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SHORT REVIEW

Assessment of advanced glycation end-products as a biomarker of diabetic outcomes

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Abstract There are substantial differences in the onset and severity of diabetes complications that are not fully explained by HbA1c levels and other risk factors. HbA1c is the gold standard for assessing metabolic control, but has limited value to identify patients at risk of developing diabetic complications. The main disadvantage of HbA1c is that it does not provide information about glycemic variability and does not reflect long-term exposure to hyperglycemia. One of the main pathogenetic mechanisms of diabetic complications is the generation and accumulation of advanced glycation end-products (AGEs). Based on its fluorescence properties, AGEs may be measured in tissues such as the skin or lens. These non-invasive measurements of AGE accumulation may be considered as promising biomarkers of late diabetic complications, and our objective is to summarize the available evidence supporting this statement. However, further translational research and prospective clinical trials are needed before these new biomarkers may be incorporated into clinical practice.

PALABRAS CLAVE
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Evaluación de forma no invasiva de los productos avanzados de la glicación como biomarcador de las complicaciones de la diabetes

Resumen La determinación de HbA_{1c} es el «estándar de oro» para evaluar el control metabólico de los pacientes con diabetes, pero tiene limitaciones en identificar los pacientes riesgo de desarrollar complicaciones. Los inconvenientes de la HbA_{1c} son que no proporciona información acerca de la variabilidad glucémica y no refleja la exposición a largo plazo a la hiperglucemia. Uno de los mecanismos patogénicos de las complicaciones de la diabetes es la acumulación de productos avanzados de la glicación (AGE). Basándose en sus propiedades

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fluorescentes, los AGE pueden determinarse en tejidos como la piel o el cristalino. Estas determinaciones no invasivas podrían contemplarse como biomarcadores de las complicaciones de la diabetes, y nuestro objetivo es resumir la evidencia disponible en referencia a ello. Sin embargo, es necesaria una mayor investigación traslacional en este campo, así como estudios prospectivos antes de que estos métodos puedan ser incorporados a la práctica clínica.

Introduction

The prevalence of diabetes is increasing worldwide and if this trend continues by 2045, 693 million people will have diabetes especially in developing countries. The burden of diabetes mellitus for both patients and society comes from the vascular complications of the disease, cardiovascular disease being a major cause of death and disability in patients with type 2 diabetes. Moreover, diabetic retinopathy is still the leading cause of vision loss in working age adults, the prevalence of ESRD (end-stage renal disease) is also up to 10 times higher in people with diabetes as those without, and diabetes is the main cause non-traumatic amputation.[1]

Limitations of HbA1c as biomarker of diabetes outcomes

The measurement of HbA1c has been the gold standard for metabolic control. However, the DCCT/EDIC Research Group showed that HbA1c values explained up to 11% of the risk of diabetic retinopathy, and that the unexplained 89% of variation in risk was due to elements of the diabetic milieu not captured by mean HbA1c value.[2,3]

The reasons why HbA1c cannot be considered a good biomarker of diabetic complications are as follows:

HbA1c does not reflect long-term hyperglycemic exposure

There is growing evidence to suggest that ''metabolic memory'' plays an important role in the development of long-term metabolic complications in both type 1 and type 2 diabetic patients.[4] HbA1c only represents the mean level of glycemia over the previous 3 months, but not the long-term exposition to hyperglycemia. Therefore, the use of new biomarkers that reflect the accumulated exposition to hyperglycemia could be useful to predict diabetes outcomes.

HbA1c does not provide information on glycemic variability

HbA1c does not provide information about the intensity of fluctuations of blood glucose levels. Glycemic variability, and in particular hyperglycemic spikes could be high enough to activate complication-causing mechanisms but too brief to affect the HbA1c value.[5] In fact, based on the available evidence it appears that glucose variability, which is not captured by HbA1c, could be a predictor of micro- and macrovascular complications as well as mortality among type 2 diabetic patients.[6]

Among the main metabolic pathways involved in the pathogenesis of late diabetic complications (i.e. oxidative stress, inflammation, AGEs), the measurement of AGEs seems the most appropriate for assessing the genuine effects of chronic hyperglycemia. The measurement of parameters related to oxidative stress and/or inflammation would also be interesting but their assessment could be significantly influenced by non-diabetic conditions (i.e. obesity, insulin resistance state) or intercurrent diseases. In addition, the different methods for determining the degree of oxidative stress or the inflammatory status inform us regarding the situation in real time rather than reflecting a sustained metabolic fingerprint. By contrast, AGEs have been implicated in the long-term nature of metabolic memory[4] and their assessment takes into account cumulative glycemia exposure and glycemic variability,[7] thus overcoming the limitations of HbA1c as a biomarker for diabetic outcomes. The objective of this review is to summarize the evidence available regarding AGEs assessment as a biomarker for diabetic complications, focusing on non-invasive techniques for its measurement. For this purpose, a comprehensive literature search of the electronic MEDLINE database was performed between August 2017 and November 2017 using Pubmed search service and the relevant articles (both originals and reviews) have been included.

AGEs as potential biomarkers of diabetes outcomes

The non-enzymatic glycation reaction is known to be one of the most significant mechanisms contributing to tissue damage that occurs in diabetes. It involves a series of chemical reactions that lead to the formation of early glycation products (like HbA1c), alpha-dicarbonyls, which are directly toxic and precursors of AGEs. Advanced glycation occurs over a prolonged period, affecting long-lived proteins, like structural components of the connective tissue matrix and basement membrane components. AGE accumulation contributes to diabetic complications through direct tissue damage, as well as through the activation of specific AGE receptors (RAGE). As a result of AGE-RAGE interaction, ROS production is incremented

and nuclear transcription factor NF-κβ is activated, thus promoting the transcription of several inflammatory mediators that have been implicated in diabetic complications.[8,9]

The plasmatic determination of AGEs, in particular N-ε-carboxymethyl lysine (N-ε-CML) and pentosidine, have been proposed as biomarkers for diabetic complications.[8] In fact, a positive association between serum levels of AGEs and the progression of atherosclerosis in common carotid artery,[10] renal failure[11] and diabetic retinopathy[8] has been reported. For example, Boehm et al.,[12] in a case-control study observed that elevated N-ε-CML was associated with proliferative diabetic retinopathy with an odds ratio of 24.5. In addition, increased plasma levels of AGEs were found to predict incident cardiovascular disease and all-cause mortality in a population with type 1 diabetes with a Hazard Ratio of 1.3 and 1.27, respectively.[13] Furthermore, in a recent prospective study, circulating AGEs were associated with the extension and severity of subclinical atherosclerosis in type 2 diabetic patients.[14] In this study, they found an association between three AGEs (glyoxal hydroimidazolone, 3-deoxyglucosone hydroimidazolone and N-ε-CML) and coronary artery calcification. These results remained significant after adjusting for age, duration of diabetes, race/ethnicity, study treatment assignment, smoking, history of cardiovascular disease and hypertension. It should be mentioned, that they also found a positive association between 2-aminoipic acid, an oxidative stress product, and coronary artery calcification. As previously mentioned AGE-RAGE interaction increases oxidative stress. At the same time, oxidative stress products accelerate AGE formation increasing the risk of presenting diabetic complications.[15–17] In this regard, the non-invasive measurement of oxidative stress parameters in the saliva of diabetic patients has been associated with a worse metabolic control and with a higher prevalence of periodontal disease.[16,17]

In a small but very illustrative study, plasma levels of two AGEs (nitrotyrosine and glyceraldehydes-derived AGE) were correlated with the mean amplitude of glycemic excursions, which was associated with more severe coronary artery disease. It is worth mentioning that the mean value of HbA1c was below 6% in all patients included in this study.[7]

However, biochemical and immunochemical assays for circulating AGE determination are complex, time-consuming, expensive and have a low reproducibility.[18] In addition, there is a significant variation with renal function in terms of an increase of AGEs associated with a reduction of glomerular filtration).[8] All these reasons limit their use in current clinical practice.

In recent years, tandem mass spectrometry has considerably facilitated the use and improved reproducibility of the assay for several AGEs. Nevertheless, serum AGEs do not necessarily reflect tissue AGE levels, as they depend on the half-life of these proteins, and in those tissues where diabetic complications develop there are also those where long lived proteins are present.[18] Therefore, it seems more reliable to measure AGEs accumulation in accessible tissues where long lived proteins are present.

Assessment of AGE accumulation in accessible tissues

Based on the fluorescent property of some AGEs, new non-invasive methods for their detection have been developed: skin and lens autofluorescence. The detection of AGEs in these tissues adds an advantage to its plasma determination. This is because lens crystallins and skin collagen are long lived proteins as a result of a low turnover. Therefore, AGEs accumulation in these proteins represents cumulative long-term glycaemia exposure.[19]

Skin autofluorescence as a biomarker for diabetic outcomes

The accumulation of AGEs in the skin (measured in skin biopsies) predicted the progression of microvascular complications in type 1 diabetic patients in a 10-year prospective study. It is worth mentioning that the predictive effect of HbA1c disappeared after adjustment for AGE levels.[20]

Skin autofluorescence (SAF) measurement using an excitation light source is a simple non-invasive examination, takes only a few minutes and has a strong correlation with the content of AGEs (including the aforementioned pentosidine and N-ε-CML) in skin biopsies.[21] There are many studies, both in type 1 and type 2 diabetic subjects exploring SAF and its association with diabetic outcomes. In type 1 diabetic subjects SAF has been associated in cross-sectional studies with the presence of subclinical atherosclerosis, coronary artery disease (OR 3.5), diabetic retinopathy, diabetic neuropathy and diabetic nephropathy (with an OR of 3.13 for the presence of any of these microvascular complications).[22,23] Moreover, in a longitudinal study (4 years of follow-up) performed in T1D, SAF predicted incident macrovascular events (OR 4.84) after an adjustment for cardiovascular risk factors.[24] Likewise, in type 2 diabetes, SAF has been associated with microvascular complications and subclinical atherosclerosis.[25,26] However, a single measurement of HbA1c and self-assessed diabetes duration was not associated with the presence of diabetic retinopathy[25] or macrovascular disease.[26] Moreover, in a prospective study within a cohort of T1D subjects that were recruited just after the onset of diabetes, SAF was associated with the mean of HbA1c values obtained after 15 years of follow-up.[23] These observations indicate that SAF measurement takes into account the cumulative exposition to hyperglycemia rather than the last few months

Although SAF correlates with the accumulated AGEs in skin biopsies and is associated with atherosclerosis, a correlation between SAF and the presence of AGEs in the arterial walls has not been proven. Schleicher et al.,[27] found that the presence of AGEs in the atherosclerotic arteries presented a similar immunostaining both in diabetic and non-diabetic patients. Moreover, in a cross-sectional study, 56 non-diabetic subjects with carotid artery stenosis age and sex matched with healthy control presented significantly elevated values of SAF measurement (2.81 versus 2.46). The difference was higher in patients with both

carotid stenosis and peripheral artery occlusive disease.[28] Likewise, Sanchez et al.[29] observed that a SAF value higher than 2 AU (arbitrary units) in a assymptomatic non-diabetic population determined a 3-fold increased risk of presenting an atheromathous plaque (assessed by carotid and femoral ultrasound). This evidence suggests that SAF could be an indicator of macrovascular risk in both diabetic and non-diabetic patients. One possible explanation is that in some patients, AGEs formation starts before the diagnosis of diabetes at least when it is made by the classical methods (HbA1c and glycemic values).

When interpreting the results of SAF, it should be taken into account that they are influenced by the presence of renal impairment. This has been demonstrated in both diabetic[30] and non-diabetic patients.[29] In diabetic subjects, Benata et al.,[30] observed that elevated SAF measurements were associated with diabetic retinopathy in patients without renal impairment, but subjects with eGFR below 60 ml/min/1.73 m^2 presented an increase in SAF measurement but without any capacity to discriminate between those with or without diabetic retinopathy. On the other hand, in non-diabetic patients, subjects with mild to moderate decrease in GFR showed significantly higher levels of SAF compared to subjects without chronic kidney disease (2.5 +/−0.6 AU vs 2.2 +/−0.4 AU). However, when the presence of subclinical atherosclerosis was taken into account, the difference only remained in the group of patients with subclinical atherosclerosis.[29]

Lens autofluorescence as a biomarker of diabetic outcomes

Lens autofluorescence (LAF) measurement is also a non-invasive technique for determining AGE accumulation in the lens which is simple, rapid and does not need pupil dilation.[31] This measurement has been validated by measuring AGE content within the lens in an animal model.[32] LAF was increased in subjects with impaired glucose tolerance or/and impaired fasting glucose and in subjects with screen-detected diabetes.[33] However, clinical studies aimed at demonstrating that LAF measurement could be a tool for diabetes screening had limited sensitivity (between 67 and 79%).[31,34,35]

As occurs with SAF, there is clinical evidence that LAF also reflects cumulative exposure to hyperglycemia. In this regard, in a longitudinal study performed in T1D subjects, LAF correlated with mean HbA1c values obtained during the study period (14 years), and 60% of the rate of increase in lens fluorescence during the study period was statistically attributable to glycaemia levels. Moreover, a higher LAF value at baseline was associated with the development of diabetic complications during follow-up.[36] Thus, both LAF and SAF measurements are particularly useful when the onset of diabetes and data regarding life-exposure to hyperglycemia is unknown, a situation that occurs more often in type 2 diabetes. It is worth mentioning that Koefoed Theil et al.[34] found a significant increase of LAF in non-diabetic patients with a first-degree relative with type 2 diabetes, suggesting once again that the mechanisms that contribute to the development of diabetic complications are activated before the diagnosis of diabetes is made by the current available methods.

Regarding diabetic complications, in a cross-sectional study among type 2 diabetic patients, LAF was associated with the presence of diabetic retinopathy: in a logistic regression model adjusting for age, sex and diabetes status, the OR for the presence of retinopathy was 4.82 in participants in the top quartile of the lens fluorescence distribution compared with participants in the lowest quartile of the LAF.[36] This effect of LAF on retinopathy persisted in a multivariate analysis adjusted also for smoking, systolic blood pressure, BMI and HbA1c (OR = 3).[37] To the best of our knowledge, there are no studies exploring the association of LAF measurement and other complications or with the presence of renal failure.

The most important limiting factor of LAF is that it is not reliable when cataracts are present and cannot be performed in those subjects who have had cataract surgery.

Future perspectives and concluding remarks

The assessment of HbA1c is currently used for determining the risk of the development of diabetic related long-term complications. However, its inability to reflect the cumulative long-term exposure to hyperglycemia and glycemic variability explains why its measurement fails to predict diabetic outcomes. Because of their capacity to give us integrative information on cumulative life-exposure to hyperglycemia, LAF and SAF measurements are two promising biomarkers of diabetic outcomes. However, the following scientific gaps need to be covered:

1) Although LAF and SAF assessments have been correlated with skin and lens AGE content, these measurements have not been validated by measuring the AGE content in the tissues affected by diabetic complications. A study recently supported by the European Foundation for the Study of Diabetes (EFSD) aimed at elucidating this issue is ongoing. In addition, comparative studies between LAF and SAF are also needed.
2) The inter-individual variability in the capacity of tissue glycation is a limiting factor that should be taken into account when analyzing the results of LAF and SAF measurements. As previously mentioned, SAF measurement was found elevated in non-diabetic subjects with atherosclerosis.[28,29] Moreover, LAF determination was increased in non-diabetic subjects with a first degree relative with T2D.[35] These observations indicate that there is a different predisposition in the capacity of AGE formation that affects both diabetic and non-diabetic patients. This is in close relationship with the inter-individual variability of the AGE's receptor (RAGE) activity. Furthermore, RAGEs are not expressed homogenously in all tissues and there is evidence that the AGE's accumulation pattern change with age,[37] thus adding more complexity to the analysis of the results.
3) Apart from AGEs formed as a consequence of the glycation of endogenous proteins, it is worth mentioning that AGEs also exist in significant amount in several foods and their quantity also depends on the type of cooking.[38] Consumption of AGE-rich diets has been associated with

elevated circulating and tissue AGEs and conditions such as atherosclerosis and kidney disease in mice. In the same direction, in healthy subjects dietary AGEs directly correlate with circulating AGEs as well as with markers of oxidative stress. Furthermore, in patients with diabetes, restriction of dietary AGEs reduces markers of oxidative stress and inflammation.[39] For all these reasons, the effect of dietary AGEs on and SAF and LAF measurements and diabetic complications is a significant topic that should be investigated in the coming years.

In summary, the assessment of AGEs by means of non-invasive methods such as LAF and SAF is a promising strategy for a better identification of diabetic patients at risk of developing late diabetic complications. This would provide a rational basis to implement a patient-centered approach in the setting of personalized medicine, which would reduce the huge economic burden associated with diabetes.

Conflict of interest

The authors declare that they have no conflicts of interest.

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