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# Interleukin-20 circulating levels in obese women: Effect of weight loss

**M.I. Maiorino [a], B. Schisano [a], C. Di Palo [a], M.T. Vietri [b], M. Cioffi [b], G. Giugliano [a], D. Giugliano [a], K. Esposito [a,*]**

[a] *Department of Geriatrics and Metabolic Diseases, Division of Metabolic Diseases, Second University of Naples, Piazza L. Miraglia, 80138 Naples, Italy*
[b] *Department of General Pathology, Second University of Naples, Piazza L. Miraglia, 80138 Naples, Italy*

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**Abstract** *Background and aims:* Obesity is associated with an increased risk of developing atherosclerosis. Interleukin-20 (IL-20) is a pleiotropic cytokine thought to be involved in the onset and progression of atherosclerosis. The aim of this study was to determine whether circulating levels of IL-20 are elevated in obese women and whether they could be affected by a substantial decrease in body weight.
*Methods and results:* Fifty obese and 50 age-matched, normal weight, premenopausal women participated in the study. Obese women entered into a medically supervised weight loss program aimed at reducing body weight to 90% of baseline. We measured anthropometric, glucose and lipid parameters, and IL-20, C-Reactive Protein (CRP) and interleukin-10 (IL-10) circulating levels. Circulating IL-20 and CRP levels were significantly higher in obese than control women ($P = 0.01$), while IL-10 levels were significantly lower; IL-20 levels were positively associated with body weight ($r = 0.35$; $P = 0.02$) and visceral fat (waist–hip ratio; $r = 0.32$; $P = 0.025$). Caloric restriction-induced weight loss (>10% of original weight) over 6 months reduced IL-20 levels from 152 (112/184) to 134 (125/153) pg/ml (median and 25%/75%; $P = 0.03$), and it was positively associated with changes in body mass index and waist–hip ratio.
*Conclusion:* In premenopausal obese women, IL-20 levels are higher than matched normal weight control women, are associated with body weight and waist–hip ratio, and are reduced by weight loss.


* Corresponding author. Fax: +39 081 5665054.
*E-mail address:* katherine.esposito@unina2.it (K. Esposito).

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## Introduction

Obesity has become nowadays a common condition and a worldwide public health problem of epidemic proportions [1]. WHO describes obesity as one of the most visible, yet most neglected, public-health problem that threatens to overwhelm both more and less developed countries [2]. The International Obesity Task Force estimates that at present 1.1 billion adults are overweight, including 312 million who are obese [3]. Individuals with a central deposition of adipose tissue can experience elevated cardiovascular morbidity and mortality, including stroke, congestive heart failure, myocardial infarction and cardiovascular death, and this is independent of the association between obesity and other cardiovascular risk factors [4]. Different mechanisms linking obesity to cardiovascular disease have been postulated. Adipose tissue is an active endocrine and paracrine organ that releases a large number of cytokines and bioactive mediators that influence lipid levels, coagulation, fibrinolysis and inflammation [5]. Increased inflammatory activity is believed to play a critical role in the development of atherogenesis and to predispose established atherosclerotic plaques to rupture [6].

IL-20 is a pleiotropic cytokine, preferentially expressed in monocytes, epithelial, and endothelial cells [7], with potent inflammatory, angiogenic, and chemoattractive effects [8]. The amino acid sequences of IL-20 and IL-10 are 28% identical and IL-20 was consequently classified as a member of the IL-10 family. Although much remains to be explained about the physiological and pathogenic mechanisms of action of IL-20, current data support its association with several diseases, including psoriasis, rheumatoid arthritis, and atherosclerosis. Chen et al. [9] have recently shown that IL-20 and its receptors are expressed in human and experimental atherosclerotic plaques; moreover, systemic delivery of IL-20 accelerates atherogenesis in the apolipoprotein E-knockout mouse model. IL-20-induced accumulation of inflammatory cells in monocytes and endothelial cells could be involved in the onset and progression of atherosclerosis [8].

To the best of our knowledge, there are no reported studies that evaluated circulating IL-120 levels in human obesity. The aims of the present study were to determine whether circulating levels of IL-20 are elevated in obese women and whether they could be affected by a substantial decrease in body weight. We also assessed the circulating levels of both C-reactive protein (CRP), which has been found associated with proxy indicators of elevated body fat [10,11] and the anti-inflammatory cytokine interleukin (IL)-10 secreted by the adipocytes [12].

## Methods

### Subjects

We studied 50 obese and 50 age-matched, normal weight, premenopausal women, aged 20—45 yr. Obese women were recruited from those attending the center for obesity management and were followed as out-patients; normal weight women were recruited from the medical and paramedical staff of our department and volunteered to serve as the control group. All women were free from type 2 diabetes, hypertension, cardiovascular disease, and alcohol abuse; none smoked or took any drug. All had normal glucose tolerance, as evidenced by a 2-h postload plasma glucose level below 140 mg/dl. Each woman gave informed written consent to participate in this study, which was approved by the institutional committee of ethical practice of our institution.

Obese women entered into a medically supervised weight loss program aimed at reducing body weight to 90% of baseline. The program consisted of a tailored hypocaloric diet with the following macronutrient composition: 50—55% carbohydrate, 30—35% lipid, and 15% protein. Behavioral and nutritional counseling were also offered to them. Women were in the weight loss program for 6 months and were followed on an out-patient basis at 1-month interval. Compliance with the program was assessed by attendance at the monthly meetings with the nutritionist and completion of the diet diaries. Women also received guidance on increasing their level of physical activity, mainly walking for a minimum of 30 min per day, but also swimming or aerobic ball games. In order to exclude seasonal variations in circulating cytokine levels, assays were repeated after 6 months in control women.

### Clinical and laboratory assessment

All women were studied after a 14-h overnight fast, within the first week after the end of menstrual bleeding and were required to refrain from drinking alcohol in the previous 10 days. Twenty-four hours nutrient intakes were calculated with food-composition tables and weekly diet diaries. All women were asked to complete for 3 days a record of food intake, and to record occupational, household, and leisure time physical activity, to assess dietary adherence and exercise activity.

Height and weight were recorded with participants wearing lightweight clothing and no shoes using a Seca 200 scale with attached stadiometer (Seca, Hamburg, Germany). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The waist to hip ratio (WHR) was calculated as waist circumference in centimeters divided by hip circumference in centimeters. Estimation of insulin sensitivity in the fasting state was assessed with HOMA (homeostasis model assessment) and calculated with the formula: fasting plasma glucose (mmol/l) $\times$ fasting serum insulin ($\mu$U/ml)/25, as described by Matthews et al. [13]. With such a method, high HOMA scores denote low insulin sensitivity (insulin resistance). Assays for serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares, Serono). Serum samples for IL-20 and IL-10 were stored at $-80\,^{\circ}$C until and assayed in duplicate using high-sensitive, quantitative sandwich enzyme assay (Quantikine HS, R&D Systems, Minneapolis, MN). Dilution curves of serum samples were parallel those of standard. All samples were run in the same assay and those showing values above the standard curve were retested with appropriate dilutions. Measurements were made in a blinded manner. Intra- and interassay coefficients of variations for IL-20 were 4% and

6%, respectively; the detection limit was 7 pg/ml. Intra- and interassay coefficients of variation for IL-10 were less than 5% and 10%, respectively. High sensitive CRP was assayed by immunonephelometry on a Behring Nephelometer 2 (Dade Behring, Marburg, Germany).

### Statistical analysis

Data are presented as the group mean (SD), except for cytokines and CRP whose values of which are presented as the median and interquartile ranges (25%/75%) as they were not normally distributed. For a desired value of $P = 0.05$ and 80% power to detect an actual difference on the pre- and post-measurements for the obese group, a sample size of 20/group was considered satisfactory. We compared baseline data using a *t* test for continuous variables and a nonparametric Wilcoxon test for IL-10, IL-20, and CRP. One-sample *t* tests were used to compare continuous variables before and after weight loss. The effects of weight loss on cytokine levels were tested by means of paired *t* test on log-transformed values and a nonparametric Wilcoxon matched test. Pearson's simple correlation allowed studying the association between two variables. Multivariate regression analysis tested the independent association and contribution of changes in body weight, metabolic variables, IL-10 and CRP levels with the dependent variable (IL-20). $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 10.05, SPSS Inc, Chicago, IL).

## Results

The characteristics of the study participants are shown in Table 1. Compared with nonobese women, obese women had higher fasting glucose and insulin concentrations, which resulted in greater values of HOMA, indicating less insulin sensitivity. Except for triglyceride concentrations, which were significantly higher in obese women, the other lipid parameters did not show significant difference between the two groups. Compared with normal weight women, IL-20 and CRP circulating levels were higher in obese women, while IL-10 levels were lower. In obese women, circulating IL-20 concentrations were positively associated with anthropometric measures of fatness, including BMI ($r = 0.35$, $P = 0.02$) and WHR ($r = 0.32$, $P = 0.025$), as well as with fasting insulin levels ($r = 0.25$, $P = 0.04$) and HOMA values ($r = 0.23$, $P = 0.04$). Associations between IL-20 levels and variables of the lipid profile were not significant. In a stepwise multiple regression analyses, both BMI and WHR were independent predictors of IL-20 levels, explaining 30% of the variance ($P = 0.02$).

All obese women completed the weight program and lost at least 10% of their initial body weight (range, 8—16 kg). Compared with baseline values, weight loss was associated with significant reductions of weight, insulin, and triglyceride levels, as well as HOMA values, and with a significant increment in HDL-cholesterol levels (Fig. 1). Weight loss also induced a significant reduction in circulating IL-20 levels, from 152 (112/184) to 134 (125/153) pg/ml (median and 25%/75%; $P = 0.03$); the magnitude and significance of the weight-loss-induced difference were similar whether parametric (paired *t* test) or nonparametric (Wilcoxon matched test) tests were used. Changes in IL-20, CRP and IL-10 circulating levels after weight loss in obese women are given in Table 2. CRP circulating levels decreased after weight loss, while IL-10 levels increased: there were no significant changes in any of these parameters in control women after 6 months. There was no significant change in body weight in the control group at 6 months (difference: −0.5 kg, 95% CI: −2.1 to 0.7 kg).

Changes in BMI ($r = 0.35$; $P = 0.01$) and WHR ($r = 0.30$; $P = 0.02$) were associated with reductions in circulating IL-20 levels. For evaluating the independent association of changes in IL-20 levels with changes in body weight, metabolic variables and cytokine levels, a multivariate analysis was performed in which the IL-20 level was the dependent variable, and BMI, insulin, triglyceride, HDL-

**Table 1** Clinical and metabolic characteristics of the study women[a].

| Parameters | Obese women ($n = 50$) | Nonobese women ($n = 50$) | *P* value |
|---|---|---|---|
| Age (yr) | 38.3 ± 4.6 | 40.2 ± 4.7 | 0.45 |
| BMI (kg/m$^2$) | 34.9 ± 4.7 | 22.5 ± 1.8 | 0.001 |
| WHR | 0.89 ± 0.08 | 0.73 ± 0.04 | 0.001 |
| Glucose (mg/dl) | 93.4 ± 8.7 | 89.5 ± 9.1 | 0.03 |
| Insulin (μU/ml) | 15.6 ± 4.9 | 9.5 ± 3.2 | 0.04 |
| HOMA | 4.1 ± 0.9 | 2.1 ± 0.7 | 0.01 |
| Serum lipids, mg/dl | | | |
| Total cholesterol | 218 ± 34 | 204 ± 47 | 0.90 |
| HDL-cholesterol | 54.6 ± 13 | 58.9 ± 16 | 0.07 |
| Triglycerides | 164 ± 55 | 115 ± 28 | 0.02 |
| IL-20 (pg/ml) | 152(112/184) | 131(99/157) | 0.01 |
| CRP (mg/l) | 3.4(1.3—5.9) | 1.7(0.9—4.1) | 0.01 |
| IL-10 (pg/ml) | 2.8(2.1—4.2) | 4.3(3.9—6.2) | 0.01 |

Abbreviations: BMI, body mass index, HDL, high-density lipoprotein. SI conversions: to convert total and HDL cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113; to convert glucose to mmol/L, multiply by 0.0555.

[a] Data are expressed as mean (SD); IL-20, CRP and IL-10 are presented as median and interquartiles range (25%/75%).

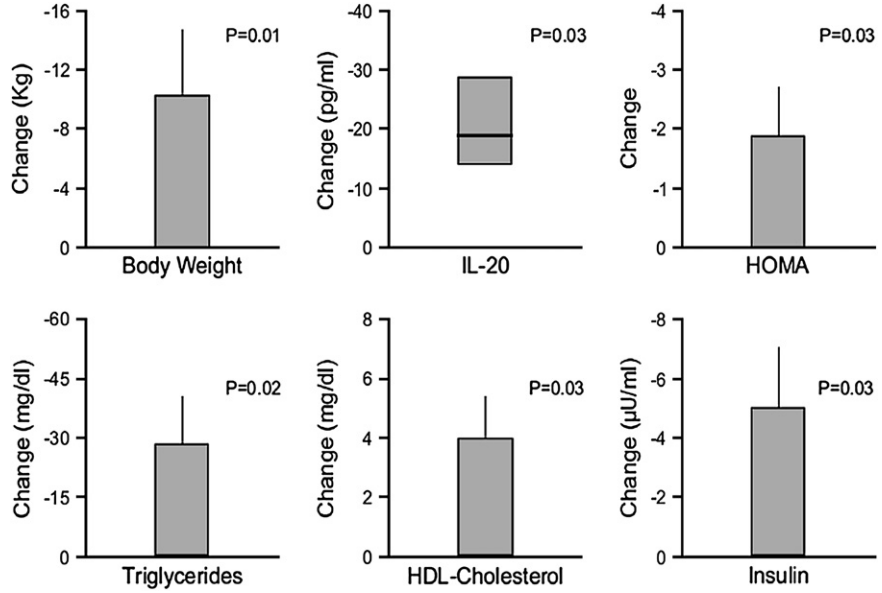


**Figure 1** Change at 6 months in body weight, lipid parameters, insulin indices and IL-20 circulating levels in 50 women participating in the weight loss program.

cholesterol levels, CRP and IL-10 levels were the independent variables. Changes in BMI, insulin and IL-10 explained 18%, 9% and 10%, respectively, of the variability in IL-20 levels.

## Discussion

To our knowledge, this is the first demonstration that circulating IL-20 levels are elevated in obese women and that weight loss is associated with proportional reductions in IL-20 levels. Our findings also confirm that weight loss is associated with reduced CRP levels [11] and increased levels of IL-10 [14]. All these suggest that weight loss may reset the proinflammatory milieu associated with increased fat mass toward a less inflammatory profile. Supporting this, effective weight loss interventions carried out in women have demonstrated reduced levels of proinflammatory cytokines, such as IL-6, IL-18, associated with increased levels of adiponectin [11], an anti-inflammatory cytokine with insulin-sensitizing properties [15].

The secretion of IL-10 by activated monocytes/macrophages and lymphocytes has led to the hypothesis that IL-10 is produced locally in atherosclerotic plaques and may offer protection from an excessive pro-inflammatory response that would result in further damage [16]. Similarly, Juge-Aubry et al. [17] demonstrated that IL-10 is secreted by explants of human white adipose tissues and is up-regulated by TNF-$\alpha$ in vitro, as well as in obese humans and rodents. They speculated that induction of IL-10 by TNF-$\alpha$ represents a counter-regulatory effect, limiting the pro-inflammatory action of this cytokine. Since obesity is classically viewed as a pro-inflammatory state, serum IL-10 levels increase after weight loss in obesity may be seen in the perspective of improvement in accompanying metabolic derangements.

**Table 2** Changes in circulating cytokine levels after 6 months[a].

| Variable | Obese women ($n = 50$) | | Control women ($n = 50$) | | Corrected difference | *P* value |
|---|---|---|---|---|---|---|
| | Mean change | *P* value | Mean change | *P* value | (95% CI)[b] | |
| IL-20, pg/ml | | | | | | |
| Mean (SD) | −21(7.7) | 0.02 | −1.1 (0.5) | 0.31 | −19.9 (−41 to −2) | 0.03 |
| Median (25%/75%) | −19.1 (−29 to −14) | 0.03 | 0.9 (−1.3 to 1.9) | 0.45 | −20.0 (−35 to −4) | 0.03 |
| IL-10, pg/ml | | | | | | |
| Mean (SD) | 1.8 (0.6) | 0.03 | 0.2 (0.1) | 0.78 | 1.6 (0.2 to 3.4) | 0.03 |
| Median (25%/75%) | 1.9 (0.9 to 3.6) | 0.03 | 0.1 (−0.2 to 0.4) | 0.81 | 1.8 (0.4 to 3.9) | 0.02 |
| CRP, mg/L | | | | | | |
| Mean (SD) | −1.2 (0.4) | 0.01 | −0.1 (0.2) | 0.12 | −1.1 (−1.9 to −0.3) | 0.01 |
| Median (25%/75%) | −1.1 (−2.7 to −0.4) | 0.01 | 0.1 (−0.3 to 0.4) | 0.24 | −1.2 (−2.3 to −0.4) | 0.01 |

[a] Data are presented as mean (SD) and median (interquartile range).
[b] CI, confidence interval.

Until now, IL-20 secretion from adipose tissue has never been reported. Our findings of higher circulating levels of IL-20 in obese women, and the relation between changes in body weight and parallel changes in IL-20 levels after weight loss, do not prove that IL-20 is produced by adipocytes. However, macrophages infiltrating the adipose tissue may be a likely candidate [18]. Obesity and type 2 diabetes mellitus are thought to be inflammatory states, consistent with the production of proinflammatory cytokines by adipose tissue [19]. In obese animals and humans, bone-marrow-derived macrophages are recruited to the fat pad under the influence of proteins secreted by adipocytes, including macrophage chemoattractant protein-1 (MCP-1) [18]. Targeted ablation of either MCP-1 or its receptor reduced macrophage infiltration of fat depots despite causing no change in body weight [20] and overexpression of MCP-1 has the opposite effect [21]. A number of atherogenic cytokines originates from non-adipose cells in adipose tissue, macrophages in particular [18]. Macrophages are found more frequently in visceral compared with subcutaneous adipose tissue [22]. Visceral fat correlates with cardiovascular risk factors [23] and is independently associated with mortality in men [24] and with CHD risk in women [25]. Although still controversial, the emerging evidence of excess release of proinflammatory and prothrombotic factors seems to be gaining more weight as the underlying mechanism than the originally proposed portal/fatty acid flux theory through insulin resistance [5]. So, macrophage infiltration into adipose tissue, mainly in visceral fat, likely makes a contribution to the emergence and maintenance of obesity-induced inflammatory responses.

IL-20-induced accumulation of inflammatory cells in various tissues could also be involved in the onset and progression of other inflammatory diseases [8]. Interestingly, psoriasis, rheumatic arthritis, and atherosclerosis are all angiogenesis-dependent disorders, suggesting the possible role of IL-20 in regulation of angiogenesis [9]. Angiogenesis plays a crucial role in the progression of atherosclerosis plaque [26]. In a rat ischemic hind-limb model, for example, IL-20 potently induces endothelial cell tube formation without affecting their proliferation and migration, suggesting that this cytokine plays an important role in vessel remodelling [27].

From a clinical perspective, it is reassuring that lifestyle changes can so effectively reduce rates of both atherosclerosis and type 2 diabetes in the population [28]. In particular, weight loss seems to represent a safe method for downregulating an individual's inflammatory status. Intervention studies aimed at evaluating the effect of weight loss on circulating inflammatory markers have found that weight reduction averaging from 5 to 15% of initial body weight, resulted in significant decrease in circulating C-reactive protein, IL-6, TNF$\alpha$, and adhesion molecule levels [11,29,30]. The present study shows that obese women present higher IL-20 circulating levels than nonobese women; moreover, IL-20 levels in obese women are associated with body weight and abdominal fat deposition, and are reduced by weight loss. Whether IL-20 is directly implicated in atherosclerosis associated with obesity deserves further studies.

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