

Progress in the Study of Glycosylated Haemoglobin Variability Index in Relation to Chronic Complications of Diabetes Mellitus

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Abstract: Diabetes mellitus (DM) is a common endocrine disease that can cause damage to tissues and organs throughout the body. Glycosylated haemoglobin (HbA1c) is considered to be the gold standard for assessing glycaemic control and treatment outcomes in patients with diabetes, but there is individual variability that affects the accurate interpretation of blood glucose. The glycosylated haemoglobin variability index (HGI) is a measure of individual variability in HbA1c and can be used in the management and treatment of patients with DM. In this paper, the relationship between HGI and chronic complications of DM is reviewed and discussed, with the aim of providing a more individualized and accurate reference for clinical management of blood glucose and risk assessment of chronic complications in DM patients, reducing and delaying the occurrence of chronic complications of diabetes and improving the quality of life of DM patients.

Keywords: Glycated Hemoglobin Variability Index; Diabetes; Chronic Complications; Glycated Hemoglobin.

1. Introduction

Diabetes is a serious global public health problem, and the prevalence of diabetes has been increasing every year in recent years, with a trend towards younger people. It is estimated that the global prevalence of diabetes will be 463 million in 2019, rising to 578 million by 2030 and 700 million by 2045[1]. Chronic hyperglycaemia can damage blood vessels and nerves, causing patients to suffer from a variety of chronic complications, greatly increasing their financial burden[2, 3] and even bringing about a high rate of disability and death[4]. The early signs and symptoms of chronic complications of diabetes mellitus are atypical and can easily be overlooked, therefore, early detection, diagnosis and treatment are the key to controlling chronic complications of diabetes mellitus. Glycosylated haemoglobin is considered to be the gold standard for assessing glycaemic control and therapeutic efficacy in diabetic patients[5]. However, in addition to being influenced by blood glucose levels, HbA1c also has complex inter-individual biological variation, which is related to genetic factors, red blood cell lifespan, haemoglobin glycation rate and other factors, thus affecting the accurate determination of the degree of glycaemic control[6]. Interindividual variation in HbA1c was described by Hempe et al. through the HGI, which is the difference between observed HbA1c and HbA1c predicted by the FPG[7]. In this paper, we will review and discuss the relationship between HGI and chronic complications of diabetes and the progress of applied research, with a view to providing a reference for early screening and intervention of chronic complications of diabetes.

2. The Relationship between HGI and Diabetic Macroangiopathy and its Application

DM has a long course, many risk factors and common

macrovascular complications, especially atherosclerotic lesions of the cardiovascular and peripheral vasculature, which predispose to coronary heart disease, ischemic stroke and lower limb arterial occlusion, and are the main causes of death in DM. Several studies have shown that HGI can be used for risk prediction and assessment of macrovascular lesions in DM, allowing for early screening and prevention [8-13]. Klara et al. conducted a multicentre, randomised, double-blind cardiovascular outcomes trial in which HGI was calculated in 7637 participants with type 2 diabetes and classified into low, medium and high HGI using the tertiles method. The results showed that the high HGI group had a higher risk of myocardial infarction and ischaemic stroke than the low HGI group and medium HGI, and also had higher risk factors for cardiovascular events such as cholesterol, LDL and triglycerides, all with statistically significant differences. This study confirmed that HGI can be an independent predictor of macroangiopathy in type 2 diabetes mellitus (T2DM)[8]. Xu et al. retrospectively analyzed 918 patients with coronary artery disease combined with T2DM who underwent PCI to explore the correlation between HGI and major adverse cardiovascular events. The study found that HGI was an independent predictor of adverse cardiovascular events. More importantly, the high HGI group had a higher risk of angina, myocardial infarction and stroke events, a worse prognosis and a significantly lower survival rate[9]. A meta-analysis examined the association between HGI and cardiovascular disease risk and all-cause mortality in patients with T2DM. This study included five observational studies of over 22,000 patients with T2DM with a median follow-up of 5 years for the meta-analysis. The results found that high HGI was associated with increased composite cardiovascular events and all-cause mortality after adjustment for multiple cardiovascular risk factors[13].

In addition Cheng et al. found that HGI was positively correlated with the degree of coronary stenosis in patients with T2DM, and that those with an excess HGI had more

coronary stenosis, more branches of coronary lesions and more stents implanted compared to those with a lower versus normal HGI, possibly because those with an elevated HGI would have accelerated protein glycation and thus endothelial damage [10]. Marini et al. found that high carotid intima-media thickness and the risk of vascular atherosclerosis was 2.7 times higher in patients with HGI than in the low HGI group [11]. However, it has also been suggested that the presence of hypertension may affect the predictive value of HGI for diabetic and pre-diabetic macrovascular disease, possibly because the superimposed effect of high HGI and hypertension accelerates the occurrence of cardiovascular events [12]. In conclusion, HGI is an independent predictor of macroangiopathy in DM, and patients with DM with high HGI are at higher risk of cardiovascular events, but clinical assessment of the condition needs to take into account the influence of multiple combined factors, including the patient's blood pressure.

3. The Relationship between HGI and Diabetic Microangiopathy and its Application

DM microangiopathy, which mainly includes diabetic nephropathy and retinopathy, is a common chronic complication of DM and is a major cause of visual impairment and renal failure in patients. Wang et al. showed that HGI is an important predictor of the development of microvascular complications in T2DM and has more predictive value and individualized guidance than HbA1c, probably because glycated haemoglobin biomutation increases the risk of microvascular complications through "metabolic memory" effects, including oxidative stress mechanisms [14]. A retrospective study by XIN et al. examined the association between HGI and diabetic kidney disease (DKD) in patients with T2DM, confirmed that HGI is a useful predictor of DKD in patients with T2DM, and constructed an HGI-based risk score to predict the risk of DKD in patients with T2DM [15]. Kim et al. conducted a 10-year prospective cohort study which showed a significant association between high HGI and new-onset chronic kidney disease in patients with impaired glucose metabolism and diabetes mellitus who were not treated with medication, and independently of HbA1c, when each unit increase in the standard deviation of HGI was associated with a 31% increase in the risk of chronic kidney disease events. It can thus be concluded that HGI can be used to predict renal dysfunction in patients with impaired glucose metabolism [16]. In addition, a growing number of scholars have confirmed that HGI is associated with the development of retinopathy in patients with DM. Tang et al. retrospectively studied 201 patients with T2DM and divided them into retinopathy and T2DM-only groups. The results of the study showed that the HGI was higher in the retinopathy group than in the T2DM-only group, and the difference was statistically significant; a binary logistic regression analysis showed that high HGI was an independent risk factor for the development of retinopathy in patients with T2DM [17]. Chen et al. also demonstrated that HGI could be a new personalized predictor of retinopathy in T2DM patients [18]. In the T1DM patient population, there appears to be an even stronger relationship between HGI and DM microvascular complications [19]. In a study with a 7-year follow-up, patients with T1DM in the high HGI group had a 3-fold higher risk of developing retinopathy and a 6-

fold higher risk of developing nephropathy compared to the low HGI group [19]. Fiorenza et al. compared HGI levels in 1505 non-DM populations and found that the risk of developing chronic kidney disease was 3.6 times higher in the high HGI group than in the low HGI patients, suggesting that HGI in non-diabetic population still serves as an independent predictor of renal dysfunction [20].

4. The Relationship between HGI and Diabetic Neuropathy and its Application

Diabetic neuropathy is a neurodegenerative disease which includes peripheral neuropathy and autonomic neuropathy and is one of the common and serious chronic complications of diabetes mellitus with significant morbidity and mortality that requires careful assessment and timely management [21, 22]. Current studies suggest that HGI is expected to be a useful indicator for early intervention and diagnosis of neuropathy in patients with DM [23-25]. Yu et al. confirmed that HGI was associated with an increased risk of developing peripheral neuropathy (DPN) in patients with T2DM, and that HGI could be a predictor of the development of DPN and a reference indicator for glycemic control in patients with T2DM, a good complement to HbA1c, and beneficial for early prevention and timely management of DPN [23]. Sheng et al. found that HGI was positively correlated with the risk of DPN, and the risk of developing DPN increased by 25.9% for each standard amount of increase in HGI, and HGI can be a better indicator for predicting the risk of developing DPN in T2DM patients [24]. HAN et al. retrospectively analyzed the relationship between HGI and diabetic cardiac autonomic neuropathy (DCAN) in 365 T2DM patients, and the results confirmed that the occurrence of DCAN was closely associated with HGI levels in T2DM patients, and that HGI was a risk factor for the development of DCAN and was positively associated with the incidence of DCAN.

5. Conclusion and Prospect

DM is a common chronic disease that can lead to a series of serious acute and chronic complications as the disease progresses, putting patients under greater emotional and financial stress. Chronic complications of DM are closely related to poor glycaemic control, and HbA1c reflects the stability of blood glucose levels over the last three months, but there is some individual variation that can affect the accurate interpretation of blood glucose. While HGI is a measure of blood glucose it can be used to predict the occurrence of chronic complications in DM, providing a new method for the individualized assessment and management of DM, which has a broad application prospect and deserves to be widely promoted in clinical practice. However, most of the current studies on the relationship between HGI and chronic complications of DM have remained in cross-sectional retrospective studies, and the mechanisms underlying the increased risk of chronic complications of DM are still unclear. This will provide clinicians with new reference indicators for the management of DM patients, reduce and delay the occurrence and development of chronic complications in DM, and reduce the disability and mortality rates of DM patients.

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