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Changes in IL-6 and IL-37 levels before and after sleeve gastrectomy in obese patients with metabolic syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is characterized as a cluster of metabolic disorders, with key components including dyslipidemia, insulin resistance, low-grade inflammation, and hypertension. Interleukins (ILs) are crucial cytokines secreted by the immune system, playing a significant role in inflammation and immune regulation. IL-37, a member of the IL-1 family (IL-1F7), is an anti-inflammatory cytokine. However, research investigating the role of IL-37 in the pathogenesis of MetS remains limited. This study aimed to evaluate plasma IL-6 and IL-37 levels in patients with MetS.

Materials and Methods: A total of 80 participants (33 males, 47 females) were included in the study. Venous blood samples obtained from individuals diagnosed with Metabolic Syndrome (MetS) (Group II, n=40) and healthy volunteers (Group I, n=40) were used for the analysis of plasma lipids, IL-6, and IL-37 levels. Among the MetS group, 20 patients underwent laparoscopic Sleeve Gastrectomy (SG) due to obesity. The total cholesterol, HbA1c, IL-6, and IL-37 levels in plasma samples collected before (Pre-SG) and after (Post-SG) the operation were compared. Plasma IL-6 and IL-37 levels were measured using a commercially available solid-phase competitive enzyme-linked immunosorbent assay (ELISA).

Results: Plasma IL-37 levels were significantly lower in Group II compared to Group I, whereas IL-6 levels were significantly higher (IL-6: Group I: 0.82±0.41; Group II: 2.06±0.5; p<0.001; IL-37: Group I: 1.47±0.51; Group II: 0.67±0.27; p<0.001). Preoperative IL-37 levels were lower compared to postoperative levels following SG, while IL-6 levels exhibited the opposite trend.

Conclusion: IL-37 may serve as a promising therapeutic target for preventing and slowing the progression of MetS. However, larger-scale, multidisciplinary studies with additional parameters are necessary to further validate these findings.

Keywords: Interleukin 37, interleukin 6, laparoscopic surgery, metabolic syndrome, obesity, sleeve gastrectomy

Introduction

Metabolic syndrome (MetS) is characterized as a cluster of metabolic disorders, primarily including dyslipidemia, insulin resistance, low-grade inflammation, and hypertension.[1] Since MetS is associated with dysfunctional adipose tissue and chronic low-grade inflammation, addressing these underlying mechanisms may provide significant benefits for its prevention and treatment.

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The development of MetS is influenced by multiple factors, including gender, age, ethnic differences, physical inactivity, diet, smoking, alcohol consumption, adipocytokines, as well as epigenetic and mitochondrial factors. Scientific evidence from experimental models and studies in both humans and animals with MetS highlights the crucial role of cytokines in the etiopathogenesis of the syndrome. Inflammatory cytokines are believed to contribute to insulin resistance and elevated plasma free fatty acids.[2,3] The discovery that precursor fat cells exhibit macrophage-like characteristics supports the hypothesis that adipose tissue is actively involved in inflammatory processes.

In healthy adipose tissue, T cells, eosinophils, and M2 macrophages produce IL-4, IL-10, and IL-13, fostering an anti-inflammatory environment that preserves insulin sensitivity. However, in obesity, M1 macrophages within adipose tissue secrete pro-inflammatory cytokines, thereby promoting inflammation and insulin resistance.[4] Additional alterations that contribute to this pro-inflammatory response include a reduction in eosinophils and regulatory T cells, as well as an increase in neutrophils, B cells, mast cells, and interferon-γ (IFN-γ)-secreting T helper (Th) 1 and cytotoxic CD8+ T cells. Scientific studies have identified key cytokines associated with MetS and its components, including tumor necrosis factor-alpha (TNF-α), IFN-γ, IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-12, IL-18, IL-21, and IL-33.[5,6]

Cytokines, which are structurally peptides or glycoproteins, play a fundamental role in modulating immune responses against foreign substances and antigens. They regulate both systemic and local inflammatory processes by facilitating intercellular communication and immune system interactions. Interleukins, a major subset of cytokines secreted by immune cells, primarily activate immune system components. By inducing the expression of proteins such as chemokines, nitric oxide synthase, and matrix metalloproteinases, interleukins are pivotal in controlling immune functions and inflammatory processes.[7-9]

IL-37, a member of the IL-1 family (IL-1F7), is an anti-inflammatory cytokine. It is secreted from various tissues at different stages of inflammation and exists in five isoforms (IL-37a, b, c, d, e). Some isoforms, however, are exclusive to specific organs: IL-37a is secreted solely from the brain, IL-37b from the kidney, IL-37c from the heart, and IL-37d from the bone marrow and testes. These isoforms undergo maturation and interact through currently unknown mechanisms involving mRNA sequencing and various enzymatic processes, ultimately forming IL-37.[10,11]

Despite its potential significance, the role of IL-37 in the pathogenesis of MetS remains poorly understood. This study is the first to evaluate IL-6 and IL-37 levels in patients undergoing sleeve gastrectomy (SG) for obesity.

Materials and Methods

Ethical Approval

The study was approved by the Biruni University Non-Interventional Ethics Committee (Decision No: 2023/79-33). It was conducted on patients diagnosed with MetS who applied to the Endocrine Clinic of Biruni University Faculty of Medicine Hospital, as well as healthy volunteers who visited the clinic for control purposes. The study was carried out in accordance with the ethical principles outlined in the World Medical Association Declaration of Helsinki (2000).

Inclusion Criteria

- Participants aged between 25 and 65 years were included
- For the patient group: diagnosis of MetS according to the NCEP ATP III criteria.
- For healthy volunteers: absence of a MetS diagnosis.
- Individuals who provided informed consent to participate in the study (for both patient and healthy volunteer groups).

Exclusion Criteria

- Were not diagnosed with MetS (for patient groups)
- Individuals with autoimmune, infectious, or malignant diseases; those taking anti-inflammatory or immunosuppressive medications; pregnant or breastfeeding women; and participants with incomplete data were excluded from the study.
- Did not consent to participate in the study or did not fall within the age range of 25-65 years (for both patient and healthy volunteer groups).

Study Group Determination

Sample size was determined using the G*Power software (version 3.1.9.4, Düsseldorf University), aiming for 80% power and an effect size of 0.7. Based on this, a minimum of 18 participants per group was calculated. A total of 80 participants were enrolled, including 40 individuals with MetS and 40 healthy controls. Of those in the MetS group, 20 underwent sleeve gastrectomy (SG) due to obesity and were evaluated both before and 6 months after surgery.

The study groups were classified as follows:

- Group I (40 individuals): Healthy volunteers
- Group II (40 individuals): Patients diagnosed with MetS. Among the patients diagnosed with MetS, only 20 underwent SG. Pre-SG (20 individuals): Patients diagnosed with MetS and obesity prior to sleeve gastrectomy. Post-SG (20 individuals): Patients diagnosed with MetS and obesity after sleeve gastrectomy (at the end of 6 months)

All participants provided written informed consent before enrollment in the study. Venous blood samples (2.5 mL) were collected from each participant into heparinized tubes.

Surgical Procedure History

The study included patients who had undergone laparoscopic sleeve gastrectomy (SG) as a surgical intervention for obesity.[12]

Analysis Method

Anthropometric measurements and blood samples were collected to assess plasma lipid levels and cytokine profiles. Plasma samples stored at -20°C were thawed in a water bath before analysis and subsequently centrifuged at 3000 rpm for 5 minutes. Changes in IL-6 (Cat. No: E0090Hu, BT LAB, China) and IL-37 (Cat. No: E1947Hu, BT-LAB, China) levels were comparatively analyzed across the four study groups. For patients with MetS who underwent laparoscopic SG, cytokine analyses were performed at the end of the 6-month postoperative period.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism 9.1.1 software. For between-group comparisons, Student's t-test was used for normally distributed variables and the Mann–Whitney U test for non-parametric data. For repeated measures within the same individuals, paired t-tests or Wilcoxon signed-rank tests were applied. Parametric data are presented as mean±standard deviation (SD), while non-parametric data are expressed as median with interquartile range (IQR). A p-value of ≤0.05 was considered statistically significant.

Results

A total of 80 participants were included in the study (33 men and 47 women). The mean age in Group I was 44.3 years (range: 27-65), while in Group II, it was 41.1 years (range: 25-65). The body mass index (BMI) was 20.88±3.1 kg/m² in Group I and 27.54±2.96 kg/m² in Group II. Plasma IL-37 levels were found to be significantly lower in Group II compared to Group I, whereas IL-6 levels exhibited the opposite trend (IL-6, Group I: 0.82±0.41; Group II: 2.06±0.5; $p<0.001$; IL-37, Group I: 1.47±0.51; Group II: 0.67±0.27; $p<0.001$).

When the results were analyzed based on gender differences, it was observed that plasma IL-37 levels were lower in men compared to women, whereas plasma IL-6 levels were lower in women compared to men. The analysis of lipid profiles (mean values) revealed that plasma triglyceride and total cholesterol concentrations were significantly elevated in the MetS group compared to the healthy group. Conversely, HDL-cholesterol (mg/dL) concentrations were significantly lower in the MetS group compared to the healthy group ($p<0.05$) (Table 1).

Our study identified four key variables that significantly influenced the improvement of MetS in patients undergoing sleeve gastrectomy (SG). These variables included total weight loss (%), body mass index (BMI, kg/m²), total cholesterol (mg/dL), and HbA1c levels at six months post-surgery. Furthermore, it was observed that all patients who underwent surgery for obesity had Type 2 diabetes mellitus (T2DM).

Pre-SG IL-37 levels were significantly lower compared to post-SG levels (IL-37, pre-SG: 0.61±0.33; post-SG: 1.65±0.47; $p<0.001$). Conversely, IL-6 levels demonstrated the opposite trend, indicating an antagonistic relationship between these two cytokines (IL-6, pre-SG: 1.97±0.38; post-SG: 0.96±0.36; $p<0.001$) (Table 2).

Table 1. Demographic data, anthropometric measurements, and IL-6 and IL-37 analysis results for patient and control groups

Variable	Control Group (Group I) (Mean±SD) (n=40)	MetS Group (Group II) (Mean±SD) (n=40)	p
Age (year)	44.3 (27-65)	41.1 (25-65)	>0.05
BMI (kg/m^2)	20.88±3.1	27.54±2.96	<0.05
HDL-cholesterol (mg/dl)	52.66± 2.09	38.4±1.29	<0.05
Total cholesterol (mg/dl)	142.22±1.87	241.16±4.53	<0.05
Triglycerides (mg/dl)	98.33±1.35	168.7±2.47	<0.05
Interluekin-6 (pg/ml)	0.82±0.41	2.06±0.5	<0.001
Interluekin-37 (pg/ml)	1.47± 0.51	0.67±0.27	<0.001

SD: Standard deviation.

Table 2. Changes in anthropometric measurements and IL-6 and IL-37 analysis before and after laparoscopic surgery for obesity

Variable	Pre-SG (Mean±SD) (n=20)	Post-SG (Mean±SD) (n=20)	p
Total Weight Loss (%)	-	25.25±4.28	-
BMI (kg/m^2)	39.75±5.44	30.03±4.92	<0.05
Total cholesterol (mg/dl)	224.56±35.77	182.43±61.68	<0.05
HbA1c	7.01±1.61	5.49±0.974	<0.001
Interluekin-6 (pg/ml)	1.97±0.38	0.96±0.36	<0.001
Interluekin-37 (pg/ml)	0.61±0.33	1.65± 0.47	<0.001

SD: Standard deviation.

Discussion

Inflammatory biomarkers play a crucial role in the etiology and progression of metabolic disorders. Several pro- and anti-inflammatory cytokines have been linked to MetS and its components (e.g., obesity, dyslipidemia, hyperglycemia); however, the combined relationship between IL-6 and IL-37 in MetS has not been extensively studied.

Interleukin-6 (IL-6) is a cytokine with both pro-inflammatory and anti-inflammatory properties, known to promote the differentiation of monocytes into macrophages.[13] The association between elevated plasma IL-6 levels and an increased risk of diabetes suggests that inflammation plays a critical role in diabetes pathogenesis.[14] Previous studies have demonstrated significantly increased serum IL-6 concentrations in individuals with MetS.[15] and in diabetic dogs compared to healthy controls.[16] In experimental models, IL-6 administration in rats has been reported to stimulate gluconeogenesis, leading to hyperglycemia and hyperinsulinemia.[17] Similarly, subcutaneous administration of recombinant IL-6 in humans has been shown to stimulate gluconeogenesis, resulting in hyperglycemia and hyperinsulinemia.[18] These findings indicate that IL-6 increases insulin resistance in adipocytes. Moreover, studies using diet-induced MetS models have shown a correlation between IL-6 levels, MetS risk factors, and cardiovascular disease.[19] Our analyses are consistent with the existing literature, demonstrating that IL-6 levels were significantly higher in the MetS group compared to the control group.

Interleukin-37 (IL-37) is an anti-inflammatory cytokine that binds to the IL-18 receptor α (IL-18Rα) to form the IL-37/IL-18Rα complex, which transmits anti-inflammatory signals. IL-37 has been detected in various inflammatory and autoimmune diseases, including rheumatoid arthritis (RA), Mycobacterium avium infection, atherosclerotic coronary disease, and Crohn's disease.[20] Through its anti-inflammatory effects, IL-37 suppresses the production

of pro-inflammatory cytokines. Scientific studies have identified key cytokines associated with MetS and its components, including TNF-α, IFN-γ, IL-1α, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-12, IL-18, IL-21, and IL-33.[21]

During inflammation, IL-37 regulates the activation of multiple signaling phosphokinases. It significantly reduces the activation of pro-inflammatory signal mediators such as FAK, STAT1, mTOR, p53, p38, paxillin, Pyk2, Syk, SHP-2, and AKT. Additionally, IL-37 upregulates anti-inflammatory mediators such as the phosphatase PTEN, thereby inhibiting inflammation mediated by the PI3K, mTOR, MAPK, and FAK pathways. In summary, IL-37 expression is upregulated by pro-inflammatory stimuli, which in turn suppress inflammation through multiple pathways.[22]

IL-37 exerts its anti-inflammatory effects through both extracellular and intracellular mechanisms. However, the factors determining the preference for one mechanism over the other remain unclear. Intracellularly, the IL-37/Smad3 complex reduces inflammatory pathways and enhances the production of anti-inflammatory cytokines. Extracellularly, IL-37 binds to IL-18Rα/IL-1R8, leading to the inhibition of pro-inflammatory pathways and the activation of anti-inflammatory pathways. However, excessive binding of IL-18BP to IL-37 reduces the anti-inflammatory activity of both IL-37 and IL-18BP. Since the IL-37 precursor undergoes processing both intracellularly and extracellularly in vivo, its N-terminus exhibits significant variability, making its functional role unclear. Studies examining IL-37 isoforms with different N-terminal ends in vivo and in vitro have revealed the biological complexity of IL-37 functions.[23]

A recent study demonstrated that IL-37 treatment (1 μg/mouse) in mice improved insulin sensitivity and reduced obesity-induced inflammation in adipose tissue after 22 weeks of a high-fat diet (HFD) compared to vehicle-treated controls. IL-37 treatment likely lowers plasma insulin levels and pancreatic islet mass by activating AMPK and inhibiting mTOR.[24-26] Thus, the anti-inflammatory effects of IL-37 may help mitigate metabolic disorders associated with obesity.

A study by Moschen et al.[27] found that IL-37 expression was significantly higher in subcutaneous and visceral adipose tissue than in the liver in obese mice. Additionally, IL-37 transgenic mice fed a high-fat diet (HFD) exhibited reduced macrophage infiltration in adipose tissue, increased circulating adiponectin levels, and improved insulin sensitivity and glucose tolerance. In vitro studies have further demonstrated that recombinant IL-37 inhibits adipogenesis and activates the AMPK signaling pathway. Human studies have also reported a positive correlation between elevated IL-37 mRNA expression in adipose tissue, improved insulin sensitivity, and a lower inflammatory state. These findings suggest that IL-37 plays a crucial role in suppressing obesity-associated inflammation and insulin resistance. Our analyses are consistent with the existing literature, demonstrating that IL-37 levels were significantly lower in the MetS group compared to the control group. The findings of our study further support the potential regulatory role of IL-37 in metabolic diseases, highlighting its therapeutic potential.

Another study examined the impact of significant weight loss on the expression of IL-1F family members. The study revealed that IL-37 expression was substantially higher in subcutaneous and visceral adipose tissue than in the liver. Furthermore, weight loss following laparoscopic adjustable gastric banding surgery shifted the expression profile of the IL-1F family toward a more anti-inflammatory phenotype. Specifically, IL-1β expression significantly decreased in subcutaneous adipose tissue, whereas IL-37 expression increased.[28] These findings, along with our study results, further support the anti-inflammatory role of IL-37 in obesity-related inflammation.

This study aimed to investigate plasma IL-6 and IL-37 levels in patients with MetS. Our findings demonstrated that plasma IL-37 levels were significantly lower in the MetS group compared to the control group, whereas the opposite was observed for IL-6. Furthermore, our study identified four key variables that significantly influenced MetS improvement in patients undergoing SG: Total weight loss.(%), Body mass index (BMI), Total cholesterol levels, HbA1c levels at six months post-surgery. In conclusion, these four factors may influence the improvement of MetS in patients undergoing SG. Additionally, plasma IL-37 levels were lower pre-SG compared to post-SG due to obesity, while IL-6 levels exhibited the opposite trend, further supporting their antagonistic relationship.

Conclusion

Given the increasing prevalence of MetS with aging worldwide, effective management strategies and identification of contributing factors are crucial for reducing the global health burden. However, there is still insufficient knowl-

edge regarding the relationship between IL-37 and MetS. The activation of inflammatory signaling pathways in MetS results in alterations in circulating and tissue levels of pro-inflammatory and anti-inflammatory cytokines, leading to systemic inflammation and tissue damage. Modulating cytokine-mediated inflammation is considered a promising therapeutic approach for MetS prevention and treatment. The novelty of this study lies in the fact that IL-37 levels were analyzed for the first time before and after SG for obesity. Given its ability to regulate inflammatory, metabolic, and immune responses, IL-37 may serve as a promising therapeutic target with potential implications in metabolic disorders and cancer development. To further substantiate these findings, larger sample sizes and multidisciplinary studies with additional parameters are required to validate the potential therapeutic role of IL-37.

Disclosures

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