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Beyond postprandial hyperglycaemia: metabolic factors associated with cardiovascular disease

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Abstract

Type II (non-insulin-dependent) diabetes mellitus is associated with a considerably enhanced risk of cardiovascular disease morbidity and mortality. Several epidemiological studies have shown an association between the 2-h glucose value after a 75 gm glucose load (2hPG) and mortality from all causes and from cardiovascular disease. The key question is whether postprandial glucose is related causally to the adverse outcomes (risk factors) or just a marker of risk. Since insulin resistance is one of the determinants of the 2hPG, factors associated with the insulin resistance syndrome, in particular postprandial hypertriglyceridaemia, also need to be considered. Glycaemic excursions could contribute to oxidative stress, endothelial dysfunction, formation of advanced glycation end-products and prolongation of the QTc interval. However, high postprandial concentrations of triglyceride rich lipoproteins, which can be partly attributed to obesity and insulin resistance, have now been recognised to affect endothelial function, to promote atherogenesis, and to be associated with coronary artery disease. On the basis of present evidence Type II diabetic patients require good overall glycaemic control, as reflected by target values of HbA_{1c}. However, postprandial hyperglycaemia should be considered as a marker of underlying metabolic abnormalities. Therefore, at present there is no evidence to support the recommendation to consider postprandial hyperglycaemia as a treatment target in itself and would thus require intervention studies showing added benefit of selectively targeting at meal-related glucose excursions in patients with an adequate HbA_{1c}. Drugs aiming at improving only postprandial glucose values are not likely to lower the excess mortality associated with Type II diabetes. [Diabetologia (2002) 45:461–475]

Keywords Type II diabetes, postprandial hyperglycaemia, postprandial hypertriglyceridaemia, dyslipidaemia, cardiovascular disease, insulin resistance, atherosclerosis, oral hypoglycaemic agents, endothelial function, oxidative stress, QT interval.

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Abbreviations: ANT, Adenine nucleotide translocator; CETP, cholesterol ester transfer protein; DECODE, diabetes epidemiology collaborative analysis of diagnostic criteria in Europe; IDL, intermediate density lipoprotein; 2hPG, plasma glucose value 2hours following a 75 gram glucose load; QTc, heart rate adjusted QT interval on the ECG

Introduction

Type II (non-insulin-dependent) diabetes mellitus is a very prevalent chronic disease occurring in 2 to 4% of the general population in the Western world and up to 20 to 30% in high risk populations [1]. Moreover, the global burden of diabetes is expected to increase dramatically in the future. The major cause of the high and rising incidence of diabetes is global westernization occurring in major parts of the world and especially in Asia.

Type II diabetes is associated with a considerably enhanced risk of cardiovascular disease; the risk is

two to fourfold for men and women, respectively, compared with non-diabetic persons [2–4]. This excess risk is not fully explained. Less than half of this excess risk can be attributed to the higher prevalence of classic risk factors as for example dyslipidaemia (high triglycerides, low HDL cholesterol) and hypertension [5, 6].

Several epidemiological studies in the past 20 years have shown an association between post 75 gm glucose load glucose concentrations (2hPG) and the occurrence of cardiovascular disease in the general population [7–18]. A recent meta-analysis including more than 95 000 people from 22 studies confirmed the association between 2hPG and incident cardiovascular events [19]. In some studies the fasting glucose concentration was also associated with cardiovascular disease [16, 20].

In addition, a few studies in persons with manifest diabetes have also shown an association of 2hPG with cardiovascular disease [21]. Of interest are the diabetic patients with isolated postprandial glucose, in whom about a twofold risk of cardiovascular disease has been found [22–24].

Two important questions arise from these observations: Is postprandial hyperglycaemia an independent risk factor, i. e. causally related to cardiovascular disease, to which the enhanced risk can fully be attributed? If so, do we need to consider the enhanced meal-related glucose excursions as a treatment target in patients with Type II diabetes?

Alternatively, postprandial hyperglycaemia might just be a marker for the increased risk of cardiovascular disease. In that case other factors need to be identified which can explain the epidemiological observations.

Before addressing these questions we briefly review the metabolic abnormalities in Type II diabetes, the known risk factors for macrovascular complications, and the possible mechanisms explaining the observed associations between meal related metabolic changes and cardiovascular disease. Finally, the therapeutic consequences, if any, will be discussed.

Factors determining fasting and postload glucose, and postprandial lipid concentrations

The most important determinants of fasting and post glucose load plasma glucose concentrations are beta-cell function and tissue sensitivity to the available insulin (insulin sensitivity). Normal glucose tolerance is dependent on an adequate insulin response and appropriate suppression of hepatic glucose production after a carbohydrate load. Beta-cell dysfunction and insulin resistance contribute to glucose intolerance and both can be found very early in the disease process resulting in Type II diabetes [25–27]. Even in normal glucose tolerant, first degree, family members

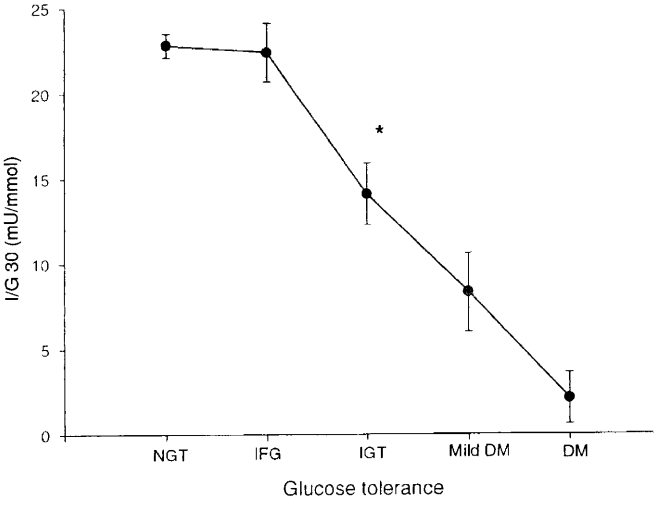

Fig. 1. Insulin secretion response to a 75 g oral glucose load expressed as delta insulin over delta glucose from 0 to 30 min in subjects with normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance and diabetes (Botnia Study). The insulin secretory response starts to decline already in the prediabetic state as illustrated by a diminished insulin 0–30' to glucose 0–30' ratio in subjects with impaired glucose tolerance (Tripathy D et al. 2000, Diabetes 49: 975–980 with permission [32])

of patients with Type II diabetes beta-cell dysfunction (e. g. loss of the normal insulin secretion pattern) and diminished insulin action can be found [28–31].

Various studies have tried to differentiate the pathophysiological mechanisms which are involved in the regulation of fasting and post challenge blood glucose concentrations. The main factor contributing to the conversion from IGT to diabetes has been shown to be the decompensation or further deterioration of beta-cell function [27, 28, 32]. These studies were carried out with the use of repeated oral glucose tolerance tests and/or intravenous glucose tolerance tests.

The traditional view is that the progression from normal glucose tolerance to IGT is predominantly due to insulin resistance, whereas the final conversion to Type II diabetes could be attributed to beta-cell failure. Recent studies, however, have shown that the factors that determine the fasting and post challenge glucose values partly overlap. For example in the Botnia study it was shown that impaired fasting glucose is characterised mainly by insulin resistance whereas impaired glucose tolerance is related to an abnormal insulin response [32] (Fig. 1). Also, a study in subjects with IGT showed that the insulin response, as reflected by the 30 min insulin-to-glucose ratio, was the major determinant of the 2-h glucose values after a 75 g glucose challenge [26]. In the Botnia study the 30 min insulin value explained 39 % of the variance in the 2hPG [32].

In contrast, a study on Pima Indians suggested that IFG was characterised by a mild impairment of the acute insulin response which was more clearly related

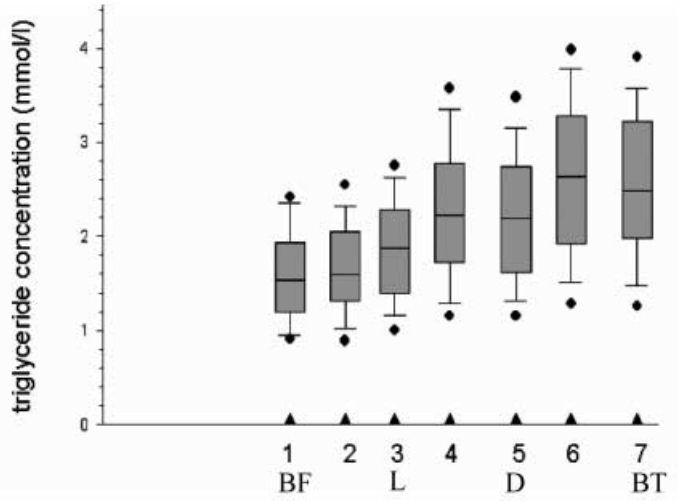

Fig. 2. Box and whisner plots (median, box [25–75th percentiles], whiskers [10–90th percentiles] and dots [5–95th percentiles]) of the home measured triglyceride concentrations in patients with Type II diabetes selected on the basis of "normal" fasting triglyceride concentrations (< 2.2 mmol/l). Measurements were made before and 2 h after the main meals and at bedtime. Since the triglyceride concentrations show a gradual rise over the day, the fasting concentrations severely underestimate the triglyceride exposure in persons with Type II diabetes. Numbers 1–7 indicate the time points of the measurements: fasting, post breakfast (B), before and after lunch (L), before and after dinner (D), and at bedtime (BT), respectively (Teno S et al. 2000, Diabetes Care 23: 1401–1406 with permission [68])

to the fasting glucose value than to the 2-h post challenge glucose concentration [33]. The apparent contradictory findings between the Finnish study and the findings in Pima Indians could be explained by the differences in applied methodology (intravenous glucose tolerance test, assessing insulin peak concentrations 3 to 5 min after the glucose challenge vs the 30 min insulin concentrations after a 75 g oral glucose load).

In either case the beta-cell defect is present and more so when allowed for the ambient insulin resistance. Moreover, as shown by the Hoorn study, the highest risk for conversion to diabetes was found in the persons with increased fasting proinsulin concentrations, indicative for an insulin secretory defect and with increased fasting and post challenge glucose values [34, 35]. These observations strongly suggest that beta-cell dysfunction is primarily responsible for the deterioration of glucose tolerance and that insulin resistance accelerates this process.

In patients with Type II diabetes and in normoglycaemic first degree relatives of Type II diabetic patients serum triglycerides (VLDL and chylomicrons) have been shown to be increased throughout most of the day [36–38]. The major contributing factors to the increased triglyceride-rich lipoproteins in the diabetic state are increased VLDL production and competition of chylomicron and VLDL particles for the removal mechanisms, as for example lipoprotein lipase and hepatic receptors [39]. A meal-related increase of chylomicron concentrations will saturate the catabolic pathways resulting in a longer residence time of triglyceride rich remnant particles. These alterations in the kinetics will promote the cholesterol ester transfer protein (CETP) mediated transfer of cholesteryl esters and triglycerides between the triglyceride enriched lipoproteins and LDL and HDL. This exchange will ultimately result in a smaller density of LDL and HDL and low HDL cholesterol concentrations, all of which are known to be independent predictors of cardiovascular disease. In addition, evidence for a direct atherogenic effect of remnant particles has been found [40–42].

Triglyceride concentrations are measured mostly in the fasting state only. The fasting value should be considered the nadir of the 24-h triglyceride profile and could therefore be misleadingly low [43, 44].

In diabetes, postprandial dyslipidaemia is a frequent feature, even in patients with apparently normal fasting triglyceride values. This also became apparent in patients with Type II diabetes with so-called normal fasting triglyceride concentrations; defined as plasma concentrations of less than 2.2 mmol/l (Fig. 2). In 81 persons the daytime triglyceride profiles were assessed with an ambulatory plasma triglyceride measurement device [45]. The average 24-h triglyceride concentrations were 2.2 ± 0.65 mmol/l with mean fasting concentrations of 1.3 ± 0.51 mmol/l. After breakfast the triglyceride concentrations gradually rose to peak concentrations between dinner and bedtime. The long duration of the so-called postprandial state can probably be explained by the insulin resistant state as discussed earlier. Postprandial hypertriglyceridaemia and the associated atherogenic alterations of the lipoproteins are now considered to be part of the insulin resistance syndrome [46, 47].

How are plasma glucose and triglyceride concentrations associated with cardiovascular disease risk?

Plasma glucose as predictor of cardiovascular disease. The substantial disagreement in the classification of individuals between the 1985 World Health Organisation (WHO-85) and the recently introduced 1997 American Diabetes Association (ADA-97) criteria raises the question as to whether the risk for mortality and for macrovascular complications is more closely associated with fasting or with postload (2hPG) hyperglycaemia. Summarising the results of several prospective studies which have addressed this question (Table 1), diabetes according to either set of diagnostic criteria was associated with an increased risk for mortality and cardiovascular complications. In the Hoorn study and in the DECODE study, the subjects

Table 1. Published risks of mortality and cardiovascular disease in glucose intolerance categories according to the WHO-85 and ADA-97 diagnostic criteria

Study	*n*	Age (years)	Follow-up (years)	End point	Reference category FPG / 2HPG (mmol/l)	RR DM WHO-85	RR DM ADA-97	RR IGT	RR IFG
DECODE Study [17]	25364	> 30	10	mortality	< 6.1 / < 7.8	2.0 [a]	1.6	1.6	1.2
Hoorn Study [48][b]	2468	50–75	9	mortality	< 7.8 / < 7.8	1.7		1.3	
					< 6.1		1.6		1.5
Mauritius, Fiji and Nauru [22]	9179	> 20	5–12	mortality	< 7.0 / < 11.1	male 2.7[a] female 2.0[a]	male 1.6 female 1.2	–	–
				CVD-mort		male 2.3[a] female 2.6[a]	male 1.3 female 1.4		
Funagata Diabetes Study [14]	2534	> 40	7	mortality	< 7.8 / < 7.8	1.2		1.3	
					< 6.1		1.7		1.2
				CVD-mort	< 7.8 / < 7.8	2.3		2.2	
					< 6.1		2.5		1.1
Cardiovascular Health Study [18]	4515	> 65	8	CVD	< 7.8 / < 7.8	1.7		1.2	
					< 6.1		1.5		1.4
					< 6.1 / < 7.8	1.7	1.7	1.2	1.5
Strong Heart Study [51]	6483	45–74	5	CHD	< 6.1 / < 7.8	2.7	2.7	0.7	0.7

FPG, fasting blood glucose; 2hPG, 2-h postload glucose; DM, diabetes; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; RR, relative risk; mort, mortality; CVD, cardiovascular disease; CHD, coronary heart disease

[a]IPH, isolated postload hyperglycaemia (FPG < 7.0 mmol/l, 2hPG ≥ 11.1 mmol/l)

[b]The Hoorn Study is participating in the DECODE study

fulfilling both sets of criteria had similar mortality risks of 2.2 and 2.3, respectively, compared to subjects with normal glucose concentrations [48, 50]. Furthermore, in the DECODE study mortality increased in subjects with normal fasting glucose ($p < 0.001$) and impaired fasting plasma glucose ($p < 0.013$) with increasing 2hPG concentrations, which was not observed for increasing concentrations of fasting plasma glucose in categories of 2hPG [17]. In the Cardiovascular Health study and the Strong Heart study the degree of risk for incident cardiovascular disease was similar for subjects diagnosed with diabetes by the WHO-85 or ADA-97 criteria [18, 51]. However, in the Cardiovascular Health study more subjects with incident cardiovascular disease were classified as having abnormal glucose concentrations by the WHO-85 criteria than by the fasting ADA-97 criteria [18]. In the Funagata Diabetes study in Japan only IGT and not IFG was a predictor for death from cardiovascular disease [14]. These and other studies, show that 2hPG especially is a good predictor for mortality, which has been attributed to the association between postload glucose concentrations and insulin resistance [16, 17, 22, 48, 52, 53]. Both the ADA-97 and WHO-85 diagnostic criteria identify subjects at risk for mortality and cardiovascular complications but the WHO-85 diagnostic criteria seem to have a greater ability to detect subjects at risk for these complications. Clearly, the 75 g OGTT and the 2hPG in particular provides additional prognostic information for mortality and macrovascular disease.

A recent study examined the association between 2hPG and atherosclerosis in subjects with various degrees of glucose intolerance, ranging from normal glucose tolerance to diabetes [54]. Glucose tolerance, carotid intima media thickness (IMT), a surrogate marker of atherosclerosis, estimated with an ultrasound technique, and cardiovascular disease risk factors were assessed in 582 subjects. The 2hPG was found to be the most important glycaemic determinant of IMT, more so than HbA_{1c} or fasting plasma glucose. An increase of the 2hPG was associated with an increase of the IMT within each tertile of HbA_{1c}. In contrast, fasting plasma glucose was not related with a rise of IMT in the HbA_{1c} tertiles. The other independent determinants of IMT were: age, male sex, proinsulin, albuminuria, total and HDL cholesterol. This study confirms the findings of the DECODE study, showing an association between the 2hPG and atherosclerotic vascular disease.

Also in persons with manifest Type II diabetes a few studies have shown that 2hPG is an independent predictor of myocardial infarction. In the Diabetes Intervention study 1139 newly diagnosed patients were followed for 11 years. The identified independent predictors for death were blood pressure, smoking, male sex, age, triglycerides and postprandial glucose [21]. Another study from the same group investigated whether isolated postchallenge hyperglycaemia constituted a risk factor for atherosclerosis as reflected by IMT. They studied 119 asymptomatic diabetic patients with either isolated fasting (IFH), postchallenge (IPH) or combined hyperglycaemia (FH-PH) [49]. The IMT increased with the deterioration of glucose tolerance, such that the lowest IMT value was found in those with normal glucose tolerance, intermediate values in subjects with IFH and IPH and the highest values in persons with combined hyperglycaemia. In multiple regression analysis the most important determinants were 2hPG, in addition to age,

sex, total and HDL cholesterol and blood pressure. The fasting plasma glucose concentration did not contribute to the IMT measure in any class of 2hPG. Hence, the authors strongly favour the OGTT for the assessment of the cardiovascular risk in persons at risk of diabetes.

An important and often overlooked group is the mostly elderly patients with isolated post challenge hyperglycaemia. They are characterised by a normal fasting glucose concentration and a diabetic 2hPG and at least three studies have shown that they suffer about a twofold risk of cardiovascular and all cause mortality [22–24].

It is therefore evident that the 2hPG is a much stronger determinant of either mortality (population based studies) and of IMT (studies in specific groups) than the other glycaemic indices, as for example fasting plasma glucose concentrations and HbA_{1c}.

Plasma triglyceride concentrations as predictors of cardiovascular disease. In 1959 an association between triglyceride concentrations and coronary heart disease events was first reported [55]. In most studies since then, the association between triglycerides and coronary heart disease was no longer statistically significant after multivariable adjustment and especially for HDL cholesterol [56]. The known inverse association between HDL cholesterol and triglycerides makes it very difficult to determine whether triglycerides are an independent risk factor for atherosclerotic vascular disease [57]. It therefore probably required a meta-analysis including data of 57 000 subjects from 17 studies to show that the triglyceride concentration is an independent risk factor for cardiovascular disease, also when adjusted for HDL cholesterol [58]. A 1 mmol/l increase was associated with a relative risk of 1.3 for men and 1.8 for women.

A more recent study, applying a nested case-control design on the data of the Physician Health study, showed that the non-fasting triglyceride concentrations strongly predicted incident myocardial infarctions. This association was independent of other risk factors, however, the known interrelation between HDL cholesterol, triglycerides and LDL size could be shown, reflecting the underlying metabolic disturbance, i. e. insulin resistance or metabolic syndrome [59]. The authors concluded that triglyceride concentrations are an important indicator of risk and can therefore be used as such. Similar results were obtained on men and women in a case-control study in the Boston area, also after adjusting for HDL cholesterol concentrations [60]. The Copenhagen Male study showed that for each tertile of the HDL cholesterol distribution an increase of triglycerides was associated with an increased risk for incident heart disease during an 8-year follow-up, also after adjustment for total and LDL cholesterol [61]. Thus the different risk factors are again shown to be closely interrelated but this analysis provided insight in the contribution of a rise of triglyceride on the risk for a given HDL-cholesterol range: a triglyceride rise from 0.88 mmol/l to 2.45 mmol/l was associated with more than double the risk in each tertile of the HDL-cholesterol distribution. In a 10-year follow-up study in Malmo on 12 510 men the interaction between total cholesterol and triglyceride concentrations on the risk of myocardial infarction was assessed whereby triglyceride values were strongly associated with incident myocardial infarctions [62]. Also an interaction between triglyceride concentrations and cholesterol was found, such that for increasing triglyceride concentrations the effect of the total cholesterol concentration became stronger. These findings suggest that triglycerides and in particular the chylomicron remnant particles are atherogenic [63]. Recent studies have addressed this issue by applying new assays for measuring remnant particles in population-based studies. In the Framingham heart study remnant like particles (RLP) - cholesterol (C) and RLP-triglycerides were measured in samples of 1567 women of whom 83 had cardiovascular disease [64]. Fasting RLP-C was associated ($p = 0.002$) with prevalent CVD in women, after adjustment of other risk factors, which further supports the concept that remnant particles should be considered atherogenic. In the past few years several clinical studies have also suggested that high postprandial triglyceride-rich lipoproteins are related to coronary heart and/or carotid artery disease in non-diabetic subjects [38, 65, 66]. Moreover, an association could be shown between postprandial chylomicron remnants and the progression of angiographically determined coronary heart disease [40]. More recently the postprandial apolipoprotein B48 and B100 response in 43 Type II diabetic patients was compared with that in healthy control subjects to differentiate between intestinal (B48) and liver derived triglyceride-rich lipoproteins (B100) in relation to the presence of coronary heart disease as estimated by quantitative coronary angiography [67]. Patients with mild and severe coronary heart disease had similar postprandial responses of B48 and B100 containing lipoprotein particles. In both groups the responses were greater than in the control group. Of interest, a correlation between maximal stenosis in the coronary angiogram (%) and postprandial concentrations of apolipoprotein B100 of IDL was found. The latter finding suggests that the smaller remnant particle is atherogenic.

In patients with Type II diabetes the association between postprandial triglyceride concentrations and the carotid (IMT) by ultrasonography was investigated [68] (Fig. 3). The IMT of the carotid artery has been shown to be predictive of incident coronary heart disease in non-diabetic populations and in Japanese Type II diabetic patients [69–72]. In 61 non-obese Type II diabetic patients in Japan plasma glucose

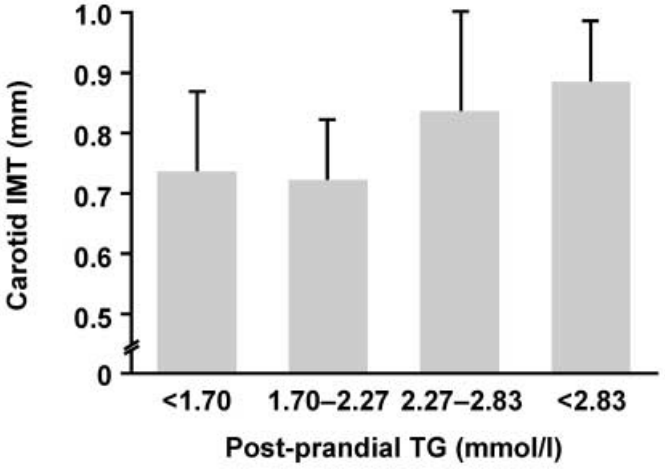

Fig. 3. Association between carotid intima media thickness, measured with ultrasonography and triglyceride concentrations in the fasting state fTG, and 4 h after a meal (pTG) in 42 Type II diabetic patients with normal fasting triglyceride concentrations (< 1.7 mmol/l) (Tripathy D et al. 2000, Diabetes 49: 975–980 with permission [68])

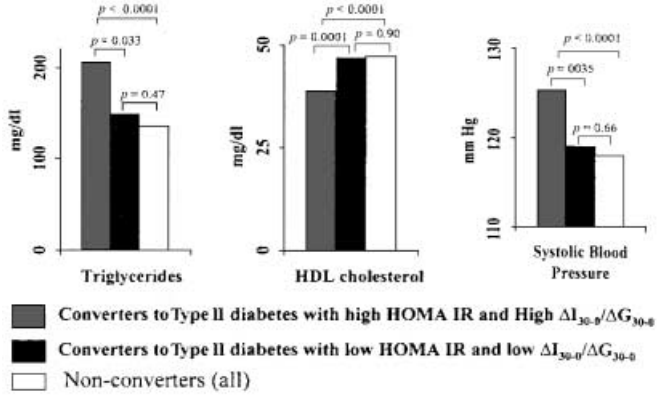

Fig. 4. Cardiovascular risk factors by insulin resistance (HOMA-IR), insulin secretion (delta insulin/delta glucose 0–30 min) and conversion status. The subjects converting to diabetes with a high HOMA-IR, indicating insulin resistance, show a worse cardiovascular risk profile than those who converted with a relatively normal insulin sensitivity (low HOMA-IR) (Haffner SM et al. 2000, Circulation 101: 975–980 with permission [78])

and serum lipid concentrations were measured before and 4 hours after a standardised meal. In univariate analysis fasting total cholesterol, LDL cholesterol and triglyceride concentrations were associated with IMT. The postprandial variables, which were associated with IMT included plasma concentrations of glucose, triglyceride, cholesterol, and C-peptide. In multivariate analysis only fasting LDL cholesterol ($p = 0.05$), and postprandial concentrations of triglyceride ($p = 0.002$) and glucose ($p = 0.02$) were independently associated with carotid IMT. Postprandial triglyceride had the strongest association with carotid IMT [68]. In the patients with normal fasting triglyceride concentrations an association was also found between postprandial triglyceride concentrations and carotid IMT.

Taken together, these associations between postprandial lipid metabolism and atherosclerosis support the concept that atherosclerosis is a postprandial phenomenon.

Are the associations of 2hPG and triglyceride concentrations with cardiovascular disease explained by insulin resistance? Insulin resistance has been shown to be associated with different cardiovascular risk factors. These include hypertension and dyslipidaemia (notably high triglyceride concentrations and low HDL cholesterol concentrations) [73]. Later insulin resistance was also found to be associated with a high waist circumference and waist-to-hip ratio [74, 75]. This clustering of risk factors for cardiovascular disease, commonly referred to as the insulin resistance syndrome or IRS, has repeatedly been shown, using different methods and in various ethnic groups [76, 77]. However these findings only explain a part of the excess risk of cardiovascular disease associated with abnormal glucose tolerance.

A recent 7-year follow-up study on 1734 non-diabetic subjects from the San Antonio Heart study showed that persons who became diabetic were more likely to harbour cardiovascular disease risk factors than those who did not become diabetic [78]. Only those who were found to be insulin resistant, as reflected by the HOMA-IR (homeostatic model assessment for insulin resistance), were showing an adverse cardiovascular disease risk profile in the prediabetic state. In contrast, those with a predominant decrease in insulin secretion (delta insulin 0–30 min/delta glucose 0–30 min, after a 75 g glucose load) with similar 2hPG values had a more favourable profile. These findings confirm that the Type II diabetic population is heterogeneous with respect to insulin resistance and beta-cell dysfunction. Moreover, the presence of atherogenic risk factors, i.e. high waist circumference, low HDL cholesterol, high triglycerides, and high blood pressure are more closely related to the presence of insulin resistance than to the presence of an insulin secretory defect (Fig. 4).

In the newly diagnosed patients with diabetes in the United Kingdom prospective diabetes study (UKPDS) the major predictor of coronary heart disease was LDL cholesterol; other independent predictors apart from age and sex were low HDL cholesterol, high HbA_{1c} and systolic blood pressure, and smoking [79]. In the UKPDS no information is available on glucose excursions. LDL cholesterol has been shown to be a risk factor for coronary artery disease in non-diabetic and diabetic subjects [80] but has not always been identified as such in diabetic cohorts [81]. LDL cholesterol has now more convincingly been recognised as a risk factor for Type II diabetes because of the post hoc analyses of the secondary

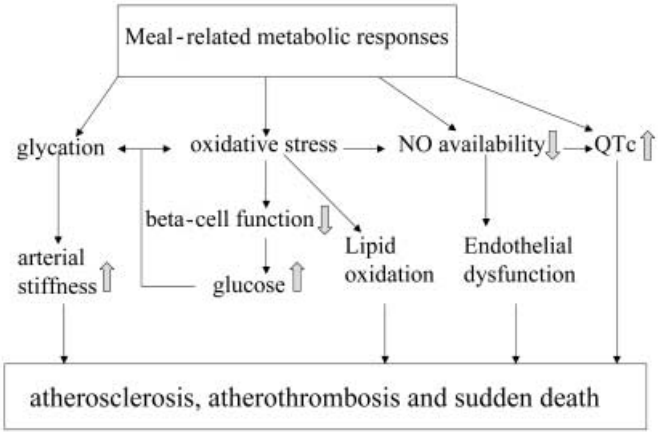

Fig. 5. Meal-related metabolic changes contributing to glycation, oxidative stress, depressed nitric-oxide (NO) availability, and prolongation of the QTc interval. These interrelated abnormalities could in turn lead to arterial stiffness, lipid oxidation, endothelial dysfunction, and manifestations of cardiovascular disease, respectively

prevention trials using cholesterol lowering drugs (HMG CoA reductase inhibitor) as for example in the 4S and CARE study, showing that LDL lowering effectively reduces recurrence of coronary heart disease events [82, 83]. To some extent it is remarkable that LDL cholesterol has emerged as an independent risk factor for Type II diabetes. Most cross-sectional studies have not or only to a very modest extent shown an increased total and/or LDL cholesterol in patients with abnormal glucose tolerance [84, 85]. In summary, the observed association between postload excursions of glucose with cardiovascular disease is at least partly explained by the presence of insulin resistance and related cardiovascular disease risk factors.

Biochemical and physiological responses to meal

Different mechanisms can potentially explain the observed associations of meal-related metabolic changes and cardiovascular disease. These include oxidative stress, glycation, depressed nitric oxide availability, and prolongation of the QTc interval. These mechanisms are strongly interrelated (Fig. 5).

Oxidative stress. This term refers to the oxidative damage incurred by reactive oxygen species. Diabetes is associated with an enhanced production of reactive oxygen species and an impaired anti-oxidant defence [86, 87]. Hyperglycaemia is known to stimulate the production of reactive oxygen species by several pathways. These include non-enzymatic glycation, auto-oxidation of glucose and stimulation of the polyol pathway. Two studies also suggested that the anti-oxidant status in the postprandial state is diminished and the susceptibility of LDL to oxidation is enhanced [88, 89]. These effects are more prominent in patients with diabetes than in healthy control subjects [88]. In particular, the total radical trapping anti-oxidant parameter, which is a global measure of plasma anti-oxidant capacity, decreased considerably during the meal. These changes were attributed to the concomitant hyperglycaemia. It is however not possible to exclude that changes in other metabolic substrates might be responsible for the observed changes in oxidative stress. The NEFA and triglyceride responses were greater and lasted longer in the Type II diabetic patients than in the control subjects. These substrates can contribute to oxidative stress [90].

We recently suggested that intracellular accumulation of long chain fatty acyl CoA in obesity is the starting point of enhanced oxidative stress and adenosine release [90, 91]. Obesity, and in particular central fat distribution, is not only associated with increased adipose tissue fat stores and increased triglyceride rich lipoprotein concentrations; also cytosolic triglyceride stores in other tissues, such as muscle tissue, liver and beta cells are increased. Increased concentrations of intracellular long-chain acyl CoA esters inhibit the mitochondrial adenine nucleotide translocator resulting in an intramitochondrial rise of the ATP:ADP ratio. Intramitochondrial ADP deficiency stimulates oxygen free radical production [92]. This could be due to a lowered proton gradient consumption by ATPase, resulting in electrons accumulating in the electron transfer chain. Tissues, which are likely to be susceptible to oxidative stress, are those that have a high-energy demand and/or a poor free radical scavenging capacity, including beta cells. Thus according to our hypothesis oxidative stress induced by intracellular triglyceride accumulation contributes to the gradual decline in beta-cell function. Data supporting that oxidative stress could be involved in the deterioration of beta-cell function has shown that gluthathione infusion potentiates glucose induced insulin secretion in persons with impaired glucose tolerance [93]. However, these findings should not be over-interpreted, since it is doubtful whether these acute responses can be attributed solely to alleviation of the oxidative stress burden on beta cells [93].

A second phenomenon related to intracellular long chain Acyl-CoA accumulation induced impairment of oxidative phosphorylation is a chronic systemic increase of adenosine [91]. Chronic increase of adenosine release is known to stimulate, amongst others, the sympathetic nervous system and to induce renal vasoconstriction. The enhanced production of adenosine could therefore also contribute to the haemodynamic alterations involved in the insulin resistance syndrome.

Together, obesity and meal-related perturbation in different substrates could stimulate via separate

routes the production of reactive oxygen species and in turn accelerate atherogenesis [89, 90]. Since obesity alone also is associated with insulin resistance and oxidative stress, the observed associations between postmeal metabolic excursions and oxidative stress are likely to be modified by body weight.

Glycation. Meal-related glucose excursions could potentially contribute to the glycation of apolipoproteins and transfer proteins enhancing the clearance of LDL via the scavenger pathway and the exchange of cholesteryl ester for triglycerides via the cholesterol ester transfer protein (CETP), rendering LDL more atherogenic [94, 95]. Also, the glycation process involving small dense LDL could enhance the susceptibility to oxidative stress, further contributing to the atherogenicity of these particles [96]. Thus, several mechanisms might increase the atherosclerotic risk associated with meal related triglyceride rich lipoproteins. However, the clinical relevance of these changes has not been established.

Accumulation of AGE is known to adversely affect several tissues and to be involved in the development of the well-known microvascular complications of diabetes [97]. The formation of AGE is also accompanied by the production of reactive oxygen species. Not only from glucose, but preferably so and at a higher rate, AGEs are formed from glycolysis intermediates as for example fructose, glucose 6-phosphate and glyceraldehyde 3-P. The high rate of AGE formation was shown in cultured endothelial cells. After only 1 week the AGE content of endothelial cells was raised about 14-fold when cultured under hyperglycaemic conditions [98]. This high rate of AGE formation is probably a result of the increase in intracellular glycolytic intermediates. Advanced glycation end products could affect large vessel function by inducing abnormalities in extracellular matrix function, affecting the structure (enhance stiffness) and function of large vessels. This has been shown in animals, where AGEs decreased the elasticity and vasodilatory response to nitric oxide [99]. Also, the administration of drugs, which break the AGE cross-links to diabetic rats reversed the diabetes induced increase of large artery stiffness [100].

Even in non-diabetic subjects fasting glucose and HbA_{1c} have been found to be associated with the carotid intima media thickness (IMT) [54, 101, 102]. In persons with impaired glucose tolerance, thus characterised by moderately increased postprandial glucose only, the major determinants of the changes in carotid artery diameter and in distensibility (stiffness) occurring over a follow-up period of 3 years were, apart from blood pressure, fasting blood glucose and HbA_{1c}, and insulin concentrations [102]. It was suggested that in women especially insulin resistance, as reflected by high insulin concentrations, could contribute to arterial stiffening. Insulin has been suggested to stimulate collagen synthesis and smooth muscle cell proliferation [52]. Thus, the observed vascular changes cannot solely be attributed to the small increase of glucose concentrations. It is very likely that other mechanisms, and insulin resistance in particular, are involved.

Depressed nitric oxide availability. In patients with diabetes a diminished vasodilatory response, measured with ultrasound techniques, has been documented [103]. This is suggestive of depressed nitric oxide availability. In both Type I and Type II diabetes chronic hyperglycaemia has been shown to impair endothelial function [104, 105].

A measure of endothelial function is the post-ischaemic flow-mediated endothelium dependent vasodilatation [106, 107]. Applying this technique in persons with and without diabetes, the vascular response to different meals has been studied. In healthy volunteers a fatty meal has been shown to induce vasodilatation and to increase forearm blood flow [108]. These changes could be related to the insulin and triglyceride responses. Possibly these haemodynamic responses could be attributed to the vasodilatory effect of insulin [109]. In vitro studies have shown that hyperglycaemia and insulinopenia can suppress nitric oxide production in human coronary endothelial cells, whereas high insulin concentrations stimulate nitric oxide production [110]. Also obesity, insulin resistance and dyslipidaemia without manifest hyperglycaemia have been associated with endothelial dysfunction [106, 108, 111–116]. In vivo and in vitro studies have shown that remnant lipoproteins affect endothelial function, as reflected by lowered nitric oxide production and activity [112, 117–119]. These observations have been confirmed in a study on 20 healthy volunteers given a fat load of 50 g of whipped cream per square metre body surface area. The consumption resulted in a rise of triglyceride concentrations from 1.0 to 1.8 mmol/l at 4 h. The flow-mediated dilatation (FMD) of the brachial artery decreased from 10.6 % before the meal to 5.8 % at 4 h after the fat load [114]. These authors also showed that the attenuation of FMD can be abolished by folic acid pre-treatment, which could be attributed to an increase of nitric oxide production. These findings are in contrast with the earlier mentioned results from studies in healthy volunteers showing a vasodilatory response after a high-fat meal [108]. This could be explained by differences in meal composition resulting in different insulin induced nitric oxide mediated vascular responses.

A recent study in 34 healthy men assessed the association between LDL particle size and endothelial function [116]. Forearm blood flow responses to intrabrachial artery infusion of acetylcholine (endothelium dependent vasodilator) and sodium nitroprusside (endothelium independent vasodilator) were as-

sessed. In this study LDL size was the only determinant of endothelium dependent vasodilatation, strongly suggesting that small and dense LDL cholesterol could, at least partly, mediate the adverse effects of insulin resistance associated with dyslipidaemia on vascular function [102, 116, 120]. These studies uniformly show that endothelial dysfunction can be related to abnormal lipid metabolism, both in the fasting state (relation with small dense LDL) and postprandially, after a fatty meal.

In a recent Japanese study in seven well controlled Type II diabetic patients the flow-mediated vasodilatation of the brachial artery was investigated before and after a mixed meal containing milk fat and sucrose [121]. The change in flow-mediated vasodilation was related to change in glucose concentrations and not to the alterations in concentrations of plasma lipids and lipoproteins (Apo B100 remnant like particles, triglycerides). The important finding in this small study is that the glycaemic parameters were found to affect FMD independently of the postprandial changes in lipids. This study is obviously too small and the subjects not representative of the obese Type II diabetic patients to exclude the potential importance of postprandial lipid metabolism on endothelial function.

The extent to which insulin resistance-associated factors are related to endothelial function has been addressed [122]. The main determinants in this study on 76 healthy subjects, as determined by forearm blood flow changes during intra-arterial acetylcholine infusions, were BMI, waist-to-hip ratio, fasting insulin and insulin resistance (HOMA-IR model). Fasting plasma concentrations of cholesterol and triglycerides were not related to the forearm blood flow changes. The investigators also showed that vitamin C and indomethacine treatment restored the attenuated forearm blood flow response in the obese. The results of this study suggest that insulin resistance in the obese is responsible for endothelial dysfunction and that oxidative stress, due to quenching and deactivating nitric oxide, is one of the contributing factors.

Prolongation of the QTc interval. In non-diabetic and diabetic subjects a prolonged heart rate-adjusted QT interval (QT_c) has been shown to be predictive for sudden death and to correlate with measures of cardiovascular disease [123–125]. These studies also have shown a prolonged QT_c associated with hyperinsulinaemia and hyperglycaemia [124, 126]. In diabetic patients the prevalence of QT_C prolongation is high (about 35 %) and is associated with autonomic neuropathy [127].

A recent study addressed the question whether acute hyperglycaemia could affect the QT_C interval in healthy subjects and whether this was dependent on the concomitant rise in insulin concentrations. The major finding was that acute hyperglycaemia, of about 15 mmol/l induced by an intravenous glucose load, increased the QT_C and several sympathetic tone dependent haemodynamic parameters [128]. In control experiments the rise of insulin was prevented by an octreotide infusion. Nevertheless, the QT_C prolongation, the rise in blood pressure, and the increase of plasma concentrations of epinephrine and norepinephrine were very similar. These data strongly suggest that hyperglycaemia alone can enhance the risk of sudden death in vulnerable persons by enhancing the sympathetic tone and by the prolongation of the QT_C interval. One of the suggested mechanisms, which could explain these effects of acute hyperglycaemia includes depressed nitric oxide formation resulting in increased intracellular calcium content [129]. In support of this hypothesis these authors found, in another set of experiments, that in patients with newly diagnosed diabetes the adverse haemodynamic effects of acute hyperglycaemia (i.e. blood pressure rise and baroreflex responses) can be reversed by L-arginine infusion, a precursor of nitric oxide. Moreover, the adverse effects of acute hyperglycaemia could also be prevented by the anti-oxidant glutathione, enhancing nitric oxide availability [130]. Also insulin could have a direct effect on QTc. Insulin lowers potassium concentrations, which in turn causes hyperpolarisation of the cell membrane [131].

It will be clear that glucose and especially the factors associated with insulin resistance could, via several biochemical pathways, affect endothelial dysfunction and promote the development of cardiovascular disease (Fig. 5).

Is there any benefit from lowering the postprandial glucose excursions?

The proportional contributions of the different, but interrelated factors that lead to the severely high risk of cardiovascular disease, have to be determined (Fig. 5).

What is known about the blood glucose lowering interventions, which have been applied to lower CVD risk and CVD risk factors? The UKPDS has taught us that maintaining good glycaemic control lowers the incidence rate of microvascular complications in Type II diabetes [132]. This was independent of the allocated treatments. No difference was observed between the blood glucose-lowering agents, sulphonylurea and insulin. Perhaps due to the gradual deterioration of glycaemic control and the small contrast in HbA_{1c} value between the intensive and conventional treatment groups (0.9 %) only a modest difference (16 %) in the occurrence of myocardial infarctions was found. Nevertheless it is now well established that long term complications of diabetes can be reduced in proportion to the achieved decrease in

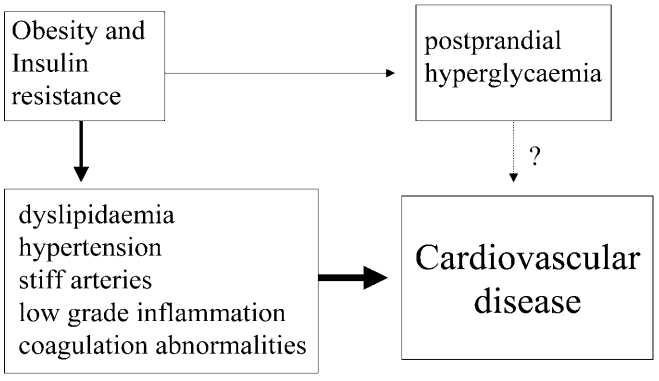

Fig. 6. Obesity and insulin resistance contribute to both postprandial hyperglycaemia and, as depicted in Fig. 5, to a cluster of cardiovascular disease risk factors. Lowering the postprandial hyperglycaemia only, thus without influencing the established risk factors will not provide the benefit one would predict from the epidemiological association between 2hPG and mortality

HbA_{1c}. Patients targeting for normalisation of the postprandial glucose concentrations could obtain a lower HbA_{1c}. Only one study in women with gestational diabetes showed that women who adjusted insulin therapy according to postprandial concentrations, rather than preprandial, achieved a lower HbA_{1c} and better pregnancy outcome [133]. In Type II diabetic patients no benefits have been reported so far of postprandial glucose monitoring. In contrast, metformin is the only blood glucose-lowering drug that has been shown in the UKPDS to lower diabetes related endpoints and all cause mortality and stroke in overweight Type II diabetic patients [134]. Even among the patients allocated to intensive blood glucose lowering, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for all cause mortality, stroke and the so-called combined ('diabetes related') endpoints. As the glucose lowering potency of metformin is not greater than that of other blood glucose lowering agents, and certainly not in terms of meal-related glucose excursions, it is of great interest to understand the mechanisms, which could explain the observed benefits. Studies over the years have shown metformin to lower the meal-related triglyceride rich lipoproteins and triglyceride excursions [135] and to decrease the methylglyoxal concentrations in Type II diabetic patients [136]. This latter finding is of interest since methylglyoxal concentrations are increased in diabetic patients and could contribute to the development of complications as a precursor of advanced glycation endproducts (AGE). Methylglyoxal and glyoxal are dicarbonyl compounds, which are known to be very reactive glycating agents and are involved in the formation of AGE products.

In vitro and animal studies have shown that metformin is able to react strongly with decarbonyl compounds and could thus decrease AGE formation [137]. Whether and how the risk can be lowered more considerably and consistently by lowering the meal-related glucose excursions has yet to be determined. The drugs which have been specifically targeted on restoring the meal-related glucose excursions are the α-glucosidase inhibitors, the short acting insulin analogues, inhaled insulin, pramlintide, and the meglitinides (repaglinide and nateglinide) [138–140]. These drugs have been effective in reducing the meal-related glucose excursions. The meglitinides for example have been shown to lower the post prandial glucose values in Type II diabetes by improving the insulin response to a meal. This resulted in a modest 0.5 to 0.6 % decline in HbA_{1c} [141]. This observation is an important proof of concept, however, the long-term benefit remains to be established.

Only a few studies have addressed the efficacy of blood glucose lowering drugs on meal-related lipoprotein excursions. A Japanese study in patients with Type II diabetes found a modest lowering of postprandial triglyceride and insulin concentrations with acarbose treatment [142]. The postprandial lipid response has not been studied with the other mentioned drugs, apart from metformin. In contrast, the meal-related glucose and insulin responses have been studied extensively. Does this in itself justify the propagation of these drugs in the treatment arsenal of Type II diabetes [143–145]? Before jumping to any kind of clinical recommendation it is crucial to learn more about these specific drugs in particular because of their intended use in the treatment of a high-risk population, i. e. the Type II diabetic patient. Lowering a risk indicator might not provide the benefit, which one would hope for or one would wrongly predict from epidemiological studies (Fig. 6). More evidence, which can only be obtained from randomised clinical trials, is certainly required. Also we need to accept that the various compounds targeted at the correction of postprandial hyperglycaemia act in different ways and thus will very likely affect the discussed established risk factors and outcomes differently. For example, insulin secretion enhancers will probably affect the postprandial lipid responses and vascular function differently from compounds, which affect the gastric emptying or glucose absorption rate. The required evidence does not necessarily include mortality or morbidity data from long-term intervention trials but at least need to include the effect on potential mechanisms as for example lipoproteins and coagulation factors, and intermediate endpoints as for example endothelial function parameters (FMD) and/or IMT measurements.

Therefore, we conclude that postprandial hyperglycaemia cannot, at least as yet, be considered to be a treatment target in itself. We have to await the evidence from convincing long-term studies showing amelioration of clinically relevant endpoints. Howev-

er, this conclusion should in no way distract from the therapeutic aim to achieve target HbA_{1c} values in patients with Type II diabetes.

Sources. This review is based on the relevant literature in the English language during the period 1990–2001 and seminal prior contributions. The sources available to the authors were integrated with sources identified through PubMed searches for "postprandial hyperglycaemia, glucose intolerance, IGT hypertriglyceridaemia, triglyceride response, postprandial lipids."

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