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Metabolism

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Decreased cardiotrophin-1 levels are associated with a lower risk of developing the metabolic syndrome in overweight/obese children after a weight loss program

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ARTICLE INFO

Article history:
Received 14 November 2012
Accepted 17 May 2013

Keywords:
Child
Intervention studies
Obesity
Cytokine

ABSTRACT

Objective. Cardiotrophin-1 (CT-1) shares some similarities with other cytokines, and participates in the control of energy metabolism. Higher circulating levels are observed in obese humans, but little information is gathered in weight loss (WL) programs. Therefore, we aimed to investigate the association of serum CT-1 levels with metabolic variables and the risk of developing metabolic syndrome (MetS) after a WL program in overweight/obese children.

Subjects and Methods. Forty-four overweight/obese children (mean age 11.5 y; 50% males) undergoing a 10-week WL program were enrolled. Subjects were dichotomized at the median of Body Mass Index-Standard Deviation Score (BMI-SDS) change, as high and low responders after intervention.

Results. CT-1 levels were significantly reduced (−48 fmol/mL, $p = 0.043$) in the high responder group after the WL program. They had significantly lower body weight (−3.7 kg, $p < 0.001$), body fat mass (−8%, $p < 0.001$), BMI-SDS (−0.78, $p < 0.001$) and waist circumference (−5.4 cm, $p < 0.001$), and a significant improvement in lipid and glucose profiles ($p < 0.05$). Interestingly, decreased CT-1 levels significantly predicted changes in total cholesterol (41%) and LDL-cholesterol (28%). Moreover, in our participants the lower the CT-1 levels, the higher the reduction in MetS risk components, after the 10-week intervention, (p-ANCOVA = 0.040, p-trend = 0.024).

Conclusion. We showed, for the first time, a reduction in serum CT-1 levels after a WL program and this decrease in CT-1 was strongly associated with a reduction in cholesterol

Abbreviations: WL, Weight loss; BMI, Body Mass Index; BMI-SDS, Body Mass Index-Standard Deviation Score; CT-1, Cardiotrophin-1; IL-6, Interleukin-6; CNTF, Ciliary Neurotrophic Factor; MetS, Metabolic Syndrome; HR, High Responder; LR, Low Responder; LAP, Lipid Accumulation Product; WC, Waist Circumference.

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http://dx.doi.org/10.1016/j.metabol.2013.05.011

levels and in MetS risk factors in overweight/obese children. Our findings may suggest that CT-1 could be an indirect marker for the diagnosis of MetS in this population.

1. Introduction

The prevalence of childhood obesity has almost tripled in US children and adolescents since 1980 [1] and in some countries there is an age-specific stabilization in these elevated values [2,3]. In Spain, a national survey in 2007 showed that 10.3% of the population aged 2–15 yr was obese and 18.8% was overweight [4]. The factors associated with overweight and obesity are complex, such as eating habits, daily physical activity and social, environmental and biological determinants. In fact, nutritional interventions are a valuable strategy to face this serious problem [3,5].

A successful weight loss (WL) program in overweight and obese children and adolescents is usually accompanied by a general metabolic improvement and a reduction in several cardiovascular risk factors [6–9]. Specifically, in intervention studies with 9–13 y obese children, increased circulating adiponectin levels and lower HOMA-IR [8,10–12] were described, together with a reduction in fat mass, Body Mass Index (BMI) or Body Mass Index-Standard Deviation Score (BMI-SDS). Previous studies have shown that an improvement in body composition and cardiometabolic risk can be seen with a BMI-SDS reduction of ≥0.25 in obese adolescents, while greater benefits accrue from losing at least 0.5 BMI-SDS [6].

Concerning changes in blood lipids, a recent systematic review with meta-analysis on the effectiveness of lifestyle interventions in obese children, showed that lifestyle intervention did significantly lower total cholesterol compared with no treatment (−0.40 mmol/L) in 440 obese children aged 8–16 yr [5]. A similar effect was found for triglycerides, the pooled mean difference being −0.20 mmol/L [5].

In recent years, cardiotrophin-1 (CT-1) has emerged as a new player in the control of energy metabolism potentially linked to obesity and type 2 diabetes [13]. CT-1 is a 201 amino acid protein member of the interleukin-6 (IL-6) superfamily of cytokines. It mediates a pleiotropic set of survival effects through a receptor system; consisting of glycoprotein 90 or leukemia inhibitory factor receptor beta (LIFRb) and a common signal transducer, the glycoprotein 130 (gp130) [14]. CT-1 is expressed in a variety of organs from human heart to liver, being nutritionally regulated [13]. It plays a role in the control of energy metabolism sharing some similarities with leptin and other cytokines such as IL-6 or CNTF (ciliary neurotrophic factor) [13,15]. Interestingly, in animals CT-1 activates fat utilization, displays glucose-lowering activity and also shows anorexigenic properties [13]. Thus, experimental data are promising for the therapeutic implication of CT-1 in obesity [16].

Endogenous CT-1 has prolonged stability in whole blood, hence permitting its development in the routine clinical investigation of patients [17]. It seems that circulating CT-1 could be considered as a promising biomarker in patients with cardiovascular diseases and the metabolic syndrome (MetS). However, few studies have been performed in obese human subjects. Two studies showed that obese adults had higher circulating CT-1 levels than normal-weight subjects [18,19] and in overweight adolescents no differences in plasma CT-1 were found when compared to control subjects [20]. There is also no information about the effect of a WL program in CT-1 levels. Thus, our aim was to evaluate changes in serum CT-1 levels after a WL program in overweight/obese children and to investigate the relationship with the risk of developing the MetS and other metabolic parameters. We hypothesized that decreased serum CT-1 levels may predict improvement in metabolic outcomes after a WL program in overweight/obese children, since it has been suggested that the high levels of CT-1 in obese subjects could be a protective mechanism to counteract the emergence of obesity-related alterations [13].

2. Subjects and methods

2.1. *Subjects*

In the study, 71 children between 7 and 15 yr and classified as overweight or obese according to the Cole *et al.* criteria [21] were invited to participate in the information session. Children were recruited from the Endocrinology Pediatric Units of the University of Navarra Clinic and Navarra's Hospital Complex in Pamplona, Navarra. All of them were Spanish or schooling foreigners for at least one year in Spain. Participants with a major psychiatric illness, significant neurological disease, bulimia nervosa, familial hyperlipidemia or any sort of either major cardiovascular or respiratory complication, were excluded. Children and their parents signed a written informed consent. The study protocol was performed in accordance with the ethical standards of the Declaration of Helsinki, and was approved by the Ethics Committee of the University of Navarra (Reference Number 038/2009). From the initial 71 volunteers, 54 successfully underwent baseline anthropometric measurements.

Forty-four participants (22 boys, 22 girls) concluded the 10-week dietary intervention (drop-out rate 18.5%) during two different periods (from April to June and from September to December, 2010) and were assessed for WL after the moderate calorie restriction treatment. BMI-SDS was calculated as a function of the subject's obesity degree when compared with BMI local reference standards [22], which is adjusted for sex and age and it is optimal for assessing adiposity in children. The response of participants to the WL program was based on changes in BMI-SDS. Subjects were dichotomized at the median of BMI-SDS (equal to 0.5). Those who lost >0.50 BMI-SDS were considered as "High Responders" (HR; n = 22) and those who lost ≤0.50 BMI-SDS as "Low Responders" (LR; n = 22) to the program. Previous studies have shown that an improvement in body composition and cardiometabolic risk can be seen with a BMI-SDS reduction of ≥0.25 in obese adolescents, while greater benefits accrue from losing at least