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Pleiotropic effects of niacin: Current possibilities for its clinical use

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Niacin was the first hypolipidemic drug to significantly reduce both major cardiovascular events and mortality in patients with cardiovascular disease. Niacin favorably influences all lipoprotein classes, including lipoprotein[a],and belongs to the most potent hypolipidemic drugs for increasing HDL-C. Moreover, niacin causes favorable changes to the qualitative composition of lipoprotein HDL. In addition to its pronounced hypolipidemic action, niacin exerts many other, non-hypolipidemic effects (*e.g.*, antioxidative, anti-inflammatory, antithrombotic), which favorably influence the development and progression of atherosclerosis. These effects are dependent on activation of the specific receptor HCA2. Recent results published by the two large clinical studies, AIM-HIGH and HPS2-THRIVE, have led to the impugnation of niacin's role in future clinical practice. However, due to several methodological flaws in the AIM-HIGH and HPS2-THRIVE studies, the pleiotropic effects of niacin now deserve thorough evaluation. This review summarizes the present and possible future use of niacin in clinical practice in light of its newly recognized pleiotropic effects.

Keywords: niacin, pleiotropic effects, HCA2 receptor, dyslipidemia, cardiovascular mortality/morbidity

INTRODUCTION

Niacin (pyridine-3-carboxylic acid, nicotinic acid, vitamin B_3,) was the first drug to significantly reduce major cardiovascular events and mortality in patients with documented myocardial infarction, as described in the randomized, double-blind CDP (coronary drug project) study (1). Even nine years after termination of the trial, mortality in the niacin group was 11 % lower than in the placebo group (2). Niacin, at a daily dose of 2–3 g, increases the

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HDL-cholesterol level by about 15–40 %, lowers triacylglycerols (TAG) by 20–50 %, LDL-cholesterol by 5–25 % and lipoprotein[a] (Lp[a]) by 20 % (3, 4). As regards increasing HDL-C, niacin is the most powerful drug of all the known lipid-lowering drugs. It has been shown that an increase in HDL due to niacin exceeds that of fibrate treatment approximately 1.6-fold (5). Niacin increases the formation of HDL in the liver by stimulating phospholipids/cholesterol efflux through transcription of the ABCA1 gene (6, 7) *via* the DR4-dependent transcription pathway (8). Moreover, as well as increasing HDL-C, niacin causes changes to the qualitative composition of lipoprotein HDL in that it selectively increases plasma HDL particles containing mainly apoA-I (LP-AI, HDL subclasses with cardio-protective properties) on the expense of HDL particles containing both apoA-I and A-II (LP-AI+AII) (9).

Lipoprotein HDL does not only increase reverse cholesterol transport (RCT) capacity by activating the ABCA1 transporter, but it also has additional effects: (*i*) anti-inflammatory – HDL inhibits the expression of VCAM-1, ICAM-1 and E-selectin in the vascular wall; (*ii*) antithrombotic – HDL suppresses blood platelet aggregation, binding of fibrinogen and secretion of thromboxane A; (*iii*) pro-fibrinolytic – HDL downregulates plasminogen activator inhibitor-1 (PAI-1) and upregulates the tissue plasminogen activator (t-PA); (*iv*) antioxidative – dependent on apolipoprotein A-I and enzymes such as paraoxonase 1, LCAT, glutathione selenoperoxidase (GSPx) and lipoprotein-associated phospholipase A2 (Lp-PLA2) (for a review, see refs. 10, 11).

Interestingly, in most studies, niacin has been combined with other lipid-lowering drugs. In the Stockholm ischaemic heart disease secondary prevention study (12), the combination of niacin with clofibrate decreased cardiovascular mortality by 36 % and total mortality by 26 %. In the angiographic studies CLAS (Cholesterol lowering atherosclerosis study) (13) and FATS (Familial atherosclerosis treatment study) (14), niacin was combined with colestipol: decreased progression and occasional regression of atherosclerotic lesions were reported along with a coincident decrease in cardiovascular events. Results from two large controlled studies (AIM-HIGH and HPS2-THRIVE) were published recently (15). HPS2-THRIVE collaborative group 2014 (16) questioned the use of niacin as a hypolipidemic drug. Both of these studies were multicenter (and in the case of HPS2-THRIVE also multiethnic), with a large number of participants, and with primary end points covering a broad range of events, including nonfatal MI, CHD death, ischemic stroke, as well as hospitalization for revascularization. Furthermore, the HPS2-THRIVE study was by far the largest niacin study at the time (17). It was concluded that the addition of niacin to statin treatment does not significantly reduce the risk of major vascular events but does increase the risk of serious adverse events. Nevertheless, in addition to its lipid metabolism-modifying action, niacin treatment is associated with multiple non-hypolipidemic effects, which favorably affect the development and progression of atherosclerosis and its complications.

These effects certainly warrant comprehensive evaluation, especially given the criticism leveled at the methodological flaws contained in the published results of the AIM-HIGH and HPS2-THRIVE studies (18–23). Indeed, both of these studies have serious drawbacks (see above): the AIM-HIGH study was underpowered, low-dose niacin was administered to patients in the placebo-group (18) and it suffered from selection bias (patients with triacylglycerols above 400 mg per 100 mL were excluded) (20). A relatively higher proportion of non-Caucasians (more than 11,000 Chinese probands, who have a higher risk of side-effects than other patient subgroups) were enrolled in the HPS2-THRIVE study (16, 22). The design of both studies ignored the pharmacokinetics of ER niacin (meal time

vs. bedtime dosages) (17, 20). The AIM-HIGH study was terminated prematurely; and the combination of niacin with laropiprant, a prostaglandin-D2 receptor antagonist, did not account for the adverse effects of laropiprant when administered exclusively (immune dysfunction, gastrointestinal bleeding, attenuation of reverse cholesterol transport) (21).

The aim of this article is to survey the pleiotropic effects of niacin on atherosclerosis, namely risk factors such as endothelial dysfunction, subclinical inflammation, the procoagulant state, oxidative stress and the metabolic/endocrine functioning of the liver, adipose tissue and pancreas. Moreover, this review summarizes the present and possible future niacin use in clinical practice.

MECHANISMS OF THE ANTIATHEROGENIC EFFECTS OF NIACIN

Niacin exerts most of its effects after binding to specific receptors. Niacin is an agonist for the G-protein-coupled receptor known as hydroxycarboxylic acid receptor 2 (HCA2, formerly known as GPR109A, HM74a and NIACR1) with endogenous ligand β-hydroxybutyrate. Lactate is recognized as an endogenous ligand for GPR81 (HCA1 receptor) and 3-hydroxyl-octanoic acid has been found to be a ligand for GPR109B (HCA3 receptor, HM74, NIACR2) (24). HCA2 is expressed in adipocytes, neutrophils, macrophages, Langerhans cells and keratinocytes (Fig. 1). Activation of HCA2, a G protein-coupled membrane receptor, in adipocytes leads to inhibition of adenylate cyclase, decreased cAMP response, reduced activity of protein kinase A and decreased hormone-sensitive lipase activity, which in turn reduces lipolysis (24). Reduced flux of non-esterified fatty acids (NEFA) to the liver leads to decreased VLDL secretion. It is also connected with suppressed expression of the PPARγ coactivator-1β (PGC-1β) and apolipoprotein C-III, with subsequent decreased secretion and increased turnover of VLDL (25). Further, in the liver, niacin enhances degradation of apolipoprotein B, inhibits the reuptake of HDL by inhibiting specific receptors (the surface-expressed ATP-synthase β-chain) (26) and non-competitively inhibits liver diacylglycerol acyltransferase-2 (DGAT 2) (27).

Activation of HCA2 in combination with niacin exerts anti-inflammatory effects in endothelial cells (28), adipocytes (29) and human monocytes (30), which are associated with reduced vascular inflammation and the anti-atheromatous effects of niacin (Fig. 1).

Niacin and endothelial dysfunction

Endothelial dysfunction (ED) is a condition characterized by an impaired ability to regulate vascular tonus, which results in a shift in the actions of the endothelium towards reduced vasodilation, a proinflammatory state and prothrombotic properties (31). Moreover, oxidative stress (OS) and systemic low-grade as well as vascular inflammation are closely connected with endothelial dysfunction. According to the current knowledge, ED is considered to be the initial phase in the development of arterial hypertension and atherosclerosis (32, 33). Oxidative stress, as a consequence of enhanced generation of reactive oxygen and nitrogen species (RONS), is a main risk factor of ED. OS suppresses the production of endothelial nitrogen oxide (NO) and inhibits its vasorelaxation effects.

Dyslipidemia and vascular inflammation are among the other risk factors for ED. Niacin has been found to improve endothelial dysfunction. Experimental studies of Ganji *et al*. (34) have shown that niacin reduces vascular OS and inflammation. The same authors

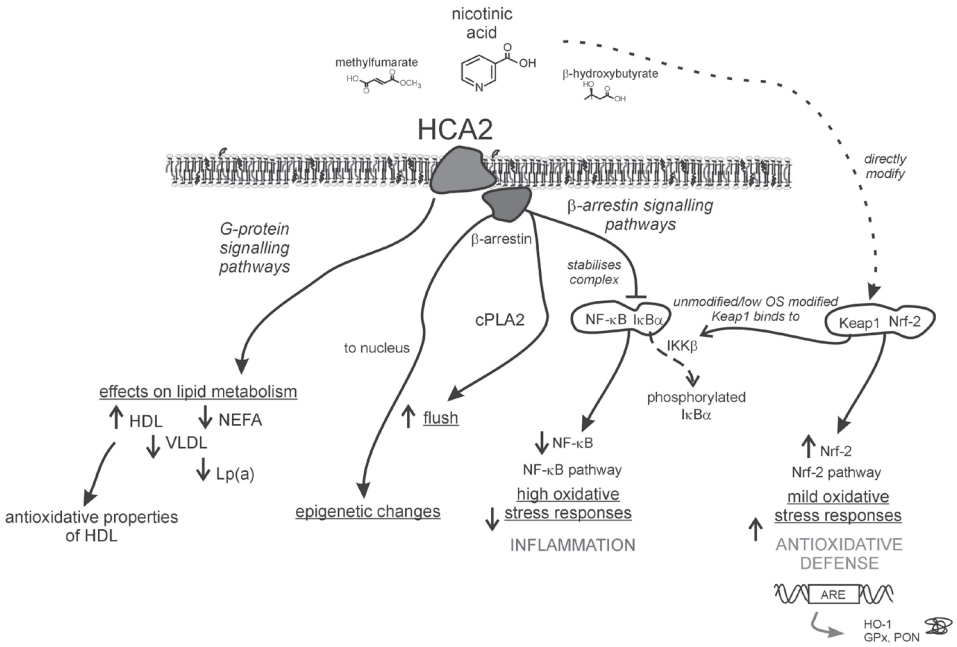

Fig. 1. Summary of the effects of nicotinic acid. The effects of niacin are mediated by its binding to the HCA2 receptor (formerly GPR109A; natural ligand: β-hydroxybutyrate), which is expressed on the surface of many cell types, or by unknown mechanisms through which niacin influences hepatocytes and endothelial cells.

have found that in cultured human aortic endothelial cells (HAEC) niacin increases nicotinamide adenine dinucleotide phosphate (NAD(P)H), reduces glutathione (GSH) and inhibits angiotensin II (ANG II)-induced RONS production, low-density lipoprotein (LDL) oxidation, tumor necrosis factor α (TNFα)-induced NF-κB activation, vascular cell adhesion molecule-1 (VCAM-1), monocyte chemotactic protein-1 (MCP-1) secretion and TNFα-induced monocyte adhesion to HAEC. In another study (35), in endothelial cells (HUVEC), niacin significantly reduced ICAM-1 (intercellular adhesion molecule 1) and PECAM-1 (platelet/endothelial cell adhesion molecule 1) levels, and lowered the cytokine-induced rise in ICAM-1 and the TNFα-induced rise in PECAM-1.

Niacin, after binding to HCA2 in adipocytes, increases the secretion of adiponectin (36), which has an anti-inflammatory and antioxidative effect on the vascular wall and improves ED (37). One of the clinically pursuable surrogate markers of ED is FMD (flow-mediated-dilation). Patients with coronary artery disease and low concentrations of HDL-C were proven to exhibit improved FMD parameters in one study (38). On the other hand, in a recent meta-analysis, the FMD-improving effect of niacin reached statistical significance only in the primary prevention of atherosclerotic cardiovascular disease, where improved FMD was associated with higher doses of niacin (39). In a small study on twenty-six patients treated with 1500 or 2000 mg niacin for 6 weeks, there was a significant reduction in plasma levels of ADMA (asymmetric dimethylarginine), which causes endothelial dysfunction through the competitive inhibition of NO synthase (40).

Niacin and oxidative stress

Transcription factor Nrf2 (nuclear erythroid 2 p45-related factor 2) and its inhibitor Keap 1 (Kelch-like ECH-associated protein1) are believed to play key roles in the regulation of homeostatic mechanisms that influence conditions linked with higher levels of oxidative stress or inflammation (33). Niacin may also have a specific role in the modulation of Nrf2 activity (41). For further information, see Fig. 2.

The antioxidative effects of niacin can be divided into indirect effects, accomplished *via* increased concentrations of HDL (see above), and direct effects or „lipid-independent" effects, which are mediated through the activation of Nrf2, as has been shown in New Zealand white rabbits (41). In experimental studies, niacin exerts beneficial effects on various parameters of oxidative stress. In rats with chronic renal failure, niacin has been shown to decrease levels of two components [p47(phox) and p22(phox)] of the NADPH oxidase system, which is an important source of superoxide molecules. Concomitantly in the same study, prothrombotic and inflammatory parameters (MCP-1, PAI-1, TGFβ COX-1, activation of NF-κB) decreased, and the extent of proteinuria, glomerulosclerosis and tubulointersticial lesions was corrected (42). In another *in vitro* study carried out on HAEC cells, niacin was proven to lower the production of reactive oxygen species (ROS) with the

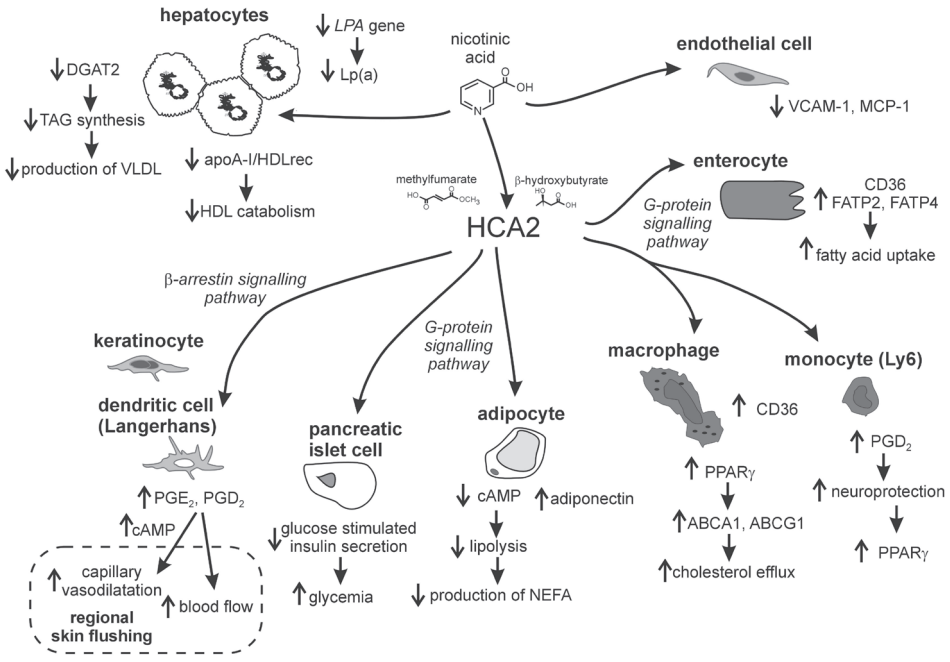

Fig. 2. HCA2 mechanisms and oxidative stress. Activation of the HCA2 receptor brings about G-protein-dependent signaling and recruitment of b-arrestins. G-protein pathways have many effects on lipid metabolism. β-arrestins stabilize the IκBα complex, thereby preventing NF-κB dissociation and consequent inflammatory responses. In addition, some HCA2 ligands are supposed to interact directly with the redox state domain of the Keap1 protein, resulting in Nrf-2 translocation into the nucleus and upregulation of genes with ARE promoter domains.

consequent oxidation of LDL and inhibition of VCAM-1 and MCP-1, which play an important role in the pathogenesis of atherosclerosis (34). A recently published study has shown that niacin treatment of paraquat-intoxicated rats decreases serum concentrations of 8-hydroxy-2′-deoxyguanosine (a marker of oxidative damage of DNA) as well as levels of tissue malondialdehyde (MDA), which is an indicator of lipoperoxidation (43). In a clinical study of 17 FHC patients with lowered HDL-C levels, niacin caused expected changes in plasma lipid concentrations and it decreased the levels of thiobarbituric acid reactive substances, lipid peroxides and paraoxonase activity (44). In the group of patients treated with rosuvastatin and additional ER NA, the concentrations of ox-LDL were lower than in those on add-on fenofibrate therapy (45). This effect was specific for rosuvastatin among other statins (simvastatin and atorvastatin).

Niacin and inflammation

Niacin has anti-inflammatory properties, which can be described according to the antioxidative effects as either indirect (stimulation of anti-inflammatory HDL synthesis) or direct. These effects stem from the activation of the receptor HCA2 in monocytes/macrophages, adipose tissue and vessel endothelium. These direct anti-inflammatory effects of niacin have been proven in experiments carried out on double knockout mice ($Ldlr^{-/-}$& $HCA2^{-/-}$) (46). Within vessel endothelium, the expression of cytoadhesive molecules (VCAM-1, ICAM-1, E-selectins) is inhibited. Furthermore, in adipose tissue, niacin suppresses TNFα-stimulated expression and secretion of proinflammatory cytokines – MCP-1, RANTES and the fractalkines supporting the recruitment of T-lymphocytes and macrophages into atherosclerotic lesions (29). In monocytes, niacin inhibits TLR-4- and TLR-2-induced expression as well as the secretion of TNFα, IL-6, and MCP-1 (30). In rats, high doses of niacin attenuated lung inflammation and improved survival during sepsis while simultaneously down-regulating the NF-κB pathway (47). Moreover, niacin can stimulate expression and secretion of adiponectin – a protein with a broad spectrum of anti-inflammatory and cardioprotective effects (see below) (24). In an *in vitro* experiment carried out on human umbilical vein endothelial cells (HUVEC) and macrophages, niacin was shown to decrease the secretion of IL-6 and TNFα and was accompanied with the inhibition of NF-κB (p65 and notch1) (48). Guinea pigs were fed a high-fat diet and under niacin administration exhibited downregulated expression of CD36 and NF-κB p65 in the arterial wall (30). The described anti-inflammatory changes were independent of modifications to lipid and eicosanoid concentrations (30).

Niacin administration to patients with stable CAD leads to a significant decrease in concentrations of high-sensitivity C-reactive protein (hs-CRP) by up to 15 % and lipoprotein-associated phospholipase A2 by up to 20 % (49). In patients with metabolic syndrome, ER niacin improved endothelial function (FMD) by 22 %, reduced hs-CRP by 20 %, and caused significant regression of carotid IMT in comparison with placebo (50).The baseline level of CRP is a strong independent predictor of the risk of future myocardial infarction, peripheral vascular disease, stroke and vascular death among healthy individuals without known vascular disease (51).

A murine experimental model of atherosclerosis was employed to examine the mechanisms at play in the antiatherogenic effects of niacin. Niacin-induced activation of HCA2 receptors expressed in macrophages within atheromatous plaques brought about higher expression of cholesterol transporter ABCG1 with consequent efflux of cholesterol. On the

other hand, it inhibited MCP-1-induced recruitment of macrophages (46). Activation of HCA2 has been shown to induce an anti-inflammatory response in macrophages and dendritic cells in the colon and enables them to support differentiation of T-regulatory lymphocytes and IL-10-producing T cells (52). It is believed that activation of HCA2 with butyrate (which is produced by an intestinal microbiome) is a part of the mechanism by which the intestinal microbiome can suppress inflammatory and pro-cancerogenic processes within the intestine. Similar effects have been ascribed to niacin administration within a pharmacological range (52).

Niacin in procoagulative and prothrombotic states

Niacin also attenuates cardiovascular risk due to its beneficial effects on the factors of coagulation and thrombolysis, some of which have been previously identified as risk factors of atherothrombotic processes. Niacin lowers the activity of coagulation factor VII, levels of fibrinogen, PAI-1 and the tissue factor (53–55). These factors are considered as independent predictors of cardiovascular disease (56–60). Niacin, as a consequence of its hypolipidemic effects, has been shown to reduce thrombocyte aggregation and blood viscosity (55). In another study of 50 patients with hyperlipidemia, niacin diminished thrombocyte counts by 20 %. Concomitantly, it led to a mild increase in MPV (mean platelet volume), which is a risk factor for atherothrombotic events. However, there was no subsequent rise in PDW (platelet distribution width) – a sign of thrombocyte activation (61). The pre-incubation of platelets with niacin inhibits their activation *via* interaction with the activated endothelium (62).

Niacin as well as omega-3 polyunsaturated fatty acids have been shown to reduce levels of lipoprotein[a] (63, 64). Lipoprotein[a] is a macromolecular complex assembled from one particle of LDL and one glycoprotein molecule of apolipoprotein[a]. Apo[a] is connected to LDL by a disulphide bond. Apo[a] is structurally homologous with plasminogen and is accountable for specific characteristics of Lp[a]. Lp[a] has been established as a risk factor of cardiovascular disease (CVD) and is not dependent on plasma lipid levels or other classical risk factors (65). The glycoprotein molecule of apo[a] has a strong structural homology to plasminogen and may account for the prothrombotic, pro-oxidative, proinflammatory and antifibrinolytic properties of Lp[a], which are the mechanisms that play an underlying role in atherogenesis (66). The atherogenicity of Lp[a] may be, in part, mediated by oxidized phospholipids associated with small apo[a] isoforms (67, 68). Moreover, niacin exerts *in vitro* effects on platelet activities due to its capacity to inhibit their aggregation along with the accompanying stimulation of prostaglandin release (thromboxane B2 and prostaglandins D2 and E2) (69).

Nevertheless, more studies should be done to elucidate the mechanism of niacin action on the Lp[a] levels in different clinical settings.

INFLUENCE OF NIACIN ON THE METABOLISM OF ADIPOSE TISSUE, LIVER AND PANCREAS

Effects of niacin on adiponectin levels

Niacin activation of the specific receptor HCA2 on adipocytes leads to an increase of adiponectin concentrations. This phenomenon has been detected only in young forms of

adipocytes. A natural ligand of HCA2 is beta-hydroxyl-butyrate. Differentiated adipocytes that do not express HCA2 receptors fail to secrete adiponectin after stimulation with niacin (36). Human adiponectin is a polypeptide of 30 kDa, containing 244 amino acid residues. This polypeptide is assembled into an array of complexes composed of multimers of 30 kDa polypeptide. Adiponectin subunits assemble into trimers [known as low molecular mass (LMW) complexes], hexamers [middle molecular mass (MMW)] or a more elaborate high molecular mass (HMW) complex composed of nine hexamers (70). The HMW form corresponds to the active form of adiponectin (71). Negative correlations have been found not only between serum adiponectin levels and the prevalence of coronary heart disease (CHD) (72) but also between adiponectin levels and the extensity and intensity of coronary lesions (73). In a prospective study, subjects with plasma adiponectin levels in the upper quintile were at a significantly lower risk of myocardial infarction in comparison with subjects in the lower quintile (odds ratio 0.39) (74). In an 18-year follow-up study, men with low adiponectin and low HDL-C values showed a 2.63 times (95 % CI, 1.66 to 4.15) increased incidence of diabetes mellitus type 2 and a 1.91 times (95 % CI, 1.20 to 3.04) increased incidence of CHD in comparison with men with high HDL-C and high adiponectin (75). On the other hand, some studies have found that high levels of adiponectin in patients with chronic heart failure (CHF) are associated with CHF severity and mortality (76–78). It has also been reported that the influence of niacin on HCA2 receptors in pancreatic islets is partially responsible for hyperglycemia. Niacin activation of HCA2 receptors in obese mice fed a high-fat diet has been shown to lead to partial dysfunction of pancreatic islets due to the induction of ROS formation and expression of PPARγ and UCP2 (79).

Influence of niacin on retinol-binding protein

One of the therapeutic targets of niacin is the lowering of retinol-binding protein 4 (RBP4) levels. RBP4 is a polypeptide of 21 kDa, which is mainly synthesized in the liver and adipocytes. The recognized function of RBP4 is vitamin A (retinol) transport. Elevated RBP4 concentrations contribute significantly to insulin resistance, as observed in obesity and diabetes mellitus type 2 in both rodents and humans (80, 81). Increasing serum RBP4 induces hepatic expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) and impairs insulin signaling in muscles (81). According to the results from the Atherosclerosis risk in community study (ARIC study), RBP4 levels may be directly involved in the pathogenesis of type 2 diabetes (T2DM) in women (82). Moreover, RBP4 may be involved in the pathophysiology of hypertriacylglycerolemia in T2DM by reducing VLDL catabolism (83). The lowering of serum RBP4 concentrations in obese mice has been shown to lead to normalization of serum RBP4 levels and to improvement in insulin sensitivity (81). Decreases in serum RBP4 levels occur independently of niacin activation of the HCA2 receptor. In experiments on mice, it was proposed that a decrease in niacin-dependent RBP4 is probably a result of increased RBP4 clearance (84).

Influence of niacin on fatty acid metabolism

Chronic treatment of a hyperlipidemic mouse model with niacin resulted in upregulation of genes involved in the unsaturated FA biosynthesis, mainly by Elovl6 (fatty acid elongase 6), Tecr (trans-2,3-enoyl-CoA reductase), and Elovl5 in gonadal white adipose tissue (gWAT). These changes were associated with increased release of DHA from gWAT

as well as increased ratio of DHA/arachidonic acid (AA) in plasma (85). It is known that plasma DHA/AA ratio has been shown to be a diagnostic marker for PUFA-associated cardiovascular health.

The study also reported a concomitant, increased ratio of DHA/AA along with elevated levels of the DHA metabolite 19,20-dihydroxy-docosapentaenoic acid (19,20-diHDPA), the precursor of the highly biologically active epoxy metabolite 19(20)-EpDPA. There were also significant correlations of both epoxy metabolites in serum.

These effects of niacin on adipose tissue and plasma PUFAs and oxylipins pose a potential contributing mechanism by which niacin treatment could reduce cholesterol levels and CVD risk. Epoxy-metabolites of eicosapentaenoic acid (EPA) and DHA could participate in the cardio-protective effects of PUFA n-3 and could be used as biomarkers in clinical studies in order to observe the influence of PUFA n-3 on the cardiovascular system (86). The abovementioned changes in the profiles of PUFA observed after niacin administration in experimental models reveal other potentially antiatherogenic and antithrombogenic effects of niacin, which should be verified in clinical trials.

POTENTIAL NOVEL CLINICAL INDICATIONS

Impact of niacin on non-alcoholic fatty liver disease

Results of experimental studies have shown that niacin treatment could favorably influence the course of non-alcoholic fatty liver disease (NAFLD), and probably also affect its etiopathogenesis. In rats with pre-existing liver steatosis induced by a high-fat diet, treatment with niacin led to considerable regression of steatosis. Niacin had no effect on the mRNA expression of fatty acid synthesis or oxidation genes but significantly inhibited mRNA levels, protein expression, and activity of diacylglycerol acyltransferase 2, a key enzyme in triacylglycerol synthesis (87).

In a murine model of steatohepatitis, niacin dramatically ameliorated the established steatohepatitis and dyslipidemia. In addition, atherogenic LDL fraction disappeared in fasting plasma and elevations in both postprandial NEFA and triacylglycerols were suppressed. Hepatic gene expression of lipogenic genes did not decrease, while expression of Fsp27 (fat-specific protein 27) decreased slightly (88). Fsp27 is a protein in adipocytes and regulates both basal and stimulated lipolysis by interacting with adipose triacylglycerol lipase (ATGL). FSP27-ATGL interactions play a crucial role in regulating lipolysis, triacylglycerol accumulation and insulin signaling in human adipocytes (89). So far, the effect of niacin treatment has not been explicitly proven in patients with NAFLD.

In a small, placebo-controlled study of obese patients with NAFLD and triacylglycerol levels under 3.4 mmol L^{-1}, a 16-week course of treatment with nicotinic acid (in a dose titrated to 2 g daily) had no effect on hepatic triacylglycerols content (90). In contrast, a study of patients with NAFLD and dyslipidemia (treated with niacin in increasing doses of up to 2 g daily over a period of 23 weeks) showed a statistically significant decrease in plasma triacylglycerols as well as reduction in the liver and visceral fat content. Simultaneously, the importance of the DGAT2 polymorphism rs3060 was identified, given that variant DGAT2 alleles (after adjustment for other covariates) were found to be connected with reduced effectiveness of niacin on the liver fat content (91).

Pleiotropic effect of niacin on chronic renal insufficiency

Niacin has a pleiotropic effect on the progression of disease in patients with chronic kidney disease (CKD). The main reason for morbidity and mortality in patients with CKD is cardiovascular disease (92, 93). The American Heart Association has recommended that patients with chronic impaired renal function should be classified in the highest risk group for developing cardiovascular events (94). High risk of CHD in persons with CKD is significantly affected by dyslipidemia (95).

The pathophysiology of dyslipidemia in CKD is complex. An important role is played by the abnormal composition and impaired clearance of triacylglycerol-rich lipoproteins and their remnants. This is caused by the down-regulation of lipoprotein lipase, hepatic lipase, the VLDL receptor, LDL receptor-related protein (LRP) and the reduction of ApoC-II/ApoC-III ratio, as well as other disturbances involved in lipid and lipoprotein metabolism (96). Increased levels of Lp[a], which is an independent risk factor of atherothrombosis, have also been identified in patients with CKD (97). Hyperphosphatemia is a further important risk factor of cardiovascular disease in persons with CKD (98).

Chronic renal insufficiency is characterized by impaired calcium-phosphate metabolism involving increased concentrations of phosphorus (99). Increased concentrations of serum phosphorus are associated with the manifestation of subclinical atherosclerosis as well as with the risk of CHD manifestations, even within limits of physiological values (100). In some studies, it has been demonstrated that nicotinic acid can reduce serum phosphorus (101, 102) by inhibiting sodium-dependent phosphate co-transporters in rat small intestine (103).

A meta-analysis of CKD studies has shown that niacin, or nicotinamide, reduces serum phosphorus levels and Ca-P products significantly, and that it has additive beneficial effects on lipid parameters (104). Niacin can contribute to the lowering of cardiovascular morbidity and mortality in patients with CKD as a result of its beneficial effect on both dyslipidemia and hyperphosphatemia. Moreover, it is the only hypolipidemic agent that lowers Lp[a] (105, 63, 64). Niacin has a unique favorable impact on factors affecting the rate of glomerular filtration decline, including number of high-density lipoprotein (HDL) particles and their function, triacylglycerol levels, oxidative stress, inflammation and endothelial function. It also lowers serum phosphorus levels by reducing dietary phosphorus absorption in the gastrointestinal tract (106). Niacin has been observed to work best in patients with lipid-profile characteristics of CKD, *i.e.*, patients with raised VLDL-TG and decreased HDL (107, 20). A significant reduction in proteinuria has also been identified in patients with CKD and hyperlipidemia treated with niacin (108).

UNWANTED EFFECTS OF NIACIN

Adverse effects of niacin are elaborated below. These effects are usually harmless but they can affect patient compliance. Some of them can be alleviated and there is continuing interest in niacin mimetics (109) that could circumvent metabolic pathways causing these effects.

Flush

The most common adverse effect in persons treated with niacin seems to be skin flushing, since about 70 % of persons receiving niacin suffer from this symptom (110). It

was suggested that flushing induced by niacin after its binding to receptor HCA2 results from an early phase of cyclooxygenase-1 dependent formation of prostaglandin D2 (PGD2) and PGE2 in Langerhans cells, followed by delayed cyclooxygenase-2 dependent production of PGE2 by keratinocytes (111). During long-term administration of niacin, tolerance to flushing develops rapidly in most individuals (112).

Gastrointestinal symptoms

Gastritis-like symptoms (such as nausea, abdominal pain) were found in 10–20 % of patients treated with IR (immediate release) nicotinic acid (6). In a small study, increased hydrochloric acid secretion was found in humans after 500 mg of nicotinic acid medication (113). Hepatotoxicity occurs predominantly at higher doses (more than 2 to 3 g per day) and in formulations with sustained release (SR-niacin), the metabolism of which is connected with production of nicotinamide and pyrimidine derivatives (114). The IR formulations of niacin in common therapeutic doses almost never cause serious liver injury (115).

Effect on glucose homeostasis and uric acid

Treatment with niacin may lead to increased insulin resistance in persons suffering from impaired glucose tolerance (116). Niacin causes insulin resistance and increases fasting serum glucose by 5 %. This increase subsides with long use of niacin (117). It was suggested that this effect could be related to the rebound increase in NEFA levels following the transient NEFA suppression induced by niacin (118), but this mechanism is questionable in long-term use of niacin (119). It was recently found in a mouse model that long-term niacin treatment resulted in insulin resistance that may be in part explained by a niacin-induced downregulation of the cAMP-degrading enzyme phosphodiesterase 3B (120) or modulated through activation of the islet beta-cell HCA2, which induce PPARγ – uncoupling protein 2 pathway (121). Moreover, HCA2 seems to play a role in jejunal glucose transport (122), which is enhanced in T2DM. In a recent meta-analysis, niacin therapy was associated with a moderately increased risk of developing diabetes regardless of the background statin or combination laropiprant therapy (123).

Nevertheless, the cardiovascular benefits of niacin were independent of fasting and 1 hour plasma glucose at baseline levels as well as after one year of therapy in the Coronary Drug Project (124).

Niacin can occasionally increase plasma uric acid levels by approximately 10 % due to competitive inhibition of tubular secretion of uric acid and induce gout in susceptible subjects (125). This effect may be due to interference with renal excretion of uric acid (126).

Other effects

Some ocular side-effects after niacin administration have been described, such as blurred vision, eyelid edema, proptosis, loss of eyelashes or macular edema. These symptoms are reversible and dose related. Most cases were found in patients in their third to fifth decades of life, who were treated with a higher dose (> 3 g of niacin per day). The mechanism of niacin's effect on the macula is unknown (127).

Acanthosis nigricans (128) or niacin-induced myopathy (129) belongs to other uncommon adverse effects of niacin. Niacin ER monotherapy has specifically amassed considerable clinical trial data that do not support an increased risk for muscle adverse experiences with niacin monotherapy (130).

CONCLUSIONS

Based on recent large clinical trials, niacin cannot be advocated as general adjunctive therapy to statins for the patients with hyperlipidemia. However, amongst those intolerant to statins, there are some subgroups that may benefit from niacin therapy, based on preclinical data and knowledge of its pleiotropic effects. Namely, (*i*) patients with a high risk of CHD with elevated Lp[a] levels; (*ii*) patients with severe hypertriacylglycerolemia, especially those intolerant to fibrates, (*iii*) patients with dyslipidemia associated with chronic kidney disease, and (*iv*) patients with non-alcoholic liver disease. The use of niacin in these subpopulations warrants further investigation.

Abbreviations, acronyms, symbols. – AA – arachidonic acid, ABC – ATP cassette binding transporter, ADMA – asymmetric dimethylarginine, apoA-I – apolipoprotein A-I, ARE – antioxidant responsive element, ATGL – adipose triacylglycerol lipase, CAD – coronary artery disease, cIMT – carotid intima media thickness, CHD – coronary heart disease, CHF – chronic heart failure, CKD – chronic kidney disease, COX-1 – cyclooxygenase 1, cPLA2 – cytosolic phospholipase A2, CRP – C-reactive protein, DGAT-2 – diacylglycerol acyltransferase 2, DHA – docosahexaenoic acid, ED – endothelial dysfunction, EPA – eicosapentaenoic acid, ER – extended release, FA – fatty acids, FATP – fatty acid transporting protein, FCH – familial hypercholesterolemia, FMD – flow-mediated dilation, GPR109A – G-protein coupled receptor 109A, *syn*. HCA2 receptor, GPx – glutathione peroxidase, GSH – glutathione, GSPx – glutathione selenoperoxidase, HAEC – human aortic endothelial cells, HCA2 – hydroxycarboxylic acid receptor 2 (formerly GPR109A), HO-1 – heme oxygenase 1, hs-CRP – high-sensitivity C reactive protein, HUVEC – human umbilical vein endothelial cells, ICAM-1 – intercellular adhesion molecule-1, IκBα – NF-κB inhibitor α, IKKβ – IκBα kinase β, IL – interleukin, Keap1 – Kelch-like ECH-associated protein1, LCAT – lecithin:cholesterol acyl transferase, Lp[a] – lipoprotein[a], Lp-PLA2 – lipoprotein associated phospholipase A2, LDL – low density lipoproteins, MCP-1 – monocyte chemotactic protein-1, MDA – malondialdehyde, NA – niacin, NAFLD – non-alcoholic fatty liver disease, NEFA – non-esterified fatty acids, NF-κB- nuclear factor κB, Nrf2 – nuclear erythroid 2 p45-related factor 2, PG – prostaglandin, OS – oxidative stress, ox-LDL – oxidatively modified LDL particles, PAI-1 – plasminogen activator inhibitor-1, PECAM-1 – platelet/endothelial cell adhesion molecule-1, PON – paraoxonase, PPARγ – peroxisome proliferator activated receptor γ, PUFA – polyunsaturated fatty acids, RANTES – regulated on activation, normal T cell expressed and secreted chemokine (*syn*. CCL5), RBP4 – retinol binding protein 4, RONS – reactive oxygen and nitrogen species, TAG – triacylglycerols, TBARS – thiobarbituric acid reactive substances, TGFβ – tumor growth factor β, TNFα – tumor necrosis factor α, t-PA – tissue plasminogen activator, T2DM – type 2 diabetes mellitus, UCP2 – uncoupling protein 2, VCAM – vascular cell adhesion molecule, VLDL – very low density lipoproteins.

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