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# Gülhane Medical Journal

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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

The latest announcement has shown a reduction in the impact factor of most journals in the field of medicine. During the pandemic, an enormous increase in published articles on COVID-19 and citations has resulted in a rapid increase in the impact factor of journals. It appears the picture will stabilize in the coming ratings.

GMJ, on the other side, has been increasing its rating through a growing number of citations from all over the world.

The number of submissions on COVID-19 to GMJ is decreasing, as with other journals. We, of course, are still motivated to increase the value of research reports on COVID-19 in GMJ.

In the third issue of GMJ, we have selected highly interesting articles and case reports. As the journal's publishing team, we try to keep covering a wide range of articles from different disciplines.

With this opportunity, I would like to express my gratitude to all submitting authors, reviewers, and editors for their contributions.

M. Ali Gülçelik, M.D., Prof.  
Editor-in-Chief

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# Platelet-rich fibrin: Current trends in periodontal regeneration

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## ABSTRACT

Autologous platelet concentrates (APCs) have witnessed a sharp rise in popularity in recent years due to their low cost and ability to promote tissue neoangiogenesis. Platelet-rich fibrin (PRF) is a platelet concentrate (PC) generated from the patient's blood without anticoagulants. PRF is a platelet-based condensation of suspended growth factors. It also has a substantial fibrin network, many leukocytes, cytokines, and glycoproteins and is used for tissue and bone regeneration. PRF plays a substantial role in wound healing. Based on the leukocyte and fibrin concentrations of PCs, Dohan Ehrenfest categorized PCs into four groups. L-PRF was used in the clot formation to fill the defect and in the membrane cover. Since then, studies, technological advances and manufacturing protocols have created newer forms and enhanced their potential as regenerative materials in numerous disciplines. In endosseous and furcation deformities, new APC varieties are being explored as biological mediators of regeneration. A computerized search of the PubMed and Google Scholar databases was performed to select relevant articles from 2006 to 2022. Screening of English language systematic reviews, meta-analyses, original research, and narrative reviews were considered in synthesizing this review. Primary subject headings like PRF, platelet-rich plasma, PCs, growth factors and PRF, periodontal regeneration and PCs were combined using Boolean 'and' with secondary terms like types, preparation, furcation, recession and intrabony defects.

**Keywords:** Platelet-rich plasma, platelet-rich fibrin, growth factors, platelet concentrates, regeneration, autologous platelet concentrates

## Introduction

Periodontal disease is an inflammatory condition that destroys supporting structures, resulting in tooth loss. Periodontal therapy mainly aims at regenerating lost periodontal tissues. Several autologous and synthetic biomaterials enhance soft tissue and bone restoration. Autologous biomaterials occurring naturally [such as autologous platelet concentrates (PC)] refer to those present within the body and act as messengers for repair, regeneration, and healing (1). Synthetic biomaterials (alloplastic) possess a few disadvantages, such as foreign body reaction and avascularity (1-3).

Platelets and fibrin are two well-known autologous biomaterials that promote wound healing and regeneration. Research has been conducted in various fields to develop blood-derived products like PCs. Due to its excellent regeneration characteristics, platelet-rich fibrin (PRF) has demonstrated promising outcomes. This review describes the history, features, and current concepts regarding the function of PRF regeneration of the periodontium.

## Methods

A computerized search of the PubMed and Google Scholar databases was performed to select relevant articles from 2006



to 2022. Screening of English language systematic reviews, meta-analyses, original research, and narrative reviews were considered in synthesizing this review. Primary subject headings like PRF, platelet-rich plasma (PRP), PCs, growth factors and PRF, periodontal regeneration and PCs were combined using Boolean 'and' with secondary terms like types, preparation, furcation, recession and intrabony defects (IBDs).

### Historical background-from fibrin glue to PCs

Due to its known properties of wound healing and regeneration, blood-derived products have been widely used in the medical field for the past 40 years (1,4). The use of fibrin glue and sealants for topical hemostasis, soft tissue healing, and as melting agents for synthetic bone substitutes grew in the 1970s (3). It was created by combining donor plasma fibrinogen, factor XIII, and fibronectin with thrombin and calcium, which causes fibrinogen to polymerize (1,3). However, there were several drawbacks such as the suboptimal stability of fibrin glue due to low concentration of fibrinogen, low resistance to physical stress, expensive processing and more importantly the risk of cross-infection and viral transmissions (5). Since these products were made from human blood in blood banks, some countries had legally restricted their use due to the risk of contamination (6). Hence, many experiments using patient blood were conducted to test various methods to obtain autologous fibrin glues.

Hematology is where the concept of PCs initially emerged (1). It is an evolution of fibrin glue technology (6). In its initial stages, PCs were used to treat patients with severe thrombocytopenia to prevent hemorrhage (7). However, its usage spread to the areas of regeneration and wound healing. The multiple functions of platelets and the widespread availability of numerous growth factors and cytokines help in regeneration. Platelets produce fibrin, fibronectin, and vitronectin which provide the matrix for connective tissue and cell migration (2).

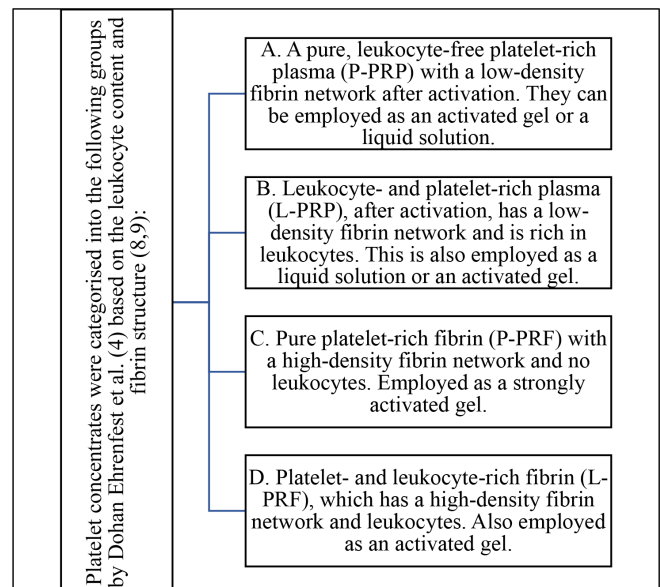
Ross et al. (3) described platelet regeneration capacity in early 1974. First-generation PC, PRP, was used in oral and maxillofacial surgery by Whitman, Berry, and Green (1997) (8) and Marx and associates (1998) (9). Combining the properties of growth factors generated by platelets and the characteristics of fibrin glue results in enhanced healing and regeneration effects of PRP (7). Due to the availability of several different systems for procuring PRP, a uniform protocol for PRP preparation needs to be revised. However, in most techniques, the patient's blood is mixed with an anticoagulant before being centrifuged to separate the blood into layers based on weight, including red blood cells (RBCs), leukocytes, platelets, and plasma (6,7). After its procurement, the stability of PRP is maintained for 8 hours, which eradicates its potential to transmit diseases or cause immunogenic reactions. Platelets start releasing growth factors within the first 10 min of PRP activation. Hence, PRP should be administered during the first ten minutes of its activation since

95% of growth factor release occurs within one hour (10). There are several drawbacks of PRP, depending on several variables, namely PC, leukocyte count, activator type, and time of fibrin scaffold placement after clotting; the characteristics of PRP can vary (1). Also, the poor handling properties due to its liquid nature, lack of uniformity in preparation protocol, and brief release of growth factors limit the clinical advantages (1). Incorporating bovine thrombin in PRP can cause the coagulation factors V, XI, and thrombin to be the target of antibodies, showing a negative impact on the coagulation process (2). Also, there are legal restrictions on handling blood, thereby paving the way for PRF (1,2).

Given the drawbacks mentioned above, Choukroun et al. (11) developed PRF in France, a second-generation PC rich in leucocytes and platelets in a fibrin network (also referred to as Choukroun's PRF). PRF is a robust regenerative biomaterial that was found to accelerate tissue healing and hence has several applications in periodontics (11).

### Platelet concentrate classification

1. PCs were categorized into the following groups by Dohan et al. (5) in 2009 based on the leukocyte content and fibrin structures (Figure 1) (10,12).
2. The PAW (platelet activation, white blood cells) categorization system established by De Long et al. (13) was based on the activation method, white blood cell and neutrophil content, and platelet number.
3. Mishra et al. (14) proposed another classification, confined to PRP and applicable only to sports medicine centered on the presence or absence of leukocytes. Four different forms of PRP were identified to determine whether PRP



**Figure 1.** Platelet concentrate classification  
PRP: Platelet-rich plasma, PRF: Platelet-rich fibrin

is activated. In addition, other classifications are proposed by various authors (15-18). However, no agreement on classification systems has yet been reached.

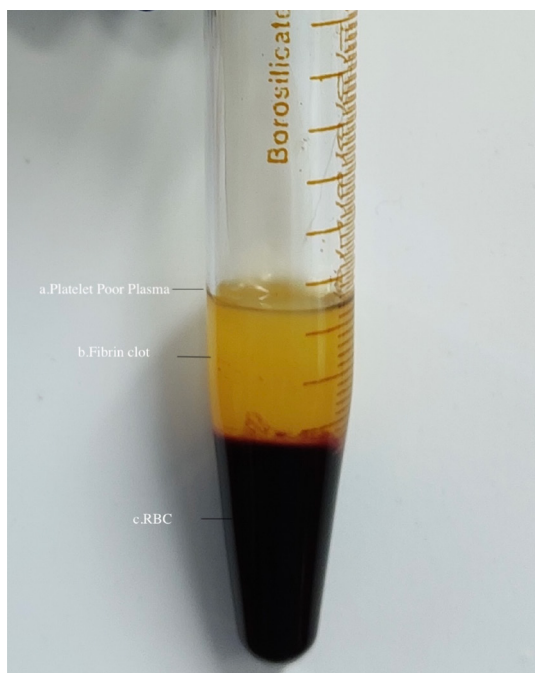
### Preparation of PRF

Unlike PRP, no anticoagulant is used; therefore, there is no need for animal thrombin or calcium for fibrin polymerization. A PC-02 table centrifuge and a blood collection kit with a 24 gauge butterfly needle and 10 mL blood collection tubes are necessary to prepare PRF.

### Protocol

5 mL of venous blood in each sterile tube was collected. It was centrifuged for 10 minutes at 3000 rpm (19). After the process, the whole blood is divided into three layers (12): a layer of platelet-poor plasma (PPP) on top, a fibrin clot with platelets and leukocytes in the middle (L-PRF) and RBCs at the bottom of the tube (Picture 1).

Plastic tubes were coated with silica and silicon to activate the coagulation process. Without anticoagulants, the platelets in contact with the inner walls become activated, progressively activating the coagulation cascade. In the beginning, fibrinogen exists at the top portion of the tube. Later, following centrifugation, thrombin is activated and converted to fibrin, forming a fibrin clot. The speed of blood collection and transfer to the centrifuge is crucial to the success of this procedure (19). The adhering RBCs were scraped off the fibrin clot obtained after centrifugation and discarded. By pressing out the fluids in the fibrin clot, L-PRF can also be transformed into the shape of a membrane.



**Picture 1.** Blood layers after centrifugation. a) Platelet-poor plasma. b) Fibrin clot. c) Red blood cells

### PRF techniques/protocols and types

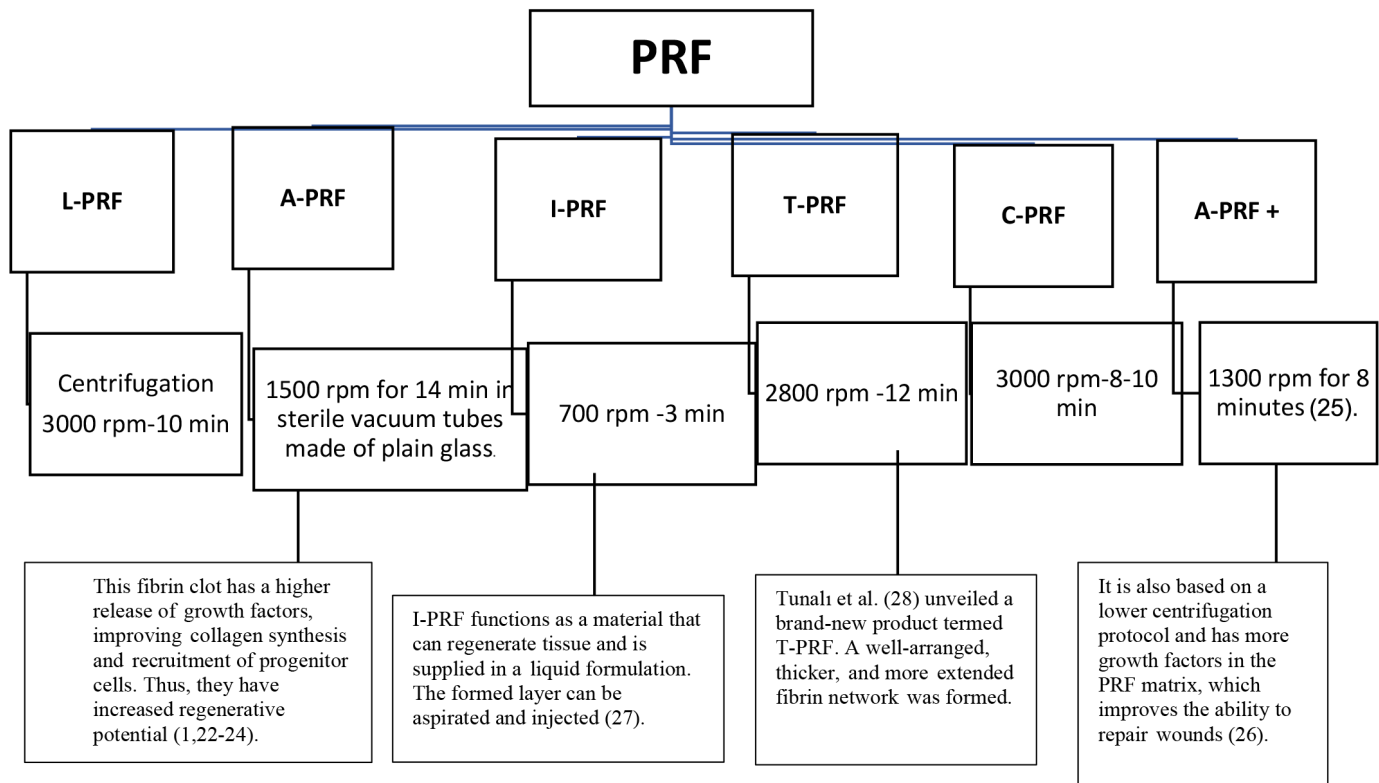
With the advance in research, several modifications in the preparation protocol of PRF were devised to enhance its wound healing and regeneration potential (Figure 2).

### Periodontal regeneration with PRF

PRF is a platelet-based consolidation of suspended growth factors. It also has a substantial fibrin network, abundant leukocytes, cytokines, glycoproteins, and several other components. The platelets contain granules that release cytokines and other factors such as serotonin, von Willebrand factor, factor V, osteonectin, and antimicrobial proteins; they cause homeostasis and enhance the clearance of pathogens. Leukocytes in PRF function in wound healing and regeneration. They also have anti-inflammatory, anti-nociceptive (20,21), and cell proliferation differentiation properties (12). PRF contains abundant growth factors such as platelet-derived growth factor (PDGF), transforming growth factor- $\beta$  (TGF- $\beta$ ), insulin-like growth factor-1 (IGF-1), fibroblast growth factor, and vascular endothelial growth factor (VEGF). VEGF is involved in various functions like osteoblast proliferation, collagen production, and angiogenesis. The Fibrin matrix promotes the invasion of various inflammatory, endothelial, and other cells. This matrix can also capture glycosaminoglycans enhancing cell migration and healing (12). They also contain stem cells, such as human bone mesenchymal stem cells that are stimulated when they come into contact with L-PRF (5,12).

In contrast to PRP, which has a rigid network, PRF has a thin, elastic fibrin network that promotes improved cytokine entrapment and cellular motility (2). The PRF matrix contains glycosaminoglycans like hyaluronic acid and heparin, which has a strong affinity for small peptides like cytokines, promoting cell migration and enhancing healing (5). PRF also promoted micro vascularization and increased cell migration (2). Furthermore, due to a natural fibrin network, there is no proteolysis of growth factors. All these properties make PRF a better healing biomaterial.

Hence, abundant growth factors in PRF have indicated its use in various regenerative and wound-healing procedures. The fundamental goal of periodontal therapy is to regenerate lost periodontal structures to restore health, function, and esthetics. As a result, the use of PRF in treating soft tissue healing, gingival recessions, IBDs, and furcation defects has gained popularity in periodontics. Also, the benefits are abundant, such as a simple process of preparation application and a cost-effective method. There is no addition of bovine thrombin and anticoagulants, and the PRF membrane is elastic and flexible owing to its three-dimensional structure, enhancing cellular migration and proliferation. PRF has certain demerits; since autologous blood is used, it is a challenge to get more significant amounts. Hence, its utility in general surgery is limited. The period between



**Figure 2.** PRF techniques/protocols and types

PRF: Platelet-rich fibrin

blood collection and centrifugation impacts the success of the procedure. It is donor-specific since it comprises immune cells and highly antigenic components. If not used immediately, the PRF membrane shrinks, resulting in the loss of structural integrity and leukocyte viability. Also, there is a risk of bacterial contamination when stored.

### The role of PRF in the regeneration of IBD

It has been demonstrated that PRF enhances bone-forming cell proliferation, differentiation, migration, and mineralization during bone formation. Several mechanisms have been suggested for bone formation through the use of PRF. The macrophages in PRF can directly promote osteogenesis. It encourages the propagation of growth factors, periodontal ligament cells, and osteoblasts, inducing osteoprotegerin production and proliferation of osteoblasts. After activation, platelets and leukocytes release cytokines that promote bone regeneration. Also, the TGF- $\beta$ 1, present in PRF stimulates collagen and fibronectin synthesis, promoting bone regeneration. VEGF promotes angiogenesis, which is required for skeletal development. PDGFs and IGF-1 promote osteoblast proliferation and differentiation (29).

Recently, the application of PRF for treating IBD was compared to other available modalities in a recent systematic review by Miron et al. (30). They obtained comparable

outcomes using open flap debridement (OFD)/PRF and OFD/bone grafts (BG). Chen et al. (31) conveyed that the benefits of OFD+PRF are more significant than that of BG+PRF, considering radiographic bone fill and depth reduction as the primary outcomes.

### The role of PRF in recession coverage (RC)

There is improved soft tissue healing because PRF membranes gradually and continuously release growth factors like VEGF, encouraging angiogenesis and accelerating tissue repair and regeneration by cell migration and repopulation in the injured site (32). When PRF was used with a coronally advanced flap for RC procedures, there was a decrease in matrix metalloproteinase-8 and interleukin beta levels but an increase in tissue inhibitors of metalloproteinase-1 levels at ten days. As a result, the initial stages of the process result in increased periodontal wound healing (33).

According to a few studies, PRF significantly enhances patient-reported outcome measures, such as postoperative pain observation and discomfort (34,35). The use of PRF was not superior to alternative treatments for Miller Class I and II gingival recessions, according to a systematic review by Moraschini and Barboza Edos (36) regarding root coverage, keratinized mucosa width, or clinical attachment level.

### The role of PRF in furcation defects

Because of the furcation location and the roots' uneven morphology, the biofilm is very challenging to access for oral hygiene procedures. Along with other well-known patient-related factors, including age, gender, smoking habit, and diabetes, the degree of furcation involvement is a risk factor for tooth loss. Several reconstructive periodontal surgical procedures and materials are used to treat these areas. Regenerative treatments are aimed at bone, cementum, and periodontal ligament regeneration in the furcation. When PRF is used, the growth factors stored in the granules are activated and released, aiding in bone regeneration (37). A systematic review and meta-analysis by Pepelassi and Deligianni (38) L-PRF demonstrated a significant clinical and radiographic additive effectiveness of OFD and osseous graft in teeth with furcation involvement. Also, in two- or three-walled periodontal endosseous defects in systemically healthy non-smokers, compared to those without L-PRF (38). PRF demonstrated better results than OFD alone in furcation treatment; however, it has fewer advantages as an adjunct to osseous graft. There is scarce literature available for any definitive conclusion regarding the combined effect of osseous graft and PRF. Also, the furcation defect studied was either maxillary or mandibular furcation with the variability of bone architecture and complexity of the furcation access.

### Other uses of PRF

PRF has several other applications in other procedures, such as socket preservation - The regenerative potential in socket preservation and following the tooth extraction is beneficial. However, more evidence is required to confirm its effectiveness (39). In implant dentistry - PRF addition to the implant surface has been shown to increase the bone-implant contact and enhance bone regeneration to enhance healing, osseointegration, and thereby the stability of implants. This could reduce the treatment time interval between implant placement and loading.

Furthermore, it improves soft tissue thickness to increase stability and minimize marginal bone loss and mucogingival surgery (40). PRF in the form of a membrane is beneficial in the palatal donor sites while harvesting free gingival grafts. The growth factors in PRF positively influence angiogenesis, cellular proliferation, and mitogenesis of wound-healing cells at the surgical site, thereby promoting fast healing (41).

### Recent advances

#### Albumin gel platelet-rich fibrin

One of the significant challenges faced with PRF was its 10-14 days period of resorption *in vivo*. To overcome this drawback, Kawase et al. (42) introduced a heat compression technique for PRF membranes used for guided tissue regeneration. However, this leads to a poor regeneration capacity as no cells or growth factors can withstand denaturation. Hence, a new technique

was developed that reintroduces the platelet-rich layer from the buffy coat into heated PPP (albumin gel) after cooling (43).

Albumin gel platelet-rich fibrin (Alb-PRF) enhanced cell migration and proliferation, biocompatibility, the release of seven key growth factors, and collagen synthesis. Centrifugation was done in plastic tubes at 700 g for 8 min. The process involved in producing the albumin gel comprised collecting the PPP layer and subjecting it to a 10-minute heating at a temperature of 75 degrees Celsius. This was allowed to cool down for 10 min at room temperature. The PRF's higher cell and growth factor content and albumin gel's low resorption properties are combined in this procedure (44).

#### BIO-PRF (horizontal centrifugation protocol) / C-PRF

Liquid PRF tubes were used in the Bio-PRF horizontal centrifuge to create C-PRF. 3000×g centrifugation protocol (C-PRF protocol) for 5-8 minutes. The following benefits are observed using horizontal centrifugation;

A) It enables an improved cellular separation by allowing cells to travel easily throughout the blood layers. Compared to traditional approaches, there is a considerable increase in leukocyte and PC.

B) It is known as a "gentle centrifugation" because the cells along the back wall of centrifugation tubes sustain less damage when low forces are used to manufacture it (45).

### Conclusion

For periodontal regenerative procedures, a range of surgical techniques, biomaterials, and BGs have been employed individually and in combination. PRF derived from autologous blood acts as a scaffold containing growth factors and living cells that potentiate wound healing and tissue regeneration. With its low cost, ease of preparation, and handling, PRF and its variants have emerged as potential regenerative materials with various applications in periodontics and other disciplines.

### Ethics

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: D.S.J., N.S., Design: D.S.J., N.S., Data Collection or Processing: D.S.J., N.S., Literature Search: D.S.J., N.S., Writing: D.S.J., N.S.

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# Maternal and paternal attachment levels in the prenatal period

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## ABSTRACT

**Aims:** This study determined maternal and paternal attachment levels and the factors affecting attachment during the prenatal period.

**Methods:** This descriptive study included pregnant women aged 18 to 48 years and their spouses admitted to a follow-up clinic. Women with risky pregnancies were excluded. Attachment was assessed using the maternal antenatal attachment scale (MAAS) and the paternal antenatal attachment scale (PAAS). The primary outcomes were the maternal and paternal attachment levels and the factors affecting attachment during the prenatal period.

**Results:** The study population consisted of 100 pregnant women and their spouses, totaling 200 individuals [age, mean±standard deviation: 27.8±5.1 years, prospective mothers; 31.5±5.9 years, prospective fathers]. The mean MAAS score was 77.87±8.08, and the mean PAAS score was 63.7±8.2. There was a statistically significant correlation between the total MAAS and PAAS scores ( $r=0.279$ ,  $p=0.005$ ). Also, mean scores of the subdimensions of quality of attachment ( $r=0.203$ ,  $p=0.042$ ) and time spent on attachment ( $r=0.236$ ,  $p=0.018$ ) of the MAAS and PAAS showed correlations. We observed that 48% of the pregnant women saw their babies with their spouses on ultrasound. Median MAAS score [81 (56 to 93) vs. 77 (45 to 93),  $p=0.002$ ] and PAAS score [66.5 (54 to 77) vs. 61 (41 to 79),  $p=0.015$ ] of the expectant mothers and fathers who saw their babies together on the ultrasound were higher than couples who did not see their babies on the ultrasound together.

**Conclusions:** This study showed a significant relationship between maternal and paternal attachment levels of couples in the prenatal period.

## Introduction

Attachment is an emotional and loving bond that starts between the parents and the fetus in the prenatal period (1). In this period, prospective mothers and fathers begin to bond with the fetus with the development of adaptation to parenting roles (2). The level of attachment in the prenatal period affects the biological, psychological, and behavioral fetal development of the fetus throughout its life (3-5) and the parent-child relations after birth (6,7).

Maternal attachment in the prenatal period is the emotion, feeling, and love that a mother feels for her unborn baby (8,9). The level of maternal attachment affects maternal and infant health (9,10). There is a linear relationship between maternal attachment and the infant's cognitive, emotional, psychological, and social development (11,12). This bond between the mother and fetus begins when the woman learns that she is pregnant and increases when the fetal movements start (12,13). Sociodemographic characteristics of the mother, marital relationship, obstetric characteristics, acceptance of pregnancy,



and mental health affect the quality of attachment (1,9,10,14). An increase is observed in adaptation to the role of motherhood and positive health behaviors in women with high levels of attachment, whereas women with low attachment levels show negative health behaviors (8,10,15,16) and, consequently, many fetal and neonatal complications may develop (14).

Paternal attachment, on the other hand, is defined as the love and care that the father feels toward his unborn baby (17,18). Similar to maternal attachment, paternal attachment impacts the infant's behavioral, emotional, and developmental outcomes (18-20). Paternal attachment begins to be established in the prenatal period and continues to increase with the first physical contact with the baby after birth (21). Factors like sociodemographic characteristics, maternal obstetric status, and father's mental health affect paternal attachment (5,22). Fathers with a high level of paternal attachment adapt better to parenting roles, support the mother more in all processes, and increase their participation in the care of the baby in the postpartum period (17,20). Paternal attachment level is also effective in alleviating mothers' need for analgesia at birth, breastfeeding problems, and postpartum psychological problems (5).

The cognitive, emotional, psychological, and social development starts in the prenatal period and continues throughout life. It is important to evaluate the quality of maternal and paternal attachment in the prenatal period and to intervene when necessary because the level and quality of attachment can affect the development of the fetus and the newborn (6,22). Although studies in the literature generally focus on maternal attachment (6), studies have also focused on paternal attachment as the effects of paternal attachment on the fetus and the newborn have been determined, and there has been an increase in fathers' participation in infant care (4). This study investigated maternal and paternal attachment levels and the factors affecting attachment.

## Methods

This descriptive study included pregnant women and their spouses admitted to the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Obstetrics and Gynecology Polyclinic for antenatal follow-up between February and December 2021. The inclusion criteria of the participants in the sample were being between the ages of 18 and 49, being able to read and write Turkish, having a healthy and single pregnancy, having a spontaneous pregnancy, and not having any psychiatric disease. The exclusion criteria were risky pregnancies, multiple pregnancies, and women diagnosed with psychiatric illness. We recruited consecutive couples who met the inclusion criteria and volunteered to participate in the study.

The power of the study was calculated using G\*Power 3.1.9.7. After the data collection process, post hoc power analysis was performed to determine the statistical power. A

sample of 100 pregnant women was sufficient at the 0.05 level of alpha error with a 95% confidence interval and 89.7% power according to the post hoc power analysis.

### Data Collection Tools

The Descriptive Information Form and the Maternal Antenatal Attachment Scale (MAAS) (12) were used to collect data from prospective mothers, and the Paternal Antenatal Attachment Scale (PAAS) (18) was used to collect data from prospective fathers.

### The descriptive information form

The form was prepared by the researchers in line with the literature (6,7,10,16,20). It includes 20 questions such as the age of women and their spouses, educational status of women and spouses, employment status, income status, duration of marriage, the quality of relationship with the spouse, being willingly pregnant, number of pregnancies, gestational week, desired and current baby gender, and breastfeeding and receiving prenatal care to reveal the sociodemographic and obstetric characteristics of the participants.

### Maternal antenatal attachment scale

The scale was developed by Condon (23) in 1993. A Turkish validity and reliability study of the scale was carried out by Golbasi et al. (12) in 2015. The scale consists of 19 items examining the feelings, attitudes, and behaviors of a prospective mother toward the fetus. Each item of the five-point Likert-type scale is scored between 1 and 5. The scale has two sub-dimensions: "quality of attachment" (items 3, 6, 9, 10, 11, 12, 13, 15, 16, 19) and "time spent on attachment" (items 1, 2, 4, 5, 8, 14, 17, 18). Since item 7 does not affect any sub-dimension, it is used only in calculating the total score. Items 1, 3, 5, 6, 7, 9, 10, 12, 15, 16, and 18 are reverse codes. The scale does not have any cutoff value. Higher scores indicate higher levels of attachment (12,23).

### Paternal antenatal attachment scale

The scale was developed by Condon (23) in 1993, and the Turkish validity and reliability study was conducted by Benli and Aksoy Derya (18) in 2019. The five-point Likert-type scale consists of 16 items measuring the father's feelings toward and thoughts about the baby. Items 1, 3, 5, 6, 7, 8, 12, 13, and 15 are reverse-coded. The scale consists of two sub-dimensions: "quality of attachment" (items 2, 3, 7, 9, 11, 12, 15, 16) and "time spent on attachment" (items 1, 4, 5, 6, 8, 10, 13, 14). The scale does not have a cutoff value. Higher scores indicate higher levels of attachment (18,23).

### Data Collection

After informing the participants about the importance, purpose and method of the study face-to-face, the data collection forms were administered to the pregnant women who agreed to

participate in the study. The expectant mothers filled out the data collection forms on paper in an empty room in the polyclinic. It took about 10-15 minutes for them to fill out the forms. After the expectant mothers completed the forms, the PAAS, which the prospective fathers should fill out, was turned into an online scale via Google Forms by the researchers. The link to the online scale was sent to the expectant mothers on WhatsApp, and they shared the online scale with their husbands. It took 10 to 15 minutes for prospective fathers to complete the scale.

### Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY: USA, 2013). Number, percentage, mean, standard deviation, median, minimum, and maximum values were calculated for descriptive statistics. The normality of continuous variables was evaluated with the Kolmogorov-Smirnov test. The independent samples t-test and one-way ANOVA were used to compare the scores showing normal distribution. The Mann-Whitney U and Kruskal-Wallis tests were used to compare the variables showing a non-normal distribution. Correlations were evaluated by calculating Spearman's coefficients. The level of statistical significance was set at 0.05.

### Outcomes

The primary outcomes were maternal and paternal attachment levels and their relationship in the prenatal period. The secondary outcome was the factors affecting maternal and paternal attachment in the prenatal period.

### Ethical Considerations

Ethics approval for the research was obtained from the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (date: 14.01.2021, decision no: 2021-24). After explaining the importance, purpose, and research methods, voluntary prospective mothers provided signed consent. An informed consent form was delivered to the prospective fathers on the screen when they clicked on the link for the online data collection form. Those who gave consent to participate were allowed to fill in the form.

### Results

The study included 100 pregnant women and their spouses, totaling 200 individuals. The mean age of the pregnant women in the study was  $27.8 \pm 5.1$  years, the mean age of the prospective fathers was  $31.5 \pm 5.9$  years, and the duration of marriage was  $5.0 \pm 4.7$  years on average. The mean gestational week of the pregnant women was  $26.2 \pm 11.4$ .

Table 1 shows the comparison of maternal and paternal attachment levels according to sociodemographic characteristics. There was no significant difference between maternal and paternal attachment levels according to

sociodemographic characteristics, including the mother's age, educational level and employment status, father's age, family income, place of residence and family type ( $p > 0.05$ ). The level of maternal attachment showed a statistically significant difference ( $p = 0.036$ ) according to the educational level of the father and the difference was related to fathers who graduated from primary school and those with a university or higher degree.

Table 2 shows maternal and paternal attachment levels according to the obstetric characteristics and pregnancy follow-up. No statistically significant difference was found between maternal and paternal attachment levels according to the number of pregnancies, miscarriage history, gestational week, having a planned pregnancy, feeling the baby's movements, the quality of the relationship between the mother and the father, the gender of the baby, and the presence of the spouse in the follow-ups ( $p < 0.05$ ). A statistically significant difference was found between maternal attachment ( $p = 0.022$ ) and paternal attachment ( $p = 0.015$ ) levels according to seeing the baby on ultrasound with the spouse.

The mean MAAS score of the prospective mothers was  $77.87 \pm 8.08$ . The mean score of the quality of attachment sub-dimension of the maternal attachment scale was  $43.12 \pm 4.25$  and the mean score of the time spent on attachment sub-dimension was  $30.28 \pm 4.58$ . The mean PAAS score of the prospective fathers was  $63.70 \pm 8.22$ . The mean score of the quality of attachment sub-dimension of the paternal attachment scale was  $35.64 \pm 3.65$  and the mean score of the time spent on attachment sub-dimension was  $28.06 \pm 5.59$ . We observed a positive correlation between the total mean maternal and paternal attachment scores ( $r = 0.279$ ,  $p = 0.005$ ). We also observed a statistically significant correlation between the quality of attachment ( $r = 0.203$ ,  $p = 0.042$ ) and time spent on attachment ( $r = 0.236$ ,  $p = 0.018$ ) sub-dimensions of maternal and paternal attachment scales.

### Discussion

A significant relationship was found between the mean total score of maternal attachment levels in the prenatal period and the mean scores on the subdimensions of quality of attachment and the time spent on attachment. As prenatal maternal attachment levels increased, paternal attachment levels also increased. It was determined that the maternal and paternal attachment levels of the couples who saw the baby with their spouses on ultrasound were significantly higher.

During pregnancy, parents form a mental and emotional bond with their unborn baby. This bond represents the mother's and father's awareness of their unborn baby, their desire to be with the baby and their interactions. Prenatal attachment is also considered the earliest form of parenting (18,24). This study revealed a positive and significant relationship between prenatal maternal and paternal attachment levels.

**Table 1.** Comparison of maternal and paternal attachment scale scores according to some sociodemographic characteristics

		Maternal attachment scale# (n=100)	p	Paternal attachment scale# (n=100)	p
<b>Mother's age</b>	n (%)				
18-30	71 (71)	79 (45-93)	0.228 <sup>a</sup>	64 (41-79)	0.584 <sup>a</sup>
31 and above	29 (29)	78 (56-86)		63 (49-76)	
<b>Father's age</b>					
18-30	51 (51)	79 (60-93)	0.709 <sup>a</sup>	65 (41-78)	0.490 <sup>a</sup>
31 and above	49 (49)	79 (45-93)		63 (46-79)	
<b>Mother's education level</b>					
Primary school	25 (25)	75 (64-85)	0.426 <sup>b</sup>	75.28±9.38 <sup>a</sup>	0.711 <sup>c</sup>
High school	38 (38)	80.5 (45-89)		77.47±7.88 <sup>ab</sup>	
University and higher	37 (37)	81 (56-93)		80.43±6.41 <sup>b</sup>	
<b>Father's education level</b>					
Primary school	29 (29)	75.2±9.3 <sup>x</sup>	0.036 <sup>c</sup>	64.5±9.4	0.776 <sup>c</sup>
High school	36 (36)	77.4±7.8 <sup>xy</sup>		63.0±7.4	
University and above	35 (35)	80.4±6.4 <sup>y</sup>		63.6±8.0	
<b>Mother's working status</b>					
Yes	84 (84)	78±8.29	0.069 <sup>d</sup>	64.1±6.1	0.797 <sup>d</sup>
No	16 (16)	77.85±8.09		63.6±8.5	
<b>Family Income status</b>					
Income less than expenses	30 (30)	77 (60-91)	0.110 <sup>b</sup>	63.4±8.1	0.966 <sup>c</sup>
Income equals expenses	60 (60)	80 (45-93)		63.7±8.4	
Income more than expenses	10 (10)	83 (71-88)		64.2±7.7	
<b>Place of residence</b>					
City center	89 (89)	78.0±8.1	0.622 <sup>d</sup>	64.2±8.2	0.053 <sup>d</sup>
Town	11 (11)	76.7±7.4		59.1±7.2	
<b>Family type</b>					
Nuclear	90 (90)	80.0 (45-93)	0.157 <sup>a</sup>	63.5±8.1	0.688 <sup>d</sup>
Extended	10 (10)	75.5 (60-85)		64.7±9.6	

<sup>a</sup>: Data are shown mean±standard deviation, and median (minimum-maximum) otherwise specified.  
<sup>a</sup>: Mann-Whitney U, <sup>b</sup>: Kruskal-Wallis, <sup>c</sup>: One-Way ANOVA (for analysis post-hoc Tukey), <sup>d</sup>: Independent two-sample t-test, <sup>xy</sup>: There is no difference between groups with the same letter

In the current study, the paternal attachment level increased parallel to the maternal attachment. Ustunsoz et al. (25) reported a significant relationship between maternal-fetal attachment and paternal fetal attachment in the prenatal period. Thus, it can be suggested that the attachment levels of couples are positively affected by each other, and interventions such as focusing on fetal movements, improving social support, and reducing parents' anxiety levels aimed at increasing maternal or paternal attachment levels may contribute positively to the attachment levels of both parents.

The present study showed no difference between the maternal attachment levels of the couples according to their sociodemographic characteristics such as age, employment status, family income level, place of residence, and family

type. Some studies examining the level of maternal attachment reported that age (14,26,27), level of education (26-28), and economic status (27) affect maternal attachment. Some studies found that the level of education (16,25), employment (26), and income status (16) of pregnant women were not related to maternal attachment. Our study revealed that the educational level of the spouse was associated with maternal attachment, and the prenatal maternal attachment level of pregnant women whose spouses were university graduates was significantly higher than those whose spouses were primary school graduates. Ustunsoz et al. (25) reported that as the level of education of the prospective father increases, the level of maternal attachment increases. More research on the effects of sociodemographic characteristics on maternal attachment level

is required, however, the role of the educational status of the spouse seems important.

Our study found that maternal attachment did not differ according to parity, gestational week, number of miscarriages, having a planned pregnancy, feeling fetal movements, fetal gender, spouse's participation in antenatal follow-ups, and the quality of the relationship between the women and the spouse. Some studies examining maternal attachment also showed that parity (14), gestational week (14), having a planned pregnancy (26,27), history of miscarriage/curtettage (27,29), and satisfaction with the partner (26) did not affect maternal attachment. However, some studies reported that gestational

week (16,27,29), number of pregnancies (16,29), number of children (16), having a planned pregnancy (26,29), feeling fetal movements (30,31), and satisfaction with the partner (32) affected maternal attachment levels. It has also been reported that having a female fetus and having the desired gender affects maternal attachment (29). Ample evidence is needed to conclude the effects of obstetrics characteristics and the quality of the marital relationship on maternal attachment level.

This study showed that paternal attachment level did not differ according to sociodemographic, obstetric, and other characteristics, except after seeing the baby on ultrasound. Similar studies on paternal attachment revealed that factors

**Table 2. Comparison of the maternal and paternal attachment scale scores according to the obstetric characteristics and pregnancy follow-up**

	n (%)	Maternal attachment scale# (n=100)	p	Paternal attachment scale# (n=100)	p
<b>Number of pregnancies</b>					
1	42 (42)	79.6±7.1	0.093 <sup>c</sup>	64.6±8.5	0.627 <sup>c</sup>
2	36 (36)	77.6±7.6		63.3±6.5	
3 and over	22 (22)	75.0±9.7		62.4±10.1	
<b>History of miscarriage</b>					
Yes	17 (17)	76 (45-89)	0.093 <sup>a</sup>	62.1±8.7	0.405 <sup>d</sup>
No	83 (83)	80 (56-93)		64.0±8.1	
<b>Gestational week</b>					
1 <sup>st</sup> trimester	19 (19)	77 (64-93)	0.296 <sup>b</sup>	61 (49-77)	0.305 <sup>b</sup>
2 <sup>nd</sup> trimester	24 (24)	81 (64-89)		67.5 (51-79)	
3 <sup>rd</sup> trimester	57 (57)	79 (45-93)		63 (41-78)	
<b>Planned pregnancy</b>					
Yes	86 (86)	78.6±7.3	0.076 <sup>d</sup>	64.3±8.0	0.050 <sup>d</sup>
No	14 (14)	73.1±10.6		59.7±8.3	
<b>Feeling baby movements</b>					
Yes	70 (70)	80 (45-93)	0.695 <sup>a</sup>	63.6±8.7	0.958 <sup>d</sup>
No	30 (30)	78.5 (69-93)		63.7±6.8	
<b>Quality of the relationship with the spouse</b>					
Good	85 (85)	79.2±6.9	0.427 <sup>d</sup>	63.9±8.1	0.427 <sup>d</sup>
Moderate/poor	15 (15)	70.0±9.5		62.1±8.6	
<b>Baby's gender</b>					
Girl	34 (34)	78.5 (45-93)	0.938 <sup>b</sup>	63.5±8.6	0.864 <sup>c</sup>
Boy	34 (34)	80 (56-91)		64.2±8.2	
Unknown	32 (32)	79 (64-93)		63.2±7.9	
<b>Spouse's attendance at the follow-ups</b>					
Yes	76 (76)	79 (56-93)	0.926 <sup>a</sup>	63.5 (41-78)	0.381 <sup>a</sup>
No	24 (24)	79.5 (45-89)		63 (47-79)	
<b>Seeing the baby on ultrasound with the spouse</b>					
Yes	48 (48)	81 (56-93)	<b>0.022<sup>a</sup></b>	66.5 (54-77)	<b>0.015<sup>a</sup></b>
No	52 (52)	77 (45-93)		61 (41-79)	

#: Data are shown mean±standard deviation, and median (minimum-maximum) otherwise specified.

<sup>a</sup>: Mann-Whitney U, <sup>b</sup>Kruskal-Wallis, <sup>c</sup>: One-Way ANOVA (for analysis post-hoc Tukey), <sup>d</sup>: Independent two-sample t-test

such as the spouse's age (25), mother's level of education (25), mother's employment status (33), number of children (33), having a planned pregnancy, and participation in prenatal courses (33) affected paternal attachment level. There are also studies stating that the level of paternal attachment does not differ according to factors such as the gender of the fetus, the desired gender of the fetus, having a planned pregnancy, and the quality of the relationship with the spouse (20). In this respect, the factors affecting the paternal attachment level in the prenatal period are still unclear. However, couples' level of education might impact a planned pregnancy.

One of the remarkable findings of our study is that both maternal and paternal attachment levels of couples who see their babies together on ultrasound are significantly higher. Türkmen and Güler (33) reported that fathers who attended antenatal follow-ups and pregnancy classes with their spouses had a significantly higher level of attachment. Øyen and Aune (34) found that ultrasound examination strengthens the attachment level of a mother to her baby. In the same study, prospective mothers preferred to attend the ultrasound examination with their spouses. Coté et al. (35) emphasized that 3D ultrasonography using 3D printed models was effective on maternal and paternal attachment levels. A systematic review of the effects of imaging techniques on parent-fetal bonds in antenatal follow-up showed a positive relationship (36). Thus, our findings are consistent with the literature. Today, obstetric ultrasound is frequently used in antenatal follow-ups. Fathers attending antenatal follow-ups may have higher responsibility toward their babies and better intrafamilial communication. Seeing the baby on ultrasound offers the opportunity to witness real-time and moving images of babies and to screen for abnormalities in the baby's development (37). Including spouses in antenatal follow-ups and ultrasound examinations may be beneficial in improving the attachment quality of parents. It is recommended that healthcare providers should include both pregnant women and their spouses in the antenatal follow-ups and raise awareness about the importance of seeing the baby on ultrasound.

### Study Limitations

There are some limitations to our study. First, since the questionnaires were delivered to prospective fathers using an online platform, some fathers did not fill in the form causing insufficient data in some cases. Second, the data were collected using scales based on self-reports.

### Conclusion

Promoting maternal and paternal attachment during the prenatal period can play a significant role in improving maternal and newborn outcomes. Determining the factors affecting the attachment level of the mother and father to the fetus may be important for the physical, emotional, and psychological

development of the child. Therefore, mothers and fathers can be provided with interdisciplinary support. Including fathers in antenatal follow-ups and seeing the baby with the mother on ultrasound may positively impact the pregnancy. In this regard, it is considered important to increase the awareness of healthcare professionals about the importance of including fathers in antenatal follow-ups. Larger studies including different populations may help gain better insights into the factors affecting the attachment levels of prospective parents.

### Ethics

**Ethics Committee Approval:** This study protocol was approved by the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (date: 14.01.2021, no: 2021/24).

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: M.U., G.A., Ö.Ö., Design: M.U., Data Collection or Processing: M.U., G.A., Ö.Ö., Analysis or Interpretation: M.U., Ö.Ö., Literature Search: M.U., G.A., Ö.Ö., Writing: M.U., G.A., Ö.Ö.

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

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# The relationship of food addiction with carbohydrate intake and stress in adolescents

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**Keywords:** Food addiction, obesity, adolescents

## ABSTRACT

**Aims:** Overweight and obesity in adulthood relate to factors at younger ages in some individuals. This study investigated the relationship of food addiction (FA) with carbohydrate intake and stress in adolescents.

**Methods:** A single-center cross-sectional study was performed using a questionnaire that included basic characteristics, anthropometric measurements (weight, height, body mass index), Yale Food Addiction Scale (YFAS), Depression, Anxiety, and Stress Scale (DASS 21), and the food frequency questionnaire for the consumption of high carbohydrates and sugar-containing foods.

**Results:** The study included 192 adolescents (146 female and 46 male) aged between 12 and 19 years. FA was detected in 8.9% of the participants. Female adolescents had a higher prevalence of FA than male adolescents (female: 10.3%; male: 4.3%,  $p=0.217$ ). FA was not observed in any underweight individuals, while its prevalence was 14.3% in obese individuals. The YFAS score was  $2.7\pm 1.8$ , and the presence of FA was significantly related to YFAS ( $p<0.001$ ). Foods that individuals with FA had the most problems with were chocolate/wafer, chips (52.9%), white bread (41.2%), deep-fried dough desserts, hamburgers/pita/lahmacun/doner, and fizzy drinks/coke (35.3%) ( $p<0.05$ ). Of the food-addicted participants, 88.2% had moderate, severe, or extremely severe levels of stress, anxiety, and depression. YFAS score correlated with stress ( $r=0.472$ ,  $p<0.001$ ), depression ( $r=0.458$ ,  $p<0.001$ ), and anxiety ( $r=0.528$ ,  $p<0.001$ ).

**Conclusions:** The results of this study suggest that high sugar content related to carbohydrates in foods might have addictive effects on adolescents.

## Introduction

Foods with high sugar content affect the brain reward system and may lead to food addiction (FA) by increasing the tendency toward more sugary food consumption (1). Processed foods with high refined sugar content may cause addiction and play a critical role in the pathogenesis of obesity by activating hedonic mechanisms (2). However, the addictive effect of sugar is an emerging topic, and the information on it is limited (3). Recently, adolescents' increasing consumption of sugary foods and their increasing obesity rates, as well as the fact that these sugary foods cause addictive behavioral changes, have led researchers to investigate the potential addictive impact of excessive consumption of sugar-containing food by adolescents (4). Jastreboff et al. (5) stated that the brain responses of obese

adolescents who consumed glucose and fructose-sweetened beverages differed from those of underweight adolescents and that the control response against the consumption of these refined sugars may have decreased, which may further maintain their consumption.

Recent studies showed that uncontrolled and chronic stress also causes changes in eating behavior and obesity development indirectly by affecting the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes, which control eating behavior (6). Chronic stress can disrupt the hypothalamic-pituitary-adrenocortical axis, followed by changes in neuropeptide Y, insulin, and cortisol levels, and ultimately increase metabolic risk factors (7). Moreover, chronic stress can disrupt the reward system and increase the desire for delicious



foods (8). Consuming delicious foods may show a relaxing effect in the presence of stress, and individuals may tend to increase food consumption as a stress response (9). Chronic stress causes compulsive eating behavior, which is the most prominent feature of FA. Posttraumatic stress disorder symptoms correlate with FA and the risk of being overweight or obese (10). Therefore, FA may contribute to stress-induced obesity (6). The relationship between emotional changes (especially stress) and eating behavior and its effects on anthropometric measurements has been extensively examined in adults. Along with this study, we determined whether there is FA among adolescents by surveying the consumption desire and consumption frequency of sugar-containing foods and carbohydrates and evaluated its relationship with stress, anxiety, depression, and anthropometric measurements. The hypotheses of the study were as follows: FA increases in stress, anxiety, and depression, and is related to body mass index (BMI).

## Methods

In this single-center, cross-sectional study, we enrolled adolescents who voluntarily agreed to participate and/or were allowed to participate by their parents/guardians. The participants were 12-19 years of age and the study period was between 20.01.2021 and 20.06.2022. Concerning the required sample size, taking alpha error 0.05 and expected power  $\beta=0.80$ , 192 participants were sufficient to test a clinically significant difference in YFAS symptom score ( $2.1\pm 1.8$ ) as shown by Tompkins et al. (11). Adolescents below 12 or above 19 years of age or those who required a restricted diet were excluded.

The study was conducted online because of the Coronavirus disease-2019 (COVID-19) pandemic. To enroll participants, we prepared a social media flyer and contacted the parents/guardians of the participants.

The study questionnaire consisted of general characteristics (e.g., sex, age), anthropometric measures (e.g., weight, height, BMI), Yale Food Addiction Scale (YFAS) (12), Depression, Anxiety, and Stress Scale (DASS 21) (13), and sections including carbohydrate and sugary food consumption frequency.

### Anthropometric measurements

In the online survey form, through detailed information and visuals, the participants (or their parents) recorded their actual weight and height. Participants were divided into groups according to age- and sex-specific BMI percentiles (World Health Organization MGRS, 2007) (14).

### Carbohydrate and sugary food consumption frequency

We prepared a food consumption questionnaire taking the literature findings as a reference. The form surveyed the frequency of food consumption in the last month, including

carbohydrate and sugar content. The foods were recorded under 24 categories as "White bread and types", "Bran bread and types", "Rice, pasta, noodles, bulgur, etc.", "Pastries such as borek (yufka-based salty), bagels, acma, pogaca (dough-based salty), etc.", "Breakfast cereals (cornflake, etc.)", "Toast, sandwich", "Pizza, lahmacun, pita, hamburger, etc.", "Salted snacks (crackers, etc.)", "Cookies, sweet biscuits", "Cake derivatives", "Dough desserts (baklava, tulumba, dessert with syrup, etc.)", "Milk desserts (rice pudding, custard, etc.)", "Fruit desserts (quince dessert, etc.)", "Ice cream, milkshake", "Coke and fizzy drinks with sugar (soda with fruit flavor, fruit juice, ice tea, etc.)", "Coke and fizzy drinks with artificial sweetener, etc.", "Packaged fruit juice", "Fresh fruit juice", "Energy/sports drinks", "Coffee with sugar and/or flavor", "Candies and jellies", "Chocolate, wafer", "Honey, marmalade, molasse, hazelnut butter, etc." and "fruits". The frequency of consumption was defined in 8 categories: every day, 1-2 times a week, 3-4 times a week, 5-6 times a week, 1 in 15 days, 1 in a month, or rarely and never.

### Yale Food Addiction Scale

We used the YFAS to determine FA, which was developed based on the diagnostic criteria of the symptoms of substance addiction from the Diagnostic and Statistical Manual of Mental Disorders 4<sup>th</sup> edition by Gearhardt et al. (12). Its validity and reliability were previously reported in adults (15) and adolescents (16,17). The YFAS 25-point questionnaire assesses addiction symptoms and food consumption in the last 12 months. The symptoms are as follows: "taking more substance than planned and for a longer period", "irresistible desire or repeated and unsuccessful withdrawal attempts", "spending more time/performance for obtaining, using, and recovering", "reducing or stopping important social, professional, or entertainment activities", "continuing to use despite knowing negative results", "developing tolerance (significant increase in amount, significant decrease in effect)", "showing typical withdrawal symptoms, continuing to use the substance to relieve the withdrawal symptoms". Symptoms are scored 0 if the criterion is not met and 1 if the criterion is met to reach a total score. The scale also includes a separate criterion to calculate a diagnostic score for FA. If the YFAS symptoms score is  $\geq 3$  (at least 3 of the 7 YFAS criteria had a score of 1) and if the 8<sup>th</sup> criterion score is 1 (intake causes clinically significant damage), the participant is considered to have FA.

### Depression, Anxiety, and the Stress Scale

In the study, DASS 21 (13) was used to determine the stress, depression, and anxiety status of the participants. It is the abbreviation for the DASS 21 developed by Lovibond and Lovibond (13). Its validity and reliability study was conducted using Scotch Pine in Turkey (18). It contains seven questions

that determine depression, anxiety, and stress levels. Its validity in adolescents has been shown in different studies (19,20). The test classifies the stress, depression, and anxiety as “normal”, “mild”, “moderate”, “severe” or “extremely severe” based on the score.

**Statistical Analysis**

The data were evaluated with the Statistical Package for the Social Sciences Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY: USA, 2015). Numerical data were expressed as mean and standard deviation (SD) or median with lower and upper values. Qualitative data were displayed as numbers and frequencies. Student’s t-test was used to test the differences between two averages showing normal distribution. Mann-Whitney U test was used to test the differences between two median values showing non-normal distribution. The chi-square test was used to test the differences between categorical variables. Correlation coefficients were calculated using Spearman’s, Pearson, or Eta squared tests. P<0.05 was considered statistically significant.

**Results**

The study included 192 adolescents (age, mean±SD = 15.3±1.6 years, 12 to 19 years, 76% female). FA was detected in 8.9% of the participants. The prevalence of FA in female and male adolescents was 10.3% and 4.3%, respectively, p=0.217).

**Anthropometric findings**

BMI classification was available for 172 individuals. Of them, 5.2% were underweight, 12.2% were at risk of being underweight, 59.3% were normal-weight, 19.2% were overweight, and 4.1% were obese. No underweight individuals than FA, whereas 14.3% of obese, 9.5% of at-risk underweight, 8.8% of normal weight, and 3.0% of overweight individuals had FA. There was no significant relationship between FA and BMI classification (p=0.643) (Table 1).

**Table 1. BMI classification according to food addiction status (World Health Organization MGRS, 2007)**

	Food addiction				p
	Yes (n=17)		No (n=175)		
	n	%	n	%	
BMI classification					0.643
Underweight (<3.p <sup>a</sup> )	0	0	9	100.0	
Underweight risk (3-15.p)	2	9.5	19	90.5	
Normal (15-85.p)	9	8.8	93	91.2	
Overweight (85-97.p)	1	3.0	32	97.0	
Obesity (>97.p)	1	14.3	6	85.7	

<sup>a</sup>Percentile, BMI: Body mass index

**YFAS scores**

The mean YFAS symptom score was 2.7±1.8 (0.0-7.0) in FA. The mean number of YFAS symptoms was 5.1±1.5 (3.0-7.0) in FA and 2.5±1.7 (0.0-7.0) without FA (p<0.001).

Table 2 shows the distribution of foods that individuals had problems with due to excessive eating and/or desire for excessive consumption across FA status. Chocolate/wafer, chips (52.9%), white bread (41.2%), deep-fried dough desserts, hamburgers/pita/lahmacun/doner, and frizzy drinks/coke (35.3%) were the most reported foods. In participants without FA, the most common foods were chocolate/wafer (32.6%), chips (26.3%), and white bread (25.7%).

**Table 2. Problematic foods according to food addiction status**

Foods that were declared problematic	Food addiction				p
	Yes (n=17)		No (n=175)		
	n	%	n	%	
Ice-cream	5	29.4	12	6.9	<b>0.002*</b>
Chocolate/wafer	9	52.9	57	32.6	0.091
Apple	0	0.0	2	1.1	0.658
Deep-fried dough desserts	6	35.3	26	14.9	<b>0.031*</b>
Broccoli	1	5.9	6	3.4	0.606
Cookies	3	17.6	12	6.9	0.114
Cakes	4	23.5	25	14.3	0.310
Candies	4	23.5	20	11.4	0.150
White bread	7	41.2	45	25.7	0.171
Pastry	4	23.5	15	8.6	0.064
Lettuce	0	0.0	2	1.1	0.658
Spaghetti	4	23.5	27	15.4	0.386
Strawberry	1	5.9	1	0.6	<b>0.039*</b>
Rice	4	23.5	13	7.4	<b>0.026*</b>
Crispbreads	2	11.8	7	4.0	0.148
Chips	9	52.9	47	26.9	<b>0.020*</b>
Bagel	1	5.9	4	2.3	0.374
French fries	5	29.4	4	2.3	0.162
Carrot	0	0.0	1	0.6	0.755
Steak	2	11.8	6	3.4	0.101
Banana	0	0.0	3	1.7	0.586
Pastrami/Turkish style fermented sausage/ sausage/salami	1	5.9	5	2.9	0.494
Hamburgers/pita/lahmacun/doner	6	35.3	23	13.1	<b>0.001*</b>
Pizza	4	23.5	14	8.0	<b>0.036*</b>
Frizzy drinks/coke	6	35.3	25	14.3	<b>0.031*</b>
None	2	11.8	51	29.1	0.126

\*Categorical qualitative data were determined by chi-square tests

The ratio of having no problems with any food type was 11.8% and 29.1%, respectively, among individuals with and without FA. Participants with FA had more problems than those without FA regarding ice cream (p=0.002), deep-fried dough-based desserts (p=0.031), strawberries (p=0.039), rice (p=0.026), chips (p=0.020), hamburger/pita/lahmacun/doner (p=0.001), pizza (p=0.036), and frizzy drinks/coke (p=0.031).

**Stress, depression and anxiety scores and FA**

Table 3 shows the relationships between stress, depression, and anxiety status and the frequency of FA. Overall, 88.2% of the food-addicted participants had moderate, severe, or extremely severe levels of stress, depression, and anxiety. There was a statistically significant difference between moderate and higher levels of stress, depression, and anxiety in FA (p<0.001).

**Carbohydrate and sugar consumption**

Table 4 shows the relationships between BMI, stress, depression, anxiety, FA and frequency of carbohydrate and sugary food consumption. Increased stress was associated with increased consumption of salted snacks (p=0.041), dough desserts (e.g., baklava, tulumba, dessert with sirup) (p=0.017), coke and frizzy drinks with artificial sweeteners (p=0.027), packaged fruit juice (p=0.014), energy/sports drinks (p=0.001), and candies and jellies (p=0.009). An increase in depression

was associated with increased consumption of cake derivatives (p=0.005), fruit desserts (e.g., quince dessert) (p=0.028), packaged fruit juice (p=0.042), energy/sports drinks (p=0.041), coffee with sugar and flavor (p=0.014), and candies and jellies (p=0.008). An increase in anxiety was associated with increased consumption of pastries such as borek (filo based salty), bagels, acma, pogaca (e.g., dough-based salty) (p=0.043), salted snacks (e.g., crackers) (p=0.016), cookies/sweet biscuits (p=0.038), cake derivatives (p=0.018), milk desserts (e.g., rice pudding, custard) (p=0.001), packaged fruit juice (p=0.007), coffee with sugar and flavor (p=0.014), candies and jellies (p=0.004), and fruits (p=0.001).

An increase in YFAS score was associated with an increase in the consumption of pastries such as borek (filo-based salty), bagels, acma, pogaca (e.g., dough-based salty) (p=0.009), salted snacks (p=0.002), cake derivatives (p=0.023), fruit desserts (e.g., quince dessert) (p=0.022), coke and frizzy drinks with artificial sweeteners (p=0.016), packaged fruit juices (p=0.025), fresh fruit juices (p=0.022), and fruits (p=0.026).

An increase in BMI was associated with increased consumption of rice/pasta/noodles/bulgur (p=0.038), salted snacks (p=0.005), coke and frizzy drinks with sugar (e.g., soda with fruit flavor, fruit juice, iced tea) (p=0.009), and coke and frizzy drinks with artificial sweeteners (p=0.025).

**Correlations between Age, BMI, YFAS score, stress, depression, and anxiety scores**

As shown in Table 5, there was a weak but significant positive correlation between age and BMI (r=0.172, p=0.024). No significant relationship was observed between BMI and YFAS score (r=0.094, p=0.222), stress (r=-0.029, p=0.710), depression (r=0.029, p=0.705), or anxiety score (r=-0.018, p=0.817). A strong positive correlation was observed between the YFAS score and stress (r=0.472, p<0.001), depression (r=0.458, p<0.001), and anxiety scores (r=0.528, p<0.001). Besides, stress, depression, and anxiety scores showed a positive and strong relationship with each other (p<0.001).

**Discussion**

In this study, the prevalence of FA in adolescents was 8.9%. In several previous studies, the prevalence of FA in adolescents ranged between 2.6% and 38.0% (11,16,17,21-25). In the current study, the prevalence of FA was 10.3% in female adolescents and 4.3% in male adolescents. We observed no significant difference in FA prevalence between females and males. Several past studies reported no difference in the prevalence of FA by sex in adolescents, while others reported a higher frequency in females (16,21-26).

We observed no relationship between BMI classification and FA status. Nevertheless, obese individuals showed the highest rate of FA. An online study by Taş Torun et al. (27) on

**Table 3. Stress, depression and anxiety according to food addiction status**

	Food addiction						p
	Yes		No		Total		
	n	%	n	%	n	%	
<b>Stress</b>							<b>&lt;0.001*</b>
Normal	2	11.8	96	54.9	98	51.0	
Mild	0		22	12.6	22	11.5	
Moderate	5	29.4	30	17.1	35	18.2	
Severe	5	29.4	18	10.3	23	12.0	
Extremely severe	5	29.4	9	5.1	14	7.3	
<b>Depression</b>							<b>&lt;0.001*</b>
Normal	1	5.9	73	41.7	74	38.5	
Mild	1	5.9	21	12.0	22	11.5	
Moderate	3	17.6	37	21.1	40	20.8	
Severe	2	11.8	16	9.1	18	9.4	
Extremely severe	10	58.8	28	16.0	38	19.8	
<b>Anxiety</b>							<b>&lt;0.001*</b>
Normal	1	5.9	75	42.9	76	39.6	
Mild	1	5.9	20	11.4	21	10.9	
Moderate	5	29.4	40	22.9	45	23.4	
Severe	1	5.9	17	9.7	18	9.4	
Extremely severe	9	52.9	23	13.1	32	16.7	

\*Categorical qualitative data were determined by chi-square tests

**Table 4.** Carbohydrate and sweetened food consumption frequency according to stress, depression, anxiety, YFAS score and BMI class

Foods and drinks	Stress		Depression		Anxiety		YFAS score		BMI class	
	Chi-square	p	Chi-square	p	Chi-square	p	Chi-square	p	Chi-square	p
White bread and types	22.107	0.776	30.307	0.349	33.203	0.228	13.328	0.065	14.298	0.940
Bran bread and types of bran bread	28.052	0.258	23.345	0.499	15.213	0.914	1.484	0.961	33.905	0.086
Rice, pasta, noodles, and bulgur	25.046	0.625	20.077	0.862	32.183	0.267	14.057	0.050	37.586	<b>0.038*</b>
Pastries such as borek (filo-based salty), bagels, acma, and pogaca (dough-based salty)	31.293	0.304	25.031	0.626	42.001	<b>0.043*</b>	18.708	<b>0.009*</b>	18.959	0.899
Breakfast cereals (cornflakes, etc.)	31.580	0.292	30.743	0.329	26.475	0.547	2.637	0.916	27.211	0.507
Toast, sandwich	30.097	0.359	20.985	0.826	29.947	0.366	4.106	0.768	18.267	0.919
Pizza, lahmacun, pita, and hamburger	32.838	0.242	32.367	0.260	32.887	0.240	8.841	0.264	30.926	0.320
Salted snacks (crackers, etc.)	42.222	<b>0.041*</b>	39.577	0.072	46.314	<b>0.016*</b>	22.538	<b>0.002*</b>	50.986	<b>0.005*</b>
Cookies, sweet biscuits	38.953	0.082	35.520	0.155	42.631	<b>0.038*</b>	10.486	0.163	25.595	0.595
Cake derivatives	31.112	0.312	51.096	<b>0.005*</b>	45.780	<b>0.018*</b>	16.230	<b>0.023*</b>	24.859	0.635
Dough desserts (e.g., baklava, tulumba, dessert with sirup)	46.201	<b>0.017*</b>	33.844	0.206	34.829	0.175	11.514	0.118	32.799	0.243
Milk desserts (rice pudding, and custard)	26.075	0.569	30.588	0.336	56.342	<b>0.001*</b>	12.456	0.087	27.362	0.499
Fruit desserts (quince dessert, etc.)	39.395	0.075	43.893	<b>0.028*</b>	34.431	0.187	16.340	<b>0.022*</b>	35.958	0.144
Ice-cream milkshake	39.314	0.076	41.245	0.051	36.333	0.134	12.646	0.081	30.552	0.337
Coke and fizzy drinks with sugar (soda with fruit flavor, fruit juice, and iced tea)	38.106	0.096	34.990	0.170	34.361	0.189	10.165	0.179	48.609	<b>0.009*</b>
Coke and fizzy drinks with artificial sweeteners	44.200	<b>0.027*</b>	37.005	0.119	27.561	0.488	17.297	<b>0.016*</b>	44.413	<b>0.025*</b>
Packaged fruit juice	46.995	<b>0.014*</b>	42.169	<b>0.042*</b>	49.661	<b>0.007*</b>	16.028	<b>0.025*</b>	30.097	0.359
Fresh fruit juice	31.435	0.298	39.090	0.079	31.569	0.292	16.367	<b>0.022*</b>	26.962	0.520
Energy/sports drinks	51.733	<b>0.001*</b>	37.311	<b>0.041*</b>	28.903	0.224	5.110	0.530	31.816	0.132
Coffee with sugar and flavor	37.982	0.099	46.953	<b>0.014*</b>	46.930	<b>0.014*</b>	4.279	0.747	25.383	0.607
Candies and jellies	48.703	<b>0.009*</b>	49.279	<b>0.008*</b>	52.052	<b>0.004*</b>	8.538	0.288	35.969	0.143
Chocolate/wafers	29.246	0.400	23.963	0.683	31.016	0.316	2.636	0.917	36.618	0.128
Honey, marmalade, molasse, and hazelnut butter	18.929	0.900	30.743	0.329	22.856	0.740	13.254	0.066	20.417	0.849
Fruits	36.360	0.134	37.589	0.106	57.841	<b>0.001*</b>	15.955	<b>0.026*</b>	20.466	0.847

YFAS: Yale Food Addiction Scale, BMI: Body mass index

**Table 5.** The correlation of stress, depression and anxiety scores with age, BMI and YFAS scores of participants

	BMI (kg/m <sup>2</sup> )	YFAS score	Stress scores	Depression score	Anxiety score
Age (years)	<b>0.172*</b>	-0.003	-0.065	-0.134	-0.034
	0.024	0.970	0.368	0.063	0.639
BMI (kg/m <sup>2</sup> )		0.094	-0.029	0.029	-0.018
		0.222	0.710	0.705	0.817
YFAS score			<b>0.472**</b>	<b>0.458**</b>	<b>0.528**</b>
			<0.001	<0.001	<0.001
Stress scores				<b>0.708**</b>	<b>0.809**</b>
				<0.001	<0.001
Depression score					<b>0.682**</b>
					<0.001

\*p<0.05. \*\*p<0.01  
SD: Standard deviation, IQR: Interquartile range, YFAS: Yale Food Addiction Scale, BMI: Body mass index

126 adolescents between the ages of 11 and 18 years showed 47.9% FA in individuals with increased BMI, much higher than 5.1% in the control group. In the present study, the prevalence of FA was 14.3% in individuals with BMI >95<sup>th</sup> percentile, while it was 8.3% in individuals with BMI <85<sup>th</sup> percentile. A meta-analysis reported a 19% average prevalence of FA in studies conducted on overweight or obese children and adolescents, and a 12% average prevalence in studies conducted on the general population (25). In the same study, there was no significant relationship between FA in adolescents and BMI z-scores (relative weight adjusted for age and sex) (25). The higher prevalence of FA in overweight and obese individuals suggests that FA is involved in the development of adolescent obesity. Nevertheless, the results may not be statistically significant due to the low number of individuals with FA and the lack of homogeneity of the groups formed according to the BMI classification. On the other hand, anthropometric measurements were performed with nonstandardized scales by the parents. This is a limitation of the study. According to the Turkish Health Survey in 2019, the rate of obesity in women aged 15 and over was 24.8%, and the rate of obesity risk was 30.4%. In males, the rate of obesity is 17.3%, and the rate of those at risk of obesity is 39.7% (28). Obesity rates were lower in adolescents than in adults in the current study. The weight reached and the nutritional habits acquired in adolescence generally continue into adulthood. It is important to evaluate and improve the anthropometric measurements of the adolescent group.

The mean YFAS symptom score we calculated in the current study ( $2.7 \pm 1.8$ ) is higher than several previous studies conducted in the general adolescent population (17,21,23). On the other hand, studies on overweight and obese individuals have reported comparable YFAS symptom scores with our findings (11,22,29-31). Vastly, the YFAS symptom score has been reported between 1.0 and 2.0 in the general population and between 2.1 and 2.9 in overweight and obese adolescents. Higher YFAS scores in the current study than in previous studies can be explained by the gender imbalance in our sample. More females participated in the current study and more females received a FA diagnosis. Furthermore, normal-weight adolescents in this study had higher YFAS scores. Lastly, the study was conducted during the pandemic, which might have adversely influenced eating habits through lockdown measures and increased distress.

The YFAS symptom score and FA status are expected to correlate. In our sample, the mean number of YFAS symptoms was  $5.1 \pm 1.5$  (3.0-7.0) in those with FA and  $2.5 \pm 1.7$  (0.0-7.0) in those without ( $p < 0.001$ ), which was very close to a previous study (16).

Individuals with FA may develop an addiction to different foods that they have problems with because of excessive eating and/or desire for excessive consumption. In this study, food-addicted individuals reported that they had more problems with

the consumption of *fast food* products than individuals without FA. These results were consistent with Keser et al. (32). We also observed that foods with higher sugar and fat content were more closely associated with FA, similar to a study by Buyuktuncer et al. (15) in adults, which reported that individuals with FA had more problems with French fries, cake derivatives, donuts, white bread, and foods with high fat and sugar contents, such as chips and chocolate.

In the current work, FA was associated with stress, depression, and anxiety. Participants with normal levels of stress, depression and anxiety constituted 51.0%, 38.5%, and 39.6% of the total participants, respectively. Other participants showed mild to severe levels of stress, depression, and anxiety. The relationship between addiction and mental problems is bidirectional. In this study, 88.2% of participants with FA had moderate, advanced, or very advanced levels of stress, depression, and anxiety. Previous studies have also reported relationships between stress, depression, and anxiety and FA assessed by DASS-21 or other methods (23,29-31,33). A review of 27 studies has concluded that many mental health problems and psychosocial disorders, including depressive symptoms, anxiety symptoms, eating disorders, low quality of life, and self-esteem, are linked to FA (33).

Concerning the food types, we observed that the consumption of some high-carbohydrate and sugary foods was particularly associated with stress, depression, and anxiety scores. Zhang et al. (34) reported that the consumption of drinks that contain more than 25 grams/day of sugar or more than 6 times a week was associated with increased anxiety and depression in adolescents. Similarly, Liu et al. (35) reported a similar association between excessive consumption of sugar-sweetened drinks and increased depression. A relationship between high sugar-containing beverage consumption and mental health issues was also shown in adolescents (36). Our findings in this regard are in agreement with the literature.

The YFAS symptom score was not affected by BMI ( $p = 0.222$ ), it showed a strong positive relationship with stress, depression, and anxiety scores ( $p < 0.001$ ). At the same time, as expected, stress, depression, and anxiety scores showed a positive and strong relationship with one another ( $p < 0.001$ ). Rose et al. (29) also did not report a significant relationship between the BMI values of the participants and the number of YFAS symptoms and mental health problems. Lin et al. (30) reported a positive correlation between BMI z-score and psychological distress, including FA and stress, depression, and anxiety. A wide variety of methodological studies have been reported in the literature. Therefore, detailed examinations are required in studies with more comprehensive and gender-distributed sampling, considering that mental health problems such as stress, depression, and anxiety may trigger overeating and lead to FA acquisition.

### Study Limitations

The study has some limitations. We experienced difficulties in data collection because we could not interview the participants face-to-face due to the pandemic measures. On the other hand, the online questionnaire was completed by the respondent and parents or guardians to ensure the quality of data as much as possible. Second, the influences of COVID-19 on stress, anxiety, depression symptoms, and eating habits (37) might have caused an overdiagnosis of FA. Third, most participants were female, causing less well evaluation of the male sex. Fourth, anthropometric data were self-reported, leaving concerns of potential errors. Fifth, the overall number of FAs remained low, making it difficult to derive well-grounded conclusions. Some peculiar values that were thought to result from erroneous measurements were excluded from the evaluation. Finally, we were not able to investigate some other ingredients like fats that might also be related to FA.

### Conclusion

In conclusion, this study suggests that FA and associated symptoms seen toward foods with higher sugar content increase because of stress, depression, and anxiety. For this reason, it is important to evaluate mental health problems to prevent nutrition-related problems in the adolescent period.

This study has also shown that foods high in sugar can cause addiction, although its cross-sectional design precludes causal inferences. Emotional states such as stress, depression, and anxiety can contribute to the development of FA. Contrary to expectations, FA, stress, depression and anxiety were not associated with BMI values. However, a more detailed evaluation of FA and mood changes may provide a new perspective on preventing and treating obesity in adolescents.

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### Ethics

**Ethics Committee Approval:** Ethical approval for the study was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (decision no: 2021/02-20, date: 20.06.2021).

**Informed Consent:** All participants gave written informed consent. Since voluntariness was taken as a basis for participation, all participants signed the volunteer consent form.

**Peer review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.T., B.A.E., N.E., Concept: M.T., B.A.E., N.E., Design: M.T., B.A.E., N.E., Data Collection or Processing: M.T., N.E., Analysis or

Interpretation: M.T., N.E., Literature Search: M.T., N.E., Writing: M.T., N.E.

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# Knowledge and practice of dental healthcare providers about disinfection of light curing units

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## ABSTRACT

**Aims:** A light curing unit (LCU) is a heat-intolerant instrument. This study aimed to assess the knowledge and practice of dental healthcare providers about the disinfection of LCUs.

**Methods:** This cross-sectional study included 350 consented dental clinicians and clinical dental students from Dakshina Kannada district of Karnataka, India, for the questionnaire part of the study. Bacterial load and debris on the LCU tips were studied in 27 LCUs from different clinics and we studied the relationship between debris and bacterial load.

**Results:** The survey included 334 healthcare providers. Only 51.8% agreed that LCUs should be disinfected after every patient. A significant proportion of the participants (62.3%) had no information about the type of disinfectant used in the clinic. Microorganism cultures were positive in approximately 80% of the 27 LCUs evaluated. Most of the LCU tips (67%) had visible debris. The numbers of colony-forming units (CFU)/cm<sup>2</sup> on blood agar and mitis salivarius agar were 57.94±92.28 and 28.56±40.63, respectively. Culture positivity was significantly lower on LCU with visibly clean tips ( $p<0.001$ ) (0.33±7.83 CFUs/cm<sup>2</sup> on blood agar and 0.78±1.39 CFUs/cm<sup>2</sup> on mitis salivarius agar).

**Conclusions:** This study showed insufficient knowledge and practice in reprocessing heat-sensitive semi-critical items among dental healthcare workers.

**Keywords:** Dentistry, disinfection, light curing unit, semi-critical items

## Introduction

The novel Coronavirus disease-2019 (COVID-19) outbreak, which started in 2019, has caused a public health emergency at a global level. The transmission of the 2019 Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) mainly occurs through inhalation, ingestion, or mucosal contact with infected respiratory droplets, either through direct or indirect contact. The origin of

droplets can be nasopharyngeal or oropharyngeal, frequently associated with saliva (1,2). Salivary secretion is a potential source for the transmission of SARS-CoV-2 because live viruses have been detected in the saliva specimens of patients with SARS-CoV-2 infection (3). The virus is thought to enter the saliva via the exchange of liquid droplets between the lower and upper respiratory tract, via crevicular fluid to blood, or through major and minor salivary glands (2).



Dental practice perpetually carries the risk of coronavirus transmission due to the following reasons; (i) frequent exposure to saliva and blood; (ii) very close proximity between patient and dental personnel during clinical procedures; and (iii) many dental procedures produce droplets and aerosols (2). Other than COVID-19, well-known diseases that can be potentially transmitted in a dental care facility are various viral infections (herpes, hepatitis, human immunodeficiency virus) and bacterial infections (tuberculosis, pseudomonas infections) (4). The prevention of cross-infection in the dental clinic is mandatory for patient care in dentistry. Hence, dentists and working staff should be aware of these infections, the route of transmission, and infection control protocols to be followed (5).

The instruments and devices used in dentistry can be categorized as critical (instruments that penetrate the soft tissue), semi-critical (non-sharp items that enter the oral cavity), or non-critical (items that have contact with intact skin) based on the risk of transmitting infections during their use and the required level of sterilization or disinfection (6). Semi-critical items contact with the mucous membrane but do not penetrate bone or soft tissues like mouth mirrors, impression trays, dental handpieces, and air-water syringe tips. These items are frequently contaminated by blood. Thus, they should be disposable or, if reused, sterilized. If sterilization is not feasible (e.g., heat-sensitive instruments), the use of a high-level disinfectant (HLD) is recommended (6).

A light curing unit (LCU) is used in dental practice to cure resin-based composites (7). It is a semi-critical item as it is introduced into the mouth and can get contaminated with saliva (8). Several methods of controlling infections on the tips of LCUs are available, including disinfectant wipes, autoclavable guides, pre-sterilized single-use plastic sheaths, and transparent disposable barriers to cover the LCU tip (9). Heat-sensitive LCU tips must be cold sterilized because they are semi-critical items and a potential source of nosocomial infections.

The COVID-19 pandemic has reminded dentists and other healthcare professionals to protect against the spread of infectious diseases diligently (2). Our ambition in this study was to increase awareness of the disinfection process of commonly used equipment in dental practice since proper disinfection techniques can reduce nosocomial infections. This study aimed to assess the knowledge and practice of dental healthcare providers about the disinfection of LCUs. Microbial loads on the LCU tips were also sought.

## Methods

### Study design and population

We conducted this cross-sectional study in 2015 in two parts. The first part consisted of a survey using a self-administered questionnaire. The second part consisted of culture studies on LCU tips.

Consented dental students with clinical exposure and dental clinicians from dentistry teaching hospitals and other dental clinics in Dakshina Kannada district of Karnataka, India, were included in the survey via convenience sampling. Finally, 350 participants working with an LCU were enrolled, including senior dental undergraduates, dental postgraduates, dental faculty, and private dental practitioners. Incomplete questionnaires were excluded from the analysis.

Institutional Ethical Committee approved the study protocol (protocol no: MCODS/I98/2013, date: 07.12.2013; and amended the protocol on 09.07.2020).

### Questionnaire

A questionnaire was designed to evaluate the knowledge and practice of the participants about the disinfection of LCUs. The questionnaire consisted of 7 close-ended questions related to infection control while using an LCU (Figure 1). Incomplete questionnaires were excluded from the analyses.

### Isolation of bacteria

We selected 27 LCUs from different clinics. Table 1 shows the type of LCUs. Swab cultures were prepared using mitis salivarius agar (HiMedia Ltd., India) and blood agar plates (HiMedia Ltd., India). Mitis salivarius agar is a selective medium for viridans streptococci, including *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus mitis*, and *Streptococcus sanguis* from mixed flora. The plates were incubated with 5% CO<sub>2</sub> at 37 °C for 48 h. Blood agar is an enriched medium that facilitates the growth of all fastidious organisms. It is ideal to use this medium for isolating and counting commensal flora of the oral cavity like *Klebsiella* spp., *Enterococcus* spp., *Staphylococcus* spp., and *Candida* spp. (10). The plates were incubated at 37 °C for 48 h. The bacterial count was assessed using a colony counter and expressed in colony-forming units per square centimeter (CFU/cm<sup>2</sup>).

### Statistical Analysis

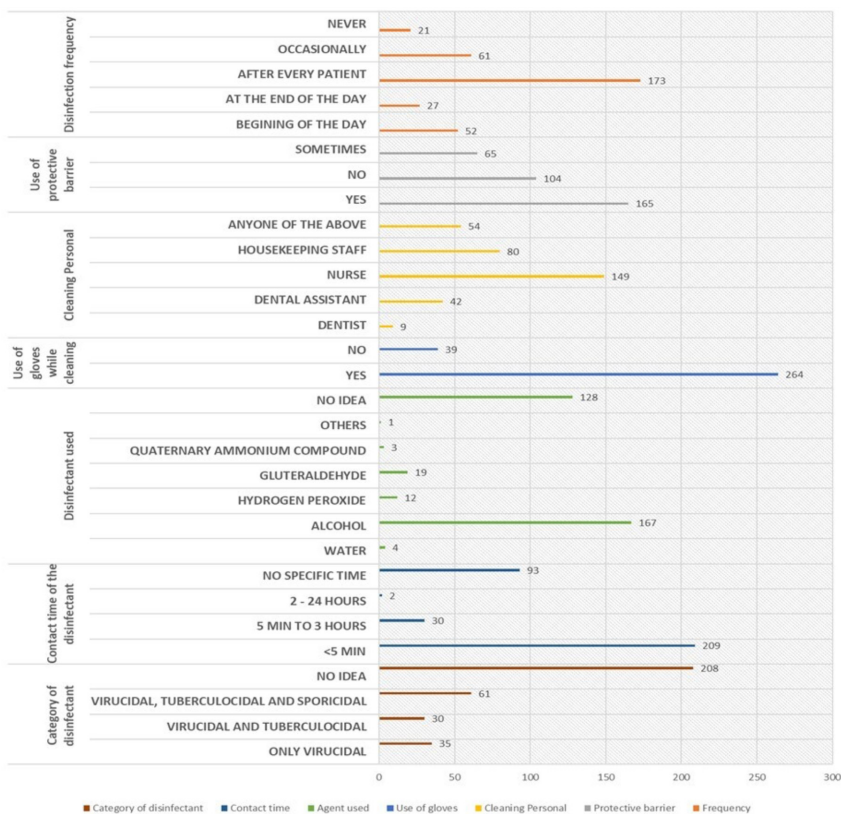
The Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 20.0 (IBM. Corp., Armonk, NY, 2011) was used for the data analysis. The distribution normality for continuous variables was tested using the Shapiro-Wilk test. Since the values were not normally distributed, Mann-Whitney U test was used to compare the variables. The significance threshold was set at 0.05.

## Results

The questionnaire part of the study included 334 responses, including 205 undergraduate dental students, 72 dental postgraduates, and 57 dentists (Figure 1). Of the participants, 51.8% thought their LCU needed disinfection after every patient. Other responses were disinfection occasionally (18.3%), at the beginning of the day (15.5%), at the end of the day (8.1%), and never (6.3%).

Only 49.5% of the participants thought using a protective cover for the LCU was essential. Other responses were occasional covering (19.5%) or never (31%). In most clinics, the auxiliary staff (dental assistant/nurse, or housekeeping staff) were responsible for cleaning of LCU (81.1%). On the other hand, there were no specific dental health care practitioners (DHCPs) assigned to this duty in some sites. Of the participants, 79% thought they needed gloves while disinfecting the LCU.

The most commonly used disinfectant was alcohol-based (50%). A significant part of the participants (38.3%) were not aware of the disinfectant composition. Others used hydrogen peroxide, glutaraldehyde, or water-based disinfectants. Most participants (62.3%) had no information about the type of disinfectant used in their clinic. Only 27.3% selected the response that the disinfectant should have tuberculocidal properties. Less than a third of the participants (27.8%) thought there was no specific time for disinfection.



**Figure 1.** Frequency distribution of participants' knowledge and practice regarding the disinfection of the LCU  
LCU: Light curing unit

Table 1. Characteristics of the dental LCUs assessed		
Item	Observation	Number (%)
Type of operatory	Hospital attached dental clinic	22 (81.5)
	Private dental clinic	5 (18.5)
Tip debris status	Visible debris present	18 (66.7)
	Visible debris absent	9 (33.3)
Bacterial count on blood agar (no. of CFUs/cm <sup>2</sup> )	No growth	5 (18.5)
	1-10 CFU/cm <sup>2</sup>	7 (25.9)
	10-100 CFU/cm <sup>2</sup>	11 (40.7)
	>100 CFU/cm <sup>2</sup>	4 (14.8)
Bacterial count on mitis salivarius agar (no. of CFUs/cm <sup>2</sup> )	No growth	6 (22.2)
	1-10 CFU/cm <sup>2</sup>	12 (44.5)
	10-100 CFU/cm <sup>2</sup>	8 (29.6)
	>100 CFU/cm <sup>2</sup>	1 (3.7)

CFU: Colony forming unit, LCUs: Light curing units

Of the 27 LCUs visible debris was identified by 67%. Culture studies showed that around 80% of the LCU tips were contaminated (Table 1). Additionally, the bacterial counts in both the agar mediums were significantly higher on the LCU tips with visible debris ( $p < 0.001$ ) (Table 2). The most common microorganisms were *Staphylococcus* spp., members of viridans *Streptococci* like *Streptococcus mutans*, *Candida* spp., and a few coliforms.

## Discussion

This study evaluated attitudes, knowledge, and practices of dental healthcare workers toward infection control practices about reprocessing semi-critical items. LCU, the heat-sensitive reusable semi-critical item in this study is used in everyday dental practice in the polymerization of photo-initiated dental materials (11). Since these devices are used intra-orally and can be contaminated with saliva and blood, they pose a risk of cross-infection (12,13). In the current scenario of the global pandemic, the need for clearer guidelines on infection control procedures in dental practice should be emphasized.

In our study, only half of the participants thought that there was a need to sterilize or disinfect the LCU after every patient, which may be related to why more than 80% of the LCUs tested showed microbial contamination. Janowalla et al. (13) detected bacterial contamination on approximately 40% of the LCUs before they were used, which was attributed by the authors to non-compliance with the recommended protocol. Such a major lapse in infection control practices (ICPs) needs to be addressed. In this regard, adequate education and training of DHCPs should be a priority (14,15). In our study, the auxiliary dental staff (dental assistant/nurse or housekeeping staff) was mainly responsible for disinfecting the LCU. Nevertheless, there was no specifically assigned DHCP at several sites, which could cause confusion among the working staff and lead to deficiencies in ICPs. Therefore, it is prudent that dentists and the auxiliary staff undergo compulsory task-specific education and training at regular intervals (14).

Based on the tolerance of the microorganisms to chemical disinfectants, it can resistance increases from the enveloped viruses (e.g., coronavirus) to vegetative bacteria (e.g., *Staphylococcus aureus*) fungi (e.g., *Candida*), non-enveloped-

viruses (e.g., adenovirus, rhinovirus), mycobacteria (e.g., *Mycobacteria tuberculosis*) and highly resistant spores (e.g., *Clostridium difficile*). Concerning such a hierarchy of tolerance, if a disinfectant can inactivate resistant microorganisms such as mycobacteria, it should be able to inactivate the least resistant COVID-19 virus (16). The chemical disinfectants that inhibit or destroy the microorganisms include liquid chemical sterilants (those which destroy all microorganisms including bacterial spores), HLD (those which may destroy all microorganisms but not necessarily high numbers of bacterial spores; used for shorter immersion time), intermediate level disinfectant or hospital disinfectant with a tuberculocidal claim (those which may destroy vegetative bacteria, most fungi, and most viruses; inactivates *Mycobacterium tuberculosis var bovis*, but not necessarily capable of killing bacterial spores) and low-level disinfectant also referred to as hospital disinfectant without a tuberculocidal claim (those that destroy most vegetative bacteria, some fungi, and some viruses, but does not inactivate *Mycobacterium tuberculosis var bovis*) (6,17). Therefore, the presence of vegetative bacteria in most LCUs tested in this study is of major concern.

As per Centers for Disease Control and Prevention guidelines, if a reusable semi-critical device or item cannot be autoclaved, it should be processed at least with HLD (14). Most sporicidal HLDs, such as glutaraldehyde and peracetic acid, are highly toxic and can pose a risk to a DHCP (18). Additionally, soaking these high-tech devices in these aggressive chemicals can sometimes damage the equipment. Therefore, the best practice for reprocessing heat-intolerant expensive semi-critical items would be to use an appropriate disposable plastic sheath or barrier to avoid contamination. This must be supplemented with an intermediate-level disinfectant with tuberculocidal properties (14). In our study, less than half of the participants thought it was essential to cover the LCU with a protective barrier. Such a low frequency of using a clear plastic sheath was in accordance with the findings of Mitton and Wilson (11).

Interestingly, we showed that LCU tips with visible debris had a significantly high microbial load, suggesting that the accumulated debris interfered with the disinfection process. Hence, using an effective barrier on the tip could assist in reducing the debris on the LCU, thereby reducing the bacterial

**Table 2. Comparison between soiled LCU tips and microbial colony counts**

Type of agar culture plate used	Debris on the LCU tip	No. of LCU	No. of colony forming units/cm <sup>2</sup>			z	p
			Mean±SD	Median (IQR)	Range		
Bacterial count on blood agar	Absent	9	3.33±7.83	0 (0.2)	0-24	-3.561	<0.001
	Present	18	57.94±92.28	29 (12.52)	1-386		
Bacterial count on mitis salivarius agar	Absent	9	0.78±1.39	0 (0.1)	0-4	-4.141	<0.001
	Present	18	28.56±40.63	12.5 (9.33)	3-174		

LCU: Light curing unit, SD: Standard deviation, IQR: Interquartile range

count. Other than the tip of the device, microorganisms were frequently identified on the body of the equipment, including the on/off buttons, in agreement with the study by Janowalla et al. (13). Therefore, these areas must be wiped, disinfected, and covered with cling film before use.

According to the current survey, the use of alcohol-based disinfectants was common. However, many participants were not aware of the disinfectant compositions. More so, they were unaware of the nature of the disinfectant and the time required for adequate disinfection. The selection of disinfectants while reprocessing heat-sensitive semi-critical items should comply with the manufacturer's instruction manual. Any chemical used should be at least tuberculocidal, compatible with the item, and should not pose undue occupational exposure risks (15), which should include any of the commercial products registered under the Environmental Protection Agency having tuberculocidal action (19). The contact time and dilution should be consistent with the chemical manufacturer's instructions. Alcohol (ethanol/isopropyl) in a concentration of  $\geq 70\%$  or even dental bleach (a minimum of 5000 ppm available chlorine i.e., 0.5% sodium hypochlorite) can also be considered as an intermediate disinfectant (20-22). Concerning the SARS-CoV-2, 1000 ppm or 0.1% for surfaces and 10,000 ppm or 1% for blood spills, 0.5% hydroxy peroxide, and 62-71% ethanol may be effective within 60 seconds of contact time (23,24). Of note, instead of spraying directly onto the device, the disinfectant should be wrapped onto a cloth soaked in the disinfectant for the recommended time. The toxic/irritant residue needs to be rinsed off with sterile water and dried (18). The reprocessed semi-critical items should be wrapped (if possible) and stored in a secure place to protect them from environmental contamination. Also, they should be kept in closed drawers, cupboards, or lidded containers to protect them from aerosols and splatters (15).

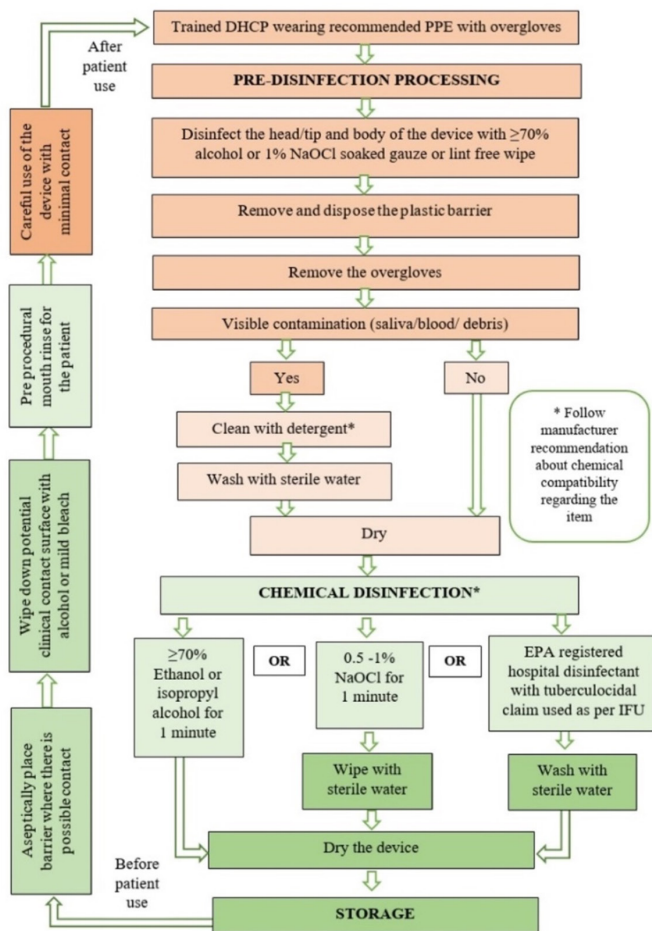
As mentioned earlier, the most crucial aspect of preventing infection control-related disasters is education and training in infection prevention. The dental operators should have written infection prevention policies and procedures aligned with national and international evidence-based recommendations (16). Reprocessing of heat-sensitive semi-critical items has a narrower margin of safety, and any deviation from the reprocessing protocol can lead to the survival of microorganisms and an increased risk of infection (14). Therefore, to assist dental practitioners in developing an evidence-based strategy to reprocess reusable heat-intolerant semi-critical items, we propose a flow chart as Figure 2.

### Study Limitations

The major limitation of this cross-sectional study was the time of the investigation. The assessment of knowledge and practice for disinfecting a reusable heat-intolerant semi-critical item was carried out much before the COVID-19 pandemic. On

the other hand, although the scenarios were different concerning dental practice before and after the COVID-19 pandemic, there has been no major change in the guidelines concerning the disinfection protocols recommended for reusable heat-intolerant semi-critical items such as LCU tips and digital intraoral radiographic sensors. Hence, the validity of the questionnaire holds good even at this point.

This survey demonstrated insufficient knowledge and training regarding the disinfection of these items among dental healthcare providers and dental students. A note of caution is that the results would be different if the investigations were performed during the COVID-19 pandemic. This is because of the increased exposure of healthcare providers to information related to ICPs. However, there are post-COVID-19 studies demonstrated that dental health professionals and students still have insufficient knowledge of disinfection (25-27). Therefore, accurate information on disinfecting different surfaces and devices used in dental practice is imperative to prevent infections.



**Figure 2.** Recommendation for reprocessing heat-sensitive semi-critical items

DHCP: Dental health care practitioner, PPE: Personal protective equipment, IFU: Information for use, NaOCl: Sodium hypochlorite

## Conclusion

The majority of the LCUs tested in this study demonstrated bacterial contamination. This could be related to the insufficient knowledge and practice of reprocessing heat-sensitive semi-critical items among dental healthcare workers. In these post-COVID-19 years, one should be more cautious in using such instruments since bacterial contamination can cause serious viral contamination. Hence, dentists and auxiliary staff must undergo compulsory task-specific education and training in infection control procedures at regular intervals.

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## Ethics

**Ethics Committee Approval:** This cross-sectional study was conducted in 2015 after obtaining Institutional Ethical Committee clearance (protocol no: MCOODS/198/2013, date: 07.12.2013; and amended the protocol on 09.07.2020).

**Informed Consent:** A consent form was filled out by all participants.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: V.N.M., S.G., M.S.T., E.S., Concept: V.N.M., M.S.T., E.S., S.N., Design: V.N.M., M.S.T., E.S., S.N., Data Collection or Processing: V.N.M., S.G., M.S.T., Analysis or Interpretation: M.S.T., E.S., S.N., Literature Search: V.N.M., S.G., M.S.T., Writing: V.N.M., S.G., M.S.T., E.S.

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# Comparison of self-esteem and anxiety levels among children with and without precocious puberty

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## ABSTRACT

**Aims:** This study compared the self-esteem and anxiety levels of children diagnosed with precocious puberty (PP) and healthy children.

**Methods:** A comparative cross-sectional study design was performed. Female children with PP and healthy controls were compared for self-esteem and anxiety using the Coopersmith Self-Esteem Inventory (CSEI) and the State-Trait Anxiety Inventory for Children with two sections including the State Anxiety Inventory for Children (SAIC) and the Trait Anxiety Inventory for Children (TAIC).

**Results:** The study included 172 children, 86 females with PP [median age (minimum-maximum) 9.41 (8-12.42) years] and 86 healthy controls [median age (minimum-maximum) 9.41 (8.08-12.08) years]. The SAIC scores of female children with PP were significantly higher than that of children without PP [27 (20-51) vs. 24 (20-43), respectively,  $p=0.002$ ]. There were no differences in TAIC scores [33 (22-53) vs. 32 (20-50),  $p=0.062$ ] and CSEI scores [80 (28-100) vs. 82 (48-100),  $p=0.196$ ] between children with and without PP. A negative correlation was observed between the CSEI and SAIC scores in both children with PP ( $r=-0.354$ ,  $p<0.001$ ) and without PP ( $r=-0.339$ ,  $p<0.001$ ). A negative correlation was observed between the CSEI scores and the TAIC scores in both children with PP ( $r=-0.684$ ,  $p<0.001$ ) and without PP ( $r=-0.504$ ,  $p<0.001$ ).

**Conclusions:** The results of this study showed that female children with PP had higher state anxiety than non-PP peers. In both groups, self-esteem scores increased while anxiety scores decreased.

## Introduction

Puberty is a process where changes such as sexual maturation, changes in body composition, and rapid skeletal growth occur (1) from 8 to 14 years of age based on ethnicity, environmental factors, and genetics (2,3). Precocious puberty (PP) is defined as atypical puberty in which secondary sexual characteristics such as pubic hair, breast, and genital development appear before 9 years of age in male children and 8 years of age in female children (1,2). The ratio of PP varies from country to country and has been increasing. The global prevalence is 3.5 per 100,000 cases, and the ratio of children diagnosed with PP in Turkey between 2011 and 2015 is 9.5% (4,5).

Pubertal changes in the early puberty period include early breast and genital development and short stature (1). The

changes in appearance can cause anxiety and a negative self-perception. In newly diagnosed patients, it is crucial to investigate the psychological effects of the disease as well as physical symptoms in order to identify risky individuals and plan appropriate interventions (6-10).

Developmental crises such as puberty are considered stressful experiences that can result in the appearance of psychopathologies (11). Some clinical symptoms of PP (e.g., thelarche, menstruation, shortness) can cause anxiety in children and their parents. Thelarche may be the biggest problem for female children, whereas menstruation or risky sexual behaviors can be a source of anxiety among parents (1,10).

In a study by Mercader-Yus et al. (12), children with PP had higher anxiety and most suffered difficulty in peer relationships, while Temelturk et al. (6) reported depressive and anxious





behaviors among female children with PP. Çoban et al. (7) determined social anxiety as the most prevalent psychiatric disorder among female children with PP. While Sontag-Padilla et al. (11) observed female children with premature adrenarche having significantly higher stress levels, Graber et al. (10) reported a correlation between premature menarche and symptoms of anxiety and panic attacks, occurring more frequently in female children with PP. Finally, Dorn et al. (13) reported that female children with PP had a higher risk of psychopathology when compared to non-PP peers.

Self-esteem is defined as a person's overall subjective sense of personal worth or value (14). In the early puberty period in which faster development of secondary sexual characteristics is observed, children tend to have difficulties in developing positive self-esteem because they regard themselves as different from their peers (15). In particular, girls who reach puberty earlier seem to find pubertal adjustment challenging, particularly due to difficulties adapting to physical and psychological changes (12,16). Temelturk et al. (6) found that female children aged 7 to 11 with PP had lower self-esteem when compared to non-PP peers.

Some studies showed a correlation between anxiety and self-esteem in girls with PP (6,12). Mercader-Yus et al. (12) showed that female children with PP had higher anxiety levels and more negative self-esteem and body image. Temelturk et al. (6) reported that anxiety correlated with self-concept in both case and control groups. Since early puberty incidence is higher in girls than in boys (1,2), more studies on the relationship between anxiety and self-esteem in girls with PP are needed. Thus, in this study, we compared the levels of anxiety and self-esteem between female children with PP and non-PP peers.

## Methods

### Study design and participants

A comparative cross-sectional study was conducted in a pediatric endocrinology outpatient clinic of a research and training hospital. The participants were female children with PP and age-matched non-PP peers from two elementary schools in Ankara between November 2020 and April 2021. The PP group included 86 female children aged 8 to 12 years and the control group included 86 female children without PP aged 8 to 12 years.

The sample size was calculated using G\*Power statistical software. Taking the study power of 0.80 and type 1 error of 0.05 in the two groups (12) 85 children were required in each group. From November 2020 through April 2021, 106 children were diagnosed with PP.

The inclusion criteria for children with PP were (i) age between 8 and 12 years and (ii) voluntary participation in the

study. The exclusion criteria were (i) refusal to participate and (ii) diagnosis of a neurologic or psychiatric disorder.

The group without PP initially included 520 students from the Yalçın Eskiyanan Primary School and Talia Yaşar Bakdur Primary School, Ankara. The inclusion criteria for children without PP were (i) age between 8 and 12 years and (ii) voluntary participation in the study. The exclusion criteria were refusing to participate and (ii) diagnosis of a neurologic or psychiatric disorder.

### Data collection

The data were collected using a descriptive information form, State-Trait Anxiety Inventory for Children (STAIC) (17) and the Coopersmith Self-Esteem Inventory (CSEI) (18). The descriptive information form consisted of eight questions, including height, weight, satisfaction with body shape, family income, education level of parent, menarche age of the mother, employment status of parents, and the number of children (6,12,15). Three more questions assessed the characteristics of early puberty in children with PP. Both parents and children were instructed to fill out the form.

### The evaluation of anxiety

STAIC was developed by Spielberger and Edwards (17) in 1973, and the Turkish validity and reliability study was conducted by Özusta (19). It tests anxiety as a state and trait in two sections named the State Anxiety Inventory for Children (SAIC) and the Trait Anxiety Inventory for Children (TAIC). The sum of the SAIC and TAIC scores is the final score. The SAIC tests how the child feels at a given moment, and the TAIC tests how the child feels in general. The Cronbach's alpha value for SAIC was previously reported as 0.82 (19), and it was 0.89 in the current study. The Cronbach's alpha value was previously reported as 0.81 for the TAIC (19), and it was 0.85 in the current study. Higher scores on SAIC and TAIC show that the child has a higher level of anxiety (17).

### The evaluation of self-esteem

CSEI was developed by Coopersmith in 1986, and the Turkish validity and reliability study of the tool was conducted by Ozogul (18,20). Cronbach's alpha value for the CSEI was previously reported as 0.77 (20), and it was 0.68 in the current study. The inventory is one of the most commonly used self-report questionnaires designed to measure attitudes toward the self in a variety of areas (family, peers, school, and general social activities) among children. The scores on the inventory range from 0 to 100, and higher scores show a higher level of self-esteem (18).

### Procedures

After obtaining informed consent from each participant and parents, the Descriptive Information Form, STAIC, and

CSEI were delivered to the participants either in the pediatric endocrinology outpatient clinic (patients) or at schools (controls). Selected teachers at schools were informed about the study protocol by the researchers. A total of 168 controls filled out the questionnaires and 86 subjects were picked up randomly from the envelopes taking age groups into account.

### Ethical considerations

Gülhane Non-Interventional Clinical Research Ethics Committee approved the study protocol (no: 2020/459, date: 30.11.2020). Official permission was obtained from the Ankara Provincial Directorate of National Education to enroll the participants without PP (E-14588481-605.99-22222278). Participation was voluntary and anonymous.

### Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences statistics for Windows, version 20.0 (IBM Corp., Armonk, NY: USA, 2011) software package. Descriptive data were presented as mean, standard deviation, median,

minimum-maximum, percentages, and frequency values. The Kolmogorov-Smirnov test was employed to assess the distribution. T-test and Mann-Whitney U test were used to compare the outcomes of the two groups.  $\chi^2$  test and Fisher's exact tests were used for categorical comparisons. Spearman's rank correlation test was used for correlations.  $P < 0.05$  was accepted as statistically significant.

### Results

The characteristics of the participants are shown in Table 1. The median age (minimum-maximum) was 9.41 (8-12.42) years in children with PP and 9.41 (8.08-12.08) years in children without PP. The two groups were similar in age ( $p=0.569$ ) and the education level of the mother ( $p=0.392$ ) and father ( $p=0.539$ ).

As shown in Table 2, children with PP had higher SAIC scores than those without PP [27 (20-51) vs. 24 (20-43), respectively,  $p=0.002$ ]. There were no significant differences in TAIC scores ( $p=0.062$ ) and CSEI scores ( $p=0.196$ ) between children with and without PP.

**Table 1. The descriptive characteristics of children and parents**

		Female children with PP (n=86)	Female children without PP (n=86)	Test	p
<b>Children</b>					
Age (years), median (min-max)		9.41 (8-12.42)	9.41 (8.08-12.08)	3.512 <sup>a</sup>	0.569
BMI, n (%)	Underweight/ Normal	66 (76.7)	61 (70.9)	1.877 <sup>b</sup>	0.391
	Overweight	12 (14)	11 (12.8)		
	Obese	8 (9.3)	14 (16.3)		
<b>Parents</b>					
Education level of the mother, n (%)	Primary school	9 (10.5)	8 (9.3)	2.997 <sup>b</sup>	0.392
	Secondary school	18 (20.9)	10 (11.6)		
	High school	28 (32.6)	33 (38.4)		
	Bachelor's and above	31 (36)	35 (40.7)		
Employment status of the mother, n (%)	Unemployed	60 (69.8)	53 (61.6)	1.264 <sup>c</sup>	0.261
	Employed	26 (30.2)	33 (38.4)		
Menarche age of the mother, median (min-max)		12 (9-15)	13 (10-15)	961.0 <sup>a</sup>	<b>0.002</b>
Education level of the father, n (%)	Primary school	6 (7.2)	5 (5.8)	2.163 <sup>b</sup>	0.539
	Secondary school	17 (20.5)	20 (23.2)		
	High school	25 (30.1)	33 (38.4)		
	Bachelor's and above	35 (42.2)	28 (32.6)		
Employment status of the father, n (%)	Unemployed	3 (3.6)	5 (5.8)	0.453 <sup>b</sup>	0.501
	Employed	80 (96.4)	81 (94.2)		
Family structure, n (%)	Nuclear family	78 (90.7)	76 (88.4)	0.977 <sup>b</sup>	0.725
	Extended family	5 (5.8)	8 (9.3)		
	Single parent family	3 (3.5)	2 (2.3)		

**Table 1. Continued**

		Female children with PP (n=86)	Female children without PP (n=86)	Test	p
Monthly income situation, n (%)	Spending exceeds income	15 (17.4)	15 (17.4)	1.304 <sup>c</sup>	0.512
	Income same as spending	50 (58.2)	56 (65.2)		
	Income exceeds spending	21 (24.4)	15 (17.4)		
Number of children, n (%)	1	22 (25.6)	20 (23.2)	2.256 <sup>c</sup>	0.324
	2	50 (58.1)	44 (51.2)		
	3 and above	14 (16.3)	22 (25.6)		

a: Mann-Whitney U test, b: Fisher's exact tests, c:  $\chi^2$  test.  
PP: Precocious puberty, BMI: Body mass index, SD: Standard deviation, Min-max: Minimum-maximum

**Table 2. The comparison of anxiety and self-esteem scores in female children with and without PP**

	Children with PP (n=86) Median (min-max)	Children without PP (n=86) Median (min-max)	Z	p
<b>STAIC</b>				
<b>SAIC (20-60)*</b>	27 (20-51)	24 (20-43)	2713.0	<b>0.002</b>
<b>TAIC (20-60)*</b>	33 (22-53)	32 (20-50)	3090.5	0.062
<b>CSEI (0-100)*</b>	80 (28-100)	82 (48-100)	3278.5	0.196

\*Represents the lowest and highest scores that can be obtained from the scale.  
PP: Precocious puberty, STAIC: State-Trait Anxiety Inventory for Children, SAIC: State Anxiety Inventory for Children, TAIC: Trait Anxiety Inventory for Children, CSEI: Coopersmith Self Esteem Inventory, Min-max: Minimum-maximum, Z: Mann-Whitney U test

The children with PP whose mothers had a bachelor's degree or above had higher SAIC scores than those without PP [28 (20-48) vs. 23 (20-40) respectively,  $p=0.016$ ] (Table 3). The children with PP whose fathers had a bachelor's degree or above had higher SAIC scores than those without PP [28 (20-48) vs. 22 (20-40), respectively,  $p=0.001$ ]. The children with PP who had a nuclear family had higher SAIC scores than those without PP [27 (20-51) vs. 24 (20-43) respectively,  $p=0.004$ ]. State anxiety was higher among children with PP who were not happy with their appearance than those without PP [(27 (20-50) vs. 24 (20-41), respectively,  $p=0.005$ ].

As shown in Table 4, there was a negative correlation between CSEI and SAIC scores ( $r=-0.354$ ,  $p<0.001$ ) and between CSEI and TAIC scores ( $r=-0.684$ ,  $p<0.001$ ) among the children with PP. There was a negative correlation between CSEI and SAIC scores in the children without PP ( $r=-0.339$ ,  $p<0.001$ ) and between CSEI and TAIC scores ( $r=-0.504$ ,  $p<0.001$ ) among the children without PP.

## Discussion

This study revealed that female children with PP had higher state anxiety than healthy peers. In addition, they had similar self-esteem and trait anxiety compared with their healthy peers.

PP is a stressful condition for preteens (16,21-23). Several studies have shown that female children with PP suffer from anxiety more than controls (8,24,25). Baumann et al. (26)

reported that PP was a source of stress for young patients in their study, and Trépanier et al. (27) showed that early menarche was associated with higher cortisol levels in relation to stress in adolescent girls. Mercader-Yus et al. (12) and Marakaki et al. (21) found that the STAIC score of children diagnosed with PP was higher than the control group. Temelturk et al. (6) found higher state anxiety levels among PP subjects. Other studies (12,21) found that female children with PP tended to have higher anxiety than controls with normal pubertal growth. These findings are consistent with our study, highlighting that female children with PP usually have more anxiety than their non-PP peers (28).

There are contradictory results in the literature regarding self-esteem among girls with PP. In the early stages of puberty, the physical appearance of girls with PP can affect psychological outcomes because of low levels of self-esteem due to changes in physical appearance compared with their peers (1,16). Children with PP often have more psychological difficulties than their non-PP peers, especially due to adjustment problems and unexpected and unusual speed of change (29). The development of self-esteem might be affected in female children whose secondary sexual characteristics develop as they recognize themselves as different from their non-PP peers (16). In the study of Temelturk et al. (6), children with PP had lower self-esteem when compared to that of the control group, contrasting with the results of some other studies (12,30,31).

Table 3. Comparison of anxiety and self-esteem scores in female children with and without PP according to demographic characteristics

Variables	SAIC				TAIC				CSEI			
	Children with PP		Children without PP		Children with PP		Children without PP		Children with PP		Children without PP	
	Median (min-max)	Z	Median (min-max)	p	Median (min-max)	Z	Median (min-max)	p	Median (min-max)	Z	Median (min-max)	p
Primary school	25 (21-42)	36.00	26 (21-43)	1.000	33 (25-47)	38 (30-46)	76 (64-92)	74 (48-100)	33.5	0.815		
Secondary school	25 (20-51)	88.5	26 (21-40)	0.944	34 (22-53)	29 (22-49)	80 (28-96)	82 (56-92)	88.5	0.944		
High school	26.5 (20-50)	335.0	24 (20-41)	0.065	35.5 (25-48)	33 (24-50)	80 (36-92)	80 (52-92)	383.5	0.252		
Bachelor's and above	28 (20-48)	355.0	23 (20-40)	<b>0.016</b>	31 (22-48)	32 (20-49)	84 (44-100)	84 (64-100)	476.5	0.392		
Primary school	29 (21-51)	9.5	25 (20-34)	0.329	34.5 (27-53)	28 (22-40)	74 (28-92)	76 (52-88)	14.0	0.931		
Secondary school	24 (20-36)	160.0	24.5 (21-43)	0.775	33 (22-48)	33 (25-49)	80 (60-96)	78 (52-100)	166.0	0.916		
High school	29 (20-50)	0.326	25 (20-41)	0.173	35 (25-48)	32 (23-50)	80 (52-92)	80 (48-100)	375.0	0.553		
Bachelor's and above	28 (20-48)	258.5	22 (20-40)	<b>0.001</b>	32 (22-46)	29 (20-44)	84 (36-100)	88 (64-96)	365.0	0.082		
Nuclear family	27 (20-51)	2176.5	24 (20-43)	<b>0.004</b>	33.5 (22-53)	33 (20-50)	80 (28-100)	80 (48-100)	262.9	0.223		
Extended family	27 (22-36)	16.0	23.5 (20-32)	0.622	33 (27-41)	31.5 (26-41)	76 (68-92)	80 (64-24)	19.0	0.943		
Single-parent family	25 (22-37)	2.0	23.5 (21-26)	0.800	33 (31-51)	28 (26-30)	80 (48-88)	86 (84-88)	1.5	0.400		
1	30 (20-48)	130.0	24 (20-41)	0.023	34 (22-51)	32 (20-50)	30 (20-48)	24 (20-41)	130.0	<b>0.023</b>		
2	25.5 (20-43)	882.5	25 (20-40)	0.098	33 (24-48)	33 (22-49)	25.5 (20-43)	25 (20-40)	882.5	0.098		
3	26.5 (20-51)	119.5	23 (20-43)	0.267	35 (22-53)	31 (21-49)	26.5 (20-51)	23 (20-43)	119.5	0.267		
Exists	27 (20-50)	1501.5	24 (20-41)	<b>0.005</b>	32,5 (22-48)	32 (20-50)	80 (52-100)	84 (52-100)	203.8	0.771		
Does not exist	26.5 (20-51)	139.5	26 (21-43)	0.459	35.5 (26-53)	35 (26-48)	76 (28-96)	76 (48-88)	152.5	0.828		

SAIC: State Anxiety Inventory for Children, TAIC: Trait Anxiety Inventory for Children, CSEI: Coopersmith Self Esteem Inventory, PP: Precocious puberty, Min-max: Minimum-maximum, Z: Mann-Whitney U test

**Table 4. Correlation analyses of SAIC and TAIC scores with CSEI scores**

Group	Inventory	CSEI			
		95%CI		Lower	Upper
		r*	p		
Female children with PP	SAIC	-0.354	<0.001	-0.535	-0.145
	TAIC	-0.684	<0.001	-0.807	-0.535
Female children without PP	SAIC	-0.339	<0.001	-0.520	-0.135
	TAIC	-0.504	<0.001	-0.660	-0.322

SAIC: State Anxiety Inventory for Children, TAIC: Trait Anxiety Inventory for Children, CSEI: Coopersmith Self Esteem Inventory, PP: Precocious puberty, r=Correlation coefficient. This coefficient takes a value between (1) and (+1), 95% CI: 95% confidence interval (lower upper bound), \*Spearman's rank correlation test

Similar to the previous works (30,31), female children with PP had similar self-esteem to that of the healthy children in this study.

Parental education level may determine anxiety among children (24). There is an inverse relationship between education level and anxiety, and individuals with higher education levels develop skills in coping with stress (22). In contrast, in our study, the state anxiety scale score was higher in children with PP whose parents had a bachelor's degree or above. These results point to the importance of qualitative and quantitative research on the differential effects of higher education levels of mothers with the stress levels of children with PP.

Any disease in a family member changes the homeostatic balance of the whole family. In such cases, the system tends to adapt to the new situation that often negatively impacts the family and the patient's health (1). The family structure is also associated with the anxiety levels of children (24). In the current study, children with PP in nuclear families had higher SAIC scores than those in the control group. This finding may be related to the limited support system for family members.

In normal puberty, as changes in the body and appearance occur, it may be difficult for the child to adapt to the new situation, and thus, a worse body image and lower self-esteem can develop (1,15). In the current study, girls with PP who were unhappy with their appearance had higher state anxiety. In children with PP, with the onset of early puberty, the children were thought to adapt to the changes in their body over time compared to their non-PP peers since no significant difference in TAIC scores was found.

The psychosocial development theory of Erik Erikson points out the importance of difficulties due to physical changes, and this is important for these children to adapt to their peers. This may lead to identity confusion in adolescence (32). In the present study, both children with PP and their non-PP peers who had problems with their body appearance were affected

by lower self-esteem levels, showing that a good body image was important for the development of self-esteem in both groups (32).

Self-esteem levels in adolescence may depend on lifestyle, family, and social environment (33). Adolescents who receive support from their families and friends have better traits, experience less anxiety, and have higher levels of self-esteem (33). In Atay et al. (33), self-esteem levels were higher in single children in the family than in children with siblings. Likewise, the reason for the lower self-esteem in the present study in children with PP without siblings than the children in the control group might be related to support from the family members. The support given by the family is also a source of avoiding and analyzing sociologic and psychological problems, overcoming difficulties, and protecting mental health (33).

We studied the potential correlations between the scores of children with and without PP on the STAIC and the CSEI. Previous studies have shown a negative correlation between anxiety and self-esteem (6,24). Temelturk et al. (6) reported that the STAIC scores correlated with Piers-Harris Children's Self-Concept Scale scores in both case and control groups. In a study by Mendle et al. (24), the anxiety scores of children with PP were correlated with lower self-esteem. Likewise, in the present study, self-esteem was one of the most related factors that affected anxiety because a negative correlation was observed between STAIC and CSEI scores in both groups.

### Study Limitations

Since the study coincided with the COVID-19 pandemic, the data of the children without PP had to be collected by their teachers outside the author group. Another limitation is the cross-sectional design precluding causal inferences from the results. Further qualitative research should evaluate the effect of PP on psychological changes.

### Conclusion

This study showed that there were no differences between female children with PP and non-PP peers in terms of self-esteem. On the other hand, the state anxiety levels among subjects with PP were higher than those of their non-PP peers. These results reveal that health professionals should be aware of changes in children with PP and determine whether children experience negative feelings about PP such as high anxiety. The results of this study demonstrate the necessity of encouraging children with PP to talk about their feelings related to early puberty.

### Ethics

**Ethics Committee Approval:** Gülhane Non-Interventional Clinical Research Ethics Committee approved the study protocol (no: 2020/459, date: 30.11.2020).

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: D.S., Design: D.S., Data Collection or Processing: B.B., D.S., Analysis or Interpretation: B.B., D.S., Literature Search: B.B., D.S., Writing: B.B., D.S.

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# Tuberculosis of the wrist

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## ABSTRACT

Mycobacterium tuberculosis (TB) is an infectious agent that can affect several organ systems and can cause various symptoms. The most common presentation is pulmonary TB. The incidence of extrapulmonary TB has become much more common worldwide due to the more frequent use of long-term immunosuppressive treatment for various indications. Examples include but are not limited to human immunodeficiency virus infection, organ transplantation, and rheumatic, hematologic, gastrointestinal, and dermatologic inflammatory conditions. Osteoarticular involvement is the third most common presentation of TB after the lung and lymph nodes, accounting for approximately 10-20% of all cases of extrapulmonary disease. The joint involvement is generally monoarticular and progresses insidiously. Skeletal TB mostly involves weight-bearing joints such as the hip and knee. Wrist involvement is rarely encountered and accounts for only 1% of skeletal TB. Herein, we describe a rare involvement of musculoskeletal TB in a renal transplant recipient.

**Keywords:** Tuberculosis, tuberculosis of wrist, arthritis, septic arthritis

## Introduction

Mycobacterium tuberculosis (TB) is an infectious agent that can affect several organ systems and cause various symptoms. The most common presentation is pulmonary TB. Extrapulmonary TB diagnoses have been increasing worldwide due to the more frequent use of long-term immunosuppressive treatment for many indications. Examples include but are not limited to human immunodeficiency virus infection, organ transplantation, and rheumatic, hematologic, gastrointestinal, and dermatologic inflammatory conditions.

Musculoskeletal involvement is the third most common presentation of TB after the lung and lymph nodes, accounting for approximately 10-20% of all cases of extrapulmonary disease. The joint involvement is generally monoarticular and

progresses insidiously. Skeletal TB commonly involves weight-bearing joints such as the hip and knee (1-3). Wrist involvement is rarely encountered and accounts for only 1% of skeletal TB. Here we describe a rare involvement of musculoskeletal TB in a renal transplant recipient.

## Case Presentation

The patient was a 57-year-old woman admitted for pain and swelling in her right wrist for seven months. There was no history of trauma, fever, infection, rheumatic disease, or psoriasis. She had significant night sweats in the last two months and 15 kg involuntary weight loss in two years. In addition to hypertension, type 2 diabetes mellitus, and chronic kidney disease, she was a renal transplant recipient for 7 years. She could not give information about the result of the purified protein derivative





(PPD) test before transplantation. She had a history of Bacillus Calmette-Guérin vaccination postpartum and no known TB cases among family members. Her treatment included mycophenolic acid, tacrolimus, prednisolone, amlodipine, furosemide, diltiazem chloride, subcutaneous insulin glargine, and glulisine.

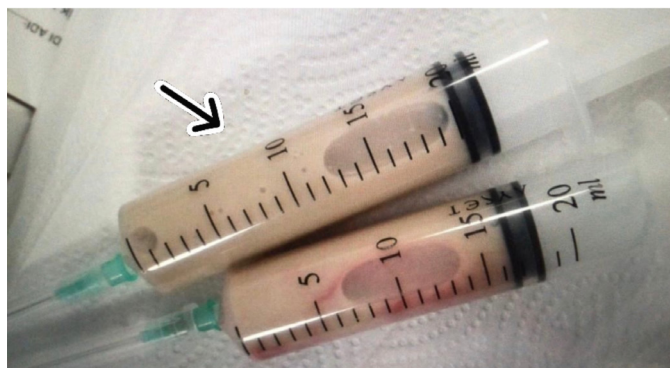
Physical examination was remarkable for local swelling, tenderness, and pain by movements in the right wrist (Figure 1). Laboratory analyses showed a white blood cell count of 18,400/microliter, neutrophil count of 17,400/microliter, lymphocyte count of 300/microliter, creatinine 1.11 mg/dL, urea 28 mg/dL, CRP 180 mg/dL, erythrocyte sedimentation rate 44 mm/h, procalcitonin 1.55 ng/mL, negative antinuclear antibody and negative anti-cyclic citrullinated peptide, complement component 3, complement component 4, normal level of antistreptolysin O, and positive rheumatoid factor. Serological tests for hepatitis B, hepatitis C, *Brucella*, and parvovirus B19 Epstein-Barr virus were non-reactive. The chest X-ray showed increased density in the upper left and lower right paracardiac areas, in the upper zones of the lung parenchyma on both sides. The patient's current tomography findings were not suggestive of TB. Sputum culture was negative for TB bacilli.

The joint aspiration showed turbid and cloudy synovial fluid. Microscopic examination of the joint fluid showed 3-4 polymorphonuclear leukocytes in each field and Gram-positive bacilli. Mononuclear cell count and acid-fast bacilli test were not available. Joint fluid was positive for the mycobacterium TB polymerase chain reaction test and rifampicin resistance was not detected. The PPD test and the quantiferon TB gold test were not available.

The patient underwent surgery with a prediagnosis of septic arthritis (Figure 2), and *Mycobacterium tuberculosis* was



**Figure 1.** Local swelling of the wrist



**Figure 2.** Joint aspirate of the patient

isolated from the joint aspirate culture. The patient was started treatment with a 2-month isoniazid 300 mg, rifampicin 600 mg, ethambutol 15-25 mg/kg, and pyrazinamide 25 mg/kg protocol, followed by a 7-month isoniazid and rifampicin treatment. Her symptoms improved remarkably, with no recurrence of arthritis.

## Discussion

The incidence of TB is increasing rapidly, including in developed countries (4). Immunosuppression from any cause except old age, nutritional status, alcohol or drug abuse, and a history of or exposure to TB predispose to clinically overt disease (4,5).

The spread of *Mycobacterium tuberculosis* to joints can occur through different mechanisms. The most common route is hematological dissemination from the primary source or a reactivated infected focus. Direct extension from osteomyelitis and direct inoculation from the infected paraarticular tissue is among the other mechanisms. Night sweats, asthenia, and loss of appetite are the most common symptoms in TB cases (5). Although our patient did not report a marked loss of appetite, other symptoms were present. On the other hand, most conditions with inflammatory arthritis can cause such symptoms. Combined with the symptoms, we proactively ordered TB tests in joint aspirate and made the diagnosis in the current case. However, in the absence of positive chest X-ray findings, diagnosis could be difficult in a reasonable time.

The most common form of musculoskeletal involvement is TB spondylitis, accounting for approximately 50-70% of all cases (6,7). Musculoskeletal TB presents in the peripheral joints in 30% of all cases (7). TB arthritis typically involves weight-bearing joints such as the hip and knee, but any joints, including the shoulder, elbow, ankle, wrist, sternoclavicular, and those of the hand and foot, can be affected (1-3). Multiple joint involvements can be observed (8). Interestingly, wrist joint involvement, like in our patient, is rare, accounting for around 1% of all skeletal TB diagnoses (9). TB arthritis may most often be confused with rheumatoid arthritis and pyogenic arthritis. Classical manifestations of TB arthritis include pain, swelling, and functional limitation, similar to any form of joint inflammation.

The abscess formation occurs in 20-25% of cases. Although rheumatoid arthritis can manifest with the typical symmetrical polyarticular disease, initial monoarticular involvement is rare and can persist for a long time. In the differential diagnosis, large bone erosion and paraarticular abscesses support the diagnosis of TB arthritis rather than rheumatoid arthritis. The diagnosis of TB is generally made using radiological, microbiological, and histopathological findings. The classical long-term treatment entails a 9-month course of isoniazid, rifampicin, pyrazinamide, and ethambutol (10). Accordingly, the recommended protocol improved the symptoms in our patient.

This rare wrist TB patient shows that TB can affect every joint. Furthermore, careful examination of symptoms, lung findings, and joint aspirate is critical in making the diagnosis, and systemic TB treatment improves joint findings.

### Ethics

**Informed Consent:** A consent form was filled out by all participants.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: B.H., E.T., İ.T., Design: B.H., E.T., İ.T., Data Collection or Processing: B.H., E.T., İ.T., Analysis or Interpretation: B.H., E.T., İ. K; Literature Search: B.H., E.T., İ.T., Writing: B.H., E.T., İ.T.

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# Autoimmune hepatitis and primary biliary cholangitis overlap syndrome after mRNA COVID-19 vaccination

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## ABSTRACT

The overlap syndrome indicates an association between autoimmune hepatitis (AIH) and sclerosis cholangitis or primary biliary cholangitis (PBC). We report a case of a 32-year-old patient who experienced overlap syndrome ten days after receiving the first dose of the mRNA Coronavirus disease-2019 (COVID-19) vaccine. Liver biopsy showed primarily AIH and "overlap syndrome" for PBC. Serum IgG was elevated, and ANA (1/100) and anti-mitochondrial antibody was positive. The patient's treatment plan included prednisolone, ursodeoxycholic acid and azathioprine. Overlap syndrome related to the mRNA COVID-19 vaccines is a very rare entity. After the histopathological diagnosis of the patient, remission was achieved following treatment.

**Keywords:** Autoimmune hepatitis, primary biliary cholangitis, COVID-19 vaccine, mRNA vaccine, overlap syndrome

## Introduction

The first case of Coronavirus disease-2019 (COVID-19) was reported in December 2019 in China. The World Health Organization declared it a pandemic on March 11, 2020 (1). Although various treatment modalities have emerged, no effective treatment has yet been found. Inactivated mRNA COVID-19 vaccines are still used as the most effective choice for protection. However, as with all other vaccines, it may have various adverse effects.

The overlap syndrome indicates an association between autoimmune hepatitis (AIH) and sclerosis cholangitis or primary biliary cholangitis (PBC) (2). Considering its immunological

and clinical features, 1 to 14 percent of patients with PBC have a variant form of AIH (3,4). Features of AIH may present at diagnosis or may develop during follow-up. Paris criteria for diagnosis of AIH and PBC (overlap syndrome) are used according to laboratory and biopsy results (5). Serum alanine aminotransferase (ALT) level 5 fold ULN, immunoglobulin G level 2 fold or the presence of smooth muscle antibodies, and interface hepatitis on histological examination are the three characteristics associated with AIH that are required by the Paris criteria for the AIP-PBC overlap syndrome. Additionally, two of the following PBC-related characteristics are required to make the diagnosis: florid duct lesions or destructive cholangitis on



histological examination and serum alkaline phosphatase level 2-fold ULN or gamma-glutamyl transferase (GGT) level 5-fold (6). Here we report a case of AIH and PBC (overlap syndrome) that developed after mRNA vaccination.

### Case Presentation

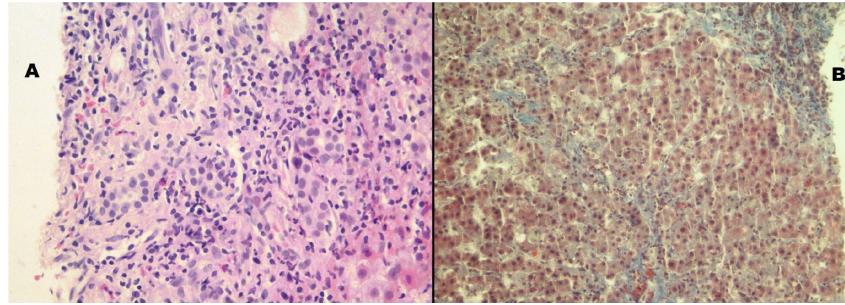
A 32-year-old male patient without a remarkable medical history was admitted to our gastroenterology clinic with icterus, dark urine, weakness, nausea, and vomiting. There was no alcohol or drug abuse history. COVID-19 history was negative. He had received the first dose of the mRNA COVID-19 vaccine 10 days ago. His physical examination revealed icterus in the sclera and mucous membranes when he was hospitalized. The patient's laboratory results were as follows; aspartate transaminase 808 U/L (range 15-40 U/L), ALT 960 U/L (range 10-40 U/L), total bilirubin 15.4 mg/dL (range 0.3-1.2 mg/dL), direct bilirubin 8.1 mg/dL (range 0-0.2 mg/dL), alkaline phosphatase 211 U/L (range 35-120 U/L), GGT 128 U/L (range 0-55 U/L), amylase 93 U/L (range 28-100 U/L), lipase 87 U/L (range 10-67 U/L), international normalized ratio 1.17 (range 0.8-1.2), C-reactive protein 9.8 mg/L (range 0-5 mg/L), antinuclear antibodies (ANA) positive (1/100) and anti-mitochondrial antibody-M2 (AMA-M2) 45.5 U/mL (range positive >10 U/mL), immunoglobulin G level was 1787 mg/dL (range 700-1600 mg/dL). The hepatitis panel, viral serology, and other serological markers were negative. The laboratory results of patients are presented in Table 1. Abdominal ultrasonography revealed gallbladder sludge.

Contrast-enhanced abdominal computed tomography showed no pathology except for edema in the periportal area and pericholecystic fluid collection. Abdominal magnetic resonance imaging/magnetic resonance cholangiopancreatography revealed periportal edema and a few minimally enlarged lymph nodes. The findings were reported to suggest inflammatory conditions of the biliary system.

A percutaneous liver biopsy was performed. The liver biopsy sample included more than 12 total portal tracts and was longer than 20 mm. Hematoxylin and eosin and Masson trichrome stains showed inflammation with moderate lymphoplasmacytic and eosinophilic leukocytes, marked cholestasis, and bile duct proliferation in the portal areas. In addition to moderate severe interface and parenchymal inflammation, local hepatocyte necrosis and degeneration were detected. Immunohistochemical studies showed disrupted reticulin framework, stage 3 fibrosis with Masson's trichrome (Figure 1B), and minimal iron deposition with iron staining. There were mixed inflammatory infiltrates including mononuclear cells, eosinophils, and scattered neutrophil infiltration in the bile ducts in the portal areas (Figure 1A). Immunohistochemical studies showed common CD38, CD138, and CD68 staining and plasma cells and histiocytes and duct proliferation with CK7 and CK19 staining. These findings suggested primarily an AIH diagnosis and fluoride duct lesion, but the presence of AMA autoantibodies and bile duct damage was suggestive of an "overlap syndrome" with PBC (7).

**Table 1. Laboratory test results**

Test	At diagnosis	After treatment	Reference range
Aspartate transaminase	808 U/L	13 U/L	15-40 U/L
Alanine aminotransferase	960 U/L	20 U/L	10-40 U/L
Total bilirubin	15.4 mg/dL	0.8 mg/dL	0.3-1.2 mg/dL
Direct bilirubin	8.1 mg/dL	0.24 mg/dL	0-0.2 mg/dL
Alkaline phosphatase	211 U/L	94 U/L	35-120 U/L
Gamma-glutamyl transferase	128 U/L	36 U/L	0-55 U/L
Amylase	93 U/L	88 U/L	28-100 U/L
Lipase	87 U/L	48 U/L	10-67 U/L
Prothrombin time	13.5 seconds	10.6	9.7-14.3 seconds
International normalized ratio	1.17	0.88	0.8-1.2
Partial thromboplastin time	38.7 seconds	22.4 seconds	22-38 seconds
C-reactive protein	9.8 mg/L	1.7 mg/L	0-5 mg/L
Erythrocyte sedimentation rate	77 mm/h	27 mm/h	0-20 mm/h
Antinuclear antibodies	Positive 1/100		
Anti-mitochondrial antibody-M2	45.5 U/mL positive		Positive >10 U/mL
Immunoglobulin G	1787 mg/dL		700-1600 mg/dL
Immunoglobulin M	178 mg/dL		40-230 mg/dL
Immunoglobulin A	407 mg/dL		70-400 mg/dL
Seruloplasmin	0.4 g/L		0.2-0.6 g/L



**Figure 1.** Liver biopsy result was compatible with an overlap syndrome. A) Mixed inflammatory infiltrate including mononuclear cells, eosinophils and scattered neutrophils in bile ducts in the portal areas (hematoxylin-eosin stain). B) Fibrotic band formation in liver parenchyma (Masson's trichrome stain)

## Discussion

mRNA COVID-19 vaccination can stimulate innate immunity (8). AIH cases have been reported after Severe acute respiratory syndrome-Coronavirus-2 vaccination in the literature (8-14). The first case of AIH after the mRNA COVID-19 vaccine was reported by Brill et al. (9). However, to the best of our knowledge, an overlap syndrome related to the mRNA COVID-19 vaccines has not been reported before. Our patient's biopsy findings were similar to those described by Brill et al. (9). We used the Paris criteria for AIH and PBC (overlap syndrome) diagnosis (5) and our patient had histological features of AIH and PBC.

The patient was seropositive for ANA and AMA, and AMA, ANA, and IgG levels were consistent with the literature (8-11,14). Biopsy findings were also consistent with overlap syndrome. Most patients reported previously were female, while our patient was male (8-13). Clayton-Chubb et al. (14) reported a similar case, a 36-year-old man who developed AIH after the mRNA COVID-19 vaccine. Another case (15) similar to the current report showed symptoms and laboratory results in a 57-year-old man who developed AIH-PBC overlap syndrome after COVID-19. Nevertheless, no liver biopsy was performed for that patient. Our patient's histopathological findings were compatible with AIH-PBC overlap syndrome.

Treatment included prednisolone 40 mg/day, ursodeoxycholic acid 15 mg/kg, and azathioprine 50 mg/day. The patient's symptoms regressed after one month of treatment, and the laboratory results were in the normal range (Table 1). Similar responses were reported in other AIH cases (8-14).

AIH has been linked to various drugs (minocycline, alpha methyl dopa, nitrofurantoin, infliximab, and statins). On the other hand, AIH/PBC coexistence is difficult to distinguish histopathologically, and making a clear differentiation between PBC and PBC-AIH overlap syndrome is important before selecting treatment options (16).

## Conclusion

We present here that the mRNA COVID-19 vaccine may be associated with a diagnosis of overlap syndrome of AIH and

PBC. Hence, clinicians should pay attention to this uncommon adverse effect of the mRNA COVID-19 vaccine and care should be taken especially in patients who develop hepatic dysfunction after vaccination.

## Ethics

**Informed Consent:** The patient consented to the publication of this report.

**Peer-review:** Externally and internally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practice - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: N.S.Ç., M.C., E.G.A.

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