Postprandial inflammation and endothelial dysfuction

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Abstract
Postprandial hyperlipidaemia is a common metabolic disturbance in atherosclerosis. During the postprandial phase, chylomicrons and their remnants can penetrate the intact endothelium and cause foam cell formation. These particles are highly atherogenic after modification. People in the Western world are non-fasting for most of the day, which consequently leads to a continuous challenge of the endothelium by atherogenic lipoproteins and their remnants. Furthermore, atherosclerosis is considered a low-grade chronic inflammatory disease. Many studies have shown that the process of atherogenesis in part starts with the interaction between the activated leucocytes and activated endothelium. Postprandial lipoproteins can activate leucocytes in the blood and up-regulate the expression of leucocyte adhesion molecules on the endothelium, facilitating adhesion and migration of inflammatory cells into the subendothelial space. Another inflammatory process associated with postprandial lipaemia is the activation of the complement system. Its central component C3 has been associated with obesity, coronary sclerosis, the metabolic syndrome and fasting and postprandial TAGs (triacylglycerols). Moreover, chylomicrons are the strongest stimulators of adipocyte C3 production via activation of the alternative complement cascade. A postprandial C3 increment has been shown in healthy subjects and in patients with CAD (coronary artery disease) and with FCHL (familial combined hyperlipidaemia). Postprandial lipaemia has been related to TAG and free fatty acid metabolism. All of these mechanisms provide an alternative explanation for the atherogenicity of the postprandial period.

Introduction
Atherosclerosis is one of the primary causes of death in the world [1]. Most of the important risk factors such as smoking, hypertension, fasting dyslipidaemia, insulin resistance, increased body fat mass and unfavourable body fat distribution are strongly interrelated and can be found in one and the same subject. One of these examples is the highly prevalent metabolic syndrome [2]. Disturbances of TAG (triacylglycerol) metabolism is one of the major abnormalities in the metabolic syndrome. Subjects with fasting hypertriglyceridaemia usually have elevated postprandial lipids due to the close correlation of fasting and postprandial TAGs. Patients with the metabolic syndrome have postprandial hyperlipidaemia [3]. However, also patients with atherosclerosis with and without the metabolic syndrome, even in the presence of normal fasting TAGs, have postprandial hyperlipidaemia [4,5].

Consequently, postprandial hyperlipidaemia is a generalized phenomenon in high-risk conditions for atherosclerosis, and chylomicrons and their remnants have been shown to penetrate intact endothelium and cause foam cell formation [6].

Key words: chylomicron, complement, inflammation, leucocyte, lipaemia, oxidative stress.
Abbreviations used: C3/ASP, C3/acylation-stimulating protein; CAD, coronary artery disease; CHD, coronary heart disease; CRP, C reactive protein; FCHL, familial combined hyperlipidaemia; FMD, flow-mediated dilation; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL, low-density lipoprotein; LPL, lipoprotein lipase; NEFA, non-esterified fatty acid; PON-1, paraoxonase 1; TAG, triacylglycerol; TRL, TAG-rich lipoprotein.

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Figure 1 | Concept of the initiation of atherosclerosis in the bloodstream

Remnants, glucose and C3b are able to induce monocyte and neutrophil activation. This will lead to adherence of these cells to the endothelium as well as to the production of chemoattractants leading to the recruitment and activation of other leucocytes. Furthermore, these activated leucocytes can activate the endothelium by the expression of CAMs (cellular adhesion molecules) and selectins, facilitating adherence of all leucocytes, including lymphocytes. The activated leucocytes can also destabilize atherosclerotic lesions by the production of ROS (reactive oxygen species) and TNFα (tumour necrosis factor α). Monocytes and lymphocytes transmigrate across the endothelial wall. Activated neutrophils cannot transmigrate through the endothelial barrier, however they are able to degranulate, resulting in release of degradative enzymes such as collagenase and gelatinase. Monocytes residing in the arterial wall become activated as a result of proinflammatory cytokines and differentiate into macrophages (MΦ). LDL and remnant particles can enter the vessel wall as well. Oxidative modification of LDL results in a highly atherogenic particle that can easily be taken up by macrophages via the scavenger receptor (CD36). Activated monocytes and macrophages in the vessel wall can activate endothelial cells, resulting in production of CAMs and cytokines such as IL-6 and 8 (interleukin-6 and 8) and MCP-1 (monocyte chemoattractant protein-1). These effects combined will lead to recruitment and activation of leucocytes, as expressed by increased selectins and integrins on the outer membrane. Other activated leucocytes are attracted to the activated endothelium and will eventually firmly adhere to the vessel wall. Monocytes and lymphocytes can then transmigrate through the endothelial barrier.

Chylomicrons and inflammation

Atherosclerosis is considered a low-grade chronic inflammatory disease [20]. Many inflammatory markers have been associated with CHD such as CRP (C-reactive protein), leucocyte count and complement C3 [3,16,21–26]. However, several studies with animal models showed reduced plaque formation [27,28] and prevention of endothelial dysfunction [29] when adherence of leucocytes to the endothelium was prevented. These findings support the theory that the process of atherogenesis in part starts with leucocyte–endothelium interaction and adherence. Obligatory for this adherence is a cytokine-controlled sequential up-regulation of selectins and adhesion molecules on activated leucocytes and endothelial cells [30].

Van Oostrom et al. have shown that postprandially, when TAG and glucose rise, neutrophil counts increase, with concomitant production of pro-inflammatory cytokines and oxidative stress, and that these changes may contribute to endothelial dysfunction [31,32]. Furthermore, TAG and glucose are able to induce leucocyte activation, as has been shown in vitro [33] and ex vivo in hypertriglyceridaemic metabolic syndrome [13]. In the postprandial phase due to limited LPL availability, competition at the level of LPL will occur, resulting in accumulation of TRLs. This competition is most likely when fasting hypertriglyceridaemia is present, as occurs in the metabolic syndrome, Type 2 diabetes and FCHL (familial combined hyperlipidaemia) [14]. However, it has also been suggested that of all patients with premature CHD, 40% have normal fasting plasma lipids [15], whereas most of these patients have impaired clearance of postprandial lipoproteins [4,16,17]. Atherosclerosis has therefore been considered to be a postprandial phenomenon [18,19].
patients [34]. In healthy volunteers and in patients with premature atherosclerosis, postprandial lipaemia was associated with the up-regulation of leucocyte activation markers [35,36]. Fasting leucocytes of patients with CVD have an increased lipid content when compared with controls and it was suggested that this was due to the uptake of chylomicrons in the bloodstream [37]. Leucocytes are also able to take up retinyl esters, as markers of intestinally derived TRLs [38]. Recently, we have shown that apolipoprotein B binds to neutrophils and monocytes and that postprandial leucocytes transport dietary fatty acids [39]. This opens the possibility that direct activation of leucocytes may occur in the blood by interaction with chylomicrons and their remnants (Figure 1). Another aspect of postprandial lipaemia involves endothelial dysfunction. Many endothelium-derived factors play a role in vasomotion, permeability, proliferation and vascular smooth cell migration; NO (nitric oxide) is clearly one of the key players [40]. In the metabolic syndrome, but also in healthy subjects, elevations in fasting and postprandial TAGs have been related to increased carotid IMT (intima-media thickness) [41] and reductions in NO-dependent post-ischaemic FMD (flow-mediated dilation) of the brachial artery [42,43]. The reduction of FMD correlates with TAG and NEFA concentrations and is reversible in postprandial studies when TAG concentrations decrease at the end of the experiment [43]. Furthermore, postprandial lipoproteins have been shown to induce expression of leucocyte adhesion molecules on the endothelium, facilitating recruitment of inflammatory cells [44]. The effects of TRLs on the endothelium appear to be related to oxidative stress generation [31,45].

Another inflammatory marker related to CHD is complement system. The C3/ASP (C3/acylation–stimulating protein) system has been recognized as a regulator of adipose tissue fatty acid metabolism [46]. ASP is identical to the desarginated form of the C3 split product C3a (C3a-desArg), which is immunologically inactive. The C3/ASP pathway stimulates re-esterification of NEFAs into TAG in adipocytes, reduces adipocyte NEFA production by inhibiting hormone-sensitive lipase and stimulates glucose uptake by adipocytes, fibroblasts and muscle cells [46]. C3 is a strong predictor of myocardial infarction [26] and it has been positively associated with obesity, CAD (coronary artery disease), insulin resistance, the metabolic syndrome [3], fasting and postprandial TAG and hypertension [16,26]. Deposition of complement co-localized with CRP has been observed in atherosclerotic plaques [47] and complement activation also plays a role in the induction of tissue damage after myocardial infarction [48]. Moreover, chylomicrons are the strongest in vitro and in vivo stimulators of adipocyte C3 production via activation of the alternative complement cascade [24,49]. A postprandial C3 increment after a fat meal has been shown in healthy subjects and in patients with CAD and with FCHL [16,24,25]. The postprandial increment has been related to TAG and NEFA metabolism [5].

Since C3 and leucocytes increase postprandially, especially after fat intake, and leucocytes become activated during the postprandial phase, a potential mechanism may be the generation of oxidative stress [31,39]. Many factors have been suggested to participate in this process. PON-1 (paraoxonase 1), a potent antioxidant closely associated with HDL-C seems to be a key player [50]. During postprandial lipaemia, HDL-C tends to decrease, impairing the reverse cholesterol transport, again providing an extra atherogenic mechanism for postprandial lipaemia.

Conclusions

TRLs are especially produced in the postprandial situation. Postprandial lipaemia leads to several metabolic dysfunctions, which directly or indirectly induce inflammation and oxidative stress in the bloodstream and at the endothelium via leucocytes and the complement system. We propose that atherogenesis most likely starts in the bloodstream, by direct interaction of leucocytes with postprandial TRLs.

References

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