Disorders in Postprandial Lipid Metabolism and the Risk of Atherogenesis

Nadmierna lipemia poposiłkowa jako czynnik ryzyka miażdżycy

Abstract

Postprandial hyperlipidemia (lipemia) is a frequent metabolic disorder observed in diabetes mellitus and atherosclerosis. The postprandial state after a high-fat meal induces endothelial dysfunction, mainly through an oxidative stress mechanism. Postprandial hyperlipidemia is known to reduce endothelium-dependent flow-mediated vasodilatation (FMD). Endothelial dysfunction has been suggested to be an early indicator of atherosclerosis. Postprandial hyperlipidemia may contribute to the development of coronary artery disease (CAD) because it is frequently observed in patients with premature atherosclerosis, despite relatively normal fasting lipemia. Hyperlipidemia has also been reported to be associated with an increased expression of cellular adhesion molecules. Postprandial intravascular inflammatory changes may be an important link in the pathogenesis of atherosclerosis (Adv Clin Exp Med 2008, 17, 5, 565–573).

Key words: atherosclerosis, postprandial lipemia, hypertriacylglycerolemia, endothelial dysfunction, inflammation.

Streszczenie


Słowa kluczowe: miażdżyca, lipemia poposiłkowa, hipertriacylglicerolemia, dysfunkcja śródbłonka, zapalenie.
thelium-dependent dilatation and oxidative stress [1, 2].

Postprandial intravascular inflammatory changes may be an important link in pathogenesis of atherosclerosis, which is a chronic inflammatory disease involving leukocytes, vascular smooth muscle cells, and metabolic disorders of lipids and glucose, leading to endothelial dysfunction. Endothelial dysfunction has been suggested to be an early indicator of atherosclerosis. Endothelium plays a crucial role in the regulation of vascular tone and the development of atherosclerosis. Endothelial function is impaired early in patients with risk factors of cardiovascular diseases and endothelial dysfunction is a strong and independent predictor of cardiovascular events. Because in healthy subjects serum levels of lipids, glucose, and insulin are increased after meals and these postprandial changes last a long time, these changes might be of importance in the initiation and progression of atherosclerosis.

**Effect of Postprandial Hyperlipidemia on Endothelial Function**

During the postprandial phase, chylomicrons and their remnants can penetrate the intact endothelium, undergo modification in the subendothelial space, and be taken up by macrophages, what results in the formation of foam cells. These particles are highly atherogenic after their prior modification. In the postprandial state the degree of endothelial function impairment is related to changes in RLP (remnant-like particle) levels. The identification of dietary or pharmacological interventions (e.g. the use of fibrates) which modulate RLP levels may provide effective tools for controlling endothelial dysfunction and, therefore, atherosclerosis and cardiovascular disease [3].

In mild hypertriacylglycerolemic subjects, a high-fat meal did not alter baseline blood pressure, heart rate, radial artery diameter, or blood flow. It also did not alter the increase in blood flow induced by four-minute ischemia, whereas it markedly attenuated the concomitant increase in arterial diameter and showed a significant correlation with the increase in serum TAGs induced by the high-fat meal \( r = 0.49, P < 0.05 \). This attenuation was not observed in control subjects and in subjects in whom the measurements were repeated after a six-hour observation period. An oral fat load (OFL) had little effect on radial artery response in controls, but it markedly altered the flow-mediated increase in radial artery diameter in hypertriacylglycerolemic subjects. OFL did not have any effect on the larger, NO-independent increase in radial artery blood flow and diameter induced by much more prolonged ischemia. This reflects a specific endothelial effect because vascular reactivity to substances other than NO that were released by long-term ischemia was unaffected by OFL in hypertriacylglycerolemic subjects and in normotriacylglycerolemic controls. These results have pathophysiological implications because endothelial dysfunction is the first step in the chain of arterial wall modifications that allow an atherosclerotic lesion to start and progress. They may thus provide an explanation for the epidemiological finding that transient increases in serum triglycerides increase the risk of coronary disease. It remains to be more fully explained whether acute hypertriacylglycerolemia affects only the ability of endothelial cells to increase their NO secretion (the endothelial function “reserve”) or if it extends to the continuous secretion of this mediator [4, 5].

Because postprandial lipemia can be acutely mitigated when proteins are added to a fatty meal, Westphal et al. investigated whether this mitigation could neutralize the lipemia-induced endothelial dysfunction. Postprandial lipemia reduced flow-mediated dilatation (FMD), the reduction reaching 58% after 3 h. This impairment of endothelial function was not observed when either of the test proteins had been added to the fatty meal. The effects of protein addition were decreases in triacylglyceroles and free fatty acids, increased insulin concentrations at all time-points, and an increased arginine/ADMA ratio between 1 and 5 h after the meal, particularly in the case of the soy protein. The authors suggested that the neutralization of the lipemia-induced endothelial dysfunction is caused by direct and indirect effects of the proteins’ insulinotropy and, secondly, by an increased supply of L-arginine. Endothelial dysfunction induced by postprandial lipemia is neutralized by addition of proteins to the fatty meal [6]. Cortés and coworkers investigated whether the addition of walnuts or olive oil to a fatty meal have differential effects on postprandial vascular reactivity, serum levels of lipoproteins, markers of oxidation, endothelial activation, and plasma asymmetric dimethylarginine (ADMA). The authors hypothesized that walnuts would reverse the postprandial endothelial dysfunction associated with the consumption of a fatty meal. Flow-independent dilatation and plasma ADMA concentrations were unchanged and the serum level of oxidized LDL decreased after either meal [51].

Concluding, endothelial function is markedly impaired by a high-fat meal that causes acute...
hypertriacylglycerolemia. This impairment is evident in dyslipidemic patients with baseline hypertriglycerolemia, but not in normotriacylglycerolemic subjects [7].

Regulation of Postprandial Lipid Metabolism – Genetic Aspects

Recent evidence suggests that common variations of the apoA5 gene locus are significant independent predictors of the risk and incidence of cardiovascular disease (CVD) and metabolic syndrome [8–10]. Apolipoprotein A5 (apoA5) polymorphisms have been consistently associated with variability in cardiovascular risk and fasting TAG levels. However, their impact on postprandial lipemia remains relatively unknown. Olano-Martín et al. investigated the putative impact of two common apoA5 polymorphisms (–1131T > C and S19W) and apoA5 haplotypes on fasting and postprandial lipid metabolism. The resulting data suggest that variation in the apoA5 gene locus is associated with differences in fasting and postprandial TAG levels in healthy adults, although the molecular basis for this association remains to be further investigated [16]. The impact of apoA5 genotype on fasting TAG has been relatively widely reported. Only three previous studies investigated the impact of common apoA5 gene variants on postprandial lipemia, with two conducted in Korean male cohorts and one in young adult Caucasian males in the European Atherosclerosis Research Study (EARS) [11]. Based on the current understanding of the role of apoA5 as a mediator of the synthesis and hydrolysis of TRL in the circulation and the association between common apoA5 SNPs and fasting TAG levels, it is likely that the increased risk may be in part attributable to an impact of genotype on TAG metabolism [12–15].

Olano-Martín et al. reported impact of the –1131T > C and S19W polymorphisms on postprandial triglyceride metabolism in healthy UK males and females, indicating that the impact of genotype may be gender specific. This indicates that the apoA5 –1131T > C SNP is significantly associated with postprandial lipemia [16]. To date, genetic susceptibility to hypertriglycerolemia has been attributed to variation in the gene for LPL or that of its cofactor, apoC2, and in some cases to apoE homozygosity. This study suggests that genotyping of individuals for the apoA5 –1131T > C SNP in addition to LPL, apoC2, and apoE may be of clinical importance, in particular in those with a family history of diabetes or CVD. It would help to identify individuals at high risk of developing exaggerated postprandial lipemia prior to presentation with clinical symptoms, which could result in more frequent monitoring and earlier intervention in the relevant subgroups. This does not rule out the possibility that variants in the apoC3 locus may have some independent effect, but it strongly suggests that apoA5 variants may be more important, which is in agreement with other studies which have examined fasting TAG levels. Further work characterizing the strength and molecular basis of as well as the impact of diet and other environmental factors on apoA5 genotype-TAG associations is merited [16].

Postprandial Lipemia and Inflammation

Emerging evidence suggests that postprandial hyperglycemia and hyperlipidemia are important risk factors in the development of atherosclerosis. Proinflammatory particles, such as IL-6, IL-8, and C3, have also been postulated to play important role in the development of vascular changes. It is thought that the release of various inflammatory mediators is initiated by resident and recruited leukocytes [17–19]. Postprandial lipoproteins can activate leukocytes in blood and enhance the expression of leukocyte adhesion molecules on the endothelium, facilitating the adhesion and migration of inflammatory cells into the subendothelial space. Another inflammatory process associated with postprandial lipemia is the activation of the complement system. Its central component, C3, has been associated with obesity, coronary artery disease, and metabolic syndrome. In addition, chylomicrons are the strongest stimulators of adipocyte C3 production due to activation of the alternative complement cascade [20].

In atherosclerotic patients, increased activation of leukocytes as determined by measurement of oxidative stress generation, surface antigen expression, and plasma levels of soluble activation markers has been already widely described. In addition, recent evidence suggests that part of the anti-inflammatory effects of statins or fibrates may be caused by inhibition of leukocyte activation apart from inhibition of HMG-CoA reductase [21] or stimulation of PPAR-α (peroxisome proliferator-activated receptor alpha), respectively.

The importance of neutrophils was underlined in an animal model which showed that prevention of leukocyte adherence to the endothelium by blocking selectins prevented endothelial dysfunction. ROS production, assessed as total plasma...
lipid hydroperoxide production, was increased postprandially in all tests that showed a reduction in flow-mediated dilatation (FMD). The postprandial phase, characterized by increased levels of glucose and TAGs, is accompanied by recruitment of neutrophils. Food intake has been suggested to induce a local enteric immune response and to activate neuro-endocrine pathways due to intestinal antigenic exposure of dietary components [22].

Postprandial lymphocyte and IL-6 increments are meal independent, suggestive of a diurnal rhythm. During the postprandial phase there is a fat- and glucose-specific neutrophil increase in vivo with a concomitant rapid postprandial IL-8 and hydroperoxide (HPO) increment that may contribute to reversible endothelial dysfunction. Postprandial intravascular inflammatory changes may be relevant in the pathogenesis of atherosclerosis [17].

According to a study performed by Esposito and coworkers, a single high-fat meal in healthy subjects impairs the antiplatelet function of endothelium and activates both coagulation and fibrinolysis. A high-carbohydrate meal also activates hemostasis, which, unlike after a high-fat meal, returns to prestimulatory values after increased nitric oxide availability by L-arginine. Food containing antioxidants partially prevents endothelial dysfunction acutely induced by a high-fat meal [23]. A few studies reported thus far have focused mainly on FVIIa and showed an increase after a fat-rich meal. Although the absolute increase in FVIIa was significantly lower after high-carbohydrate meal than after high-fat meal, activation of coagulation occurred after both meals. This suggests that the process is independent, at least in part, of the type of food. This may indicate that L-arginine may play a role, at least after acute administration, in resetting activated hemostasis and that this putative effect, specific or nonspecific, may be impaired during a high-fat meal. Both procoagulant and anticoagulant events may be influenced by the same food. This is possibly the result of interactions between different components of the system and the compensatory adjustments in one part when another is affected in an attempt to maintain hemostasis [24].

Adhesion molecules, particularly intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), and E-selectin, have been associated with cardiovascular disease [25]. Elevated levels of these molecules have been reported in diabetic patients. The adhesion of circulating leukocytes to endothelial cells plays an important role in the initiation of atherosclerosis. Cellular adhesion molecules are poorly expressed by the resting endothelium, but they are up-regulated during atherogenesis. Soluble forms of some cellular adhesion molecules may be an index of endothelial activation or even a molecular marker of early atherosclerosis. Circulating levels of some cellular adhesion molecules, particularly ICAM-1, VCAM-1, and E-selectin, have been found to be increased in diabetic patients [26, 27].

A high fat load and glucose alone produced increases in nitrotyrosine, ICAM-1, VCAM-1, and E-selectin plasma levels in normal and diabetic subjects [28]. These effects were more pronounced when high fat and glucose were combined. Short-term simvastatin treatment had no effect on lipid parameters, but reduced the effect on adhesion molecules and nitrotyrosine, which was observed during every different test. Long-term simvastatin treatment was accompanied by a lower increase in postprandial triglycerides followed by smaller variations in ICAM-1, VCAM-1, E-selectin, and nitrotyrosine during the tests. This study showed an independent and cumulative effect of postprandial hypertriacylglycerolemia and hyperglycemia on ICAM-1, VCAM-1, and E-selectin plasma levels, suggesting oxidative stress as a common mediator of such effects. The beneficial effect of simvastatin against oxidative stress and the plasma levels of adhesion molecules may be ascribed to a direct effect in addition to the lipid-lowering action of the drug [29]. However, hyperlipidemia has also been reported to be associated with increased levels of cellular adhesion molecules and evidence also suggests that postprandial hyperlipidemia may condition an increase of these molecules.

**Oxidative Stress as a Common Mediator of Metabolic Disorders**

An oxidative mechanism might be responsible for impaired flow-mediated brachial artery vasodilation after a high-fat meal. The mechanism underlining free-radical generation during an acute increase of both glycemia and triacylglycerolemia seems to be mediated by the induction of NADPH activity [30]. Postprandial hyperglycemia and postprandial hypertriacylglycerolemia may have direct and cumulative effect in stimulating endothelial dysfunction and nitrotyrosine (NT) generation [31].

In one study, pretreatment with vitamins C and E blocked the progression of endothelial dysfunction [32]. Impairment of endothelium-dependent vasodilation after a high-fat meal was previously reported. Postprandial hypertriacylglycerolemia has been related to endothelial dysfunction. There might be an inverse relation between the magnitude of decrease
in blood pressure after L-arginine and the increase in triacylglycerol level after the high-fat meal [33].

Indeed, recent studies demonstrate both an independent and a cumulative effect of postprandial hypertriacylglycerolemia and hyperglycemia on endothelial function, with oxidative stress as the common mediator. The production of oxidative stress in such conditions may involve the overgeneration of superoxide anion (O$_2^-$) at the mitochondrial level, which in turn inactivates nitric oxide (NO), producing peroxynitrite, a potent long-lived oxidant [34]. It is also thought that reactive oxygen species (ROS) interfere with the bioavailability of endothelial nitric oxide; however, the exact mechanism remains uncertain. In addition, it has been suggested that endothelial cells could become indirectly activated due to interaction with adhering activated neutrophils. Those adhering neutrophils could impair vessel endothelial function via production of ROS and proteolytic enzymes [35].

Bae et al. analyzed the effects of postprandial hypertriacylglycerolemia with or without antioxidant supplementation on endothelial function as related to lipid oxidation in young healthy subjects. Endothelium-dependent flow-mediated brachial artery vasodilatations (FMDs) and serum malonyldialdehydes (MDAs), lipid oxidation products, did not significantly change following ingestion of any of the three types of meal. This study suggests that postprandial hypertriacylglycerolemia-induced endothelial dysfunction is not associated with lipid oxidation and that the protective effects of tocopherol on endothelial function may be due to some alternative, yet unknown, mechanism [36].

**Postprandial Disorders of Glucose and Lipid Metabolism – Independent Risk Factors or a Common Pathophysiological Link Leading to CVD?**

Meal absorption is a complex phenomenon, and postprandial hyperlipidemia and hyperglycemia are simultaneously present in the postabsorptive phase, particularly in diabetic subjects and in subjects with impaired glucose tolerance. Therefore, a specific and direct role of hyperglycemia, independent of concomitant hyperlipidemia, has been frequently questioned. Hyperglycemia has an earlier effect on both cellular adhesion molecules and nitrotyrosine (NT) during the postprandial period, whereas hypertriacylglycerolemia has a delayed but lasting effect and the combination of both has an early and lasting effect. Nitrotyrosine is a suitable marker of peroxynitrite and increased NT plasma levels have been found in diabetic patients. Moreover, when hyperglycemia and hypertriacylglycerolemia are simultaneously present there is a greater increase in cellular adhesion molecule level compared with that observed during either hyperglycemia or hypertriacylglycerolemia alone. These data suggest that postprandial hyperglycemia and hypertriacylglycerolemia have an independent but cumulative effect on the development of atherosclerosis and that their combination may favor an atherogenic postprandial profile for over 4 h [37].

There is evidence that postprandial hypertriacylglycerolemia is a risk factor for cardiovascular diseases in nondiabetic subjects, whereas in diabetic subjects, postprandial hyperglycemia has recently been suggested as an independent risk factor for CVD. Because in diabetic patients the postprandial phase is characterized by increase in both plasma triacylglycerols and glucose, the distinct roles and relative importance of these two factors in the pathogenesis of CVD in diabetes are a subject of current research [38].

Plasma apolipoprotein A4 (apoA4) level has been shown to be a good marker of triglyceride changes after a high-fat diet. However, the distribution of apoA4 between apoB- and non-apoB-containing lipoproteins (Lp) during the postprandial state has not been described nor has the influence of obesity on this distribution. Fasting Lp B:A4 may represent a good marker of the postprandial triglyceride increase in obese women. Changes in apoA4 concentrations in apoB- and non-apoB-containing Lp after a fat meal depend mainly on the degree of obesity rather than on insulin resistance [39].

Abnormalities during the postprandial state contribute to the development of atherosclerosis. Postprandial hyperglycemia and hypertriacylglycerolemia independently cause postprandial cytokine activation. However, it is not clear which dietary composition preferentially affects postprandial endothelial function in healthy subjects. Postprandial endothelial function was impaired only after a high-fat diet and not after a high-carbohydrate or standard test meal in healthy subjects [40].

**Postprandial State in Association with the Development of CVD and its Clinical Manifestation**

The risk of coronary artery disease (CAD) increases with the consumption of a high-fat diet.
The paradigm that dietary fats act exclusively through effects on serum lipids and lipoproteins has been already challenged [41]. It is generally accepted that postprandial hyperlipidemia may contribute to the development of CAD because it is frequently present in patients with premature atherosclerosis despite relatively normal fasting lipids. Therefore, postprandial hyperlipidemia with accumulation of atherogenic chylomicron remnants might be a risk factor for CAD [42]. Recently, much attention has been paid to prove that the abnormalities in postprandial state are important contributing factors to the development of atherosclerosis, even in diabetics. Since in diabetic patients the postprandial phase is characterized by the simultaneous increase of plasma TAGs and glucose, the distinct role and relative importance of these two factors in the pathogenesis of CVD in diabetes is a matter of debate. Evidence that this is the case is not conclusive, however, because TAGs were reported both to worsen and to have no measurable effect on endothelial function [43, 44]. Furthermore, little evidence has been obtained on whether TAGs affect endothelial function in individuals with more complex alterations in lipid profile, despite the evidence that under this circumstance the role of triacylglycerols as a cardiovascular risk factor may be enhanced. Hypercholesterolemia markedly impairs endothelial function. Whether this is the case for hypertriacylglycerolemia is less clear; however, there is some limited evidence on the effect of an acute increase in triacylglycerolemia caused by a high-fat meal. Postprandial increases in the serum level of TAGs appear to be predictive of coronary disease more than chronic TAGs levels [45].

Several studies have shown that an increased level of serum triacylglycerols can be an independent risk factor for coronary disease when occurring alone as well as against the background of other alterations in lipid profile [46]. This has stimulated research into whether triacylglycerols are able to cause endothelial dysfunction, which starts the cascade of events leading to the atherosclerosis [47].

Postprandial hypertriacylglycerolemia may represent an independent predictor of CVD in nondiabetic patients and a predictor of carotid intima media thickness in patients with type 2 diabetes. However, recent studies support the hypothesis that postprandial hyperglycemia is also a risk factor for CVD. The notion that postprandial hypertriacylglycerolemia and hyperglycemia may be important factors in the development of CVD is supported by evidence that both induce increases in the adhesion molecules ICAM-1, VCAM-1, and E-selectin, which have been shown to predict the development of atherosclerosis in diabetes [48, 49].

Bell et al. investigated the association of postprandial dysmetabolism, i.e. hyperglycemia, and hyperlipidemia with myocardial disease in diabetic glucose-intolerant and -tolerant patients. The authors showed a direct and proportional association between postprandial dysmetabolism and both coronary artery disease and cardiac events [50].

**Reduction of Postprandial Hyperlipidemia as a New Therapeutic Target**

According to Cortés and coworkers, fat meals enriched with walnuts or olive oil acutely improve FMD independently of changes in oxidation, inflammation, or ADMA. Both walnuts and olive oil preserve the protective phenotype of endothelial cells [51]. The plasma concentrations of soluble inflammatory cytokines and adhesion molecules decreased independently of meal type, except for E-selectin, which decreased more after the walnut meal.

The possibility of preventing hyperglycemia and hypertriacylglycerolemia-induced endothelial dysfunction and oxidative stress by short-term treatment with statins has been reported. The possibility of reducing NT generation during acute hyperglycemia with irbesartan has also been demonstrated recently [29]. Statins and angiotensin type 1 receptor blockers (ARBs) have been shown to reduce oxidative stress and inflammation, improving endothelial function. Short-term atorvastatin and irbesartan treatments significantly counterbalanced these phenomena, and their combination was more effective than either therapy alone [52]. Statins and ARBs work as antioxidants in various pathways. Blocking the enzyme HMG-CoA reductase, statins inhibit the synthesis of mevalonic acid, a precursor of many nonsteroidal isoprenoid compounds, and cholesterol biosynthesis. The intermediate compounds are responsible for the intracellular trafficking of several membrane-bound proteins, such as Rho and Ras GTPase, which modulate NADPH activity. Atorvastatin has been shown to reduce NADPH-mediated superoxide generation in endothelial cells exposed to high glucose levels [53]. ARBs also modulate NADPH activity, particularly in the presence of high glucose. However, the effect is due to the blockade of the specific receptor, which favors the translocation of Rac1-induced NADPH overexpression [54].
Conclusion

It is well recognized that post-prandial lipoproteins play an important role in the development of atherosclerosis; however, the mechanisms underlying this role remain unclear. An attractive working hypothesis is that the pathogenic link is endothelial dysfunction. The available data seem to corroborate this theory and recognize triggering by oxidative stress, but some of the evidence is still contradictory.

References


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