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Lipaemia, Inflammation and Atherosclerosis: Novel Opportunities in the Understanding and Treatment of Atherosclerosis

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Abstract

Atherosclerosis is the major cause of death in the world. Fasting and postprandial hyperlipidaemia are important risk factors for coronary heart disease (CHD). Recent developments have undoubtedly indicated that inflammation is pathophysiologically closely linked to atherogenesis and its clinical consequences. Inflammatory markers such as C-reactive protein (CRP), leucocyte count and complement component 3 (C3) have been linked to CHD and to hyperlipidaemia and several other CHD risk factors. Increases in these markers may result from activation of endothelial cells (CRP, leucocytes, C3), disturbances in adipose tissue fatty acid metabolism (CRP, C3), or from direct effects of CHD risk factors (leucocytes). It has been shown that lipoproteins, triglycerides, fatty acids and glucose can activate endothelial cells, most probably as a result of the production of reactive oxygen species. Similar mechanisms may also lead to leucocyte activation. Increases in triglycerides, fatty acids and glucose are common disturbances in the metabolic syndrome and are most prominent in the postprandial phase. People are in a postprandial state most of the day, and this phase is proatherogenic. Inhibition of the activation of leucocytes, endothelial cells, or both, is an interesting target for intervention, as activation is obligatory for adherence of leucocytes to the endothelium, thereby initiating atherogenesis. Potential interventions include the use of unsaturated long-chain fatty acids, polyphenols, antioxidants, angiotensin converting enzyme inhibitors and high-dose aspirin, which have direct anti-inflammatory and antiatherogenic effects. Furthermore, peroxisome proliferator activating receptor gamma (PPARγ) agonists and statins have similar properties, which are in part independent of their lipid-lowering effects.

1. Dyslipidaemia and Atherosclerosis

Atherosclerosis is the major cause of death in western societies.[1] Important risk factors include smoking, hypertension, dyslipidaemia, insulin resistance, increased body fat mass, unfavourable body fat distribution and a prothrombotic state.[2-6] Most of these risk factors are strongly inter-related and are part of the insulin resistance/metabolic syndrome, as was elegantly described by Reaven in 1988.[7] The incidence of the metabolic syndrome is rapidly increasing in western societies and therefore a dramatic increase in coronary heart disease (CHD) has to be expected.[8,9] Most

probably, these effects are a result of a changing western lifestyle that is more and more sedentary and characterised by a hypercaloric diet rich in saturated fatty acids and carbohydrates.[9] Among all lipid parameters, triglycerides and high-density lipoprotein (HDL) cholesterol are the most important predictors of CHD in the metabolic syndrome, whereas total cholesterol or low-density lipoprotein (LDL) cholesterol are not closely linked to this syndrome.[10-12] The fact that, in addition to triglycerides, HDL cholesterol also predicts CHD is not unexpected, because both are closely inversely correlated, as a result of the transfer of cholesteryl esters from HDL to triglyceride-rich particles in exchange for triglycerides from triglyceride-rich particles, by cholesteryl ester transfer protein. This transfer, in concert with hepatic lipase and phospholipid transfer protein, leads to small, dense, relatively cholesterol-depleted and triglyceride-enriched HDL particles, a process that mainly occurs under conditions of triglyceride excess.[13] In addition, when hypertriglyceridaemia is present, small dense LDL cholesterol particles will be generated via similar mechanisms. These are highly atherogenic after oxidative or glycaemic modification, as a result of processing by upregulated scavenger receptors on activated monocytes, transforming them into macrophages and eventually leading to foam cell formation.[14] A high prevalence of small dense LDL is very common in patients with the metabolic syndrome.[15,16]

1.1 Dyslipidaemia: the Importance of the Postprandial Phase

It is important to acknowledge that triglyceride-rich particles are produced mainly postprandially, and that people are non-fasting during most of the day.[17-20] Endogenous triglyceride-rich particles (very-low-density lipoprotein, VLDL) and exogenous triglyceride-rich particles (chylomicrons) share the same metabolic pathway – endothelium-bound lipoprotein lipase hydrolyses triglycerides into glycerol and free fatty acids. Fatty acids differ in carbon chain length and the degree of saturation, depending on the type of dietary fat. Increased concentrations of free fatty acids (FFA) as a result of obesity and, more importantly, a hypercaloric diet, are regarded as one of the key aetiological components of the metabolic syndrome.[21] In the postprandial phase, because of the limited availability of lipoprotein lipase, competition at the level of this enzyme will occur, resulting in accumulation of triglyceride-rich particles. This competition is most likely to manifest in the presence of fasting hypertriglyceridaemia, such as occurs in the metabolic syndrome, type 2 diabetes and familial combined hyperlipidaemia, and is confirmed by strong positive correlations between fasting and postprandial triglyceride concentrations.[22] However, it has also been shown that, among all patients with premature CHD, 40% have normal fasting plasma lipids,[23,24] although many have impaired clearance of postprandial lipoproteins.[25-29] It is for that reason that atherosclerosis has been considered to be a postprandial phenomenon.[30,31] Further evidence is provided by a study that demonstrated that carotid artery intima-media thickness, which provides a good clinical estimate of atherosclerosis, is better predicted by postprandial triglycerides than by concentrations of individual triglyceride-rich particles.[32] As with plasma triglycerides, postprandial changes in glucose concentrations also may play a more important part in the atherosclerotic process than fasting glucose.[33-35]

1.2 Assessment of Postprandial Lipaemia

In most studies, postprandial lipaemia has been investigated under metabolic ward conditions after administration of a standardised oral fat load.[36] Separation of lipoproteins according to density by ultracentrifugation is regarded as the golden standard for lipoprotein subfractionation. Very recently, quantification of remnant-like particle cholesterol has been shown to be a simple and useful tool with which to estimate the plasma concentration of remnants of triglyceride-rich particles.[37] In addition, remnant-like particle cholesterol is an independent risk factor for

CHD [38] and is strongly related to intima-media thickness, independently of LDL cholesterol and plasma triglycerides.[39] Metabolic ward studies, however, may not provide a realistic impression of the free-living daytime situation and can not be applied in clinical practice in large populations.

A novel method has recently been developed to assess postprandial lipaemia using serial measurements of capillary triglycerides in an out-of-hospital situation.[17-20,40,41] Day-long triglyceride profiles are closely related to postprandial lipaemia as assessed by standardised oral fat loading tests and can easily be applied in clinical practice for routine population-based screening.[17] Furthermore, repeated measurements of total day-long triglyceridaemia were less variable than repeated measurements of fasting and postprandial capillary triglycerides in normolipidaemic individuals and in patients with familial combined hyperlipidaemia.[18] Day-long triglyceridaemia has been associated with insulin resistance, body composition and diet.[19,20,42,43] We have also demonstrated that day-long triglyceride profiles distinguish better between normolipidaemic CHD patients and healthy controls matched for age, sex and body mass index than do other lipid and non-lipid risk factors.[26] However, we should point out that, despite the growing number of postprandial studies suggesting an association with CHD, postprandial hypertriglyceridaemia has not yet been investigated in a prospective study and it is not known if it is a more powerful modifiable factor than LDL cholesterol or fasting triglycerides.[44,45] However, as fasting triglycerides, even in 'normal' concentrations, are strong predictors of CHD,[46,47] and in view of the close association between fasting triglycerides and postprandial hypertriglyceridaemia and the lesser variability of the latter, postprandial triglyceridaemia is a risk factor that is worthy of consideration in clinical practice.

2. Atherosclerosis and Inflammation

Coronary heart disease is nowadays regarded as a low-grade chronic inflammatory process.[48,49] Atherogenesis is initiated by endothelial injury triggered by several CHD risk factors.[48,49] In the early phase of atherogenesis, resident and recruited leucocytes release various inflammatory mediators, bind to the endothelium and eventually transmigrate into the lesion.[49] The latter characteristic is most specific for monocytes and lymphocytes, whereas neutrophils are usually present only in ruptured plaques.[48-51] Most certainly, a greater content of inflammatory cells in the atherosclerotic lesion renders the plaque vulnerable, with an increased risk of rupture.[52] The importance of leucocytes in the atherosclerotic process is supported by animal studies that have shown reductions in plaque formation and endothelial dysfunction when adherence of leucocytes was prevented.[53,54] Obligatory for the interaction between leucocytes and endothelial cells is a sequential cytokine-controlled upregulation of integrins and selectins on activated leucocytes and endothelial cells.[55]

2.1 C-Reactive Protein

Currently, there is a growing body of evidence for a positive relation between systemic inflammation and the presence of CHD.[56,57] Of all the inflammatory markers, high-sensitivity CRP is the strongest independent predictor of the development of CHD events in healthy individuals and patients with established CHD.[58] Increased CRP is most prominent in patients with unstable angina[59] and predicts the outcome after a cardiovascular event.[60] CRP is not only a marker of CHD, but is most certainly a proatherogenic and proinflammatory agent also. One of the mechanisms involved is endothelial cell activation as a result of complement system activation.[61,62]

CRP is closely related to traditional CHD risk factors, with obesity – visceral fat deposition in particular – as the strongest correlate.[63,64] In contrast, data concerning relationships with other CHD risk factors are inconsistent after correction for body composition parameters. Some studies have shown a correlation with markers of insulin sensitivity, triglycerides and HDL cholesterol concentrations, whereas the relationship with total

cholesterol and LDL cholesterol remains equivocal.[63-65] Currently, the theories behind the relationship between CRP and CHD most often include endothelial cell activation leading to synthesis of interleukin-6 (IL-6).[66] IL-6 is the major cytokine responsible for hepatic production of CRP and is itself also associated with CHD.[67] In contrast, it has been shown that adipose tissue, and the visceral depot in particular, is a major contributor of plasma IL-6, explaining approximately 33% of plasma IL-6 concentrations.[68,69] The importance of the adipose tissue is underlined by the strong correlations with both CRP and IL-6,[64,70] and can be explained by the fact that adipose tissue veins drain directly into the portal vein. As adipose tissue is an important player in the metabolism of triglycerides and FFAs, a relationship between lipid metabolism and IL-6 is plausible. Indeed, IL-6 has been reported to be associated with changes in FFA concentrations,[70] which may be the result of an inhibitory effect of IL-6 on lipoprotein lipase activity.[69,70] Postprandial changes after an acute oral fat load may also be expected. In the postprandial phase, increments in IL-6 have been described; however, a circadian rhythm seems more important than feeding.[69,71-73] In contrast, CRP has been shown to lack a diurnal rhythm.[74]

2.2 Leucocytes

Blood leucocyte count is another inflammatory marker that predicts CHD morbidity and mortality.[75,76] Among all leucocyte subpopulations, neutrophil counts demonstrated the best epidemiological association,[76] despite the finding that these cells usually are not present in plaques. In contrast to CRP concentration, the leucocyte count is consistently related to traditional CHD risk factors such as smoking, hyperlipidaemia and insulin resistance.[77-79]

The relationship between leucocyte count, hyperlipidaemia and insulin resistance may in part be explained by plasma triglycerides and glucose concentrations, because of their capacity to induce leucocyte activation, as has been shown *in vitro* and *ex vivo* in patients with hypertriglyceridaemia.[80-87] In addition, we have recently shown *in vivo* that postprandially, when triglyceride and glucose concentrations increase, leucocyte counts increase, with concomitant production of proinflammatory cytokines and oxidative stress, and that these changes may contribute to endothelial dysfunction.[72,88] The observed increments in leucocyte count were attributable to a specific increase in neutrophils, whereas the increase in lymphocyte count was independent of food ingestion, as this also occurred after a water (control) test.[72,88] In most studies, activation of leucocytes has been assessed by gene expression,[84,86] nuclear factor kappa B (NF-κB) activation,[84] secretion of cytokines, enzymes and reactive oxygen species [82,84,85] and intracellular signalling.[87] A more direct way to study leucocyte activation could be quantification of the expression of markers of leucocyte activation that are involved in the interaction with the endothelium. Increased expression of leucocyte markers has been shown *in vitro* after incubation with artificial triglyceride-rich emulsions[80] and with native lipoproteins.[81,83] In agreement with these data, we have recently observed an increased expression of markers of activation on monocytes and neutrophils after an acute oral fat load in healthy volunteers (data on file). In this study, the increase in expression was positively related to the postprandial increment in triglycerides. Similar results have been found after an acute glucose load in healthy volunteers and in patients with type 2 diabetes; however, in that study the increased expression was unrelated to the change in glucose.[89] In the case of triglyceride-induced activation of leucocytes, the type of fatty acids seems to be of importance. *In-vitro* leucocyte activation was most striking with medium-chain fatty acids, whereas it was not observed after stimulation with long-chain fatty acids.[80,87,90]

2.2.1 Leucocytes and the Endothelium

Increased expression of markers of leucocyte activation is suggestive of proinflammatory and proatherogenic conditions and most probably represents an increased capacity of these cells to

adhere to the endothelium. Indeed, it has been shown that monocytes and neutrophils from patients with hyperlipidaemia show enhanced endothelial cell adhesion *in vitro*, when compared with controls.[91-93] Furthermore, the expression of markers of leucocyte activation has been linked to CHD,[94,95] was greatest in patients with unstable angina[96-98] and predicted re-stenosis after coronary angioplasty.[99,100] It has been shown in patients with CHD that the greatest activation was measured on leucocytes obtained from coronary blood, which makes underestimation of leucocyte activation in peripheral blood likely.[96]

Leucocyte activation may result, not only from direct effects of CHD risk factors on these cells, but also indirectly, as a result of activation of endothelial cells.[101] Conversely, activated leucocytes can stimulate endothelial cells, as has been shown, for example, in myocardial ischaemia-reperfusion injury and in models of endotoxaemia.[102,103] This leucocyte-induced endothelial cell activation most probably occurs via production of reactive oxygen species, proinflammatory cytokines and degradative enzymes such as gelatinase and collagenase.[103] Endothelial cells produce a variety of proinflammatory cytokines upon activation, which may facilitate recruitment and activation of leucocytes.[103,104] Artificial endothelial injury induced by coronary angioplasty has been shown to result in concomitant activation of leucocytes.[93,100] Classical CHD risk factors, such as glucose and hyperlipidaemia, are also able to induce endothelial cell activation *in vitro*.[105,111] With respect to lipoproteins, most attention has been paid to LDL cholesterol, and to oxidised LDL cholesterol in particular.[105,106] However, other lipoproteins, amongst them lipoproteins that are specific for the postprandial phase, have shown similar properties.[105,108,110,111] *In-vivo* evidence of the involvement of both endogenous and exogenous lipoproteins was provided in animal studies showing that these particles can cross the endothelial barrier and reside in the subendothelial space, where they may have local effects on endothelial cell activation and foam cell formation.[112] In hyperlipidaemia, and in particular in the postprandial phase when lipolysis pathways are overloaded, the residence time of atherogenic lipoproteins will increase, leading to a marginated pool of these particles, theoretically increasing the risk of atherosclerosis. Recent evidence from our laboratory has shown that this marginated pool of atherogenic lipoproteins is larger in patients with familial combined hyperlipidaemia than in normolipidaemic controls, and that it decreases significantly after treatment with atorvastatin (data on file).

The type of fatty acids may attenuate the effect of triglycerides on endothelial cells. Linolenic acid, an omega-3 or *n*-3 fatty acid present in fish oils, which is the origin of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is believed to have cardioprotective properties. Reduced activation of endothelial cells has been shown *in vitro* after they were incubated with these fatty acids.[113-115]

In-vivo measurement of endothelial function is a good surrogate marker of atherosclerosis.[116] Endothelial dysfunction in peripheral arteries and combined carotid intima-media thickness both correlate well with endothelial function of the coronary artery, which is regarded as the gold standard.[117-119] In agreement with *in-vitro* data, endothelial dysfunction after acute changes in glucose, triglyceride and FFA concentrations has been reported.[72,120-123] Again, different types of fatty acid showed different responses; in particular, *n*-3 fatty acids have shown to exert beneficial effects on endothelial function.[113,115,124]

2.2.2 Proposed Mechanisms for Leucocyte and Endothelial Cell Activation

In the case of glucose, activation and dysfunction of endothelial cells is a result of overproduction of superoxide by the endothelial cell mitochondrial electron transport chain.[125-127] Other sources of reactive oxygen species may be uncoupled endothelial nitric oxide synthase (eNOS), cytochrome P450 and membrane-associated NAD(P)H oxidase.[128] The production of reactive oxygen species will lead to formation of advanced glycation endproducts, increased hexosamine and polyol pathway fluxes and activation of

protein kinase C.[126,127] It has been shown that, in endothelial cells, activation of protein kinase C subsequently results in activation of NF-κB, which is a transcription factor of proinflammatory mediators.[125,127,128] These effects will result in increased expression of proinflammatory cytokines and adhesion molecules. Reactive oxygen species will also reduce the availability of nitric oxide, which is an important endothelial-cell-derived atheroprotective and vasodilatory agent.[115,128,129] The mechanism behind the effects of lipoproteins and FFAs on endothelial cells has not yet been fully elucidated, but is believed to comprise the production of reactive oxygen species also.[105,110,115,130,131] The beneficial effects of *n*-3 fatty acids most probably include a decrease in production of reactive oxygen species, resulting in reduced activation of the summarised cascades.[115,132] Furthermore, fatty acids are natural ligands of PPARs, which appear to have a variety of effects in different types of cells.[133] The mechanisms behind direct effects of lipoproteins and glucose on leucocytes are less well understood, but may be similar to their effects on endothelial cells.[84,87] With respect to lipoproteins, an initial step may involve binding or uptake of triglyceride-rich particles by phagocytosing monocytes or neutrophils. It has been demonstrated that neutrophils are able to take up retinyl esters, which are markers of triglyceride-rich lipoproteins.[134] Unpublished data from our laboratory suggest that neutrophils accumulate lipids in their cytoplasm during the postprandial phase, suggesting that opsonisation may occur *in vivo*, thus providing a novel pathway for *in-vivo* activation of leucocytes and clearance of remnants in humans (figures 1 and 2). Supportive evidence for the validity of our observation has been provided by the fact that leucocytes from patients with CHD have an increased lipid content when compared with those of controls.[135]

2.3 Complement System

A third inflammatory marker related to CHD is complement component 3 (C3). C3 is a strong predictor of myocardial infarction [136,137] and has been positively associated with obesity, type 2 diabetes, dyslipidaemia and hypertension.[25,138,139] It is produced in the liver and in extrahepatic tissues such as fibroblasts, mononuclear cells, endothelial cells and adipocytes.[140,141] The complement system is the most important and phylogenetically best conserved mechanism in human immunology and comprises three different pathways: the alternative, the classical and the mannose-binding lectin pathways.[142] Activation of these pathways results in cleavage of C3 into C3a and C3b. In plasma, C3a exits only in the desarginated form (C3adesArg), as a result of the action of carboxypeptidase B on the carboxyl terminus of C3a.[138] Under normal circumstances, C3b will not enter the terminal complement activation pathway that leads to inflammation, as there are abundant inactivators in the blood.[142] When inflammation is initiated, C3b leads to formation of the membrane attack complex. C3b attached to pathogens will facilitate opsonisation and other terminal complement components such as C5a serve as chemoattractants.[142] Deposition of complement co-localised with CRP has been observed in atherosclerotic plaques,[143,144] and complement activation also has a role in the induction of tissue damage after myocardial infarction.[145]

2.3.1 Involvement of the Complement System in Lipid Metabolism

The strong correlation between C3 and obesity is most probably a result of the ability of the adipose tissue to synthesize C3. *In-vitro* studies have shown that chylomicrons are among the most potent stimulators of adipose tissue production of C3 and subsequent activation of the alternative complement pathway, leading to the formation of C3b and C3adesArg.[141] As there is not a true inflammation, the terminal routes of the complement cascade are not activated. However, C3adesArg has been found not to be an innocent bystander: it has been demonstrated that this protein was identical to acylation-stimulating protein (ASP), a newly recognised adipocyte-

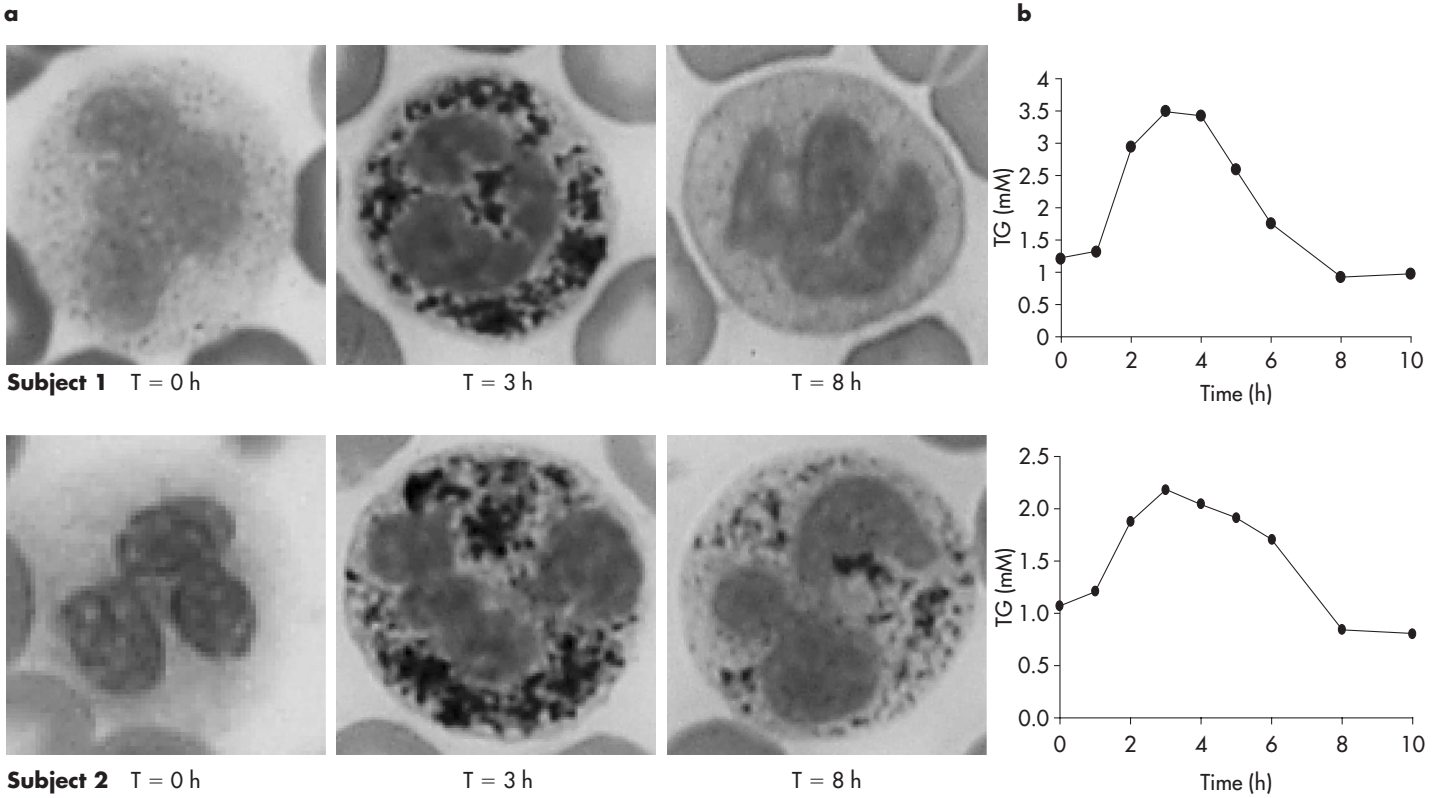

Fig. 1. Representative pictures of lipid-specific (Sudan black) staining of whole blood (**a**) and plasma triglyceride (TG) curves (**b**), before and during a standardised oral fat-loading test in two healthy individuals (Subjects 1 and 2). Blood smears were made immediately after blood sampling, dried and fixed, and stained with Sudan black, which specifically stains lipids. At baseline (fasting samples; **a**, left panels) in both individuals there was no staining of the cytoplasm; however, 3h postprandially (**a**, middle panels), when in both individuals maximum plasma TG values were attained (**b**), there was an increased staining of cytoplasmic material. After 8h, the cytoplasmic staining was virtually absent (**a**, right panels). Note the different *Y*-axis scales in (**b**). **T** = time.

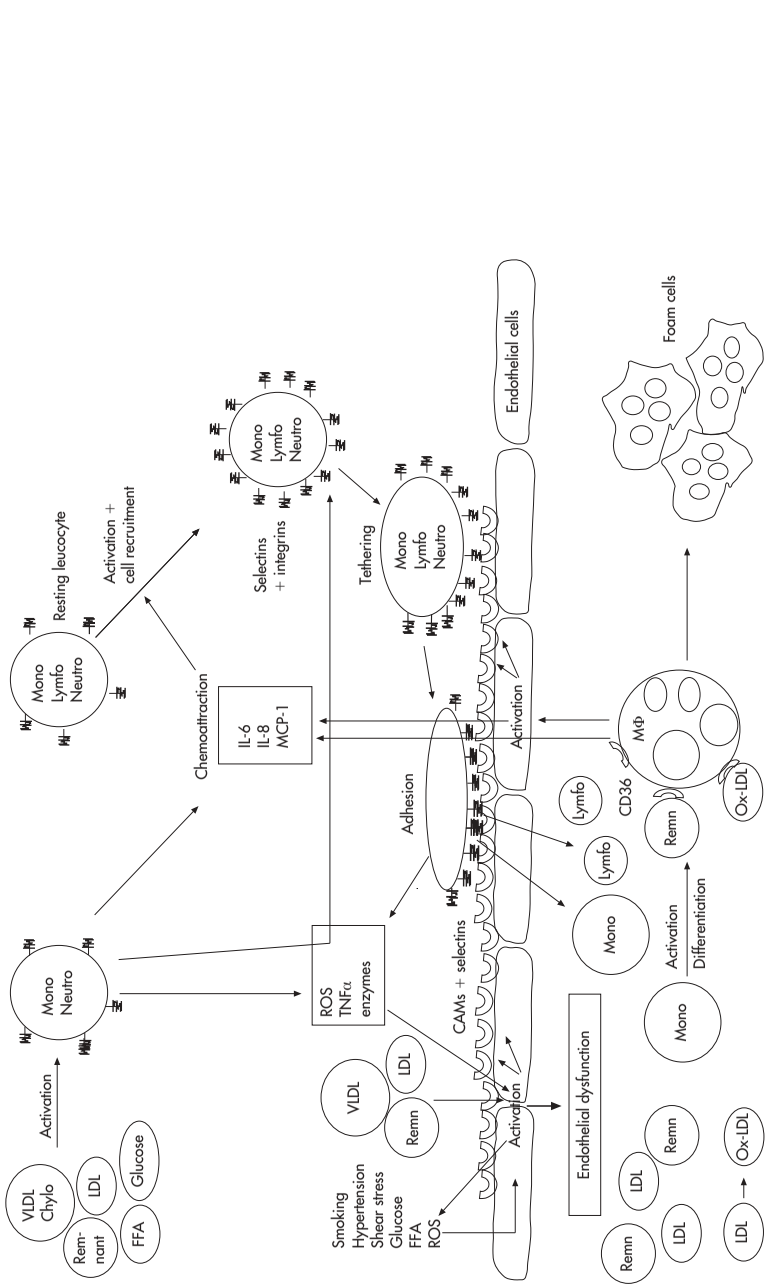

Fig. 2. Inflammatory pathogenesis of atherosclerosis. Endothelial cells become activated as a result of smoking, hypertension, shear stress, hyperglycaemia, reactive oxygen species (ROS) and dyslipidaemia. The last can be caused by very-low-density lipoprotein (VLDL) and chylomicron (Chylo) particles, remnant particles (Remn), low-density lipoprotein (LDL) particles and free fatty acids (FFA). The results of endothelial cell activation are ROS production, dysfunction of the endothelium and expression of cellular adhesion molecules (CAMs) and selectins, facilitating adherence of all leucocytes and transmigration of monocytes (Mono) and lymphocytes (Lympho), but not neutrophils (Neutro). Monocytes residing in the arterial wall become activated by proinflammatory cytokines and differentiate into macrophages. LDL and remnant particles can enter the vessel wall also. Oxidative modification of LDL results in a highly atherogenic particle (Ox-LDL) that can easily be taken up by macrophages (MΦ) 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 interleukins-6 (IL-6) and -8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1). These effects combined will lead to recruitment and activation of leucocytes, as expressed by increased selectins and integrins on the outer membrane. Activated leucocytes are attracted to the activated endothelium and will eventually adhere firmly to the vessel wall. Monocytes and lymphocytes can then transmigrate through the endothelial barrier. Furthermore, monocytes and neutrophils can also become directly activated by lipoproteins, FFA and glucose. This will lead to adherence of these cells to the endothelium, in addition to production of chemoattractants, leading to recruitment and activation of additional leucocytes. Moreover, these directly activated leucocytes can activate the endothelium or destabilise atherosclerotic lesions by the production of ROS, tumour necrosis factor α (TNFα) and degradative enzymes syuch as collagenase and gelatinase.

derived hormone involved in FFA metabolism.[138] The mechanisms are not yet fully elucidated, but include stimulation of re-esterification of FFA into triglycerides in adipocytes and fibroblasts, reduction of endogenous production of FFA by inhibiting-hormone-sensitive lipase in the adipocyte, and stimulation of intracellular glucose uptake by adipocytes, fibroblasts and muscle cells.[138,146,147] The effects of the C3/ASP system are believed to be additional to, but independent of, the effects of insulin.[138,146,147]

Efficient FFA trapping, in particular postprandially, is desirable, because increases in FFA are believed to have a pivotal role in the pathogenesis of insulin resistance and type 2 diabetes.[148] It has recently been shown that fasting ASP predicts postprandial clearance of triglycerides and FFA;[149] therefore, as chylomicrons are potent activators of the C3/ASP pathway *in vitro*, involvement of this system in the postprandial phase is likely. However, using standardised oral fat loads it has been shown that plasma ASP does not change postprandially in healthy lean or obese individuals, or in patients with familial combined hyperlipidaemia.[150-152] These findings could be explained by the relatively low concentrations of ASP in plasma and the paracrine action of the hormone. Indeed, when ASP was measured locally in adipose tissue by venous cannulation and estimation of arterio–venous gradients, the expected postprandial increase was demonstrated unequivocally.[153] In contrast, C3, which is present in much greater concentrations in plasma (g/L amounts), does change postprandially, although this has not been shown invariably. Two studies demonstrated unchanged postprandial plasma C3 after a mixed meal in healthy individuals, whereas in obese subjects a small significant increase was observed.[150,151] When standardised oral fat loads were administered, increments in C3 were observed in healthy individuals, in patients with CHD who were normolipidaemic and in patients with familial combined hyperlipidaemia.[25,139,154] We have recently shown that the discrepancies between reports in the literature concerning postprandial changes in C3 were attributable to the differences between the meals ingested for the study.[155] When healthy insulin-sensitive individuals ingested a standardised oral fat load, a 10% postprandial increase in C3 was observed that was blunted when glucose was added to the fat load.[155] We hypothesised, therefore, that the C3/ASP system is a backup system for postprandial FFA trapping that is active in low-insulin or insulin-resistant situations, explaining the strong positive relationship between C3/ASP and the metabolic syndrome.[155] Our hypothesis is supported by the findings of a recent study showing that, on dramatic weight reduction, insulin sensitivity improved, with a concomitant decrease in plasma ASP concentrations.[156]

Similar to those of leucocytes and endothelial cells, the inflammatory response of the C3/ASP system has been shown to depend on the type of fatty acids in the diet. Low ASP and high FFA concentrations were seen in response to a diet enriched in *trans* fatty acids, whereas a diet enriched in unsaturated fatty acids resulted in the opposite.[157]

Finally, many other interesting inflammatory markers, which will not be discussed in this review, have been proposed that may be related to the process of atherosclerosis. They comprise soluble markers of endothelial cell adhesion molecules and selectins, CD40 and CD40-ligand and many other new promising markers.[56,57,143]

3. Strategies to Reduce Inflammation

Mechanistically, strategies to reduce inflammatory changes should interfere with the production of reactive oxygen species or, more desirably, with protein kinase C and NF-κB pathways.

3.1 Lifestyle and Diet

Without any doubt, the first intervention should be lifestyle improvement. Weight reduction by decreasing dietary energy intake and increased physical activity has been shown, not only to improve plasma lipids and insulin sensitivity, but also to reduce CRP, IL-6 and ASP.[158-160] The benefit of these effects was underlined by a study

showing reduced progression of atherosclerosis as determined by intima-media thickness.[161]

3.1.1 Fatty Acids

As previously discussed, a balanced diet should be low in saturated fatty acids and enriched in polyunsaturated fatty acids – *n*-3 fatty acids in particular. These fatty acids have been shown to be effective in improvement of endothelial function [113-115] and reduction of inflammatory processes.[115,132] In addition, plaque-stabilising effects via reduction in migration of monocytes and vascular smooth muscle cells have been described.[132] Furthermore, these fatty acids can indirectly influence these processes by reducing triglyceridaemia, decreasing small dense LDL cholesterol and increasing HDL cholesterol.[132,162,163] It is believed that the beneficial effects of these fatty acids are via reduction in reactive oxygen species,[115,132] but they may also involve activation of PPARs.[133]

The effects of *n*-3 fatty acids suggest an atheroprotective effect. Indeed, CHD is less common in populations with a high dietary fish content, such as Alaskan natives, Greenland Eskimos and Japanese islanders.[164-166] In addition, people from western European countries with a high fish intake have a lower CHD risk than individuals who rarely consume fish.[167,168] Intervention studies based on a diet enriched in *n*-3 fatty acids showed a reduced CHD mortality also.[168,169] Recommendation of a diet enriched with *n*-3 fatty acids has also been shown to improve survival after a primary CHD event.[168,170]

3.1.2 Antioxidants and Polyphenols

Of particular interest are the effects of antioxidants and polyphenols on inflammatory processes. Most probably via reduction of reactive oxygen species, vitamins E (α-tocopherol) and C (ascorbate) and folic acid have been associated with improvement in triglyceride- and glucose-induced endothelial dysfunction.[121,171-173] Furthermore, vitamins E and C are believed to reduce LDL oxidation and adhesion of leucocytes to the endothelium.[173] The latter effect may occur via inhibition of protein kinase C, as has been demonstrated with vitamin E.[173] Polyphenols present in green tea and in red wine have been demonstrated to produce an improvement in endothelial dysfunction and reduced adherence of leucocytes to the endothelium.[174,175] Most probably, these agents directly inhibit activation of NF-κB, resulting in decreased activation of both leucocytes and endothelial cells.[174,175] Unfortunately, although numerous studies have shown promising effects of antioxidants, cardiovascular endpoint trials with these agents have provided disappointing results.[121,131,176] In contrast, there is suggestive evidence that polyphenols contribute to the atheroprotective effects of the Mediterranean diet.[177,178]

3.2 Anti-Inflammatory Drugs

An evolving target of pharmacotherapeutic treatment of inflammatory disorders is the NF-κB pathway.[179] Two frequently prescribed classes of drugs that directly inhibit NF-κB are glucocorticoids and non-steroidal anti-inflammatory drugs.[179] The effects of corticosteroids in CHD have not been studied extensively. Most studies were performed in patients with angioplasty- or stent-induced inflammatory responses. Single-dose treatment before or after the endothelial injury did not show a significant effect on the occurrence of re-stenosis.[180,181] In contrast, in a selected group of patients with CHD with a high CRP response after stent placement, prolonged administration of prednisone resulted in a reduction of angiographic re-stenosis and concomitant CHD events.[182] Furthermore, a combination of immunosuppressive agents to prevent allograft rejection in cardiac transplant patients resulted also in a reduction in progression of intima-media thickness.[183] Stents coated with one of these immunosuppressants, sirolimus, showed a lower occurrence of re-stenosis and cardiovascular events when compared with conventional stents.[184] It should be pointed out that the mode of action of sirolimus is not via NF-κB, but via arrest of the cell cycle.[185]

Aspirin, a known inhibitor of platelet aggregation by interacting with cylo-oxygenase, is also an inhibitor of NF-κB.[186] It has been shown that

aspirin inhibits adhesion of leucocytes to the endothelium *in vitro* via a reduction in the activation of both cell types.[187,188] However, these studies revealed that the effective dose of aspirin required to induce these anti-inflammatory effects is beyond the order of grams/day.[187,188] In agreement with this finding, it has recently been shown in healthy volunteers that short-term low-dose aspirin (75–500 mg/day) had no effect on CRP, IL-6 and markers of activation of leucocytes and endothelial cells.[189,190] However, if high CRP reflects unstable plaques,[59] patients in this category may derive greater *a-priori* benefit from the antithrombotic effect of aspirin. Indeed, in primary prevention, aspirin 325 mg/day showed the strongest CHD risk reduction in the individuals in the greatest CRP quartile.[191] In addition, the predictive value of CRP has been shown to be weakened when patients are pretreated with aspirin.[192]

3.3 The Renin–Angiotensin System

Angiotensin II is known as a proatherogenic and proinflammatory hormone, with receptors expressed on both leucocytes and endothelial cells.[193] Via production of reactive oxygen species, angiotensin II promotes the activation of NF-κB, LDL oxidation and endothelial dysfunction.[193-196] In clinical studies, a reduction in CRP and proinflammatory cytokines by inhibition of the renin–angiotensin system has been demonstrated.[196-198] Several studies have shown that inhibition of the renin–angiotensin system by inhibitors of angiotensin converting enzyme and angiotensin II resulted in a significant reduction in CHD morbidity and mortality in various groups of patients.[193,195] Although angiotensin converting enzyme inhibitors increase bradykinin, which has some atheroprotective effects, it is believed that most of the anti-inflammatory effects can be explained by a reduction in angiotensin II.[193,195,198]

3.4 Peroxisome Proliferator Activating Receptors

As mentioned previously, the beneficial effect of certain fatty acids is in part mediated via PPARs.[199,200] PPARs are nuclear receptors that, after ligand-induced activation, form a heterodimer with a ligand-activated retinoic acid receptor. This activated complex then binds to a nuclear PPAR responsive element, which subsequently leads to gene transcription and synthesis of proteins with a variety of effects. PPARs has a role in protein, glucose and lipid metabolism, cellular differentiation, proliferation and apoptosis, neoplastic proliferation, inflammatory processes and endothelial function.[201-205] Three subtypes, PPARα, PPARβ/δ and PPARγ, which have distinct functions and distribution, have been identified.

3.4.1 PPARα Agonists

PPARα is expressed in liver, heart, muscle and kidney and has hypolipidaemic effects resulting in reduced triglycerides, increased HDL cholesterol and a reduction in the formation of small dense LDL cholesterol.[199,203,205] Furthermore, it is believed that, via activation of PPARα, proinflammatory pathways such as NF-κB and mitogen-activated protein kinase cascades are controlled.[210,205] Expression of PPARα has been described in macrophages, dendritic cells, B and T lymphocytes and also in vascular cells.[201,206] It is likely that, through activation of PPARα in these cells, leucocyte–endothelial interaction, transmigration of inflammatory cells, proliferation of vascular smooth muscle cells, thrombus formation and apoptosis of cells in the plaque can be repressed.[205,207] Besides natural ligands such as *n*-3 polyunsaturated fatty acids, the synthetic fibrates have also been shown to bind PPARα.[199] Acting through the mechanisms described above, these drugs have shown hypolipidaemic properties and may therefore be anti-inflammatory and anti-atherogenic.[205,208,209] In addition, direct anti-atherogenic effects of fibrates have been described.[205] In animals fed a high-cholesterol diet, fibrate treatment resulted in plaque regression[210] and, very recently, improvement in endothelial function has been described in patients with increased triglycerides in response to treatment with fibrates.[211] The clinical use of fibrates

has been shown to reduce proinflammatory cytokines and CRP.[207,212] In a series of large intervention studies, the combined effects of fibrates have shown benefit in the primary and secondary prevention of CHD events and mortality.[205]

3.4.2 PPARβ/δ Agonists

The second type of PPAR, PPARβ/δ, is ubiquitously expressed. However, this receptor has not been well investigated, as a lack of specific agonists has hampered further study. Recently, however, this receptor has been implicated in wound healing and it is believed to increase HDL cholesterol.[201,205,213]

3.4.3 PPARγ Agonists

The third member of the PPAR family is PPARγ, which is highly expressed in adipocytes and macrophages. In lower concentrations, this receptor is also found in the pancreas, skeletal muscle, vasculature, T lymphocytes, neutrophils and smooth muscle cells.[201,202,204] PPARγ promotes adipogenesis in favour of the subcutaneous depots, whereas visceral fat is reduced, and it also reduces plasma triglycerides and FFA and increases HDL-cholesterol.[203,204] Furthermore, as with PPARα, efflux of cholesterol from macrophages is stimulated on activation of PPARγ.[205,214] More importantly, activation of PPARγ leads to improvement in insulin sensitivity. However, the mechanisms involved remain a matter of debate.[201-205] In addition, a variety of anti-inflammatory and vascular effects have been ascribed to PPARγ activation, most of them via inhibition of NF-κB activation. Furthermore, activation of PPARγ may lead to reductions in prothrombotic markers, decreased vascular intimal hyperplasia and a decrease in blood pressure, although plasma volume tends to increase.[202,204,205] Recently, it has also been suggested that activation of PPARγ may have a protective role in carcinogenesis, as a result of the beneficial effect on cell differentiation and apoptosis.[215] Among the emerging roles of PPARs, it is also becoming evident that PPARα and PPARγ have important roles in innate and adaptive immunity.[201]

To date, two different clinically applicable PPARγ agonists (thiazolidinediones) have become available: rosiglitazone and pioglitazone. As described, these drugs have profound effects on insulin sensitivity and lipid metabolism and thus are very promising agents in the treatment of the metabolic syndrome. Regarding the triglyceride-decreasing and HDL-cholesterol-increasing effects of both agents, a recent meta-analysis suggested benefit in favour of pioglitazone.[216] In animal studies, treatment with PPARγ agonists resulted in reductions in plaque size and in patients with type 2 diabetes, inhibition of re-stenosis after angioplasty was observed.[217-219] In clinical studies, thiazolidinediones have shown numerous anti-inflammatory effects, which may be direct or indirect – for instance via lipid decreasing. Among these effects are inhibition of the formation of reactive oxygen species and reduction in NF-κB, CRP, proinflammatory cytokines, leucocyte count and plasma concentrations of markers of endothelial cell activation.[220,221] Furthermore, improvement in endothelial function has been described in animal studies and in humans.[204,222,223] Unfortunately, long-term studies investigating the effects on the development of the metabolic syndrome and cardiovascular outcome are not yet available. Present and future research on PPAR agonists will be focused on the development of tissue selective PPAR agonists, such as selective PPARγ agonists. These drugs have shown a more pronounced effect on insulin sensitivity than on adipogenesis, and may therefore result in a reduction in the weight gain that is an undesirable side effect of the conventional PPARγ agonists.[224,225] In addition, dual PPARα/γ agonists have been developed that may have major effects on different components of the metabolic syndrome.[226,227]

3.5 Statins

3.5.1 Lipid-Lowering Effects of Statins

HMG-CoA reductase inhibitors (statins) competitively inhibit HMG-CoA reductase, the rate-

limiting enzyme in cholesterol synthesis. The resulting decrease in hepatic intracellular cholesterol concentration leads to an upregulation of LDL receptors, enabling enhanced clearance of apoB- and apoE-containing lipoproteins, LDL in particular, but also VLDL and intermediate-density lipoprotein.[228] Furthermore, it is believed that, to some extent, statins inhibit hepatic synthesis of VLDL and stimulate lipoprotein-lipase-mediated lipolysis, which may explain the triglyceride-decreasing properties of these drugs.[229,230] In general, statins tend to induce a modest reduction in fasting plasma triglycerides and the efficacy increases with the concentration of the triglycerides before treatment.[231] When baseline triglycerides were less than 1.7 mmol/L, no significant or dose-dependent effects on triglycerides were found and the maximal triglyceride-decreasing response at any dose was only modest (12%). Weakly dose-related reductions, varying from 9% to 37%, occurred when baseline triglycerides were between 1.7 and 2.8 mmol/L. The largest and most consistent dose-dependent reductions (22–45%) were seen with all statins in individuals with baseline triglyceride concentrations greater than 2.8 mmol/L. A reduction in fasting plasma triglycerides is usually accompanied by significant decreases in postprandial lipaemia, as a result of decreased competition for the common lipolytic pathway. Essentially, the reduction in postprandial lipaemia is similar to the reduction in fasting plasma triglycerides.[25,26,154,232-237] Statin-induced improvement in peripheral FFA trapping has been suggested by two studies showing decreases in fasting and postprandial C3 concentrations.[25,154] A summary of the effects of different statins on postprandial lipaemia is shown in Table I.

Table I. Effects of different statins on postprandial lipaemia

Study	Statin	Patient category	n	Outcome variable	Effects on fasting plasma TG (%)	Effects on postprandial lipaemia (%)
Weintraub et al.[237]	Lovastatin	Types IIa and IIb	10	RP	−27	−28
Cianflone et al.[233]	Lovastatin	Types IIa and IIb	12	TG and RP	−16	−5 and −30
Castro Cabezas et al.[232]	Simvastatin	FCHL	7	TG and RP	−30	−25 and −3
O'Keefe et al.[234]	Pravastatin	Type IV	18	TG and RP	−15	−2 and −25
Parhofer et al.[235]	Atorvastatin	Normal	10	TG and RP	−30	−27 and −34
Sheu et al.[236]	Simvastatin	DM type 2	24	TG	−22	−26
Halkes et al.[25]	Simvastatin	CHD	16	TG	−27	−27
Verseyden et al.[154]	Atorvastatin	FCHL	12	TG	−29	−23
van Oostrom (unpublished)	Rosuvastatin	CHD/IIb	20	TG	−37	−33

Types IIa, b and **IV** = Fredrickson classification of dyslipidaemia; **FCHL** = familial combined hyperlipidaemia; **DM** = diabetes mellitus; **CHD** = coronary heart disease; **TG** = triglycerides; **RP** = retinyl palmitate

3.5.2 Non-Lipid-Decreasing Effects of Statins

Other actions of statins may include partial agonism of PPARα and PPARγ.[238,239] Further evidence for this theory is given by the overlap between the non-lipid-decreasing (pleiotropic) effects of statins and the variety of effects of PPAR agonists. Besides the pleiotropic effects relevant for cardiovascular disease, statins may have anti-

cancer properties, may reduce osteoporosis, and may decrease the development of dementia and multiple sclerosis.[240,241] Pleiotropic effects of statins that in theory affect the process of atherosclerosis comprise acute improvement in endothelial function and anti-inflammatory, antithrombotic and antiproliferative effects.[242-245] The anti-inflammatory effects of statins include reduced adherence and transmigration of leucocytes as a result of lower activation of leucocytes and endothelial cells.[92,108,246-248] Furthermore, a reduction in generation of reactive oxygen species, a lower production of proinflammatory mediators and reduced T cell activation via inhibition of major histocompatibility complex class II have been described.[249-252] It is believed that at least part of the anti-inflammatory effects result from the inhibition of NF-κB[253] or induction of eNOS,[254] in part independently of PPAR activation. It has also been shown that, via binding to a specific leucocyte domain, statins reduce adherence of these cells to the endothelium.[255]

3.5.3 Statins: Clinical Evidence

In clinical studies, the anti-inflammatory effects of statins are reflected by reduced plasma concentrations of proinflammatory cytokines, CRP and endothelial cell activation markers which, in some but not all studies, were independent of the lipid-decreasing effects.[256-258] Recently, in a large observational study, it was demonstrated that patients with hyperlipidaemia who were receiving statins had a lower leucocyte count,[258] but this was not confirmed in a prospective statin-intervention study in hyperlipidaemic patients.[81] Furthermore, as a result of decreases in lipids, but probably also by a pleiotropic effect, statins have been shown to reduce the expression of several markers of leucocyte activation *in vitro* [108,248,255] and *in vivo*.[81,92,259] The immune-modulating effect of statins was shown in transplantation patients, in whom reduced rejection occurred.[260,261]

To date, it remains unclear whether the pleiotropic effects of statins are a class effect or rather result from specific actions of the different statins. Benefit from pleiotropic effects is likely, because statin trials do not show a linear relationship between on-treatment reduction in LDL and the occurrence of CHD events.[242] Furthermore, statins have proven beneficial across the whole range of pretreatment cholesterol concentrations.[262,263] It has been shown that normocholesterolaemic patients with increased CRP still derive benefit from statins.[264]

The combined effects of statins have demonstrated enhancement of re-endothelialisation [265] and, more importantly, resulted in plaque stabilisation and in some trials were even associated with plaque regression.[266] In a series of large clinical studies, statins have been associated with reductions in CHD morbidity and mortality in various groups of patients and in healthy individuals.[262,267-270]

3.6 Perspectives of Anti-Inflammatory Intervention in Atherosclerosis

Therapeutic options to modulate inflammatory processes in atherosclerotic disease will remain a matter of great interest in forthcoming years. It has recently been shown that platelet glycoprotein IIb/IIIa receptor blockers may reduce cardiovascular events, not only via antithrombotic effects, but also via anti-inflammatory effects. These drugs inhibit platelet–leucocyte and leucocyte–endothelium interactions and reduce CRP and IL-6 concentrations.[271,272] Furthermore, experimental studies are in progress to investigate the effects of anticytokine treatment; in addition, specific inhibitors of ligands involved in leucocyte–endothelium binding are being studied.[103,273-275]

4. Conclusion

Atherosclerosis is an inflammatory disease and has been linked to inflammatory markers such as CRP, C3 and leucocytes. It has become apparent that these markers have direct proatherogenic effects and that C3, via involvement in lipid metabolism, is also indirectly associated with atherosclerosis. Activation of leucocytes is obliga-

tory for atherogenesis and results, not only from endothelial cell activation, but most certainly also from direct effects of lipoproteins, triglycerides, FFA and glucose. These metabolic factors are most often increased in the metabolic syndrome, but also in the postprandial phase, which means that this period is proatherogenic. This knowledge will help to improve our understanding and the treatment of atherosclerotic disease.

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