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Effect of Weight Reduction on Inflammatory Mediators in Patients with and without Metabolic Syndrome

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ABSTRACT

Background: Obesity is now considered a low grade, chronic inflammatory disease that is associated with metabolic disorders like type 2 diabetes and insulin resistance**.** Weight loss in obese and overweight subjects, achieved both by energy-restricted diet or surgery, was found to be a critical factor for reducing the level of inflammatory markers.
Objective: To find if the effect of weight loss on inflammatory mediators in overweight and obese patients will be affected by the presence or absence of metabolic syndrome (MetS).
Methods: The final patient sample was (114) patients. According to BMI and presence or absence of MetS, they were divided into 4 groups: Group (1): overweight with MetS. Group (2): overweight without MetS. Group (3): obese with MetS. Group (4): obese without MetS.
An eight-week program for weight reduction including dietary restrictions and physical activity was followed by all patients. Obesity parameters and inflammatory mediators were measured before and after weight reduction.
Results: Adiponectin, TNFα and IL6 (the significantly different inflammatory mediators before the weight loss program) showed that the highest degree of significant difference was in TNFα between group 2 and 4. Delta change showed that after the weight loss program the changes were significant between the four groups in CRP, TNFα, and IL6. Group 2 and 3 were the only two groups showing significant difference in the 3 parameters.
Conclusions: Presence of MetS augments the beneficial effect of weight loss in those patients in comparison to patients who lack the criteria of MetS.
Keywords: Weight reduction; Inflammatory mediators; Metabolic syndrome.

INTRODUCTION

Obesity is now accepted as a low grade, chronic inflammatory disease that is linked to metabolic disorders, including type 2 diabetes and insulin resistance [(1)]. Overweight persons (those who have body mass index (BMI) ≥ 25 kg/m^2) are nearly 30% of the world population, i.e., 2.1 billion people, more than 600,000 of them are classified as obese (defined as BMI ≥ 30 kg/m^2) [(2)]. Inflammation is a physiological reaction of the organism to injurious stimuli, be they biological, chemical, or physical. If working well, the damaging factor is cleared leading to inflammation resolution with healing of tissues. However, if the dealing with the injurious stimuli or even if the removal of apoptotic inflammatory cells fails, the inflammation process will continue with development of chronic inflammation or autoimmunity [(3)].

Visceral adiposity is considered now as an initial trigger for most of the pathways implicated in metabolic syndrome (MetS). From all the suggested mechanisms, insulin resistance, activation of neurohormones, and chronic inflammation seem to be the leading players in the commencement, advancement, and transformation of MetS [(4)].

Visceral adiposity increases free fatty acids (FFAs), which impede the antilipolytic effect of insulin. FFAs prevent the activation of protein kinase in the muscle which leads to reduced glucose uptake with subsequent insulin resistance development [(5)]. In turn, insulin resistance leads to the development of hypertension as the vasodilator effect of insulin is lost [(6)]. Insulin resistance also increases serum viscosity, induces a hypercoagulable state, and produces pro-inflammatory cytokines, which are released from the adipose tissue promoting the increased risk of cardiovascular disease (CVD) [(7).]

In a meta-analysis including 76 articles, weight loss in obese and overweight subjects, achieved both by energy-restricted diet or surgery, was found to be a critical factor for reducing the level of inflammatory markers [(8)].So, the value of weight loss on level of inflammatory markers is well known now.

Not all patients with obesity have a MetS. As stated by the International Diabetes Federation (IDF) 2006; the MetS can be diagnosed by presence of waist > 94 cm (men) or > 80 cm (women) in addition to the presence of two at least from the following: 1. Blood glucose higher than 5.6 mmol/L (100 mg/dl) or having treatment for diabetes mellitus (DM) -2. High-density lipoprotein cholesterol (HDL-C) < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or taking medications for low high-density HDL-C -3. Blood triglycerides (TG) > 1.7 mmol/L (150 mg/dl) or taking medications for hypertriglyceridaemia -4. Blood pressure > 130/85 [(9)].

In this research, we tried to find if the effect of weight loss on inflammatory mediators in overweight and obese patients will be affected by the presence or absence of MetS. Up to our knowledge, no previous studies examined this effect.

PATIENTS AND METHODS

This is a prospective cohort study. Willing overweight or obese subjects were recruited from

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outpatient's clinic. The inclusion criteria were age 18–65-year, and 25≤ BMI <35. Patients with clinical evidence of active inflammation or infection, uncontrolled DM or organ failure (liver, kidney, and heart), severe comorbidity (i.e., chronic pulmonary disease, active cancer) were excluded from the study. Acetylsalicylate (75-100 mg / day) was the only allowed medication from non-steroidal anti-inflammatory group.

- **Anthropometric assessment:**

Height, weight (while wearing lightweight clothing and bare footed), waist circumference (the midpoint from the lower costal margin to the iliac crest), were measured. BMI was calculated as weight (kg)/ height $(m)^2$. Overweight was defined as (25≤BMI<30) and obese (30≤BMI<35).

- **Weight loss program:**

Using the Mifflin St Jeor equation, resting energy expenditure was calculated for all patients and according to daily activity per week, energy requirements were estimated. Dietary food list was designed to offer energy requirements minus 500-800 kcal/day. A simplified "Food Exchange Lists" was provided to the patients with a 60-minute round training for each 10 patients. Patients were instructed to exercise or have a brisk walking 150 minute per week as a 30 minute per day for 5 days per week. Patients were reinforced every 7 days to make sure that dietary instructions and physical activities were followed. The program duration was eight weeks.

- **Patients' categorization:**

The original sample consisted of 140 patients. Patients who failed to lose at least 4 % of their weight were excluded from the results (11 patients). Some patients did not come on time or lost connection with the authors (15 patients) so also were excluded from the results, so the final patient sample was (114) patients. According to BMI and presence or absence of MetS, they were divided into 4 groups:

Group (1): overweight patients (25 ≤BMI <30) with MetS (n =30). *Group (2):* overweight patients (25 ≤BMI <30) without MetS. (n =28). *Group (3):* obese patients (30 ≤BMI <35) with MetS (n =29). *Group (4):* obese patients (30 ≤BMI <35) without MetS (n =27).

- Laboratory investigations:

For each patient, 2 sets of blood sample (before and after the weight loss program) were obtained. Each set consists of 3 venous blood samples.

One sample (1.8 ml) was collected in purple-topped vacutainer tube (Greiner Bio-One, Germany). Using this sample, complete blood count (CBC) was measured using Sysmex XN-2000 autoanalyzer (Siemens Diagnostic, Erlangen, Germany) for calculation of neutrophil to lymphocyte ratio (NLR).

The other 2 venous blood samples were collected on 2 yellow-topped gel vacutainer tube (ELDAWLIA ICO, Asyut, Egypt) for serum separation. Serum from one tube was used for immediate measurement of CRP, TG, HDL-C using Cobas c702/8000 autoanalyzer (Roche diagnostic, Mannheim, Germany), and interleukin 6 (IL6) on Cobas e602/8000 autoanalyzer (Roche diagnostic, Mannheim, Germany).

The separated serum from the 2nd tube was frozen at -80˚C until TNFα, and adiponectin quantification.

A quantitative measurement of TNFα was done using TNFα PicoKine ELISA kit (Boster Biological Technology, Pleasanton CA, USA, Catalog # EK0525). And quantitative measurement of adiponectin was done using human adiponectin ELISA kit PicoKine® (Boster Biological Technology, Pleasanton CA, USA, Catalog # EK0595). Both were measured according to manufacturer protocol.

Ethical consent:

The study was approved by Zagazig University's Research Ethics Committee. Informed consent forms were signed by all patients and submitted them to Zagazig University. We ensured adherence to the Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.

Statistical analysis

Data were analyzed using SPSS program (Statistical Package for the Social Sciences) version 24. The Shapiro-Wilk test was used to test normality of data. All data were non-normally distributed (non-parametric). Quantitative data were expressed as median and interquartile (IQ) range. Wilcoxon test was used to compare the changes along time for non-parametric paired variables. Kruskal-Wallis test was used to calculate difference between quantitative variables in more than two groups. Post hoc test for multiple comparisons was done by using Dunn's Multiple Comparison Post-hoc test, to detect which groups were significantly different from each other. Spearman's correlation test was used to detect correlation between variables. All statistical comparisons were two tailed with significance level of P-value ≤ 0.05.

RESULTS

The characteristics of the study subjects before the 8 weeks of weight loss program are shown in **(Table 1).** There was a significant difference between the four groups in BMI, weight, triglycerides, and diastolic blood pressure (DBP). Regarding the inflammatory markers, IL6, TNFα, and adiponectin showed a significant difference. There was no significant difference in CRP and NLR.

Table (1): **Anthropometric and biochemical features of studied population among groups before the 8 weeks of weight loss program**

	Overweight-MetS (group 1) N=30	Overweight– no MetS (group 2) N=28	Obese – MetS (group 3) N=29	Obese – no MetS (group 4) N=27	*p*
Weight (kg)	79 (77-82)	80 (77-82.8)	94 (88-99)	99 (95-103)	<0.001
BMI	26.9 (25.9-27.8)	27.4 (26.7-28.1)	32.5 (31.4-33.7)	32.7 (31.9-33.7)	<0.001
Waist (cm)	102 (96-106.2)	99 (95.3-103)	101 (95-105)	95 (89-101)	0.026
SBP (mm Hg)	137 (131-140)	135.50 (128.5-140)	138 (129-140)	138 (133-140)	0.936
DBP (mm Hg)	79 (75-84)	86.50 (84.3-90)	80 (75-83)	80 (76-84)	<0.001
TG (mg/dL)	155.5 (112-177)	105 (95 -118.8)	152 (140-177)	142 (113-156)	<0.001
HDL (mg/dL)	45 (40.7-46)	45 (40-46)	48 (41.5-53)	44 (42-51)	0.595
Adiponectin (ng/ml)	11.4 (10.5-16.8)	11.7 (10-18.6)	11 (8-13.8)	9.3 (8.3-12.2)	0.027
CRP (mg/L)	8 (6.2-9.0)	7.9 (6.4-9.2)	8.3 (7.3-11)	7 (5.2-8.8)	0.054
TNFα (pg/mL)	8.5 (7.9-12.4)	8.5 (7.6-9.4)	9.8 (8.6-12.5)	11.6 (9.3-12.9)	<0.001
IL6 (pg/mL)	5.2 (3.9-6.7)	6 (4.4-7.6)	6.7 (5.3-8.4)	6.3 (4.6-7.5)	0.018
NLR	2.6 (2.3-2.9)	2.4 (1.7-2.7)	2.7 (2.5-3)	2.4 (2-2.9)	0.168

MetS: metabolic syndrome. BMI: body mass index. SBP: systolic blood pressure. DBP: diastolic blood pressure. TG: triglycerides. HD: high-density lipoproteins. CRP: C reactive protein. TNFα: tumor necrosis factor. IL6: interleukin 6. NLR: neutrophil to lymphocyte ratio.
-Data are non-parametric and expressed as median (IQ range)

Post hoc analysis was done for significantly different parameters (**Table 2).**

Table 2: P values of the post-hoc analysis to indicate which groups were significantly different from each other

Post-hoc	Group 1 vs. group 2	Group 1 vs. group 3	Group 1 vs. group 4	Group 2 vs. group 3	Group 2 vs. group 4	Group 3 vs. group 4
BMI	0.163	<0.001	<0.001	<0.001	<0.001	0.304
Weight (kg)	0.878	<0.001	<0.001	<0.001	<0.001	0.008
Waist (cm)	0.076	0.414	0.003	0.333	0.222	0.03
TG (mg/dL)	<0.001	0.195	0.242	<0.001	0.003	0.016
DBP (mm Hg)	<0.001	0.706	0.724	<0.001	<0.001	0.474
Adiponectin (ng/ml)	0.892	0.099	0.089	**0.024**	0.123	0.932
TNFα (pg/mL)	0.066	0.196	**0.041**	**0.002**	**<0.001**	0.437
IL6 (pg/mL)	0.201	**0.001**	**0.037**	**0.037**	0.411	0.21

TG: triglycerides. DBP: diastolic blood pressure. TNFα: tumor necrosis factor. IL6: interleukin 6.

To study the correlations within each group between inflammatory markers (TNFα, IL6, and adiponectin), which showed significant difference, and obesity parameters before the 8-week weight loss program, Spearman's correlation test was used. All inflammatory markers did not show significant correlation with obesity parameters within each group **(Table 3).**

Table (3): Correlations between adiponectin, TNFα, and IL6 level and obesity parameters before the 8-week weight loss program within each group

Groups	Variables	Adiponectin		TNFα		IL6	
		r	P	r	P	r	P
group 1	Weight	0.101	0.596	-0.113	0.553	0.300	0.107
	BMI	-0.181	0.338	-0.026	0.890	-0.156	0.411
	Waist	-0.080	0.676	-0.150	0.427	-0.155	0.414
group 2	Weight	0.006	0.974	-0.143	0.467	0.061	0.758
	BMI	0.030	0.880	-0.098	0.620	-0.074	0.708
	Waist	-0.197	0.314	0.284	0.143	0.144	0.465
group 3	Weight	0.028	0.887	0.213	0.268	-0.202	0.293
	BMI	0.040	0.838	0.176	0.361	-0.256	0.181
	Waist	-0.088	0.649	0.134	0.489	-0.238	0.213
group 4	Weight	-0.229	0.251	0.062	0.758	0.001	0.999
	BMI	-0.112	0.577	0.248	0.211	-0.069	0.733
	Waist	-0.050	0.805	0.321	0.103	0.347	0.076

r = Correlation coefficient. TNFα: tumor necrosis factor. IL6: interleukin 6. NLR: neutrophil to lymphocyte ratio.

(Table 4) shows changes within each group in weight, waist, lipid profile, and inflammatory markers after the 8 weeks weight loss program. Apart from HDL in group 1, all other parameters in all the other groups showed some degree of significant difference.

Table (4): Changes in obesity parameters, lipid profile, and inflammatory markers after the 8-week weight loss program

	Group 1 (N=30)			Group 2 (N=28)			Group 3 (N=29)			Group 4 (N=27)		
	before	**after**	***p***	**before**	**after**	***p***	**before**	**after**	***p***	**before**	**after**	***p***
Weight (kg)	79 (77-82)	76 (73.8-77)	<0.001	80 (77-82.8)	75 (67-77)	<0.001	94 (88-99)	90 (84-95.5)	<0.001	99 (95-103)	94 (89-99)	<0.001
Waist (cm)	102 (96-106.2)	97.5 (91-103)	<0.001	99 (95.3-103)	93.5 (80-98.8	<0.001	101 (95-105)	96.7 (93-100.5)	<0.001	95 (89-101)	91 (84.2-10597.4)	<0.001
TG (mg/dL)	155.5 (112-177)	141.5 (111-157.5)	0.004	105 (95 - 118.8)	102.5 (90-114)	<0.001	152 (140-177)	142 (126-163)	0.008	142 (113-156)	142 (111-147)	<0.001
HDL (mg/dL)	45 (40.7-46)	45.5 (43.8-49.3)	0.447	45 (40-46)	46 (43-48.8)	0.017	48 (41.5-53)	48 (40.5-54.5)	<0.001	44 (42-51)	46 (40-52)	0.001
Adiponectin (ng/ml)	11.4 (10.5-16.8)	13 (11.3-17.9)	<0.001	11.7 (10-18.6)	12.8 (10-19.3	0.004	11 (8-13.8)	12 (8.9-14.7)	0.025	9.3 (8.3-12.2)	9.5 (9.1-12.6)	0.002
CRP (mg/L)	8 (6.2-9.0)	7 (5.7-8)	<0.001	7.9 (6.4-9.2)	7.7 (6.6-9)	<0.001	8.3 (7.3-11)	7.7 (6.2-9)	0.017	7 (5.2-8.8)	6.2 (4.1-7.1)	0.002
TNFα (pg/mL)	8.5 (7.9-12.4)	8.5 (6.7-10.4)	<0.001	8.5 (7.6-9.4)	8.2 (7.4-9)	<0.001	9.8 (8.6-12.5)	9 (7.3-12.1)	<0.001	11.6 (9.3-12.9)	10.3 (8.6-11.7)	<0.001
IL6 (pg/mL)	5.2 (3.9-6.7)	5 (3.2-6.5)	0.005	6 (4.4-7.6)	5.8 (4.6-7.2	<0.001	6.7 (5.3-8.4)	3 (5-7.2)	0.012	6.3 (4.6-7.5)	5.8 (4.4-7.5)	0.002
NLR	2.6 (2.3-2.9)	2.3 (2-2.6)	0.005	2.4 (1.7-2.7)	2.2 (1.5-2.5	<0.001	2.7 (2.5-3)	2.4 (2-2.9)	<0.001	2.4 (2-2.9)	2.3 (2-2.7)	<0.001

TG: triglycerides. HDL: high-density lipoproteins. CRP: C reactive protein. TNFα: tumor necrosis factor. IL6: interleukin 6. NLR: neutrophil to lymphocyte ratio.
-Data are non-parametric and expressed as median (IQ range)

(Table 5) shows the delta change in inflammatory markers in response to weight reduction among groups. The delta value was defined as post-intervention value minus pre-intervention value. It was significant for TNFα, IL6, and CRP.

Table (5): Delta change in inflammatory markers in response to weight reduction among groups

	Group 1	Group 2	Group 3	Group 4	*P*
Delta adiponectin	1.05 (-1.80 to 5.20)	0.85 (-2.20 to 2.90)	0.90 (-1.10 to 2.90)	0.70 (-1.30 to 1.60)	0.344
Delta CRP	-0.95 (-3.30 to 1.10)	-0.20 (-2.00 to 0.30)	-0.90 (-3.80 to 1.70)	-1.10 (-2.90 to 1.10)	0.029
Delta TNFα	-0.90 (-2.50 to 1.00)	-0.40 (-0.80 to 0.50)	-1.20 (-4.30 to 1.30)	-0.70 (-2.70 to 0.40)	0.001
Delta IL6	-0.25 (-2.20 to 0.50)	-0.15 (-1.50 to 0.30)	-0.60 (-2.20 to 0.40)	-0.40 (-1.30 to 0.40)	0.005
Delta NLR	-0.20 (-0.70 to 0.40)	-0.20 (-0.80 to 0.20)	-0.20 (-0.80 to 0.20)	-0.20 (-0.50 to 0.20)	0.175

(Negative delta value means that the second value is less than the first one)

-Data are non-parametric and expressed as median (IQ range)

Post-hoc analysis was done for these significant changes **(Table 6)**.

Table (6): P values of the post-hoc analysis of delta changes in inflammatory markers in response to weight reduction among groups

	Group 1 vs. group 2	Group 1 vs. group 3	Group 1 vs. group 4	Group 2 vs. group 3	Group 2 vs. group 4	Group 3 vs. group 4
Delta CRP	0.020	0.902	0.745	0.015	0.010	0.839
Delta TNFα	0.008	0.127	0.781	<0.001	0.019	0.077
Delta IL6	0.278	0.017	0.775	<0.001	0.436	0.009

DISCUSSION

The effect of weight loss on inflammatory mediators in obese patients has been already proved in other studies [(10)]. The hypothesis that, presence of MetS in obese patients can change this effect, was tested in this work. The pathophysiological rationale behind this hypothesis is that over-weight and obese persons without MetS could be free of the pro-inflammatory effect of insulin resistance and dyslipidemia.

Significant research to identify initiators for chronic inflammation in MetS has been done. The liver, the intestine, and adipose tissue have been proposed as the triggers of such inflammation [(11)]. Inflammatory mediators release from one site triggers inflammation in other tissues, expanding the generalized tissue dysfunction and damage [(12)].

The levels of inflammatory mediators before intervention showed significant difference in adiponectin, TNFα, and IL6. The CRP, a common marker, and the NLR, a newly and not commonly used one, showed non-significant difference.

Adipocytes behave as immune cells that release an enormous amount of adipokines and cytokines which are proinflammatory mediators [(13)]. The inflammatory state following the MetS shows a quite distinct presentation, as it is not marked by infection or indications of autoimmune process or massive tissue damage. Furthermore, the magnitude of the inflammation is not great and so it is often referred to as "low-grade" chronic inflammation [(14)]. Others named this inflammatory state as "meta-inflammation", to indicate that it is a metabolically triggered inflammation, or "para-inflammation" [(15)].

Post hoc analysis for adiponectin, TNFα and IL6 (the significantly different inflammatory mediators) showed that the highest degree of significant difference was in TNFα between group 2 and 4. The three mediators were significantly different between group 2 and 3, TNFα and IL6 between group 1 and 4 and IL6 only between group 1 and 3. It seems that the presence of MetS adds to the effect of weight on inflammatory mediators' level.

We observed that the degree of weight loss and the change of waist circumference was significant within each group and not affected by the presence of MetS or the initial weight. This may indicate that adherence to the weight loss program is the major affecting factor in weight loss. The changes in inflammatory mediators -within each group after weight loss- were statistically significant. **Monzillo *et al.*** studied the effect of 6-month weight loss program on 24 insulin resistant obese subjects. After an average 7% reduction in body weight, IL-6 levels decreased

significantly but there was no significant change in the mean CRP values [16]. The same study found that TNFα decreased with reduction of weight but with a significant reduction only in the impaired glucose tolerance subgroup. **Bastard *et al.*** failed to find a change in TNFα after weight loss [17]. **Pedersen *et al.*** used low energy diet for 12 weeks in 29 non-diabetic participants with CAD, no significant changes were seen in CRP and IL6 while TNFα showed a statistically significant 9.5% decrease [18].

Delta change, reflecting the dynamic changes in inflammatory mediators, showed that the changes was significant between the four groups in CRP, TNFα, and IL6. Post hoc analysis showed that group 2 and 3 are the only two groups showing significant difference in the 3 parameters with a highly significant difference in TNFα and IL6, a result which can indicate the patients with MetS and a higher degree of obesity will experience greater decrease in inflammatory mediators in response to weight reduction in comparison to those with a lesser degree of obesity and having no Mets.

More similar studies are needed to compare results and to confirm the findings of this study.

CONCLUSION

Our study suggests that the presence of MetS augments the valuable role of weight loss in patients with MetS in comparison to patients who lack the criteria of MetS.

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Conflict of Interest:

The authors have no conflict of interest to report.

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