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Preliminary report

Adipokines and treatment with niacin

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Abstract

Adipokines may serve as an important etiologic link between atherosclerosis and obesity. Because adipose tissue is one site of action of the lipid-lowering drug niacin, we investigated whether niacin treatment would affect not only lipids but also adipokines. Twenty-four patients were treated with extended-release niacin. During the first 4 weeks the daily dose was increased at weekly intervals from 375 to 1000 mg, which was maintained for 4 weeks. Thereafter, the dose was 1500 mg for another 6 weeks. Adiponectin increased by 54% and 94%, respectively, resistin was lowered only moderately, and leptin not at all. Because adiponectin has repeatedly been shown to be negatively associated with atherosclerotic risk, its pronounced increase may bring about additional atheroprotection by niacin beyond its improvement in lipids.

1. Introduction

Visceral obesity is closely associated with the development of cardiovascular diseases, although the underlying molecular mechanisms are still not fully understood. One possible link may be substances secreted by adipocytes, such as adiponectin, resistin, or leptin. Adiponectin is of particular interest because, unlike other adipokines, this abundant protein is the only known physiologic atheroprotective substance besides high-density lipoprotein (HDL) in humans. It is low in patients with obesity, insulin resistance, type 2 diabetes mellitus, and coronary artery disease, but high in lean individuals free from atherosclerosis. Its atheroprotective role may be based on influences on endothelial function such as expression of adhesion molecules, attachment of monocytes, and stimulation of nitric oxide production (for a review, see reference [1]). Furthermore, adiponectin has been suggested to be actively involved in the improvement of insulin resistance [2].

Adipose tissue is also a major site of action of the lipid-lowering drug niacin, which has recently attracted renewed interest in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 study [3] in which it was found to slow down the intima-media thickness in patients with coronary heart disease. Against this background we investigated whether the new extended-release niacin would not only alter lipid levels, but also affect the concentrations of the adipokines previously mentioned.

2. Methods

Twenty-four patients from the lipid clinic (20 males/4 females) with HDL cholesterol (HDL-C) of less than 0.9 mmol/L were included consecutively in this open-label treatment study. Their age and body mass index were 41 to 74 years and 21 to 42 kg/m^2, respectively. Patients with type III hyperlipoproteinemia, thyroid dysfunction, and creatinine >160 μmol/L (>1.8 mg/dL) were excluded. An ethics committee had approved the protocol, and all patients had given their written informed consent.

The patients and the investigators remained blinded to all laboratory results until the end of the study. The study medication was extended-release niacin (Niaspan, Merck, Darmstadt, Germany), taken shortly before sleeping. Twenty-four patients were treated with extended-release niacin. During the first 4 weeks the daily dose was increased at weekly intervals from 375 to 1000 mg, which was maintained for 4 weeks. Thereafter, the dose was 1500 mg for another 6 weeks.

At baseline and after the treatment periods with 1000 and 1500 mg, fasting blood samples were taken for determinations of lipids, adiponectin, leptin, and resistin. The samples were immediately cooled and serum was prepared within 2 hours and stored at −20°C. Triglycerides and cholesterol were determined by commercial enzymatic

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methods (Roche Diagnostics, Mannheim, Germany), as well as HDL-C, which was separated by a slight modification of a Lipid Research Clinics method. Glucose was determined by the hexokinase method on a Modular-System random-access analyzer (Roche Diagnostics) and insulin by commercial radioimmunoassay (BI-Insulin IRMA, BIO-RAD, Munich, Germany). The following formula was used: homeostatic assessment of insulin resistance (HOMA-IR) = fasting insulin (U/L) × fasting glucose (mmol/L)/22.5. Plasma resistin (BioVendor, Brno, Czech Republic) and adiponectin (BioCat, Heidelberg, Germany) were measured using enzyme-linked immunosorbent assays, and leptin with the leptin coated-tube immunoradiometric assay kit (DSL, Sinsheim, Germany). All samples were assayed in duplicate, samples from the same patient being measured in 1 run at the end of the study. The intra-assay coefficient of variation for the determination of leptin was 3.2%, for adiponectin 3.3%, and for resistin 2.8%. The inter-assay coefficients of variation were 5.4%, 5.7%, and 5.1%, respectively. Statistical analysis was performed using SPSS 10.0 software (SPSS, Chicago, IL). All results are expressed as means with SDs. The Wilcoxon signed rank test was used to test all differences before and after treatments with 1000 and 1500 mg niacin, respectively, for significance. The study was sponsored in part (12 patients for lipids) by Merck. The sponsor was not in any way involved in the study design, in collection, analysis, and interpretation of the data, or in writing and submission of the paper for publication.

3. Results

All patients finished the study according to the protocol. The extent of the lipid lowering was as expected on the basis of literature. A good patient compliance is indicated by the lowering of triglycerides and the increase of HDL-C after treatment with 1000 mg/d for 4 weeks as well as with 1500 mg/d for another 6 weeks (Table 1). With regard to the parameters of glucose homeostasis, slight increases in glucose, insulin, and the HOMA-IR index calculated from these 2 parameters did not reach the level of statistical significance. Adiponectin was raised from 4.83 ± 2.39 to 7.45 ± 5.71 μg/mL under 1000 mg niacin and to 9.35 ± 6.06 μg/mL under 1500 mg in 23 of 24 patients (both $P < .001$). This increase was independent of baseline adiponectin concentrations, HDL-C, BMI, and, age. Resistin was lowered only after 1000 mg niacin by 8.3% ($P < .028$). Leptin concentrations remained unchanged.

4. Discussion

The major result of this study is the marked increase in adiponectin. This increase by almost 100% is intriguing in the light of its negative association with the risk of atherosclerosis. Treatment with niacin virtually normalized adiponectin to its level in risk-free and lean individuals. At present it, is not possible to translate this increase into the health benefit, but when the lowest adiponectin quartile was compared with the highest quartile in a case-control study in 225 male patients undergoing coronary angiography, the odds ratio for risk of coronary artery disease was found to be 2.05 [4]. It is therefore possible that the increase in adiponectin after niacin brings about additional atheroprotection beyond the improvement in lipids. In this case this effect might be regarded, by analogy with effects after statin therapy, as a pleiotropic effect.

We can only speculate about the mechanisms underlying the increase in adiponectin by niacin. Synthesis and secretion of adiponectin have been reported to be modulated via a functional peroxisome proliferator-activated receptor (PPAR)-responsive element in the human adiponectin promoter. Rubic et al [5] have speculated that niacin stimulated translocation and transcription of PPAR-γ indirectly by stimulating prostaglandin D_2 and subsequently prostaglandin J_2, an endogenous ligand of PPAR-γ. A mechanism involving PPAR-γ would be in line with the action of thiazolidinediones [6], the only other drug class known to increase adiponectin. The moderate lowering of resistin in this study is also compatible with this hypothesis, because resistin, like adiponectin, is influenced via the PPAR-γ mechanism and has been shown to be lowered by rosiglitazone. Finally, this

Table 1
Lipids, adiponectin, leptin, resistin, and parameters of glucose homeostasis before and after therapy with, respectively, 1000 mg and then 1500 mg extended-release niacin

	Baseline	After therapy (n = 24) 1000 mg	After therapy (n = 24) 1500 mg	Change from baseline (%)	P^a
HDL-C (mmol/L)	0.78 ± 0.20	0.92 ± 0.19	0.94 ± 0.21	+17.9/+20.5	.001/.001
Triglycerides (mmol/L)	4.2 ± 3.6	3.1 ± 1.8	2.7 ± 2.1	−26.2/−35.7	.028/.021
Cholesterol (mmol/L)	5.1 ± 1.6	4.9 ± 1.7	4.6 ± 1.5	−3.9/−9.8	.440/.006
LDL-C (mmol/L)	2.7 ± 1.2	2.4 ± 1.0	2.4 ± 1.1	−11.1/−11.1	.394/.347
Adiponectin (μg/mL)	4.83 ± 2.39	7.45 ± 5.71	9.35 ± 6.06	+54.2/+93.6	.001/.001
Leptin (ng/mL)	18.1 ± 13.6	21.04 ± 12.3	19.9 ± 16.2	+16.2/+9.9	.053/.192
Resistin (ng/mL)	3.97 ± 2.25	3.64 ± 1.28	3.77 ± 2.21	−8.3/−5.0	.028/.088
Glucose (mmol/L)	6.2 ± 1.6	6.4 ± 1.8	6.3 ± 1.4	+3.2/+1.6	.074/.381
Insulin (pmol/L)	100 ± 52	107 ± 59	106 ± 55	+7.0/+6.0	.655/.368
HOMA-IR	4.7 ± 3.0	5.3 ± 3.2	4.9 ± 4.2	+12.8/+4.2	.110/.314

All values are expressed as means ± SD. LDL-C indicates low-density lipoprotein.
[a] According to the Wilcoxon signed rank test.

mechanism might also be responsible for the trendwise increase of leptin, which has also been observed after therapy with acipimox [7,8], an analogue of nicotinic acid.

Regarding one of the beneficial effects of adiponectin, namely, the improvement of insulin resistance, we did not find an improvement of the HOMA index but rather a trend to deteriorate by +12% ($P = .110$) after 1000-mg extended-release niacin (Table 1). This question ought to find further interest in future studies, particularly in the light of earlier reports that niacin might promote insulin resistance [9-11].

A limitation of this study is the lack of a control group. Therefore, a confirmation of this result is warranted by another investigation including a placebo arm. Underlying mechanisms must be addressed in studies using cell cultures. In addition, further studies must investigate if an increase of adiponectin might contribute to cardiovascular risk reduction.

Taking all this together, the hitherto unreported normalization of adiponectin by niacin may constitute additional atheroprotection beyond its action on lipids.

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