

## Postprandial triglycerides and endothelial function

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**Summary:** Several studies support the association between postprandially elevated triglyceride levels and atherosclerosis. Histological and cell culture investigations revealed, that triglyceride rich postprandial lipoproteins are taken up by macrophages and smooth muscle cells and are detectable as part of foam cells in vascular lesions. Remnant particles, generated by lipolysis of postprandial lipoproteins in vitro and fatty acids increase the permeability of the endothelium and are cytotoxic for endothelial cells. – Besides these morphological changes of cells, lipoproteins have been shown to exert effects on cellular functions like the expression of membrane proteins and the production or release of several bioactive substances regulating communication with blood cells and other cell systems of the vascular wall, blood pressure and hemostasis. – This review concentrates on the influence of postprandial lipoproteins on factors involved in the interaction of endothelial cells with blood leukocytes and factors mediating blood pressure regulation. Increased expression of adhesion molecules has been detected immunohistochemically in atherosclerotic plaques in animals and humans. It was demonstrated that patients with elevated triglyceride levels have increased levels of soluble adhesion molecules. Furthermore, postprandial lipoproteins were shown to induce membrane expression of adhesion molecules. This effect seems to be at least in part mediated by the oxidative modification of the particles. Accordingly chylomicrons separated after ingestion of safflower oil, rich in polyunsaturated linoleic acid, induced higher adhesion molecule expression at higher oxidant concentration compared with chylomicrons sepa-

rated after ingestion of olive oil, rich in monounsaturated oleic acid. – Several authors described effects of fatty acids on the expression of adhesion molecules. On the one hand, they may exert stimulatory effects as such, on the other hand cytokine induced adhesion molecule expression may be enhanced by certain fatty acids and inhibited by others, implying an interference with signal transduction processes. – Effects of lipoproteins on vasoactive substances seem to be implicated in endothelial dysfunction, too. The endothelium-derived relaxing factor nitric oxide (NO) has gained increasingly attention in the last two decades and is regarded as protective against hypertension and atherosclerosis. It was demonstrated that chylomicrons and their remnants inhibited endothelium-dependent relaxations in isolated aortas. Vasodilatory responses and nitric oxide metabolism were shown to be affected by the amount and composition of dietary fat. Cell culture experiments revealed modulation of NO release by certain fatty acids. – Plasma levels of endothelin-1, a strong vasoconstrictor, have been shown to be increased in patients with type 2 diabetes and metabolic syndrome, respectively. Postprandially elevated triglycerides increased endothelin-levels in addition to insulin in patients with metabolic syndrome. – In summary, there is evidence that the association between postprandial triglycerides and the metabolic syndrome is driven by direct influences on endothelial functions because plasma triglyceride levels are associated with levels of humoral risk markers of endothelial origin, and postprandial lipoproteins stimulate the release and/or expression of endothelial mediators in vitro, which induce atherogenesis and hypertension.

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### Role of the endothelium in the pathogenesis of vascular disease

A crucial step in the pathogenesis of vascular disease seems to be the increased adhesion of monocytes (and other leukocytes) to the vascular endothelium. Adherent monocytes enter the vascular wall, differentiate into macrophages and finally transform into foam cells by accumulating lipoproteins. Foam cells present – together with T-lymphocytes – characteristic components of fatty streaks, the first stage in atherogenesis. Macrophages and T-cells can recruit more macrophages by secretion of cytokines and induce the migration and proliferation of smooth muscle cells by release of growth factors. Necrosis of

foam cells and proliferation of smooth muscle cells in the intima, that accumulate lipids and secrete extracellular matrix substances, result in the development of fibrous plaques and disease progression (Ross, 1993).

Endothelial cells play a central role in this process since they produce a spectrum of bioactive substances which regulate communication with blood cells on the one hand and with cell systems of the vascular wall on the other hand, and modulate blood pressure and hemostasis. Therefore, the role of the endothelium is not simply a permeability barrier, but an active mediator between blood cells and cells of the vascular wall.

The interaction with blood leukocytes is mediated by adhesion molecules (VCAM-1, ICAM-1, E-

selectin, P-selectin), cytokines like interleukins (e.g. IL-1, IL-6, IL-8), monocyte-chemotactic-protein (MCP-1) and granulocyte- or monocyte-colony-stimulating factors. Growth factors modulate the proliferation of fibroblasts and smooth muscle cells. Blood pressure is regulated by relaxing factors like prostacyclin or nitric oxide on the one hand and vasoconstricting factors like endothelin-1 and angiotensin-II on the other hand. Regulation of hemostasis is mediated by secretion of antithrombotic factors like e.g. prostacyclin or tissue plasminogen activator, and on the other hand by prothrombotic factors like e.g. platelet-activating factor or tissue factor. In the healthy individual, these systems are in a balance. Several factors can disturb the balance between pro- and antithrombotic and between vasoconstrictor and vasorelaxing agents and modulate the physiological production of cytokines, adhesion molecules and growth factors, leading to a prothrombotic, hypertensive and hyperadhesive state, a phenomenon described as endothelial dysfunction.

## Postprandial lipoproteins and vascular disease

### Clinical and epidemiological studies

A link between elevated triglyceride levels and atherosclerosis is supported by several epidemiologic studies (Pelkonen et al., 1977; Heyden, 1980; Carlson et al., 1985; Castelli, 1986; Cambien et al., 1986). However, it was questioned whether triglyceride levels are an independent risk factor, since in many studies hypertriglyceridemia was associated with other risk factors, especially low High-Density-Lipoprotein (HDL) levels (Hulley et al., 1980; Austin, 1989). Moreover, one has to admit, that most studies only assessed the fasting state and did not account to the fact that triglyceride levels increase after ingestion of a meal. Several authors, however, have demonstrated, that patients with precocious coronary heart disease have postprandially elevated triglyceride levels and the accompanying lipoprotein fractions, chylomicrons, VLDL and their remnants have been shown to be associated with atherosclerosis (Simons et al., 1987; Simpson et al., 1990; Groot et al., 1991; Patsch et al., 1992; Karpe et al., 1994; Weintraub et al., 1996).

Studies in our group revealed that of 15% healthy male volunteers had excessively elevated triglyceride levels after a standard lipid load test (Schrezenmeir et al., 1992, 1993). The phenomenon of "Triglyceride-High-Response" was associated with postprandially increased levels of insulin, proinsulin and free fatty acids, higher abdominal adipose tissue and postprandial energy expenditure and therefore interpreted as early marker for the manifestation of the metabolic syndrome (Schrezenmeir et al., 1996, 1997). There-

fore, it seems to be important to elucidate the atherogenic potential of postprandial lipoproteins.

The postprandial elevation of triglycerides is mainly due to an increase of chylomicrons of intestinal origin, characterized by Apolipoprotein B<sub>48</sub> (ApoB<sub>48</sub>), but higher concentrations of Very-Low-Density-Lipoproteins (VLDL) of hepatic origin, characterized by ApoB<sub>100</sub>, also may contribute (Schrezenmeir et al., 1993; Cohn et al., 1993; Schneemann et al., 1993). This was explained by a diminished degradation of VLDL because of the preferential lipolysis of chylomicrons (Schneemann et al., 1993; Karpe et al., 1993). Chylomicrons are generally not regarded as atherogenic, because those types of dyslipoproteinemias that are characterized by excessive elevation of chylomicrons (lipoprotein lipase (LPL) deficiency, ApoC<sub>II</sub> deficiency) are not associated with increased prevalence of atherosclerosis (Brunzell et al., 1976). Only one study could detect signs of atherosclerosis in patients with chylomicronemia (Benlian et al., 1996), but those suffered in part also from diabetes which might have been the primary cause of vascular disease.

### Effects on endothelial barrier function

It is well known, that cholesterol-rich low-density lipoproteins (LDL) are taken up by macrophage scavenger receptors leading to cholesterol ester deposition in the cells (Goldstein et al., 1979; Parthasarathy et al., 1987). Histological and cell culture experiments revealed, that also triglyceride rich postprandial lipoproteins are taken up by macrophages and smooth muscle cells and are detectable as part of foam cells in vascular lesions (Floren and Chait, 1981; Gianturco et al., 1982, 1988; Yu and Mamo, 1997).

Chylomicrons and VLDL are rather heterogeneous concerning size and composition. In general, it is assumed that intact chylomicrons are too big to enter the vascular wall (Nordestgaard and Tybjaerg-Hansen, 1992). However, smaller VLDL are able to permeate the endothelium and it was suggested that even chylomicrons could enter if the endothelium is already damaged (Hamsten, 1990; Proctor and Mamo, 1996).

An often cited hypothesis was published by Zilversmit (1973, 1979) who postulated that lipolysis of postprandial lipoproteins by LPL generates highly atherogenic remnants, relatively enriched with cholesterol, that lead to foam cell development. In addition, the local release of high concentrations of free fatty acids is thought to damage endothelial cells.

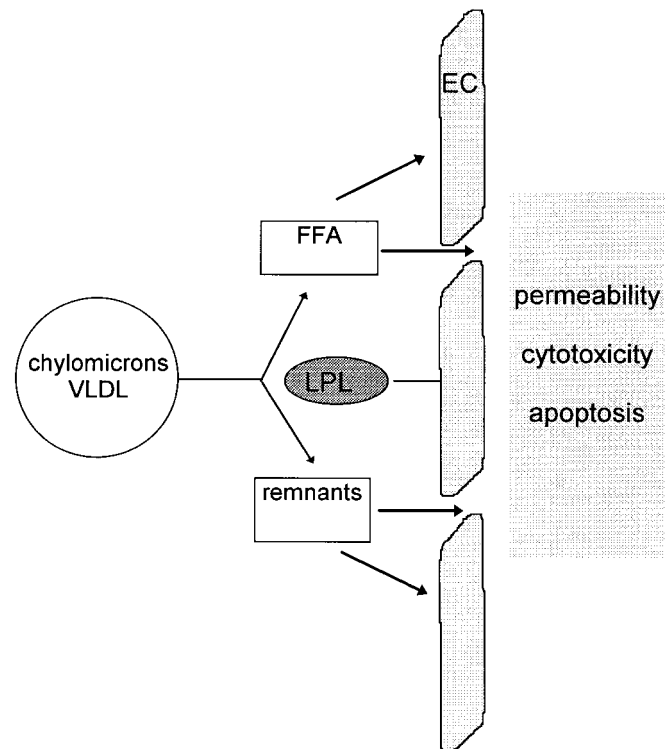
Indeed it was shown in endothelial cell culture experiments that *in vitro* lipolysis of postprandial lipoproteins with lipoprotein lipase (LPL) resulted in the generation of particles that increased the perme-

ability of the endothelium – measured as albumin transfer across the endothelial monolayer – and were cytotoxic to endothelial cells, whereas lipolysis products of fasting serum had no such effect (Speidel et al., 1990; Hennig et al., 1992; Chung et al., 1998). Chung et al. (1998) determined the effects of the fat composition of a single meal on the cytotoxic potential of the fatty acids lipolytically released from the postprandial lipoprotein fractions. Postprandial lipemia was induced by feeding fasted normolipidemic human subjects with a meal rich in saturated fat and another meal rich in polyunsaturated fat, or vice versa. The polyunsaturated/saturated fatty acid ratio of serum fatty acids in postlipolysis serum (fasting and postprandial) were consistently higher than that of fatty acids or triglycerides associated with triglyceride-rich lipoproteins in prelipolysis serum. This indicates that polyunsaturated triglycerides in VLDL and/or chylomicrons are more susceptible to lipolysis than saturated ones. FFA in postlipolysis postprandial serum after ingestion of polyunsaturated fat were consistently more cytotoxic than that in postlipolysis postprandial serum after ingestion of saturated fat. The authors pointed out that – despite the general belief that saturated fat is more atherogenic than polyunsaturated fat – lipolytic remnant products of postprandial lipoproteins produced after a meal rich in polyunsaturated fat seem to be more injurious to the endothelium than those produced after a meal rich in saturated fat.

Incubation of cells with singular free fatty acids similarly resulted in endothelial damage, with linoleic acid having the most prominent effect (Hennig et al., 1984, 1993). Interestingly, saturated fatty acids (palmitic and stearic acid), and also higher unsaturated fatty acids (linolenic acid) had no influence on permeability. Therefore, it is unclear to which degree the effects of linoleic acid are due to induction of oxidative stress (Fig. 1).

### Effects on endothelial cell functions

Besides these effects on endothelial integrity, lipoproteins have been shown to exert effects on cellular functions like the expression of membrane proteins and the production or release of several mediators related to atherogenesis. Most in vitro studies on the impact of lipoproteins on endothelial cells concentrated on oxidized LDL. LDL oxidation is mediated by interaction with endothelial cells and other cells of the vascular wall (Morel et al., 1984; Steinbrecher et al., 1984; Parthasarathy et al., 1987). Modification of ApoE in oxLDL results in diminished binding to the LDL receptor and excessive uptake of oxLDL via scavenger receptors into macrophages (Goldstein et al., 1979; Steinbrecher et al., 1984, 1987; Partha-



**Fig. 1** Influence of postprandial lipoproteins on endothelial integrity.

EC endothelial cell; FFA free fatty acid; LPL lipoprotein lipase; VLDL very-low density lipoprotein

sarathy et al., 1987). Another consequence of oxidation are changes in the chemical composition of the lipid portion, mainly generation of fatty-acid hydroperoxides and transformation of phosphatidylcholine into lyso-phosphatidylcholine (Steinbrecher et al., 1984; Parthasarathy et al., 1985).

OxLDL were shown to stimulate adhesion molecule expression (Lehr et al., 1994; Khan et al., 1995; Gebuhrer et al., 1995; Amberger et al., 1997), release of chemotactic factors like MCP-1 (Cushing et al., 1990) and production of colony-stimulating-factors (Rajavashisth et al., 1990). Furthermore, interactions with blood pressure regulators have been described, like a stimulation of endothelin-1 secretion (Boulangier et al., 1992) and an inhibition of NO production or release (Kugiyama et al., 1990; Tanner et al., 1991). Procoagulatory activity has been demonstrated in a stimulation of Plasminogen Activator Inhibitor (PAI-1) synthesis (Latron et al., 1991) and inhibition of Tissue Plasminogen Activator (tPA) synthesis and release (Kugiyama et al., 1993).

Several recent studies in endothelial cells imply, that also postprandial triglycerides are associated with endothelial dysfunction and the accompanying lipoproteins directly affect cellular functions. The following sections will summarize the current knowledge on the impact of postprandial triglycerides and postprandial lipoprotein fractions on endothelial

functions. In addition to chylomicrons and VLDL, effects of their lipolysis products, i.e. remnants on the one hand and free fatty acids on the other, will be discussed. This review concentrates on factors mediating the interaction with blood leukocytes and on agents involved in blood pressure regulation.

### *Interaction with blood leukocytes*

#### Adhesion molecules

The critical adhesion of blood monocytes to the endothelium is at least in part mediated by several adhesion molecules. Increased expression of adhesion molecules has been detected immunohistochemically in atherosclerotic plaques in animals and humans (Cybulsky and Gimbrone, 1991; Poston et al., 1992; O'Brien et al., 1993; Li et al., 1993; Davis et al., 1993; Richardson et al., 1994). The membrane expression of adhesion molecules is accompanied by occurrence of soluble forms of adhesion molecules (lacking membrane-spanning and cytoplasmic domains), which have been shown to be highly related to atherosclerosis and therefore likely to be humoral markers for endothelial dysfunction (De Caterina et al., 1997; Zeitler et al., 1997; Rohde et al., 1998).

E-selectin, a member of the selectin family, mediates the rolling of leukocytes at the vascular wall, whereas Intercellular-Adhesion-Molecule-1 (ICAM-1) and Vascular-Cell-Adhesion-Molecule-1 (VCAM-1), members of the immunoglobulin superfamily, mediate firm adhesion of blood cells to the endothelium and finally the extravasation of leukocytes. Adhesion molecule expression is low in unstimulated endothelium, with the exception of ICAM-1, which is constitutively expressed to a higher degree (Pober et al., 1986). Cytokines (TNF $\alpha$ , IL-1) and bacterial endotoxins induce the expression of E-selectin after 4–6 h of incubation (Bevilaqua et al., 1989) and later on the expression of VCAM-1 and ICAM-1 (Pober et al., 1986; Pober and Cotran, 1991). P-Selectin (GMP-140, CD62) is constitutively expressed in the membrane of Weibel-Palade-bodies of endothelial cells and is translocated few minutes after stimulation with thrombin or histamine (McEver et al., 1989). De novo synthesis of P-selectin can be induced by cytokines (IL-1, TNF $\alpha$ ) (Bevilaqua and Nelson, 1993).

#### Impact of postprandial triglycerides on soluble adhesion molecule levels

Elevated levels of soluble adhesion molecules have been demonstrated in diabetic patients (Steiner et al., 1994; Ceriello et al., 1996; Cominacini et al., 1995). The underlying mechanisms of increased adhesion molecule levels are not fully elucidated and their relation to glycaemic control was discussed contro-

versely (Steiner et al., 1994; Cominacini et al., 1995, 1997). Studies of Cominacini et al. (1997) imply that glycaemic control per se is not directly implicated in increased E-selectin plasma concentration, but could affect E-selectin concentration through its effect on oxidative stress. In accordance, De Mattia et al. (1998) demonstrated a reduction of soluble VCAM-1 levels after treatment with the antioxidant N-acetyl-L-cysteine in non-insulin dependent diabetic patients.

It was suggested that the occurrence of advanced glycation end products in diabetic patients is responsible for the induction of adhesion molecule expression and accelerated vasculopathy (Schmidt et al., 1995). There is evidence that not only disturbances in glucose metabolism and related plasma factors, but also disorders of lipid metabolism are associated with alterations of adhesion molecule levels: In diabetic patients, increased levels of E-selectin were shown to correlate with triglyceride levels (Bannan et al., 1998). In a recent study, the association between soluble adhesion molecules and other risk factors occurring with hypertriglyceridemia and the effect of triglyceride reduction on adhesion molecule levels were analysed (Abe et al., 1998). Compared with normal control subjects, patients with severe hypertriglyceridemia and low HDL had significantly increased levels of soluble ICAM-1, VCAM-1 and E-selectin, independently of diabetes mellitus and other risk factors. In those patients who received purified n-3 fatty acids, triglyceride levels and simultaneously ICAM-1 and E-selectin levels were reduced, with the greatest reduction in diabetic patients.

#### Impact of postprandial lipoproteins on adhesion molecule expression

The relationship between disorders in lipid metabolism and adhesion molecule levels is supported by in vitro studies of interactions between triglyceride-rich lipoproteins and membrane expression of adhesion molecules: VLDL treated in vitro with lipoproteinlipase were shown to induce increased monocyte adhesion to endothelial cells (Saxena et al., 1992).

We have previously demonstrated that chylomicrons induce E-selectin and VCAM-1 expression in endothelial cells (Moers et al., 1997). This was done by immunocytochemical detection of adhesion molecules expression in endothelial cells from human umbilical veins. However, differences were observed between chylomicron preparations from different individuals, all separated from plasma 4 h after ingestion of a standard lipid load test (Schrezenmeir et al., 1992, 1993). To elucidate, which factor or component of chylomicrons could be responsible for these differences, we analysed, if oxidative modification of chylomicrons results in an increased stimulation of adhesion molecule expression. Indeed,

we could demonstrate that chylomicrons oxidized in vitro with copper sulphate induced E-Selectin expression depending on the dosage of oxidant (Jagla and Schrezenmeir, 1998).

In a next step we intended to find out, whether the fatty acid composition and the oxidation propensity of dietary fat determines the effect of oxidized chylomicrons. Indeed, chylomicrons separated after ingestion of safflower oil, rich in polyunsaturated linoleic acid, induced higher levels of adhesion molecule expression at the higher copper concentration (10  $\mu\text{mol/l}$ ) compared to chylomicrons separated after ingestion of olive oil, rich in monounsaturated oleic acid (Fig. 2).

Another group demonstrated stimulation of monocyte adhesion to the endothelium by oxidized chylomicrons (Kurtel et al., 1995). The effect was shown to be mediated at least in part by ICAM-1. Involvement of E-selectin and VCAM-1 was not analysed. Other authors demonstrated cytotoxic effects of oxidized chylomicrons – separated after ingestion of different oils – on endothelial cells after prolonged incubation (Mabile et al., 1997). Similarly to our findings concerning adhesion molecule expression, the degree of cytotoxicity was related to the degree of unsaturation of the dietary fat.

It was questioned, whether in vitro oxidation of lipoproteins reflects processes occurring in vivo. With regard to LDL, it was demonstrated that oxidation with metall ions results in a similar composition of oxidation products than oxidation in vivo by interaction with cells. However, the mechanisms by which LDL are oxidized in vivo are not yet fully elucidated. Concerning chylomicrons, a practical significance of oxidative modification is given by the finding, that ingestion of oxidized fats is related to the content of oxidation products in the chylomicron fraction

(Naruszewicz et al., 1987; Staprans et al., 1993, 1994). Therefore, oxidized chylomicrons – in contrast to LDL – circulate in the blood, are hydrolyzed by LPL at the endothelium and the released oxidized fatty acids can directly affect endothelial cells. This would suggest, that postprandial lipoproteins promote atherogenesis by a different mechanism of action than LDL.

Impact of fatty acids on adhesion molecule expression

Several authors described effects of fatty acids on the expression of adhesion molecules. On the one hand, there seem to be stimulatory effects as such, on the other hand augmentation or inhibition of cytokine induced adhesion molecule expression was demonstrated for certain fatty acids, implying an interference with signal transduction processes.

A stimulation of ICAM-1 expression was shown for butyric acid (Justus et al., 1995), but very high concentrations (1 mmol/l) have been used in this approach. Young et al. (1998) described that exposure of endothelial cells to linoleic acid increased cellular oxidative stress, activated nuclear transcription factor  $\text{NF}\kappa\text{B}$ , increased interleukin-8 (IL-8) production, and elevated intercellular adhesion molecule-1 (ICAM-1) levels.

Another group demonstrated that linoleic acid-derived hydroxy- and hydroperoxy derivatives (HETE, HPETE) stimulate E-Selectin, ICAM-1 und VCAM-1 expression (Sultana et al., 1996). This finding would support our hypothesis, that oxidation products of fatty acids are the mediators of oxidized chylomicron-induced adhesion molecule expression. Linoleic acid has furthermore been shown to stimulate  $\text{TNF}\alpha$ -induced adhesion molecule expression (Toborek et al., 1996) However, effects of a combined exposure to linoleic acid and  $\text{TNF}\alpha$  on IL-8 production and ICAM-1 levels were dependent on the time of exposure. For example, ICAM-1 levels increased at 12 hours but decreased ICAM-1 levels at 24 hours compared with treatment with  $\text{TNF}\alpha$  alone (Young et al., 1998).

Inhibitory and thus protective effects on cytokine-induced expression of adhesion molecules have been demonstrated for n-3 fatty acids. Weber et al. (1995) found, that preincubation of HUVEC with docosahexaenoic acid (DHA), but not eicosapentaenoic acid (EPA) or arachidonic acid (AA) resulted in inhibition of  $\text{TNF}\alpha$ -mediated VCAM-1 expression; expression of ICAM-1 and E-selectin and VCAM-1 stimulation by other cytokines ( $\text{IFN}\gamma$ ,  $\text{IL-1}\beta$ ) were not changed significantly. Similar results were reported by De Caterina et al. (1994). Other authors demonstrated effects of EPA and AA on adhesion molecule expression using other stimulators and

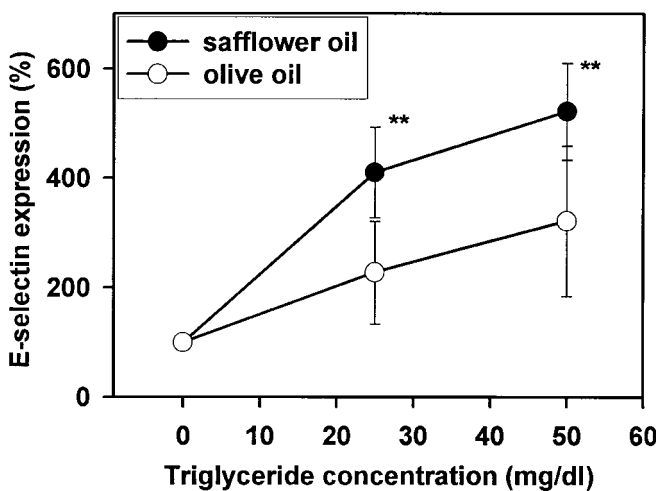
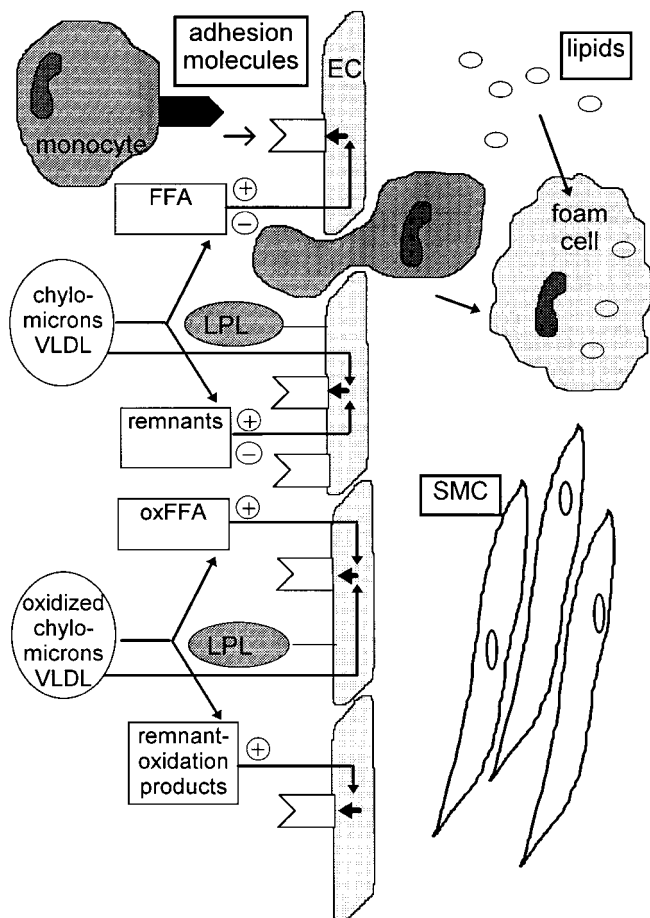


Fig. 2 Stimulation of E-selectin expression by chylomicrons, separated after ingestion of olive oil and safflower oil, oxidized in vitro by 10  $\mu\text{M}$   $\text{CuSO}_4$  (mean  $\pm$  SEM, \*\*  $p < 0,001$ )

different incubation procedures (Kim et al., 1995; Collie-Duguid and Wahle, 1996). Recently, also oleic acid was shown to inhibit adhesion molecule expression (Carluccio et al., 1999). In contrast, Sethi et al (1996) showed that only (in vitro) oxidized n-3 fatty acids inhibit activation of E-selectin and VCAM-1 expression induced by LPS or phorbol esters and Huang et al. (1997) described inhibitory effects of arachidonic acid and its hydroxy- and hydroperoxy derivatives, results that are in contrast to the above cited study of Sultana et al. (1996) (Fig. 3).



**Fig. 3** Influence of postprandial lipoproteins on leukocyte adhesion. Adhesion molecules mediate the recruitment of monocytes. Adherent monocytes can transmigrate the endothelium, differentiate into macrophages and transform into foam cells by accumulation of lipids. Postprandial lipoproteins have been shown to modulate adhesion molecule (AM) expression. On the one hand, non-oxidized chylomicrons and fatty acids as well as oxidized chylomicrons and their lipolysis products *stimulate* AM expression, on the other hand *inhibitory* effects on AM expression have been described for non-oxidized as well as for oxidized fatty acids. EC endothelial cell; FFA free fatty acid; oxFFA oxidized fatty acid; LPL lipoprotein lipase; SMC smooth muscle cell; VLDL very-low density lipoprotein

### Blood pressure regulation

Nitric oxide (NO) has gained increasingly attention during the last two decades due to its close relation to hypertension and atherosclerosis. NO, formerly called “endothelium derived relaxing factor” is produced from L-arginine by NO synthase (Palmer et al., 1988) and acts by activating guanyl cyclase in smooth muscle cells (Rapoport and Murad, 1983). Besides its vasodilatory activity, NO inhibits adhesion and aggregation of platelets (Radomski et al., 1997), adhesion of leukocytes to the endothelium (Kubes et al., 1991) and migration and proliferation of smooth muscle cells (Garg and Hassid, 1989).

NO production has been shown to be impaired in hypercholesterolemia and atherosclerosis (Verbeuren et al., 1986; Förstermann et al., 1988; Minor et al., 1990; Bossaller et al., 1991). Interference of oxLDL with nitric oxide activity has been detected in various cell culture studies. Effects on NO synthase expression (Liao et al., 1995) and substrate availability (Tanner et al., 1991) were discussed. It was, however, suggested that oxLDL do not inhibit the synthesis or release of NO, but even stimulate NO production and inactivate NO afterwards, possibly by generation of superoxide anions (Kugiyama et al., 1990; Galle et al., 1991; Chin et al., 1992).

### Effects of postprandial triglycerides on blood pressure

Several authors investigated effects of postprandial lipoproteins on endothelium-dependent relaxation, which is supposed to be mediated by NO. Grieve et al. (1998) demonstrated that perfusion of isolated aortas with native and oxidized chylomicron remnants resulted in an inhibition of endothelium-dependent relaxations, measured as response to relaxing agents after contraction of ring preparations of the previously perfused vessel with phenylephrine. Since the relaxation induced by the agents used in this approach was shown to be inhibited by the NO synthase inhibitor N<sup>G</sup>-nitro-L-arginine, remnant-mediated inhibition was attributed to an interference with NO production.

A similar experimental design was used by Doi et al. (1998) to test effects of postprandial lipoproteins on endothelium-dependent vasorelaxation. After precontraction with phenylephrine, remnant lipoproteins, but not the VLDL fraction, impaired vasorelaxation in response to the vasodilators acetylcholine, substance P and calcium-ionophor A23187. Incubation with lipid extracts from the remnant lipoproteins also inhibited vasorelaxation, indicating that the lipid component of lipoproteins was responsible for the effect.

Kugiyama et al. (1998) analysed the correlation of responses of coronary arterial diameter and coronary

blood flow to intracoronary infusion of acetylcholine with remnant lipoprotein levels in subjects with normal coronary angiograms. It was shown that remnant lipoprotein levels were independently associated with abnormal endothelium-dependent vasomotor function in large coronary arteries, indicating that remnant lipoproteins may impair endothelial vasomotor function in human coronary arteries. A decrease in coronary nitric oxide bioactivity seemed to be responsible in part for the inhibitory effects of remnant lipoproteins, since constrictor responses of epicardial coronary diameters to intracoronary infusion of the NO synthase inhibitor N<sup>G</sup>-monomethyl-L-arginine at baseline, had an inverse and independent correlation with remnant lipoprotein levels by use of multivariate analysis.

Inoue et al. (1998) assessed endothelial function by an acetylcholine provocation test in patients suspected of having ischaemic heart disease because of chest pain, but without angiographic evidence of atherosclerotic coronary artery disease. Acetylcholine (ACh)-induced vascular relaxation is mediated by nitric oxide released from the endothelium. The percent change in coronary artery diameter after intracoronary injection of ACh was smaller in patients with high remnant lipoprotein cholesterol (RLP-C), compared with the normal RLP-C group. There were no significant differences in other lipid levels, suggesting that there is an association between high serum RLP-C and coronary vascular endothelial cell dysfunction.

In another study the effect on a single high fat meal, compared to an isocaloric low fat meal, on endothelial function was investigated in healthy, normocholesterolemic volunteers (Vogel et al., 1997). Endothelial function, in the form of flow-mediated vasoactivity, was assessed in the brachial artery using ultrasound as percent arterial diameter change 1 minute after 5 minutes of upper-arm arterial occlusion. Flow-dependent vasoactivity decreased after the high-fat meal, whereas no changes were observed after the low-fat meal. The postprandial change in vasoactivity strongly correlated with the postprandial increase in triglycerides. These results imply that a single high-fat meal transiently impairs endothelial function and were interpreted as a potential mechanism by which a high-fat diet might be atherogenic independent of changes in cholesterol.

#### Effects of fatty acids on nitric oxide activity

Turpeinen et al. (1998) analysed the effect of polyunsaturated fatty acid intake on endothelial function by measuring urinary concentrations of nitric oxide metabolites in healthy subjects after diets rich in either linoleic acid or oleic acid. Urinary levels of 8-iso-PGF2 $\alpha$  were measured as an *in vivo* marker for lipid peroxidation processes. After a baseline diet rich

in saturated fatty acids (SFA) for 4 weeks, volunteers were switched to either a high linoleic acid diet or a high oleic acid diet also for 4 weeks. Urinary excretion of 8-iso-PGF2 $\alpha$  was significantly increased after the linoleic acid diet, whereas the urinary concentration of nitric oxide metabolites decreased. No significant changes were seen in the oleic acid group. Again, the modulation of NO production by the LA diet was attributed to the induction of oxidative stress. In contrast, supplementation with fish oils rich in n-3 fatty acids has been shown to improve forearm blood flow responses to acetylcholine in humans, whereas olive oil had no effect (McVeigh et al., 1993). Neither fish oil nor olive oil supplementation produced any significant changes in forearm blood flow when an endothelium-independent vasodilator was used. Accordingly, administration of fish oil and eicosapentaenoic acid resulted in increased levels of urinary nitric oxide metabolites (Harris et al., 1997).

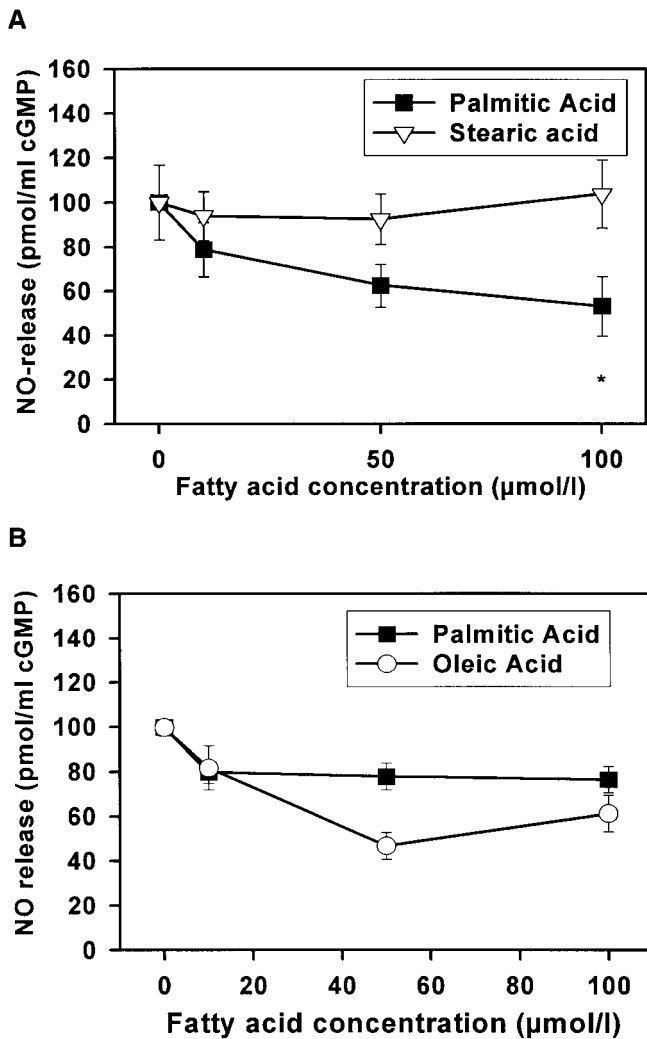
*In vitro* experiments revealed interactions of fatty acids with NO release. An inhibition of NO release was demonstrated for oleic acid (Davda et al., 1995) and palmitic acid (Moers and Schrezenmeir, 1997). Eicosapentaenoic acid in contrast (and in accordance with the above cited results) was shown to stimulate nitric oxide release (Okuda et al., 1997).

In our experiments (Moers and Schrezenmeir, 1997) the influence of fatty acids on NO release was analysed in HUVEC, measured by a bioassay technique (Ishii et al., 1991) as NO-induced cGMP production of a fibroblast cell line. NO production was stimulated by calcium ionophore A23187 and the effect of fatty acids on this stimulated NO production was analysed. We could demonstrate that palmitic acid and oleic acid inhibited NO-release, whereas stearic acid had no effect (Fig. 4).

This would suggest, that intake of saturated fat rich in palmitic acid, followed by prolonged postprandial elevations in palmitic acid levels could lead to an increase in vascular tone and to diminished protective effects of NO, namely its inhibitory action on platelet aggregation and monocyte adhesion.

#### Effects of postprandial lipoproteins on endothelin-1 production

As mentioned above, endothelial cells do not only produce vasorelaxing factors but also their counterpart. The 21 amino-acids comprising peptide endothelin-1 is a strong local vasoconstrictor, which is even more potent than angiotensin II. ET-1 is generated from its precursor big-endothelin by endothelin-converting-enzyme (ECE) and leads to a long-lasting blood pressure elevation (Yanagisawa et al., 1988). Besides this, ET-1 has been shown to stimulate mitogenesis of smooth muscle cells (Kanse et al., 1995). Increased levels of endothelin-1 have



**Fig. 4** A Inhibition of stimulated NO release of HUVEC by palmitic acid. (mean  $\pm$  SEM). B Inhibition of stimulated NO release of Eahy.926 endothelial cells by palmitic and oleic acid (mean  $\pm$  SEM, \*  $p < 0.05$ ). NO release was measured as cGMP production in rat fibroblasts. Stimulated NO release was set as 100%

been related to cardiovascular disease. In rats, plasma ET-1 concentrations increased after cholesterol feeding and ET-1 levels correlated with plasma total cholesterol, LDL, and VLDL concentrations (Horio et al., 1991).

Endothelin-levels have been shown to be increased in patients with type 2 diabetes or metabolic syndrome, respectively (Takahashi et al., 1990; Ferri et al., 1997). After an insulin bolus, endothelin-levels peaked in patients (Piatti et al., 1996). Cell culture experiments revealed that endothelin release is stimulated by insulin (Hu et al., 1993). In one study, endothelin-levels were shown not to correlate with hypertriglyceridemia (Haak et al., 1994) but it was demonstrated by another group that in patients with metabolic syndrome postprandially elevated triglycerides increased endothelin-levels in addition to insulin (Piatti et al., 1996).

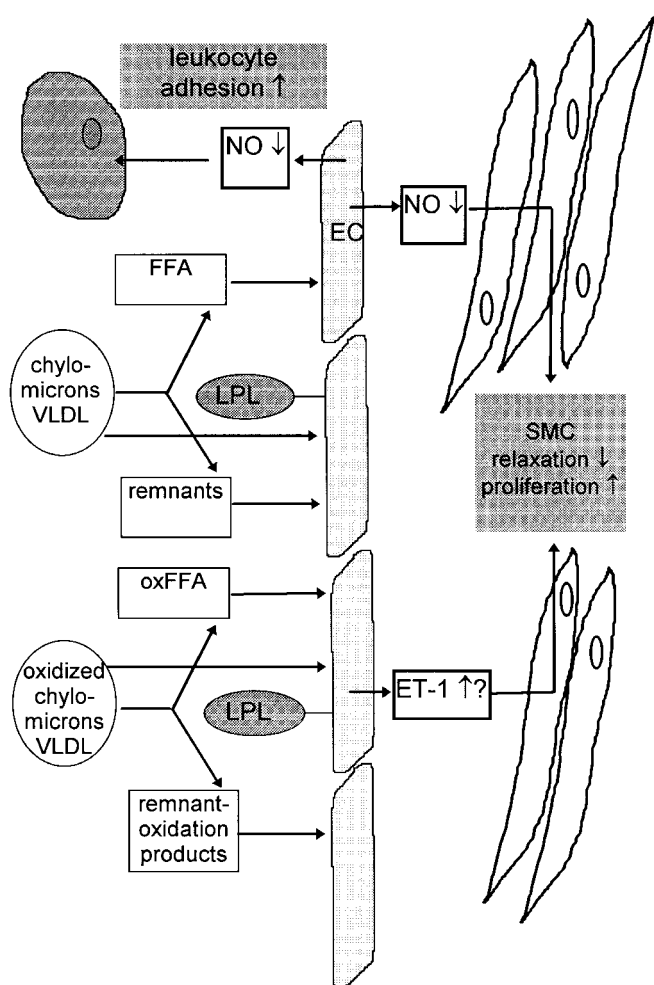
In vitro experiments revealed that ET-1 secretion from endothelial cells increased significantly after incubation with oxidized LDL, and also higher doses of VLDL increased ET-1 secretion (Horio et al., 1993).

So far, there are no in vitro observations about an effect of chylomicrons or the triglyceride component of lipoproteins on endothelin release, but one could imagine, that triglyceride-rich lipoproteins or fatty acids can affect endothelin-secretion similarly to LDL. Since ET-1 secretion is counterbalanced by NO production (Boulanger and Lüscher, 1990), impairment of NO release by postprandial lipoproteins is likely to be associated by increment of ET-1 levels. It was concluded from the finding that chylomicron remnants potentiate phenylephrine induced vasoconstrictions and addition of the NO-inhibitor  $N^G$ -nitro-L-arginine increased rather than inhibited this effect (Grieve et al., 1998), that lipoproteins act also by other mechanisms, potentially by stimulation of the release of contracting factors. Whether direct effects on ET-1 mRNA synthesis or ECE-activity including the underlying signal pathways occur, remains to be clarified (Fig. 5).

#### Components of lipoproteins mediating interaction with cellular functions

To which components can effects of lipoproteins be attributed? With regard to oxidized LDL fatty acid hydroperoxides and phospholipids, especially lysophosphatidylcholine were identified as effective compound mediating endothelial dysfunction (Quinn et al., 1988; Kugiyama et al., 1990; Kume et al., 1992; Khan et al., 1995).

Concerning postprandial lipoproteins one can think of remnants at first, which have been shown to cause foam cell development and are assumed to act atherogenic because of its relatively high cholesterol content, but only few effects on endothelial cells have been directly related to remnants. Another point of view is, that fatty acids released by LPL are the component that initiates endothelial dysfunction, since singular fatty acids were shown to affect adhesion molecule expression and NO production. However, pro- and antiatherogenic effects have been described for some fatty acids (e.g. oleic acid, linoleic acid) and for non-oxidized fatty acids as well as for oxidation products. Effects of singular fatty acids are difficult to interpret, since experimental conditions show great variations. Strikingly, especially linoleic acid was shown to exert several negative effects in endothelial cell culture studies and linoleic acid rich diets have been found to provoke atherogenic effects in humans; from this point of view, linoleic acid can be suspected to be more atherogenic than oleic acid. The difference was



**Fig. 5** Influence of postprandial lipoproteins on vasomotor function. NO induces vasorelaxation by activation of guanyl cyclase in smooth muscle cells and acts furthermore protective by inhibition of leukocyte adhesion. Endothelin-1 is in contrast a potent vasoconstrictor and stimulates mitogenesis of SMC. NO release was shown to be inhibited by fatty acids in vitro. Furthermore, non-oxidized and oxidized chylomicrons and remnants seem to be involved in diminished endothelium-dependent relaxation. If this effect is exclusively mediated by inhibition of NO release or additionally by stimulation of endothelin-1 release remains to be determined.

EC endothelial cell; ET-1 endothelin-1; FFA free fatty acid; oxFFA oxidized fatty acid; LPL lipoprotein lipase; SMC smooth muscle cell; VLDL very-low density lipoprotein

attributed to the higher oxidation propensity of linoleic acid; however, polyunsaturated fatty acids, supposed to be much more sensitive towards oxidation, seem to have contrary effects on adhesion molecule expression as well as on endothelium-dependent vasorelaxation. Therefore, the role of oxidation processes induced by fatty acids needs further clarification. With regard to the fact, that lipolysis can result in a local rise of fatty acid concentrations over those levels normally measured in plasma it is important to note potential pro- and atherogenic effects on endothelial functions.

Based on the presented experimental data, fatty acids (equally or even more than remnants) seem to be mediators of endothelial dysfunction. Therefore, triglyceride rich postprandial lipoproteins have – in contrast to LDL – atherogenic effects not related to cholesterol.

### Mechanisms of interaction between lipoproteins and cellular functions

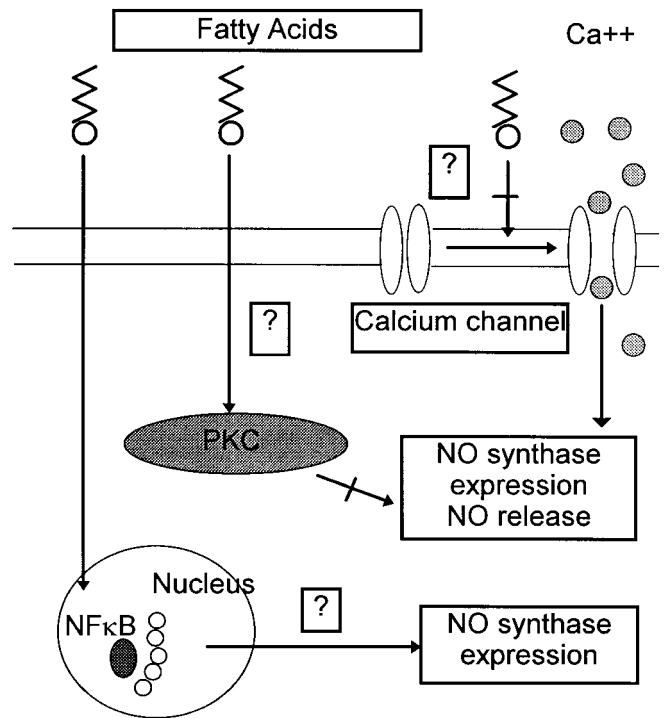
Several possible mechanisms by which lipoprotein components influence expression or release of endothelial mediators may be suggested. Fatty acids incorporated into cell membrane phospholipids affect membrane fluidity and thereby the function of receptors and ion channels (Flavahan, 1992). Indeed, interactions of fatty acids with ion channels have been described in vitro (Ordway et al., 1991; Allen et al., 1998). Furthermore they could influence signal transduction processes or act as second messengers. The protein kinase C (PKC) pathway seems to play a central role in regulation of endothelial functions like adhesion molecule expression and NO synthase expression (Lane et al., 1990; Deisher et al., 1993; Davda et al., 1994; Hirata et al., 1995). Lyso-PC, the effective component of oxLDL was shown to activate PKC (Kugiyama et al., 1992; Ohgushi et al., 1993). Effects on PKC activity have furthermore been demonstrated for monounsaturated fatty acids (Murakami et al., 1986; Khan et al., 1992) and oxidized fatty acids (Huang et al., 1997; Sultana et al., 1996).

Furthermore, fatty acids seem to be directly involved in regulation of gene expression since they have been shown to stimulate nuclear transcription factor  $\text{NF}\kappa\text{B}$  (Hennig et al., 1996; Sugiyama et al., 1998) which seems to play a key role in regulation of inflammation and to be involved in expression of cytokines, adhesion molecules and other endothelial mediators (Marui et al., 1993; Barnes and Karin, 1997). It was suggested, that this activation is mediated by induction of oxidative stress (Hennig et al., 1996). Recently, it was shown that VLDL activate  $\text{NF}\kappa\text{B}$  (Dichtl et al., 1999). Interestingly, oxidation of VLDL reduced its capacity to activate  $\text{NF}\kappa\text{B}$  in vitro, whereas free fatty acids such as linoleic and oleic acid activated  $\text{NF}\kappa\text{B}$  to the same extent as did VLDL. In the same study, intravenous injection of human VLDL into rats resulted in arterial activation of  $\text{NF}\kappa\text{B}$  as assessed by electrophoretic mobility shift assay. There was also a parallel expression of the adhesion molecules intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, as well as the cytokine  $\text{TNF}\alpha$ . Pretreatment of the rats with diet containing of the antioxidant probucol for 8 weeks did not inhibit arterial activation of  $\text{NF}\kappa\text{B}$  in response to injection of

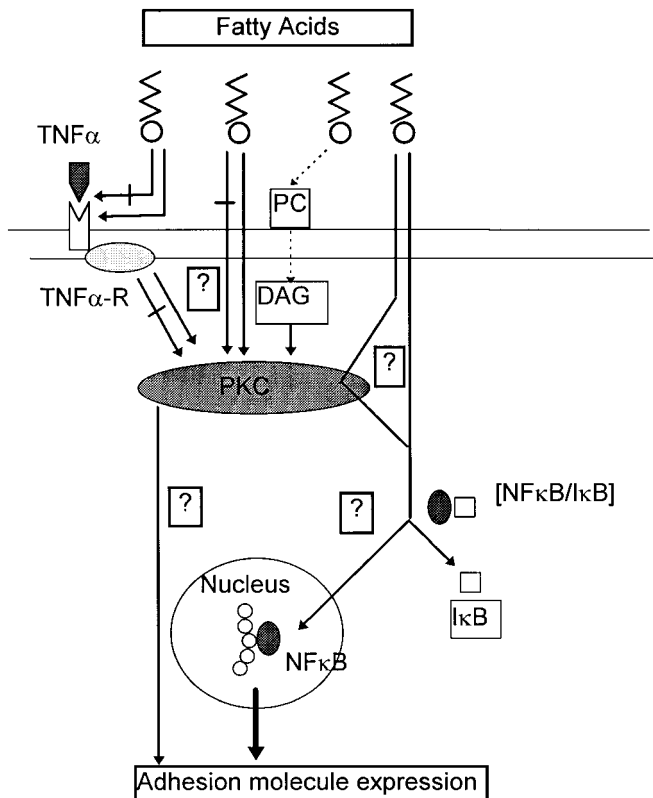
VLDL. Moreover, injection of triglycerides activated arterial expression of NFκB to the same extent as VLDL. These results imply that activation of the proinflammatory transcription factor NFκB is mediated by a release of VLDL fatty acids but does not involve VLDL oxidation. The role of oxidative modification of lipoproteins or their components, respectively, remains to be elucidated (Fig. 6, Fig. 7).

**Conclusion**

In summary, postprandially elevated triglyceride levels have to be regarded as risk markers for the metabolic syndrome similarly to cholesterol levels. There is evidence that the association between postprandial triglycerides and the metabolic syndrome or atherosclerosis, respectively, is driven by direct influences on endothelial functions because plasma triglyceride levels are associated with levels of humoral risk markers of endothelial origin and postprandial lipoproteins and their lipolysis products (remnants, free fatty acids) mediate the release and/or expression of endothelial mediators driving atherogenesis and hypertension in vitro. As a consequence, postprandial lipoprotein particles are taken up by cells of the vascular wall producing



**Fig. 7** Potential mechanisms by which fatty acids modulate signalling pathways involved in nitric oxide release or NO synthase expression. NFκB nuclear transcription factor κB; PKC protein kinase C



**Fig. 6** Potential mechanisms by which fatty acids modulate signalling pathways involved in adhesion molecule expression. DAG diacyl glycerol; NFκB nuclear transcription factor κB; PC phosphatidylcholine; PKC protein kinase C; TNFα-R TNFα receptor

foam cells, an early step in the development of atherosclerotic lesions. One could postulate, that after lipolysis fatty acids taken up by the endothelial cell induce expression or release of mediators of increased monocyte attachment, whereas remnant particles are in a second step taken up by macrophages and generate foam cells by cholesterol ester accumulation. In conclusion, more attention has to be paid to the potential atherogenic activity of postprandial lipoproteins.

**References**

Abe Y, El-Masri B, Kimball KT, Pownall H, Reilly CF, Osmundsen K, Smith CW, Ballantyne CM: Soluble cell adhesion molecules in hypertriglyceridemia and potential significance on monocyte adhesion. *Arterioscler Thromb Vasc Biol* 18: 723–731, 1998  
 Allen S, Khan S, Al-Mohanna F, Batten P, Yacoub M: Native low density lipoprotein-induced calcium transients trigger VCAM-1 and E-Selectin expression in cultured human endothelial cells. *J Clin Invest* 101: 1064–1075, 1998  
 Amberger A, Maczek Ch, Jürgens G, Michaelis D, Schett G, Trieb K, Eberl T, Jindal S, Xu Q, Wick G: Co-expression of ICAM-1, VCAM-1, ELAM-1 and Hsp60 in human arterial and venous endothelial cells in response to cytokines and oxidized low-density lipoproteins. *Cell Stress & Chaperones* 2: 94–103, 1997  
 Austin MA: Plasma triglyceride as a risk factor for coronary heart disease: the epidemiologic evidence and beyond. *Am J Epidemiol* 129: 249–259, 1989

- Bannan S, Mansfield MW, Grant PJ: Soluble vascular cell adhesion molecule-1 and E-selectin levels in relation to vascular risk factors and to E-selectin genotype in the first degree relatives of NIDDM patients and in NIDDM patients. *Diabetologia* 41: 460–466, 1998
- Barnes PJ, Karin M: Nuclear factor- $\kappa$ B – a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 336: 1066–1071, 1997
- Benlian P, De Gennes JL, Foubert L, Zhang H, Gagné SE, Hayden M: Premature atherosclerosis in patients with familial chylomicronemia caused by mutations in the lipoprotein lipase gene. *N Engl J Med* 335: 848–854, 1996
- Bevilaqua MP, Stengelin S, Gimbrone MA Jr, Seed B: Endothelial-leukocyte-adhesion molecule 1: An inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 243: 1160–1165, 1989
- Bevilaqua MP, Nelson RM: Selectins. *J Clin Invest* 91: 379–387, 1993
- Bossaller C, Habib GB, Yamamoto H, Williams C, Wells S, Henry PD: Impaired muscarinic endothelium-dependent relaxation and cyclic guanosine 5'-monophosphate formation in atherosclerotic human coronary arteries. *Circulation* 83: 652–660, 1991
- Boulanger C, Lüscher TF: Release of endothelin from the porcine aorta. Inhibition by endothelium-derived nitric oxide. *J Clin Invest* 85: 587–590, 1990
- Boulanger CM, Tanner FC, Bea ML, Hahn AWA, Werner A, Lüscher TF: Oxidized low density lipoproteins induce messenger RNA expression and release of endothelin from human and porcine endothelium. *Circ Res* 70: 1191–1197, 1992
- Brand K, Page S, Rogler G, Bartsch A, Brandl R, Knuechel R, Page M, Kaltschmidt C, Baeuerle PA, Neumeier D: Activated transcription factor nuclear factor-kappa B is present in the atherosclerotic lesion. *J Clin Invest* 97: 1715–1722, 1996
- Brunzell JD, Schrott HG, Motulsky AG, Bierman EL: Myocardial infarction in familial forms of hypertriglyceridemia. *Metabolism* 25: 313–320, 1976
- Cambien F, Jacqueson A, Richard JL, Warnet JM, Ducimetiere P, Claude JR: Is the level of serum triglyceride a significant predictor of coronary death in “normocholesterinemic” subjects? The Paris Prospective Study. *Am J Epidemiol* 124: 624–632, 1986
- Carlson LE, Böttiger LE, Ähfeldt PG: Risk factors for ischemic heart disease in men and women: Results of a 19-year follow-up of the Stockholm Prospective Study. *Acta Med Scand* 218: 207–211, 1985
- Carluccio MA, Massaro M, Bonfrate C, Siculella L, Maffia M, Nicolardi G, Distante A, Storelli C, De Caterina R: Oleic acid inhibits endothelial activation: A direct vascular antiatherogenic mechanism of a nutritional component in the mediterranean diet. *Arterioscler Thromb Vasc Biol* 19: 220–228, 1999
- Castelli WP: The triglyceride issue: A view from Framingham. *Am Heart J* 112: 432–437, 1986
- Ceriello A, Falletti E, Bortolotti N, Motz E, Cavarape A, Russo A, Gonano F, Bartoli E: Increased circulating intercellular adhesion molecule-1 levels in type II diabetic patients: the possible role of metabolic control and oxidative stress. *Metabolism* 45: 498–501, 1996
- Chin JH, Azhar S, Hoffman BB: Inactivation of endothelial derived relaxing factor by oxidized lipoproteins. *J Clin Invest* 89: 10–18, 1992
- Chung BH, Hennig B, Cho BH, Darnell BE: Effect of the fat composition of a single meal on the composition and cytotoxic potencies of lipolytically-releasable free fatty acids in postprandial plasma. *Atherosclerosis* 141: 321–332, 1998
- Cohn JS, Johnson EJ, Millar JS, Cohn SD, Milne RW, Marcel YL, Russell RM, Schaefer EJ: Contribution of ApoB<sub>48</sub> and ApoB<sub>100</sub> triglyceride-rich lipoproteins (TRL) to postprandial increases in the plasma concentration of TRL triglycerides and retinyl esters. *J Lipid Res* 34: 2033–2040, 1993
- Collie-Duguid ESR, Wahle KWJ: Inhibitory effect of fish oil n-3 polyunsaturated fatty acids on the expression of endothelial cell adhesion molecules. *Biochem Biophys Res Commun* 220: 969–974, 1996
- Cominacini L, Fratta Pasini A, Garbin U, Davoli A, De Santis A, Campagnola M, Rigoni A, Zenti MG, Moghetti P, Lo Cascio V: Elevated levels of soluble E-selectin in patients with IDDM and NIDDM: relation to metabolic control. *Diabetologia* 38: 1122–1124, 1995
- Cominacini L, Fratta Pasini A, Garbin U, Campagnola M, Davoli A, Rigoni A, Zenti MG, Pastorino AM, Lo Cascio V: E-selectin plasma concentration is influenced by glycaemic control in NIDDM patients: possible role of oxidative stress. *Diabetologia* 40: 584–589, 1997
- Cushing SD, Berliner JA, Valente AJ, Territo MC, Navab M, Parhami F, Gerrity R, Schwartz CJ, Fogelman AM: Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. *Proc Natl Acad Sci USA* 87: 5134–5138, 1990
- Cybulsky MI, Gimbrone MA Jr: Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. *Science* 251: 788–791, 1991
- Davda RK, Chandler LJ, Guzman NJ: Protein kinase C modulates receptor-independent activation of endothelial nitric oxide synthase. *Eur J Pharmacol* 266: 237–244, 1994
- Davda RK, Stepniakowski KT, Lu G, Ullian ME, Goodfriend TL, Egan BM: Oleic acid inhibits endothelial nitric oxide synthase by a protein kinase C-independent mechanism. *Hypertension* 26: 764–770, 1995
- Davis MJ, Gordon JL, Gearing AJH, Pigott R, Woolf N, Katz D, Kyriakopoulos A: The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM and E-selectin in human atherosclerosis. *J Pathol* 171: 223–229, 1993
- De Caterina R, Basta G, Lazzarini G, Dell’Omo G, Petrucci R, Morale M, Carmassi F, Pedrinelli R: Soluble vascular cell adhesion molecule-1 as a biohumoral correlate of atherosclerosis. *Arterioscler Thromb Vasc Biol* 17: 2646–2654, 1997
- De Caterina R, Cybulsky MI, Clinton SK, Gimbrone MA, Libby P: The omega-3 fatty acid docosahexaenoate reduces cytokine-induced expression of proatherogenic and proinflammatory proteins in human endothelial cells. *Arterioscler Thromb* 14: 1829–1836, 1994
- De Mattia G, Bravi MC, Laurenti O, Cassone-Faldetta M, Proietti A, De Luca O, Armiento A, Ferri C: Reduction of oxidative stress by oral N-acetyl-L-cysteine treatment decreases plasma soluble vascular cell adhesion molecule-1 concentrations in non-obese, non-dyslipidaemic, normotensive, patients with non-insulin-dependent diabetes. *Diabetologia* 41: 1392–1396, 1998
- Deisher TA, Sato TT, Pohlman TH, Harlan JM: A protein kinase C agonist, selective for the beta I isozyme, induces E-Selectin and VCAM-1 expression on HUVEC but does not translocate PKC. *Biochem Biophys Res Commun* 193: 1283–1290, 1993
- Dichtl W, Nilsson L, Goncalves I, Ares MP, Banfi C, Calara F, Hamsten A, Eriksson P, Nilsson J: Very low-density lipoprotein activates nuclear factor-kappaB in endothelial cells. *Circ Res* 84: 1085–1094, 1999
- Doi H, Kugiyama K, Ohgushi M, Sugiyama S, Matsumura T, Ohta Y, Nakano T, Nakajima K, Yasue H: Remnants of chylomicron and very low density lipoprotein impair endothelium-dependent vasorelaxation. *Atherosclerosis* 137: 341–349, 1998
- Ferri C, Bellini C, Desideri G, Baldoncini R, Properzi G, Santucci A, De Mattia G: Circulating endothelin-1 levels in obese patients with the metabolic syndrome. *Exp Clin Endocrinol Diabetes* 105 (Suppl 2): 38–40, 1997

- Flavahan NA: Atherosclerosis or lipoprotein-induced endothelial dysfunction. *Circulation* 85: 1927–1938, 1992
- Floren CH, Chait A: Uptake of chylomicron remnants by the native LDL receptor in human monocyte-derived macrophages. *Biochim Biophys Acta* 665: 608–611, 1981
- Förstermann U, Mügge A, Alheid U, Haverich A, Frölich JC: Selective attenuation of endothelium-mediated vasodilatation in atherosclerotic human coronary arteries. *Circ Res* 62: 185–190, 1988
- Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle cells by acetylcholine. *Nature* 288: 373–376, 1980
- Galle J, Mülsch A, Busse R, Bassenge E: Effects of native and oxidized low density lipoproteins on formation and inactivation of endothelium-derived relaxing factor. *Arterioscler Thromb* 11: 198–203, 1991
- Garg UC, Hassid A: Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. *J Clin Invest* 83: 1774–1777, 1989
- Gebuhrer V, Murphy JF, Bordet JC, Reck MP, McGregor JL: Oxidized low-density lipoprotein induces the expression of P-selectin (GMP140/PADGEM/CD62) on human endothelial cells. *Biochem J* 306: 293–298, 1995
- Gianturco SH, Bradley WA, Gotto AM, Morrisset JD, Peavy DL: Hypertriglyceridemic very low density lipoproteins induce triglyceride synthesis and accumulation in mouse peritoneal macrophages. *J Clin Invest* 70: 168–178, 1982
- Gianturco SH, Bradley WA: Lipoprotein-mediated cellular mechanisms for atherogenesis in hypertriglyceridemia. *Sem Thromb Hemost* 14: 165–169, 1988
- Goldstein JL, Ho YK, Basu SK, Brown MS: Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. *Proc Natl Acad Sci USA* 76: 333–337, 1979
- Grieve DJ, Avella MA, Elliott J, Botham KM: The influence of chylomicron remnants on endothelial cell function in isolated perfused rat aorta. *Atherosclerosis* 139: 273–281, 1998
- Groot PHE, van Stiphout WAHJ, Krauss XH, Jansen H, van Tol A, van Ramshorst E, Chin-On S, Hofmann A, Crosswell SR, Havekes L: Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease. *Arterioscler Thromb* 11: 653–662, 1991
- Haak T, März W, Jungmann E, Hausser S, Siekmeier R, Gross W, Usadel KH: Elevated endothelin levels in patients with hyperlipoproteinemia. *Clin Invest* 72: 580–584, 1994
- Hamsten A: Hypertriglyceridaemia, triglyceride-rich lipoproteins and coronary heart disease. *Bailliere's Clin Endocrinol Metab* 4: 895–922, 1990
- Harris WS, Rambjor GS, Windsor SL, Diederich D: n-3 fatty acids and urinary excretion of nitric oxide metabolites in humans. *Am J Clin Nutr* 65: 459–464, 1997
- Hennig B, Shasby DM, Fulton AB, Spector AA: Exposure to free fatty acid increases the transfer of albumin across cultured endothelial monolayers. *Circ Res* 57: 776–780, 1984
- Hennig B, Chung BH, Watkins BA, Alvarado A: Disruption of endothelial barrier function by lipolytic remnants of triglyceride-rich lipoproteins. *Atherosclerosis* 95: 235–247, 1992
- Hennig B, Ramasamy S, Alvarado A, Shanta NC, Boissoneault GA, Decker EA, Watkins BA: Selective disruption of endothelial barrier function by pure fatty acids and fatty acids derived from animal and plant fats. *J Nutr* 123: 1208–1216, 1993
- Hennig B, Toborek M, Joshi-Barve S, Barger SW, Barve S, Mattson MP, McClain CJ: Linoleic acid activates nuclear transcription factor- $\kappa$ B (NF $\kappa$ B) and induces NF $\kappa$ B-dependent transcription in cultured endothelial cells. *Am J Clin Nutr* 63: 322–328, 1996
- Heyden S: Fasting triglycerides as predictors of total and CHD mortality in Evans County, Georgia. *J Chronic Dis* 33: 275–282, 1980
- Hirata K, Kuroda R, Sakoda T, Inoue N, Kawashima S, Yokoyama M: Inhibition of endothelial nitric oxide synthase activity by protein kinase C. *Hypertension* 25: 180–185, 1995
- Horio T, Kohno M, Murakawa K, Yasunari K, Yokokawa K, Ueda M, Takeda T: Increased plasma immunoreactive endothelin-1 concentration in hypercholesterolemic rats. *Atherosclerosis* 89: 239–246, 1991
- Horio T, Kohno M, Yasunari K, Murakawa K, Yokokawa K, Ikeda M, Fukui T, Takeda T: Stimulation of endothelin-1 release by low density and very low density lipoproteins in cultured human endothelial cells. *Atherosclerosis* 101: 185–190, 1993
- Hu RM, Levin ER, Pedram A, Frank HJL: Insulin stimulates production and secretion of endothelin from bovine endothelial cells. *Diabetes* 42: 351–358, 1993
- Huang ZH, Bates EJ, Ferrante JV, Hii CST, Poulos A, Robinson BS, Ferrante A: Inhibition of stimulus-induced endothelial cell intercellular adhesion molecule-1, E-Selectin, and vascular cell adhesion molecule-1 expression by arachidonic acid and its hydroxy and hydroperoxy derivatives. *Circ Res* 80: 149–158, 1997
- Hulley SB, Rosenman RH, Bawol RD, Brand RJ: Epidemiology as a guide to clinical decisions: The association between triglycerides and coronary heart disease. *N Engl J Med* 302: 1383–1389, 1990
- Inoue T, Saniabadi AR, Matsunaga R, Hoshi K, Yaguchi I, Morooka S: Impaired endothelium-dependent acetylcholine-induced coronary artery relaxation in patients with high serum remnant lipoprotein particles. *Atherosclerosis* 139: 363–367, 1998
- Ishii K, Sheng H, Warner TD, Förstermann U, Murad T: A simple and sensitive bioassay method for detection of EDRF with RFL-6 rat lung fibroblasts. *Am J Physiol* 261: H598–H603, 1991
- Jagla A, Schrezenmeier J: Induction of E-Selectin expression by oxidized chylomicrons. *Diabetologia* 41 (Suppl 1): A317, 1998
- Justus AC, Hoggatt AM, Faulk WP: Heparan-dependent endothelial antithrombin binding is increased by butyrate. *Tromb Res* 80: 125–133, 1995
- Kanse SM, Wijelath E, Kanthou C, Newman P, Kakkar VV: The proliferative responsiveness of human vascular smooth muscle cells to endothelin correlates with endothelin receptor density. *Lab Invest* 72: 376–382, 1995
- Karpe F, Steiner G, Olivecrona T, Carlson LA, Hamsten A: Metabolism of triglyceride-rich lipoproteins during alimentary lipemia. *J Clin Invest* 91: 748–758, 1993
- Karpe F, Steiner G, Uffelman K, Olivecrona T, Hamsten A: Postprandial lipoproteins and progression of coronary atherosclerosis. *Atherosclerosis* 106: 83–97, 1994
- Khan BV, Parthasarathy SS, Alexander RW, Medford RM: Modified low density lipoprotein and its constituents augment cytokine-activated vascular cell adhesion molecule-1 gene expression in human vascular endothelial cells. *J Clin Invest* 95: 1262–1270, 1995
- Khan W, Blobel GC, Hannun YA: Activation of protein kinase C by oleic acid. *J Biol Chem* 267: 3605–3612, 1992
- Kim DN, Eastman A, Baker JE, Mastrangelo A, Sethi S, Ross JS, Schmeel J, Thomas WA: Fish oil, atherogenesis, and thrombogenesis. *Ann NY Acad Sci* 748: 474–480, 1995
- Kubes P, Suzuki M, Granger DN: Nitric oxide: an endogenous modulator of leukocyte adhesion. *Proc Natl Acad Sci USA* 88: 4651–4655, 1991
- Kugiyama K, Kerns SA, Morrisett JD, Roberts R, Henry PD: Impairment of endothelium-dependent arterial relaxation by lysolecithin in modified low density lipoproteins. *Nature* 344: 160, 1990

- Kugiyama K, Ohgushi M, Sugiyama S, Murohara T, Fukunaga K, Miyamoto E, Yasue H: Lysophosphatidylcholine inhibits surface receptor-mediated intracellular signals in endothelial cells by a pathway involving protein kinase C activation. *Circ Res* 71: 1422–1428, 1992
- Kugiyama K, Sakamoto T, Misumi I, Sugiyama S, Ohgushi M, Ogawa H, Horiguchi M, Yasue H: Transferable lipids in oxidized low-density lipoprotein stimulate plasminogen activator inhibitor-1 and inhibit tissue-type plasminogen activator release from endothelial cells. *Circ Res* 73: 335–343, 1993
- Kugiyama K, Doi H, Motoyama T, Soejima H, Misumi K, Kawano H, Nakagawa O, Yoshimura M, Ogawa H, Matsumura T, Sugiyama S, Nakano T, Nakajima K, Yasue H: Association of remnant lipoprotein levels with impairment of endothelium-dependent vasomotor function in human coronary arteries. *Circulation* 97: 2519–2526, 1998
- Kume NM, Cybulsky MI, Gimbrone MA: Lysophosphatidylcholine, a component of atherogenic lipoproteins, induces mononuclear leukocyte adhesion molecules in cultured human and rabbit arterial endothelial cells. *J Clin Invest* 90: 1138–1144, 1992
- Kurtel H, Liao L, Grisham MB, Tso P, Aw TY, Anderson DC, Miyasaka M, Granger DN: Mechanisms of oxidized chylomicron-induced leukocyte-endothelial cell adhesion. *Am J Physiol* 268: H2175–H2182, 1995
- Lane TA, Lamkin GE, Wancewicz EV: Protein kinase C inhibitors block the enhanced expression of intercellular adhesion molecule-1 on endothelial cells activated by interleukin-1, lipopolysaccharide and tumor necrosis factor. *Biochem Biophys Res Commun* 172: 1273–1281, 1990
- Latron Y, Chautan M, Anfosso F, Alessi MC, Nalbone G, Lafont H, Juhan-Vague I: Stimulating effect of oxidized low density lipoproteins on plasminogen activator inhibitor-1 synthesis by endothelial cells. *Arterioscler Thromb* 11: 1821–1829, 1991
- Lehr HA, Olofsson AM, Carew TE, Vajkoczy P, von Andrian UH, Hübner C, Berndt MC, Steinberg D, Messmer K, Arfors KE: P-Selectin mediates the interaction of circulating leukocytes with platelets and microvascular endothelium in response to oxidized lipoprotein in vivo. *Lab Invest* 71: 380–386, 1994
- Li H, Cybulsky MI, Gimbrone MA Jr, Libby P: An atherogenic diet rapidly induces VCAM-1, a cytokine-regulatable mononuclear leukocyte adhesion molecule, in rabbit aortic endothelium. *Arterioscler Thromb* 13: 197–204, 1993
- Liao L, Starzyk RM, Granger DN: Molecular determinants of oxidized low-density lipoprotein-induced leukocyte adhesion and microvascular dysfunction. *Arterioscler Thromb Vasc Biol* 17: 437–444, 1997
- Mabile L, Salvayre R, Bonnafé MJ, Nègre-Salvayre A: Oxidizability and subsequent cytotoxicity of chylomicrons to monocytic U937 and endothelial cells are dependent on dietary fatty acid composition. *Free Radical Biol Med* 19: 599–607, 1995
- Marui N, Offermann MK, Swerlick R, Kunsch C, Rosen CA, Ahmad M, Alexander RW, Medford RM: Vascular cell adhesion molecule-1 (VCAM-1) gene transcription and expression are regulated through an antioxidant-sensitive mechanism in human vascular endothelial cells. *J Clin Invest* 92: 1866–1874, 1993
- McEver RP, Beckstead JH, Moore KL, Marshall-Carlson L, Bainton DF: GMP-140, a platelet alpha-granule membrane protein, is also synthesized by vascular endothelial cells and is localized in Weibel-Palade bodies. *J Clin Invest* 84: 92–99, 1989
- McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGrath LT, Henry WR, Andrews JW, Hayes JR: Dietary fish oil augments nitric oxide production or release in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 36: 33–38, 1993
- Minor RJ, Myers PR, Guerra RJ, Bates JN, Harrison DG: Diet-induced atherosclerosis increases the release of nitrogen oxides from rabbit aorta. *J Clin Invest* 86: 2109–2116, 1990
- Moers A, Fenselau S, Schrezenmeir J: Chylomicrons induce E-Selectin and VCAM-1 expression in endothelial cells. *Exp Clin Endocrinol Diab* 105 (Suppl 2): 35–37, 1997
- Moers A, Schrezenmeir J: Palmitic acid but not stearic acid inhibits NO-production in endothelial cells. *Exp Clin Endocrinol Diab* 105 (Suppl 2): 78–80, 1997
- Morel DW, DiCorleto PE, Chisholm GM: Endothelial and smooth muscle cells alter low density lipoprotein in vitro by free radical oxidation. *Arteriosclerosis* 4: 357–364, 1984
- Murakami K, Chan SY, Routtenberg A: Protein kinase C activation by cis-fatty acid in the absence of Ca and phospholipids. *J Biol Chem* 261: 15424–15429, 1986
- Naruszewicz M, Wozny E, Mirkiewicz E, Nowicka G, Szostak WB: The effect of thermally oxidized soya bean oil on metabolism of chylomicrons: increased uptake and degradation of oxidized chylomicrons in cultured mouse macrophages. *Atherosclerosis* 66: 45–53, 1987
- Nordestgaard BG, Tybjaerg-Hansen A: IDL, VLDL, chylomicrons and atherosclerosis. *Eur J Epidemiol* 8 (Suppl 1): 92–98, 1992
- O'Brien KD, Allen MD, McDonald TO, Chait A, Harlan JM, Fishbein J, McCarty J, Ferguson M, Hudkins K, Benjamin CD, Lobb R, Alpers CE: Vascular cell adhesion molecule-1 is expressed in human atherosclerotic plaques: implications for the mode of progression of advanced coronary atherosclerosis. *J Clin Invest* 92: 945–951, 1993
- Ohgushi M, Kugiyama K, Fukunaga K, Murohara T, Sugiyama S, Miyamoto E, Yasue H: Protein kinase C inhibitors prevent impairment of endothelium-dependent relaxation by oxidatively modified low-density lipoprotein. *Arterioscler Thromb* 13: 1525–1523, 1993
- Okuda Y, Kawashima K, Sawada T, Tsurumaru K, Asano M, Suzuki S, Soma M, Nakajima T, Yamashita K: Eicosapentaenoic acid enhances nitric oxide production by cultured human endothelial cells. *Biochem Biophys Res Commun* 232: 487–491, 1997
- Ordway RW, Singer JJ, Walsh JV: Direct regulation of ion channels by fatty acids. *TINS* 14: 96–100, 1991
- Palmer RMJ, Ashton DS, Moncada S: Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature* 333: 664–666, 1988
- Parthasarathy S, Steinbrecher IP, Barnett J, Witztum JL, Steinberg D: Essential Role of phospholipase A2 activity in endothelial cell-induced modification of low density lipoprotein. *Proc Natl Acad Sci USA* 82: 3000–3004, 1985
- Parthasarathy S, Fong LG, Otero D, Steinberg D: Recognition of solubilized apoproteins from delipidated, oxidized low density lipoprotein (LDL) by the acetyl-LDL receptor. *Proc Natl Acad Sci USA* 84: 537–540, 1987
- Patsch JR, Miesenböck G, Hopferwieser T, Mühlberger V, Knapp E, Dunn JK, Gotto AM Jr, Patsch W: Relation of triglyceride metabolism and coronary artery disease. *Arterioscler Thromb* 12: 1336–1345, 1992
- Pelkonen R, Nikkilä EA, Koskinen S, Penttinen K, Sarna S: Association of serum lipids and obesity with cardiovascular mortality. *Br Med J* 2: 1185–1187, 1977
- Piatti PM, Monti LD, Conti M, Baruffaldi L, Galli L, Phan CV, Guazzini B, Pontiroli AE, Pozza G: Hypertriglyceridemia and hyperinsulinemia are potent inducers of endothelin-1 release in humans. *Diabetes* 45: 316–321, 1996
- Pober JS, Cotran RS: What can be learned from the expression of adhesion molecules in tissues? *Lab Invest* 64: 301–305, 1991
- Pober JS, Gimbrone MA Jr, Lapierre LA, Fiers W, Rothlein R, Springer TA: Overlapping patterns of activation by human endothelial cells by interleukin 1, tumor necrosis factor and immune interferon. *J Immunol* 137: 1893–1896, 1986

- Poston RN, Haskard DO, Coucher JR, Gall NP, Johnson-Tidey R: Expression of intercellular adhesion molecule-1 in atherosclerotic plaques. *Am J Pathol* 140: 665–673, 1992
- Proctor SD, Mamo JCL: Arterial fatty lesions have increased uptake of chylomicron remnants but not low-density lipoproteins. *Coron Artery Dis* 7: 239–245, 1996
- Quinn MT, Parthasarathy S, Steinberg D: Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. *Proc Natl Acad Sci USA* 85: 2805–2809, 1988
- Radomski MW, Palmer RMJ, Moncada S: The anti-aggregatory properties of vascular endothelium: interactions between prostacyclin and nitric oxide. *Br J Pharmacol* 92: 639–646, 1987
- Rajavashisth TD, Analibi A, Territo MC, Berliner JA, Navab M, Fogelman AM, Lusis AJ: Induction of endothelial cell expression of granulocyte and macrophage colony-stimulating factors by modified low-density lipoproteins. *Nature* 344: 254–257, 1990
- Rapoport RM, Murad F: Agonist-induced endothelium-dependent relaxation in rat thoracic aorta may be mediated through cGMP. *Circ Res* 52: 352–357, 1983
- Richardson M, Hadcock SJ, DeReske M, Cybulsky MI: Increased expression in vivo of VCAM-1 and E-selectin by the aortic endothelium of normolipemic and hyperlipemic rabbits. *Arterioscler Thromb* 14: 760–769, 1994
- Rohde LE, Lee RT, Rivero J, Jamacochian M, Arroyo LH, Briggs W, Rifai N, Libby P, Creager MA, Ridker PM: Circulating cell adhesion molecules are correlated with ultrasound-based assessment of carotid atherosclerosis. *Arterioscler Thromb Vasc Biol* 18: 1765–1770, 1998
- Ross R: The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 362: 801–809, 1993
- Saxena U, Kulkarni NM, Ferguson E, Newton RS: Lipoprotein lipase-mediated lipolysis of very low density lipoproteins increases monocyte adhesion to aortic endothelial cells. *Biochem Biophys Res Comm* 189: 1653–1658, 1992
- Schmidt AM, Hori O, Chen JX, Li JF, Crandall J, Zhang J, Cao R, Yan SD, Brett J, Stern D: Advanced glycation endproducts interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. A potential mechanism for the accelerated vasculopathy of diabetes. *J Clin Invest* 96: 1395–1403, 1995
- Schneemann BO, Kotite L, Todd KM, Havel RJ: Relationships between the responses of triglyceride-rich lipoproteins in blood plasma containing apolipoproteins B<sub>48</sub> and B<sub>100</sub> to a fat containing meal in normolipidemic humans. *Proc Natl Acad Sci USA* 90: 2069–2073, 1993
- Schrezenmeir J, Weber P, Probst R, Biesalski HK, Luley C, Prellwitz W, Krause U, Beyer J: Postprandial pattern of triglyceride-rich lipoprotein in normal-weight humans after an oral lipid load: exaggerated triglycerides and altered insulin response in some subjects. *Ann Nutr Metab* 36: 186–196, 1992
- Schrezenmeir J, Keppler I, Fenselau S, Weber P, Biesalski HK, Probst R, Laue C, Zuchhold HD, Prellwitz W, Beyer J: The phenomenon of a high triglyceride response to an oral lipid load in healthy subjects and its link to the metabolic syndrome. *Ann NY Acad Sci* 683: 302–314, 1993
- Schrezenmeir J: Hyperinsulinemia, hyperproinsulinemia and insulin resistance in the metabolic syndrome. *Experientia* 52: 426–432, 1996
- Schrezenmeir J, Fenselau S, Keppler I, Abel J, Orth B, Laue C, Sturmer W, Fauth U, Halmagyi M, März W: Postprandial triglyceride high response and the metabolic syndrome. *Ann NY Acad Sci* 827: 353–368, 1997
- Sethi S, Eastman A, Eaton JW: Inhibition of phagocyte-endothelium interactions by oxidized fatty acids: A natural anti-inflammatory mechanism? *J Lab Clin Med* 128: 27–38, 1996
- Simons LA, Dwyer T, Simons J, Bernstein L, Mock P, Poonia NS, Balasubramaniam S, Baron D, Branson J, Morgan J, Roy P: Chylomicrons and chylomicron remnants in coronary artery disease: a case-control study. *Atherosclerosis* 65: 181–189, 1987
- Simpson HS, Williamson CM, Olivecrona T, Pringle S, Maclean J, Lorimer AR, Bonnefous F, Bogaeievsky Y, Packard CJ, Sheperd J: Postprandial lipemia, fenofibrate and coronary artery disease. *Atherosclerosis* 85: 193–202, 1990
- Speidel MT, Booyse FM, Abrams A, Moore MA, Chung BH: Lipolyzed hypertriglyceridemic serum and triglyceride-rich lipoprotein cause lipid accumulation in and are cytotoxic to cultured human endothelial cells. High density lipoproteins inhibit this cytotoxicity. *Thromb Res* 58: 251–258, 1990
- Staprans I, Pan XM, Miller M, Rapp JH: Effect of dietary lipid peroxides on metabolism of serum chylomicrons in rats. *Am J Physiol* 264: G561–G568, 1993
- Staprans I, Rapp JH, Pan XM, Kim KY, Feingold KR: Oxidized lipids in the diet are a source of oxidized lipid in chylomicrons of human serum. *Arterioscler Thromb* 14: 1900–1905, 1994
- Steinbrecher UP, Parthasarathy S, Leake DS, Witztum JL, Steinberg D: Modification of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. *Proc Natl Acad Sci USA* 81: 3883–3887, 1984
- Steinbrecher OP: Oxidation of human low density lipoprotein results in derivatization of lysine residues of apolipoprotein B by lipid decomposition products. *J Biol Chem* 262: 3603–3608, 1987
- Steiner M, Reinhardt KM, Krammer B, Ernst B, Blann AD: Increased levels of soluble adhesion molecules in type 2 (non-insulin dependent) diabetes mellitus are independent of glycaemic control. *Thromb Haemost* 72: 979–984, 1994
- Sugiyama S, Kugiyama K, Ogata N, Doi H, Ota Y, Ohgushi M, Matsumura T, Oka H, Yasue H: Biphasic regulation of transcription factor nuclear factor- $\kappa$ B activity in human endothelial cells by lysophosphatidylcholine through protein kinase C-mediated pathway. *Arterioscler Thromb Vasc Biol* 18: 568–576, 1998
- Sultana C, Shen Y, Rattan V, Kalra VK: Lipoxigenase metabolites induced expression of adhesion molecules and transendothelial migration of monocyte-like HL-60 cells is linked to protein kinase C activation. *J Cell Physiol* 167: 477–487, 1996
- Takahashi K, Ghatei MA, Lam HC, O'Halloran DJ, Bloom SR: Elevated plasma endothelin in patients with diabetes mellitus. *Diabetologia* 33: 306–310, 1990
- Tanner FC, Noll G, Boulanger CM, Lüscher TF: Oxidized low density lipoproteins inhibit relaxations of porcine coronary arteries. Role of Scavenger receptor and endothelium-derived nitric oxide. *Circulation* 83: 2012–2020, 1991
- Toborek M, Barger SW, Mattson MP, Barve S, McClain CJ, Hennig B: Linoleic acid and TNF $\alpha$  cross-amplify oxidative injury and dysfunction of endothelial cells. *J Lipid Res* 37: 123–135, 1996
- Turpeinen AM, Basu S, Mutanen M: A high linoleic acid diet increases oxidative stress in vivo and affects nitric oxide metabolism in humans. *Prostaglandins Leukot Essent Fatty Acids* 59: 229–233, 1998
- Verbeuren T, Jordaens F, Zonnekeyn L, Van Howe C, Coene M, Herman A: Effect of hypercholesterolemia on vascular reactivity in the rabbit: 1. Endothelium-dependent and endothelium-independent contractions and relaxations in isolated arteries of control and hypercholesterolemic rabbits. *Circ Res* 58: 552–564, 1986
- Vogel RA, Corretti MC, Plotnick GD: Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol* 79: 350–354, 1997
- Weber Ch, Erl W, Pietsch A, Danesch U, Weber PC: Docosa-hexaenoic acid selectively attenuates induction of vascular cell

- adhesion molecule-1 and subsequent monocytic cell adhesion to human endothelial cells stimulated by tumor necrosis factor- $\alpha$ . *Arterioscler Thromb Vasc Biol* 15: 622–628, 1995
- Weintraub MS, Grosskopf I, Rassin T, Miller H, Charach G, Rotmensch HH, Liron M, Rubinstein A, Iaina A: Clearance of chylomicron remnants in normolipidaemic patients with coronary artery disease. *BMJ* 312: 936–939, 1996
- Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332: 411–415, 1988
- Young VM, Toborek M, Yang F, McClain CJ, Hennig B: Effect of linoleic acid on endothelial cell inflammatory mediators. *Metabolism* 47: 566–572, 1998
- Yu KC, Mamo JC: Binding and uptake of chylomicron remnants by cultured arterial smooth muscle cells from normal and Watanabe-heritable-hyperlipidemic rabbits. *Biochim Biophys Acta* 1346: 212–220, 1997
- Zeitler H, Ko Y, Zimmermann C, Nickenig G, Glanzer K, Walger P, Sachinidis A, Vetter H: Elevated serum concentrations of soluble adhesion molecules in coronary artery disease and acute myocardial infarction. *Eur J Med Res* 2: 389–394, 1997
- Zilversmit DB: A proposal linking atherogenesis to the interaction of endothelial lipoprotein lipase with triglyceride-rich lipoproteins. *Circ Res* 33: 633–638, 1973
- Zilversmit DB: Atherogenesis: A postprandial phenomenon. *Circulation* 60: 473–485, 1979

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