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LETTER TO EDITOR

Is Glycemic Control the Primary Goal in Diabetes Treatment?

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Abstract

The prevalence of Diabetes is steadily increasing, raising public health concerns. Hyperglycemia leads to microvascular and macrovascular diseases through several metabolic and biochemical pathways. Previous clinical trials and observational studies have demonstrated that tight glycemic control can reduce the incidence of diabetic complications, with the greatest benefit shown in younger patients with diabetes of shorter duration and those who have no prior history of cardiovascular disease. Moreover, previous studies highlight the concept of metabolic memory and legacy effect, since controlling diabetes early can have an impact on long-term prognosis of the disease. As to whether it is time to consider shifting the treatment focus for patients with type 2 diabetes from a glucose-centric to a weight-centric or a cardio-centric approach, the dilemma remains theoretical; glucose control, weight loss and effective treatment of metabolic and cardio-vascular co-morbidities are interrelated components of an integrated plan of care that should be addressed simultaneously and effectively.

Key Words: *Type 2 diabetes; Glycemic control; Primary goal; Legacy effect; Metabolic memory*

The prevalence of Diabetes is steadily increasing, raising public health concerns; according to the International Diabetes Federation, more than 500 million adults suffer from diabetes, a number that is expected to rise up to 783 million by 2045 [1]. Type 2 diabetes mellitus (T2DM), which accounts for over 90% of diabetes cases, is a group of metabolic disorders characterized by hyperglycemia in combination with disorders of lipid and protein metabolism [2,3].

The disease is primary caused by a combination of insufficient secretion of insulin from the pancreas and reduced insulin action in insulin-sensitive peripheral tissues such as muscle, liver and adipose tissue [4,5]. However, during the last decade, more insight in the etiology of T2DM was gained and other pathophysiological disorders involving the kidney (increased reabsorption of glucose), the brain (increased appetite, increased sympathetic tone), the digestive system (increased glucose absorption,

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impaired incretin effect) and the immune system (inflammation) have been recognized as factors that can cause or aggravate hyperglycemia [5]. Decreased insulin secretion and action usually coexist in T2DM patients, and it is usually unclear which abnormality predominates and which is the primary cause of hyperglycemia. Genetic predisposition also plays an important role in the appearance of T2DM by affecting both insulin sensitivity and secretory function of the pancreas [6,7]. In addition to the genetic burden, many environmental factors (diet high in fat and carbohydrates, sedentary lifestyle, smoking, stress, environmental pollution, etc.) have been shown to participate in the clinical manifestation and/or worsening of hyperglycemia [8].

The risk of T2DM increases linearly with increased body weight [9]. Visceral obesity worsens insulin resistance, resulting in decreased glucose uptake from muscle and adipose tissue. Moreover, obesity and subsequent insulin resistance eliminate the suppressive effect of insulin on hepatic glucose production, resulting in an increase in circulating glucose levels [9,10]. However, clinical manifestation of T2DM is evident when compensatory insulin secretory pancreatic response fails to maintain glucose homeostasis, the exact cause of which is not fully elucidated [5].

Patients with diabetes are subjected to an increased risk of developing microvascular and macrovascular complications that adversely affect their quality of life (due to blindness, kidney failure, neuropathic pain, lower limb amputations, etc.) and reduce their life expectancy by 5-15 years, depending on the age at diagnosis [11,12]. To date, there is highly reliable evidence from epidemiological and pathophysiological studies that hyperglycemia per se is largely responsible for the development of chronic complications in subjects with diabetes mellitus [13].

Glucose variability is a term, used to describe either short-term or long-term fluctuations in plasma glucose values. Glycated hemoglobin (HbA1c) is the main marker for assessing long-term glycemic control and treatment efficacy. However, it has been shown that HbA1c cannot accurately predict short-term fluctuations in glucose values, since an HbA1c value within target can be found in individuals with euglycemia (low glucose variability), as well as in patients with a combination of hyperglycemic spikes and hypoglycemic episodes (high glucose variability) [14]. In patients using continuous glucose monitoring devices, detailed glycemic data are available and can be used to estimate glucose variability. Time in range (glucose values: 3.9-10.0 mmol/L) is a useful index of glycemic control, which correlates well with both HbA1c, and risk of complications. Additionally, time below range (<3.9 mmol/L) and time above range (>10.0 mmol/L) are useful indices for the identification of hypoglycemic episodes and hyperglycemic spikes respectively. Although to date it has not been proven whether glycemic variability is an independent risk factor for cardiovascular disease, several studies support the association of glucose variability with adverse cardiovascular outcomes [14].

Glucose variability leads to microvascular and macrovascular diseases through several metabolic and biochemical pathways [14,15]. Advanced glycation end-products (AGEs) are increased as a result of hyperglycemia, resulting in permanent abnormalities in extracellular matrix and intracellular protein modification [16,17]. Moreover, overproduction of reactive oxygen species via enzymatic pathways, glucose oxidation and mitochondria dysregulation have been shown to contribute to vascular disease not only in diabetes mellitus, but in stroke and peripheral arterial disease, as well [18]. Oxidative damage can also affect unsaturated fatty acid constituents of triglycerides and

cholesteryl esters. As with glucose, reactive aldehydes are formed, and these can impair amino acids and proteins [19]. The combined effect of hyperglycemia, dyslipidemia and increased free radical oxidation proposed as glycoxidation and lipoxidation can cause much more severe protein damage and impairment of vascular contractility and permeability than each of them separately [19,20]. In addition, there is growing evidence that extracellular matrix synthesis, hormone receptors turnover, cell growth/proliferation and angiogenesis, are impaired in diabetes and correlated to increases in diacylglycerol levels and protein kinase C (PKC) activity [20]. Investigation of aldose reductase (AR) and polyol pathways have also shed light in the pathogenesis of diabetic complications; hyperglycemia leads to aldose reductase overexpression, intracellular sorbitol accumulation, increased production of NADH, lack of NAD+ and enhanced NADPH use [21]. Based on the above, AR and polyol pathways are new targets for the prevention or early treatment of diabetic complications [22]. The above biochemical and metabolic pathways should not be considered as competitive or mutually exclusive [23]. Given that, atherosclerosis and neoangiogenesis are linked to enhanced proliferation of endothelial and/or smooth muscle cells, it is highly possible that glycation of proteins, oxidative stress and activation of PKC, may lead to hypoxia and altered growth factor metabolism which in turn could mediate diabetic vascular complications [24].

Inflammatory responses induced by even a short-term episode of hyperglycemia can persist for several days [24]. In this point of view, hyperglycemic spikes and acute inflammatory responses contribute to a vicious cycle reducing insulin sensitivity, accelerating β-cell loss, impairing endothelial function, and leading to microvascular and macrovascular complications [25].

As shown in large clinical trials, tight glycemic control can reduce the risk of microvascular complications in patients with type 1 diabetes mellitus (T1DM), as well as in T2DM patients [25,26]. An increase in diabetic nephropathy and/or retinopathy is observed even with marginally increases of HbA1c, while the incidence of microvascular disease increases exponentially in subjects with HbA1c more than 7%. Conversely, a reduction in HbA1c lower or equal to 7% leads to a statistically significant reduction in the incidence and worsening of microvascular complications, according to prospective randomized intervention studies, in subjects with T1DM and T2DM [26,27].

According to therapeutic intervention studies (Multiple Risk Factor Intervention Trial, EPIC Norfolk study) diabetes mellitus is linked with increased mortality rates by two to four times compared to people without diabetes [28,29]. These studies (which included both overweight and normal weight subjects) demonstrated that hyperglycemia is a major risk factor for both cardiovascular and all-cause mortality [28,29]. Interestingly, small increases of glycated hemoglobin (within the range of normoglycemia) have been found to be associated with a risk of cardiovascular disease and death from any cause, in nondiabetic adults [30]. In Pacific Study, fasting plasma glucose was shown to be an independent predictor factor of cardiovascular events even at levels of 5.2 mmol/L [31].

Based on the above, it is reasonable to expect that lowering glucose levels with intensive therapy will lead to a reduction in cardiovascular complications and cardiovascular death [13,32]. However, the reduction of HbA1c below 7% does not always result in a statistically significant reduction in the incidence of macrovascular complications and/or death in patients with T2DM. In three large clinical studies

(ACCORD, ADVANCE, VADT), including older patients with a diabetes duration of more than eight years and a history of cardiovascular disease in one-third of the participants, there was no significant difference of cardiovascular events between intensified and standard treated patients [33-35]. On the opposite, an increase in mortality was evident, which on sub-analyses appeared to affect older people, those with longer duration of diabetes and those with pre-existing cardiovascular disease [36]. Moreover, according to a meta-analysis of intervention studies in T2DM, despite of a 15% reduction of cardiovascular events per 1% of HbA1C over 5 years of treatment, there was not any significant effect on mortality rates [32]. A hypothesis for the explanation of these results could be increased rates of hypoglycemia which is known to increase mortality rates in older subjects with prior cardiovascular diseases and metabolic co-morbidities [13]. On the contrary, a significant benefit of tight glycemic control in all-cause mortality was evident in patients with newly diagnosed T2DM during long-term follow-up [37]. These findings point out the need for individualization, avoidance of hypoglycemic episodes, as well as a need for early diagnosis and treatment of co-morbidities, such as hypertension and dyslipidemia.

Interestingly, in a recent systematic review of randomized clinical trials and observational studies (in 40,346 patients), the intensive glucose-lowering therapy (compared to conventional therapy) reduced the incidence of major cardiovascular events, with the greatest benefit shown in studies conducted in patients with diabetes of shorter duration (less than 10 years), with no prior history of cardiovascular disease. These results reinforce the need of intensive glucose control in patients with short duration of diabetes, no prior cardiovascular disease and long survival expectance [37].

Legacy effect and metabolic memory are terms used to highlight the fact that glucose values in the early stages of diabetes have an impact on long-term prognosis of the disease [38,39]. The legacy effect of tight glucose control was evident during post-trial 10-year observational period of DCCT and UKPDS studies. During the observation period a statistically significant reduction in cardiovascular benefit was evident in the group of subjects who were well controlled during the initial year study, despite the worsening of their glucose control during follow-up. In contrast, in patients who had poor glycemic control during the initial study, no reduction in the incidence of cardiovascular events was observed despite the improvement of their glycemic control during the observation period of follow-up [38-41]. These findings demonstrate that a period of euglycemia offers protection, even if glucose dysregulation follows. In contrast, a long period of hyperglycemia results in a reduction of the favorable effect that a possible future better control of glucose values may have on the incidence of complications [38-41].

Interestingly, cardiovascular morbidity and mortality remain increased in subjects with T2DM, compared with subjects without diabetes, even after tight glycemic control. This residual risk can be further decreased by cardio-protective drugs such as glucagon-like peptide 1-receptor agonists (GLP-1RA) and/or sodium-glucose co-transporter 2 inhibitors (SGLT2i). Previous Cardiovascular Outcome Trials (CVOTs) have shown a beneficial effect of both classes in the risk of the composite outcome of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke). In addition, SGLT2i have shown beneficial effects in the incidence of hospitalization for heart failure [42].

Moreover, weight loss exerts benefits that extend beyond glycemic control, since it has been shown to decrease the majority of risk factors for cardiovascular disease and improve quality of life [43].

As a conclusion, it seems that hyperglycemia is a dominant cardiovascular risk factor for T2DM patients and therefore targeting the reduction of glucose levels is expected to have a favorable effect in the incidence of microvascular and macrovascular complications and an improvement in life expectancy and patients' quality of life [13]. Prerequisites for the above are, early initiation of treatment, avoidance of hypoglycemia and individualized treatment considering age and co-morbidities. As to whether it is time to consider shifting the treatment focus for patients with type 2 diabetes from a glucose-centric to a weight-centric or a cardio-centric approach, the dilemma remains rather theoretical; glucose control, loss of visceral fat, and cardiovascular risk factor management are interrelated components of an integrated plan of care that should be addressed simultaneously and effectively [44].

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