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IMPORTANCE OF PRANDIAL GLUCOSE REGULATION IN THE MANAGEMENT OF CARDIOVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS

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Abstract

There is a worldwide epidemic increase in the number of type 2 diabetes (T2DM) patients who frequently associate with cardiovascular disease (CVD). There are data suggesting that glycemic control does not substantially reduce CVD risk but hyperglycemia increases the risk of CVD. This apparent paradox could be explained by the role of post-prandial hyperglycemia in the pathogenesis of cardiovascular complications in T2DM. There is numerous evidences, both experimental and clinical, for this association but controversies on this topic persist. The aim of this paper was to review the current literature regarding the role of postprandial glucose in the genesis of CVD in T2DM.

key words: *post prandial glucose, cardiovascular risk factor*

Introduction

During the last years there were controversies related to diabetes care, especially due to the lack of uniformity in the recommended targets for post prandial glucose [1]. There is a frequent lack of acknowledgment of the risks posed by elevated post prandial glucose levels [2], despite the fact that post prandial glucose levels were shown to be an independent risk factor for cardiovascular disease (CVD) and mortality [3]. The variation of cardiovascular (CV) risk factors during the post prandial phase induced by an acute blood glucose increase is very important and may be due to the production of free radicals Normalizing post prandial glucose value is a rational therapeutic goal at all stages of diabetes mellitus.

Cardiovascular mortality in type 2 diabetes mellitus (T2DM)

Diabetic patients have a high mortality due to cardiovascular disease. For non-diabetic and type 2 diabetic (T2DM) patients, hyperlipidemia, hypertension, obesity, lack of exercise, smoking and a positive family history contribute to the genesis of macro vascular complications.

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Progress in reducing mortality rates among diabetic patients has been limited to men but diabetes continues to greatly increase the mortality risk, particularly among women [4]. The major public health success in the United States over the past 40 years was the decline in CVD mortality rates and the accompanying increases in overall longevity [5]. Aggressive cardiovascular disease risk factor management has been shown to be particularly effective among persons with diabetes and aggressive diabetes care should result in increased longevity [6]. It was shown that mortality rates are double in diabetic women compared to non-diabetic control females. However, other studies have shown that mortality declined both in men and women with diabetes in North Dakota [7], Ontario [8], and in the Framingham Heart Study cohort were incidence and mortality rates for CVD have declined [9].

In the National Health and Nutrition Examination Survey (NHANES) III [10] mortality data were analyzed for a group of 1507 diabetic patients, mainly with T2DM. A number of 642 patients died during the follow up period, 53% from CV causes. Only three factors remained significantly associated with mortality in this diabetic subset: poor glycemic control (HbA1c > 8% vs. HbA1c < 6%), absence of physical activity and current smoking status. A conclusion of this study was that mortality rates can be reduced in the diabetic population by 15.3% through improving glycemic control. However, accelerated atherosclerosis in diabetes especially increases the risk for macro vascular complications [11].

Postprandial glycemia is an independent risk factor for cardiovascular disease

In 2002, Bonora described a remarkable increase in plasma glucose two hour after breakfast and/or lunch in most non-insulin treated diabetic patients [12]. As many as 70% of patients with HbA1c below 7% had postprandial glycemic values over 160 mg/dl (8.9 mmol/l) after meals. In the same article [12], Bonora states that in T2DM patients the incidence of CVD is independently related to post prandial glycemia or post oral glucose tolerance test blood glucose values. According to Bonora et al., subjects with impaired glucose tolerance and isolated post challenge hyperglycemia have an increased cardiovascular risk comparative to those with normal glucose tolerance. They found that impaired glucose tolerance subjects had a risk of carotid stenosis which is three fold higher than subjects with normal glucose tolerance. They concluded that diabetes is not only "fasting glucose care" or "HbA1c care" but must be also "post prandial glucose care" and suggested targets for postprandial peaks < 135 mg/dl (7.5 mmol/l) to reduce arterial risk and < 160 mg/dl (8,9 mmol/l) to reduce micro-vascular risk [12].

Findings from the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study (1998), Hanefeld et al. (2002) [13] and Meigs et al. (2002) [14] showed that post prandial glucose values at 1 h and 2 h are independent risk factors for CVD and mortality, knowing that diabetics exhibit a two-to-three fold increase in the incidence of CVD [13] and a substantial reduction in life expectancy [15,16].

According to Peter et al. [17], almost 75% of T2DM patients die because of CVD. International Diabetes Federation (IDF) recommended that 2 hour post meal glucose must be kept under 140 mg/dl (7.8 mmol/l) and post prandial glycemia is or should become a therapeutic target to minimize cardiovascular risk. Later Peter et al. [17] underlined that the therapeutic strategy must address also the postprandial glucose excursions.

In Jan 2005, Ceriello suggested that there is an increasing body of evidence showing that a contributing factor for the development of atherosclerosis in diabetes is the postprandial state and that the postprandial blood glucose may be relevant for the onset of cardiovascular complications [18]. The modification of CV risk factors during the post prandial phase by an acute increase of glycemia is very important and maybe the mechanism involved is the production of free radicals. In conclusion Cerriello said that correcting post prandial hyperglycemia should be part of the strategy for the management and prevention of CVD in diabetes [18].

It was shown that diabetes mellitus magnifies risk of cardiovascular morbidity and mortality [19]. Thus, the UKPDS (United Kingdome Prospective Diabetes Study) showed that above the threshold of HbA1c > 6.2%, the CV risk increases in parallel with the blood glucose levels [20]. Moreover, data from the meta-analysis of 95.000 diabetic patients have shown that the increase in CV risk begins even below the diabetic threshold [21]. Improvement of diabetic therapy and a better glycemic control will reduce atherosclerotic macro vascular complications. Thus, in the UKPDS study, improving insulin resistance with metformin decreased macro vascular events [20].

Targets for glycemic control

Both the UKPDS in T2DM and the Diabetes Control and Complication Trial in type 1 diabetes demonstrated that the relationship between glycemia and the risk of developing complications was evident across the range of HbA1c and that the lower the levels of blood glucose achieved, the lower the risk of micro vascular complications will be [22]. Thus, epidemiological analysis of the UKPDS study showed that each 1% increase in HbA1c elevated the risk of diabetes related death with 21%, the risk of myocardial infarction with 14%, the risk for micro vascular disease with 37% and for peripheral vascular disease with 43% [20,22]. In addition, UKPDS data have shown that tight control of blood glucose combined with an early T2DM diagnosis is associated with significant delays or even prevention of the development of complications, both macrovascular (myocardial infarction and stroke) and microvascular (retinopathy and neuropathy) [20,22]. The patients must be identified at an early stage and the treatment must be implemented early with safe and effective treatment modalities [20,22,23].

Post prandial hyperglycemia is a risk indicator for both micro and macrovascular complications in T2DM

Da Ros et al. [24] showed that most of the cardiovascular risk factors are modified in the postprandial phase in diabetes by an acute increase of glycemia and hypothesized that the mechanism could be the labile non-enzymatic glycation of target proteins and the production of free radicals.

Heine et al. [25] showed that post prandial hyperglycemia is a risk indicator for both micro and macrovascular complications in patients with impaired glucose tolerance or T2DM. The cardio-vascular morbidity and mortality is high also in metabolic syndrome patients. The authors suggested that in the prevention and management of micro-vascular complications in T2DM we must take into account both chronic and acute fluctuations of glycemia while in order to lower the risk of macro-vascular complications we must control post prandial triglyceride levels and the other components of the metabolic syndrome [25].

Woerle et al. [26] performed a prospective intervention trial to assess the contribution of controlling fasting and postprandial glycemia for achieving recommended HbA1c goals. One hundred and sixty four patients with HbA1c higher than 7.5% received an intensified treatment program. The authors concluded that for achieving HbA1c < 7%, control of fasting hyperglycemia is necessary but usually insufficient, controlling postprandial hyperglycemia being essential [26].

Physicians continue to rely on fasting plasma glucose and HbA1c to guide management of T2DM even if the primary disorder is postprandial glycemia deregulation. Thus Leiter et al. [27] reviewed articles regarding the contribution of postprandial hyperglycemia to overall glucose load or cardiovascular risk. They found that 33% T2DM patients were diagnosed having at that moment post prandial hyperglycemia and fasting normoglycemia and concluded about a linear relationship between the 2 hours oral glucose tolerance test and the risk of cardiovascular death [27]. The authors suggested the existence of a glucose triad including fasting plasma glucose, glycated hemoglobin and post prandial glucose, all these factors being important in the management of T2DM [27]. When the therapy is targeted on post prandial glucose, a reduction in the progression of cardiovascular events and atherosclerosis is obtained but all three factors: (fasting plasma glucose, post prandial glucose and HbA1c) should be controlled [27].

Charpentier et al. [28] sustained that even in individuals with impaired glucose tolerance postprandial glycemia increases the CV risk, a relation which is more important than that observed for HbA1c or fasting glycemia. In the same review, they report studies showing that decrease of postprandial glycemia with acarbose, reduces cardiovascular events and the progression of intima-media thickness, treatment of postprandial glycemia with glinides improves also intima-media thickness, interleukin-6 and C reactive protein while treatment with rapid acting insulin analogs improves endothelial dysfunction [28].

In 1997 Heller H et al. underlined the hypothesis that postprandial glucose spikes are important in the apparition of micro and macrovascular diabetes complications. The paper states that in vitro data show that the form alpha of proteinkinase C is activated in the endothelial cells by high glucose concentrations and stimulate the production of adhesion molecules which affect the permeability of tight junctions between endothelial cells [29].

Finally, Madsbad at al. [30] suggested that the importance of postprandial hyperglycemia for the development of diabetic complications

and atherosclerosis is unclear and one of the explanations is that no randomized controlled trials exist regarding the specific treatment of postprandial hyperglycemia [30].

Cardiovascular risk management in T2DM

In 2007 Chenniappan [31] showed that an aggressive cardiovascular risk management in combination with glycemic control is necessary in patients with T2DM and insulin resistance. When HbA1c is nearly at goal, postprandial glycaemia should be assessed. Insulin sensitizer oral agents in combination with lifestyle modification may be used. The authors stress out the importance of reducing LDL cholesterol and triglycerides and improving HDL cholesterol using lipid lowering agents and life style modification [31]. They also state physicians can use 3 or more antihypertensive agents but ACE inhibitor should be the first line therapy for the prevention of microalbuminuria in hypertensive diabetic patients. As the data from the Diabetes Prevention Program and Steno-2 study have shown, multifactorial intervention has significant cardiovascular benefits among patients at risk, especially in those with T2DM and microalbuminuria [31].

Furtado at al. [32] in their review article showed that several studies demonstrated the importance of reducing the CV burden by adopting prevention strategies. They concluded upon the importance of lifestyle changes, low carbohydrate diet, regular physical activity and weight control. Targets for the high risk patients or patients with established CVD should be: HbA1c < 7%, fasting glycemia levels < 100 mg/dl, LDL < 100 mg/dl, HDL cholesterol > 50 mg/dl and triglycerides < 150 mg/dl. As first option for blood pressure control ACE inhibitors (combined or not with tiazides) are preferred mainly in patients with renal disease, the blood pressure target being < 130/80 [32].

Charpantier et al. [33] described a nationwide French survey showing that the prevalence of cardiovascular risk factors remains high and that recommendations need to be reinforced since glycaemia, blood pressure and LDL cholesterol targets were not reached. Dussol at al. [34] showed that T2DM and hypertension are frequently associated and the cardiovascular morbidity is very important. Renal disease appears in 40% of these patients and whatever the stage of renal disease, it increases cardiovascular risk. These patients die of CV complications usually before reaching the End Stage Renal Disease [34].

Standl et al. [35] tried to evaluate the pro and cons of specific impact of postprandial hyperglycemia and glycemic variability on the vascular complications in diabetes and concluded that measures of oxidative stress and endothelial dysfunction are high when there are glucose peaks and by preventing glucose peaks or wide glucose excursions it might be possible to restore to normal these dysfunctions [35]. In a more recent follow up of the Australian Diabetes Obesity and Lifestyle (Aus-Diab) Study, Barr et al. [36] reported a continuous relationship between the metabolic status (including fasting plasma glucose, postprandial glucose and HbA1c) and all cause and cardiovascular mortality [36].

In overt diabetes there are few prospective studies which have analyzed the relationship between postprandial glucose and cardiovascular risk. For example the Diabetes Intervention Study (Hanefeld et al. 1996)

found that newly diagnosed T2DM patients with postprandial glucose higher than 180 mg/dl (10 mmol/l) had a 40% higher risk of myocardial infarction than those with a mean postprandial glucose below 144 mg/dl (8 mmol/l) [37]. In another prospective study Cavalot at al. [38] confirmed that postprandial glucose is an independent risk factor for cardiovascular disease in T2DMwomen.

Finally, Haffner et al. [39] showed that postprandial hyperglycemia plays an important role in the development of coronary heart disease in subjects with impaired glucose tolerance. In addition the Diabetes Prevention Program showed that, reducing postprandial glycemia by means of diet, weight loss, increased physical exercise and smoking cessation reduces the risk of T2DM development by 58% compared with placebo, regardless of ethnicity, body mass index, sex and level of glycaemia. The lifestyle modifications were more effective than metformin treatment [39].

Conclusions

Worldwide there is an epidemic of T2DM associated with CVD. The number of individuals with type 2 diabetes continues to increase from 135 million worldwide in 1995 to 160 millions in 2000 and in 2015 is predicted that the number will be 300 million individuals with diabetes [19,41]. There are many reasons for this increase: the real increase in prevalence of the condition due to westernization and life style changes, the increased survival of T2DM patients, the intensive screening campaigns and the introduction of new diagnostic criteria with lower threshold values.

Glycemic control does not substantially reduce CVD risk but hyperglycemia increases the risk of CVD. Apparently this is a paradox, probably due to the role of metabolic syndrome and postprandial hyperglycemia associated with T2DM [40]. It is now recognized that the most effective strategies for managing CVD risk in diabetes involve reducing not only blood glucose but also all other risk factors like unhealthy lifestyle, hypertension, lipid profiles etc. Complications in T2DM might be minimized by early implementation of tight glycemic control targeting both insulin resistance and impaired insulin secretion. Physicians must consider the early use of combination therapy in patients with recently diagnosed T2DM, chosing medications that reduce the adverse events like hypoglycemia and weight gain.

Post prandial glycemia should be measured when glucose concentration in the blood is at its highest peak, usually 2 hours after a meal. The ideal levels of postprandial glycemia should be not different than from individuals without diabetes. It would be ideal to safely keep patients with diabetes within the normal blood glucose range, or to achieve the lowest levels that are possible while minimizing the risk of hypoglycemia.

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