necessary to know the general variability of the scattering coefficient under stable glycaemic conditions. For that purpose the time course of light scattering in healthy volunteers was investigated. In a series of 30 experiments it was shown that considerable variations of the scattering coefficient (up to 2% in 4 h) take place under euglycaemic conditions. During the experiments the volunteers moved as little as possible, similar to the glucose clamp experiments. The glucose independent light scattering variations may be due to factors such as variable hydration of skin layers, rearrangement of tissue structures (e.g. diameter of blood vessels, swelling of stratum corneum), changes of the sensor/skin interface and skin temperature. For example, skin temperature variations induced by local heating of skin were shown to change scattering coefficients linearly by 1%/°C (temperature range: 25–28°C). Preliminary results of studies with recently developed devices indicate that the sensor/skin interface is a major source of the observed drifts.

## Discussion

Our results demonstrate that variations of blood glucose in diabetic patients induce respective variations in light scattering of skin. The results can be regarded as a substantiation of concept that a continuous non-invasive blood glucose monitor based on scattering coefficient determination might be feasible. Nevertheless, the glucose independent variations of the

scattering coefficient of skin are a major obstacle for the development of a reliable non-invasive glucose monitor. It is mandatory to reduce profoundly the effect of glucose independent processes on the determination of scattering coefficient. This could be done by modified sensor geometry, optimised attachment conditions of the sensor head to skin or by modifications in the algorithms of scattering coefficient calculations.

Of course, the results do not provide definitive evidence that the described effect of glucose on refractive indices is the only cause of glucose related variations in light scattering. Other physiological processes taking place simultaneously with blood glucose variations might be involved as well. This issue can be reliably addressed only after considerable advances in the reduction of those variations of scattering coefficient which are independent of glucose have been achieved. Nevertheless, the accordance of the observed in-vivo sensitivity of the glucose effect on scattering coefficient with theoretical considerations and experimental in-vitro results indicate that the variation of the refractive index of body fluids is a predominant factor for glucose related variations in light scattering of skin tissue [19, 20, 23].

In comparison with spectrophotometry, the scattering approach is more sensitive in respect of glucose variations [19, 20]. It does not need any specific absorption bands of glucose since the scattering coefficient in the VIS/NIR wavelength range is relatively independent from wavelength. Thus, there is no restriction to glucose specific absorption bands and the most advantageous wavelength can be used. Relatively simple and cheap light sources and light detectors that emit and detect discrete wavelengths in the NIR-range can be used. Another advantage of this approach is that variations in light absorption (e.g. due to blood volume or blood oxygenation changes) affect the scattering properties of skin to a minor degree. In contrast, scattering is a major obstacle for spectrophotometry.

Due to a considerable local variability of the 'base line' absolute scattering coefficient in skin, individual in-vivo calibration of the scattering signal after attachment of the sensor to the skin by a conventional measurement of the actual blood glucose concentration will be necessary at regular intervals. Nevertheless, the measurement of relative changes of the scattering coefficient should allow diabetic patients to monitor glucose levels continuously over time, providing the advantages associated with such a measurement.

In conclusion, our preliminary studies suggest a possibility of monitoring variations of glucose concentration in extracellular fluid non-invasively and continuously by measuring the scattering properties of human skin. Nevertheless, the substantiation of the concept does not guarantee that it will be possible to develop a practical and applicable optical glucose sensor device though its availability would be of great help to diabetic patients.

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