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ORIGINAL ARTICLE

Pregabalin inhibits proinflammatory cytokine release in patients with fibromyalgia syndrome

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ABSTRACT

Objectives: The main goal of the study was to investigate how pregabalin (PGB) affects proinflammatory cytokine release in patients with fibromyalgia syndrome (FMS).

Patients and methods: This experimental research study was conducted with 85 female participants (mean age: 49.6±10.1 years; range, 30 to 73 years) between April 2020 and November 2020. Of the participants, 30 were FMS patients using PGB 150 mg/day for at least three months, 30 were FMS patients not using PGB, and 25 were healthy individuals. The detection of FMS was carried out according to the 2010 American College of Rheumatology diagnostic criteria. Levels of proinflammatory cytokines (interleukin [IL]-2, IL-6, IL-12, IL-17, interferon-gamma, and tumor necrosis factor-alpha) were measured by enzyme-linked immunosorbent assay.

Results: Serum concentrations of proinflammatory cytokines were remarkably decreased in FMS patients using PGB ($p<0.001$) and were higher in patients with FMS not using PGB than in healthy subjects ($p<0.001$). The highest values of proinflammatory cytokines were found in the group of FMS patients not using PGB ($p<0.001$).

Conclusion: These results indicate that PGB inhibits the release of proinflammatory cytokines, suggesting that it can be used as an anti-inflammatory agent in inflammatory cases.

Keywords: Cytokines, fibromyalgia, immunity, inflammation, pregabalin.

Fibromyalgia is a pain-related disease that is commonly encountered in the community and manifests itself with distinctive symptoms.[1] It usually occurs more frequently in the age range of 50 to 65 years. The distribution rate of the disease is lower in men than in women.[2] Since there is no clear laboratory diagnostic method used in the diagnosis of fibromyalgia syndrome (FMS), the determination of the disease is made based on the clinical observation and history of the patient. However, renewed American College of Rheumatology (ACR) criteria have recently been used for the diagnosis.[3] Although it is thought that many different mechanisms are effective in its development, the etiopathogenesis of FMS is still not established.[4] In current studies on FMS, the importance of immune system components has been emphasized, and it is thought to play an important role in the development of neuropathic pain.[4,5] Cytokines are the major mediators of the immunity and have anti-or proinflammatory effects in the

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body. Proinflammatory cytokines are mostly produced by macrophages and orchestrate the inflammatory pathways. There are many studies suggesting that proinflammatory mediators, such as interleukin (IL)-6, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), are associated with pain-related conditions.[4,6] Research has shown that proinflammatory cytokine concentrations are lower in healthy individuals than in FMS patients.[6,7] Several cytokines (IFN-γ, TNF-α, and IL-6) have been reported to support central nervous system responses.[8] In addition, a relationship was observed between TNF-α and IL-17A plasma concentrations of FMS patients, while a significant correlation was found between clinical findings, such as pain and anxiety, and the IL-17 level in serum samples taken from rheumatoid arthritis (RA) patients.[9,10] However, it has been reported that the concentration of IL-6 is associated with pain grade in these patients.[11] In another study examining the connection between neuropathic pain pathways and IL-2, it was found that IL-2 has an analgesic effect on the central and peripheral nervous system.[12] Sturgill et al.[13] also reported that the concentrations of IFN-γ in the healthy group were lower than in patients with FMS. Furthermore, different studies have also suggested that IL-12 as a proinflammatory mediator has noticeable effects in inflammatory conditions.[14,15] Nonetheless, the cause of FMS is not clear, and its treatment varies with different medications in use recently. One of the most known agents is pregabalin (PGB). It is suggested that the pharmacological effects of PGB are mostly on the nervous system. In support of this, studies in mouse models have shown that even high doses of PGB have no significant effect on blood pressure or heart rhythm.[16] The binding of PGB to the α2δ region inhibits calcium flow in the central nervous system and accordingly decreases the release of several substances (glutamate, substance P, and noradrenaline).[16] Additionally, PGB is an antiepileptic drug used for the management of pain-related cases, such as epilepsy and anxiety. Antiepileptic drugs can directly affect the immune system, modifying the expression and the synthesis of some molecules, mainly cytokines.[17] However, there is not enough information about the immunomodulator effect of PGB on cytokine release. The main purpose of this study was to investigate the function of PGB on serum proinflammatory cytokine levels in FMS patients.

PATIENTS AND METHODS

This experimental research study was conducted with 85 female participants (mean age: 49.6±10.1 years; range, 30 to 73 years) at the Physical Therapy and Rehabilitation Clinic of the Uludağ University Hospital between April 2020 and November 2020. Of the participants, 30 were FMS patients using PGB 150 mg/day for at least three months, 30 were FMS patients not using PGB, and 25 were healthy individuals. The patients were collected from the physical medicine and rehabilitation outpatient clinic. Patients were evaluated using the 2010 ACR criteria and scoring was done using Fibromyalgia Impact Questionnaire (FIQ).[18,19] Inclusion criteria were being diagnosed with FMS in the last two to three years and having symptoms in accordance with the ACR diagnostic criteria. The terms of exclusion were autoimmune, metabolic, allergic, or acute/chronic inflammatory disease and pregnancy.

Blood samples taken from FMS patients and healthy individuals were centrifuged at 3000 rpm for 10 min, and the serums obtained were transferred to Eppendorf tubes to be kept in the freezer at -80°C until they were used. The concentrations of proinflammatory cytokines (IL-2, IL-6, IL-12, IL-17, IFN-γ, and TNF-α) were measured by an enzyme-linked immunosorbent assay kit (BT-LAB, Shangai, China) and studied in accordance with the instructions for use. Serum samples were added to the wells of plates precoated with human IL-2, IL-6, IL-12, IL-17, IFN-γ, and TNF-α antibodies. Afterward, biotinylated human antibodies were added and bound to antigens in the samples. Streptavidin-HRP (horse radish peroxidase) was added and bound to the biotinylated antibodies. After incubation, unbound portions of streptavidin-HRP were removed, and then substrate solution was added. The intensity in the color of the wells varied in proportion to the amount of human IL-2, IL-6, IL-12, IL-17, IFN-γ, and TNF-α. In the last step, the stop solution was added, and the plate was read at 450 nm. All samples were measured twice, and the values of cytokine

levels were computed using standard curves. The validated detection limits were 2.51 ng/L for IL-2, 1.03 ng/L for IL-6, 0.13 ng/L for IL-12, 1.06 ng/L for IL-17, 0.49 ng/L for IFN-γ and 1.52 ng/L for TNF-α.

Statistical analysis

Data were analyzed using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test the variables for normal distribution. Continuous variables were presented as median (min-max) and mean ± standard deviation. According to the normality test results, analysis of variance or the Kruskal-Wallis test was used if the number of groups was more than two. Multiple comparison procedures were performed using the Dunn-Bonferroni approach to identify the different group or groups after the Kruskal-Wallis test. A *p* value <0.05 was considered statistically significant.

RESULTS

The mean age of FMS patients using PGB, FMS patients not using PGB, and the healthy controls was 50.9±9.9, 49.8±11.9, and 48.6±10.6 years, respectively. The mean age was similar in all groups, and no significant difference was observed (p=0.731). The IL-2 concentration was remarkably increased in FMS patients not using PGB (0.36 ng/L) compared to FMS patients using PGB (0.17 ng/L) and healthy controls (0.24 ng/L). A statistically significant difference was found between FMS patients using or not using PGB and healthy individuals (p<0.001 and p<0.002, respectively; Table 1, Figure 1). However, a significant difference was determined between the patients using and not using PGB in terms of IL-6 levels (p<0.001). IL-6 levels were higher in the patient group not using PGB (0.41 ng/L) than in the group using PGB (0.23 ng/L), and IL-6 levels of healthy controls (0.31 ng/L) were lower than in FMS patients (Table 2, Figure 2). IL-12 levels of the healthy control group (0.20 ng/L) were lower than both patient groups, whereas IL-12 levels of the group not using PGB (0.31 ng/L) were higher than the group using PGB (0.14 ng/L). Additionally, a noticeable difference was detected between the patient groups (p<0.001, Table 3, Figure 3). Furthermore, there was a significant difference between the groups in terms of the

Table 1. IL-2 levels in healthy controls and FMS patients

	Healthy controls		FMS patients (using PGB)		FMS patients (not using PGB)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
IL-2 (ng/L)	0.24	0.11-1.04	0.17	0.08-1.20	0.36	0.21-1.89	<0.001

FMS: Fibromyalgia syndrome; PGB: Pregabalin; IL: Interleukin.

Table 2. IL-6 levels in healthy controls and FMS patients

	Healthy controls		FMS patients (using PGB)		FMS patients (not using PGB)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
IL-6 (ng/L)	0.31	0.15-1.53	0.23	0.06-1.45	0.41	0.22-1.98	<0.001

FMS: Fibromyalgia syndrome; PGB: Pregabalin; IL: Interleukin.

Table 3. IL-12 levels in healthy controls and FMS patients

	Healthy controls		FMS patients (using PGB)		FMS patients (not using PGB)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
IL-12 (ng/L)	0.20	0.11-0.91	0.14	0.10-1.45	0.31	0.21-1.64	<0.001

FMS: Fibromyalgia syndrome; PGB: Pregabalin; IL: Interleukin.

Table 4. IL-17 levels in healthy controls and FMS patients

	Healthy controls		FMS patients (using PGB)		FMS patients (not using PGB)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
IFN-γ (ng/L)	0.24	0.13-0.95	0.17	0.09-1.02	0.36	0.28-1.23	<0.001

IL: Interleukin; FMS: Fibromyalgia syndrome; PGB: Pregabalin; IFN-γ: Interferon gamma.

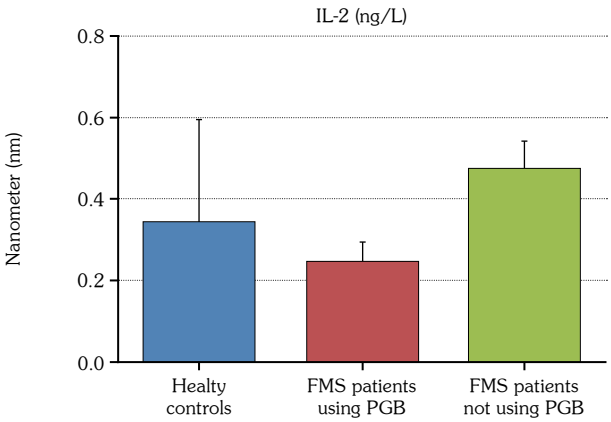

Figure 1. IL-2 levels in healthy controls and FMS patients, p<0.001.
IL: Interleukin; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

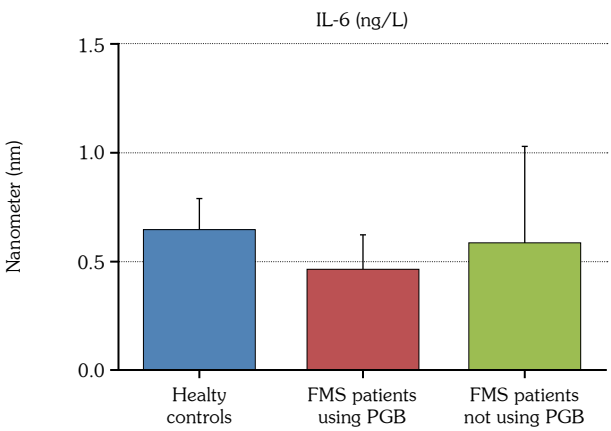

Figure 2. IL-6 levels in healthy controls and FMS patients, p<0.001.
IL: Interleukin; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

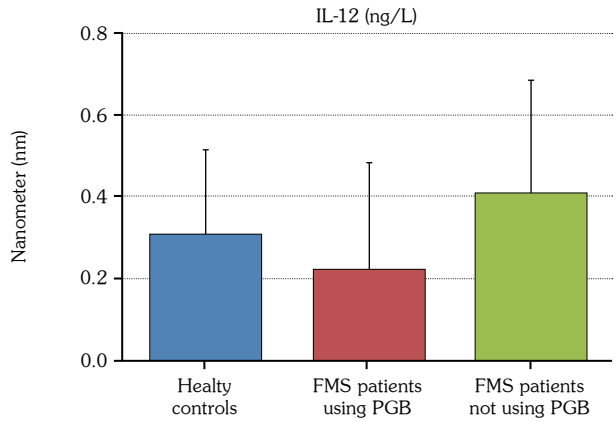

Figure 3. IL-12 levels in healthy controls and FMS patients, p<0.001.
IL: Interleukin; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

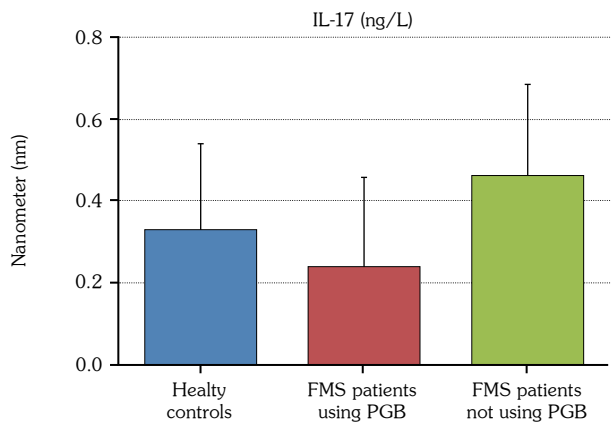

Figure 4. IL-17 levels in healthy controls and FMS patients, p<0.001.
IL: Interleukin; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

IL-17 value (p<0.001). The IL-17 level of the FMS patients not using PGB (0.36 ng/L) was higher than the healthy controls (0.24 ng/L) and patients using PGB (0.17 ng/L) (Table 4, Figure 4). The FMS patients not using PGB had the highest IFN-γ level (0.43 ng/L), and a remarkable difference was obtained between the patients and healthy subjects (p<0.001). However, a variation between the FMS groups was observable, and the levels of FMS patients using PGB (0.16 ng/L)

Table 5. IFN-γ levels in healthy controls and FMS patients

	Healthy controls		FMS patients (using PGB)		FMS patients (not using PGB)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
IFN-γ (ng/L)	0.19	0.12-0.88	0.16	0.09-1.59	0.43	0.10-0.88	<0.001

IFN-γ: Interferon gamma; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

Table 6. TNF-α levels in healthy controls and FMS patients

	Healthy controls		FMS patients (using PGB)		FMS patients (not using PGB)		
	Median	Min-Max	Median	Min-Max	Median	Min-Max	*p*
TNF-α (ng/L)	0.23	0.14-1.10	0.14	0.08-1.18	0.93	0.35-2.94	<0.001

TNF-α: Tumor necrosis factor alpha; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

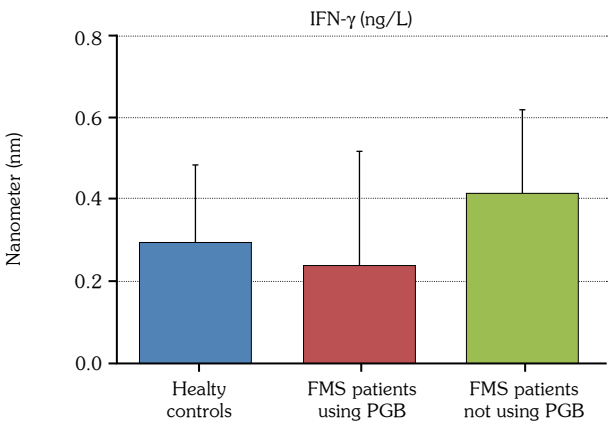

Figure 5. IFN-γ levels in healthy controls and FMS patients, p<0.001.

IFN-γ: Interferon gamma; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

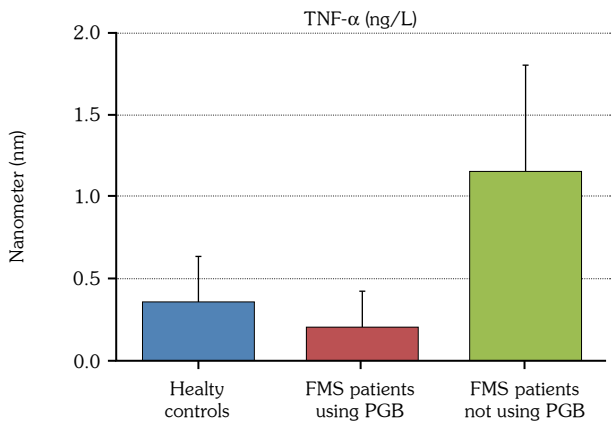

Figure 6. TNF-α levels in healthy controls and FMS patients, p<0.001.

TNF-α: Tumor necrosis factor alpha; FMS: Fibromyalgia syndrome; PGB: Pregabalin.

were lower than nonuser patients (p<0.001, Table 5, Figure 5). Additionally, TNF-α levels of the healthy group (0.23 ng/L) and FMS patients using PGB (0.14 ng/L) were lower than in the patient group not using PGB (0.93 ng/L), and there was a significant difference between the FMS patients using and not using PGB (p<0.001, Table 6, Figure 6).

DISCUSSION

Fibromyalgia syndrome is a common pain disease that has negative effects on the lives of individuals, and its cause is still not clearly understood. In the light of the findings obtained from patients with FMS, it has been observed that more than one parameter may be a factor in the occurrence of this disease.[20] Current approaches are that immunological markers affect the course of the disease. For example, it has been shown that inflammatory cytokines can cause inflammation by activating various pathways in the nervous system through microglia cells.[21] Cytokines are the main mediators of immunity and are involved in inflammatory responses. They may show anti-or proinflammatory activity in pain-related inflammation. It is suggested that

in FMS patients with chronic widespread pain, any change in cytokine release will disrupt the immune system balance, and this supports the persistence of pain.[22] Many studies demonstrated that proinflammatory mediators are critical in patients with FMS.[4-6] It was reported that IL-2, a proinflammatory cytokine, concentrations were lower in healthy individuals compared to FMS patients.[7] However, Peter and Wallace[22] detected an increase in the IL-2 concentrations of FMS patients. In our study, IL-2 concentrations of the patient group were also higher than the healthy group. There is not enough information about IL-2 action in FMS, but it is suggested that it may be used for clinical therapies on FMS-like symptoms. Interleukin-6, also a proinflammatory cytokine, has crucial effects on immunity and is highly expressed in the central nervous system.[23] It is known that IL-6 promotes pain formation mediated by central nervous system sensitization. In addition, it has a connection with nociceptive plasticity. In studies on pain, increased secretion of gp130, IL-6, and IL-6R was found in the dorsal root ganglia and spinal cord, which has been associated with disease pathology.[23,24] However, the levels of IL-6 in the patient group were also higher than in the healthy group in the present study, and this increase was statistically significant. Interleukin-6 is suggested to have an important function in the underlying mechanisms of FMS[24] but the efficacy of IL-6 in pain-related diseases is still a subject of study. Although IL-12, another proinflammatory cytokine, is mostly researched in autoimmune diseases, there are also studies showing that it may be associated with pain. Recently, it has been shown that IL-12 also induces inflammatory hypernociception.[25] A mechanical hypernociception mediated by endothelin-1 and endothelin-B receptor interaction was obtained in rats injected with IL-12. This finding is significant since pain at the IL-12 injection site was reported in human treatment.[26] Furthermore, IL-12 is a significant mediator for the development of arthritis, and a significant association was detected between IL-12 concentration and severity of disease in RA patients by Kim et al.[27] In addition, IL-12 is included in the release of proinflammatory cytokines, so it has been predicted that IL-12 blockade may be therapeutically beneficial in the treatment of RA. In our study, IL-12 concentration was higher in the patient group compared to the healthy group. IL-17 is the principal cytokine released from Th17 cells and is upregulated in various inflammatory cases like RA. Additionally, it was determined that the symptoms of FMS patients, such as pain, depression, and anxiety, showed a positive correlation with IL-17A levels.[28] Although the studies on the efficacy of Th17 cells in FMS are inadequate, most of the research demonstrates that IL-17 levels rise in FMS patients.[9,10] In our study, IL-17 concentration was lower in the patient group than in the healthy group, and this result was consistent with the other studies performed.

Tumor necrosis factor-α is one of the most important cytokines released by macrophages and microglia cells and shows activity in neural pain pathways.[29] It can regulate pain signals by binding to the TNFR1 (TNF receptor 1) and has a crucial role in the inflammation area where pain occurs.[29] In addition, substance P and corticotropin-releasing hormone are chemicals that are secreted in the body during stress.[29] Both of these substances trigger inflammation and support the release of TNF-α.[29] In a study, it was detected that the concentrations of substance P, TNF-α, and corticotropin-releasing hormone in FMS patients were higher than in healthy individuals.[30] There are different findings about the efficacy of TNF-α in FMS. In some studies, there was no difference in TNF-α levels between patients and healthy individuals,[11,31,32] while in other studies, TNF-α levels were found to be lower in people with FMS.[31-33]

Interferon-γ is another proinflammatory cytokine that we recently investigated. The results of studies on IFN-γ showed that there was no noticeable difference between the patients and healthy subjects, and values of IFN-γ were similar in each group.[7,34] On the contrary, we determined a marked increase in the concentrations of TNF-α and IFN-γ of FMS patients compared to the healthy subjects. In addition to all these, FMS patients using and not using PGB were also compared in our study, and the effect of PGB on proinflammatory cytokines was investigated. Although there are a few studies on the effectiveness of PGB,[35,36] the results of our study were consistent with the earlier findings. We found that the levels of FMS patients using PGB were lower than nonuser patients and healthy

controls. However, Kilic et al.[35] reported that the effect of each dose of PGB was anti-inflammatory in relation to cytokine levels in adult female rats. Although PGB acts by binding to voltage-gated calcium channels and is pointed for the medication of pain, it is thought to also have an effect on inflammation.[35] Studies have reported that it inhibits IL-6 and TNF-α levels.[35,36] This effect of PGB may explain the unexpected results in FMS. The pathogenesis of FMS is still not fully understood. The lack of appropriate laboratory diagnostic methods to help detect the disease also makes it difficult to understand the causes of FMS. It is thought that the severity of the symptoms of FMS may be affected by the modifications in the immune pathways. Based on this, it is suggested that the level of cytokine release has a crucial area in the development of FMS. Moreover, since the information about the methods used in the treatment of FMS and how the drugs are effective is not clear, the data in our study can support the clarification of this issue and guide the therapeutic applicability of PGB-like drugs.

In conclusion, this is the first study to show how PGB use affects cytokine profile in FMS patients. Significant differences were obtained in cytokine levels of patients with PGB treatment. These results prove that immune mediators play an important role in the neurological pain process. In addition, our results provide a perspective on how PGB regulates the immune system in neuroinflammatory cases, such as pain-related diseases, FMS, and anxiety. The anti-inflammatory function of PGB may help explain its working system in the treatment of similar pain-related cases. More detailed studies should be conducted to understand the relationship of PGB with immune mediators in various pain-related diseases and to investigate these effects on different immune mediators.

Ethics Committee Approval: The study protocol was approved by the Uludağ University Ethics Committee (date: 2020, no: 2020/2). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization: P.E., A.A.; Methodology: P.E.; Data collection and processing: P.E., M.Ç.; Data analysis: A.C.M.; Writing-original draft preparation: A.A., P.E.; Writing-review and editing: P.E., A.A., S.Ç.; Visualization: A.A., P.E.; Supervision: S.Ç., All authors have read and agreed to the published version of the manuscript.

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