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Biomarkers as a predictor for diabetic retinopathy risk and management: A review

Authors:
Kevin C. Phillips[1]
Peter C. Clarke-Farr[1]
Tandi E. Matsha[2]
David Meyer[3]

Affiliations:
[1]Department of Ophthalmic Sciences, Cape Peninsula University of Technology, South Africa

[2]Department of Biomedical Sciences, Cape Peninsula University of Technology, South Africa

[3]Division of Ophthalmology, University of Stellenbosch, South Africa

Corresponding author:
Kevin Phillips,
kcphil@iafrica.com

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Background: The systemic and ocular manifestations of diabetes are an increasing burden on both private and public healthcare systems. The ability to accurately predict patient susceptibility and prognostic implications of the disease is essential to its optimal management and planning.

Aim: The purpose of this paper was to review alternative biomarkers to those currently in use regarding the diagnosis and prognosis of diabetes and the ocular effects of the disease. Current biomarkers include Fasting Plasma Glucose (FPG), Oral Glucose Tolerance Test (OGTT) and Glycolated Haemoglobin (HbA1c).

Methods: The research strategy comprised of a comprehensive literature review of articles from Mendeley, Cochrane and Elsevier with additional input from experts in the field serving as co-authors.

Results: The review found that there are alternative biomarkers to those currently utilised. These include adiponectin, apolipoprotein B, C-reactive protein and ferritin. Fructosamine, while useful where whole blood is available, is unreliable as a diagnostic biomarker resulting in a 10% variation coefficient. Post-prandial glucose (PPG) measurement most closely predicted HbA1c.

Conclusion: With prediction of risk for diabetes in individuals, a value combination, expressed as either a numerical score or a percentage, consisting of adiponectin, apolipoprotein B, C-reactive protein and ferritin, almost doubled the relative risk of contracting the disease. Eye care practitioners need to question diabetic patients about their FPG and HbA1c levels and encourage them to have the relevant tests regularly, including PPG. The importance of biomarkers should be emphasised and used as an educational tool to facilitate better diabetes management and treatment adherence.

Introduction

As a global health concern, diabetes has become a major focus for both epidemiological research and public health planning.[1] It is estimated that excess deaths attributable to diabetes worldwide are approximately 3.96 million in the age group 20–79 years, accounting for 6.8% of global (all ages) mortality.[2] Global estimates from 2013 indicated that 382 million people suffered from diabetes – a number that is expected to rise to 592 million by 2035.[3] The largest populations with diabetes live in low- and middle-income countries and these will experience the greatest increase in the incidence of diabetes over the next 17 years.[3] In regional terms, diabetes accounted for 6.0% of deaths in adults in Africa and 15.7% in North America.[4] Beyond 49 years of age, diabetes was responsible for a higher proportion of deaths in females than in males in all regions, reaching over 25.0% in some regions and age groups.[2] In South Africa, the lack of current statistics regarding the prevalence of diabetes mellitus among the urban Cape mixed-race population prompted the Bellville South Diabetes Study.[5] This investigation found that the prevalence of diabetes had increased markedly since the previous 1985 study,[6] indicating a crude prevalence of nearly 29.0% of the target population, up from 7.1% in 1985. Both studies included an assessment of the modifiable risk factors of obesity, sedentary lifestyle and co-morbidities of hypertension and dysglycaemia, all of which appear to be linked in some way to urbanisation and lifestyle choices. As a descriptive term, diabetic retinopathy is referred to as diabetic eye disease, while optic nerve disease (papillopathy), ocular surface diseases, cataracts and primary or secondary glaucoma are ocular complications associated with the condition.[7] Clearly, those trained to examine the eye are ideally placed to recognise diabetic eye disease and the ocular complications associated with diabetes. These practitioners include ophthalmologists and optometrists, both of whom possess the necessary skills and equipment to perform this valuable task. This article intends to review the relatively new field of physiological biomarkers as a predictor for diabetic retinopathy risk and management.

Systemic and ocular complications of diabetes

The complications of diabetes include vasculopathy, nephropathy, retinopathy and even dementia. It is well-documented that prolonged hyperglycaemia has devastating cardiovascular outcomes,[8] and the risk for cardiovascular disease (CVD) and all-cause mortality independent from other risk factors is significantly higher in individuals with chronic hyperglycaemia.[9] Furthermore, chronic hyperglycaemia has also been associated with an increased risk of microangiopathy, a further major risk factor for CVD. A definitive relationship has been demonstrated between microvascular complications and prolonged hyperglycaemia, including retinopathy, nephropathy and neuropathy.[10] The United Kingdom Prospective Diabetes Study (UKPDS 35)[11] concluded that, while the risk of diabetic complications was strongly associated with hyperglycaemia, each 1% reduction in HbA1c value reduced any end point related to diabetes by 21% and microvascular complications by 37%. Aiello[10] states further that the presence of proteinuria is also associated with retinopathy and that hypertension, a common co-morbidity with diabetes, is an established risk factor for diabetic macular oedema, associated with the presence of proliferative diabetic retinopathy.

Diabetic retinopathy has been redefined to be neurovascular in nature, rather than microvascular, as neurodegenerative changes precede and coexist with microvascular changes.[12] Diabetic retinopathy is a specific microvascular complication of uncontrolled diabetes and remains the leading cause of preventable blindness in people of working-age.[13] Up to one-third of the diabetic population are affected, and it is associated with an increased risk of life-threatening systemic vascular complications, including stroke, coronary heart disease and heart failure.[13] Retinal nerve fibre loss (RNFL) is common in diabetes and the identification of RNFL thinning, by means of optical coherence tomography (OCT), in the inferior retina, is associated with peripheral neuropathy in patients with type 2 diabetes and is more pronounced in those at higher risk of foot ulceration.[14] This has been confirmed more recently where cardiac autonomic neuropathy (CAN) was associated with superior RNFL defects, leading to the possibility that specific diabetic neuropathies may be predicted by the area of RNFL loss.[15] The use of retinal imaging as an adjunct to OCT[16] is adding value to the improvement of primary care diabetes management in general and retinopathy treatment in particular.

The current role of biomarkers in diabetes and systemic complications

Because diabetic retinopathy is inextricably linked to diabetes, it follows that in order to curb the prevalence of the consequences of diabetes, specifically retinopathy, the ability to predict the potentiality of individuals to develop the condition has become increasingly important. To this end, clinicians resort to certain diagnostic aids, including the use of biomarkers. The term 'biomarker' is literally a combination of 'biological' and 'marker'[16] and has been used in clinical practice for many years. They are normally, but not exclusively, measured in body fluids (blood or urine)[17] and refer to objective medical signs that can be measured. These biomarkers indicate the medical state of a patient, including the severity of the pathology and often the prognosis of a disease. Biomarkers also play an integral part in conducting clinical trials and in the diagnosis and treatment of patients.[18] Moreover, the prudent use of biomarkers can assist in the predictability of diabetes in individuals susceptible to the disease[19] and can be utilised to ascertain certain risk factors for contracting the disease.[17] In terms of the prediction of diabetes in individuals, a value combination, expressed as either a numerical score or a percentage, consisting of adiponectin, apolipoprotein B, C-reactive protein (CRP) and ferritin, almost doubled the relative risk of contracting the disease.[20]

Adiponectin, a plasma protein secreted by adipocytes, enjoys an inverse relationship with fat storage.[21] An adiponectin insufficiency results in an increased deposition of adipose tissue and consequent obesity through insulin resistance.[21] The addition of thiazolidinedione drugs in adiponectin-insufficient individuals improves insulin sensitivity and antidiabetic outcomes.[21] It follows therefore that adiponectin as a biomarker is a quantifiable entity that can provide predictability in terms of insulin resistance and concomitant diabetes. A decreased level of apolipoprotein A5, involved in triglyceride metabolism, is a further biomarker in obesity incidence, with consequent insulin resistance.[22] Apolipoprotein regulates plasma lipid metabolism[23] and, whereas conventional clinical diabetes diagnostic processes involve the measurement of cholesterol, current models appear to prefer the measurement of apolipoprotein B and apolipoprotein A-I as markers of vascular risk. The conclusion is that the definition of dyslipidaemia in metabolic syndrome should include the apolipoprotein biomarkers.[24] C-reactive protein is commonly used to detect inflammation and is predominantly secreted by the liver and adipose tissue in the presence of inflammation.[25] It is readily and regularly quantified as a diagnostic tool for the presence of inflammation in the body, serving mainly as a biomarker for vascular inflammation.[25] Ferritin is an iron-regulatory protein that actively promotes iron release in times of deficiency or inhibits release in times of over-abundance; excessive levels have been linked, *inter alia*, to coronary artery disease.[26] Apolipoprotein Al (apoAl), apolipoprotein B (apoB) and the apoB:apoAI ratio have been significantly and independently associated with diabetic retinopathy and its severity. Serum apolipoprotein levels appear to be stronger biomarkers of diabetic retinopathy than traditional lipid measures.[27]

Further analysis has confirmed a difference in gender specificity, where the male predictability was greatest with four biomarkers: adiponectin, apolipoprotein B, ferritin and interleukin-1 receptor antagonist (IL-1RA). The female predictability of diabetes risk includes higher levels of adiponectin, apolipoprotein B, CRP and insulin.[20] Recently, the associations of glycoprotein acetyls (GlycA), IL-1RA and high-sensitivity C-reactive protein (hs-CRP) with insulin secretion, insulin sensitivity, incident type 2 diabetes, hypertension, CVD events and total mortality was investigated in the prospective Metabolic Syndrome in Men

(METSIM) study. In this instance, GlycA was associated with impaired insulin secretion, hyperglycaemia, incident type 2 diabetes and CVD. Interleukin-1 receptor antagonist and hs-CRP were associated with adverse changes in insulin sensitivity and obesity-related traits and with total mortality, the conclusion being that inflammatory biomarkers differentially predicted changes in insulin secretion and insulin sensitivity.[28] Current research involves the use of proteomics, and the investigation of proteins and metabolomics where significant metabolic variation in pre-diabetic individuals distinct from commonly used and known diabetes risk indicators, such as glycolated haemoglobin levels, fasting glucose and insulin, is evident.[29] Three metabolites have been identified, namely, glycine, lysophosphatidylcholine and acetylcarnitine, which, in insulin-resistant patients, exhibit significantly different quantities than in normoglycaemic individuals.[29] There have also been significant advances in genetic identification, where seven T2D-related genes associated with these three IGT-specific metabolites have been recognised.[29]

The role of biomarkers as a predictor for diabetic retinopathy

Traditionally, the clinical diagnosis of diabetes mellitus is based on the measurement of certain biomarkers, for example, glycolated haemoglobin (HbA1c) levels; fasting, or random, blood glucose levels; and oral glucose tolerance tests (OGTT).[30] The HbA1c test has been the standard measure to monitor blood glucose control and is a biomarker of future cardiovascular risk.[31] This test provides a measure of average blood glucose levels over the preceding 2–3 months, expressed both in mmol/mol and as a percentage, helping clinicians evaluate treatment options and efficacy.[32] The National Glycohaemoglobin Standardization Program (NGSP) was initiated in 1996 with the goal of standardising HbA1c results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (DCCT/UKPDS).[33] The International Expert Committee (IEC) and the American Diabetes Association (ADA) proposed that diagnostic criteria for diabetes and pre-diabetes be based on HbA1c levels,[34] but these authors postulate that screening for diabetes and pre-diabetes with these measurements would differ from using oral glucose tolerance tests (OGTT). It is traditionally accepted that high HbA1c levels are an important predictor of mortality; however, new research indicates that low HbA1c can be as dangerous and that newer clinical guidelines should include minimum levels of HbA1c.[35]

The link between HbA1c and periodontal disease has been studied, with the conclusion that the mean HbA1c was significantly elevated with periodontal deterioration.[36] The link between retinopathy and HbA1c appears to be at a level of 6.5%.[37] While fructosamine and glycated albumin appear to be especially useful where whole blood is not available and are strongly associated with microvascular conditions, HbA1c as a long-term predictor of vascular outcomes remains the standard.[38] Owing to prolonged hyperglycaemia being associated with diabetes complications, including retinopathy, the time-dependent effect of HbA1c is significant when investigating the link between HbA1c and retinopathy.[39]

Other diagnostic biomarkers have been utilised in the diagnosis of diabetes, namely, fructosamine and glycated albumin. While both are associated with vascular outcomes and mortality similar to HbA1c, they appear to be utilised as short-term markers of glycaemic control.[38] A 1987 study evaluating fructosamine for the measurement of plasma protein glycation showed results, obtained on plasma samples drawn at different times of the day, differed by up to 1.0 mmol/L, corresponding to a variation coefficient of greater than 10%. The consequence was that the average glycaemia in this study of fructosamine determination was subject to an uncertainty of 7.8 mmol/L. It was found that factors other than protein concentration, such as lipid content, also influence the results of fructosamine determinations.[40] Albumin is one of the most abundant plasma proteins and is heavily glycated in diabetes.[41] When comparing the levels of plasma glucose with HbA1c, glycated albumin and fructosamine, the results were 100 days, 40 days and 30 days, respectively.[42] In a study to determine the correlation between glucose monitoring by fasting plasma glucose (FPG) or 2 h postprandial (PPG) blood glucose with HbA1c and fructosamine in type 2 diabetic patients, results showed that PPG correlated better than FPG to HbA1c and both equally correlated to fructosamine levels. It appears that PPG predicted overall glycaemic control better than FPG. This study showed that, compared to HbA1c, fructosamine correlated least well with mean glucose profiles, the conclusion being that HbA1c use in monitoring overall glycaemic control is better than fructosamine.[43] The limitations of fructosamine use in place of HbA1c to evaluate the efficacy of antidiabetic treatments were further exposed in a later study where the risk of misclassification was around 10% when fructosamine was used to estimate HbA1c.[44] It is important for eye care practitioners to question diabetic patients about their FPG and HbA1c levels and to encourage them to have the relevant tests regularly. The importance of these biomarkers should be emphasised and used as an educational tool to facilitate better diabetes management.

Treatment and management of diabetic retinopathy

The prevention of diabetic retinopathy is achieved by good blood glucose control coupled with blood pressure control and possibly blood lipid regulation.[13] The ADA has determined the level of HbA1c for the prediction of diabetic retinopathy to be 6.5% and this threshold has been confirmed by a further 2013 study by Cho et al.[37] This study supported the judicious use of HbA1c for the diagnosis of diabetes and the detection of diabetic retinopathy. Poor blood glucose control, confirmed by a high HbA1c level, was the most important factor associated with the prevalence of diabetic retinopathy in Taiwanese type 2 diabetic patients.[45] For patients who progress to levels of vision-threatening retinopathy (proliferative retinopathy and macular oedema),

laser photocoagulation treatment is effective in preserving the remaining vision, but the treatment is not vision-restorative in nature. Surgical procedures such as vitrectomy are occasionally needed for advanced retinopathy, while promising advances in the medical treatment of retinopathy utilising intraocular injections of steroids and antivascular endothelial growth-factor agents (anti-VEG-F), which are less destructive, are being employed more frequently.[13] However, not all patients respond to anti-VEG-F agents, reinforcing the fact that diabetic retinopathy is a multifactorial disease.[12] While therapeutic approaches used for patients with, or at risk for, diabetic retinopathy are advancing along with risk factor modification strategies, screening plays an important role in early detection and intervention to prevent the progression of diabetic retinopathy.[46]

In the context of a national screening programme for referable retinopathy, digital imaging has been shown to be an effective method for any programme for referable retinopathy. It has also been shown to be more sensitive for optometric evaluation than slit-lamp examination.[47] Furthermore, digital imaging has proven time–benefit qualities, reducing image evaluation time by 28% and reducing the ungradable rate to less than 3%.[48] Single-field digital fundus photography was found to be an acceptable, accurate and valid screening tool for diabetic retinopathy in remote communities of central Australia, where the sensitivity (the percentage of referable images) and specificity (the percentage of non-referable images) for detecting any diabetic retinopathy were 74% and 92%, respectively.[49] In Singapore, non-physician diabetic retinopathy graders were able to provide good detection of diabetic retinopathy and maculopathy from fundus photographs,[47] while, locally, non-mydriatic digital fundoscopy has been shown to be a reliable and cost-effective measure in the screening and diagnosis of diabetic retinopathy in a primary care setting in South Africa.[50] In essence, because the eye offers easy non-invasive access to the vasculature, retinal screening can save vision at a relatively low cost. The ability to image the vasculature of the retina could also assist in the early diagnosis of CVD. Substantial advances in photographic technology have now enabled the photography of undilated fundus to be performed by suitably trained non-medical personnel, with accurate results.[47] In this regard, it has been shown that the observation of a high microaneurysm formation rate over time on colour fundus photographs appears to be a good biomarker for diabetic retinopathy with progression to Clinically Significant Macula Oedema in type 2 diabetic patients with NPDR.[51]

It is undisputed that obesity has increased worldwide and is a major risk factor for diabetes, CVD, cancer, sleep apnoea, non-alcoholic fatty liver disease, osteoarthritis and other ailments. Obesity has further been associated with disability, mortality and enormous health costs.[52] The body mass index (BMI) is the dominant means of defining and diagnosing obesity in national and international public health policy.[53] Virtually all social science research related to obesity utilises BMI, despite wide agreement in the medical literature that BMI is seriously flawed because it does not distinguish fat from fat-free mass such as muscle and bone.[53] In spite of BMI being a somewhat inaccurate measuring tool, it is still the best simple assessment screening tool available for assessing obesity. Science needs another more accurate tool than only weight and height as a measure of fatness.[53] Notwithstanding the above, BMI is a quick and cost-effective screening tool, facilitating effective primary healthcare in a clinical setting.[54] It is therefore important that not only eye care practitioners but all health care practitioners are cognisant of the BMI concept and screen obese patients appropriately for diabetic eye disease and refer for biomarker assessment to determine their diabetes risk.

Conclusion

Medical science continues to explore newer and more effective ways to screen for diabetes. The investigation of biomarkers and their relation to insulin resistance, obesity and clinical diabetes has far-reaching consequences and significance for populations most susceptible to the disease. Certain clusters or cohorts in the population exhibit a higher than normal prevalence of diabetes, such as in the Bellville South community.[5] Research opportunities exist, both epidemiologically and clinically, to scrutinise the biomarker profile of these populations in order to determine their relevance and possible interventions to retard the progression into diabetes. The utilisation of novel biomarkers like adiponectin levels in association with the more traditional HbA1c, OGTT and FPG, alongside clinical observations of BMI and obesity, can further facilitate the predictability of the disease, while fundus examination can assist with the monitoring of the disease progression. By being at the forefront of eye care, suitably skilled optometrists can assist ophthalmology and primary care medicine in performing valuable screening of patients, referring those potentially at risk for appropriate biomarker testing and assessing any diabetic eye disease or ocular complications of diabetes.

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Competing interests

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Authors' contributions

K.C.P. was the lead author and the primary contributor to the writing of this article. T.E.M. was the originator of the study concept, while P.C.C-F. provided input and guidance on the writing, structure and article content. D.M. provided expertise on ophthalmology content.

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