Editorial

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Innovative approaches in diabetes diagnosis and monitoring: less invasive, less expensive... but less, equally or more efficient?

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Criteria for screening, diagnosing and monitoring diabetes mellitus rely on well-defined protocols, which have been based for decades on venous (for screening/diagnosis) or capillary (for monitoring) glucose determinations. It is now well admitted that HbA_{1c} may also be used in current practice, not only for monitoring but also for diagnosis of diabetes [1]. HbA_{1c} is a typical product of non-enzymatic glycation, a general process that refers to the irreversible binding of simple oses or their by-products to proteins. In particular, HbA_{1c}, which results from the binding of glucose to the N-terminal extremities of globin β chains, retrospectively reflects the cumulative binding of glucose to hemoglobin depending on glycemia levels during the 4–8 weeks preceding the assay [2]. Although there is still some debate on the respective use of the two biomarkers, these recommendations indicate that both instantaneous glucose concentrations and integrated markers of glycation can be used in these circumstances, both approaches seeming equally efficient in providing valuable clinical information.

However, although these worldwide strategies have been established, the development of new approaches using innovative methods of protein glycation evaluation cannot be disregarded. Two types of reasons justify this research: (i) economical constraints, especially in developing countries, and (ii) implementation of non invasive techniques. In this issue of *Clinical Chemistry and Laboratory Medicine*, Monteyne et al. [3] describe a technique of near-infrared (NIR) spectroscopy for evaluating glycation in nails meeting the two criteria.

It has been shown for several years, especially using *in vitro* approaches, that physical methods like infrared (IR) or Raman spectroscopies could be valuable tools for evaluating protein glycation [4–6] or other nonenzymatic posttranslational modifications (NEPTMs) like carbamylation [7]. Spectroscopic methods provide specific spectra reflecting structural characteristics of proteins, especially regarding secondary and tertiary structures, which are

altered by NEPTMs-induced changes, especially in the case of glycation [8]. For example, Raman spectroscopy has proved to be able to distinguish between spectra generated by glycated and non glycated forms of both hemoglobin [9] and albumin [4], allowing the development of semiquantitative methods for glycation evaluation. Different applications of IR spectroscopy have also been applied to the detection of glycation-induced changes in proteins. Before the present publication, the same team had evaluated the ability of attenuated total reflection Fourier-transform infrared (ATR-FTIR) spectroscopy to detect glycation on the same materials [10]. However, this approach required that the nail clippings are powdered prior analysis, thus limiting its use in a routine practice. The NIR equipment used in the present publication may be connected to optic fibers allowing the analysis to be directly performed on complete fingernails, which makes this method more convenient and suitable for a routine practice [3].

The use of nails as primary materials is also an interesting approach. It is well known that glycation products, especially advanced glycation end products (AGEs), accumulate in extracellular matrix-rich tissues like skin, and that their evaluation provides an integrative retrospective view of glycemic control on long time periods, depending on the half-life of constituting proteins [11, 12]. As these investigations generally require biopsies, they cannot be carried out in current practice. However, original non-invasive investigations, precisely using spectroscopy, must be mentioned, such as those performed on human lips with a FTIR spectroscopy device [13]. Practically speaking, nails constitute valuable materials because they can be obtained without causing skin damage. Besides, they are physiologically more relevant than other easy-to-obtain samples like hair because they are continuously in close contact with blood vessels and interstitial fluid [14]. Nail protein glycation has been proposed as marker in diabetes more than 30 years ago [15]. However, the application in clinical settings had rarely been proposed [16] until the authors of the commented paper proposed different new

strategies to assess glycemic control in African countries [3, 14, 17]. All these studies used nail clippings as materials for evaluating glycation, not only by spectroscopic methods but also by assaying fructosamine directly on the nail samples [17]. In the latter case, nail clippings were simply dipped into a fructosamine assay reagent, providing a simple way to measure protein glycation, especially suitable for countries with low economical outcome. The present study has the additional advantage to be performed without needing any reagent.

The paper published in this issue focuses on the application of NIR spectroscopy to the diagnosis of diabetes mellitus, claiming that it could be considered an alternative technique. However, broader applications could be considered because these approaches could also constitute valuable tools in diabetes follow-up. The road has been opened several years ago with the non-invasive measurement of skin autofluorescence as a direct reflect of skin glycation due to AGE deposition [18]. As a matter of fact, this measurement has proven to be a valuable mean to assess patient “metabolic burden”, and skin autofluorescence has been shown to be correlated with systemic AGE concentrations and to the development of various diabetes mellitus complications [19, 20]. The physical spectroscopic methods described here could also represent promising applications for non-invasive investigations.

Thus, this approach and comparable ones are promising and should lead to new developments. However, their use must still be considered preliminary in clinical situations, and there is probably a long way before their use in routine. Indeed, many markers of glycation, especially AGEs, have been proposed in the last decades for providing additional information to established biomarkers in the follow-up of patients with diabetes mellitus [21, 22]. However, because of the lack of method comparison, harmonization or standardization [23], the use of these promising markers remains limited [24]. Comparable remarks apply to this NIR spectroscopy method and other similar ones. Glycation-induced spectral changes have clearly been evidenced, allowing the use of the method in clinical situations, but the subtle molecular changes responsible for spectral alterations have not yet been clearly identified. Therefore, at that step, the method is only qualitative allowing discriminating between diabetic and non-diabetic subjects, but challenges related to the establishment of reliable and transferable quantification procedures have still to be faced. Indeed, the ability of these methods to provide quantitative information is a key factor for reaching the intended clinical purposes. When this goal is reached, calibration processes must be

established with suitable materials and procedures, and then harmonized in order to allow between-center comparability of results. Such pitfalls limit the comparisons of results from autofluorescence measurements, which can however reach a satisfactory degree in precision when performed in a single center. Additional aspects have to be considered like the expertise of the operators, which must be strictly assessed and controlled, and the costs of the devices, which must be taken into account in the economical assessment, even if they are eventually paid off.

To conclude, screening, diagnosis and monitoring of diabetes mellitus will probably benefit in the future from the input of new methodological approaches, like the NIR spectroscopic method described here. However, their strengths, relying mainly on their non-invasiveness and their low cost, must be considered in light of their currently limited quantitative properties and the necessary demonstration of their effectiveness for clinical purpose when compared to currently accepted methodologies and protocols. A long way of stimulating experimentations is still to go!

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