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Levels of adiponectin, C-reactive protein and interleukin-1 receptor antagonist are associated with the relative change in body mass index between childhood and adulthood

JUHA SALTEVO, MAUNO VANHALA, HANNU KAUTIAINEN, MARKKU LAAKSO

Abstract

Obesity has been related to subclinical inflammation and decreased levels of adiponectin. We examined the relationship between inflammatory markers and adiponectin and the change in body mass index (BMI) between childhood and adulthood. Our study included 368 subjects (176 men and 192 women) from a population-based cohort whose weight and height had been recorded at the age of seven years. They participated in this study as adults (with a mean age of 46 years); levels of adiponectin, interleukin-1 receptor antagonist (IL-1 Ra) and high-sensitivity C-reactive protein (hs-CRP) were measured. The relative change of BMI from childhood to adulthood was significantly associated with levels of IL-1 Ra (men: $r=0.27$ [95% CI: 0.12 to 0.40] and women: 0.64 [0.55 to 0.72]), hs-CRP ($r=0.15$ and 0.52, respectively) and adiponectin ($r=-0.13$ and -0.29 , respectively) in both genders.

Decreased levels of adiponectin and elevated levels of IL-1 Ra and hs-CRP at adulthood appear to be related to the change in BMI between childhood and adulthood.

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Key words: adiponectin, C-reactive protein, interleukin 1 receptor antagonist, obesity, relative weight change.

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Introduction

Obesity, especially central obesity, is associated with a clustering of cardiovascular risk factors, particularly insulin resistance, hypertriglyceridaemia, low levels of high-density lipoprotein cholesterol (HDL-C), abnormal glucose tolerance and hypertension.¹

Adipose tissue is hormonally active and involved in the action of insulin as well as glucose and lipid metabolism.² Adiponectin, which is expressed exclusively in adipose tissue and is abundant in human plasma, is decreased in individuals with obesity, type 2 diabetes and coronary heart disease.^{3,4} In a cross-sectional study, obese adolescents had approximately 50% lower adiponectin levels compared to adolescents of normal weight.⁵ Adiponectin has also been implicated as an important regulator of cell growth and tissue remodelling. Some of these functions may be mediated by specific interactions of adiponectin with several growth factors.⁶

Low-grade inflammation is associated with cardiovascular disease,^{7,9} and with diabetes, insulin resistance and metabolic syndrome.^{10,11} C-reactive protein (CRP), an acute-phase reactant, is synthesised in the liver largely in response to interleukin 6 (IL-6). In addition, IL-1 receptor antagonist (IL-1 Ra), a naturally occurring antagonist of the pro-inflammatory cytokine IL-1 β , has been shown to be a central mediator of inflammatory reactions,¹² and it is significantly elevated in the metabolic syndrome.¹³ IL-1 Ra has anti-inflammatory properties, because it binds competitively to IL-1 β membrane receptors. It is also an acute-phase reactant produced by the liver in large quantities during inflammatory states.¹⁴ Thus, high circulating concentrations of CRP and IL-1 Ra are generally considered to indicate an obesity-associated pro-inflammatory state, but it is unknown how they are related to changes in weight.

The aim of this study was to examine the association of IL-1 Ra, hs-CRP and adiponectin with relative weight gain between childhood and adulthood.

Materials and methods

Subjects

Subjects were recruited from a population-based study, which included a total of 1,294 middle-aged subjects born

Table 1. Demographic, clinical and biochemical characteristics of the study subjects

Characteristics	Men	Women	p value
	n=176 Mean (SD)	n=192 Mean (SD)	
Demographic			
At 7 years			
Height, cm	122 (5)	121 (5)	0.17
Weight, kg	23 (4)	23 (4)	0.22
Body mass index, kg/m ²	15.4 (1.3)	15.4 (1.7)	0.91
Adulthood			
Age, years	46 (4)	46 (5)	0.11
Height, cm	177 (6)	163 (6)	<0.001
Weight, kg	82 (12)	70 (13)	<0.001
Body mass index, kg/m ²	26.3 (3.4)	26.2 (4.9)	0.81
Clinical			
Blood pressure, mmHg			
Systolic	135 (16)	130 (17)	0.002
Diastolic	83 (10)	79 (9)	<0.001
Biochemical			
Total cholesterol, mmol/L	5.9 (1.0)	5.6 (1.0)	0.009
HDL cholesterol, mmol/L	1.3 (0.3)	1.5 (0.3)	<0.001
Total triglycerides, mmol/L	1.6 (0.9)	1.3 (0.8)	0.002
Fasting plasma glucose, mmol/L	6.0 (1.0)	5.7 (1.0)	<0.001

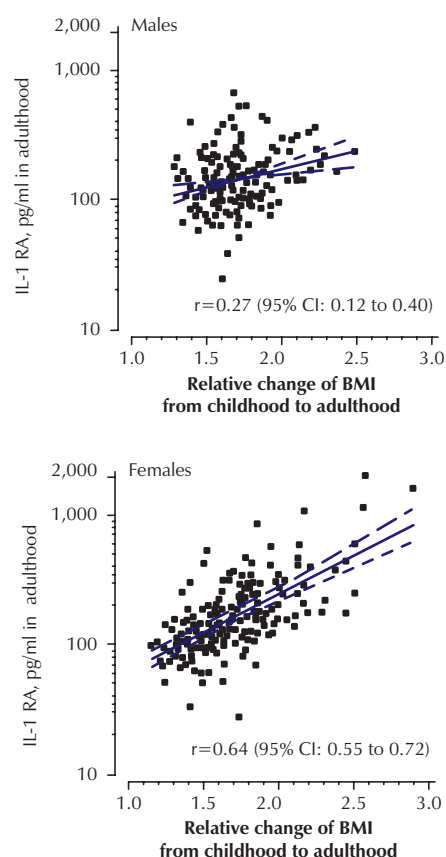
Key: NS = non-significant; HDL = high-density lipoprotein

during 1942, 1947, 1952, 1957 and 1962 (the entire age group) in Pieksämäki, eastern Finland. No exclusion criteria were applied. Altogether, 923 subjects participated in this cross-sectional study; they gave their written informed consent. The study protocol was approved by the Ethics Committee of Kuopio University Hospital and the University of Kuopio. Information on weight and height at the age of seven years (the start of primary school) was obtained from local health registries and was available for 368 subjects. These subjects did not differ from subjects not having weight and height measurements at the age of seven years with respect to clinical characteristics and laboratory data (data not shown).

Clinical and laboratory methods

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Even though BMI cannot distinguish between lean and fat mass, it is considered a reasonable measure of childhood overweight and obesity after the age of two years.^{15,16} The relative change from childhood to adulthood was calculated as adult BMI divided by childhood BMI.

Fasting blood samples were drawn after 12 hours of fasting. The analysis of serum adiponectin was performed using an enzyme immunoassay (human adiponectin ELISA Kit, B-Bridge International Inc., Mountains View, CA, US). Plasma concentration of IL-1 Ra was measured with high-sensitivity assay kits from R&D Systems, Minneapolis, MN, US. CRP was measured with an Immulite analyser and a DPC high-

Figure 1. Relationship between interleukin-1 receptor antagonist (IL-1 RA) levels in adulthood and the relative change of BMI between childhood and adulthood in males and females

Key: BMI = body mass index; r = correlation coefficient; CI = confidence intervals

sensitivity CRP assay (hs-CRP). Serum cholesterol and triglycerides were measured from fresh serum samples using enzymatic colorimeter methods (CHOD-PAP, GPO-PAP, Boehringer Mannheim GmbH, Germany).

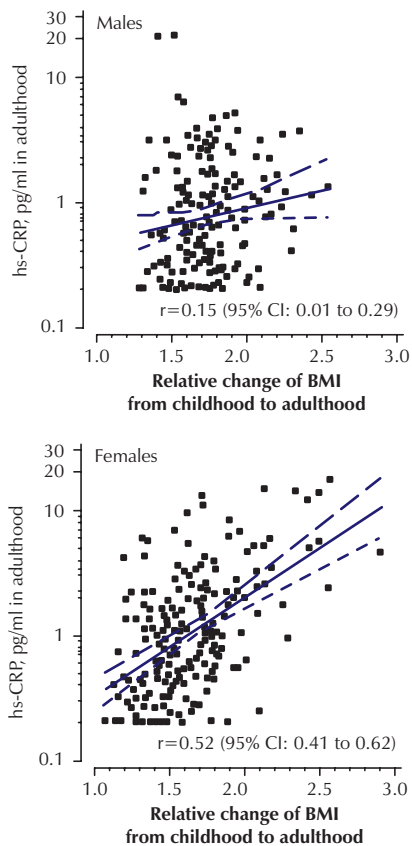
Statistical analysis

The results are given as mean \pm standard deviation (SD), with 95 per cent confidence intervals (CI). The statistical significance between the groups was evaluated by chi-squared test, *t*-test or permutation test (Monte Carlo *p* value). The normality of variables was evaluated by the Shapiro-Wilk *W* test. Variables with skewed distribution were logarithmically transformed for statistical analysis. Correlation coefficients were calculated by the Pearson method and 95 per cent CIs obtained using bias and accelerated bootstrapping (5,000 replications).

Results

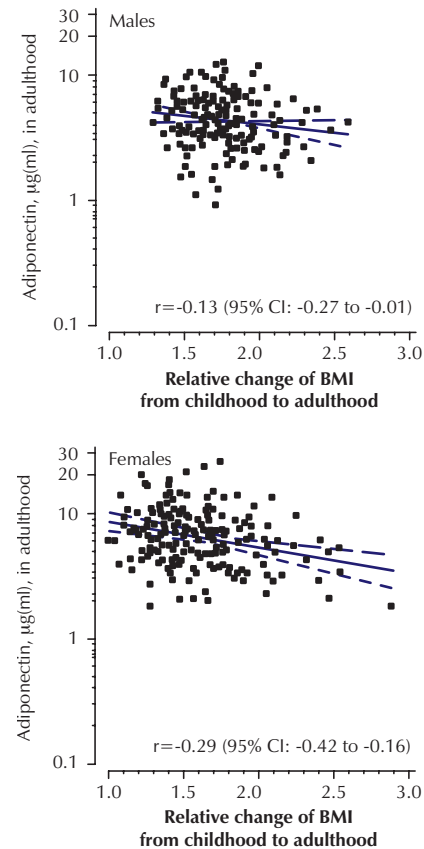
Table 1 shows the height, weight and BMI of the subjects at the age of seven years as well as demographic, clinical and biochemical characteristics of the study population at follow-up (at a mean age of 46 years in men and women).

Figure 2. Relationship between high-sensitivity C-reactive protein (hs-CRP) levels in adulthood and the relative change in BMI between childhood and adulthood in males and females



Key: BMI = body mass index; r = correlation coefficient; CI = confidence intervals

Figure 3. Relationship between adiponectin level in adulthood and relative change of BMI between childhood and adulthood in males and females



Key: BMI = body mass index; r = correlation coefficient, CI = confidence intervals

Levels of measured cytokines were lower in men than in women. Adiponectin levels were 4.6 ± 2.2 in men vs. 8.0 ± 4.8 $\mu\text{g/ml}$ in women, $p < 0.001$; hs-CRP levels were 1.4 ± 2.4 vs. 2.0 ± 2.8 pg/ml , $p = 0.03$; and IL-1 Ra levels 166 ± 97 vs. 209 ± 223 pg/ml , $p = 0.02$, respectively.

Figures 1 and 2 show the significant positive relationship between levels of the inflammatory markers (IL-1 Ra and hs-CRP) in adulthood and the relative change of BMI between childhood and adulthood. Figure 3 shows the significant negative relationship between adiponectin measured at adulthood and the relative change of BMI from childhood to adulthood. The strongest correlation was seen in women with IL-1Ra ($r = 0.64$ [95% CI 0.55 to 0.72]) and in men with IL-1 Ra ($r = 0.27$ [95% CI 0.12 to 0.40]).

Discussion

The novel finding in our study is an association between the relative change of BMI between childhood and adulthood and the levels of adiponectin and markers of low-grade inflammation. This might mean that decreased levels of adiponectin and elevated levels of IL-1 Ra and hs-CRP are also indicators of relative weight gain. The association was particularly strong among women, but it was also significant

among men. The growth pattern and fat distribution may differ between females and males. Studies in this area have conflicting results: some show that intra-abdominal fat tends to be higher in men than in women,¹⁷ and others that women and men have similar amounts of liver and intra-abdominal fat, but women have more subcutaneous fat.¹⁸ In general, women have a higher percentage of body fat than men and markers of inflammation strongly correlate with measures of adiposity.¹⁹

In our study, the elevated levels of pro-inflammatory markers (IL-1 Ra and hs-CRP) and low levels of adiponectin predicted weight gain retrospectively. IL-1 Ra had the strongest correlations with relative weight change in our study. This finding is in line with observations that IL-1 Ra protects human beta cells from glucose-induced functional impairment and apoptosis in obesity.²⁰ The level of IL-1 Ra has been shown to be markedly and reversibly elevated in human obesity and to be predicted by lean body mass and insulin levels.^{21,22} IL-1 Ra has also been shown to be the most sensitive marker of cytokine response in the prediabetic state in the offspring of patients with type 2 diabetes.²³ Later, the levels of IL-1 Ra fall once type 2 diabetes develops.²⁴ A recent 13-week preliminary study with anakinra (a recombinant

human IL-1 Ra) improved glycaemia and beta-cell function and reduced markers of systemic inflammation.²⁵

Levels of adiponectin are decreased in obesity even though this substance comes primarily from adipose tissue. The explanation could be that the inflammation associated with obesity inhibits adiponectin expression.²⁶ Our results support the hypothesis that adiponectin may be the link between overnutrition, weight gain, insulin resistance and cardiovascular disease.^{27,28} The recent finding that obesity at the age of 18 years increases the lifetime risk of diagnosed diabetes²⁹ may reflect the effects of lower levels of adiponectin and higher levels of cytokines over many years. A study in non-diabetic Japanese women showed that a decrease in plasma adiponectin level was associated with low-grade chronic inflammation, as measured by the elevation of hs-CRP.³⁰ In agreement with this notion, a Swedish six-year follow-up study of 2,821 non-diabetic healthy men demonstrated a significant correlation between positive inflammation-sensitive plasma proteins (fibrinogen, orosomucoid, α 1-antitrypsin, haptoglobin and ceruloplasmin) and weight gain.³¹ The inflammatory process, which may be genetically determined, could be the driving force to weight change from childhood to adulthood, not simply a marker of current obesity. A study in Pima Indians failed to demonstrate the association of low adiponectin levels and weight gain in a prospective study, but the follow-up period was only 2–3 years.³²

The limitations of the current study are that adiponectin and the inflammatory markers were measured when subjects were already middle-aged and we do not have these data from their childhood. For this reason, we used the relative change of BMI from childhood to adulthood. Prospective studies are needed to verify this new finding and to show whether inflammation occurs first and whether it predicts future adiposity. The childhood data were obtained from a third of the whole study population, but the clinical characteristics and laboratory data of these subjects did not differ from those of the whole group, which was a population-based cohort of five age groups from the same city with no exclusion criteria.

We conclude that elevated levels of the inflammatory markers IL-1 Ra and hs-CRP and decreased levels of adiponectin are related to relative weight gain between childhood and adulthood, both in females and males.

Conflict of interest statement

None declared.

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