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Investigation of DNA damage and inflammatory marker profile in patients after bariatric surgery

Obezite ameliyatı sonrası hastaların DNA hasarı ve inflamatuar marker profilinin araştırılması

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Abstract

Purpose: Obesity is a significant risk factor in the development of many serious diseases. The most prominent ones among them are diabetes and coronary heart disease. Elevated blood sugar levels in obese individuals lead to increased susceptibility to infections due to the suppression of the immune response. Moreover, fatty skin folds can cause topical infections, ulcers, and delayed/impaired wound healing. Therefore, inflammatory and pro-inflammatory markers in the serum have gained importance in diseases such as diabetes and obesity. Furthermore, in obesity, reactive oxygen species (ROS) lead to DNA damage. 8-oxo-dG, which is the primary product of DNA oxidation, can be detected in the serum, saliva, and urine, making it an ideal biological marker for DNA damage in large population-based studies. The Comet assay analysis is a method used to demonstrate the double-strand breaks in DNA. Induction of γ-H2AX in tissue indicates the initiation of a well-regulated mechanism to reverse double-strand breaks in DNA. Potential benefits of monitoring the genomic health in obesity include creating a sense of urgency for personalized intervention measures and evaluating their progress. DNA damage in obesity is believed to be a reversible condition. Chronic inflammation is an etiological factor known to support DNA damage and neoplastic transformations in cells. Cytokines secreted from adipose tissue, especially TNF-alpha, IL-6, and IL-1β, promote the accumulation of various cells, including neutrophils, macrophages, and dendritic cells, and it indicates the initiation of an inflammatory process. In this project, it was aimed to investigate possible changes in inflammation markers and DNA damage in individuals undergoing bariatric surgery, who were beginning to improve endocrine and metabolic syndrome markers.

Materials and methods: For this purpose, blood and urine samples were collected from 45 obese patients, who had undergone bariatric surgery and 45 healthy volunteers matched for age and gender. The levels of inflammatory markers (IL-1β, IL-6, IL-8, and TNF-α) and the DNA damage marker γ-H2AX in serum, as well as the amount of 8-oxo-dG in urine, were determined using ELISA. Additionally, the percentage of DNA damage was determined using the Comet assay analysis.

Results: Weight control achieved through bariatric surgery and the subsequent reduction in fat tissue resulted in a significant decrease in the levels of γ-H2AX and 8-oxo-dG, as well as a parallel significant reduction in the percentage of DNA damage in the Comet assay results. The significant decrease in inflammatory markers IL-1β, IL-6, IL-8, and TNF-α levels indicated that bariatric surgery also affects inflammation indirectly.

Conclusion: Although there are numerous studies in the literature on individual parameters related to DNA damage in various diseases and obesity, it is believed that the present study determining DNA damage, oxidation, and repair mechanisms simultaneously with inflammatory marker levels serves as a guiding example for comparing genomic health and stability in pre-obese, post-obese, and non-obese individuals.

Keywords: Obesity, DNA damage, inflammation, bariatric surgery.

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Öz

Amaç: Obezite, birçok ciddi hastalığın gelişmesinde önemli bir risk faktörüdür. Bunlar arasında en büyük payı diyabet ve koroner kalp hastalıkları oluşturmaktadır. Yüksek kan şekeri immün yanıtı baskıladığından obezlerde enfeksiyona yatkınlık artmaktadır. Ayrıca yağlı deri katlantıları topikal enfeksiyon, ülser ve gecikmiş-bozulmuş

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yara iyileşmesi sorunlarına neden olmaktadır. Bu nedenle diyabet ve obezite gibi hastalıklarda serumdaki inflamatuar ve pro-inflamatuar markerlar önem kazanmıştır. Ayrıca obezitede reaktif oksijen türleri (ROS), DNA hasarına neden olur. DNA oksidasyonunun başlıca ürünü olan 8-oxo-dG serum, tükürük ve idrarda tespit edilebilir, bu da büyük popülasyon bazlı çalışmalar için ideal bir DNA hasarı biyolojik belirleyicisidir. Komet assay analizi DNA çift zincir kırıklarının gösterilmesi için kullanılan bir yöntemdir. Dokuda γ-H2AX indüksiyonu, DNA'nın çift iplik kırıklarının tersine çevrilmesi için iyi düzenlenmiş bir mekanizmanın başladığını göstermektedir. Obezitede genom sağlığını izlemenin potansiyel faydaları, kişiselleştirilmiş müdahale önlemlerinin aciliyetini oluşturmak ve ilerlemelerini değerlendirmek için önemlidir. Obezitedeki DNA hasarının, geri dönüşümlü bir durum olduğu düşünülmektedir. Kronik inflamasyon, DNA hasarı ve hücrelerde neoplastik dönüşümlerin destekleyicisi olarak bilinen bir etiyolojik faktördür. Adipoz dokudan salgılanan sitokinler, özellikle TNF-alfa, IL-6 ve IL-1β, nötrofiller, makrofajlar ve dendritik hücreler dahil olmak üzere çeşitli hücrelerin toplanmasını teşvik eder ve bu da inflamatuar bir sürecin başladığını göstermektedir. Biz bu proje ile obezite operasyonu ile endokrin ve metabolik sendrom belirteçleri düzelmeye başlayan bireylerde inflamasyon markerları ve DNA hasarı üzerine olası değişimlerini araştırmayı amaçladık.

Gereç ve yöntem: Bu amaçla 45 adet obezite ameliyatı geçirmiş hasta ve bu hastalarla yaş ve cinsiyet açısından uyumlu olan 45 adet sağlıklı gönüllüden kan ve idrar örnekleri alınmıştır. İnflamatuar marker IL-1β, IL-6, IL-8 ve TNF-α ve DNA hasar markerı γ-H2AX'in serum miktarı ve ayrıca idrarda 8-oxo-dG miktarı ELISA ile tespit edilmiştir. Komet assay analizi ile de DNA hasar yüzdesi tespit edilmiştir.

Bulgular: Obezite ameliyatı ile sağlanan kilo kontrolü ve dolayısı ile yağ dokusundaki azalma, DNA hasarı üzerinde γ-H2AX ve 8-oxo-dG miktarının azalması ve buna paralel olarak komet assay sonuçlarında da DNA hasar yüzdesinin anlamlı derecede azalması ile sonuçlanmıştır. İnflamasyon markerları IL-1β, IL-6, IL-8 ve TNF-α miktarlarının anlamlı derecede azalması obezite ameliyatının dolaylı olarak inflamasyon üzerine de etkili olduğunu göstermiştir.

Sonuç: Literatürde DNA hasarına ilişkin tekil parametrelerle ilgili birçok hastalıkta ve obezitede çalışma bulunmakla birlikte, DNA hasarının, oksidasyonunun ve tamir mekanizmasının belirlenmesi ve inflamasyon markerlarının da eş zamanlı seviyelerinin belirlenmesi sayesinde genom sağlığı ve stabilitesinin obezite öncesi, sonrası ve non-obez bireylerde karşılaştırılması açısından çalışmamızın yol gösterici olduğunu düşünmekteyiz.

Anahtar kelimeler: Obezite, DNA hasarı, inflamasyon, obezite ameliyatı.

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Introduction

Obesity arises from the disparity between calorie intake and expenditure, leading to the accumulation of excess fat when more food is consumed than the energy consumed in the body [1]. Obesity is a serious health issue in today's world. It is estimated that there are approximately 700 million obese individuals in the world. It is projected that, as of the year 2030, 2.16 billion individuals (38%) will be overweight, and 1.12 billion individuals (10%) will be considered obese [2].

Obesity is a significant risk factor for the development of several serious diseases. Diabetes and coronary heart disease have the largest share among them. The treatment of obesity, especially for patients with morbid obesity (BMI >40), is often more costly and time-consuming than expected. Bariatric surgery is offered as a preferred treatment due to its long-lasting effects and low risk. Various surgical techniques with varying efficiency levels have been developed for this purpose [3]. Individuals with a BMI of 40 kg/m² or a BMI of 35 kg/m² with comorbidities (such as diabetes, hypertension, dyslipidemia, cardiovascular disease, and respiratory diseases) despite the diet and exercise can be treated with bariatric surgery [4]. Laparoscopic Sleeve Gastrectomy (LSG) and Roux-en-Y Gastric Bypass are currently the most widely preferred surgical methods nowadays [5]. In the LSG method, the procedure starts with the dissection of the omentum attached to the greater curvature of the stomach. Starting from 2.5 to 4 cm proximal to the pylorus, the greater curvature is resected up to the angle of His at the cardioesophageal junction. The gastrocolic and gastrosplenic ligaments are cut first. To completely resect the stomach fundus, where ghrelin, also known as the hunger hormone, is secreted, the omentum is freed up to the left diaphragmatic crus. With an average calibration of 36 French (1.2 cm), the orogastric tube is inserted into the stomach by the anesthesia team. Resection is performed by using cutting and stapling devices, ensuring that there is neither stricture nor excessive volume in the remaining stomach portion [6].

In obesity, the disruption of the balance between reactive oxygen species (ROS) mediated signaling mechanism and antioxidant defense causes comorbid diseases. ROS are known to be mutagenic, and they cause DNA damage and altered protein expression, as well as interfering with signaling pathways that support tumor formation [7]. 8-oxo-deoxyguanosine (8-oxo-dG) is a product of free radical-induced oxidation of guanosine. 8-oxo-dG can be detected in serum, saliva, and urine; this makes it an ideal biological marker for DNA damage in large population-based studies [8]. The comet assay analysis is a method used to demonstrate double-strand breaks in DNA. Tail length and the percentage of DNA within the tail are considered measures of DNA damage [9].

The induction of nuclear γ-H2AX foci indicates the initiation of a significant repair process potentially following a carcinogenic DNA lesion. The induction of γ-H2AX in tissues suggests the initiation of a well-regulated mechanism for reversing double-strand DNA breaks [10].

Previous studies reported a positive correlation between BMI and DNA damage. The potential benefits of monitoring “genomic health” in obesity are important in order to emphasize the urgency of personalized intervention measures and assess their progress. It is believed that DNA damage in obesity is a reversible condition [11].

Since high blood sugar suppresses the immune response, obese individuals are more susceptible to infections. Moreover, fatty skin folds can lead to topical infections, ulcers, and delayed/impaired wound healing. Therefore, in diseases such as diabetes and obesity, inflammatory and pro-inflammatory markers in the serum have gained importance. Bariatric surgery has become a widely preferred method for individuals with reduced responsiveness to medical treatment, compromised vital functions, and affected vital organs, leading to decreased mobility [12].

Chronic inflammation is an etiological factor known to support DNA damage and neoplastic transformations in cells. In the case of obesity, the release of pro-inflammatory molecules from adipose tissue, including CRP, TNF-α, and IL-8, was reported in previous studies [13]. It is known that plasma levels of IL-6, TNF-α, and TNF receptors increase in obese individuals [14]. Cytokines released from adipose tissue, especially TNF-alpha, IL-6, and IL-1β, promote the accumulation of various cells, such as neutrophils, macrophages, and dendritic cells, which indicates the initiation of an inflammatory process [15].

With this project, it was aimed to examine potential changes in inflammatory markers and DNA damage among individuals, in whom endocrine and metabolic syndrome markers started improving with bariatric surgery.

Material and methods

Sample collection

In the present study, 45 obese patients, who had undergone bariatric surgery, and 45 healthy volunteers matching with these patients in terms of age and sex were included. Approximately 5 ml of peripheral venous blood samples were collected from both healthy controls and obese patients before the surgery and one year after the surgery by using biochemical tubes (yellow cap), 3 ml of peripheral blood samples were collected into hemogram tubes (purple cap), and approximately 3 ml of urine samples were obtained.

DNA damage detection with the comet method

A 3 ml blood sample from the hemogram tube was added to a sterile 15 ml falcon tube after gently pipetting it following the addition of 3 ml histopaque. Following the centrifugation performed at 3000 rpm for 30 min. at 12°C, the intermediate phase containing lymphocytes was transferred to a new sterile 15 ml falcon tube. Subsequently, 3 ml of PBS was added, followed by centrifugation at 3000 rpm for 10 minutes at 12°C. The isolated lymphocytes were then stored at -80°C until the completion of other study samples.

DNA damage in lymphocytes was detected by using the classic alkaline comet assay method. In this method, lymphocytes were seeded on coverslips coated with agarose solution with a low melting temperature after being covered with agarose solution with a

high melting temperature. After treatment with a lysis solution, electrophoresis was performed in the electrophoresis solution at +4°C. After the electrophoresis process, neutralization was performed. Then, the coverslips treated with methanol were prepared for staining. Ethidium Bromide dye was used to stain the coverslips, and imaging was performed using a fluorescent microscope. DNA damage was evaluated based on parameters such as head length, head intensity, tail length, tail intensity, and tail moment of cells using a fluorescent microscope.

Detection of the serum levels of inflammatory markers IL-1β, IL-6, IL-8, TNF-α, and DNA damage marker γ-H2AX by using ELISA

Blood samples in the biochemical tube obtained from patient and control groups were centrifuged at 2500 rpm for 10 min. at +4°C to obtain serum. The sera obtained were stored at -80°C until the completion of the samples.

The quantities of inflammatory markers IL-1β, IL-6, IL-8, and TNF-α, as well as the DNA damage marker γ-H2AX, were determined by using the ELISA (BT Lab, China) method in all serum samples. In this system that is based on the biotin double-antibody (sandwich) principle, the wells were coated with specific antibodies. Standards were prepared in serial dilutions, starting from the stock standard, with concentrations of 1x, 1/2, 1/4, 1/8, 1/16, and 1/32. To the standard well, 50µl of standard and 50µl of Streptavidin-HRP were added. For the sample wells, 40µl of sample + 10µl of antibody + 50µl of Streptavidin-HRP were added. After incubation at 37°C for 60 minutes, washing process was performed with the washing solution. Then, 50µl of chromogen solution A and 50µl of chromogen solution B were added to the wells sequentially. After incubating in the dark at 37°C for 10 minutes, 50µl of stop solution was added (the blue color will turn yellow). The absorbance changes were measured at 450 nm wavelength with the resulting color change.

Detection of the level of 8-oxo-dG in urine by using ELISA

Urine samples obtained from patient and control groups were transferred to sterile 15 ml falcon tubes and centrifuged at 3000 rpm for 5 minutes at room temperature. The supernatant was transferred to sterile Eppendorf tubes and stored at -80°C until the completion of samples.

The amount of 8-oxo-dg indicating DNA damage due to oxidative stress was determined in all urine samples using the same ELISA (BT Lab, China) procedure.

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study.

Statistical analyses

A strong effect size (dz=1.6) was observed in the reference study. Considering that a lower effect size could be obtained (dz=0.4), a power analysis was performed, indicating that a 95% confidence level with 80% power could be achieved when at least 41 participants were included in the study. In order to make comparisons with the control group, a similar number of participants were included in the patient group (minimum n=41). Data were analyzed by using SPSS 25.0 software. Continuous variables were presented as mean ± SD, whereas categorical variables were presented as numbers and percentages. Independent group differences were compared with the Two-Sample t-test when parametric test assumptions were met, and the Mann-Whitney U test was used when parametric test assumptions were not met. For dependent group comparisons, the Two-Sample Paired t-test was used when parametric test assumptions were met, and the Wilcoxon test was used when parametric test assumptions were not met. Moreover, correlations between continuous variables were examined by using Spearman or Pearson correlation analyses, while differences between categorical variables were examined using the Chi-Square analysis.

Results

DNA damage between groups

Examining the results of comet analysis for DNA damage detection among groups, it was observed that the DNA damage of patients had significantly decreased at the post-surgery control performed 1 year after the surgery (p=0.0081). When evaluated in terms of head length, tail length, head intensity, tail intensity, and tail moment at the 1-year follow-up, a statistically significant difference was found in head length (the median value before surgery was 69.05 with an interquartile range of 14.37, while the median value was 84.35 with an

interquartile range of 23.74 in the 1st year control, *p*=0.010). No statistically significant difference was observed between the control group and the post-surgery group (median value for the control group was 89.35 with an interquartile range of 21.74, *p*=0.285) (Figure 1).

Serum levels of inflammatory markers IL-1β, IL-6, IL-8, TNF-α, and the DNA damage marker γ-H2AX among the groups

Comparing the IL-1β levels of the groups, it was observed that the IL-1β levels of patients significantly decreased at the 1st-year follow-up after bariatric surgery (*p*=0.003). No significant difference was determined between the control group and the 1st-year post-surgery control group (*p*=0.763) (Table 1).

Examining the IL-6 levels of the groups, significant differences in IL-6 levels of patients were observed at the 1st-year follow-up after bariatric surgery (*p*=0.001). No significant difference was observed between the control group and the 1st-year post-surgery control group (*p*=0.873) (Table 2).

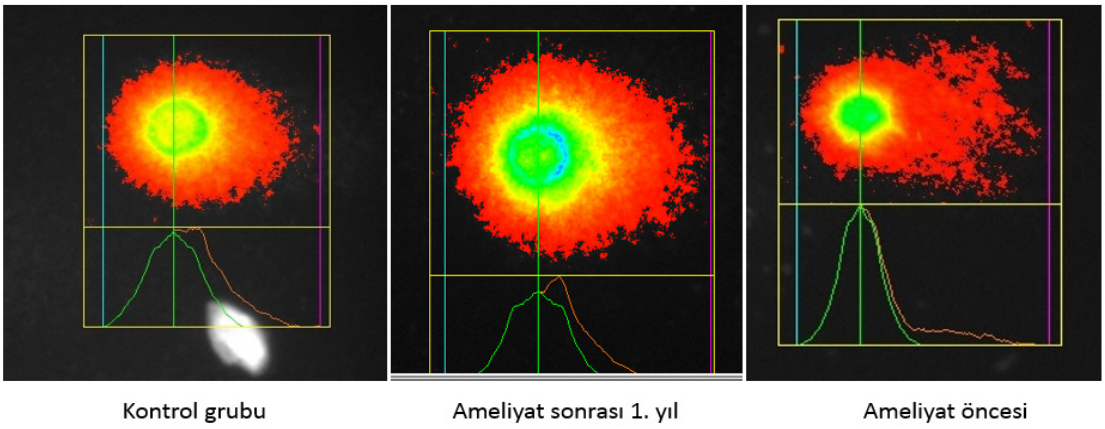

Figure 1. Comet images of control group, pre surgery and 1st year follow up

Table 1. Pre-surgery, 1st year postop, and control groups' IL-1β levels (pg/ml)

Group	Mean	Standard Deviation	Standard Error	*p*
Pre-surgery	498.96	352.91	52.64	0.003
1st year follow-up	333.58	207.31	30.902	0.763
Control	303.165	180.7	23.44	

Table 2. Pre-surgery, 1st year follow-up, and control groups' IL-6 levels (ng/L)

Group	Mean	Standard Deviation	Standard Error	*p*
Pre-surgery	60.45	37.56	5.59	0.001
1st year follow-up	31.42	7.63	1.138	0.873
Control	28.23	6.75	1.03	

Analyzing the IL-8 levels of the groups, it was determined that there was a statistically significant difference in IL-8 levels of patients at the 1st-year follow-up after bariatric surgery (p=0.001). While there was a significant difference in IL-8 levels between the control group and pre-surgery IL-8 levels, no significant difference was observed at the 1st-year post-surgery follow-up (p=0.6996) (Table 3).

Examining TNF-α levels of the groups, significant differences in TNF-α levels of patients were observed at the 1-year follow-up after bariatric surgery (p=0.000). While a statistically significant difference was found TNF-α levels of the control group and pre-surgery group, no significant difference was observed at the 1st-year post-surgery follow-up (0.723) (Table 4).

Considering the γ-H2AX levels of the groups, a significant difference was found in γ-H2AX levels of patients at the 1st-year follow-up after bariatric surgery (p=0.000). Although a significant difference was determined between γ-H2AX levels of the control group and pre-surgery γ-H2AX levels, no significant difference was observed at the 1st-year post-surgery follow-up (p=0.124) (Table 5).

Urinal 8-oxo-dG levels of the groups

Examining the 8-oxo-dG levels of the groups, there was a significant difference in 8-oxo-dG levels of patients at the 1st-year follow-up after bariatric surgery (0.002). Even though a significant difference was found between 8-oxo-dG levels of the control group and pre-surgery 8-oxo-dG levels, there was no significant difference in the 1st-year post-surgery follow-up (p=0.378) (Table 6).

Table 3. Pre-surgery, 1st year follow-up, and control groups' IL-8 levels (ng/L)

Group	Mean	Standard Deviation	Standard Error	*p*
Pre-surgery	233.2966	104.18029	15.53028	0.001
1st year follow-up	106.5141	31.60977	4.71211	0.6996
Control	90.85	22.03	2.36	

Table 4. Pre-surgery, 1st year follow-up, and control groups' TNF-α levels (ng/L)

Group	Mean	Standard Deviation	Standard Error	*p*
Pre-surgery	98.50	57.14	8.51	0.000
1st year follow-up	63.50	9.76	1.45	0.723
Control	61.25	10.85	2.43	

Table 5. Pre-surgery, 1st year follow-up, and control groups' γ-H2AX levels (ng/ml)

Group	Mean	Standard Deviation	Standard Error	*p*
Pre-surgery	7.35	5.81	0.866	0.001
1st year follow-up	2.87	1.52	0.227	0.124
Control	3.23	2.13	0.452	

Table 6. Pre-surgery, 1st year follow-up, and control groups' 8-oxo-dG levels (ng/ml)

Group	Mean	Standard Deviation	Standard Error	*p*
Pre-surgery	7.2	4.8	0.763	0.002
1st year follow-up	4.85	2.22	0.492	0.378
Control	3.12	1.73	0.397	

Discussion

The relationship between obesity and genotoxic damage is a relatively new research subject, and previous studies reported an accumulation of DNA damage among individuals with obesity and its association with obesity-related diseases [16, 17]. The results of a previous study carried out on the potential effects of weight loss on DNA damage by using the single-cell gel electrophoresis technique showed that weight loss can lead to a decrease in DNA damage levels in the body [18]. Furthermore, weight loss was shown to reduce inflammation markers such as C-reactive protein (CRP), Tumor Necrosis Factor-Alpha (TNF-α), and interleukin-6 (IL-6), as well as a decrease in oxidative stress [19]. In addition, high levels of proinflammatory cytokines, including prostaglandin E2, TNF-α, IL-2, IL-8, IL-10, and monocyte chemoattractant protein-1, were associated with increased levels of body fat. It was claimed that inflammation triggered by the activation of the nuclear factor kappa light chain-enhancer of activated B cells (NF-κB) complex may promote cancer development. Inflammation and immunological changes can also cause malignancy and progression by affecting DNA repair mechanisms, gene functions, and cellular mutation rates [20, 21]. In addition to endogenous antioxidant systems, a diet rich in antioxidants can protect DNA and enhance cellular resistance to oxidative stress [22, 23]. Consuming a diet rich in fruits and vegetables was shown to reduce the risk of metabolic diseases and cancer [24]. Furthermore, the quality and quantity of dietary fat were shown to be correlated with DNA stability and a diet rich in polyunsaturated fatty acids might reduce DNA damage [25].

It is known that obesity alters the DNA double-strand break repair mechanism caused by genotoxic chemicals [26]. Previous scientific studies have revealed that individuals with obesity have double-strand breaks, single-strand breaks, oxidized bases, and DNA damage that are twice as high as in normal-weight individuals [27, 28]. Obesity can lead to an increase in DNA damage or disruptions in DNA repair mechanisms, resulting in the accumulation of DNA damage in cells, leading to inflammation, changes in gene expression, and disruptions in cellular metabolism [26]. Studies carried out on experimental animals reported an increase in genotoxic damage to mitochondrial DNA (mtDNA) in animals fed a high-fat diet [29, 30]. During the development of obesity, the accumulation of T lymphocytes and macrophages in adipose tissue promotes the production of reactive oxygen species (ROS) by NADPH oxidase and nitric oxide 2 protein [31-33]. ROS formation can lead to increased insulin levels, fatty acids, and glucose levels, and indirectly contribute to inflammation [34]. Disruptions in the oxidant/antioxidant balance can negatively affect cellular biomolecules, including DNA [35]. According to the results of a previous study, obesity was associated with inflammation and oxidative stress, which induce DNA damage, and the prevention of DNA repair results in the accumulation of DNA damage in adipocytes [26]. A study carried out on young adults aged between 18 and 30 years revealed a negative correlation between BMI and nucleotide excision repair (NER) capacity [36]. The results of a study comparing the evaluation of DNA damage in peripheral lymphocytes of obese and normal-weight adolescents in cell culture environments indicated that obesity can alter the repair mechanism of DNA double-strand breaks caused by genotoxic agents [37].

In this study, comparing the preoperative and postoperative results of DNA damage markers, γ-H2AX, and 8-oxo-dG, in both whole blood and serum, it was demonstrated that there was a reduction in the amount of DNA damage among obese patients after bariatric surgery. In addition, comparing the levels of inflammation

markers, IL-1β, IL-6, IL-8, and TNF-α, before and one year after the surgery, a decrease was observed in inflammation markers after surgery, reaching similar levels to the control group.

In conclusion; weight control achieved through sleeve gastrectomy, which is a restrictive method in morbidly obese individuals, resulted in a reduction in DNA damage and inflammation. Although there are many studies carried out on individual parameters related to DNA damage in various diseases and obesity, it is believed that the present study provides valuable insights into genome health and stability, both before and after obesity, and in non-obese individuals, by determining DNA damage, oxidation, and repair mechanisms simultaneously, as well as evaluating inflammation markers.

Conflict of interest: No conflict of interest was declared by the authors.

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Conceptualization, A.B.E.U.; methodology, S.S., I.A., A.B.E.U.; software, I.A., A.B.E.U.; validation, S.Y., M.R.A.; formal analysis, T.S.; investigation, T.S., S.Y., M.R.A.; resources, I.A., A.B.E.U.; data curation, S.S., I.A., A.B.E.U.; writing, A.B.E.U. original draft preparation, T.S., A.B.E.U.; writing, review and editing, T.S., B.E.U.; project administration, T.S., S.Y., M.R.A., S.S., I.A., A.B.E.U.; funding acquisition, All authors have read and agreed to the published version of the manuscript.