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ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

The Relationship of MIF and PBMC Telomerase Activity in Obese Individuals

Obez Bireylerde MIF ve PBMC Telomeraz Aktivitesi Arasındaki İlişki

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ABSTRACT

Introduction: To determine the relationship between circulating macrophage migration inhibitory factor (MIF) concentrations and telomerase activity in obese individuals.

Material and Methods: The study included 62 obese individuals (BMI >25 kg/m²) and 20 age– and sex-matched healthy volunteers. Participants were eligible if they were 18–60 years old, free of chronic systemic diseases, non-smokers, non-alcohol users, and had not taken any medications or dietary supplements in the previous three months. Exclusion criteria included acute infection, pregnancy or lactation, and recent surgical interventions (within six months). Plasma MIF and p53 levels were determined using ELISA, PBMC Telomerase activity was assessed using a PCR-based assay.

Results: Plasma MIF levels were significantly higher in obese individuals (median=173,64 pg/mL) compared to controls (median=39,5 pg/mL; p=0,005). Similarly, median p53 levels were higher in obese individuals (13,37 U/mL) than in controls (0,85 U/mL; p=0,001). Telomerase activity was also significantly higher in obese individuals; it was positive in 32,3% and negative in 67,7% of the obese group, whereas it was positive in only 5% and negative in 95% of the control group (p=0,015). A significant correlation was found between BMI and MIF, p53, and telomerase activity. Additionally, there was a significant correlation between MIF and p53 (r=0,39; p=0,001), and between MIF and telomerase activity (r=0,326; p=0,003). However, no significant correlation was observed between p53 and telomerase activity (p=0,53).

Conclusion: Plasma levels of MIF and p53, as well as PBMC telomerase activity, were significantly higher in obese individuals than in healthy controls. Significant positive correlations between MIF, p53, and telomerase activity suggest that these molecules may jointly contribute to the pathophysiology of obesity.

Keywords: Macrophage migration inhibitory factor (MIF), obesity, p53, telomerase activity

ÖZ

Giriş: Bu çalışmanın amacı, obez bireylerde telomeraz aktivitesi ile dolaşımdaki makrofaj migrasyon inhibitör faktörü (MIF) konsantrasyonu arasındaki ilişkinin belirlenmesidir.

Materyal ve Metodlar: Çalışmaya, Vücut Kitle İndeksi (VKİ) 25 kg/m²'nin üzerinde olan 62 birey ile yaş ve cinsiyet açısından eşleştirilmiş 20 sağlıklı gönüllü dâhil edildi. Dâhil edilme kriterleri; 18–60 yaş aralığında olmak, kronik sistemik hastalığı bulunmamak, son üç ay içinde herhangi bir ilaç veya besin takviyesi kullanmamış olmak ve sigara veya alkol kullanmamak olarak belirlendi. Dışlanma kriterleri arasında akut enfeksiyon varlığı, gebelik veya emzirme durumu ile son altı ay içinde cerrahi girişim öyküsü yer aldı. Plazma MIF ve p53 düzeyleri ELISA yöntemiyle, periferal kan mononükleer hücre (PBMC) telomeraz aktivitesi ise polimeraz zincir reaksiyonu (PCR) yöntemiyle değerlendirildi.

Bulgular: Plazma MIF düzeyleri obez bireylerde (medyan: 173,64 pg/mL) kontrol grubuna (medyan: 39,5 pg/mL; p=0,005) göre anlamlı düzeyde yüksek bulundu. Benzer şekilde, p53 düzeyleri de obez bireylerde (medyan: 13,37 U/mL) kontrol grubuna kıyasla (medyan: 0,85 U/mL; p=0,001) önemli ölçüde artmıştı. Telomeraz aktivitesi obez grubun %32,3'ünde pozitif, %67,7'sinde negatif iken; kontrol grubunda yalnızca %5'inde pozitif, %95'inde negatifti (p=0,015). VKİ ile MIF, p53 ve telomeraz aktivitesi arasında anlamlı korelasyon saptandı. Ayrıca, MIF ile p53 (r=0,39; p=0,001) ve MIF ile telomeraz aktivitesi (r=0,326; p=0,003) arasında da anlamlı ilişki belirlendi. Ancak, p53 ile telomeraz aktivitesi arasında istatistiksel olarak anlamlı bir ilişki gözlenmedi (p=0,53).

Sonuç: Obez bireylerde plazma MIF ve p53 düzeyleri ile PBMC telomeraz aktivitesinin anlamlı şekilde arttığı saptanmıştır. MIF, p53 ve telomeraz aktivitesi arasındaki anlamlı ilişkiler, bu moleküllerin obezitenin patofizyolojisinde potansiyel bir rol oynayabileceğini göstermektedir.

Anahtar Sözcükler: Makrofaj migrasyon inhibitör faktörü (MIF), obezite, p53, telomeraz aktivitesi

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Introduction

Obesity is an important risk factor for dyslipidemia, cardiovascular disease, type 2 diabetes, and cancer. The prevalence of obesity has increased in Türkiye over the past decade (1). Adipose tissue is not only a lipid storage organ but also an active endocrine organ that secretes various substances, including proinflammatory cytokines such as TNF-α, and macrophage migration inhibitory factor MIF (2,3). Macrophage migration inhibitory factor is a pleiotropic cytokine that plays a pivotal role in the pathogenesis of numerous inflammatory conditions, cardiovascular disorders and cancer (4). Macrophage migration inhibitory factor is expressed by many immune system cells such as monocytes, macrophages, B cells, and T cells. In addition, MIF is also expressed in various tissues including the lungs, skin, endocrine system, and gastrointestinal and genitourinary tracts. Previous studies have shown that MIF acts as an upstream activator of both innate and adaptive immune responses by inducing the production and expression of proinflammatory molecules such as TNF-α, IFN-γ, IL-1β, IL-2 and IL-6 (5). Obesity is characterized by a chronic low-grade inflammation (6). Rudolf Ludwig Carl Virchow was among the first to recognize that inflammatory mechanisms play a role in the pathogenesis of cancer (7). p53 is an important tumor suppressor gene. The metabolic pathways in healthy and tumor cells differ, and studies have indicated that p53 is involved in maintaining metabolic homeostasis and regulating metabolic pathways (8). In response to chronic nutrient abundance p53 can be induced, which may contribute to the development of obesity and insulin resistance (9). Unlike p53, MIF supports maintenance of monocyte and macrophage function and has effects that promote cell growth and survival (5). Studies have shown that aging and oxidative stress can lead to increased telomerase activity in peripheral blood mononuclear cells (PBMCs) (10). Other studies have demonstrated high telomerase activity in most tumor types, suggesting a role for telomerase in extending telomeric DNA and enabling the unlimited proliferation of cancer cells (11).

Despite growing evidence linking obesity to inflammation and oxidative stress, the interplay between MIF, p53, and telomerase activity in obese individuals has not been fully elucidated. Given that MIF and p53 have opposing effects on apoptosis and cell survival, and that telomerase activity reflects cellular aging and proliferative potential, we hypothesized that these markers might be interrelated in obesity. Therefore, this study aimed to evaluate plasma MIF and p53 levels together with PBMC telomerase activity in obese individuals and to investigate the potential relationship between these parameters.

Material and Methods

Subjects and clinical protocol

The study included 82 apparently healthy subjects who were recruited between February and October 2019. The Local Bioethics Committee of Ankara Yıldırım Beyazıt University, Yenimahalle Education and Research Hospital, Ankara, Türkiye, approved the study protocol, and written informed consent was obtained from all participants. Anthropometric measurements were taken using a Body Composition Analyzer (X-Contact 350). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Participants were then divided into two groups based on their BMI: overweight/obese (51 women and 11 men; BMI >25 kg/m^2), and normal-weight controls (14 women and 6 men; BMI <25 kg/m^2).

Ethics Approval and Informed Consent:

The study protocol was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University, Yenimahalle Education and Research Hospital (Approval No.: 49; Date: September 25, 2018). All participants provided written informed consent before enrollment, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Blood sampling

Blood samples were collected in the morning after an overnight fast, using tubes containing heparin as an anticoagulants. The blood sample was divided into two portions. the first portion was centrifuged at 5000× g for 5 min; plasma was isolated and stored at -80°C until analysis. The second portion was used to isolate PBMCs using commercially available Lymphocyte Separation Medium (Capricorn Scientific, Germany). Heparinized whole blood was diluted 1:1 with phosphate buffered saline (PBS) and carefully poured over the 5 ml of lymphocyte separation solution. Separation was performed by centrifugation at 1200× g for 20 min. PBMCs were then collected from the interphase layer using a sterile Pasteur pipette, washed twice with PBS, spined for 10 min at 300× g and resuspended in 0.5 mL of PBS. The cell count was determined using a Thoma counting chamber, and the cells were stored at -80°C until the time of analysis. PBMCs were selected for telomerase activity measurement because obtaining tissue samples from healthy volunteers was not ethically or practically feasible. PBMCs provide an accessible peripheral source for assessing systemic telomerase activity.

Cytokines and p53 Analysis

Plasma MIF levels were measured using a human MIF ELISA kit (Sigma-Aldrich, RAB0360, USA). Circulating concentrations of p53 were determined using a human p53 ELISA kit (Abcam, ab46067, UK). All assays were performed according to the manufacturer's instructions. Absorbances were measured at wavelength of 450 nm using a CLARIOstar Plus microplate reader (BMG Labtech, Germany). Data analysis was performed using GraphPad Prism software, version 8.4.1.

Telomerase Assay

PBMCs were resuspended in 200 µL of lysis reagent and incubated for 30 min on ice. The lysates were centrifuged at

16.000× g for 20 min at 6°C, and 175 µl of each supernatant was transferred into a fresh Eppendorf tube. Telomerase activities were then assessed using the TeloTAGGG Telomerase PCR ELISA kit (Roche, Germany). Absorbance was measured at a wavelength of 450 nm using CLARIOstar Plus microplate reader (BMG Labtech, Germany).

Statistical Analysis

Data on anthropometric and biochemical parameters are shown as median (minimum-maximum), mean ± standard deviation (SD). Some of the data were also expressed as percentages (%). Since the distribution of the variables was not normal and the sample size was small (n <30) in one of the compared groups, differences between medians were assessed using the Mann-Whitney U test. Chi-square tests were used to compare categorical variables. Spearman's rank correlation coefficient (r) was applied to examine relationships between MIF, p53, and telomerase activity. A p-value <0,05 was considered statistically significant. All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 22.0).

Results

Table 1. Anthropometric and biochemical characteristics of the study participants

	Obese (n=62)	Control (n=20)	*P*
n (F/M)	62 (51/11)	20 (14/6)	*p*=0,34
Age (Year)			
Median	34,5	28,5	0,063
Mean ± standard deviation	34,8±8,5	30,6±8,75	
(Minimum-maximum) value	(21–47)	(21–51)	
BMI (Kg/m²)			
Median	31,44	21,91	0,001**
Mean ± standard deviation	32,65±5	21,71±1,63	
(Minimum-maximum) value	(27–43,85)	(19–24,11)	
Lean body mass (kg)			
Median	52,1	34,1	0,001**
Mean ± standard deviation	55,53±13,69	35,74±9,49	
(Minimum-maximum) value	(25,57–88,60)	(24,65–55,7)	
Body fat mass (kg)			
Median	31,45	15	0,001**
Mean ± standard deviation	33,52±10,21	21,86±14,64	
(Minimum-maximum) value	(16,9–57,3)	(7,26 – 47,65)	
Total body water (%)			
Median	39,2	32,72	0,057
Mean ± standard deviation	41±9,07	34,9±6,64	
(Minimum-maximum) value	(29,8–63,8)	(25–48,7)	
Body fat (%)			
Median	36	21,5	0,001**
Mean ± standard deviation	35,88±6,5	21,32±7,74	
(Minimum-maximum) value	(15,4–47)	(10,4–31,4)	
Waist-hip ratio (%)			
Median	0,9	0,8	0,001**
Mean ± standard deviation	0,89±0,06	0,76±0,08	
(Minimum-maximum) value	(0,79–1,03)	(0,64–0,81)	
MIF (pg/ml)			
Median	173,64	39,5	0,005**
Mean ± standard deviation	298,32±411,9	94,7±121,28	
(Minimum-maximum) value	(8,92–2389,69)	(8,92–438,65)	
P53 (u/ml)			
Median	13,37	0,85	0,001**
Mean ± standard deviation	22,74±31,26	6,14± 9,54	
(Minimum-maximum) value	(0,65–131,81)	(0,5–31,41)	
Telomerase activity			
Positive (%)	20 (32,3%)	1 (5%)	0,015*
Negative (%)	42 (68,9%)	19 (95%)	

Data are presented as median, and mean ± standard deviation (SD); comparisons between the obese and control groups were performed using the Mann-Whitney U test; F: Female; M: Male; BMI: Body mass index; MIF: Macrophage migration inhibitory factor; PBMC: Peripheral blood mononuclear cells.

Table 2. Correlation between plasma MIF, p53, telomerase activity, and anthropometric parameters

		MIF	p53	Telomerase activity
Age	r	0,102	0,003	-0,115
	p	0,363	0,98	0,305
BMI	r	0,235	0,243	0,219
	p	0,034*	0,028*	0,048*
Waist –hip ratio	r	0,228	0,037	0,005
	p	0,119	0,802	0,974
Body fat	r	0,087	0,096	0,089
	p	0,475	0,43	0,463
Body fat mass	r	0,095	0,093	0,161
	p	0,425	0,434	0,173
Lean body mass	r	0,314	0,149	0,160
	p	0,007**	0,207	0,1675
Total body water	r	0,164	0,053	0,130
	p	0,165	0,653	0,274
p53	r	0,39	-	0,07
	p	0,001**		0,53
Telomerase activity	r	0,326	0,07	-
	p	0,003**	0,53	

Spearman's correlation coefficients (r) and p-values are shown; BMI: Body mass index; MIF: Macrophage migration inhibitory factor; PBMC: Peripheral blood mononuclear cells; statistical significance: * $p < 0.05$; ** $p < 0.01$.

Discussion

The result obtained in the present study are in agreement with previous reports (12,13) showing that plasma MIF levels are significantly increased in obese individuals compared with controls and that this increase is positively corelated to BMI. These findings support the presence of a chronic proinflammatory state associated with obesity. Although the effects of excessive caloric intake on p53 levels in adipose tissue have been investigated, studies examining its impact on plasma p53 levels have been not encountered. In the current study, plasma p53 levels were significantly higher in obese individuals than in controls, and this increase was also positively correlated with BMI. Previous studies have demonstrated that elevated p53 expression in the adipose tissue of obese individuals may counteract the lipogenic effects of insulin, thereby preventing excessive fat accumulation. This mechanism may be related to increased insulin levels and insulin resistance commonly observed in obesity. Activation of p53 in the tissues of obese individuals may thus represent a protective response against the carcinogenic effects of insulin (14). Telomerase is usually expressed at low to undetectable levels in PBMCs; therefore, only a few studies have investigated telomerase activity in these cells (15). To our knowledge, this is the first study to report that telomerase activity in PBMCs is significantly higher in obese individuals than in controls, and that it correlates positively with BMI. This increase may be explained by the fact that obesity is characterized by proinflammatory state accompanied by increased oxidative stress (16). Due to its high guanine content, telomeric DNA is highly susceptible to oxidative damage (17), and oxidative base lesions in telomeres may induce moderate telomere lengthening through telomerase activation (18). In the present study, we also found a positive correlation between MIF and telomerase activity. Previously, Xia and Hou demonstrated that the anticancer drug Doxorubicin, causes senescence in mesenchymal stem cells (MSC), and that pretreatment with MIF increases cell viability, telomere length, and telomerase activity (18). Another study indicated that MIF reduces cellular susceptibility to radiation and helps restore telomere length and telomerase activity (19). In the context of obesity, the positive correlation between MIF and telomerase activity observed in our study may reflect underlying biological mechanisms driven by chronic low-grade inflammation and oxidative stress. Macrophage migration inhibitory factor activates intracellular signaling pathways, including NF-κB and PI3K/Akt, which are known to enhance telomerase activity (18). In addition, elevated oxidative stress in obesity may further stimulate MIF secretion from adipocytes and immune cells as a compensatory mechanism to counteract ROS-induced DNA damage. Increased telomerase activity in PBMCs may therefore represent part of a systemic adaptive response aimed at preserving chromosomal stability under persistent oxidative and inflammatory stress. These findings suggest that the MIF–telomerase relationship in obesity reflects a coordinated molecular network linking inflammation, oxidative stress, and telomere maintenance. Previous studies investigating the relationship between MIF and p53 have yielded conflicting results. Marvast et al. found no significant correlation between MIF and p53 expression in gastric adenocarcinoma (20). Similarly, Liu H et al., reported no association in adenoid cystic carcinoma tissue (21). In contrast, other study showed that MIF can promote Akt signaling and inhibit apoptosis in the p53-null cervical carcinoma (HeLa) and in the p53-null breast cancer (MDA-MB-468) cell line (22). Conversely, a significant positive correlation between p53 and MIF expression was found in 58 patients with prostate cancer (23). In our study, we found a significant positive correlation between MIF and p53 levels. This finding supports the notion that p53 may participate in the inflammatory processes associated with obesity. Moreover, this positive correlation may indicate that MIF-mediated inhibition of apoptosis can occur independently of p53. Although previous studies have demonstrated a negative correlation between telomerase activity and p53 expression (24,25), no significant association was observed between these parameters in the present study. This discrepancy may be explained by differences in study context and tissue type. Most existing studies have examined the relationship between telomerase activity and p53 expression in cancer tissues, whereas our investigation focused on obesity-related changes in peripheral blood mononuclear cells. Therefore, the contrasting results may reflect distinct regulatory or pathological mechanisms underlying cancer and

obesity. However, to more accurately assess the relationship between p53 and telomerase activity in obesity, future studies should examine this association at the adipose tissue level, where metabolic and inflammatory signaling are more directly involved in obesity-related molecular changes.

Study Limitations

This study has several limitations that should be considered when interpreting the findings. First, the control group sample size was smaller than that of the obese group, primarily due to the difficulty of recruiting healthy volunteers willing to donate blood. However, the control group size remained adequate for statistical analyses, and the data exhibited low variability, supporting the reliability of the comparisons. Second, the cross-sectional design limits the ability to draw causal inferences. Third, telomerase activity was measured in PBMCs instead of tissue samples because collecting tissues from healthy participants was ethically and practically unfeasible. PBMCs provide an accessible peripheral source for assessing systemic telomerase regulation; however, the measured activity likely reflects a systemic response to chronic inflammation and oxidative stress associated with obesity rather than tissue-specific telomere maintenance. Therefore, while PBMC-based measurements are informative, extrapolation to tissue-specific mechanisms should be interpreted with caution.

Conclusion

This study demonstrated that plasma MIF and p53 levels, as well as telomerase activity in PBMCs, are significantly increased in obese individuals compared with healthy controls. The positive correlations between MIF, telomerase activity, and BMI suggest that these factors may participate in a shared regulatory network involving inflammation and oxidative stress in obesity. Further studies at the adipose tissue level are needed to clarify the mechanistic interactions among MIF, p53, and telomerase in obesity.

Ethical Considerations: This study was approved by the Ankara Yildirim Beyazit University, Yenimahalle Education and Research Hospital Ethics Committee with the decision dated 25/09/2018 and numbered 49

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Consent of Patients: The participants were informed in detail, and informed consent was obtained.

Data Availability Statement: All relevant data are within the paper and they are available from the corresponding author on reasonable request.

Author Contributions: Concept - SR; Design - SR; Supervision -SR, FB, MSK; Data Collection and/Or Processing - SR; Providing Resources and Funding - FB; Literature Search - SR; Analysis or Interpretation - SR; Writing - SR; Critical Review - SR, FB, MSK

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