HORMONES 2016, 15(3):321-344

Review

Postprandial dysmetabolism: Too early or too late?

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ABSTRACT

Postprandial dysmetabolism is a postprandial state characterized by abnormal metabolism of glucose and lipids and, more specifically, of elevated levels of glucose and triglyceride (TG) containing lipoproteins. Since there is evidence that postprandial dysmetabolism is associated with increased cardiovascular mortality and morbidity, due to macro- and microvascular complications, as well as with conditions such as polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD), it is recommended that clinicians be alert for early detection and management of this condition. Management consists of a holistic approach including dietary modification, exercise and use of hypoglycemic and hypolipidemic medication aiming to decrease the postprandial values of circulating glucose and triglycerides. This review aims to explain glucose and lipid homeostasis and the impact of postprandial dysmetabolism on the cardiovascular system as well as to offer suggestions with regard to the therapeutic approach for this entity. However, more trials are required to prevent or reverse early and not too late the actual tissue damage due to postprandial dysmetabolism.

Key words: Dysmetabolism, Dysglycemia, Dyslipidemia, Insulin resistance, PCOS, Steatohepatitis

INTRODUCTION

Postprandial dysmetabolism comprises a new parameter for the assessment of carbohydrates and lipids homeostasis. While the conventional risk factors defining cardiovascular disease are evaluated in a fasting state, postprandial dysmetabolism is a postprandial state distinguished by abnormally increased circulating levels of glucose and lipids and therefore constitutes an independent risk factor for the onset of cardiovascular events.[1] In this review we will focus specifically on a) mechanisms that disturb the postprandial homeostasis of glucose and lipids, b) the impact of the impaired metabolism of these nourishing substrates on cardiovascular disease and c) therapeutic interventions aimed at correcting postprandial dysmetabolism.

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Received: 25-04-2016, Accepted: 15-09-2016

PHYSIOLOGY OF GLUCOSE AND LIPID METABOLISM AND MECHANISMS CONTRIBUTING TO THEIR DYSREGULATION

Homeostasis of glucose metabolism: Postprandial

glucose metabolism is regulated by the action of hormones, such as insulin, glucagon, amylin and the incretin hormones, glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic peptide (GIP).[2] (Figure 1).

Insulin is produced by the beta cells of the pancreas as proinsulin before being secreted and is subsequently cleaved into insulin and C-peptide. During a meal insulin is secreted in two phases: the first consists of a rapid short-term rise which lasts a few minutes and the second of a more progressive release proportional to the glycemic load of the meal.[1,3] Data suggest that an impaired first phase of insulin secretion is an indicator of beta cell dysfunction encountered in patients with early diabetes and prediabetes.[1,2,4-6] The effect of insulin on glucose homeostasis is to reduce the postprandial glucose levels, a goal that is achieved via three actions. a) It increases the glucose uptake by peripheral tissues, mainly by skeletal muscles. This action is mediated mainly through an isoform of a family of glucose transporters proteins, GLUT4. The GLUT4 protein transporter is a major regulator of whole-body glucose homeostasis and its recruitment to the cell surfaces of muscle and adipose cells is stimulated by insulin.[7] b) It promotes glycogen synthesis. c) It inhibits glucagon secretion, thus resulting in reduced glucose production by the liver.[2]

Glucagon is secreted from alpha pancreatic cells into the portal vein and promotes hepatic glucose production during fasting via glucogenolysis and gluconeogenesis.[2,8] After food consumption glucagon secretion is suppressed by insulin, amylin and GLP1. Glucagon plays a significant role in postprandial hyperglycemia. In diabetic patients the suppression of glucagon secretion is not adequate, leading to hyperglucagonemia and subsequent increased glucose production by the liver.[9]

Amylin (also known as islet amyloid polypeptide-IAPP) is synthesized by beta pancreatic cells and released with insulin in response to the same stimulus. Amylin contributes to maintaining glucose homeostasis by delaying gastric emptying, suppressing glucagon release and controlling satiety.[2,10] In diet-induced obese rats, amylin reduced their body weight and body fat with relative preservation of lean tissue.[11]

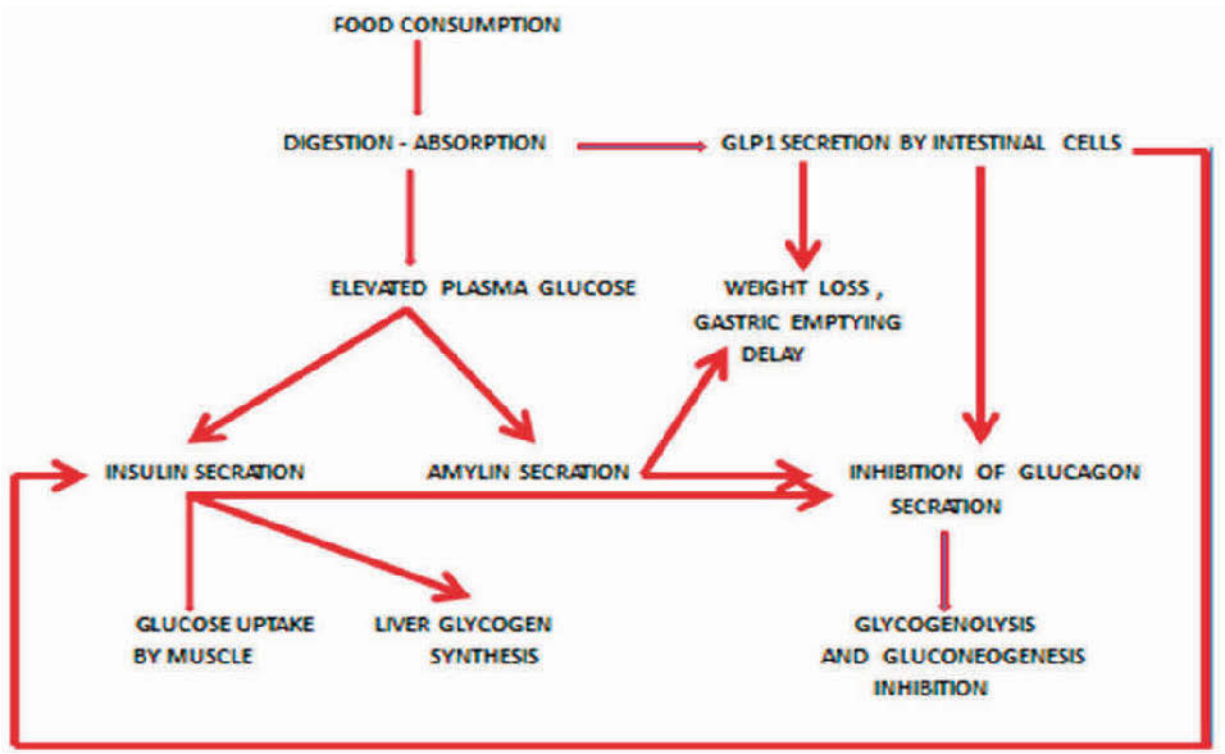

Figure 1. Postprandial plasma glucose homeostasis.

The GLP1 and GIP are peptides secreted from intestinal cells during nutrient ingestion. GLP1 is produced by L cells which are located primarily in the ileum but also in the colon, while GIP is produced by K cells which are located in the proximal parts of the small intestine.[12] The incretin effect refers to the amplification of insulin secretion that is observed when glucose is taken orally, as opposed to being infused intravenously, to provide identical plasma glucose concentrations.[13] Incretin hormones act directly on the pancreas stimulating insulin secretion by beta cells in a glucose-dependent manner. In addition, GLP1 inhibits glucagon secretion by pancreatic cells and delays gastric emptying. The latter defines the main mechanism contributing to reducing postprandial overproduction of glucose. Furthermore, animal and in vitro studies have shown that it enhances beta cell proliferation and differentiation and seems to inhibit apoptosis.[12,15] After their release, incretin hormones are rapidly broken down in the circulation by dipeptylpeptidase-4 inhibitor enzyme (DDP-4).[2,14]

While it is known that the incretin effect is reduced in patients with type 2 diabetes,[13,16] there has been debate as to whether the impairment of the incretin effect is due to reduced secretion of GIP and GLP1. Recent data indicate that reduced incretin secretion per se is not the factor responsible for the diminished stimulation of insulin secretion seen in type 2 diabetes;[16-19] moreover, it appears that in type 2 diabetes, GIP no longer modulates glucose-dependent insulin secretion even at pharmacological plasma levels.[19] A meta-analysis of 688 participants (363 patients with type 2 diabetes vs 325 non-diabetic controls) demonstrated that patients with type 2 diabetes are in general characterized by preserved GIP secretion in response to oral glucose and meal tests. However, post hoc subgroup analyses showed that high BMI, younger age and low HbA1c level seem to positively affect the GIP responses in diabetic patients.[16] Another meta-analysis evaluating the secretion of GLP1 in 554 participants (275 patients with type 2 diabetes and 279 non-diabetic controls) suggested that diabetic patients in general do not exhibit reduced GLP1 secretion in response to an oral glucose tolerance test (OGTT) or meal test.[17] However, meta-regression analyses exhibited independent effects of HbA1c and fasting plasma glucose levels on GLP1 iAUC responses and, moreover, a post hoc subgroup analysis showed that increasing levels of HbA1c associated negatively with GLP1 iAUC.[17] The latter observations may explain the conflicting results from other studies which included older patients with a long history of diabetes and relatively high HbAic and fasting plasma glucose levels, thus implying that the GLP1 secretion profile may be preserved in the early stages of diabetes and subsequently alter during the progression of diabetes.[17] Xu et al studied the expression of GIP and GLP1 beta cell receptors in hyperglycemic rats and found that they were significantly decreased in 90% of pancreatectomized rats. Sub-expression was reversible when glucose levels were normalized.[18] This verification indicates that downregulation of pancreatic incretins receptors due to chronic hyperglycemia may be an important determinant of a reduced incretin effect in diabetic patients.

GLP2 is another proglucagon-derived peptide produced by a subset of enteroendocrine cells within the epithelium of the small and large intestine and by a population of neurons in the brainstem.[20] GLP2 increases absorption of nutrients, while it has been shown that parenteral infusion in non-obese humans increases glucagon secretion.[21] However, though it was once considered to have no effect on insulin secretion,[22] recent data from animal model experiments indicate that GLP2 may promote insulin sensitivity, particularly in conditions associated with obesity.[20] Although the underlying mechanisms have yet to be determined, some possible actions include food intake reduction mediated by the central nervous system, neuroendocrine signals which suppress hepatic glucose production and reduced gut permeability with subsequent bacterial-endotoxemia.[20] Nevertheless, results from human studies still remain inconsistent and future research is needed.[20]

Homeostasis of lipid metabolism: The role of lipids in postprandial dysmetabolism is important. Postprandial dysmetabolism is mainly characterized by elevated levels of triglycerides (TG) and their remnant lipoprotein particles (RLPs),[1] therefore a brief overview of TG metabolism and homeostasis is essential (Figure 2).

After the consumption of a meal containing lipids, dietary origin triglycerides are hydrolyzed in the

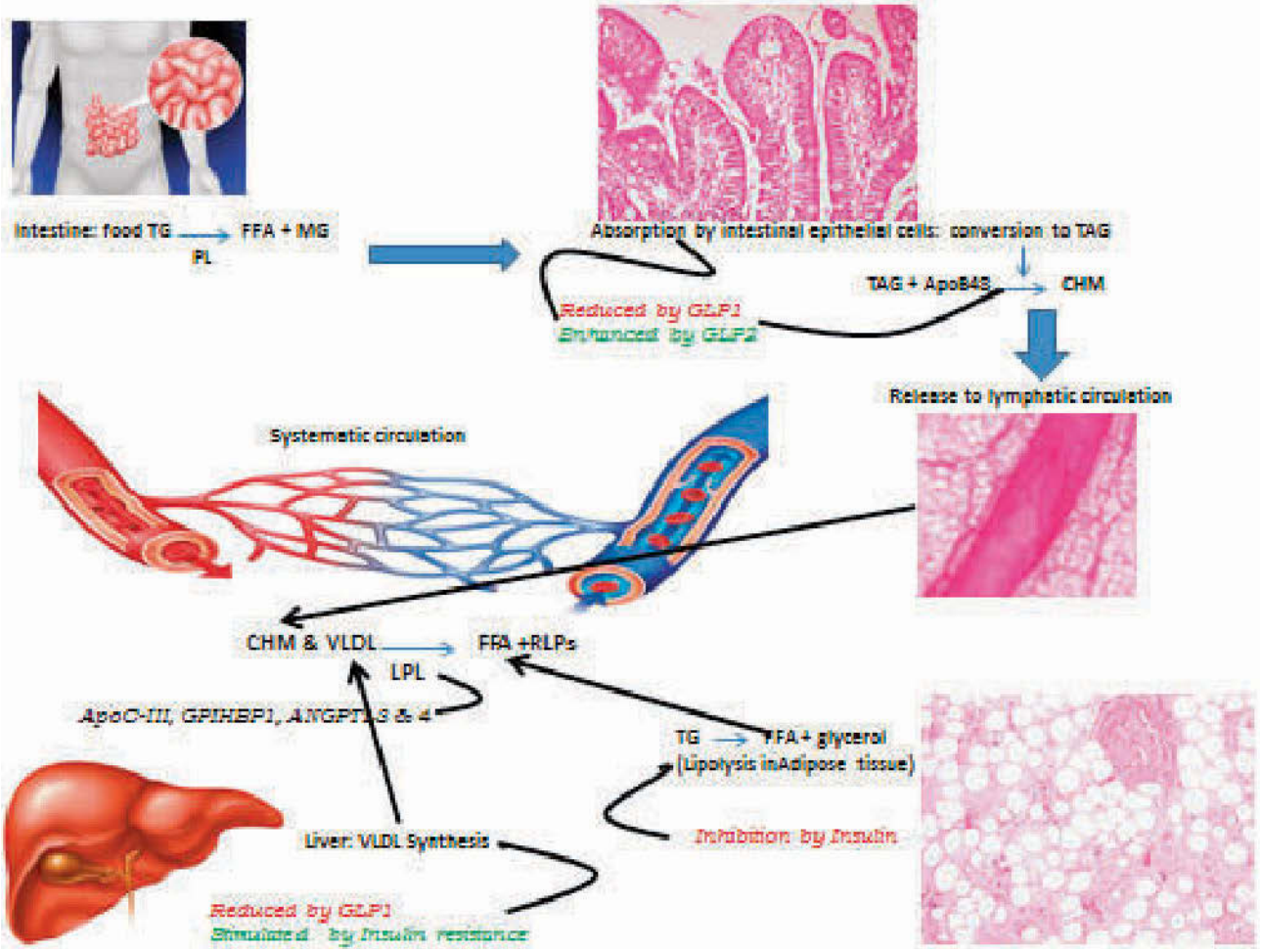

Figure 2. Triglycerides plasma homeostasis. TG: triglycerides, PL: pancreatic lipase, FFA: free fatty acid, MG: monoglycerides, TAG: triacyloglyceroles, CHM: chylomicrons, LPL: lipoprotein lipase, RLPs: remnants lipoprotein particles, VLDL: very low density lipoproteins, GPIHBP1: Glycosylphosphatidylinositol-anchored high density lipoprotein 1, GLP1: glucagon-like peptide 1, GLP2: glucagon-like peptide 2.

intestine to free fatty acids and monoglycerides by the enzyme pancreatic lipase Subsequently, they are absorbed by intestinal epithelial cells, converted to triacylglyceroles and packed with ApoB48 into chylomicrons, which are then secreted in the lymphatic circulation.[23-25]

Very low density lipoproteins (VLDL) are produced and secreted by the liver and contain triglycerides packed with ApoB100. They are initially synthesized in the hepatic endoplasmatic reticulum as pre-VLDL and subsequently form $VLDL_2$. In the Golgi apparatus $VLDL_2$ may then be converted to larger $VLDL_1$ by the addition of lipids.[24] Large VLDL particles are considered to be more atherogenic as they are associated with endothelial dysfunction and the formation of foam cells in vessel walls.[24]

Chylomicrons and VLDL break down by several lipases (lipoprotein lipase-LPL, hepatic lipase) into fatty acids and RLPs and compete in clearance.[23-25] LPL is located in capillary endothelial cells, mainly in the heart, adipose tissue and skeletal muscle.[26,27]

Lipolysis is a catabolic pathway which occurs mainly in adipose tissue and is characterized by the hydrolysis of TG into fatty acids and glycerol which are subsequently released into the circulation, providing peripheral tissues with the necessary energy demands.[28] Lipogenesis, on the other hand, is an anabolic pathway which occurs principally in adipose tissue, but

also in other organs such as the liver, muscle, heart and pancreas. It leads to TG production through free fatty acid esterification and is distinguished from lipogenesis originating from free fatty acids derived from the diet and de novo lipogenesis which occurs principally in the liver and mainly after a high carbohydrate meal.[28] Insulin plays a critical role in the regulation of lipid homeostasis and is implicated in the subtle balance between lipolysis and lipogenesis, since it stimulates lipid synthesis and adipogenesis and inhibits lipolysis.[28]

Apart from insulin action on lipid metabolism, it seems that gut peptides like GLP1 and GLP2 may also play an important role in lipid homeostasis affecting postprandial hypertriglyceridemia. It has been reported that GLP1 ameliorates postprandial hyperlipidemia via several mechanisms, including reduction of intestinal lymph flow, TG absorption, gastric emptying and gut motility and decreased intestinal lipoprotein production and secretion.[25] It has also been noted in experimental animal models that administration of GLP1 analogs may result in reduced VLDL production by the liver and decreased expression of genes involved in hepatic de novo lipogenesis.[29] On the other hand, GLP2 appears to be associated with high postprandial TG, ApoB48 and free fatty acids concentrations, probably via enhancement of intestinal lipid absorption and intestinal lipoprotein particles release.[30]

The risk factors which seem to contribute to postprandial hypertriglyceridemia are obesity, insulin resistance, VLDL hypersecretion, reduced lipolysis by LPL, reduced RLPs clearance by hepatic receptors and genetic factors.

It has been found that obese individuals, and especially those exhibiting visceral obesity, develop increased response in postprandial TG after the consumption of a fatty meal compared to non-obese subjects.[31,32] Meanwhile, it has been proposed that elevated adiposity results in a high flow of free fatty acids to the liver, leading to increased hepatic TG synthesis.[23] Hepatic free fatty acid delivery is also increased in humans with insulin resistance resulting in excess secretion of VLDL.[23,33] In fact, obesity and insulin resistance are closely associated, leading to dysregulation of TG homeostasis. During adipose tissue expansion, adipocytes become hyperplastic and dysfunctional and subsequently resistant to the antilipolytic effect of insulin.[28] As subjects' resistance increases, plasma free fatty acid levels also rise: the resulting excess free fatty acid release is toxic for many tissues and leads to reduced glucose uptake by liver and muscle, pancreatic beta cell dysfunction and stimulation of hepatic TG synthesis and VLDL production.[28] Blackburn et al. compared post-challenge triglyceride (TG)-rich lipoprotein (TRL) levels after a high fat content breakfast in men with impaired glucose tolerance (IGT) versus men with normal glucose tolerance (NGT): the results showed that men with IGT had a higher increase in the post-challenge TG-TRL levels including all TG fractions (large, medium and small).[34]

It is likely that reduced LPL activity contributes to postprandial increase of TG in diabetic patients.[35] Regarding LPL, there is evidence that several modifiers may, through their interference, alter its activity, thus leading to TG accumulation. Specifically, ApoC-III, which is produced by the liver and intestine, is an exchangeable apolipoprotein located in the ApoA-I/C-III/A-IV gene cluster on chromosome 11q23. ApoC-III, consisting of an independent factor for CVD in humans, is found in both fasting and postprandial TG and chylomicrons.[26] It has been reported that ApoC-III increases plasma TG through inhibition of LPL activity as well through enhancement of hepatic production of VLDL,[26] although novel data suggest that ApoC-III may also increase plasma TG levels via an LPL-independent mechanism.[36] In addition, results from experimental animal models show that ApoC-III contributes to hypertriglyceridemia mainly by inhibiting hepatic clearance of TG-rich lipoproteins via low density lipoprotein receptors (LDLRs) and LDL-related protein 1 (LRP1) which mediate the endocytotic clearance of RLPs.[37] In addition, its impact on CVD prevalence is also due to stimulation of inflammatory processes in vessels and the pancreas.[26] Glycosylphosphatidylinositol-anchored high density lipoprotein 1 (GPIHBP1) is expressed in capillary endothelial cells and is hypothesized to be a binding site for LPL in the capillary lumen, thereby facilitating LPL activity and TG hydrolysis along the luminan surface of capillaries.[27] Moreover, it has been shown from both animal models[38] and in humans with various GPIHBP1 mutations that GPIHBP1 deficiency

or dysfunction seems to be associated with elevated TG levels.[27] Finally, ANGPTL 3 and ANGPTL 4 are secreted proteins expressed mainly in the liver and adipose tissue, respectively, which are structurally similar to angiopoietins and their expression appears to be upregulated in insulin resistance states.[39] Animal experiments have indicated that they may interfere in TG metabolism by inhibiting LPL, thus exacerbating hypertriglyceridemia.[39]

Another factor contributing to postprandial hypertriglyceridemia is lack of hepatic receptors (HSPG, LDLR, LRP1), which interfere with the clearance of chylomicrons and VLDL from the circulation.[40] Of note, some of the hepatic lipoprotein remnant clearance receptors may interact with insulin. Specifically, it has been shown that insulin may stimulate the translocation of LRP1 to the plasma membrane, thus contributing to RLPs clearance.[41] On the other hand, it has been found that inactivation of LRP1 could be associated with reduced expression of surface insulin receptors and suppressed GLUT2 translocation to plasma membrane. This will account for the fact that in experimental animals with inactivated LRP1 receptors, consumption of a high-fat diet results in insulin resistance and metabolic syndrome.[42]

Given that most people consume fat-containing meals frequently during the day, the usual metabolic state of lipids is postprandial, since after a typical fatty meal, consumption serum triglycerides rise within an hour and remain elevated for 5-8 hours. This contrasts with glucose metabolism which displays transient elevations after a meal.[43]

COMPLICATIONS OF POSTPRANDIAL DYSMETABOLISM

Complications of postprandial hyperglycemia

Postprandial hyperglycemia seems to contribute significantly to the development of cardiovascular complications, since it has been shown to enhance injury in both the macro- and microvascular systems, thus resulting in increased morbidity and mortality (Tables 1-3). Indeed, several reports strongly indicate that severe postprandial hyperglycemia is correlated with increased incidence of cardiovascular events and mortality.[44-49]

Table 1. Association of postprandial hyperglycemia with cardiovascular morbidity and mortality

Postprandial hyperglycemia and mortality/cardiovascular disease								
Study	**Participants**	**Results**						
		All cause mortality	**CV mortality**	**CHD mortality**	**Stroke mortality**	**Cancer mortality**	**CVD events/ morbidity**	**MI/ACS**
Shaw et al, 1999	9,179 subjects	√	√			√		
Saydah et al, 2001	3,092 US adults	√						
DECODE Study Group, 2001	15,388 men and 7,126 women	√	√	√	√			
Cavalot et al, 2006	529 type 2 diabetics						√	
Barzin et al, 2013	3,794 subjects						(-)	
Strojek et al, 2016	1,115 patients		√				√	√

CV: cardiovascular, CHD: coronary heart disease; CVD: cardiovascular disease; MI: myocardial infarction; ACS: acute coronary syndrome.

Table 2. Association of postprandial hyperglycemia with the development of atherosclerosis

Postprandial hyperglycemia and atherosclerosis				
Study	**Participants**	**Results**		
		Increased carotid IMT	**Coronary stenosis/ atherosclerosis**	**Increased aPWV**
Hanefeld et al, 1999	403 subjects	√		
Temelkova-Kurktschiev et al, 2000	582 individuals	√		
Brohal et al, 2006	24,111 subjects (DM or IGT)	√		
Saely et al, 2008	1,040 patients		√	
Gong et al, 2009	Newly diagnosed untreated type 2 diabetics and IGT			√
Ando et al, 2010	2,842 subjects			√
Hu et al, 2010	474 type 2 diabetics	√		
Tanaka et al, 2014	108 subjects	√		
Gordin et al, 2016	46 type 2 diabetics and 25 controls			√

IMT: intima media thickness, aPW: arterial pulse wave velocity.

Table 3. Association of postprandial hyperglycemia with microvascular complications

Postprandial hyperglycemia and microvascular complications				
Study	**Participants**	**Results**		
		Retinopathy	**Neuropathy**	**Nephropathy**
Shiraiwa et al, 2005	232 type 2 diabetics	√	√	√
Sartore et al, 2013	68 type 1 and 2 diabetics	√		
Sun ZJ et al, 2015	12,833 subjects			√

Data analyzed from the prospective cohort Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study, which included 3,092 adults 30-74 years old who underwent an oral glucose tolerance test, suggest that post-challenge hyperglycemia is associated with increased risk of all-cause and CVD mortality independently of other CVD risk factors.[44] Similarly, pooled data from three population-based longitudinal studies showed that individuals with isolated post-challenge hyperglycemia had an increased risk of all-cause and cardiovascular mortality compared to those without diabetes. Furthermore, men with isolated post-challenge hyperglycemia had a high risk of cancer death.[45] In addition, recent data have shown that the average challenge in 2-hour blood glucose level after meals was associated with the greatest difference in event-free survival probability for a composite endpoint which included CV death, nonfatal MI, nonfatal stroke, hospitalization for acute coronary syndromes or coronary revascularization.[46] On the other hand, another study compared newly diagnosed diabetes patients who exhibited isolated post-challenge hyperglycemia (fasting plasma glucose <126 mg/dL and 2-h post-challenge plasma glucose ≥200 mg/dL) with patients without diabetes. During an 8-year observation period, the HR, adjusted for potential confounders for incident cardiovascular disease, was not significant [1.32 (95% CI: 0.88-1.99; p = 0.2)] in the newly diagnosed diabetic patients with isolated post-challenge hyperglycemia (fasting plasma glucose <126 mg/dL and 2-h postprandial glucose ≥200 mg/dL) compared to those without diabetes.[47]

Regarding the contribution of fasting versus postprandial hyperglycemia to cardiovascular events, there

are reports indicating that postprandial hyperglycemia comprises a better predictor of deaths from all causes and cardiovascular disease as well as an independent factor for cardiovascular events than fasting blood glucose.[48,49] Specifically, in adults of advanced age (mean age 78), postprandial glucose was associated with atherosclerotic cardiovascular disease and mortality independently of fasting glucose.[50]

Pulse wave velocity (PWV) is the simplest non-invasive robust assay for evaluation of arterial stiffness and, specifically, carotid-femoral PWV has been used in epidemiological studies demonstrating the predictive value of aortic stiffness for CV events.[51] There are studies in subjects with post-challenge hyperglycemia detected by an OGTT or by measuring glucose levels after meal consumption. Results suggest that post-challenge/postprandial hyperglycemia correlates with a higher brachial or brachial-ankle pulse wave velocity, thus indicating a possible involvement of postprandial hyperglycemia in early-stage atherosclerosis.[52-54] Carotid intima media thickness (IMT) may predict the occurrence of stroke and myocardial infarction.[55] Several studies have evaluated the impact of postprandial hyperglycemia on IMT in diabetic or IGT patients.[56-60] In non-diabetic patients who exhibit impaired glucose tolerance after an OGTT, post-challenge hyperglycemia appears to be associated with increased IMT.[56-58] In one study, the 2h post-challenge plasma glucose and post-challenge glucose spikes were more strongly associated with carotid IMT than fasting plasma glucose and HbA1c.[57] Another study noted that in non-diabetic IGT patients early hyperglycemia, and specifically the 60 minutes plasma glucose after an 75g OGTT, was significantly and positively correlated with IMT.[58] Regarding diabetic patients, post-challenge glucose spikes have been shown to be independently associated with carotid IMT, implying that they may contribute to development of atherosclerosis.[59] In a systematic review including 24,111 subjects (4,019 with diabetes and 1,110 with IGT), diabetic patients seemed to have a threefold increase in carotid IMT compared to patients with IGT. The authors attributed this difference to the advanced age (>10 years older) and the increased relative risks of myocardial infarction and stroke (>40%) of the diabetic participants.[60] In addition, data from an experimental animal study revealed that intermittent glucose administration in female mice leads to an approximately fourfold greater atherosclerotic lesion size in their aortic sinus, thereby indicating that repetitive glucose spikes may accelerate atherosclerotic lesions formation.[61] Concerning coronary atherosclerosis, Saely et al. evaluated the impact of postprandial hyperglycemia on coronary vessels in individuals with conventional diabetes (diabetes diagnosed on the basis of fasting glucose), isolated post-challenge diabetes (blood glucose ≥200 mg/dl after a 75g OGTT), IGT and normal glucose tolerance who underwent a coronary angiography for the evaluation of coronary artery disease (CAD). The results showed that coronary atherosclerosis was more frequent in patients with IGT, isolated post-challenge diabetes or conventional diabetes, with significant coronary stenosis (≥50%) being higher in patients with isolated post-challenge diabetes or conventional diabetes.[62]

Apart from the fact that postprandial hyperglycemia is known to cause macrovascular complications, there is evidence that it also contributes to microvascular complications. In a cross-sectional study of 232 subjects with type 2 diabetes, multiple regression analysis showed that postprandial hyperglycemia correlated independently with the incidence of diabetic retinopathy and neuropathy and non-independently with the incidence of diabetic nephropathy.[63] One study also reported that in Japanese patients with type 2 diabetes, postprandial hyperglycemia was an even stronger predictor of the progression of diabetic retinopathy than HbA1c.[64] Data from another study of 68 patients with DM1 and DM2 suggest that glucose variability may constitute a risk factor for diabetic retinopathy, particularly in the context of acute fluctuations and acute hyperglycemia, regardless of HbA1c.[65] As far as nephropathy is concerned, a study of 12,833 individuals without a history of renal disease or diabetes indicated that impaired glucose tolerance, but not isolated impaired fasting glucose, is associated with increased GFR and a higher risk of glomerular hyperfiltration (estimated GFR above the age- and gender-specific 95th percentile for apparently healthy subjects) (OR 1.34, 95%CI: 1.107-1.66, p=0.009).[66]

A cross-sectional analysis of a large epidemiological study showed that postprandial hyperglycemia may affect the metabolism of certain lipoproteins. Specifically, it was demonstrated that isolated impaired glucose

tolerance is associated with increased triglycerides, large very low density lipoprotein subclass particles and structural remodeling of LDL particles, in contrast to isolated impaired fasting glucose which is associated with increased ApoB and total LDL particles.[67]

Studies to identify the possible complications of postprandial hyperglycemia could simultaneously evaluate its contribution to overall diurnal hyperglycemia. It seems that postprandial hyperglycemia defines the main hyperglycemic state when HbA1c is low, such as in early or well controlled diabetes. In contrast, fasting hyperglycemia is much more closely associated with higher values of HbA1c (Table 4).[68-70]

Complications of postprandial hyperlipidemia

Large epidemiological studies have shown that postprandial hypertriglyceridemia is an additional risk factor for the development of cardiovascular disease (Tables 5, 6). Twenty-four thousand fine hundred and thirty-five (24,535) Norwegian women aged 35-49 years old were followed up for a mean of 14.6 years. Results showed that mortality from coronary heart disease, cardiovascular disease and all-cause mortality steadily increased with increasing non-fasting triglyceride concentrations.[71] In addition, data from a prospective study with 26,509 initially healthy US women who underwent a follow-up for a median of 11.4 years indicated that both fasting and non-fasting triglycerides levels were predictors of such cardiovascular events as nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization or cardiovascular death. Furthermore, non-fasting triglyceride levels maintained a strong independent relationship with cardiovascular events in contrast to fasting levels, which demonstrated a weaker association with cardiovascular events when adjusted for total and high density lipoprotein cholesterol and measures of insulin resistance.[72]

As in the female population, cardiovascular risk increases in men with elevated postprandial triglycerides. A prospective cohort study including 14,916 men aged 40 to 84 years old determined that the occurrence of myocardial infarction was the main outcome during a 7-year follow-up. Triglyceride levels (85% of

Table 4. Contribution of postprandial hyperglycemia in overall hyperglycemia

	HbA1c						
	<6.2	**<6.5**	**<7.3**	**≥9**	**>9**	**>10.2**	
% contribution of postprandial hyperglycemia	80%						Woerle HJ et al, 2007
		61%					Schernthaner G, 2010
			70%				Monnier L et al, 2003
				22%			Schernthaner G et al, 2010
					40%		Woerle HJ et al, 2007
						30%	Monnier L et al

Table 5. Association of postprandial hypertriglyceridemia with cardiovascular mortality and morbidity

Postprandial hypertriglyceridemia and cardiovascular mortality–morbidity							
Study	**Participants**	**Results**					
		Total deaths	**Deaths from CVD**	**Deaths from CHD**	**CVE**	**MI**	**CHD**
Stensvold et al, 1993	24,535 women	√	√	√			
Stampfer et al, 1996	14,916 men					√	
Bansal et al, 2007	26,509 women				√		
Nordestgaard et al, 2007	7,587 women and 6,394 men	√				√	√

CVD: cardiovascular disease; CHD: coronary heart disease; CVE: cardiovascular events; MI: myocardial infarction.

Table 6. Association of postprandial hypertriglyceridemia with the development of atherosclerosis

Postprandial hypertriglyceridemia and atherosclerosis			
Study	**Participants**	**Results**	
		Carotid IMT	**aPWV**
Teno et al, 2000	61 type 2 diabetics	√	
Chen et al, 2003	78 type 2 diabetics	√	
Mori et al, 2005	68 type 2 diabetics	√	
Ahmad et al, 2005	86 newly detected type 2 diabetics and 45 non-diabetics	√	
Daskalova et al, 2005	45 individuals		√

Carotid IMT: carotid intima media thickness; aPWV: arterial pulse wave velocity.

blood samples collected at baseline were non-fasting) exhibited a linear association with the risk for myocardial infarction, with men in the highest quintile having an approximately 2.5 greater risk than those in the lowest quintile.[73] Another prospective cohort study of 7,587 women and 6,394 men aged 20-39 years from Copenhagen pointed to an association of elevated non-fasting triglycerides with myocardial infarction, ischemic heart disease and death during a mean follow-up of 26 years. Hazard ratios were higher as triglycerides levels increased.[74] Additionally, it has been reported that elevated postprandial TG is linked to an increased risk of myocardial infarction, ischemic stroke and early death in women and men in the general population.[75]

The role of postprandial hypertriglyceridemia in the development of atherosclerosis seems to be important. There are several studies evaluating the impact of postprandial hypertriglyceridemia on carotid intima thickness in type 2 diabetic patients of various origins.[76-79] The studies concluded that increased postprandial triglycerides are associated with higher IMT. Additionally, in 45 patients who underwent a standardized fatty meal test and whose triglycerides levels were subsequently measured after 2, 4, 6 and 8 hours, it was shown that high post-challenge triglycerides correlated positively with an increase in aortic pulse wave velocity (aPWV) 6 hours after the fatty meal consumption and, specifically, a 0.88 m/s rise of aPWVA was found for a 100mg/dl increase in triglycerides.[80]

Waist circumference, which is an index of central obesity, constitutes a well-recognized cardiovascular risk factor in hypertensive patients[55] and has also been reported to be associated with such conditions as, inter alia, idiopathic portal vein thrombosis,[81] asthma in children and adolescents and uncontrolled asthma in women,[82,83] non-alcoholic liver disease[84] and dementia.[85] Oka et al conducted a study including 1,505 men and 798 women who were not taking medications for diabetes or dyslipidemia. Both fasting and 2-hours postprandial TG levels were measured and a possible association with waist circumference was tested. The results showed that waist circumference had a stronger association with postprandial TG than fasting TG.[86] This finding may suggest that postprandial hypertriglyceridemia plays a role in many pathologic conditions related to central obesity.

PATHOPHYSIOLOGY OF POSTPRANDIAL DYSMETABOLISM INDUCED CARDIOVASCULAR COMPLICATIONS

The main pathophysiologic mechanisms participating in development of cardiovascular damage are endothelial dysfunction and oxidative stress, activation of inflammation and coagulation, and penetration of lipoprotein particles in the arterial wall (Figure 3).

Endothelial dysfunction is an early process in the development of cardiovascular disease and is defined as a reduced response to vasodilatory stimuli.[87] It has been shown that postprandial hyperglycemia and hyperlipidemia is associated with increased production of reactive oxygen species (ROS) leading to increased oxidative stress, which subsequently

mediates the development of endothelial dysfunction.[87-89] It has been proposed that excess of post-meal nutrients overburden the electron transport chain in mitochondria, exceeding their metabolic ability in muscle and adipose tissue mitochondria and thus resulting in increased ROS production.[1,87] Specifically regarding postprandial hypertriglyceridemia, it seems that endothelial function is mainly impaired after a high saturated fatty acid intake, while the effects of high-monounsaturated or polyunsaturated are more controversial.[87]

Inflammation and the pro-inflammatory state have been shown to be another significant contributor to the pathogenesis of atherosclerosis. There is evidence that postprandial hyperglycemia is associated with increased circulating cytokines levels such as IL-6 and TNFa in subjects with IGT[90] and in type 2 diabetic patients.[91] Concerning non-diabetic individuals, intake of a high fat meal, which leads to postprandial triglycerides increase, results in elevated cytokines.[91] It has been proposed that upregulation of endothelial cells adhesion molecules plays an important role in the pathogenesis of atherosclerosis through enhanced adhesion of circulating leukocytes in the endothelium.[92] Circulating adhesion molecules such as the intracellular adhesion molecule (ICAM)-1 and vascular cellular adhesion molecule (VCAM)-1 have been proposed as markers of atherosclerosis and future cardiovascular events.[93-95] There are data that postprandial dysmetabolism is associated with elevated circulating adhesion molecules,[91,92] suggesting that postprandial

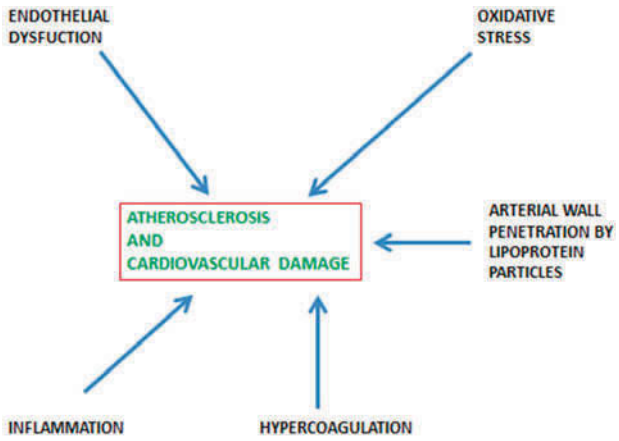

Figure 3. Mechanisms involved in cardiovascular damage caused by postprandial dysmetabolism

dysmetabolism-induced pro-inflammatory response is a significant pathophysiologic mechanism for the development of atherosclerosis. In addition, experiments in rat models have shown that postprandial hypertriglyceridemia is associated with overexpression of ICAM-1 and increased monocyte adhesion in the aortic arterial wall.[96] Recent data also demonstrate that postprandial hyperglycemia is involved in increased leucocyte activation in patients with type 2 diabetes and familial combined hyperlipidemia.[97]

Concerning the coagulation system, there are data demonstrating that postprandial hyperglycemia constitutes a significant predictor of platelet activation, as this was shown by measurement of urinary 11-dehydro-thromboxane (TX)B(2), a marker of in vivo platelet activation, in subjects with type 2 early diabetes.[98] It has also been found that induction of acute short-term hyperglycemia in type 2 diabetic patients results in increased platelet activation markers, such as shear-induced platelet activation, P-selectin and LIMP expression on platelets, urinary 11-dehydro-TxB2 excretion and plasma vWF.[99] Similarly, postprandial lipemia after the intake of fatty diets results in increased plasminogen activator inhibitor (PAI)[100] and activated factor VII, with saturated fats causing a lesser increase in FVIIa than unsaturated.[101]

Additionally, postprandial lipids appear to have a direct impact on vessels structure and establishment of atherosclerosis, since RLPs infiltrate the subendothelial space of the arterial wall, are subsequently enriched in cholesterol and ApoE and are then phagocytized by arterial wall macrophages.[23]

POSTPRANDIAL DYSMETABOLISM AND OTHER SYNDROMES

It is noteworthy that postprandial dysmetabolism, apart from being a risk factor for cardiovascular disease, also seems to be involved in other conditions like polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD). A recent study in 163 adolescents fulfilling diagnostic criteria for PCOS showed that 17.2% of PCOS patients exhibited abnormal glucose metabolism after an OGTT (16% had IGT and 1.2% had diabetes), while only two patients were detected with hyperglycemia based on fasting glucose values. In addition, all patients with

abnormal glucose metabolism were overweight or obese.[102] Kyaw Tun et al. compared glucose, insulin and lipids responses after a mixed meal in 26 obese PCOS women and 26 obese controls: the results revealed that AUC-TG, AUC-glucose and AUC-insulin were higher, while AUC-HDL was lower in PCOS women after the meal, with AUC-insulin and iAUC-insulin remaining higher after adjustment for BMI and HOMA-IR.[103] Another study compared post-challenge glucose and lipids responses after an OGTT and an oral fat tolerance test (OFTT) between 20 lean (BMI 23.5±2.6 Kg/m^2) PCOS women and 20 BMI-matched controls (BMI: 23.1±3.1 kg/m^2): it was found that HOMA-IR, AUC-glucose, AUC-TG, AUC-VLDL and AUC-total cholesterol were higher in PCOS women.[104] All the aforementioned findings indicate that postprandial dysmetabolism is involved in PCOS syndrome, with obesity and insulin resistance playing an important role in its occurrence in these patients. In fact, the actual pathogenetic mechanisms of glucose dysmetabolism in PCOS women appear to be multifactorial with impaired insulin action, beta cell dysfunction and decreased hepatic clearance of insulin being implicated. Moreover, insulin resistance and hyperinsulinemia appear to contribute to hyperandrogenemia and anovulation which characterize PCOS.[105]

Of note, a proportion of PCOS women also exhibit NAFLD. In a study of 83 PCOS women (without a history of alcohol intake, chronic liver disease or medication causing hepatotoxicity or elevated liver enzymes) who were compared to 64 healthy controls, it was found that overweight/obese, but not lean, PCOS subjects exhibited higher serum levels of ALT and γGT. In addition, multiple regression analysis revealed that BMI and HOMA-IR were major determinants of ALT and γGT.[106]

Regarding NAFLD in the non-PCOS population, there is also evidence that there is a correlation with postprandial dysmetabolism. One hundred seventy-three (173) biopsy-proven NAFLD patients without prior known type 2 diabetes underwent a 75g OGTT. Impaired glucose tolerance, including diabetes, was detected in 60% of the NAFLD patients. In addition, post-challenge hyperinsulinemia at 120 min after the test was associated with advanced fibrosis (P = 0.0001, OR: 3.56; 95% CI, 1.61-7.86).[107] Similarly, another study with 111 NAFLD patients showed that when an OGTT was performed in patients with non-established type 2 diabetes, 33% of them revealed abnormal glucose tolerance (IGT or diabetes). In addition, fasting hyperglycemia was of limited sensitivity (46%) but high specificity (89%) for identifying those patients, while all of them had post-challenge hyperinsulinemia.[108] Concerning NAFLD and postprandial lipids, there is evidence that non-obese non-diabetic normolipidemic patients with non-alcoholic steatohepatitis (NASH) manifest postprandially pronounced intestinal and hepatic VLDL1 accumulation and LDL lipid peroxidation and, moreover, that steatosis is independently associated with postprandial intestinal VLDL1.[109] It has also been shown in healthy subjects who underwent an oral fat load that those with increased liver fat (>5% as determined by magnetic resonance spectroscopy) exhibit increased post-challenge AUC-plasma TG, AUC-chylomocron TG, AUC-VLDL2TG and AUC-chylomicron ApoB100 compared to those with normal liver fat.[110]

SCREENING AND DIAGNOSIS OF POSTPRANDIAL DYSMETABOLISM

a) Detecting postprandial hyperglycemia

The conventional methods for the detection of postprandial hyperglycemia are the 75g OGTT and self-monitoring of blood glucose (SMBG). IGT is defined as plasma glucose levels 140-199mg/dl after a 75g OGTT, while levels ≥200mg/dl are a criterion for the diagnosis of diabetes.[111]

Guidelines for management of post-meal glucose in diabetes currently recommend SMBG as being the optimal method for assessing plasma glucose levels in insulin and non-insulin treated type 2 diabetic patients and propose that the timing and frequency of SMBG be individualized to each person's treatment regimen and level of glycemic control.[112]

Emerging technologies for the evaluation of postprandial glucose levels include continuous glucose monitoring (CGM) and plasma 1,5-anhydroglucitol (1,5-AG).[112] CGM employs a sensor measuring interstitial glucose every 1-10 min, which then transmits this reading to a data storage device. 1,5-AG is a natural dietary polyol and has been proposed as a marker for post-meal hyperglycemia. Stettler et al.

performed a prospective study at three large Swiss hospitals and found that 1,5-AG best reflected the 2-hour postprandial glucose values of the two previous weeks.[113] These findings are consistent with recent data from type 1 diabetic patients monitored with CGM in whom the change in 1,5-AG level was significantly correlated with changes in glycemic control, mean post-meal maximum glucose and area under the curve for glucose above 180mg/dL.[114]

b) Detecting postprandial hypertriglyceridemia

In contrast to postprandial hyperglycemia, there are currently no available standardized or validated protocols and cut-off points for the assessment of postprandial hypertriglyceridemia.[1] The Endocrine Society Clinical Practice Guidelines for the evaluation and treatment of hypertriglyceridemia indicate that although postprandial lipid levels may be a more potent predictor of cardiovascular disease risk than fasting triglycerides, it is recommended that the diagnosis of hypertriglyceridemia at present be based on fasting TG levels due to lack of standardization and reference levels of non-fasting TG or RLPs.[115] Similarly, the American Association of Clinical Endocrinologists Guidelines for management of dyslipidemia and prevention of atherosclerosis point out the lack of an assessment and of a standardized reference range for non-fasting TG. They however emphasize that elevated postprandial TG can no longer be ignored as indicative of no increased CHD risk and also refer to several studies which suggest that non-fasting TG exceeding the usual fasting cut-off points (≥150mg/dl) are independently associated with increased CAD risk.[116] The 2011 European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemias state that the use of non-fasting TG is still debated.[154] Also mentioned is the fact that non-HDL-C has proved to be a good surrogate marker of TG and remnants.[154] Several biochemical procedures have been used for the evaluation of postprandial plasma chylomicrons and their remnants (triglyceride-rich lipoprotein fractions, remnant-lipoprotein cholesterol, retinylesters, chylomicron-like emulsion, sodium dodecyl sulphate-polyacrylamide gel electrophoresis, immunoblotting, enzyme-linked immunoabsorbent assays, C13 breath test capillary finger prick), which nevertheless are not equivalent in specificity, cost and applicability.[117] Su et al propose identification of ApoB48 with ELISA, along with capillary triglyceride measurements, as the most clinically potent methods for the determination of postprandial lipid metabolism.[117] There are also data indicating that in young healthy subjects, fasting triglyceride-rich lipoproteins are useful predictors of postprandial hyperlipidemia, thereby pointing to a potential effective method that avoids the use of inconvenient meal loading tests.[118] It would be interesting to evaluate the utility of this assay in other population groups, such as in older, obese or diabetic individuals. Regarding the determination of optimal cut-off points for the detection of postprandial hyperlipidemia, White et al. suggest an optimal non-fasting triglyceride threshold of 175mg/dl, which corresponds to a HR for cardiovascular events of 1.88 (95% CI 1.52-2.33, P <0.001).[119]

TREATMENT OF POSTPRANDIAL DYSMETABOLISM

Major curative interventions aiming at postprandial dysmetabolism treatment are dietary modification, exercise, weight loss and medication aiming at amelioration of postprandial glucose and triglycerides values. The American Diabetes Association Guidelines recommend a target of peak postprandial capillary plasma glucose (measurements should be made 1-2 hours after the beginning of the meal) <180mg/dl (10mmol/l) for non-pregnant adults with diabetes.[111] Given the fact that postprandial glucose values >7.8mmol/l are associated with an increase in all-cause mortality and values, while >10mmol/l is associated with both microvascular complications and higher risk for MI, the Canadian Diabetes Association Guidelines recommend a 2-hour postprandial glucose target of 5-10mmol/l in diabetic patients in order to achieve an A1c ≤7%. If, however, the A1c target of ≤7% cannot be achieved, they recommend a further lowering of the postprandial glucose target to 5-8 mmol/l.[120]

Dietary modification and exercise

The international guidelines recommend lifestyle modification in individuals with IGT in order to delay conversion to type 2 diabetes. Weight loss, increased physical activity and an appropriate intake of total energy with a diet in which fiber and low fat

protein sources predominate have been seen to be effective.[111,120,121]

The contribution of a well-designed and balanced diet is important for postprandial dysmetabolism treatment. Modern diets have been shown to be involved in meal-induced inflammation and postprandial oxidative stress.[122] In addition, recent data indicate that fast food consumption induces greater and sustained overall cardiac workload (prolonged elevations in resting heart rate and prolonged elevations in diastolic workload) in patients with type 2 diabetes.[123] In contrast, the Mediterranean diet which is low in caloric density but rich in nutrient density has been associated with better cardiovascular health.[1]

Consumption of fiber is beneficial for postprandial dysmetabolism amelioration. Specifically, it has been shown that a diet rich in vegetables, fruits and whole cereals decreases both postprandial glucose and triglyceride-rich lipoproteins.[124,125] In addition, a meal high in fruit and fiber is associated with alterations in several factors which may result in improved postprandial glucose and lipid values and in restriction of inflammatory response. These alterations include higher proinsulin, insulin, C-peptide, GIP and peak GLP-1 secretion and lower plasma glucagon, dipeptidyl peptidase-IV (DPP-IV) and CD26 expression in mononuclear cells (MNC) compared to a high fat and carbohydrate meal.[126]

Regarding carbohydrates, both the type and amount of carbohydrates consumed are crucial for the increase of postprandial glucose. A low glycemic index diet appears to result in lower postprandial glucose levels as well as in lower fasting apolipoprotein B concentration.[127] The glycemic index measures the glycemic effect of meal carbohydrate compared to the effect of an equal amount of glucose and is estimated as a percentage of the blood glucose area under the curve 2 hours after food consumption compared to the same area under the curve after the same amount of carbohydrate was taken as glucose.[128,129] In addition, it seems that consumption of meals containing high amounts of carbohydrates contributes to post-meal glucose excursions in individuals both with impaired glucose regulation and with normal glucose tolerance, with postprandial glucose fluctuations increasing gradually with increased proportions of consumed carbohydrates.[130]

The ESC and the EAS Guidelines for the management of dyslipidemias state that a high monounsaturated fat diet significantly improves insulin sensitivity and reduces postprandial TG levels compared to a high saturated fat diet.[154] There is evidence that consumption of omega-3 fatty acids may improve postprandial lipid metabolism, curbing elevations of triglycerides, ApoB48, remnant lipoprotein-cholesterol levels in healthy subjects, decreasing postprandial triglyceride and ApoB48 in obese individuals combined with an hypocaloric diet and reducing postprandial triacylglycerol levels in hypertriglyceridemic patients.[131-133]

It is noteworthy that type 2 diabetic patients seem to exhibit reduced post-breakfast glucose excursion when consuming a high protein breakfast compared to a high carbohydrate breakfast meal.[134] Similarly, hypertriglyceridemic individuals who consume a low protein diet appear to develop an exaggerated postprandial chylomicron response, as indicated by increased postprandial ApoB48.[135]

Exercise and concomitant weight loss also have an important role in the management of postprandial dysmetabolism. The American Diabetes Association Guidelines recommend a target of 7% weight loss and increase of their moderate-intensity physical activity to at least 150 min/week.[111] A meta-analysis of 11 studies, including aerobic exercise, resistance exercise or a combination of these, concluded that exercise decreased significantly average glucose concentrations (-0.8 mmol/L, $p < 0.01$) and daily time spent in hyperglycemia (-129 minutes, $p < 0.01$) but did not have an impact on fasting glucose in patients with type 2 diabetes.[136] This finding strengthens the beneficial impact of exercise on postprandial glucose metabolism. As far as postprandial lipid metabolism is concerned, it seems that exercise improves postprandial triglyceride levels in overweight young women and men with metabolic syndrome and in type 2 diabetic patients.[137-139] Moreover, there are data indicating that weight loss after bariatric surgery may result in lower postprandial plasma glucose values in both obese and non-obese type 2 diabetic patients.[140,141]

Pharmacological treatment targeting postprandial hyperglycemia

Concerning IGT, the Canadian Diabetes Association recommends pharmacological therapy with

metformin or acarbose for individuals with IGT in order to reduce the risk of type 2 diabetes (Grade A, Level 1A).[120] The American Diabetes Association Guidelines, on the other hand, do not distinguish between individuals with IGT and those with IFG and recommends consideration of metformin therapy in individuals with prediabetes and BMI >35, in those aged <60 years, in women with prior gestational diabetes mellitus and in those with rising A1C despite lifestyle intervention.[111]

The International Diabetes Federation Guideline Development Group states that the pharmacologic agents that mainly affect postprandial glucose values in diabetic patients are: α-glucosidase inhibitors (AGIs), meglitinides, short-acting sulfonylureas, short-acting insulin, GLP1 analogs, DDP4 inhibitors and pramlitidine.[112]

AGIs act in the intestine through inhibition of α-glycosidases which are located in the gut epithelium and convert oligosaccharides and polysaccharides to easily absorbed monosaccharides. AGIs thus reduce carbohydrates absorption. They are effective in lowering postprandial glucose levels and, of note, they also blunt postprandial lipids spikes. Moreover, they possess additional pleiotropic effects, such as increase of GLP-1 postprandial circulating levels, oxidative stress reduction, prevention of endothelial dysfunction and promotion of weight loss. Their main adverse effect is flatulence and other gastrointestinal symptoms.[142,143]

Meglitinides (repaglinide and nateglinide) are short-acting insulin secretagogues which act to restore the disrupted early-phase secretion of postprandial insulin. They are administered 15 minutes before a meal and their action begins within 30 minutes of meal inception. Their main adverse effect is hypoglycemia.[144] A randomized multicenter clinical trial in type 2 diabetic patients showed that after a 16-week therapy, both repaglinide and nateglinide seemed to have a similar postprandial glycemic effect, although repaglinide was more effective in reducing HbA1c and fasting plasma glucose.[145] Concerning the effectiveness of meglitinides in reducing postprandial hyperglycemia complications compared to other insulin secretagogues, a randomized single-blind trial on 175 drug-naïve type 2 diabetic patients showed that repaglinide for 12 months resulted in regression of carotid intima-media thickness in a greater proportion of diabetics compared to glyburide (52% vs 18%, $p<0.01$). In addition, inflammation markers, such as CRP and IL-6, decreased more in the repaglinide vs the glyburide group. These observations were accompanied by statistically significant changes in postprandial but not fasting hyperglycemia.[146]

GLP1 receptor agonists (exenatide, exenatide LAR, liraglutide, lixisenatide) are synthetic GLP1 analogs resistant to DDP4 disruption which demonstrate the same actions as endogenous GLP1.[14] The GLP1 analogs that primarily aim at lowering postprandial glucose are exenatide and lisixenatide, while exenatide LAR and liraglutide mainly affect fasting plasma glucose.[14] The main reason that short-acting GLP1 receptor agonists (exenatide, lisixenatide) seem to be more effective in reducing postprandial glucose levels appears to be related to the rate of gastric emptying rather than their effect on insulin release.[147] It seems that short-acting GLP1 receptor agonists cause a more sustained delay in gastric emptying than the longer-acting ones.[147] There is clinical evidence that exenatide improves postprandial hyperglycemia through deceleration of gastric emptying, enhancement of visceral glucose uptake, inhibition of glucagon secretion and stimulation of insulin secretion. These mechanisms contribute to an improvement of prandial glycemia and a reduction of body weight.[148] The American Diabetes Association Guidelines propose adding a GLP-1 receptor agonist in order to cover postprandial glucose excursions in diabetic patients treated with basal insulin when A1C remains above target despite achievement of an acceptable fasting glucose level.[111] Moreover, recent large double-blind trials have evaluated the impact of GLP1 receptors agonists on cardiovascular morbidity and mortality in patients with type 2 diabetes.[149,150] The ELIXA trial is a multicenter, randomized, double-blind, placebo-controlled trial which enrolled 6,068 type 2 diabetic patients with a recent acute coronary heart syndrome who were randomized to receive lixisenatide or placebo in addition to concomitant glucose-lowering agents in accordance with the local clinical guidelines. After a median of 25 months of follow-up, results showed non-inferiority of lixisenatide to placebo ($p<0.001$) with respect to a primary composite endpoint of

cardiovascular death, myocardial infarction, stroke or hospitalization for unstable angina.[149] The LEADER trial is a multicenter, double-blind, placebo-controlled trial which included 9,340 patients with type 2 diabetes and high cardiovascular risk who were randomized to receive liraglutide or placebo in addition to standard care. The primary composite outcome was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or nonfatal stroke. After a 3.8-year median follow-up, it was shown that the primary outcome was achieved in fewer patients in the liraglutide group (608 of 4,668 patients [13.0%]) than in the placebo group [694 of 4,672 (14.9%)] [hazard ratio, 0.87; 95% confidence interval (CI), 0.78 to 0.97; P<0.001 for non-inferiority; P=0.01 for superiority].[150]

DPP4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin) inhibit the DPP4 enzyme which physiologically inactive GLP1 and GIP through disintegration. They are effective in reducing plasma glucose levels in the postprandial and the fasting state. They have no effect on body weight and they are safe with respect to causing hypoglycemia.[151] The various DPP4 inhibitors are similar concerning their antihyperglycemic properties.[151] Regarding the effectiveness of DPP4 in reducing postprandial hyperglycemia compared to other hypoglycemic agents targeting postprandial glucose, a recent study in 19 type 2 diabetics inadequately controlled by diet and exercise indicated that the effects of sitagliptin on postprandial glucose levels were similar to those of nateglinide.[152]

Pramlitidine is a synthetic analog of amylin which may be used with mealtime insulin in type 1 and type 2 diabetic patients.[153] Moreover, it may be used in type 2 diabetics in addition to monotherapy with metformin or sulfonylurea or to combined therapy with metformin and sulfonylurea, with or without insulin therapy. It is effective in reducing postprandial glucose by 4-6 mmol/l and may be useful in reducing the dose of administered insulin.[153] In addition, it may contribute to weight reduction, which however seems to be transient. The most common adverse effect is transient nausea.[153]

Pharmacological treatment targeting postprandial hypertriglyceridemia

So far, the guidelines do not recommend pharmacological treatment aiming to ameliorate postprandial hypertriglyceridemia, nor do they delineate specific targets.[115,116,154] Antilipidemic agents are typically used for treatment of fasting hyperlipidemia. Nevertheless, there are data suggesting that they may also play an important role in the management of postprandial hyperlipidemia.

Statins

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity and they are moreover considered as useful pharmacologic therapy for the treatment of fasting hypertriglyceridemia.[154] There is evidence that they may also improve postprandial lipoprotein metabolism.[155] There are data indicating that 4 weeks therapy of atorvastatin 10mg daily may decrease postprandial large triglyceride-rich lipoproteins (containing chylomicrons) in hypertriglyceridemic patients.[156] In addition, it has been shown that pitavastatin 2mg/day may result in reduction of both postprandial hypertriglyceridemia and endothelial dysfunction in obese subjects and in patients with stable coronary artery heart disease.[157,158] Simvastatin 80mg has also been seen to be effective in reducing postprandial plasma triglyceride levels and triglyceride-content in lipoprotein fractions in male obese patients with metabolic syndrome.[159]

Ezetimibe

Ezetimibe inhibits the intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients, thus resulting in upregulation of hepatic LDL receptor and subsequently in increased LDL-cholesterol clearance from the circulation.[154] Trials in overweight/obese men with hypertriglyceridemia report that the administration of ezetimibe at a dose of 10mg/day resulted in reduction in postprandial serum triglyceride excursion as well as in fasting and postprandial ApoB48 levels.[160,161] Similar results have been noted in type 2 diabetic subjects when the same dose of ezetimibe (10mg/day) was added to a lipid lower treatment with simvastatin 20mg.[162] In addition, it seems that this medication may suppress postprandial endothelial dysfunction, as this has been assessed by brachial artery flow-mediated dilation.[163] In respect to ezetimibe efficacy in ameliorating postprandial hyperlipidemia compared to statin

therapy, a multicenter, double-blind, crossover trial in 100 abdominally obese patients with metabolic syndrome showed that adding 10mg ezetimibe to a low dose statin treatment (10mg simvastatin) has an equal effect compared to a high dose statin treatment (simvastatin 80mg) in postprandial plasma lipids as well as in fasting and postprandial change of endothelial function.[164]

Fibrates

Fibrates interfere with lipoprotein metabolism, decreasing the production and increasing the catabolism of triglyceride-rich lipoproteins through the activation of peroxisome proliferator-activated receptor-alpha (PPAR-α). They are effective in lowering both fasting and postprandial triglycerides and triglyceride-rich lipoprotein (TRL) remnant particles.[154,165] It has also been suggested that fenofibrate may reduce fasting and postprandial inflammatory response and oxidative stress as it has been shown to reduce inflammation markers such as soluble vascular cell adhesion molecule-1 (VCAM-1) and soluble intercellular adhesion molecule-1 (ICAM-1) as well as oxidized fatty acids.[166] Concerning the comparison of fibrates efficacy with other lipid lowering agents or their potential synergistic effect, a randomized controlled clinical trial with 47 type 2 diabetics with hypertriglyceridemia showed that gemfrozile 1200mg/d alone did not differ in decreasing postprandial serum triglyceride compared to gemfrozile 1200mg/d plus ezetimibe 10mg/d or atorvastatin 10mg/d plus ezetimibe 10mg/d, and that fasting serum ApoB was reduced only in subjects receiving a regimen containing ezetimibe.[167]

The ACCORD lipid trial evaluated the effect of intensive lipid plasma treatment on cardiovascular outcomes in type 2 diabetic patients. Five thousand five hundred eighteen (5,518) type 2 diabetics who were treated with simvastatin were randomly assigned to receive fenofibrate or placebo and the primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes after a 4.7-year mean follow-up.[168] No significant difference was found between the fenofibrate group and the placebo group with respect to the primary outcome. However, there was a subgroup of patients with both a baseline TG level in the highest third (mean 284mg/dl) and an HDL level in the lowest third (mean 29.5 mg/dl) who seemed to benefit from treatment with fenofibrate.[168] High fasting TG and low fasting HDL forms a well-recognized component of the metabolic syndrome which is also characterized by several other lipid and lipoprotein abnormalities, such as elevated postprandial TG, small dense LDL and ApoB containing particles including chylomicrons and VLDL.[154] Moreover, an ancillary study in a subset of subjects of the ACCORD lipid trial showed that administering fenofibrate 145mg/dl to type 2 diabetics receiving simvastatin resulted in reduction of both postprandial triglycerides and postprandial ApoB levels.[169] However, it seems that the overall baseline TG levels in these subjects were lower (median=99) and the HDL levels were higher (mean=38.9±10mg/dl) than in the subgroup, who appeared to have benefited from fenofibrate therapy in the original ACCORD lipid trial.[168,169] These data may indicate that fenofibrate therapy may ameliorate postprandial dyslipidemia in subjects with low HDL and high fasting TG, such as type 2 diabetics and individuals with metabolic syndrome, but further studies need to be conducted.

Apart from the well-established hypolipidemic agents, it seems that orlistat, a drug which promotes weight loss by inhibiting intestinal lipase, may lower postprandial TG levels as stated by the Endocrine Society Clinical Practice Guidelines for evaluation and treatment of hypertriglyceridemia.[115] It is also interesting that pharmacological agents targeted at postprandial hyperglycemia could also play a role in amelioration of postprandial hypertriglyceridemia. Specifically, there is clinical evidence that incretin-based therapies like exenatide and DPP4 inhibitors may play an important role in lowering postprandial lipids and lipoproteins concentrations and postprandial lipids spikes.[25] It has been also shown that acarbose might reduce postprandial triglycerides, serum-remnant like particle (RLP) cholesterol, chylomicrons and free fatty acids.[142]

CONCLUSIONS

Postprandial dysmetabolism is a non-fasting state characterized by elevated levels of plasma glucose and triglyceride containing lipoproteins (chylomicrons, VLDL, RLPs). Accumulating data indicate

that postprandial dysmetabolism contributes to the development of atherosclerosis, while it has also been demonstrated that it comprises a risk factor for increased cardiovascular morbidity and mortality. Clearly, postprandial hyperglycemia contributes to microvascular complications such as nephropathy and retinopathy. The main pathophysiologic mechanisms participating in development of cardiovascular damage are endothelial dysfunction and oxidative stress, activation of inflammation and coagulation mechanisms and facilitating the penetration of lipoprotein particles into the arterial wall.

The conventional methods for the detection of postprandial hyperglycemia are the 75g OGTT and SMBG, while emerging technologies for the evaluation of postprandial glucose levels include CGM and plasma 1,5-anhydroglucitol (1,5-AG). In contrast to postprandial hyperglycemia detection and screening, there are no currently available standardized or validated protocols and cut-off points for the assessment of postprandial hypertriglyceridemia.

The management of postprandial dysmetabolism includes firstly lifestyle modification strategies with diet, exercise, weight loss and, if deemed necessary, the administration of a variety of pharmaceutical agents. Regarding medical treatment, acarbose, meglitinide analogs, short-acting insulin and the novel GLP-1 receptor agonists, DDP-4 inhibitors and pramlitidine are effective in ameliorating postprandial hyperglycemia, while some of these hypoglycemic agents such as acarbose, exenatide and DPP-4 receptor agonists seem also to be effective in postprandial hyperlipidemia treatment. Drugs which are conventionally used for the treatment of fasting dyslipidemias, such as statins, ezetimibe and fibrates, also appear to play an important role in managing postprandial dyslipidemia. However, future trials are required exploring not just isolated blood measurements, but mainly the actual tissue damage and the reversibility of postprandial dysmetabolism long-term complications.

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