

# Enthesitis: an obscured extraintestinal manifestation in pediatric inflammatory bowel disease

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## ABSTRACT

**Background.** Enthesitis is an extra-intestinal manifestation of inflammatory bowel disease (IBD) which often remains underdiagnosed in children. We aimed to evaluate the frequency of enthesitis in pediatric IBD patients using physical examination and ultrasound (US) assessment as the reference standard.

**Methods.** 31 children, 7 -18 years of age, diagnosed with IBD were recruited for a cross-sectional study. All subjects completed a study questionnaire and underwent both physical and US examination for the presence of the enthesitis.

**Results.** Of 31 subjects (17girls; median age 14(6) years) enrolled, 17 (55%) had ulcerative colitis, 11 (35%) had Crohn's disease, and 3 (10%) had indeterminate colitis. The median time from IBD diagnosis was 1.2 years. At least one enthesitis (range 1–4) was identified in 14 (45%) patients of whom nine had more than one enthesitis with symmetric involvement in eight. The quadriceps femoris insertion at the superior portion of the patella was the frequently involved site (32%, 9 of 28 sites), followed by patellar ligament insertion at tibial tuberositas. The presence of enthesitis was associated with a higher intensity of the musculoskeletal pain ( $p=0.018$ ), but physical activity remained unaffected ( $p=0.056$ ).

**Conclusions.** Enthesitis is a common underestimated extra-intestinal manifestation of IBD that may impact the musculoskeletal health of children. Future studies with more extensive cohorts are needed to evaluate enthesial involvement both with physical examination and US in order to predict the long-term outcomes of the enthesitis on children with IBD.

**Key words:** pediatric inflammatory bowel disease, extraintestinal manifestations, enthesitis.

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory disorders affecting the gastrointestinal tract, which may be associated with extraintestinal manifestations involving the eyes, skin, hepatobiliary and musculoskeletal systems.<sup>1</sup> Musculoskeletal involvement, affecting especially the peripheral or axial joints, can precede, concur, or succeed IBD. Enthesitis which is an inflammation at the insertion site of the ligaments or tendons to the bone is a sign of musculoskeletal involvement.<sup>2,3</sup> It is a distinct clinical hallmark

of spondyloarthropathies (SpA) in both children and adults, observed also in healthy children<sup>4</sup> as well as in children with juvenile idiopathic arthritis (JIA), particularly those with enthesitis-related arthritis (ERA).<sup>5,6</sup> Articular-peripheral complications occur in 23%, and axial involvement in 4% of adult patients with IBD.<sup>7,8</sup> Data are limited in children. One study that evaluated children with IBD-associated arthropathy found enthesitis and sacroiliitis (SI) in 7% and 25% of patients, respectively.<sup>9</sup> The pathophysiology of enthesitis includes the innate and adaptive immunity with overlap of the interleukin (IL)-23 and IL-17 axis. The IL-23 is a key driver of enthesitis in rats and acts via previously unidentified T cells.<sup>10</sup> Accordingly abnormal gut microbiome as seen in IBD

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patients may play a role in the emerging of enthesal pathology.<sup>11</sup> Moreover, biomechanical factors such as obesity and physical activity may confound the pathogenesis of the enthesitis and might explain predominately lower limb distribution.<sup>12</sup> Enthesitis is generally independent of IBD activity index, and may be asymptomatic in the majority of patients.<sup>13,14</sup> Children with IBD are usually not examined for enthesitis and additionally there is no standard protocol for such examination. Yet, clinical findings including localized pain, tenderness, and swelling are suggestive of enthesitis.<sup>15</sup> If left untreated, enthesitis may cause osteopenia, erosions, soft tissue calcifications, and new bone formation. Osteopenia, which is present in many patients with IBD, may also aggravate enthesitis.<sup>16</sup> Ultrasonography (US) and power Doppler ultrasonography (PDUS) are used for the diagnosis of inflammatory enthesitis.<sup>17</sup> This study aimed to investigate the frequency of enthesitis in children with IBD.

## Material and Methods

The study included 31 children, 7 to 18 years of age, who had been diagnosed with Crohn's disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC), at the Pediatric Gastroenterology Unit. The trial was approved by the University of Health Sciences Umraniye Research and Training Hospital Ethics Committee (approval number 19/12/2019-26670).

Inclusion was made regardless of the duration, phenotype, severity or current activity of the disease and all patients had been on 5 amino salicylic acid (5-ASA) and azathioprine treatment, with or without low dose of methylprednisolone. Disease activity indexes for CD and UC or IC were calculated using the Pediatric Cohn's Disease Activity Index (PCDAI) and the Pediatric Ulcerative Colitis Activity Index (PUCAI), respectively.<sup>18,19</sup> Disease phenotype at diagnosis was categorized according to the Paris classification.<sup>20</sup> All IBD patients were evaluated for coexistence of

familial Mediterranean fever (FMF), using FMF diagnostic criteria.<sup>21,22</sup> Clinical information about previous diagnoses, anthropometric measurements and laboratory tests (albumin, C-reactive protein (CRP), complete blood count (CBC), and erythrocyte sedimentation rate (ESR)) were obtained from the hospital's medical record system. Informed consent was taken from the parents and children prior to inclusion. Patients who had been previously diagnosed with arthritis or SpA, had overuse tendinitis, were on non-steroidal anti-inflammatory drugs or were unable to describe pain accurately were excluded.

Initially, a questionnaire was given to the parents or the children themselves for demographic and historical characteristics and the presence or absence of musculoskeletal pain, joint symptoms and the degree of the daily physical activity. The level of the sportive activities done by the children was also detailed to exclude overuse tendinitis. Musculoskeletal pain intensity within the previous month was designed to range from 0 (no pain) to 10 (intense pain) using numerical pain rating scale (NPRS).<sup>23,24</sup> Physical activity score ranged from 0 (not active) to 5 (very active).<sup>25</sup>

**Musculoskeletal examination:** The subjects were examined by the same pediatric rheumatologist who was blinded to the diagnosis of the disease phenotype and clinical history of the patients including musculoskeletal symptoms and medications. The patients were also examined for signs suggesting spondyloarthropathies as well as peripheral extraintestinal manifestations as dactylitis. Enthesitis was defined as the presence of tenderness on a vigorous tendon palpation.<sup>26</sup> A standardized bilateral examination for enthesitis was performed, including the humeral supraspinatus insertion at the greater tuberosity, common flexor tendon insertion at the medial epicondyle, common extensor tendon insertion at the lateral epicondyle, hip extensor insertion at the greater trochanter, quadriceps femoris insertion at the superior patella, patellar ligament insertion at the patella and tibial tuberosity, Achilles tendon

insertion at the calcaneus, and plantar fascial insertion at the calcaneus.<sup>27</sup>

**Ultrasound (US) examination:** Patients with signs of enthesitis were further evaluated by the same pediatric rheumatologist who was also experienced in musculoskeletal US examination (certified by EULAR, the European League Against Rheumatism). Philips IU22 US device with a high-frequency linear array 12 MHz transducer was used.<sup>26,27</sup> Grey-scale and power Doppler evaluation of each enthesial site in both longitudinal and transverse planes- included assessment of the abnormalities in the tendon appearance, hypoechogenicity, lack of normal fibrillar aspect, enthesophytes, bony erosions, bursitis and power Doppler signal at enthesitis. Power Doppler imaging was standardized with a pulse repetition frequency of 500–750 Hz and gain adjusted to the highest level without background noise artefact.<sup>28,29</sup> Enthesitis was graded according to its intensity: 0, absent; 1, minimal (1 spot); 2, moderate (2 spots); and 3, severe ( $\geq 3$  spots).<sup>5</sup> Minimal power Doppler findings of enthesitis may be detected in normal children, thus findings of grade 2 or above were considered positive.<sup>6,30</sup> Patients with and without enthesitis were compared. Entheses thickness [expressed in millimeters and defined with Balint cut-off for quadriceps  $>6.1$  mm, inferior pole of patella (proximal rotuleus) and tibial tuberosity (distal rotuleus)  $>4$  mm, Achilles  $>5.29$  mm, plantar fascia  $>4.4$  mm] were recorded at each site and scored with US according to Glasgow Ultrasound Enthesitis Scoring System (GUESS), ranging from 0 to 36, which was validated by Balint et al.<sup>31,32</sup>

### Statistical analysis

The results were analyzed by the Statistical Package for the Social Sciences (SPSS) version 11 for Windows (SPSS Inc.; Chicago, IL, USA). Shapiro-Wilks test was used to determine the distribution of the variables. Independent samples t-test was used for comparison of normally distributed variables and the results were shown as mean and standard deviation (SD). Mann-Whitney U test was used for non-

normally distributed variables and the results were shown as interquartile range (IQR). Pearson correlation test, Fisher's exact test, and chi-square test were used to compare the absence or presence of enthesitis and p values of less than 0.05 were accepted as significant.

### Results

The study included 31 children with a female to male ratio of 1.2 (F/M: 17/14). The median (IQR) age of the study population was 14 (6) years. Of 31 children, 17 (55%) had UC, 11 (35%) had CD, and 3 (10%) had indeterminate colitis (IC). The median (IQR) time from IBD diagnosis was 8 (6) months and all patients were receiving one or more medication (Table I). Pediatric disease activity index and bowel involvement are listed in Table I. All IBD patients had negative p-ANCA results and none had coexisting FMF disease. There was no relationship between enthesitis and clinical variables, including IBD phenotype, IBD activity index and levels of inflammatory markers. However, patients with enthesitis had younger age ( $p=0.048$ ), and higher body mass index SDS (BMI SDS) ( $p=0.041$ ), compared to those with no enthesial involvement (Table II). Musculoskeletal pain intensity score within the previous month ranged from 1 (no pain) to 10 (severe intense pain) points. Children, having at least one enthesitis reported a greater intensity of pain than those without enthesitis ( $p=0.001$ ). The level of physical activity was not found to be affected by the presence of pain or enthesitis ( $p=0.066$ ). The results of blood tests obtained at the time of examination are summarized in Table II. A total of 28 inflamed enthesial sites were detected in 14 of 31 (45%) patients. Nine (64%) of the 14 patients with enthesitis had more than one tender enthesitis (range 1–4), with symmetric involvement in eight (57%) of them. Only one patient with IC had enthesial involvement. The most common sites of enthesitis were the quadriceps femoris insertion at the superior portion of the patella (9 of 28 sites), patellar ligament insertion at tibial tuberositas (7 of 28 sites) and the Achilles tendon insertion at the calcaneus (7 of 28

**Table I.** Demographic and clinical characteristics of children with inflammatory bowel disease.

Characteristics	All (N=31)	Ulcerative colitis (N=17)	Crohn's disease (N=11)	Indeterminate colitis (N=3)
Age (years), median (IQR)	14 (6)	15 (6)	14 (6)	9 (0)
Disease duration (months), median (IQR)	8 (6)	6 (6)	11 (17)	6 (15)
Disease location, n (%)				
Rectosigmoid	5(16%)	3 (18%)		2 (67%)
Left sided disease	5 (16%)	4 (24%)		1 (33%)
Pancolitis	10 (33%)	10 (59%)		
Large intestine only	21 (68%)	17 (100%)	1 (9%)	3 (100%)
Small intestine only	1 (3%)		1 (9%)	
Small and large intestine	9 (29%)		9 (82%)	
Medications, n (%)				
5-Acetylsalicylic acid	31(100%)	17 (100%)	11 (100%)	3 (100%)
Azathioprine	28 (90%)	17 (100%)	11 (100%)	0 (0%)
Methylprednisolone	4 (13%)	0 (0%)	4 (36%)	0 (0%)

IQR: interquartile range

sites). The least affected ligament was the hip extensor insertion at greater trochanter (Table III). The most frequently observed enthesal pathology on ultrasonographic examination was thickening of tendon 12 (38%) followed by peritendinous edema 10 (31%), hypoechogenicity 6 (19%), loss of thickness 2 (6%) and increased Doppler signal (6%). No tendon tears, intratendinous calcifications, enthesophytes or bone erosions were observed (Table IV). Bursitis was detected in four patients, three with bilateral retrocalcaneal and one with bilateral infrapatellar involvement. The treatment for enthesitis was arranged as sulfasalazine or ibuprofen for mild cases (9 patients), methylprednisolone dosage adjustment for moderate (2 patients) and in three patients with severe disease the treatment was switched to anti-TNF agent (infliximab).

## Discussion

The present study reports the frequency of enthesitis in children with IBD, which to our knowledge is the first pediatric study investigating ultrasound-guided diagnosis of enthesitis. As far as we could find in the literature, only one study reported enthesitis in pediatric IBD patients with diagnosis based

solely on physical examination findings,<sup>33</sup> another study reported enthesitis in a study investigating spondyloarthropathies in pediatric IBD.<sup>9</sup> The rate of enthesitis in pediatric IBD study was 21%, where 12% of the subjects had 3 or more tender entheses.<sup>33</sup>

Compared with previous studies, the frequency of enthesitis in patients with IBD was higher in our study, with at least one ultrasonographically verified enthesitis in 45% of all patients. This was thought to be due to the diagnostic approach using both physical examination and US. This was similar to adult IBD studies in which both physical and US examinations had been performed and the frequencies had been reported to be between 44.3- 84.1%.<sup>34,35</sup> In a meta-analysis performed for the prevalence of the axial and peripheral manifestation in adults with CD and UC, the prevalence of the peripheral manifestations such as enthesitis was reported to range between 1- 54%.<sup>36</sup>

Jousse-Joulin et al.<sup>5</sup> found that enthesal tenderness does not always correspond to ultrasound abnormalities while radiographic enthesitis is also not associated with positive physical examination findings, suggesting subclinical enthesitis. In accordance, a

**Table II.** Comparison of clinical features, musculoskeletal pain and activity levels between patients with and without enthesitis.

Features	No enthesitis (N=17)	Enthesitis (N=14)	p-value
Age (years), median (IQR)	16 (6)	11 (6)	0.048
Gender, n (%)			0.015
Male	9 (53%)	5 (36%)	
Female	8 (47%)	9 (64%)	
BMI SDS, mean $\pm$ SD	-0.57 $\pm$ 1.4	0.19 $\pm$ 0.79	0.041
Disease duration (months), median (IQR)	9 (17)	6 (6)	0.570
Inflammatory bowel disease type, n (%)			
Crohn's disease	5 (29%)	6 (43%)	0.715
Ulcerative colitis	10 (59%)	7 (50%)	0.480
Indeterminate colitis	2 (12%)	1 (7%)	-
Pediatric Activity Index (PCAI or PUCAI), median (IQR)			
Crohn's disease (PCDAI)	20.0 (25.0)	30.0 (5.0)	0.452
Ulcerative colitis (PUCAI)	20.0 (1.25)	20.0 (10.0)	0.229
Inflammatory bowel disease activity, n (%)			0.778
Remission	7 (33%)	6 (38%)	
Mild to moderate disease	10 (67%)	8 (62%)	
Musculoskeletal pain score during last one month, median (IQR)	3.0 (4.5)	7.0 (3.25)	0.001
Physical activity level, n (%)			0.066
Not active	0 (0%)	0 (0%)	
A little active	0 (0%)	0 (0%)	
Regular activity	0 (0%)	1 (7%)	
Pretty active	3 (17%)	5 (36%)	
Very active	14 (83%)	8 (57%)	
Laboratory, median (IQR)			
WBC ( $\times 10^3/\mu\text{l}$ )	9.31 (2.9)	8.6 (4.4)	0.894
Hemoglobin (gr/dl)	12.6 (1.1)	12.5 (1.85)	0.116
Platelets ( $\times 10^3/\mu\text{l}$ )	346 (103)	352 (116)	0.642
Albumin (gr/dl)	4.1 (0.4)	3.9 (0.3)	0.226
ESR (mm/h)	16 (10)	28 (13)	0.673
CRP (mg/L)	0.2 (0.1)	0.4 (0.5)	0.370

BMI SDS: body mass index standard deviation score, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IQR: interquartile range, PCDAI: Pediatric Crohn's Disease Activity Index, PUCAI: Pediatric Ulcerative Colitis Activity Index, WBC: white blood cell

research in adult IBD patients without any musculoskeletal symptoms showed that a majority of the subjects had ultrasonographic findings suggestive of enthesitis, not observed in controls.<sup>37</sup> This trial supports the hypothesis that enthesitis is prevalent and asymptomatic in patients with IBD. Of note, compared with

clinical examination US is a more sensitive method in detecting enthesitis. In a recent study, US detected enthesitis in 25 of 30 patients whereas clinical enthesitis was seen only in 15 of them.<sup>6</sup> Similar results had been reported in studies on concomitance of psoriasis and enthesitis, emphasizing that US is a valuable

**Table III.** Distribution of enthesitis among ligaments of lower limbs in children with inflammatory bowel disease (N=28 sites).

Enthesitis	Left	Right	Bilateral
Hip extensor insertion at greater trochanter, n (%)		1 (4%)	
Quadriceps femoris insertion at superior portion of patella, n (%)	1 (4%)	2 (7%)	6 (21%)
Patellar ligament insertion at tibial tuberositas, n(%)	1 (4%)	2 (7%)	4 (14%)
Plantar fascial insertion at the calcaneus, n (%)		2 (7%)	2 (7%)
Achilles tendon insertion at calcaneus, n (%)	1 (4%)	2 (7%)	4 (14%)

**Table IV.** Observed enthesial pathologies and involved sites.

Enthesial pathology	Involved sites				
	Hip extensor insertion at the greater trochanter	Quadriceps femoris insertion at the superior portion of patella	Patellar ligament insertion at the tibial tuberositas	Achilles tendon and fascia	Plantar fascia
Thickening of tendon (n=12)	1	4	2	4	1
Hypoechoogenicity of tendon (n=6)		3	1	1	1
Peritendinous edema (n=10)		3	2	5	
Doppler signal (n=2)			1	1	
Loss of thickness (n=2)		1			1

examination tool.<sup>38-41</sup> The introduction of power Doppler increased the sensitivity, allowing visualization of abnormal vascularisation and hyperemia of the soft tissue.<sup>41,42</sup>

The current study also revealed that patients with increased BMI had statistically higher enthesial involvement, which had not been previously reported in pediatric patients with IBD. Similar data had been reported in several adult studies especially in patients with psoriasis related enthesitis where the increased BMI was found to be correlated with enthesial involvement.<sup>36,37</sup> The authors supposed that the increased BMI may have burdened ligaments of lower extremities.<sup>38,44</sup>

The frequency of enthesitis was found to be almost equal in both UC and CD, similar with recent trials which reported that concurrence of enthesitis was not different among patients with UC or CD.<sup>33-36</sup> Nevertheless patients with enthesial involvement had relatively younger age ( $p=0.048$ ) with female predominance ( $p=0.015$ ). Horton et al.<sup>33</sup> showed that there was no age and sex differences in patients

with enthesitis, however Jose et al.<sup>55</sup> showed that extra-intestinal manifestations had been observed more frequently in girls with IBD. A female predominance of enthesial involvement was also found in studies performed on patients with psoriasis.<sup>37,41</sup>

Familial Mediterranean fever and inflammatory bowel disease association was reported in many studies. The prevalence of FMF in Turkish children with IBD was found to range between 15-21.2%.<sup>42,43</sup> Children with CD had increased FMF prevalence, whereas in UC the rate was found to be similar with Turkish healthy controls.<sup>42,43</sup> When patients with FMF were investigated for the presence of IBD a concomitant IBD was diagnosed in 15.4% of them.<sup>44</sup> Interestingly Yurtcu et al.,<sup>45</sup> did not find an association between FMF gene mutations and IBD phenotypic characteristics, but IBD patients without Mediterranean fever (MEFV) mutations had a statistically significant increase in extraintestinal disease frequencies. As enthesitis is also prevalent among patients with severe FMF<sup>46</sup> it is important to exclude FMF concurrence in children with IBD, however none

of our patients met the diagnostic criteria of FMF, hence we did not perform FMF mutation analysis.

Quadriceps femoris insertion at superior portion of patella was the most affected enthesal site, similar to the results of Weiss et al.<sup>17</sup> who showed that 30% of enthesitis-related arthritis in pediatric patients was at the quadriceps insertion of superior patella, followed by common extensor (12%) and Achilles (10%) tendons. Nevertheless, Cantini et al.<sup>34</sup> reported that the Achilles' tendon had been mostly affected, followed by proximal and distal insertions of the patellar tendons. According to other trials the patellar tendon insertion at the tibial tuberosity was affected mostly.<sup>6,47-49</sup> In our trial, increased tendon thickness was the most commonly detected finding which was consistent with most previous studies.<sup>50,51</sup> These results would help understand the differences in enthesal involvement between pediatric and adult patients, and as well as the differences between concurrent diseases.

The patients with enthesitis were more likely to have increased musculoskeletal pain than those without enthesitis.<sup>33,51</sup> In the current study the enthesitis was detected in patients who had more intensive pain within the previous month ( $p=0.001$ ). Horton et al.<sup>33</sup> supposed that presence of enthesitis may reflect an inflammatory process which may cause pain or patients with enthesitis could have lower pain thresholds, or a combination of the two. The other hypothesis is that undertreated enthesitis could predispose affected individuals to experience more pain elsewhere.<sup>33</sup> The study of healthy school children showed that those with enthesitis reported tenderness at control sites at lower applied pressures.<sup>52</sup>

Even so, the presence of enthesitis did not seem to affect the level of activity in our patients. Horton et al.<sup>33</sup> also reported that the presence of enthesitis did not affect the level of activity in children with IBD. Palm et al.<sup>53</sup> investigated physical activity and quality of life in adult IBD patients with non-inflammatory joint pain

(NIJP) and reported that NIJP could decrease physical activity and quality of life in these subjects. Accordingly a study on enthesitis and quality of life in patients with juvenile rheumatoid arthritis showed a marked decrease in both physical activity and quality of life.<sup>54</sup> The issue could be explained by the fact that these subjects had associated co-morbidities like arthritis. Further studies will provide a better understanding of these issues.

Enthesitis is responsive to treatment, but it is unclear, beyond pain relief, if the response translates to true resolution and reversal of the underlying morphological destruction.<sup>56</sup> There is no specified therapy for enthesitis in children with IBD, but treatment for JIA, psoriasis and SpA associated enthesitis is broadly discussed.<sup>56-58</sup> The first line of choice for active enthesitis are non-steroidal anti-inflammatory drugs (NSAIDs), whereas in severe active enthesitis, American College of Rheumatology/Arthritis recommends using anti-TNF, anti-IL-17 agents and Janus kinase inhibitors. In children and adolescents with chronic active enthesitis unresponsive to NSAIDs, the bridging therapy with an oral glucocorticoids are recommended.<sup>58</sup> In our case, the treatment was tailored as sulfasalazine or ibuprofen for mild enthesitis, whereas for those with moderate disease the methylprednisolone was the choice and severe cases were switched to anti-TNF therapy.

The present study had a few limitations. First, the study was conducted with a limited number of patients. In addition, many of the drugs used to control IBD, including salicylate derivatives (used by all of our patients), cytotoxic medications such as azathioprine (used by 90%) and oral steroids (used by 12%), are also effective in the treatment of arthritis and enthesitis. This may interfere with the percentage of enthesal involvement. Moreover, we performed the study in a cohort of patients with a well-controlled disease. One could speculate that patients with more active intestinal disease and who are drug-free may have increased risk for other extraintestinal inflammatory conditions.

Two or more enthesal examinations, first at the diagnosis and second at the time of remission, would most likely give more extensive information about the enthesal involvement and response to treatment in children with IBD.

In conclusion, this trial supports the hypothesis that enthesitis is a prevalent extraintestinal manifestation of IBD regardless of the type of disease. The concurrence of enthesitis causing subclinical sign and symptoms may have impacts on musculoskeletal health of pediatric patients with IBD. A higher BMI could contribute to enthesal involvement, especially in lower extremities and aggravate the pain. Being different from adult IBD, children could have associated musculoskeletal pain which does not deteriorate their physical activity. To our knowledge, this is the first study using both physical examination and US to evaluate enthesitis in children with IBD. We supposed that powered Doppler evaluation is a more sensitive method to detect enthesitis, therefore, a combined clinical and US evaluation is probably the best approach to evaluate the presence of enthesitis in children with IBD. Further studies with more extensive cohorts are needed to evaluate the long-term impact of enthesitis in children with IBD.

#### Author contribution

The authors confirm contribution to the paper as follows: study conception and design: Nelgin Gerenli and Betül Sözeri, data collection: Nelgin Gerenli, analysis and interpretation of results: Nelgin Gerenli and Betül Sözeri, draft manuscript preparation: Nelgin Gerenli.

All authors reviewed the results and approved the final version of the manuscript.

#### Ethical approval

The trial was approved by the University of Health Sciences Umraniye Research and Training Hospital Ethics Committee (approval number 19/12/2019-26670).

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#### Conflicts of interest

We declare no conflicts of interest associated with this publication.

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