Original paper

Short-term lifestyle intervention significantly increases fasting adiponectin and induces a decline in serum adiponectin during oral glucose tolerance test, without changes in insulin resistance

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Abstract

Introduction: Metabolic syndrome is associated with insulin resistance (IR) and low concentrations of adiponectin, an adipocytokine that improves insulin sensitivity and has anti-inflammatory and anti-atherogenic properties. An increase in circulating adiponectin may, therefore, have beneficial effects in terms of reduction of cardiovascular risk. We aimed to establish whether short-term (two-week) lifestyle intervention alters serum concentrations of adiponectin, and whether there are changes in adiponectin during oral glucose tolerance test (OGTT).
Material and methods: We measured adiponectin levels during 75.0 gram OGTT before and after two weeks of a hospital-based lifestyle modification programme that consisted of hypocaloric diet and moderate exercise in 16 severely obese, non-diabetic subjects (4 males), aged 42.0±14.18 years, BMI 42.65±7.82 kg/m^2 (mean ±SD). IR indices were assessed before and after intervention.
Results: Exercise and diet programme resulted in a decline of BMI (to 40.21±7.14 kg/m^2, $p<0.001$) and fasting glucose ($p=0.002$), although without significant improvement in IR. There was, however, a significant rise in fasting adiponectin (from 32.1±13.2 nmol/l to 35.38±11.04 nmol/l, $p=0.008$). Furthermore, though initially there was no change in serum adiponectin levels during OGTT, there was a significant decline in serum adiponectin during OGTT at the end of the study ($p<0.001$).
Conclusions: A two-week period of lifestyle modification (hypocaloric diet and moderate exercise) increases fasting adiponectin and induces a decline in serum adiponectin during OGTT in severely obese subjects. Favourable changes in serum adiponectin in subjects at high risk of cardiovascular disease are observed after a relatively short period and precede significant changes in insulin resistance.

Key words: adiponectin, oral glucose tolerance test, obesity, metabolic syndrome

Introduction

Metabolic syndrome is associated with central obesity, dyslipidaemia, hypertension, type 2 diabetes and atherosclerotic cardiovascular disease [1]. Adipose tissue is now considered to represent not only an energy storage organ, but is also a source of several adipocytokines, such as leptin, resistin and adiponectin, known to be involved in regulation of energy homeostasis, insulin resistance, atherosclerosis and inflammatory processes [2–4].

Adiponectin is an adipose tissue-specific adipocytokine [5] that circulates in human plasma in high concentrations, and in addition to its anti-diabetic effects [6] adiponectin is also anti-atherogenic [7] and anti-inflammatory [8]. Plasma levels of adiponectin have been found to be decreased in obesity [5], dyslipidaemia [9] and type 2 diabetes [10, 11], i.e. in conditions typically associated with the metabolic syndrome. Previous studies have demonstrated that reduced circulating adiponectin levels are partially reversible by weight reduction in obese and in insulin-resistant subjects [11–13]. Such an increase in circulating adiponectin may therefore potentially attenuate increased cardiovascular risk associated with the metabolic syndrome. Patients with the metabolic syndrome are typically encouraged to lose weight and to undertake regular exercise. There is, however, conflicting evidence on the minimum duration of such intervention that may result in any appreciable changes in circulating adiponectin.

In our study, we have therefore endeavoured to assess whether short-term, but highly supervised, lifestyle intervention consisting of diet and exercise may lead to a change in circulating adiponectin concentrations in severely obese subjects with the metabolic syndrome. Additionally, we assessed whether adiponectin levels are altered following oral administration of glucose during standardised 75 gram oral glucose tolerance test.

Material and methods

The study involved 16 subjects (4 males) (age mean±SD 42±14.18 years, BMI 42.65±7.14 kg/m^2) who were recruited from the Obesity and Metabolic Syndrome Outpatient Clinic of the Medical University of Lodz, Poland. Following initial assessment in the clinic (history, full clinical examinations, assessment of baseline fasting glucose, lipids, TSH and free T4, ECG) they were admitted to our department for a two-week lifestyle modification programme. This involved dietary advice followed by a weight-reducing hypocaloric diet of 1200±200 kcal/24 hours for female subjects and 1400±200 kcal/24 hours for males. Individual caloric content was calculated according to the FAO/WHO criteria which take into account sex, age and individually calculated ideal body weight. According to these recommendations, calculated protein intake should be 1 gram/kg of ideal body mass, with 20-25% of total energy derived from fat, limitation of saturated fats intake and complete elimination of fried foods. In addition to dietary intervention each subject participated in a physical exercise programme that included swimming for 45 minutes a day and three 15 min sessions on a cycloergometer per day. All subjects were also encouraged to take regular walks throughout the day. 75 gram oral glucose tolerance test was performed in each subject before behavioural intervention (day 1) and after completion of a two-week period (day 15). During oral glucose tolerance test (0, 60, 120 minutes) blood samples were taken for the assessment of serum glucose, insulin and adiponectin. Exclusion criteria included treated diabetes mellitus, treated dyslipidaemia, and active ischaemic heart disease, lung disease or heart failure that precluded participation in the exercise programme because of anginal pain or dyspnoea. None of the studied subjects received any medication that could significantly influence insulin sensitivity (such as metformin or thiazolidinediones). The study received ethical approval of the Ethics Committee of the Medical University of Lodz, Poland.

Insulin resistance indices [Homeostasis Model Assessment (HOMA), Quantitative Insulin-Sensitivity Check Index (QUICKI) and Insulin Resistance Index (IRI)] were calculated as specified below.

HOMA: was calculated as G_0 (mmol/l)* I_0 (µU/ml)/ 22.5 [14].

QUICKI: was also calculated from fasting glucose and insulin values, according to the formula: $1/[\log(I_0) + \log(G_0)]$, where I_0 is fasting insulin (microunits per millilitre) and G_0 is fasting glucose (milligrams per decilitre). QUICKI is the reciprocal of the log-transformed product of fasting glucose and insulin; it is a dimensionless index without units. Some authors believe that QUICKI is superior to HOMA [15, 16].

Insulin Resistance Index is a method based on changes of glycaemia and insulinaemia during an oral glucose tolerance test (OGTT) [17]. IRI was calculated through the formula: 2/[1/(INSp x GLYp)]+1, where INSp and GLYp are the measured insulin and glycaemic areas. This method is based on changes of glycaemia and insulinaemia during OGTT, and correlates well with the euglycaemic hyperinsulinaemic glucose clamp technique [18]. According to the same authors the assessment of free fatty acids (FFA) during OGTT is equally effective for the purpose of calculation of the insulin resistance index [18].

During the OGTT blood was sampled at 0, 60 and 120 min for determination of plasma insulin and FFA. Tubes were immediately transported to the laboratory. Serum insulin was determined by an immunoenzymatic assay (IMMULITE, DPC) and serum concentrations for total FFA were determined by an enzymatic method (Boehringer Mannheim). The samples for FFA determination were spun down with minimal delay and frozen at -20°C until analysis.

Serum adiponectin levels were measured as previously described [19]. Briefly, adiponectin antiserum was generated in rabbits using a C-terminal fragment of adiponectin (aa189-202, Biotrend). The amino acid sequence for antibody generation had a 93% homology between human and murine adiponectin. Full-length recombinant human and murine adiponectin or adiponectin-fragment was used as a standard (data not shown). The inter- and intra-assay CV was <6.5%.

Statistical analysis

Statistical analysis of the data was performed with simple descriptive statistics. Paired-samples t-tests were used to compare the means of two variables for a single group. It computes the differences between values of the two variables for each case and tests whether the average differs from 0. The one-way ANOVA procedure produced a one-way analysis of variance for a quantitative dependent variable by a single factor (independent) variable. Analysis of variance was used to test the hypothesis that several means are equal. This technique is an extension of the two-sample t-test.

The assessment of bivariate correlations was performed by Pearson's correlation coefficient. In all analyses $p<0.05$ was considered to indicate statistical significance.

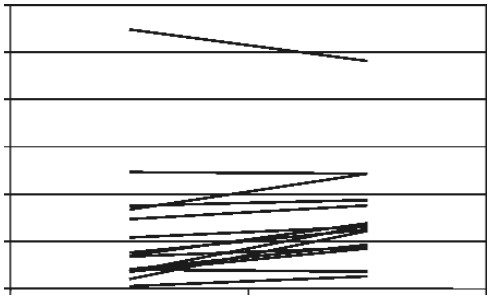

Figure 1. Fasting Serum Adiponectin (nmol/l) before (1) and after (2) short-term lifestyle intervention. Individual (n=16) fasting adiponectin concentrations before and after two weeks of lifestyle intervention (diet and exercise programme) in hospital settings

Results

Results of the study are presented in Tables 1-3 and Figure 1. There was a highly significant fall of BMI, from 42.65±7.82 kg/m^2 to 40.21±7.14 kg/m^2, $p<0.001$. This was accompanied by a significant rise in fasting adiponectin from 32.11±13.25 nmol/l to 35.38±11.04 nmol/l (t-test: p=0.007) (Figure 1).

There was, however, only a trend towards improvement of QUICKI, from 0.34±0.04 to 0.34±0.04, p=0.063, and no significant change of HOMA (p=0.64) or IRI (p=0.88) as assessed by paired t-test (Table I). Seven out of 16 subjects were found to have impaired glucose tolerance during OGTT before lifestyle intervention. None of the study subjects had glucose levels in the diabetic range during OGTT. After a two-week period of lifestyle intervention only four subjects still had evidence of impaired glucose tolerance during OGTT.

There was no significant change in adiponectin concentrations during OGTT before lifestyle intervention, but there was a significant fall in adiponectin concentrations during OGTT after a two-week period of lifestyle intervention (see Table II). There

Table I. Effects of behavioural intervention on BMI, insulin resistance indices and fasting adiponectin in 16 subjects (4 males) during the study

Parameter ±SD	Before intervention	After intervention	P value
Age	42.0±14.18		
BMI	42.65±7.82	40.21±7.14	p<0.001
Fasting glucose (mg/dl)	90.13±15.34	82.07±12.88	0.002
Fasting insulin (µg/dl)	12.67±6.66	13.43±10.77	0.97
HOMA	2.89±1.66	2.69±2.9	0.64
QUICKI	0.34±0.04	0.34±0.04	0.06
IRI	1.29±0.30	1.27±0.29	0.88
Adiponectin (nmol/l)	32.11±13.25	35.38±11.04	0.008

Table II. Adiponectin levels during 75 gram oral glucose tolerance test before and after two-week period of lifestyle interventio

	Adiponectin before (nmol/l)	Adiponectin after (nmol/l)	Glucose before (mg/dl)	Glucose after (mg/dl)	FFA before (mmol/l)	FFA after (mmol/l)
0 min	32.11±13.25	35.38±11.04	90.13±15.34	82.07±12.88	11.07±0.38	1.00±0.45
60 min	31.28±13.25	31.94±10.66	166.25±40.73	161.20±37.65	0.55±0.23	0.49±0.18
120 min	32.94±11.80	31.57±11.12	132.38±37.70	118.53±22.68	0.28±0.17	0.31±0.17
p0 *vs* 60 min	p=0.50	p=0.0005	p<0.005	p<0.001	p<0.0001	p=0.0008
p0 *vs* 120 min	p=0.35	p=0.0001	p<0.0005	p<0.001	p<0.0001	p=0.0003

Table III. Correlation of fasting adiponectin with insulin resistance indices before and after behavioural intervention, as assessed by Pearson's correlation coefficient

	Before intervention	After intervention
HOMA	r=0.01, p=0.97	r=0.04, p=0.88
QUICKI	r=-0.05, p=0.85	r=0.02, p=0.32
IRI (insulin)	r=0.43, p=0.09	r=0.37, p=0.16
IRI (free fatty acids)	r=0.46, p=0.11	r=0.48, p=0.20

was, however, no significant correlation between serum adiponectin and insulin resistance indices, with the exception of a trend towards a positive correlation between serum adiponectin and IRI obtained both from the measurements of glucose and insulin or glucose and FFA during OGTT (see Table III).

Discussion

Our study demonstrates a significant increase in adiponectin levels after two weeks of lifestyle intervention that resulted in moderate weight loss in obese subjects; BMI before lifestyle modification programme was 42.65±7.82 kg/m^2 and after lifestyle modification programme was 40.21±7.14 kg/m^2 ($p<0.001$), average decline of BMI of 2.4 kg/m^2 (average weight loss of 6 kg). This weight loss was accompanied by mild but not significant improvement in insulin resistance indices. The lack of significant change in insulin resistance indices is not surprising given the relatively short intervention period, and given that body composition studies [20] indicate that initial weight loss is related mostly to the loss of glycogen and water with only minor reduction of fat mass. In our study, we did not detect a clear association between serum adiponectin and insulin resistance indices though there was a trend towards positive correlation between serum adiponectin and a dynamic measure of insulin resistance, i.e. the insulin resistance index. There is a possibility that a larger number of subjects might be needed to detect a significant association between insulin resistance indices and total adiponectin, given that a recent study on adiponectin levels in polycystic ovary syndrome, based on data from 62 subjects, showed in multiple linear regression analysis that insulin resistance explained only 13% of the variability of plasma total adiponectin, suggesting a significant role of other, as yet unexplained factors in determination of plasma adiponectin concentrations [21].

Another possible explanation of the lack of correlation between serum adiponectin and insulin resistance might be related to the polymeric structure of adiponectin, where higher molecular weight isoforms tend to correlate better with insulin resistance [22]. Indeed, a recent study of Lara-Castro et al. [23] also confirms that higher molecular weight adiponectin complexes and not total adiponectin are responsible for the association between adiponectin and increased insulin sensitivity.

Interestingly, we have demonstrated a significant increase in serum adiponectin after a relatively short period of intervention (diet and exercise) in a closely supervised hospital environment. Though long-term intervention studies (over 6 months) demonstrated a significant increase in adiponectin levels [24–26], the effects of shorter interventions in most cases failed to demonstrate a significant change in serum adiponectin [27–30]. In contrast to these studies, Balagopal et al. [31] reported a 34% increase in adiponectin concentrations in a 3-month randomised trial, where, similar to our design, intervention consisted both of dietary advice and an exercise programme. Hotta et al. [32] also described a significant (about 50-60%) increase in adiponectin in hospitalised patients after gradual decrease in caloric content from 2000 kcal/day to 800 kcal/day over a two-month period. Though adiponectin levels were measured in that study only after two months, it is possible that a significant increase in adiponectin might have been detected at a much earlier stage. In this context it is interesting to note that beneficial changes in serum adiponectin were observed in our study after only a two-week intervention period. What, however, might be the reason behind the lack of significant changes in adiponectin levels in some other short duration (4-week to 3-month) studies mentioned above? We point out that our study was conducted in a highly supervised hospital environment. This ensured almost 100% compliance with the diet and exercise programme. Though exercise is not invariably associated with changes in serum adiponectin [11, 33], other studies show increase in adiponectin after about one week of exercise programme in obese and overweight males [34] as well as after a longer (6 month) period of lifestyle modification consisting of diet and moderate physical activity [24]. Furthermore, because of our hospital regulations all subjects were forbidden to smoke, and smoking is known to reduce adiponectin levels [35]. In our case 3 out of 4 males and 3 out of 12 women were smokers, but it should be noted that some increase in adiponectin was present in almost all our subjects, regardless of their smoking habits.

Another potentially interesting aspect of our study might be related to the significant change in adiponectin during the oral glucose tolerance test after intervention. The effect of oral glucose tolerance test on adiponectin levels is controversial. Osei et al. [36] showed a non-significant rise in plasma adiponectin during OGTT in subjects with BMI <30 kg/m^2 (from 10.75±5.82 µg/ml to 13.01±5.55 µg/ml, p=0.08, n=8) and no change in those with BMI>30

kg/m^2 and normal glucose tolerance (8.79±4.61 *vs* 8.71±4.59 µg/ml, n=11, p=0.42). Peake et al. [37] also reported no change in adiponectin isoforms (high molecular weight, hexameric adiponectin and trimers) after oral glucose. In contrast, Panidis et al. [38] showed a significant decrease in serum adiponectin in both overweight and normal weight women with and without the polycystic ovary syndrome (PCOS) (overweight: controls n=38, PCOS n=25, normal weight: controls n=10, PCOS n=21). In this context, our study demonstrates that adiponectin response to oral glucose tolerance test may be altered by lifestyle intervention. The mechanism behind this response and its clinical significance remain unclear, though it is known that weight loss not only influences fasting adiponectin levels, but may also restore adiponectin pulsatility [39]. Formal studies on the effects of glucose administration on adiponectin pulsatility before and after weight loss are needed, however, to establish whether such a mechanism might be related to the change in response to oral glucose tolerance after a diet and exercise programme.

Conclusions

In summary, our study demonstrates a significant rise in fasting adiponectin after a two-week lifestyle modification period in a supervised environment. This suggests that even relatively short intervention might be enough to induce favourable changes in concentrations of this adipocytokine. Such intensive intervention might be potentially more effective in inducing favourable and lasting changes in lifestyle than repeated consultations in an outpatient clinic. It remains, however, to be established whether the observed changes may be maintained after discharge from the hospital, i.e. during standard outpatient management.

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