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Increased total and high–molecular weight adiponectin after extended-release niacin

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Abstract

Niacin has recently been shown to increase serum total concentrations of the adipocyte-derived protein adiponectin. Adiponectin possesses important vascular anti-inflammatory and metabolic properties that have been attributed to the active high–molecular weight (HMW) complex of the protein. Our purpose was to examine the influence of extended-release niacin on the distribution of HMW and low–molecular weight (LMW) adiponectin complexes. Fifteen men with the metabolic syndrome were treated for 6 weeks with extended-release niacin. Serum total adiponectin concentrations increased by 46% after the niacin intervention ($P < .05$). High–molecular weight adiponectin accounted for 63% of the increase in total adiponectin, which was reflected by a shift in the HMW/LMW adiponectin ratio from 0.69 to 0.86 (+25%) ($P < .05$). Serum insulin concentrations increased by 20% after the niacin intervention despite an increase in HMW adiponectin concentrations ($P < .05$). These results suggest that the increase in total adiponectin concentrations observed with extended-release niacin is primarily due to an increase in the active HMW complex. Therefore, at least part of the cardioprotective benefits of niacin may be attributed to a shift in the HMW/LMW adiponectin ratio in obese men with the metabolic syndrome.

1. Introduction

The incidence of obesity and related metabolic disease conditions has reached epidemic proportions in the United States and worldwide [1]. Obesity is associated with a cluster of interrelated metabolic and cardiovascular disease (CVD) risk factors that include insulin resistance, dyslipidemia, and hypertension, which are collectively referred to as the *metabolic syndrome* [2]. Obesity-related insulin resistance leads to elevations in serum nonesterified fatty acids (NEFAs) and concomitant elevations in hepatic glucose and triglyceride synthesis and secretion. Therefore, interventions designed to target adipose tissue lipolysis and/or hepatic glucose and triglyceride production would be expected to improve metabolic characteristics of obese individuals in the absence of weight loss or changes in lifestyle.

The effects of niacin (nicotinic acid) on serum blood lipids and lipoproteins have been well described. Niacin reduces fasting serum triglycerides by 15% to 35%, lowers lipoprotein (a), raises high-density lipoprotein cholesterol (HDL-C) by 18% to 45%, and has moderate effects on low-density lipoprotein cholesterol (LDL-C) [3-5]. Although the mechanisms responsible for improvements in blood lipids and lipoproteins remain unclear, the recent identification of a G-protein coupled receptor (GPR109A) for niacin has provided valuable insight for future research [6]. Receptor-mediated reductions in adipose tissue lipolysis and the subsequent reduction of serum NEFAs have been proposed as a primary mechanism for the improvements in blood lipids associated with niacin [7]. Although the lipid-altering effects of niacin have been presumed to be responsible for reductions in CVD morbidity and mortality, recent evidence suggests that niacin may also have important vascular anti-inflammatory and antimitogenic properties [8]. Furthermore, extended-release niacin has been shown to increase

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serum total adiponectin and leptin concentrations by 56% and 26%, respectively, providing further evidence that other factors may contribute to niacin-mediated reductions in CVD risk [9].

Adiponectin (Acrp30) is secreted exclusively by adipocytes and is one of the most abundant plasma proteins in humans, making up 0.01% to 0.05% of total plasma proteins [10]. Adiponectin is secreted primarily as an active high–molecular weight (HMW) complex and a low–molecular weight (LMW) complex [11,12]. The HMW complex is closely associated with the known physiological and metabolic effects of adiponectin [13]. High–molecular weight adiponectin has been shown to improve insulin receptor tyrosine kinase phosphorylation, lipoprotein lipase activity, fatty acid transport, and fatty acid oxidation [14]. Unlike many other adipokines such as leptin, which are upregulated, adiponectin secretion is decreased in obesity, metabolic syndrome, type 2 diabetes mellitus, and CVD [15]. Decreased adiponectin expression and secretion have been positively associated with insulin sensitivity [16].

Insulin resistance is one of the most common and poorly explained adverse effects of niacin administration. It has been proposed that "rebound" increases in serum NEFAs are responsible for insulin resistance as niacin concentrations diminish in the blood [17]. Studies using extended-release niacin have observed no changes in serum NEFAs when measured 10 to 12 hours after niacin treatment [9]. However, serum NEFAs were reduced up to 4 hours and increased 3-fold above baseline for up to 5 hours when blood samples were obtained over 9 hours after the administration of extended-release niacin [18]. Therefore, it is possible that changes in fatty acid secretion may play a role in the reduction in insulin sensitivity and adiponectin secretion and/or expression after extended-release niacin administration.

The purpose of this investigation was to examine the influence of extended-release niacin on serum total and HMW adiponectin in men with the metabolic syndrome and to examine the relationship between the adiponectin complex distribution and insulin resistance. We report that niacin increases adiponectin concentrations by increasing the HMW complex, resulting in a shift from primarily the LMW complex to the HMW complex in the absence of changes in body weight or body composition.

2. Materials and methods

2.1. Participant selection

Adult male volunteers were recruited in the local community and surrounding areas by word of mouth, newspaper and radio advertisements, community presentations, and mail outs. Volunteers were considered for the study if they were between the ages of 30 and 65 years, previously sedentary, obese (body mass index $\geq$30 kg/m^2, waist girth >88 cm), hypertriglyceridemic (triglycerides $\geq$150 mg/dL), and nonsmokers. Individuals taking medications known to influence lipid, lipoprotein, or glucose metabolism and those with known history of or active gout, peptic ulcer disease, diabetes, or liver disease were excluded from the study. Volunteers who met the initial criteria for the study were invited to the laboratory for additional preliminary screening. At the preliminary screening, volunteers were fully informed about the nature of the study and were asked to complete an institutionally approved informed consent. A venous blood sample was obtained during the visit and sent to a Centers for Disease Control and Prevention–certified laboratory to verify blood lipid, glucose, and liver enzyme concentrations. All participants who were allowed to participate in this study were examined by an attending physician of the Exercise Technology Laboratory and were cleared for entrance in the study.

2.2. Experimental procedures

Participants who met all criteria for the study were asked to record all physical activity and food consumed 3 days before starting the niacin intervention. Body weight and height, waist circumference, and body fat percentage were obtained on each participant. Body fat percentage was estimated using dual-energy x-ray absorptiometry. A fasting blood sample was obtained from each participant to evaluate baseline adiponectin, glucose, and insulin concentrations. A prescription for extended-release niacin was then provided by the attending physician. Participants were asked to return to the laboratory on a weekly basis for blood sampling to evaluate changes in liver enzyme and biochemical profiles. Participants returned to the laboratory after the 6-week extended-release niacin intervention for blood sampling. All blood samples were obtained after an 8- to 12-hour fast at approximately the same time each morning (before 9:00 AM). Whole blood was centrifuged at 1500*g* for 20 minutes to isolate serum. Aliquots of serum were stored at −80°C until analyses were conducted. Food logs were analyzed using a commercially available software package (Food Processor for Windows, version 7.40; ESHA Research, Salem, OR). Total caloric intake and the amount of protein, fat, and carbohydrate (in grams) were estimated from the food log.

2.3. Extended-release niacin protocol

Niacin was provided at a dose of 500 mg/d during the first week, 1000 mg/d during the second week, and 1500 mg/d during weeks 3 through 6. Niacin was taken once a day in the evening with a low-fat snack before bedtime. In addition, each participant was asked to take an enteric-coated aspirin (300 mg) 30 to 60 minutes before the evening dose of niacin. Participants were asked to record and report all adverse reactions experienced on a weekly basis.

2.4. Biochemical analysis

Clinical chemistries were evaluated by a Centers for Disease Control and Prevention–certified laboratory on a

weekly basis during the niacin intervention. Serum glucose concentrations were analyzed using a commercially available colorimetric enzymatic kit (Raichem, Columbia, MD). Insulin, total adiponectin, and HMW adiponectin concentrations were determined by enzyme-linked immunosorbent assay (Millipore, St Charles, MO). The intraassay coefficients of variation for glucose and insulin were 0.5% and 3.3%, respectively. The intraassay coefficients of variation for total and HMW adiponectin were 2.9% and 4.5%, respectively.

2.5. Statistical analysis

The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: [fasting insulin (in microunits per milliliter) × fasting glucose (in millimoles per liter)]/22.5. The LMW adiponectin was calculated as the difference between total and HMW adiponectin concentrations. Formal and graphical tests for normality were conducted for each variable before analysis. All variables were normally distributed; therefore, a pairwise Student *t* test was used to examine differences before and after the niacin intervention. Relationships between physiological characteristics and changes in the variables of interest were determined using Pearson product-moment correlation coefficients. Power analyses suggested that 14 participants would be required to meet statistical significance for total adiponectin at an effect size of 0.8 and an α level of .05. All data were analyzed using the Statistical Analysis System (SAS for Windows, version 9.1; SAS Institute, Cary, NC). The comparison-wise error rate was set at $P < .05$.

3. Results

Baseline physiological and metabolic characteristics of the participants are presented in Table 1. All participants met the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome [2] and the hypertriglyceridemic waist phenotype (waist circumference >90 cm and serum triglycerides >176 mg/dL) [19]. Body weight was correlated with glucose (r = 0.64), total adiponectin (r = 0.57), and HMW adiponectin concentrations (r = 0.62); HMW to total adiponectin ratio (r = 0.56); and HMW/LMW ratio (r = 0.63) at baseline. There were no correlations between baseline serum lipids, insulin, or adiponectin.

Table 1
Baseline physiological characteristics

	Means ± SEM	Minimum-maximum
Age (y)	45 ± 2	32-57
Height (cm)	175.4 ± 2.4	161.3-195.6
Weight (kg)	105.2 ± 4.6	85.7-146.7
BMI (kg/m^2)	34.0 ± 0.8	29.3-39.2
Waist girth (cm)	107.9 ± 2.1	95.3-123.8
% Fat	36 ± 1.1	23-44
SBP (mm Hg)	130 ± 3	108-154
DBP (mm Hg)	84 ± 2.1	66-102
Insulin (μg/mL)	15.6 ± 3.1	5.1-52.1
HOMA-IR	3.9 ± 0.8	1.2-12.4
Diabetes (n)	0	
Known CVD (n)	2	

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Diabetes (n), number of individuals included in the study with type 2 diabetes mellitus; Known CVD (n), number of individuals included in the study with known CVD.

The LMW complex of adiponectin accounted for approximately 60% of the total serum adiponectin concentrations at baseline. Individual and mean ± SEM total, HMW, and LMW adiponectin responses to niacin are provided in Fig. 1. The HMW and LMW adiponectin increased in 14 of 15 participants after niacin treatment. Total adiponectin concentrations increased by 46% from 5.7 ± 0.5 to 8.4 ± 0.7 μg/mL. The increase in total adiponectin concentrations was primarily accounted for by a 63% increase in HMW adiponectin concentrations from baseline (2.4 ± 0.2 to 3.9 ± 0.3 μg/mL). Although niacin increased the concentration of the LMW complex by 37%, there was a 25% increase in the HMW/LMW adiponectin ratio after niacin treatment, indicating a shift in complex distribution from the LMW complex to the HMW complex. Changes in HMW and LMW concentrations were both correlated with the increase in total adiponectin concentrations after niacin (r = 0.91 and 0.92, respectively).

Insulin concentrations and the HOMA-IR model assessment index were 22% and 20% higher, respectively, after the niacin intervention despite significant increases in total and HMW adiponectin ($P < .05$ for both) (Fig. 2). There was no relationship between the percentage changes in insulin concentrations, NEFAs, and adiponectin total or complex concentrations. However, percentage changes in total cholesterol, LDL-C, and HDL-C were significantly correlated with changes in adiponectin concentrations (Table 2). Niacin was tolerated well, with only 3 reports of isolated flushing and no changes in liver enzymes. Body weight and energy density and composition were evaluated on a weekly basis and were not changed throughout the study.

4. Discussion

Niacin is one of the most effective pharmacological agents for the treatment of hypertriglyceridemia and low HDL-C [20]. Although improvements in blood lipid and lipoprotein metabolism are clearly associated with reductions in CVD morbidity and mortality, the influence of niacin on vascular inflammation and the emerging biomarkers of disease suggest that other factors may be involved [21,22]. Indeed, extended-release niacin dramatically increased serum concentrations of the adipocyte-derived protein adiponectin in individuals with the metabolic syndrome [9]. Adiponectin has recently been identified as a biomarker of the metabolic syndrome and is strongly associated with

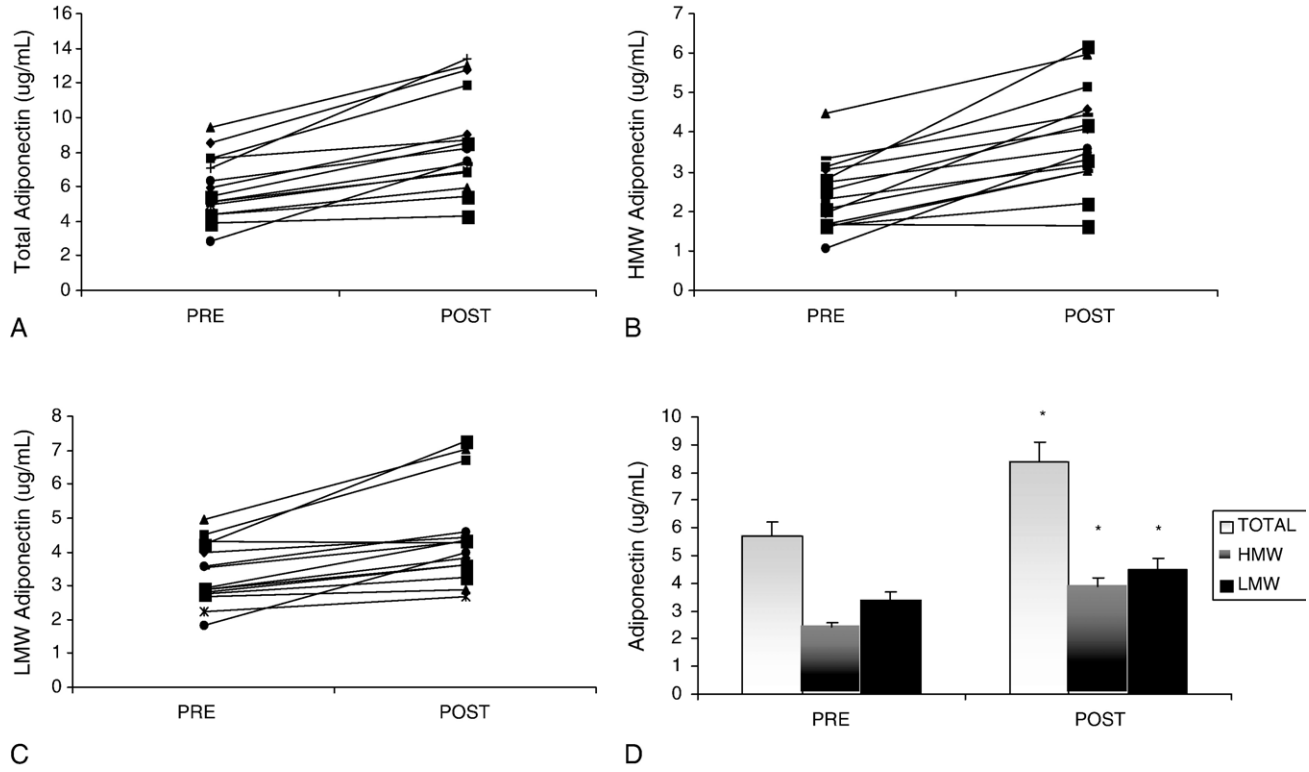

Fig. 1. Individual responses to 6 weeks of extended-release niacin for serum total adiponectin (A), HMW adiponectin (B), and LMW adiponectin (C). Mean ± SEM (D) changes in total, HMW adiponectin, and LMW adiponectin after 6 weeks of extended-release niacin. Total adiponectin increased by 47%. The HMW and LMW adiponectin concentrations increased by 63% and 37%, respectively, after the niacin intervention. *$P < .05$ for all compared with preintervention. PRE indicates preintervention; POST, postintervention.

CVD [23]. Because adiponectin concentrations are low in men with the metabolic syndrome, an increase in adiponectin concentrations would be expected to lower CVD risk [24]. However, total adiponectin concentrations provide no information regarding the relative abundance of the metabolically active HMW complex (HMW/LMW ratio) that is thought to confer the greatest cardioprotective benefits. Therefore, the purpose of this investigation was to examine the effects of extended-release niacin on the distribution of adiponectin complexes in men with the metabolic syndrome. We report that total adiponectin concentrations were increased by 46%, with the HMW complex accounting for 63% of the increase in total adiponectin. The HMW/LMW ratio increased from 0.69 to 0.86 (25%) after the niacin treatment, providing further evidence that niacin shifts the adiponectin complex distribution in men with the metabolic syndrome from a primarily LMW to HMW distribution.

Adiponectin is secreted exclusively by adipocytes primarily as HMW and LMW complexes and, to a lesser extent, as a trimer [14]. Adiponectin is thought to have novel vascular anti-inflammatory, antimitogenic, and insulin-sensitizing properties and is involved in energy homeostasis [25,26]. It has been proposed that adiponectin reduces vascular inflammation by reducing the activation of adhesion molecules and smooth muscle cell infiltration [27,28]. Adiponectin has also been shown to increase insulin receptor tyrosine kinase phosphorylation, fatty acid translocase CD36 expression, adenosine monophosphate–activated protein kinase activity, and fatty acid oxidation. Pajvani and colleagues [13] found that the proportion of adiponectin in the HMW form rather than absolute circulating levels was responsible for the amelioration of insulin resistance.

Westphal and colleagues [9] found that 8 weeks of extended-release niacin increased total adiponectin and leptin concentrations by 56% and 26%, respectively, in a group of men with the metabolic syndrome but observed no changes in resistin, C-reactive protein, or other emerging biomarkers of disease. Similarly, the investigators found that extended-release niacin increased adiponectin concentrations by 97% from baseline after 8 weeks of treatment in individuals with known CVD [29]. Our results confirm these observations in that we found a 46% increase in serum total adiponectin concentrations in men with the metabolic syndrome but provide evidence for the first time that the increase in total adiponectin appears to be the result of a shift in the distribution of adiponectin from primarily the LMW form to the HMW form. Furthermore, despite significant increases in HMW adiponectin concentrations, we also found that niacin increased insulin concentrations and insulin resistance (HOMA-IR) by 20% and 22%, respectively. The

reductions in insulin sensitivity reported here are similar to those previously reported with extended-release niacin.

Thiazolidinediones are the only other pharmacological agents known to improve HMW adiponectin concentrations in humans. Thiazolidinediones are considered potent insulin-sensitizing agents despite evidence that more than 50% of individuals show no changes in insulin sensitivity [13]. Recent evidence suggests that adiponectin is more closely associated with blood lipid metabolism than insulin sensitivity [30]. Therefore, the well-known metabolic and cardiovascular benefits of thiazolidinediones as agonists of the peroxisome proliferator–activated receptor (PPAR) γ nuclear factors may be partially explained by associated elevations in HMW and total adiponectin concentrations independent of changes in insulin sensitivity [31]. A recent investigation found that PPAR-γ expression was increased in a dose-dependent fashion when primary adipocytes from high-cholesterol New Zealand rabbits were exposed to niacin [32]. Therefore, it is possible that niacin-mediated activation of the GPR109A receptor increases PPAR-γ expression, leading to an increase in adiponectin expression and secretion.

Results from the current investigation confirm other reports that extended-release niacin increases insulin concentrations and insulin resistance in men with the metabolic syndrome [9]. The increase in insulin concentrations may be explained by the pharmacokinetics of extended-release niacin. For example, extended-release niacin has been shown to reduce adipose tissue lipolysis for at least 4 hours after administration. This is followed by a 3-fold rebound in lipolysis for up to 5 hours as niacin levels diminish in the blood. It is possible that the increase in serum insulin concentrations may be attributed to the increase in serum NEFAs as niacin concentrations diminish in the blood because serum NEFAs would be expected to increase hepatic glucose production and reduce hepatic and skeletal muscle glucose oxidation. Future studies will be required to examine the effects of extended-release niacin on serum NEFA, insulin, and adiponectin concentrations in the hours after the last dose of niacin to help determine the mechanisms responsible for changes in insulin concentrations and insulin sensitivity. Knowledge of these mechanisms would assist in the development of pharmacological and molecular strategies to exploit the benefits of niacin while minimizing its adverse effects on insulin sensitivity.

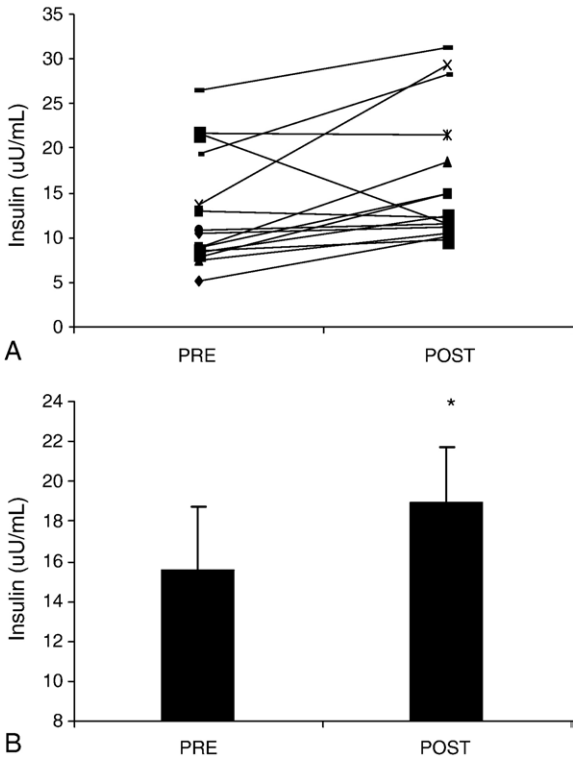

Fig. 2. Individual (A) and mean ± SEM (B) changes in fasting serum insulin concentrations after 6 weeks of extended-release niacin. *$P < .05$ compared with preintervention.

Table 2
Correlation between percentage changes in serum adiponectin and lipids

	Total adiponectin	HMW adiponectin	LMW adiponectin
Total cholesterol	−0.60 *	−0.58 *	−0.55 *
HDL-C	0.68 *	0.63 *	0.81 *
LDL-C	−0.57 *	−0.54 *	−0.55
Triglyceride	−0.34	−0.46	−0.39
NEFA	−0.24	−0.41	−0.10
Insulin	0.42	0.30	0.36

All values represent Pearson product moment correlation coefficients (r) between percentage changes in serum adiponectin and lipid variables.

* $P < .05$.

A limitation of this study was the absence of a control group. Although it is possible that the effects of niacin on the parameters studied may be caused by the effect of time, changes in insulin, glucose, and total adiponectin concentrations were similar to those observed by Westphal and colleagues [9]. Furthermore, there were no changes in any of the variables examined in a placebo-treated group, suggesting that the effects observed were due to the effects of niacin and not due to time.

In conclusion, the results of this study provide evidence for the first time that extended-release niacin increases total adiponectin concentrations primarily by increasing the active HMW complex form in the absence of changes in body weight. Therefore, it is possible that niacin may be an effective strategy to increase adiponectin concentrations in obese individuals at risk for CVD. Future studies will be required to determine the mechanisms by which niacin increases adiponectin secretion and/or expression.

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