Short Communication

Serum adiponectin levels predict the effect of short-term dietary interventions on insulin sensitivity in humans

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Abstract

Aims/hypothesis. Fat-rich diets can acutely induce insulin resistance. Data from adiponectin knock-out mice suggest that this effect might be increased in the absence of adiponectin. In the present study we tested whether plasma adiponectin concentrations influence changes in insulin sensitivity induced by a short-term dietary intervention in humans.

Methods. We analysed data from 27 healthy, non-obese men with normal glucose tolerance. These men ate a diet high in fat and a diet high in carbohydrates for three days each.

Results. The high-fat diet induced a significant drop in insulin sensitivity (determined by euglycaemic–hyperinsulinaemic clamp) compared to baseline (0.100 ± 0.009 vs 0.083 ± 0.007 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot (\text{pmol} \cdot \text{l}^{-1})$, $p=0.01$). The drop in insulin sensitivity was more pronounced in subjects with low serum adiponectin (0.094 ± 0.011 vs 0.077 ± 0.010 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot (\text{pmol} \cdot \text{l}^{-1})$, $p=0.02$) than in subjects with high serum adiponectin (0.103 ± 0.011 vs 0.090 ± 0.040 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot (\text{pmol} \cdot \text{l}^{-1})$, $p=0.16$). In the

whole group the high-carbohydrate, low-fat diet did not cause an increase in insulin sensitivity (0.095 ± 0.007 vs 0.102 ± 0.009 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot (\text{pmol} \cdot \text{l}^{-1})$, $p=0.06$). However, insulin sensitivity was significantly increased in the subgroup with low serum adiponectin levels (0.084 ± 0.013 vs 0.099 ± 0.018 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot (\text{pmol} \cdot \text{l}^{-1})$, $p=0.01$). In an additional multivariate analysis post-intervention insulin sensitivity was predicted by pre-intervention insulin sensitivity ($p<0.001$) and adiponectin concentrations ($p=0.001$).

Conclusions/interpretation. These data indicate that the reduction in insulin sensitivity achieved by a short-term high-fat diet is more pronounced in non-obese subjects with low serum adiponectin. Thus it is possible that the restriction of dietary fat and a diet high in carbohydrates might be particularly effective in subjects with low adiponectin such as obese or Type 2 diabetic individuals.

Keywords Adiponectin · Dietary intervention · Insulin sensitivity · Obesity

Introduction

In animal models and in humans obesity and insulin resistance are associated with reduced serum concen-

trations of the adipocyte-derived hormone adiponectin [1]. Treatment with adiponectin has been shown to reverse insulin resistance in mouse models [2]. Human studies strongly suggest that adiponectin is an important determinant of the insulin sensitivity of both glucose and lipid metabolism [3]. The effects of adiponectin seem to be mediated by stimulation of glucose uptake and fatty acid oxidation in skeletal muscle and liver [4].

Insulin sensitivity in humans can be modulated by an acute dietary intervention. In a previous study we have shown that a dietary lipid load causes a reduction of insulin sensitivity and an increase in intramyocellu-

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lar lipid stores [5]. Subsequently we observed that the increase in intramyocellular lipids induced by a high-fat diet was negatively correlated to adiponectin serum levels [6]. Based on these findings, we tested in the present study the hypothesis that the negative effect of a high-fat diet on insulin sensitivity might depend on individual serum adiponectin levels. In order to reduce influences of other obesity-related factors, we studied a non-obese population, which was divided into a low- and a high-adiponectin subgroup.

Subjects and methods

Subjects. A total of 27 men, who were non-diabetic according to World Health Organization criteria, underwent the diet protocol described below. The local ethics committee approved all protocols. All subjects gave informed written consent.

For statistical analyses the group was divided in two subgroups with high and low serum adiponectin concentrations. For that purpose we performed univariate linear regression analyses with BMI as a dependent and adiponectin as an independent variable, using a database that had been previously published ($n=265$ men) [3]. Using the equation of the resulting regression curve ($\ln \text{adiponectin} = 5.77 - 1.16 \times \ln \text{BMI}$), we calculated a statistically expected adiponectin serum level for every subject in this study. This statistically expected serum adiponectin level was subtracted from the serum adiponectin level actually measured. Subjects with a negative result were assigned to the low-adiponectin group and vice versa. Subjects in the low-adiponectin group thus had lower serum adiponectin levels than those statistically predicted from their BMI.

Analytical procedures and measurements. Serum insulin was determined with a micro particle enzyme immunoassay (Abott, Wiesbaden, Germany). Adiponectin serum concentrations were measured using a commercially available radio immunoassay (LINCO Research, St Charles, Mo., USA).

Hyperinsulinaemic-euglycaemic clamp. Subjects underwent a hyperinsulinaemic-euglycaemic clamp as previously described [3, 5, 6].

Diet protocol and composition. A detailed description of the composition of the diet has been published before [5]. In that paper a sub-cohort of the group presented here was already analysed. The subjects ate a fat-rich and a carbohydrate-rich diet for three consecutive days each. The high-fat diet contained 11159 to 12314 kJ/day, with 55 to 60% of energy derived from fat. With the carbohydrate-rich, low-fat diet the average intake in energy and in fat was lower than in the high-fat diet (7954–8891 kJ/day, with 18 to 23% of energy derived from fat). Fasting serum adiponectin levels were determined before the subjects were enrolled in the study.

Statistical analysis. All data are given as means $\pm$ SEM unless otherwise stated. Distribution was tested for normality using the Shapiro-Wilk W test. A paired Student's *t* test was used to analyse the effect of dietary interventions. Non-normally distributed parameters were log-transformed to achieve normal distribution before statistical analyses. To adjust the effects of covariates and identify independent relationships, we performed multivariate linear regression analyses. A *p* value of less than 0.05 was considered to be statistically significant. The statistical software package JMP (SAS Institute, Cary, N.C., USA) was used.

Results

Subject characteristics. Anthropometric data of all subjects and of the subgroups with high and low serum adiponectin are shown in Table 1. Anthropometric data of the group of subjects with low serum adiponectin and of subjects with high serum adiponectin were comparable (Table 1).

Effects of fat-rich diet. In the whole group insulin sensitivity was significantly reduced upon eating the fat-rich diet ($p=0.01$). This reduction reflects the strong effect of the high-fat diet in the subgroup of subjects with low serum adiponectin ($p=0.02$). No effect was observed in the subgroup with high serum adiponectin ($p=0.16$; see Table 1 for details). On the

Table 1. Subject characteristics

Characteristic	Low-adiponectin group	High-adiponectin group	<i>p</i>
Number	11	16	
Age (years)	29 $\pm$ 1	30 $\pm$ 1	0.59
BMI (kg/m ²)	25.2 $\pm$ 2	24.1 $\pm$ 3	0.23
Percent body fat	21 $\pm$ 2	20 $\pm$ 4	0.77
Waist-to-hip-ratio	0.91 $\pm$ 0.07	0.91 $\pm$ 0.07	0.94
Fasting glucose (mmol/l, OGTT)	5.3 $\pm$ 0.1	4.9 $\pm$ 0.1	0.02
2-h glucose (mmol/l, OGTT)	5.4 $\pm$ 0.4	4.8 $\pm$ 0.3	0.28
Fasting insulin (pmol/l, OGTT)	47 $\pm$ 7	38 $\pm$ 6	0.24
2-h insulin (pmol/l, OGTT)	218 $\pm$ 68	181 $\pm$ 53	0.19
Adiponectin (μ g/ml)	5.9 $\pm$ 1.1	11.5 $\pm$ 3.0	
ISI (μ mol $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹ $\cdot$ (pmo $\cdot$ l ⁻¹)) before fat-rich diet	0.094 $\pm$ 0.011	0.103 $\pm$ 0.011	0.79
ISI (μ mol $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹ $\cdot$ (pmo $\cdot$ l ⁻¹)) after fat-rich diet	0.077 $\pm$ 0.010 ^a	0.090 $\pm$ 0.040 ^b	0.61
ISI (μ mol $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹ $\cdot$ (pmo $\cdot$ l ⁻¹)) before low-fat diet	0.084 $\pm$ 0.013	0.102 $\pm$ 0.009	0.13
ISI (μ mol $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹ $\cdot$ (pmo $\cdot$ l ⁻¹)) after low-fat diet	0.099 $\pm$ 0.018 ^c	0.105 $\pm$ 0.007 ^d	0.46

All data are means $\pm$ SD. ISI, insulin sensitivity index. ^a $p=0.02$ vs pre-intervention; ^b $p=0.16$ vs pre-intervention; ^c $p=0.01$ vs pre-intervention; ^d $p=0.76$ vs pre-intervention

basis of multivariate analyses, the effect of serum adiponectin on post-intervention insulin sensitivity was not significant ($p=0.38$) after adjusting for pre-intervention insulin sensitivity.

Effects of carbohydrate-rich, low-fat diet. Eating a diet that was low in fat and high in carbohydrates for three days did not cause an increase in insulin sensitivity in the group studied, when compared to baseline insulin sensitivity ($p=0.06$). An improvement in insulin sensitivity with this diet was only seen in subjects with low serum adiponectin ($p=0.01$), but not in subjects with high serum adiponectin ($p=0.76$; see Table 1 for details). In an additional multivariate analysis the effect of serum adiponectin remained significant ($p=0.001$) after adjusting for baseline insulin sensitivity.

Discussion

In the present study we provide indirect evidence that adiponectin predicts the effect of a dietary intervention on insulin sensitivity in healthy non-obese subjects. A negative effect of a high-fat diet on insulin sensitivity is only seen in subjects with low serum adiponectin levels. Moreover, in subjects with low adiponectin levels, a short-term high-carbohydrate, low-fat diet increases insulin sensitivity.

The interpretation of our results, however, is limited by the protocol. First of all, the two diets eaten were not isocaloric. The high-fat diet contained more energy than the high-carbohydrate, low-fat diet. This makes it impossible to distinguish between effects primarily caused by oversupply of fatty acids and effects caused by caloric excess. In addition, our subjects were young and healthy, non-obese men undergoing a short-term intervention. Therefore, before extrapolating our results to obese and/or Type 2 diabetic patients or to women, they need to be confirmed over a longer period in a more heterogeneous population.

The finding that a short-term high-fat diet reduces insulin sensitivity has already been reported [5] in a sub-cohort of the subjects analysed here. In that study no statistically significant effect of a low-fat diet on insulin sensitivity was found. However, a high interindividual variance was observed in the changes in insulin sensitivity induced by the dietary intervention in that study. Due to this, it appeared likely that the change in insulin sensitivity was influenced by sus-

ceptibility factors. Our present analysis suggests that adiponectin serum levels might be one of these postulated factors. This suggestion is consistent with animal data showing that adiponectin knock-out mice are extremely sensitive to severe diet-induced insulin resistance [7].

The conclusion that, in subjects with low adiponectin levels, a reduced intake of dietary fat and energy might have a beneficial effect on insulin sensitivity could be of practical importance. People with reduced adiponectin levels are known to have an increased risk of developing Type 2 diabetes [8]. Thus reducing intake of dietary fat and/or energy might be an especially effective tool for preventing Type 2 diabetes in this population.

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