Current Topic

Postprandial glycaemic excursions and cardiovascular risk

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During the last few years there is increasing recognition regarding the role of postprandial hyperglycaemia (PPHG) in contributing to the development of micro- and macrovascular complications of diabetes. PPHG has a harmful effect on the vascular endothelium, which is mainly mediated by oxidative stress. Numerous epidemiological and longitudinal studies have shown elevated PPHG to be an independent risk factor for cardiovascular disease and increased mortality risk. In addition, PPHG contributes significantly to glycosylated haemoglobin levels particularly in relatively well controlled type 2 diabetic subjects. PPHG is thus emerging as a valid therapeutic target to minimise cardiovascular disease risk. This review looks at the association of postprandial excursions and the risk for cardiovascular disease.

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Type 2 diabetes mellitus is one of the most common metabolic disorders, characterised by abnormalities in insulin action (insulin resistance) and insulin secretion (pancreatic beta-cell dysfunction)[1,2]. In the natural history of type 2 diabetes mellitus, it is the postprandial plasma glucose level that rises initially (stage of impaired glucose tolerance) even before the fasting plasma glucose levels begin to increase. The pancreas responds by secreting much higher insulin levels in an effort to keep the postprandial glucose values under check. With time, the ability of the pancreas to secrete such supraphysiological doses of insulin diminishes (Starling's law of the pancreas) and overt diabetes results with an increase in fasting plasma glucose (FPG) as well[3]. The Diabetes Control and Complications Trial (DCCT)[4], the United Kingdom Prospective Diabetes Study (UKPDS)[5] and the Kumamoto study[6] have all demonstrated that maintaining glycaemic control to levels as close to physiological levels, prevents the development and progression of microvascular disease and to some extent macrovascular complications as well.

Traditionally the fasting plasma glucose has been the standard to assess the control of diabetes and the efforts to control the postprandial plasma glucose were not very aggressive. However, the recent focus on the contribution of the postchallenge or postprandial hyperglycaemia (PPHG) to the development of complications has changed the attitude of physicians as now the postprandial plasma glucose receive similar attention as the fasting plasma glucose. Indeed, postprandial glycaemic excursions do contribute to the sustained hyperglycaemia of diabetes[7]. According to Monnier[8,9], the postprandial period lasts at least for four to six hours after a meal, followed by a postabsorptive period. Using 24-hour continuous glucose monitoring system it has been shown that deterioration of glucose homeostasis in individuals with type 2 diabetes occurs in stages with an initial loss of postprandial glycaemic control, which progresses later to fasting hyperglycaemia.

There is continuing debate as to what degree of postprandial glucose contributes to the development of microvascular and macrovascular complications. Recent studies[10,11] have found PPHG to be an independent risk factor for cardiovascular comorbidities and all-cause mortality in diabetes. In this article we will discuss about postprandial excursions and the risk for cardiovascular disease.

Definition of Postprandial Hyperglycaemia (PPHG) :

The term 'postprandial' is broadly defined as the period following meal, therefore, postprandial hyperglycaemia refers to plasma glucose concentrations after eating[12]. Generally in diabetic individuals the plasma glucose levels start to increase 10 minutes after the start of a meal and in non-diabetic individuals peak around 1 hour later, rarely crossing 140mg/dl. It returns to preprandial levels by 2 to 3 hours. The profile of postprandial hyperglycaemia is determined by multiple factors including the timing, quantity and composition of the meal, carbohydrate content (both quantity and quality), insulin and glucagon secretion, etc. Because the absorption of food persists for 5 to 6 hours, this makes it difficult to define the time at which the postprandial value has to be measured. It is generally the 2-hour postplasma glucose that is used but some centres use the 1.5 hours value. Since differences in diet habits

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and preferences between various cultures, and even within the same day (eg, breakfast, lunch and dinner) can markedly reflect the glycaemic excursions, it is difficult to fix a standard time for taking the postprandial sample and it largely depends on local customs and habits[13].

However, the American Diabetes Association has suggested that in general, a measurement of plasma glucose 2 hours after the start of a meal is practical, generally approximates the peak value in patients with diabetes, and provides a reasonable assessment of PPHG[14].

Relationship between Postprandial Hyperglycaemia and Cardiovascular Risk:

Cardiovascular disease accounts for most of the increased morbidity and mortality associated with type 2 diabetes[15]. An acute elevation of the plasma glucose level triggers a series of tissue responses that may contribute to the development of macrovascular complications of diabetes. Concomitant increase of glycaemia in the postprandial phase can amplify an increase in cardiovascular risk factors while producing by itself several functional alterations favouring cardiovascular disease[16]. According to Haller[17] the development of atherosclerosis often predates a diagnosis of type 2 diabetes and it is possible that postprandial changes contribute to atherosclerosis before fasting plasma glucose concentrations are elevated. Indeed there is increasing evidence that PPHG is an important contributing factor for the development of atherosclerosis in non-diabetic individuals. There are also several experimental studies that have demonstrated the potential proatherogenic role of PPG peaks[18].

Numerous cross-sectional and prospective epidemiological studies, mostly using the oral glucose tolerance test, have shown elevated postprandial/postglucose challenge values to be independent risk factors for macrovascular complications and increased mortality risk. Table 1 provides various studies[19-38] reporting on association of postprandial hyperglycaemia with risk of cardiovascular disease since 1979. The Honolulu Heart Study[23] found a strong correlation between postchallenge glucose levels and the incidence of cardiovascular mortality. The German Diabetes Intervention Study[24], which followed newly diagnosed patients with type 2 diabetes, found moderate postprandial hyperglycaemia to be more indicative of arthrosclerosis than was fasting glucose, and found postprandial, but not fasting glucose to be an independent risk factor for cardiovascular mortality. A meta-analysis which included 95,783 subjects followed on average for 12.4 years, demonstrated an exponential relationship between the incidence of cardiovascular events and the 2-hours PPG[28]. Similar to these findings, de Vegt *et al*[30] found that the degree of risk conferred by the 2-hour postprandial glucose concentration was nearly twice that conferred by glycated haemoglobin level. The DECODE Study[35], which followed more than 25,000 subjects for a mean period of 7.3 years, confirmed that, the, 2-hour postchallenge hyperglycaemia after an OGTT is associated with increased mortality, and also that , the postchallenge glucose level is a better predictor of mortality than the fasting plasma glucose level.

Cavalot *et al*[38] in the San Luigi Gonzaga Diabetes Study in a 5-year follow-up type 2 diabetic subjects have concluded that postprandial, but not fasting, blood glucose is an independent risk factor for cardiovascular events, with a stronger predictive power in women than in men. The same group after a 14-year follow-up recently have again demonstrated that both postprandial blood glucose and HbA1c predicts CVD events and all-cause mortality in diabetic subjects.

Additionally, the Helsinki Policemen study conducted in early 1980s[22] and the Paris Prospective Study done in early 1990s[39] have also demonstrated that postprandial hyperinsulinaemia is an independent risk factor for macrovascular complications. Longitudinal studies conducted in Mauritius, Figi and Nauru have shown that isolated postchallenge hyperglycaemia ($\geq$ 11.1 mmol/l) with normal fasting plasma glucose($<$7.0 mmol/l) doubles the risk of mortality[30]. Similarly, in the Rancho Bernardo Study, isolated postchallenge hyperglycaemia was a predictor of fatal cardiovascular disease (CVD) in older women and men.

Some, studies[23,25,40] have demonstrated that even moderate postprandial hyperglycaemia (148-199 mg/dl) is not only more indicative of artherosclerosis than is fasting glucose, but also may have direct adverse effects on the endothelium. A recent study by Mah *et al*[41] hypothesise that postprandial hyperglycaemia would decrease vascular function in healthy men by inducing oxidative stress and proinflammatory responses and increasing asymmetric dimethylarginine:arginine (ADMA:arginine), a biomarker that is predictive of reduced NO biosynthesis. Many alterations found in the postprandial state could initiate a cascade of proatherogenic disturbances, which leads to endothelial dysfunction and plaque instability and furthermore, a rapid decrease in flow mediated vasodilatation has also been demonstrated in the postprandial phase in type 2 diabetic patients which is inversely correlated with the magnitude of PPHG[42].

Experimental studies have also shown a link between carotid intima media thickness(IMT), a surrogate marker for atherosclerosis and PPHG[18]. The RIAD (Risk factors in Impaired glucose tolerance for Atherosclerosis and Diabetes) study[19], conducted in 119 subjects showed that 2-hours PPG correlated better than FPG with carotid IMT. In another study[18] conducted in 582 subjects with varying degrees of glucose intolerance, 2-hours PPG was found to

Table 1 — *Studies on Association of Postprandial Hyperglycaemia with Risk of Cardiovascular Disease*

Study/year	Study	No of cases	Follow-up in years	Conclusions
Pyorala *et al* (1979)[20]	Social Insurance Institution's (SII) Coronary Heart Disease Study and Helsinki Policemen Study	4326	4 years in SII and 10 years in Helsinki Policemen study	1-hour and 2-hour OGTT glucose predicted incidence CHD risk
Jarrett *et al* (1982)[21]	Bedford Study	241	10	Protection was in CAD was lost in patients with increased PPG
Pyorala *et al* (1985)[22]	Helsinki Policemen Study	982	9.5	2-hour OGTT glucose predicted incidence CAD better than FPG
Donahue *et al* (1987)[23]	Honolulu Heart Programme	6394	12	Strong correlation between PPG levels and the incidence of cardiovascular mortality
Jackson *et al* (1992)[24]	Islington Diabetes Survey	223	-	2-hour glucose –better predictor of CAD than HbA1c
Vaccaro *et al* (1992)[25]	Chicago Peoples Gas Company Study	873	19	PPG is associated with coronary and cardiovascular mortality independent of other factors
Hanefeld *et al* (1996)[26]	German Diabetes Intervention Study	984	11	2-hour PPG but not fasting glucose is associated with increased all-cause and CVD mortality.
Balkau *et al* (1998)[27]	Whitehall Study, Paris Prospective Study and Helsinki Policeman Study	17,000	20	2-hour PPG associated with increased all-cause and CVD mortality
Barrett-Connor and Ferrare (1998)[28]	Rancho Bernardo Study	1,858	7	Isolated PPG doubles the risk-fatal CVD and heart disease in older women and men
Coutinho *et al* (1999)[29]	Meta-analysis of 20 studies	95,783	12	Progressive relationship between FPG and 2-hour glucose and CVD
De Vegt *et al* (1999)[30]	Hoorn Study	2,363	8	2-hour-glucose –better predicts mortality than HBA1c and increases CVD mortality by 62%
Shaw *et al* (1999)[31]	-	9,179	5-12	Isolated PPG doubled the mortality risk
Tominaga *et al* (1999)[32]	Funagata Diabetes Study	2,651	7	IGT – a risk factor for CVD, but not IFG
Barzilay *et al* (1999)[33]	Cardiovascular Health Study	4,515	8	Subjects with IGT – 22% increased risk of CVD compared with NGT subjects
Saydah *et al* (2001)[34]	National Health and Nutrition Examination Survey (NHANES) Mortality Study	3,174	12-16	Relative risk for death from CVD – 20% more in IGT and 70% in previously undiagnosed type 2 diabetes
DECODE Study Group (2001)[35]	Diabetes Epidemiology Collaborative analysis of Diagnostic criteria in Europe (DECODE) Study	25,364	10	2-hour PPG is associated with increased mortality, and a better predictor than FPG level
Meigs *et al* (2002)[36]	Framingham OffSpring Study	3,370	4	2-hour glucose predicts CVD events better than HBA1C
Esposito *et al* (2004)[37]	Campanian Postprandial Hyperglycaemia Study	75	1	Reduction of PPG is associated with carotid intima media thickness
Cavalot *et al* (2006)[38]	San Luigi Gonzaga Diabetes Study	529	5	PPG, but not FPGs an independent risk factor in women than men for cardiovascular events in type 2 diabetes
Cavalot *et al* (2011)[39]	San Luigi Gonzaga Diabetes Study	505	14	Both PPG and HbA1C predict cardiovascular events and all-cause mortality

OGTT: Oral glucose tolerance test; PPG : Postprandial glucose; CAD: Coronary artery disease; CVD: Cardiovascular disease; FPG: Fasting plasma glucose; HbA1c: Glyosylated haemoglobin; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; NGT: Normal glucose tolerance

be the most important glycaemic determinant of carotid IMT, compared to HbA1c or FPG.

Evidence also suggests that control of PPHG may reduce the development of CVD. There are few intervention studies which showed that by controlling PPGH there was a reduced risk of the development of cardiovascular events[43] and also a significant decrease in the progression of carotid IMT[36,44]. However the recent multinational, randomised, controlled trial, the Hyperglycaemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D)[45], which compared the effects of prandial *versus* fasting glycaemic control on risk for cardiovascular outcomes in patients with type 2 diabetes after acute myocardial infarction (AMI) identified a linear relationship between the risk of CVD death and PPHG[11]. According to Ceriello[45], negative result of the HEART2D study is in line with the ACCORD trial[46], ADVANCE study[47], longterm follow-up of the UK Prospective Diabetes Study[48] and STOPNIDDM[44] studies. It appears that if the control of hyperglycaemia (either fasting [ACCORD and ADVANCE] or postprandial [HEART2D]) is started too late, the possible beneficial effect of treating hyperglycaemia with re-

spect to preventing CVD may be lost.

It has been shown that PPHG leads to postprandial lipaemia (mainly triglyceride rich particles and free fatty acids), a state during which lipoprotein moieties of high atherogenicity circulate in the blood[48-50]. In a study investigating the effects of postprandial lipaemia on CIMT, postprandial triglycerides had the strongest correlation with CIMT, although PPHG, postprandial triglycerides and fasting LDL-C levels were all independently related[50]. Enhanced lipid peroxidation is also associated with postprandial elevations of blood glucose[51,52], leading to oxidative stress which may contribute to the development of micro- and macrovascular complications of diabetes mellitus.

Conclusions :

Nearly 75% of mortality in individuals with type 2 diabetes can be accounted for by CVD. It is now being increasingly realised that PPHG plays an important role in the development of macrovascular and microvascular complications in individuals with diabetes and impaired glucose tolerance. During PPHG, hyperglycaemic spikes cause endothelial dysfunction, inflammatory reactions and oxidative stress, which may lead to progression of atherosclerosis and occurrence of cardiovascular events. There is an alarming body of epidemiological and interventional evidence suggesting that postprandial, but not fasting hyperglycaemia, independently predicts CVD events. Thus attempts should be made to correct PPHG in addition to FPG, to reduce the risk of CVD and the earlier these strategies are initiated the better would be the outcomes.

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