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Original Paper

Relationship between Changes in Plasma Adiponectin Concentration and Insulin Sensitivity after Niacin Therapy

Gemma Fraterrigo[a, c] Elisa Fabbrini[a] Bettina Mittendorfer[a]
Stephen O'Rahilly[d] Philipp E. Scherer[b] Bruce W. Patterson[a]
Samuel Klein[a]

[a]Division of Geriatrics and Nutritional Science, Center for Human Nutrition, Washington University School of Medicine, St. Louis, Mo., and [b]Touchstone Diabetes Center, University of Texas Southwestern Medical Center, Dallas, Tex., USA; [c]Department of Endocrinology and Metabolism, University Campus Bio-Medico, Rome, Italy; [d]Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Cambridge, UK

Key Words
Adiponectin · Insulin sensitivity · Obesity · Nicotinic acid · Glucose uptake

Abstract
Background: Niaspan® (extended-release niacin) is a nicotinic acid formulation used to treat dyslipidemia in obese subjects. Niaspan binds to the GPR109A receptor in adipose tissue and stimulates adiponectin secretion, which should improve insulin sensitivity. However, Niaspan therapy often causes insulin resistance. The purpose of this study was to evaluate whether Niaspan-induced changes in plasma adiponectin concentration are associated with a blunting of Niaspan's adverse effect on insulin action in obese subjects with non-alcoholic fatty liver disease (NAFLD). ***Methods:*** A hyperinsulinemic-euglycemic clamp procedure was used to assess muscle insulin sensitivity before and after 16 weeks of Niaspan therapy in 9 obese subjects with NAFLD [age 43 ± 5 years; BMI 35.1 ± 1.3 (means ± SEM)]. ***Results:*** Niaspan therapy did not affect body weight (99.1 ± 4.2 vs. 100 ± 4.4 kg) or percent body fat (37.8 ± 2.5 vs. 37.0 ± 2.5%). However, Niaspan therapy caused a 22% reduction in insulin-mediated glucose disposal ($p < 0.05$). The deterioration in glucose disposal was inversely correlated with the Niaspan-induced increase in plasma adiponectin concentration ($r = 0.67$, $p = 0.05$). ***Conclusions:*** These results demonstrate that Niaspan causes skeletal muscle insulin resistance, independent of changes in body weight or body fat, and the Niaspan-induced increase in plasma adiponectin concentration might partially ameliorate Niaspan's adverse effect on insulin action in obese subjects with NAFLD.

Samuel Klein, MD

Center for Human Nutrition, Washington University School of Medicine
660 South Euclid Avenue, Campus Box 8031
St. Louis, MO 63110 (USA)
Tel. +1 314 362 8708, E-Mail sklein@wustl.edu

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Background

Obesity is associated with insulin resistance and dyslipidemia (i.e. increased triglyceride and LDL cholesterol and decreased HDL cholesterol concentrations in plasma), which are risk factors for type 2 diabetes and cardiovascular disease [1]. The mechanisms responsible for the relationship between excess adiposity and metabolic dysfunction are likely related to multiple factors, including alterations in fatty acid metabolism, circulating inflammatory proteins, and decreased plasma adiponectin concentration [2–8].

Niaspan® (extended-release niacin; Abbott Laboratories, Abbott Park, Ill., USA) is a nicotinic acid formulation used to treat dyslipidemia in obese subjects because it increases plasma HDL cholesterol and decreases triglyceride and LDL cholesterol concentrations [9–13]. Moreover, Niaspan therapy should theoretically improve insulin action because it binds to the GPR109A receptor in adipose tissue, which increases the secretion of adiponectin [14–16], an adipokine that increases insulin sensitivity [17]. However, the use of Niaspan to treat dyslipidemia in obese people has potential limitations, because niacin derivatives are associated with a decrease in insulin sensitivity [16, 18–21]. The mechanism responsible for the deleterious effect of niacin therapy on insulin sensitivity is not known.

The purpose of this study was to evaluate the relationship between Niaspan therapy-induced changes in plasma adiponectin concentration and insulin sensitivity. We hypothesized that Niaspan therapy increases plasma adiponectin concentration, which would help ameliorate the adverse effects of Niaspan on insulin action. Skeletal muscle insulin sensitivity, assessed by using the hyperinsulinemic-euglycemic clamp procedure, and plasma adiponectin concentration were determined in obese subjects with non-alcoholic fatty liver disease (NAFLD) before and after 16 weeks of Niaspan therapy.

Methods

Subjects

Nine obese subjects (6 women and 3 men; age 43 ± 5 years; BMI 35.1 ± 1.3) with NAFLD (intrahepatic triglyceride content ≥5.6%), who were previously studied to evaluate the effect of Niaspan therapy on metabolic function [22], participated in this study. None of the subjects smoked cigarettes, consumed ≥20 g/day of alcohol or had severe hypertriglyceridemia (>3.4 mM), diabetes or other significant organ system dysfunction. All subjects were weight stable (≤2% change in weight) and sedentary (<1 h of exercise per week) for at least 3 months before enrollment and throughout the entire duration of the study. Subjects provided their written informed consent before participating in this study, which was approved by the Human Research Protection Office of Washington University School of Medicine.

Experimental Protocol

Subjects were admitted to the Clinical Research Unit on the evening before the hyperinsulinemic-euglycemic clamp procedure, where they consumed a standard meal and then fasted until completion of the clamp procedure the next day, as previously described [22]. During the hyperinsulinemic-euglycemic clamp procedure, [6,6-$^2H_2$]glucose was infused to assess plasma glucose rates of appearance (Ra) and rates of disappearance (Rd) during basal conditions and during insulin infusion (50 mU/m^2 body surface area per minute). One blood sample was obtained immediately before starting the tracer infusion to determine the background glucose enrichment and adiponectin concentration in plasma; blood samples to determine glucose and insulin concentrations and glucose enrichment to evaluate glucose kinetics were obtained every 10 min during the final 30 min of the basal period and every 10 min during the final 30 min of the insulin infusion.

After the baseline clamp procedure was performed, subjects began treatment with Niaspan for 16 weeks (titrated from 500 mg/day during the first 3 weeks to a final dose of 2,000 mg/day for the remaining 13 weeks). Compliance with therapy was enhanced by contact with the study research nurse every

Table 1. Niaspan therapy-induced changes in factors involved in glucose homeostasis and insulin action

	Change, %
Adiponectin	34 ± 15[b]
Glucose	7.6 ± 3.8
Insulin	82 ± 29[a]
HOMA-IR score	98 ± 32[a]
Basal glucose Ra	17 ± 7[a]
Insulin-mediated stimulation of glucose Rd	–25 ± 9[a]

Values are means ± SEM. HOMA-IR = Homeostasis model assessment of insulin resistance. [a] $p < 0.05$ and [b] $p = 0.08$ for Niaspan therapy-induced change.

week (i.e. outpatient visits in the Clinical Research Unit every 2 weeks and contact by phone every other week). Compliance with therapy was also monitored by pill count during the bimonthly visits. The hyperinsulinemic-euglycemic clamp procedure performed before treatment was repeated after 16 weeks of Niaspan therapy, 12 h after the last dose of Niaspan was given.

Sample Processing and Kinetic Analyses

Total plasma adiponectin concentration during basal conditions was determined by using an enzyme-linked immunosorbent assay system (ALPCO Diagnostics, Salem, N.H., USA). Plasma insulin concentration was determined by using a radioimmunoassay (Linco Research, St. Louis, Mo., USA). Plasma glucose concentration was determined by using an automated glucose analyzer (Yellow Springs Instruments, Yellow Springs, Ohio, USA). Plasma glucose tracer-to-tracee ratios (TTR) were determined by using gas chromatography mass spectrometry [23].

Total glucose Ra in plasma, which equals total glucose Rd (an index of glucose uptake), was calculated by dividing the glucose tracer infusion rate by the average plasma glucose TTR during the last 30 min of the basal period of the clamp procedure [23]. During basal conditions, total glucose Ra provides an index of hepatic glucose production rate. During the clamp procedure, total glucose Ra represents endogenous glucose Ra plus exogenous glucose Ra; endogenous glucose Ra during the clamp was therefore calculated by subtracting the exogenous glucose infusion rate from total glucose Ra.

Statistical Analysis

All data sets were normally distributed. Therefore, Student's t test for paired samples was used to evaluate the effect of treatment on glucose kinetics and plasma substrate and hormone concentrations. Pearson's correlation coefficient was determined to evaluate the relationship between the Niaspan-induced change in plasma adiponectin concentration and the change in insulin-mediated stimulation of glucose Rd. Data are presented as means ± SEM. A p value <0.05 was considered statistically significant.

Results

Basal plasma glucose concentration was not affected by Niaspan therapy (table 1). Basal plasma insulin concentration nearly doubled ($p < 0.05$) and basal plasma adiponectin concentration increased by ~30% ($p = 0.08$) with Niaspan therapy (table 1). Basal glucose Ra increased by ~20% ($p < 0.05$) and insulin-mediated glucose Rd decreased by ~25% ($p < 0.05$) after 16 weeks of Niaspan therapy (table 1). The change in insulin-mediated stimulation of glucose disposal correlated ($r = 0.67$; $p < 0.05$) with the change in plasma adiponectin concentration (fig. 1).

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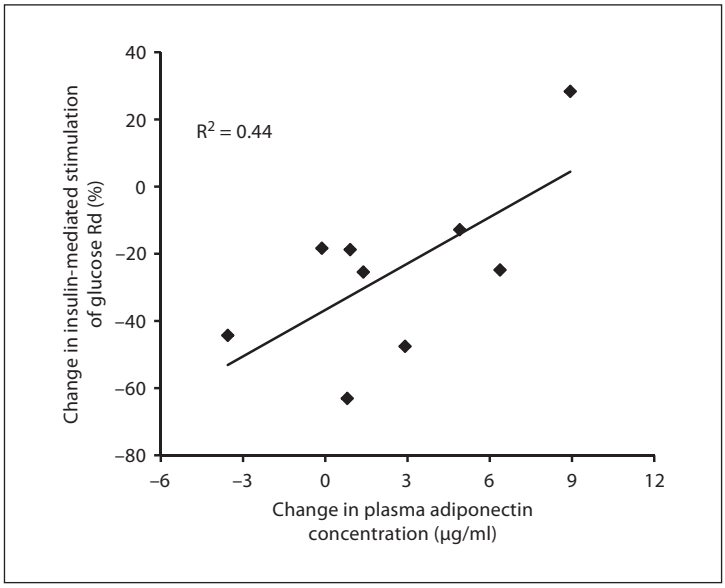

Fig. 1. Relationship between the Niaspan treatment-induced change in plasma adiponectin concentration and insulin-mediated stimulation of glucose Rd.

Discussion

Niaspan is used to treat dyslipidemia because it raises serum HDL cholesterol and reduces serum triglyceride and LDL cholesterol concentrations [9–13]. Although Niaspan binds to the GPR109A receptor in adipose tissue, which stimulates adiponectin secretion and should improve insulin sensitivity [17, 24], treatment with nicotinic acid derivatives often causes insulin resistance [16, 18–21]. The results from our study demonstrate that the degree of Niaspan-induced insulin resistance is inversely related with Niaspan-induced changes in plasma adiponectin concentration. These data suggest that the Niaspan-induced increase in adiponectin secretion ameliorates Niaspan's adverse effect on insulin sensitivity.

The exact mechanism(s) responsible for the deleterious effect of Niaspan therapy on insulin sensitivity is not known. Nicotinic acid derivatives cause a transient suppression of lipolysis followed by a characteristic rebound increase in fatty acid release from adipose tissue [25]. Therefore, it is possible that Niaspan impairs insulin sensitivity by increasing plasma free fatty acids, which are then delivered to muscle and liver tissues and generate intracellular fatty acid metabolites that reduce insulin signaling [3, 5–8]. However, Niaspan is an extended-release nicotinic acid formulation, and the rebound effect is much less than that observed with crystalline nicotinic acid [26]. In fact, we have found that 16 weeks of Niaspan therapy do not affect basal adipose tissue lipolytic rates [22], which suggests that the increase in circulating insulin associated with Niaspan therapy compensates for Niaspan-induced adipose tissue insulin resistance to maintain normal lipolytic rates.

Although we found that plasma adiponectin concentration increased by ~30% after 16 weeks of Niaspan therapy in our subjects, this increase did not achieve statistical significance ($p = 0.08$), presumably because of the small number of subjects and a type 2 statistical error. Nonetheless, the increase we observed is similar to that reported by other investigators, who found a ~50% increase in plasma adiponectin concentration after 6 weeks to 6 months of Niaspan therapy [9, 16, 27]. Moreover, we found a significant inverse correlation between the increase in plasma adiponectin concentration and the change in insulin-mediated glucose disposal, consistent with a metabolic effect of adiponectin.

An increase in circulating adiponectin increases skeletal muscle insulin sensitivity. The insulin-sensitizing effect of adiponectin is likely mediated through several mechanisms. Data from studies conducted in mouse models demonstrate that adiponectin's activation of the adiponectin receptor 1 (AdipoR1) stimulates AMPK, mitochondrial biogenesis, and fatty acid oxidation and glucose uptake [28, 29], and blocking AdipoR1 or AMPK activation inhibits these effects [28, 29]. It is thought that adiponectin-induced AMPK activation relieves the negative regulation of IRS1 through serine phosphorylation via mTOR/S6K [30]. In addition, adiponectin stimulates ceramidase activity and ceramide catabolism through an AdipoR1-dependent but AMPK-independent mechanism [31]. Ceramides can inhibit insulin signaling by inhibitory serine phosphorylation of IRS1 [5, 8, 32]. These data suggest that adiponectin blunts the Niaspan-induced decrease in skeletal muscle insulin sensitivity by reducing the intramyocellular availability of harmful fatty acid metabolites and enhancing the insulin signaling cascade.

There are several limitations to our study. First, we measured total adiponectin concentration but did not evaluate potential changes in high-molecular weight and low-molecular weight subfractions, which have different biological activities [33]. However, this limitation does not affect the conclusions from our study because the Niaspan-induced increase in total adiponectin concentration is predominately due to an increase in the biologically active high-molecular weight isoform [27, 34]. Second, the association between changes in insulin sensitivity and plasma adiponectin concentration observed in our study does not establish a cause-and-effect relationship, and additional studies are needed to evaluate this issue.

In summary, the results from our study demonstrate that treatment with Niaspan causes skeletal muscle insulin resistance, independent of changes in body weight or body fat. The deterioration in insulin sensitivity was inversely related to an increase in plasma adiponectin concentration. These data suggest that Niaspan-induced stimulation of adipose tissue adiponectin secretion might help protect against Niaspan's adverse effect on insulin sensitivity in obese subjects with NAFLD.

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Disclosure Statement

The authors do not have any relevant conflicts of interest.

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