Effects of Ursodeoxycholic Acid on Inflammatory Markers IL-6 and IL-17 in Patients with Metabolic Syndrome

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ABSTRACT

Metabolic syndrome encompasses a cluster of factors that significantly heighten the risk of cardiovascular disease and type 2 diabetes mellitus. This study explores the impact of Ursodeoxycholic acid on inflammatory markers, specifically interleukins IL-6 and IL-17, in patients with MS. Forty patients with MS, aged 25–55, were evaluated, with a control group of 30 healthy individuals. Serum levels of IL-6 and IL-17 were measured before and after 30 days of UDCA therapy (500 mg daily), alongside a hypocaloric diet. Patients were stratified by blood pressure (BP) and body mass index (BMI) to examine associations with cytokine levels. Pre-treatment, IL-6 and IL-17 levels in MS patients were significantly higher than in controls. Post-treatment results indicated a notable reduction in IL-6, particularly in the obese subgroup (BMI >30 kg/m^2), though IL-17 levels remained largely unchanged. These findings suggest that UDCA may help modulate IL-6-driven inflammation in MS, especially among obese patients, while IL-17 requires additional therapeutic targeting. Limitations include the study's short duration, small sample size, and absence of placebo control. Future research should investigate long-term outcomes and the effects of UDCA on broader inflammatory pathways in MS to enhance therapeutic approaches.

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Introduction

Metabolic syndrome is a complex of interconnected factors that significantly increase the risk of developing atherosclerotic cardiovascular disease and type 2 diabetes mellitus (DM-2) [4-17]. This syndrome has become a focal point for research in recent years, drawing heightened attention from cardiologists, endocrinologists, and primary care physicians. The growing prevalence of metabolic syndrome in diverse populations underscores its importance as a major public health concern [6].

One of the primary contributors to the progression of cardiovascular disease is immune-mediated inflammation. Elevated inflammatory markers, such as interleukins (IL)-1 and IL-6, as well as tumor necrosis factor-alpha (TNF-α), are strongly associated with an increased risk of complications in cardiac pathology. These markers are not only reflective of an underlying inflammatory process but are also predictive immunological indicators of cardiovascular risk [2]. The core "metabolic risk factors" include atherogenic dyslipidemia, hypertension, elevated plasma glucose, a prothrombotic state, and a pro-inflammatory state. This cluster of conditions, often collectively referred to as "metabolic syndrome," does not require all factors to be present for diagnosis, although each contributes significantly to overall risk [18].

In recent studies, Interleukin-6 (IL-6) has emerged as a pivotal cytokine in both immune response and metabolic regulation. IL-6 is synthesized primarily by monocytes and macrophages, as well as by endothelial cells and fibroblasts in response to various stressors, including inflammation, trauma, hypoxia, and bacterial endotoxins [1]. Initially recognized for its role in immune protection, IL-6 stimulates a cascade of responses, including T-cell activation, B-cell maturation, and C-reactive protein synthesis in the liver. Importantly, IL-6 also acts to temper inflammatory responses by inhibiting the synthesis of other pro-inflammatory mediators, such as TNF-α [1].

Over the past decade, researchers have established IL-6 as a critical factor in metabolic regulation. This cytokine has become particularly relevant with the discovery of adipose tissue inflammation as a pathogenic mechanism in obesity. The association of IL-6 with metabolic disturbances, especially in the context of metabolic syndrome, has been substantiated by studies linking elevated IL-6 levels to insulin resistance, obesity, and DM-2. High levels of IL-6 are also associated with increased atherosclerotic plaque formation and related cardiovascular complications. Furthermore, recent evidence highlights the role of IL-6 in contributing to endothelial dysfunction, promoting atherosclerosis, and potentially accelerating the progression of cardiovascular diseases [5].

In light of the rising prevalence of metabolic diseases such as obesity, metabolic syndrome, and DM-2, as well as their complications, the inflammatory and metabolic roles of IL-6 hold both research and clinical significance. Elevated IL-6 levels are not only a marker of inflammation but also contribute directly to the pathogenesis of these diseases through mechanisms that include inducing insulin resistance and altering lipid metabolism [3,8].

The exploration of treatment options for metabolic syndrome and its associated inflammatory states has led to increased interest in pharmacological agents with pleiotropic properties. Ursodeoxycholic acid , a formulation of ursodeoxycholic acid (UDCA), has been shown to exert a variety of beneficial effects due to its multiple mechanisms of action, including choleretic, cytoprotective, immunomodulatory, anti-apoptotic, hypocholesterolemic, and litholytic properties [3-4]. Recent studies suggest that UDCA not only enhances bile flow and reduces cholesterol absorption but also has anti-inflammatory effects that may lower IL-6 and TNF-α levels, potentially contributing to reduced cardiovascular risk.

The implications of IL-6's role in metabolic and inflammatory pathways make agents like Ursodeoxycholic acid a promising adjunct in the management of metabolic syndrome. The potential of UDCA to modulate inflammation and lipid metabolism aligns with the need for therapeutic strategies that target both metabolic dysregulation and chronic inflammation. Ongoing research aims to clarify the impact of UDCA and similar agents on cytokine profiles and metabolic parameters, potentially offering new avenues for addressing the complex pathophysiology of metabolic syndrome and associated conditions. The purpose of this study was to assess the levels of interleukins 6 and 17 in patients with metabolic syndrome, both before and after treatment with Ursodeoxycholic acid.

Materials and Methods

We evaluated the clinical and immunological parameters of 40 patients, comprising 18 females and 22 males aged between 25-55 years, with a body mass index (BMI) ranging from 25.0 to 32.2 kg/m². A control group of 30 healthy individuals was also included. The diagnosis of metabolic syndrome was made according to the International Diabetes Federation (IDF) criteria (2007).

Interleukin IL-6 and IL-17 levels in blood serum were measured for all participants using an enzyme-linked immunosorbent assay (ELISA) with the Vector-Best test system (Russia). Anthropometric measurements, including height, weight, BMI, waist circumference, and hip circumference, were recorded for each participant.

All patients received ursodeoxycholic acid at a dosage of 500 mg taken nightly for 30 days, accompanied by a hypocaloric diet. Patients were thoroughly informed about the treatment process and provided written consent to participate in the study.

The patients were stratified into groups based on blood pressure (BP) and BMI:

- *Blood Pressure Groups:* Participants were divided into two groups based on their BP levels: 19 patients with BP ≤140/80 mmHg and 21 patients with BP >140/80 mmHg.
- *BMI Groups:* Group 1 consisted of 20 patients with a BMI less than 30 kg/m², while Group 2 included 20 patients with type I obesity (BMI >30 kg/m²).

Statistical Analysis: The collected data were statistically processed using a PENTIUM-IV personal computer with appropriate statistical software for analyzing clinical and immunological data. Descriptive statistics were calculated, and comparative analyses were conducted to assess the effects of Ursodeoxycholic acid therapy on IL-6 and IL-17 levels in the context of metabolic syndrome. Statistical significance was set at $p<0.05$ for all analyses, providing insights into the therapeutic potential of Ursodeoxycholic acid in modulating inflammatory markers in metabolic syndrome patients.

Results

Table 1 presents the concentrations of IL-6 and IL-17 in blood serum among patients with metabolic syndrome (MS) stratified by blood pressure (BP) levels, both before and after monotherapy with Ursodeoxycholic acid. The analysis reveals that, prior to treatment, patients with MS but without arterial hypertension (AH) exhibit IL-6 levels that are 2.8 times higher than those in healthy controls, with IL-17 levels surpassing control values by over sixfold ($p<0.001$). Similar patterns were observed in MS patients with AH, where IL-6 levels measured at 5.3 ± 0.5 pg/mL and IL-17 at 2.8 ± 0.23 pg/mL, representing increases of more than threefold and sixfold, respectively, compared to controls. Following Ursodeoxycholic acid treatment, a general downward trend in IL-6 and IL-17 levels was noted in both groups. However, their levels remained elevated relative to the control group, showing statistically significant differences ($p<0.001$), indicating a partial response to the therapy.

The data were further analyzed by stratifying MS patients based on body mass index (BMI). In Group 1 (BMI <30 kg/m²), serum IL-6 and IL-17 levels were significantly higher than normative values. Specifically, IL-6 levels rose from a control mean of 1.55 ± 0.25 pg/mL to 3.01 ± 0.18 pg/mL ($p<0.001$). IL-17 levels also exhibited a substantial sixfold

increase, with a mean value of 2.7 ± 0.15 pg/mL compared to 0.45 ± 0.22 pg/mL in the healthy cohort.

Table 1. Analysis of the levels of IL-6 and IL-17 in comorbid MS

Parameters	Pre - treatment		Post treatment	
	IL-6	IL-17	IL-6	IL-17
MS	4,4±0,75	2,9±0,19	3,1±2,8*	2,7±1,3
MS + AH	5,3±0,5**	2,8±0,23**	3,02±1,7	2,8±1,5*
Controls	1,55±0,25	0,45±0,22	1,55±0,25	0,45±0,22

Note: *p-validity relative to the control group, p1-validity relative to the 2 groups.*

In Group 2, which included MS patients with obesity (BMI >30 kg/m²), IL-6 levels were markedly elevated, reaching 6.94 ± 0.34 pg/mL, approximately 4.5 times higher than the levels found in healthy individuals ($p<0.001$), and over twice the levels recorded in Group 1. IL-17 levels in the obese subgroup exceeded control values by more than sixfold ($p<0.001$), though the IL-17 increase did not significantly differ between Groups 1 and 2 ($p>0.05$).

After a 30-day course of Ursodeoxycholic acid therapy, Group 1 showed a mild decrease in IL-6 and IL-17 levels. Notably, patients in Group 2 experienced a statistically significant reduction in IL-6 ($p<0.001$), though IL-6 levels remained substantially elevated compared to those in the control group ($p<0.001$). However, no statistically significant reduction in IL-17 levels was observed in either group, suggesting that IL-17 may be less responsive to this treatment.

Table 2. IL-6 and IL-17 content in MS depending on BMI pre and post treament.

Parameters	Pre-treatment		Post- treatment	
	IL-6	IL-17	IL-6	IL-17
BMI <30kg/m^2	3,01±0,18*	2,7±0,15	2,3±1,4*	2,3±0,9
BMI >30kg/m^2	6,94±0,34*	2,9±0,28*	5,1±1,9*	3,2±1,6*
Controls	1,55±0,25	0,45±0,22	1,55±0,25	0,45±0,22

Note: *p-validity relative to the control group, p1-validity relative to the 2 groups.*

These findings indicate that metabolic syndrome is strongly associated with an activated cytokine system, manifesting as substantial elevations in serum IL-6 and IL-17 levels. Importantly, there were no significant differences in IL-6 and IL-17 levels between patients with MS, with or without AH, suggesting that elevated BP does not further exacerbate cytokine levels in MS. Therapy with Ursodeoxycholic acid demonstrated a positive effect on the cytokine profile, particularly with respect to IL-6, although IL-17 levels remained largely unaltered.

Patients with obesity (BMI >30 kg/m²) exhibited significantly higher levels of IL-6 and IL-17 than overweight patients (BMI <30 kg/m²), underscoring the role of adiposity in amplifying inflammation. Ursodeoxycholic acid therapy successfully reduced IL-6 levels, particularly in the obese subgroup, but had minimal impact on IL-17, suggesting the need for targeted therapies that can address both cytokines in metabolic syndrome management.

Discussion

The study highlights a significant association between metabolic syndrome (MS) and an elevated inflammatory response, particularly as measured by IL-6 and IL-17 levels in the blood serum. These findings align with existing literature suggesting that chronic low-grade inflammation is a hallmark of MS, contributing to its progression and the development of associated complications, such as cardiovascular disease and type 2 diabetes mellitus. Elevated IL-6 and IL-17 levels in MS patients underscore the role of cytokine activation in this condition, with both cytokines involved in mediating inflammatory pathways that can exacerbate insulin resistance, endothelial dysfunction, and other metabolic disturbances [8,11,15].

The results further indicate that the degree of inflammation is more pronounced in MS patients with higher body mass indexes (BMIs), specifically those classified as obese (BMI >30 kg/m²), compared to those who are merely overweight. The observation that IL-6 levels are particularly elevated in the obese subgroup supports findings from other studies that link obesity with increased adipose tissue inflammation. Adipocytes in obese individuals secrete higher levels of pro-inflammatory cytokines, particularly IL-6, which has been implicated in the worsening of insulin resistance and the promotion of atherosclerosis [3,9].

Interestingly, our study did not find significant differences in IL-17 levels between patients with hypertension (AH) and those without, suggesting that IL-17 may be more closely

associated with adiposity-related inflammation than with blood pressure variations in the context of MS. This lack of difference could indicate that the pro-inflammatory state in MS operates through mechanisms that are somewhat independent of hypertension status, with obesity playing a central role in modulating IL-6 and IL-17 levels [14,19].

The administration of Ursodeoxycholic acid had a notable effect on cytokine levels, although its impact varied between IL-6 and IL-17. Specifically, Ursodeoxycholic acid was effective in reducing IL-6 levels, particularly in the subgroup of patients with obesity, albeit levels remained significantly above those of the healthy control group. This finding aligns with Ursodeoxycholic acid 's known anti-inflammatory properties, which may attenuate the chronic inflammatory state associated with metabolic disturbances. However, its effect on IL-17 was less pronounced, suggesting that additional therapeutic strategies may be needed to target IL-17–mediated pathways. This selective cytokine response may reflect the complex, multifaceted nature of cytokine regulation in MS, where different inflammatory mediators might respond to therapy in variable ways depending on their role in metabolic or immune pathways [4,7,20].

The persistence of elevated cytokine levels, despite treatment, indicates that long-term management of MS might require combination therapies aimed at both metabolic and inflammatory pathways. The observed reduction in IL-6 but limited response in IL-17 implies that Ursodeoxycholic acid may not fully address the immune-modulatory requirements in MS, particularly in severely obese individuals. This observation opens avenues for further research into adjunctive treatments that could more comprehensively modulate cytokine responses and better manage the inflammatory profile associated with MS [6,17].

This study is limited by a small sample size and short treatment duration, which may reduce generalizability and hinder insight into long-term effects of Ursodeoxycholic acid on inflammatory markers in metabolic syndrome. The absence of a placebo control, reliance on self-reported dietary adherence, and focus solely on IL-6 and IL-17 leave gaps in understanding the broader inflammatory profile and therapeutic mechanisms. Additionally, potential confounding factors like lifestyle variables and comorbidities were not controlled. Future research with larger, diverse cohorts, extended follow-up, and mechanistic exploration is needed to validate and expand on these findings.

Conclusions

Metabolic syndrome is associated with the activation of the cytokine system, manifesting as a significant increase in IL-6 and IL-17 in blood serum. IL-6 and IL-17 levels are significantly higher in obese patients compared to overweight patients, indicating an intensified inflammatory response with increasing adiposity. Therapy with Ursodeoxycholic acid demonstrated a positive effect on cytokine status, particularly in reducing IL-6 levels; however, it had limited efficacy on IL-17, suggesting the potential need for combination treatments to comprehensively manage cytokine-driven inflammation in MS patients.

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