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THE RELATIONSHIP OF BODY MASS INDEX WITH SERUM TGF-BETA LEVEL AND CLINICAL FINDINGS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Abstract

Aim: Systemic sclerosis (SSc) is an inflammatory disease characterized by a widespread fibrosis of affected tissue. Obesity is characterized as a chronic inflammatory state and affects the production of cytokines. The aim of the present study was to evaluate whether obesity alters clinical characteristics and serum were transforming growth factor-beta (TGF-β) levels in patients with SSc.
Material and Methods: Eighty-six patients with SSc were enrolled in this study. Body mass indexes (BMI) were calculated and the cases were divided into 3 groups (normal, overweight and obese). In each group, the extent of skin involvement was determined by modified Rodnan skin score, pulmonary function test, and carbon monoxide diffusing capacity were measured. TGF-β levels were measured by the enzyme-linked immunosorbent assay.

Results: Thirty-eight patients were of normal weight (BMI: ≤25 kg/m^2), 27 patients were overweight (BMI: 25-30 kg/m^2) and 21 patients were obese (BMI >30 kg/m^2). Their clinical and laboratory findings were similar. However, serum TGF-β level was significantly lower in obese SSc patients compared with those with normal weight.

Conclusion: These results suggest that obesity does not affect the severity of SSc. The cause of decreased serum TGF-β level in obese patients may be increased by fat tissue instead of SSc. Despite decreased TGF-β level, the severity of SSc is not different between obese and non-obese patients. These differences apart from TGF-β may be responsible for the SSc severity in obese SSc patients.

Keywords: Systemic sclerosis, obesity, body mass index, transforming growth factor-beta

INTRODUCTION

Systemic sclerosis (SSc) is a chronic inflammatory autoimmune disease characterized by fibrosis of the skin and internal organs. Although SSc is a rare disease, it has high morbidity and mortality due to difficulties in treatment (1). Although the etiology of SSc has not been fully elucidated, it is thought that its pathogenesis consists of several steps that result in vasculopathy and immune activation-triggered fibrosis (2). It is thought that some cytokines secreted because of immune activation trigger fibrosis. At the beginning of these cytokines, transforming growth factor-beta (TGF-β) appears first. It has been shown that TGF-β levels are increased in fibrotic (skin and lung) tissues taken from patients

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with SSc and are associated with disease activity (3). All these suggest that TGF-β cytokine plays a central role in the pathogenesis of SSc. However, there is also a study showing that there is an inverse correlation between TGF-β level and modified Rodnan skin scores (mRSS) (4). This can be explained by the fact that TGF-β has both anti-and pro-inflammatory effects (5) and that SSc has different subtypes and different clinical stages. Moreover, both overexpression and insufficient expression of TGF-β are thought to cause vascular pathology (3). According to data from the World Health Organization in 2016, more than 1.9 billion adults aged 18 years and older were overweight, and more than 650 million of these were obese (6). In recent years, it has been shown by many studies that obesity is closely associated with chronic systemic inflammation. In obesity, it is thought that pro-inflammatory cytokines secreted from increased subcutaneous adipose tissue play an important role in triggering the systemic acute phase response (7,8). The role of obesity and thus adipose tissue in the pathogenesis and disease activity of inflammatory rheumatic diseases has been the subject of research. There is increasing evidence that adipose tissue contributes significantly to the pathogenesis of SSc. It has been shown that in SSc, adipose tissue fat cells transform into myofibroblasts and contribute to fibrosis (9). In this study, we investigated the effect of obesity on clinical findings and serum TGF-β levels in SSc patients.

MATERIAL AND METHODS

Newly diagnosed or followed scleroderma patients who met the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013 Scleroderma Classification Criteria and who applied to the Rheumatology outpatient clinic of Fırat University Faculty of Medicine, Department of Internal Medicine between 2013 and 2014 were included in the study. Before starting the study, the approval of the Fırat University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee was obtained with the decision number 97521439-8b dated 02.05.2013.

Inclusion criteria;

- Being between the ages of 18 and 65,
- To establish cooperation,
- To be diagnosed according to the 2013 ACR/EULAR SSc Classification Criteria.

Exclusion criteria;

- Having Overlap syndrome
- Having additional systemic disease that can affect TGF-β levels
- Patients with a diagnosis of malignancy
- Patients who did not accept participation in the study.

Written informed consent was obtained from all subjects included in the study regarding the purpose of the study and the issues related to blood sampling. Demographic characteristics, clinical findings, organ involvement, and other follow-up parameters of the patients were evaluated in terms of SSc. 8-10 mL of venous blood samples taken into biochemistry tubes from the patients and control groups included in the study were centrifuged at 4000 rpm for 5 min, and serum samples were stored in a deep freezer at -80 °C until they were studied. Complete blood count, sedimentation, C-reactive protein (CRP), anti-nuclear antibody (ANA), anti-topoisomerase I (anti-Scl-70), and anti-centromere antibody (ACA) were recorded simultaneously. The severity of skin involvement of all patients was calculated and noted with mRSS, and pulmonary function test was performed. High-resolution lung computed tomography was performed in patients with abnormal findings on posteroanterior chest X-ray. Pulmonary arterial pressure (PAP) was measured using transthoracic echocardiography, and systolic PAP above 40 mmHg were considered pulmonary arterial hypertension. Body mass index (BMI) of patients was calculated as weight/height (2). They were divided into 3 groups according to their BMI. Those with a BMI of ≤25 kg/m^2 were considered "normal", those with a BMI of 25-30 kg/m^2 as "overweight", and those with a BMI >30 kg/m^2 as "obese" (10). Serum TGF-β levels were measured using the ELISA method using an appropriate commercial kit (Boster Biological Technology Co., Ltd., Pleasanton, USA). Results were expressed as pg/mL.

Statistical Analysis

IBM SPSS 22.0 for Windows statistical package program was used for the statistical evaluation of our research data. Measured variables were presented as mean ± standard deviations, while categorical variables were presented as numbers and percentages (%). It was checked whether the data fit the normal distribution or not. Showing a normal distribution; Independent samples t-test was used to compare the two groups. The Mann-Whitney U test was used to compare the two-choice groupings that did not show a normal distribution. Normally distributed; one-way analysis of variance in the comparison of groupings with more than two options; non-normal distribution; Kruskal-Wallis H test was used to compare groupings with more than two options. Correlation analysis was performed by choosing either Pearson or Spearman correlation analysis depending on whether the parametric test conditions were met or not. Chi-square (χ^2) test was used for the comparison of qualitative variables. The hypotheses will be taken in two directions; a p value of <0.05 was considered statistically significant.

RESULTS

Eighty-six patients with a diagnosis of SSc were included in the study. Thirty-eight (44.2%) patients were of normal weight, 27 (31.4%) patients were overweight, and 21 (24.4%) patients were obese. Demographic, clinical, imaging, and laboratory characteristics are shown in Table 1. No statistically significant difference was observed between the groups in terms of age and gender (p value 0.158 and 0.808, respectively). While limited SSc was common in overweight and obese patients, diffuse SSc was more common in patients with normal BMI, but this difference was not statistically significant (p=0.585). There was no statistically significant difference between the groups in terms of ANA, ACA, and anti-Scl-70 antibody positivity (p value 0.178, 0.920, 0.931, respectively). No statistically significant findings were observed in terms of forced vital capacity, diffusing capacity of the lungs for carbon monoxide, systolic PAP, or pulmonary fibrosis findings. When laboratory findings were evaluated, there was no statistically significant difference in terms of CRP, erythrocyte sedimentation rate, hemoglobin level, and leukocyte level (p values 0.478, 0.228, 0.708 and 0.285, respectively).

When the level of TGF-β1 was evaluated, it was measured as 65.1±163.7 pg/mL in those with normal weight, 28.1±24.1 pg/mL in those with overweight, and 16.7±14.7 in those who were obese. Although TGF-β1 levels were significantly higher in normal-weight individuals, no statistically significant difference was observed (Kruskal-Wallis p=0.124). However, when TGF-β1 levels were evaluated in post hoc analyses, there was a statistically significant difference between those with normal weight and those with obesity (Mann-Whitney U p=0.045, Figure 1).

DISCUSSION

Systemic sclerosis is a chronic, multisystemic, autoimmune disease. Due to the difficulties in its treatment, it can cause serious morbidity and mortality. The clues to be discovered regarding the pathogenesis and the factors affecting the clinical course may guide new treatment searches. Among the multiple cytokines associated with SSc, TGF-β is considered to be the main regulator of physiological and pathological fibrogenesis (11). In a study examining the effect of TGF-β on the differentiation of human adipocyte precursor cells, it was found that TGF-β had

Table 1. Clinical and laboratory characteristics in SSc patients with different BMI

BMI (kg/m^2)	≤25 (Normal) (n=38)	25-30 (Overweight) (n=27)	>30 (Obese) (n=21)	p
Age, years	48.4±15.1	54.4±10.1	52.5±10.8	0.158
Disease duration, years	6.5±5.7	6.2±4.8	5.6±4.1	0.808
mRSS	11.6±7.1	10.3±5.9	10.9±4.9	0.589
Limited SSc, %	40.3	34.3	25.4	0.585
Diffuse SSc, %	58.3	25.3	16.7	0.585
ANA positive, %	81.6	96.3	90.5	0.178
ACA positive, %	15.8	18.5	14.3	0.920
ATA positive, %	47.4	51.9	47.6	0.931
DL_{co}, %	86.8±30.1	87.6±25.9	88.1±21.9	0.985
FVC, %	72.1±16.2	76.1±15.2	78.3±115.6	0.319
sPAP, mm/Hg	37.7±12.9	34.6±10.7	37.5±7.5	0.495
Pulmonary fibrosis, %	55.3	63.0	42.9	0.380
PAH, %	26.3	11.1	33.3	0.163
Hemoglobin, g/dL	12.7±2.1	12.4±1.1	12.8±1.1	0.708
Leukocyte, 10^3/μL	7.1±2.8	9.9±1.2	8.3±2.6	0.285
ESR, mm/h	28.5±18.9	31.1±15.8	22.8±13.2	0.228
CRP, mg/dL	1.2±2.3	1.8±4.1	2.5±5.6	0.478
TGF-β1, pg/mL	65.1±163.7	28.1±24.1	16.7±14.7	0.124

BMI: Body mass index, SSc: Systemic sclerosis, ANA: Anti-nuclear antibody, ACA: Anti-centromere antibody, ATA: Anti-topo antibody, FVC: Forced vital capacity, PAH: Pulmonary arterial hypertension, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TGF-β: Transforming growth factor-beta, DL_{co}: Diffusing capacity of the lungs for carbon monoxide, mRSS: Modified Rodnan skin scores, sPAP: Systolic pulmonary arterial pressure

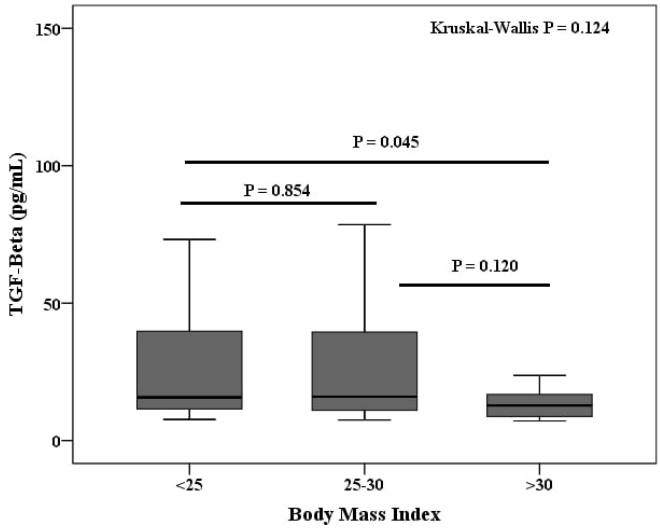

Figure 1. Serum TGF-β; levels in normal, overweight and obese patients
TGF: Transforming growth factor

an inhibitory effect on adipocyte precursor cells (12). In the literature review, we could not find any study that investigated the effects of obesity on TGF-β levels and clinical parameters in SSc patients. In this preliminary study, we investigated the serum TGF-β levels of normal weight, overweight, and obese patients in SSc patients and the relationship between obesity and clinical findings. The main source of pro-inflammatory cytokines in obese individuals is thought to be the visceral adipose tissue. It is known that the levels of some cytokines (adiponectin, resistin, leptin, interleukin-6, TNF-alpha, vascular endothelial growth factor, and TGF-β) associated with visceral adipose tissue are altered in obese individuals (13). Some of these cytokines are associated with inflammation and their roles in the pathogenesis of SSc have been the subject of research (14). Tomčík et al. (15) found that adiponectin was negatively correlated with the skin involvement in SSc. In the study of Winsz-Szczotka et al. (16), it was observed that adiponectin was lower in patients with diffuse skin involvement and negatively correlated with acute phase responses. Similarly, in the study of Budulgan et al. (17), it was shown that leptin levels were negatively associated with disease activity. On the other hand, contrary to this study, Pehlivan et al. (18) showed that serum levels of leptin were higher than in the control group, but this study did not show any correlation with disease activity. As it can be understood from these studies, it can be predicted that certain cytokine profiles may change in obese patients, and thus the severity of SSc disease may also change. In the study of Petruschke et al. (12), in which they examined the effect of TGF-β on human adipocyte precursor cells *in vitro*, it was shown that TGF-β had an inhibitory effect on human adipose tissue development and reduced the activity of a lipogenic enzyme in newly formed adipose cells. In our study, the low TGF-β level in obese SSc patients may have resulted in an insufficient inhibitory effect on adipose tissue and an increase in subcutaneous adipose tissue. On the other hand, gastrointestinal involvement is seen in more than 70% of SSc patients, which limits oral food intake and results in a low BMI (19). As we have shown in our study, considering that patients with low BMI have higher TGF-β, it can be said that these patients may be more active. There is a need for studies in which the BMI of the patients at the time of diagnosis and during follow-up is compared with the control group in order to state more clearly the paradox that whether SSc has an effect on BMI or whether BMI has an effect on SSc disease severity.

In Brezovec et al. (9), it was shown that in the pathogenesis of SSc, adipose fat cells turn into myofibroblasts and contribute to fibrosis. It is expected that patients with high TGF-β levels will inhibit adipose fat cells, preventing myofibroblast formation and therefore having a lower mRSS. These conflicting results may be explained by the fact that myofibroblasts originate from many cells. In addition, it is thought that different cytokines and pathways play a role in SSc patients and different clinical presentations have different pathogenic processes (2). Our results suggest that pathways other than TGF-β may be responsible for SSc severity in obese SSc patients. The fact that normal weight patients, which we confirmed in our study, have a higher rate of diffuse disease and higher TGF-β levels than overweight and obese patients confirms the relationship between high TGF-β and high disease activity in the literature (20).

TGF-β has both anti-and pro-inflammatory effects (5). There is low-grade chronic inflammation in overweight and obesity (21). In our study, we found that obese patients had lower TGF-β levels. This result suggests that low TGF-β level in obesity triggers inflammation by causing disruption of the inflammatory/anti-inflammatory balance. In the study of Oeser et al. (22) on 33 normal BMI, 28 overweight and 39 obese systemic lupus erythematosus patients, it was shown that obese patients had worse functional capacity, reported more fatigue complaints and had a higher acute phase response. In the review of Moroni et al. (23), it was observed that obesity has negative effects on both disease activity and treatment response in patients with rheumatoid arthritis and psoriatic arthritis (PsA), and relapses are higher in obese individuals. Obesity was associated with a lower rate of disease remission, according to the results of 12-month follow-up in rheumatoid arthritis patients by Ellerby et al. (24). In a study by di Minno et al. (25), 135 obese PsA patients

compared with 135 normal-weight control groups showed that obese patients reached low disease activity at a lower rate at 12-month follow-up, and obesity was found to be an indicator of relapse. In our study, we could not detect a clinically unfavorable difference in obese individuals.

Study Limitations

There are some limitations to our study. One of the limitations of the study is that the patients included in the study were under the treatment regimen at the time of enrollment. Because, TGF-β level may have been affected by treatment regimens. Another limitation of our study is that SSc patients have not been compared with healthy individuals with the same BMI. Another limitation of our study is the relatively small number of cases.

CONCLUSION

These results suggest that obesity does not affect SSc severity. The cause of decreased serum TGF-β level in obese patients may be increased by fat tissue instead of SSc. Despite decreased TGF-β level, the severity of SSc is not different between obese and non-obese patients. These differences apart from TGF-β may be responsible for the SSc severity in obese SSc patients. To better understand the effect of obesity on TGF-β level, which play an important role in the pathogenesis of SSc, there is a need for new clinical studies with a larger number of patients, including untreated patients, and to compare them with control groups.

Ethics

Ethics Committee Approval: Before starting the study, the approval of the Fırat University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee was obtained with the decision number 97521439-8b dated 02.05.2013.

Informed Consent: Written informed consent was obtained from all subjects included in the study regarding the purpose of the study and the issues related to blood sampling.

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Authorship Contributions

Surgical and Medical Practices: B.Ö., A.K., Concept: İ.G., B.G., Design: B.G., Data Collection or Processing: B.G., Analysis or Interpretation: B.G., S.A., Literature Search: F.A., B.Ö., Writing: İ.G., A.K.

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REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-99.
2. Koca SS, Özgen M, Işık A. Etiopathogenesis of systemic sclerosis. J Turk Soc Rheumatol 2012;4:39-46.
3. Lafyatis R. Transforming growth factor β--at the centre of systemic sclerosis. Nat Rev Rheumatol 2014;10:706-19.
4. Dziadzio M, Smith RE, Abraham DJ, Black CM, Denton CP. Circulating levels of active transforming growth factor beta1 are reduced in diffuse cutaneous systemic sclerosis and correlate inversely with the modified Rodnan skin score. Rheumatology (Oxford) 2005;44:1518-24.
5. Sanjabi S, Zenewicz LA, Kamanaka M, Flavell RA. Anti-inflammatory and pro-inflammatory roles of TGF-beta, IL-10, and IL-22 in immunity and autoimmunity. Curr Opin Pharmacol 2009;9:447-53.
6. World Health Organization (WHO). Obesity and overweight. Available from: URL: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
7. Rodríguez-Hernández H, Simental-Mendía LE, Rodríguez-Ramírez G, Reyes-Romero MA. Obesity and inflammation : epidemiology, risk factors, and markers of inflammation. Int J Endocrinol 2013;2013:678159.
8. Karczewski J, Śledzińska E, Baturo A, et al. Obesity and inflammation. Eur Cytokine Netw 2018;29:83-94.
9. Brezovec N, Burja B, Lakota K. Adipose tissue and adipose secretome in systemic sclerosis. Curr Opin Rheumatol 2021;33:505-13.
10. National Institutes of Health (NIH). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. 1998. Available from: URL: https://www.hhs.gov/guidance/document/clinical-guidelines-identification-evaluation-and-treatment-overweight-and-obesity-adults
11. Pannu J, Trojanowska M. Recent advances in fibroblast signaling and biology in scleroderma. Curr Opin Rheumatol 2004;16:739-45.
12. Petruschke T, Röhrig K, Hauner H. Transforming growth factor beta (TGF-beta) inhibits the differentiation of human adipocyte precursor cells in primary culture. Int J Obes Relat Metab Disord 1994;18:532-6.
13. Ahima RS, Scolaro LM, Park HK. Adipokines and Metabolism. In: Ahima, R. (eds). Metabolic Syndrome. Springer; Cham. 2016.
14. Żółkiewicz J, Stochmal A, Rudnicka L. The role of adipokines in systemic sclerosis: a missing link? Arch Dermatol Res 2019;311:251-63.
15. Tomčík M, Arima K, Hulejová H, et al. Adiponectin relation to skin changes and dyslipidemia in systemic sclerosis. Cytokine 2012;58:165-8.
16. Winsz-Szczotka K, Kuźnik-Trocha K, Komosińska-Vassev K, Kucharz E, Kotulska A, Olczyk K. Relationship between adiponectin, leptin, IGF-1 and total lipid peroxides plasma concentrations in patients with systemic sclerosis: possible role in disease development. Int J Rheum Dis 2016;19:706-14.
17. Budulgan M, Dilek B, Dağ ŞB, et al. Relationship between serum leptin level and disease activity in patients with systemic sclerosis. Clin Rheumatol 2014;33:335-9.
18. Pehlivan Y, Onat AM, Ceylan N, et al. Serum leptin, resistin and TNF-α levels in patients with systemic sclerosis: the role of adipokines in scleroderma. Int J Rheum Dis 2012;15:374-9.

19. Miller JB, Gandhi N, Clarke J, McMahan Z. Gastrointestinal Involvement in Systemic Sclerosis: An Update. J Clin Rheumatol 2018;24:328-37.

20. Ihn H. Autocrine TGF-beta signaling in the pathogenesis of systemic sclerosis. J Dermatol Sci 2008;49:103-13.

21. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415-45.

22. Oeser A, Chung CP, Asanuma Y, Avalos I, Stein CM. Obesity is an independent contributor to functional capacity and inflammation in systemic lupus erythematosus. Arthritis Rheum 2005;52:3651-9.

23. Moroni L, Farina N, Dagna L. Obesity and its role in the management of rheumatoid and psoriatic arthritis. Clin Rheumatol 2020;39:1039-47.

24. Ellerby N, Mattey DL, Packham J, Dawes P, Hider SL. Obesity and comorbidity are independently associated with a failure to achieve remission in patients with established rheumatoid arthritis. Ann Rheum Dis 2014;73:e74.

25. di Minno MN, Peluso R, Iervolino S, et al. Obesity and the prediction of minimal disease activity: a prospective study in psoriatic arthritis. Arthritis Care Res (Hoboken) 2013;65:141-7.