

# The Relationship Between Idiopathic Heavy Menstrual Bleeding and Periodontitis: A Case-Control Study

Ülkü METE URAL<sup>a</sup>, Gülbahar USTAOĞLU<sup>b</sup>, Zeynep KARAS<sup>b</sup>, Emre AVCI<sup>c</sup>

<sup>a</sup>Bolu Abant İzzet Baysal University Faculty of Medicine Department of Gynecology and Obstetrics, Bolu, Türkiye

<sup>b</sup>Bolu Abant İzzet Baysal University Faculty of Dentistry, Department of Periodontology, Bolu, Türkiye

<sup>c</sup>Health Sciences University Gülhane Faculty of Pharmacy, Department of Basic Pharmaceutical Sciences, Division of Biochemistry, Ankara, Türkiye

**ABSTRACT Objective:** The cause of idiopathic heavy menstrual bleeding has not been identified, but increased systemic inflammation may be a factor. Periodontitis has an impact on general health and may cause systemic low-grade inflammation. The aim of the study was to investigate the relationship between idiopathic heavy menstrual bleeding and periodontitis. **Material and Methods:** A total of 60 women were included in the study. Thirty women with idiopathic heavy menstrual bleeding constituted the study group, and 30 healthy age-matched participants with normal menstrual bleeding constituted the control group. Evaluation of menstruation was performed using a pictorial-based assessment chart (PBAC) score. Periodontal status was evaluated with the gingival index, plaque index, bleeding on probing, probing depth, clinical attachment loss, total teeth number, and decay teeth number. Saliva samples were obtained to analyze the total antioxidant status, total oxidant status, arylesterase activity, and oxidative stress index levels. **Results:** There were no statistically significant differences in age and BMI between the study and the control groups. All the periodontal clinical parameters were found to be statistically significantly deteriorated in the idiopathic heavy menstrual bleeding group. Total antioxidant status, total oxidant status, and oxidative stress index were significantly high, and arylesterase activity was low in the study group. **Conclusion:** Periodontitis causes systemic inflammation and can be associated with increased endometrial inflammatory effects. Local endometrial inflammation may interfere with normal endometrial healing and reduce the ability of endometrial cells to proliferate. Inadequate restoration of normal cytoarchitecture of endometrial tissue may contribute to prolonged menstrual bleeding.

**Keywords:** Idiopathic heavy menstrual bleeding; periodontitis; oxidative stress; saliva; inflammation

Heavy menstrual bleeding (HMB) is a common gynecological problem impressing up to 30% of reproductive-age women and is clinically characterized as menstrual blood loss of 80 mL or more each menstrual cycle.<sup>1</sup> HMB is one of the most frequent reasons for referrals to gynecological clinics and negatively influences physical, social, emotional, economic status, and sexual activity. Abnormal uterine bleeding can be classified into 2 categories based

on the International Federation of Gynecology and Obstetrics classification system: non-structural causes (COEIN: Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified) and structural causes (PALM: Polyps, Adenomyosis, Leiomyoma, Malignancy and hyperplasia).<sup>2</sup> The definition of idiopathic HMB (IHMB) is used in cases with no pelvic pathology or general bleeding disorder.<sup>3</sup> Half of the patients with HMB are

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**Correspondence:** Ülkü METE URAL

Bolu Abant İzzet Baysal University Faculty of Medicine İzzet Baysal Training and Research Hospital,  
Department of Gynecology and Child Unit Gynecology and Obstetrics, Bolu, Türkiye  
E-mail: ulkumete2004@yahoo.com



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categorized as idiopathic HMB and have no such problems.<sup>4</sup>

Periodontitis is a chronic, multifactorial inflammatory disease caused by dysbiotic plaque biofilms and related to increasing damage to the tissues that support teeth and impacts 10%-15% of adults.<sup>5</sup> Periodontal diseases lead to bacteraemia, inflammation, and a severe immune response. Inflammatory mediators, including interleukin-1 and tumor necrosis factor- $\alpha$ , and oral pathogens rapidly enter the circulation, inducing systemic inflammatory reactants. The detrimental consequences of periodontitis affect not just oral health but overall systemic well-being as well. Bacteremia, endotoxemia, and systemic inflammation are all potential side effects of periodontitis that have been linked to the onset and progression of systemic diseases, including rheumatoid arthritis, respiratory disorders, diabetes mellitus, adverse pregnancy outcomes, and cardiovascular diseases including atherosclerosis, myocardial infarction, and stroke.<sup>6-8</sup>

The exact cause of IHMB is yet unknown; however, research points to delayed endometrial repair and increased inflammation.<sup>9,10</sup> We hypothesize that increased systemic inflammation due to periodontitis may also increase endometrial inflammation, leading to heavy menstrual blood loss. The present study aimed to explore whether periodontitis is related to the occurrence of IHMB. A growing amount of scientific research indicates that moderate untreated periodontitis might have systemic effects, and a substantial correlation between periodontitis and systemic disorders has been demonstrated.<sup>11-13</sup> However, we could not identify any research in the literature that investigated the relationship between periodontitis and IHMB.

## MATERIAL AND METHODS

### STUDY POPULATION

The present cross-sectional study was conducted in the period from January 2020 to January 2024 following the approval from the Clinical Research Ethics Committee of Bolu Abant İzzet Baysal University (date: January 7, 2020; no:2019/175) in accordance with the Helsinki Declaration. Before enrollment in the study, all participants provided writ-

ten informed permission. A total of 60 patients aged 25-45 years were included. 30 women with idiopathic HMB constituted the study group, and 30 healthy age-matched participants with normal menstrual bleeding constituted the control group.

In this study, to show the severity of menstrual bleeding, pictorial-based assessment chart (PBAC) was used. The PBAC is a simple, pictorial tool used in women to assess menstrual blood loss. The PBAC score records the number of tampons or towels used and the degree to which they are stained with blood. The PBAC is a validated procedure designed to provide a semi-quantitative assessment of menstrual blood loss and has similar results with objective measurements derived from the alkaline haematin method.<sup>14</sup> It takes into account many factors, such as how many sanitary products are used, the percentage of blood contamination on these products, the quantity and size of blood that was passed, and the frequency of flooding occurrence. Images of tampons and sanitary towels with light, moderate, and heavy stains (rated as 1, 5 and 20, respectively) are included in the chart. Additionally, the passage of clots (scored as ascending scores from 1-5) and flooding occurrences are noted. PBAC score >100 was used to define HMB.<sup>15</sup>

Patients complaining of HMB between the ages of 25-45 with a PBAC score >100 formed the study group. PBAC is a potential self-screening method for heavy menstrual bleeding, but a brief information was given to the participants and explained the process for filling out the PBAC using their previous or current cycle. After changing their tampon or menstrual pads throughout a menstrual cycle, participants were prompted to complete the PBAC each time.

The participants were evaluated in terms of ultrasonography and hormone profile on the 3<sup>rd</sup> day of menstruation. The reproductive-age women with normal hormone profiles who did not have leiomyoma, polyps, adenomyosis or increased endometrial thickness were included in the study. Women in a similar age group with normal menstrual bleeding, normal ultrasonographic and hormone profiles formed the control group. The individuals with a history of polycystic ovarian syndrome, endometrial hyperplasia, in-

fertility, and recurrent pregnancy loss were excluded from the study. All participants have given healthy birth at least once and not undergone uterine surgery before. Patients who required endometrial biopsy due to menorrhagia and those with normal pathology results were included in the study.

History of coagulation disorder and chronic inflammatory systemic diseases such as diabetes mellitus and rheumatoid arthritis, cardiovascular diseases, and respiratory diseases, and women with a diagnosis of acute or chronic infections, malignancy, platelet dysfunction, thrombocytopenia, chronic liver or renal dysfunction, endocrine diseases, connective

tissue, and infiltrative disorders, metabolic diseases were not included in the study. Smokers, obese, pregnant, and breastfeeding women, and individuals who use anticoagulants, antiplatelets, hormone preparations, and any other medical treatment were excluded from the study. The inclusion and exclusion criteria are shown in the flow chart (Figure 1).

## CLINICAL EXAMINATION

One experienced periodontist assessed all clinical periodontal parameters, such as the clinical attachment level (CAL), probing depth (PD), bleeding on probing (BOP), plaque index (PI), and gingival index

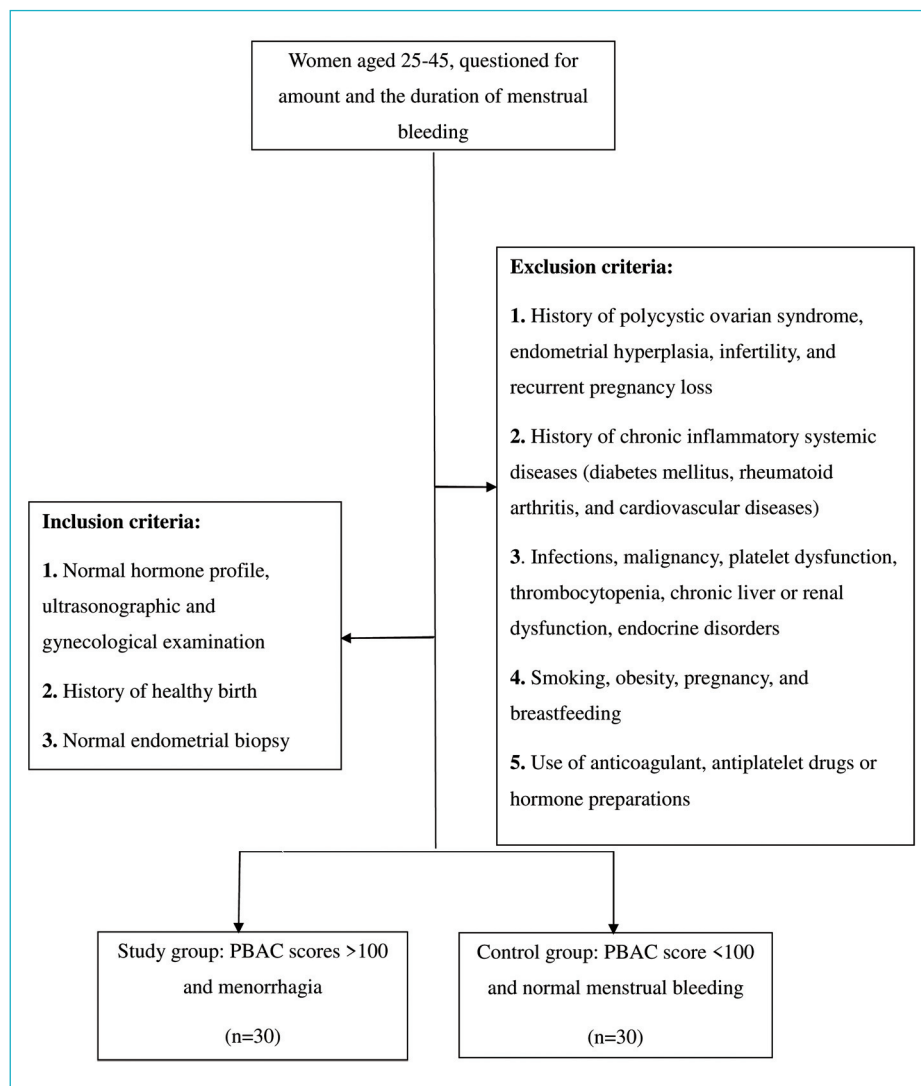


FIGURE 1: Flow chart of inclusion and exclusion criteria.

(GI).<sup>16,17</sup> A calibration exercise was carried out to achieve satisfactory reproducibility between examiners. A Williams probe (Hu-Friedy, Chicago, IL, USA) was used to perform periodontal examinations. For each tooth in the oral cavity, the clinical values of PD and CAL were assessed. The distolingual, midlingual, mesiolingual, distobuccal, midbuccal, and mesiobuccal regions were the 6 locations at which the measurements were conducted. The obtained results were recorded with an estimate to the closest entire millimeter. The distance between the cemento-enamel junction and the bottom of the pocket was measured and recorded, and this distance was designated as CAL. The total score acquired from all teeth was divided by the total number of teeth examined during the study to determine the mean values of PD and CAL. To determine the proportion of BOP, the periodontal probe was very gently and carefully inserted into the gingival sulcus, even one site with BOP was noted as (+) for every single tooth.

#### SILNESS&LÖE PIAQUE INDEX<sup>16</sup>

Score 0: No microbial plaque present. Score 1: A thin layer of microbiological plaque lining the free gingival edge; Score 2: A moderate buildup of plaque within the sulcus; Score 3: A large amount of free gingival margin plaque in a pocket or sulcus.

#### LÖE&SILNESS GINGIVAL INDEX<sup>17</sup>

Score 0: Normal gingiva; Score 1: Mild inflammation, with a little edema and color change. No bleeding on probing; Score 2: Moderate inflammation, with redness, edema, and glazing. Bleeding on probing; Score 3: Severe inflammation, with evidenced redness, edema, ulceration. Propensity for spontaneous bleeding.

#### SALIVA SAMPLES AND MEASUREMENT OF OXIDATIVE STRESS BIOMARKERS IN SALIVA

The saliva samples were collected for 10 minutes before clinical periodontal measurements. After an overnight fast, 3 mL of unstimulated saliva samples were taken between 9:00 and 10:00 in the morning in order to prevent any alterations in the patients' circadian rhythms and kept at -80°C until the oxidative

stress parameters were analyzed. Before sampling, all patients were advised not to eat or drink anything. Oxidative stress biomarkers, including total antioxidant status (TAS), total oxidant status (TOS) levels, and arylesterase activity (ARE) were analyzed spectrophotometrically and commercially available kits (Relassay, Türkiye) were used.<sup>18</sup> ARE activity was expressed as kilo units per 1 liter of sera (kU/L). The ratio of TOS to TAS, which constitutes the oxidative stress index (OSI), is an essential marker within this dynamic oxidative network.<sup>19</sup> The following formula was used to determine the OSI value:

$$\text{OSI (arbitrary unit)} = \frac{\text{TOS } (\mu\text{mol H}_2\text{O}_2 \text{ equivalent/L})}{\text{TAS (mmol Trolox equivalent/L)}}$$

#### STATISTICAL ANALYSIS

The acquired data in this study were tested for conformance to a normal distribution using the Kolmogorov-Smirnov test. The student t-test for normally distributed variables was employed to evaluate the differences between these groups (GI, PI, PD, CAL, BOP, total teeth number, decay teeth number, BMI, and age), and the Mann-Whitney U test for variables without normal distribution (TAS, TOS, OSI, and ARE). Statistical significance was set as  $p < 0.05$ .

## RESULTS

There were no statistically significant differences in age and body mass index (BMI) between the study and the control groups ( $p > 0.05$ ). The mean age was  $36.03 \pm 6.01$  years in the IHMB group and  $34.33 \pm 6.03$  years in the control group. The mean BMI was  $24.87 \pm 1.84 \text{ kg/m}^2$  and  $24.77 \pm 1.43 \text{ kg/m}^2$  for the IHMB group and the control group, respectively. Median PBAC score and median length of menstrual bleeding were higher in the IHMB group ( $p < 0.001$ ) [Table 1](#) displays the participant's demographic information.

The periodontal clinical parameters (GI, PI, CAL, BOP, total teeth number, and decay teeth number) were shown in [Table 2](#) and found to be statistically different between the groups. All the parameters were deteriorated in the IHMB group. It was determined that oxidant and antioxidant markers in saliva showed significant differences between groups.

**TABLE 1:** Demographic data.

	IHMB group (n=30)	Control group (n=30)	p value
Age	36.03±6.01	34.33±6.03	0.279
BMI	24.87±1.84	24.77±1.43	0.817
Menstrual bleeding (PBAC score)	396 (162-948)	58 (41-74)	<0.001
Duration of menstrual bleeding (days)	9 (7-14)	6 (4-8)	<0.001

IHMB: Idiopathic heavy menstrual bleeding; BMI: Body mass index;  
PBAC: Pictorial blood loss assessment chart.

**TABLE 2:** Comparison of clinical parameters between the groups.

	IHMB group (n=30)	Control group (n=30)	p value
GI	1.72±0.44	1.38±0.32	0.001
PI	1.92±0.62	1.41±0.50	0.001
PD	2.35±0.53	2.07±0.56	0.056
CAL	2.39±0.58	2.08±0.57	0.039
BOP (%)	68.35±37.83	37.40±32.33	0.001
Total teeth number	24.2±2.80	26.20±2.26	0.004
Decay teeth number	1.23±1.04	0.66±1.02	0.038

IHMB: Idiopathic heavy menstrual bleeding; GI: Gingival index; PI: Plaque index;  
PD: Probing depth; CAL: Clinical attachment level; BOP: Bleeding on probing.

**TABLE 3:** Comparison of total antioxidant status, total oxidant status, oxidative stress index, and paraoxonase 1 arylesterase levels between two groups.

	IHMB group (n=30)	Control group (n=30)	p value
TAS			
$\bar{X}$ ±SD	0.80±0.30	0.61±0.28	0.005
Median (minimum-maximum)	0.77 (0.16-1.48)	0.55 (0.20-1.29)	
TOS			
$\bar{X}$ ±SD	18.94±16.60	5.77±3.50	<0.001
Median (minimum-maximum)	10.71 (1.28-55.87)	6.15 (0.44-13.67)	
OSI			
$\bar{X}$ ±SD	2.34±1.91	1.11±1.00	0.003
Median (minimum-maximum)	1.85 (0.27-9.13)	0.90 (0.08-4.87)	
ARE			
$\bar{X}$ ±SD	326±3.89	327.90±3.35	0.031
Median (minimum-maximum)	325 (320-335)	328 (322-334)	

IHMB: Idiopathic heavy menstrual bleeding; TAS (mmol Trolox equivalent/L): Total antioxidant status; SD: Standard deviation; TOS ( $\mu\text{mol H}_2\text{O}_2$  equivalent/L): Total oxidant status; OSI (arbitrary unit): Oxidative stress index; ARE (kU/L): Paraoxonase 1 arylesterase.

Women with idiopathic HMB had higher salivary TAS, TOS, OSI, and lower ARE activity compared to women with normal menstrual bleeding (Table 3).

## DISCUSSION

This study evaluated the relationship between periodontal diseases and IHMB. According to our results, the periodontal clinical parameters and oxidative stress markers were found to be significantly distorted in the IHMB group compared to the healthy group. We hypothesized that the increased chronic inflammation due to periodontitis would result in increased and persistent endometrial inflammation and delayed endometrial repair, contributing to the symptoms of heavy menstrual bleeding. To our knowledge, the relationship between idiopathic HMB and periodontitis has not been studied.

A growing amount of research in recent years has indicated that reactive oxygen species play a crucial role in creating an oxidatively stressed environment, which is the basis of the pathophysiology of numerous chronic inflammatory diseases.<sup>20</sup> Periodontitis is one of the most prevalent chronic inflammatory diseases of humans. The chronic systematic inflammatory response due to periodontitis may contribute to increased pro-inflammatory mediators and oxidative stress in the endometrium. HMB has been linked to increased endometrial inflammation and delayed endometrial repair during menstruation.<sup>10,21</sup>

Menstrual bleeding is a pattern of self-limiting inflammation. Because of the leukocytic invasion, tissue edema, and subsequent production of inflammatory mediators in the endometrium, menstruation is considered as an inflammatory event.<sup>22</sup> This type of physiological inflammation does not exist beyond the reproductive tract. During menstruation, an exaggerated or prolonged inflammatory response will cause excessive tissue damage and may result in HMB.<sup>23</sup> Research analyzing endometrial tissue from women with HMB has identified significantly increased levels of the endometrial pro-inflammatory cytokines such as tumor necrosis factor, interleukin-8, prostaglandin, and cyclo-oxygenase-2 mRNA expression.<sup>22,24</sup>

As first-responder cells, neutrophilic polymorphonuclear leucocytes play a major role in periodontal health. They achieve this by utilizing a variety of special defense mechanisms, such as phagocytosis,



chemotaxis, degranulation, and the release of reactive oxygen species. Remarkably, periodontal disease seems to be linked to a neutrophil phenotype that is hyperactivated and characterized by the overproduction of reactive oxygen species and proteases.<sup>25</sup> Although reactive oxygen species play a crucial role in gene regulation, cell signaling, and antimicrobial defense, an excess of these species raises the oxidant load in the affected tissues, causing oxidative stress that in turn causes pathological changes that ultimately destroy host tissues and cause chronic inflammation.<sup>20,26</sup>

Periodontitis likely has a potential impact on up-regulating oxidative stress both locally and systemically, leading to a persistent imbalance that favors systemic inflammatory disorders. Saliva is accepted as the primary antioxidative barrier against oxidative stress due to its rich content of antioxidant enzymes.<sup>27</sup> Arylesterase activity has an important role in modulating oxidative stress and inflammation by protecting against lipid peroxidation, making it a potential marker for assessing inflammation. In our study, saliva arylesterase activity was found to be significantly lower in patients in the IHMB group, indicating impaired antioxidant defense mechanisms and inflammation.

The strict regulation of the endometrium acts as a complex multicellular system that comprises interactions of immune, endocrine, and vascular systems to allow periodic injury and repair at menstruation. The progesterone withdrawal creates a condition resembling an inflammatory event in the endometrium. The population of endometrial neutrophils increases dramatically after progesterone withdrawal.<sup>28</sup> Neutrophils, as key mediators of the inflammatory response, quickly move to the site of injury. While neutrophils in circulation only live for a few hours, those in inflamed tissue can endure for several days. Pro-inflammatory mediators and hypoxia reduce neutrophil apoptosis.<sup>29</sup> Reduced apoptosis causes a sustained neutrophil response, which is a hallmark of chronic inflammation.<sup>30</sup> The extended neutrophil response causes tissue damage and function loss.<sup>28</sup> The mouse model showed the significance of this neutrophil inflow during menstruation by demonstrating how neutrophil depletion impacted endometrial breakdown and remarkably postponed endometrial repair.<sup>31</sup>

Obesity is a chronic inflammatory situation. A study of animal models demonstrated that the endometrium of obese mice had higher levels of inflammatory mediators and hypoxia-regulated gene panel, which is compatible with a pro-inflammatory local endometrial environment. This study indicated that obesity-related systemic chronic inflammation raises local inflammation in the mouse endometrium.<sup>32</sup>

The importance of inflammation in optimal endometrial repair was emphasized in the study that investigated the relationship between decreased glycolysis and HMB.<sup>33</sup> The insufficient repair of the normal cytoarchitecture of endometrial tissue concerning HMB was highlighted in another study examining the linkage between pathological menstrual symptoms and the development of extragenital forms of local inflammation.<sup>34</sup> A review examining the pathogenesis of adenomyosis indicates that persistent endometrial inflammation may represent a cause of decidualization dysfunction.<sup>35</sup>

Our study had some limitations. Endometrial sampling was not performed to isolate local endometrial environmental differences that cause HMB. Systemic and endometrial oxidative stress markers were not examined simultaneously.

We found that periodontitis is associated with heavy menstrual bleeding. Women with IHMB should be investigated for increased inflammation in the body; periodontitis may be one possible cause of this condition.

## CONCLUSION

The cause and severity of menstruation problems may be influenced by inflammatory processes. Since periodontitis also leads to systemic inflammation in the body, oral health should be kept in mind in women with heavy menstrual bleeding. Prospective researches are required to clarify the possibility of targeting oxidative stress and inflammatory processes to ameliorate menstrual symptoms.

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*During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-*

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### Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

### Authorship Contributions

**Idea/Concept:** Ülkü Mete Ural, Gülbahar Ustaoglu; **Design:** Ülkü Mete Ural, Gülbahar Ustaoglu; **Control/Supervision:** Gülbahar Ustaoglu, Zeynep Karas; **Data Collection and/or Processing:** Gülbahar Ustaoglu, Ülkü Mete Ural; **Analysis and/or Interpretation:** Gülbahar Ustaoglu, Emre Avci, Zeynep Karas; **Literature Review:** Ülkü Mete Ural, Gülbahar Ustaoglu; **Writing the Article:** Ülkü Mete Ural; **Critical Review:** Gülbahar Ustaoglu; **References and Fundings:** Emre Avci, Zeynep Karas; **Materials:** Emre Avci, Zeynep Karas.

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