European Journal of Therapeutics

DOI: 10.58600/eurjther-28-4-0104

Original Research

# Comparison of Pineal Gland Volume Between Patients with Fibromyalgia and Healthy Controls

Çağlar Karabaş[1], Samet Karahan[2], Havva Talay Çalış[3], Ali Koç[4]

[1]Kastamonu Physical Therapy and Rehabilitation Center, Department of Physical Medicine and Rehabilitation, Kastamonu, Turkey
[2]Kayseri City Hospital, Department of Internal Medicine Division of Rheumatology, Kayseri, Turkey
[3]Kayseri City Hospital, Department of Physical Medicine and Rehabilitation, Kayseri, Turkey
[4]Kayseri City Hospital, Department of Radiology, Kayseri, Turkey

**ABSTRACT**

**Objectives:** The pineal gland is an important neuroendocrine organ accounting for the melatonin secretion and chronobiology that regulate circadian rhythm. This study was designed to compare pineal gland volume (PGV) with healthy controls and patients with fibromyalgia syndrome (FM), in which sleep quality and efficiency is reduced.

**Patient and Methods:** In this cross-sectional study, PGV and functional pineal gland volume (FPGV) of FM patients with age- and sex-matched healthy controls were compared. All MR imaging studies were performed using a 3 Tesla scanner with a multi-channel phased array head coil. The volume of pineal glands and pineal cysts were calculated from 3D MP RAGE images using the formula: volume= AP x transverse x craniocaudal diameter x 0.523.

**Results:** There was no significant difference in PGV and FPGV between the FM group and healthy controls (p=0.374 and p=0.421, respectively). In the correlation analysis, age was negatively correlated with PGV and FPGV in the FM group (r=-0.496, p=0.010; r=-0.477, p=0.014, respectively). No significant correlation was detected between age, PGV and FPGV in the control group (r= 0.022, p=0.916; r= -0.019, p=0.925, respectively).

**Conclusions:** Based on the results, there was no significant difference between the FM group and healthy controls regarding PGV and FPGV. However, PGV and FPGV were decreased by advancing age in the FM group in which melatonin therapy is offered as an option.

**Keywords:** Fibromyalgia syndrome, pineal gland volume, functional pineal gland volume, pineal gland magnetic resonance imaging

## INTRODUCTION

The pineal gland is an endocrine organ adjacent to the posterior wall of the third ventricle between the posterior and dorsal habenular commissures, accounting for the melatonin secretion and chronobiology that regulates circadian rhythm (1). Melatonin is a hormone that regulates the sleep/wake cycle. There is a correlation between pineal gland volume (PGV) and melatonin secretion (2). It has been seen that individuals with a smaller PGV secrete less melatonin (3). It was suggested that "functional parenchymal volume" (FPGV), which excludes cysts and calcification from pineal gland volume, is actually responsible for melatonin secretion (1, 4).

In previous studies, PGV was found to be lower in chronic systemic diseases such as obesity, primary insomnia, and schizophrenia, leading to an impaired sleep circadian rhythm when compared to the general population, suggesting that lower PGV may play a role in disease pathogenesis (2, 3, 5).

Fibromyalgia (FM) is a clinical entity involving many symptoms such as chronic generalized pain, fatigue, sleep disorder, cognitive dysfunction, and depressive episodes (6). Wikner et al. compared FM patients with healthy individuals and found lower levels of nocturnal melatonin secretion in FM patients (7). To the best of our knowledge, there is no study showing a relationship between PGV and FM, which influences daily quality of life and leads to depression and sleep disorders.

In this study, we aimed to evaluate the relationship between FM and PGV and FPGV.

**How to cite:** Karabaş Ç, Karahan S, Çalış HT, Koç A. Comparison of Pineal Gland Volume Between Patients with Fibromyalgia And Healthy Controls. Eur J Ther 2022; 28(4): 301–5.

**Corresponding Author:** Çağlar Karabaş **E-mail:** drckarabas@gmail.com

**Received:** 12.10.2021 • **Accepted:** 11.01.2022

## MATERIAL AND METHOD

### Study Design and Participation

A cross-sectional experimental design was made to compare PGV and FGPV obtained by magnetic resonance imaging (MRI) in FM patients with healthy controls. The study was approved by the lolocal Ethics Committee (Approval No: 2019/564-24.07). The study was conducted in accordance with the Helsinki Declaration and all participants gave written informed consent.

The study included 26 patients (23 women and 3 men), who presented to the Physical Therapy & Rehabilitation and Rheumatology outpatient clinics of the Kayseri City Hospital and were diagnosed as having FM based on the American College of Rheumatology (ACR) 2016 Diagnostic Criteria between September, 2016 and December, 2019 and age-, sex-, and body mass index (BMI)-matched 26 healthy individuals (23 women, 3 men) as controls (8). Patients with chronic systemic diseases, inflammatory rheumatoid disease (rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, etc.), history of malignancy, history of autoimmune disorder, with psychiatric disorders such as depression or schizophrenia, and patients with regular or excessive alcohol consumption were excluded.

All patients with FM were asked to answer the Fibromyalgia Impact Questionnaire (validated in Turkish), which assesses physical function, occupational status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being (9, 10). The pain was assessed using the Visual Analog Scale (VAS), which is rated by a 0-100 mm ruler (0: no pain, 100, intractable pain). The patients were asked to mark on the ruler according to their pain level. The VAS score was defined as the distance from point 0 (no pain) to the point marked by the patient and recorded in mm (11). All subjects underwent MR imaging in accordance with the protocol. No complication was observed during the imaging studies.

MR Imaging Protocol and Measurement of Pineal Gland Volume

All MRI exams were performed with a 3 T scanner (MAGNETOM®, Skyra; Siemens Healthcare, Erlangen, Germany) using a multi-channel phased array head coil. The protocol was composed of axial T1-weighted three dimensional magnetization-prepared rapid acquisition gradient echo (3D MP RAGE) sequence (Time to echo, 3 ms; Time repetition, 22 ms; Flip angle, 30°; Field of view, 200 mm; matrix, 256 × 256; slice thickness, 0.5 mm), sagittal T1-weighted three dimensional magnetization-prepared rapid acquisition gradient echo (3D MP RAGE) sequence (Time to echo, 2 ms; Time repetition, 20 ms; Flip angle, 30°; Field of view, 180 mm; matrix, 256 × 256; slice thickness, 0.5 mm), and axial T2-weighted fluid attenuated inversion recovery (FLAIR) sequence (Time to echo, 85 ms; Time repetition, 9000 ms; Field of view, 100 mm; matrix, 256 × 256; slice thickness, 3 mm). MRI images were reviewed by a radiologist with 15 years of experience in neuroradiology. Pineal cysts were identified as circular areas isointense to the cerebrospinal fluid. The volume of the pineal glands and pineal cysts were calculated from the 3D MP RAGE images using the formula:

Volume= X x Y x Z (AP x transverse x craniocaudal diameters) x 0.523.

For patients with pineal cysts, cyst volume was subtracted from the gland volume in order to find the functional gland volume.

**Main Points:**

- This is the first study assessing PGV in patients with FM and healthy controls using MR imaging.
- There is no significant difference in PGV and FPGV between FM and control groups.
- Age was negatively correlated with PGV and FPGV in the FM group while no correlation was detected in the control group.

### Statistical Analysis

To evaluate the effect size, Cohen's d coeficient was calculated for between- group variables that showed a significant change. An effect size of 0.20 to <0.50 was regarded as small, 0.50 to <0.80 as medium, and >0.80 as large (12). To detect a clinically important difference of 30 mm3 on the PGV between groups, with an estimated SD of 20 mm3, 80% power, and 5% significance level using the Mann- Whitney U test, 24 participants were needed in each group. To account for dropout, 2 participants were recruited. Statistical analyses were performed using SPSS version 23.0 (IBM, Armonk, NY, USA). Categorical variables were presented using descriptive statistics (frequency counts and percentages), while numeric items were summarized using mean ± standard deviation or median (IQR25-75). The normal distribution of data was assessed using the Shapiro-Wilk test and histogram. The chi-square test was used in comparisons between groups. A Student's t test was used to compare variables with normal distribution while the Mann Whitney U test was used to compare variables with skewed distribution between groups. Spearman's correlation analysis was performed for data with skewed distribution and quantitative data. The variables used in Spearman correlation analysis were age, gender, BMI, symptom duration, VAS, Fibromyalgia Impact Questionnaire (FIQ), FGV, and FGPV. Statistical significance of correlation coefficients estimated was assessed by a determination coefficient of 0.01 and 0.05. A p value < 0.05 was considered as statistically significant.

## RESULT

In both the FM and control groups, there were 23 women (88.5%) and 3 men (11.5%). The mean age was 40.62 ± 9.02 years in the FM group and 37.42 ± 6.06 years in the control group (p=0.140). There were no significant differences in age, gender, and body mass index between the groups. Table 1 presents the demographic and clinical characteristics of the participants.

No significant difference was detected in PGV and FPGV between the FM and control groups (p=0.374 and p=0.421, respectively; Table 2). In correlation analysis, age was negatively correlated with PGV and FPGV in the FM group (r=-0.496, p=0.010; r=-0.477, p=0.014, respectively). No significant correlation was detected between age, PGV and FPGV in the control group (r= 0.022, p=0.916; r= -0.019, p=0.925, respectively). In the FM group, no significant correlation was detected between BMI, PGV and FPGV (r= -0.253, p=0.213; r= -0.236, p=0.245, respectively). In the FM group, no significant correlation was detected between duration of symptoms, PGV and FPGV (r= -0.112, p=0.587; r= -0.106,

p=0.606, respectively). In addition, no significant correlation was detected between BMI, PGV and FPGV in the control group (r= 0.154, p=0.453; r= 0.127, p=0.536, respectively). In the correlation analysis among VAS, PGV and FPGV, it was found that PGV and FPGV were reduced by increasing FIQ in the FM group but the difference did not reach statistical significance (r= -0.352, p=0.078; r= -0.344, p=0.085, respectively). Again, no significant difference was detected between FIQ and PGV and FPGV in the FM group (r= -0.261, p=0.199; r= -0.239, p=0.240; Table 3). Figure 1a and 1b present correlation between age and PGV and FPGV in the FM group. Figure 1c and 1d present correlation between age and PGV and FPGV in the control group. Figure 2a and 2b present correlation between VAS and PGV and FPGV while Figure 2c and 2d present correlation between FIQ and PGV and FPGV in the FM group.

Figure 1. a and b, correlation between VAS, PGV and FPGV in FM patients; c and d, correlation between FIQ, PGV and FPGV in FM patients

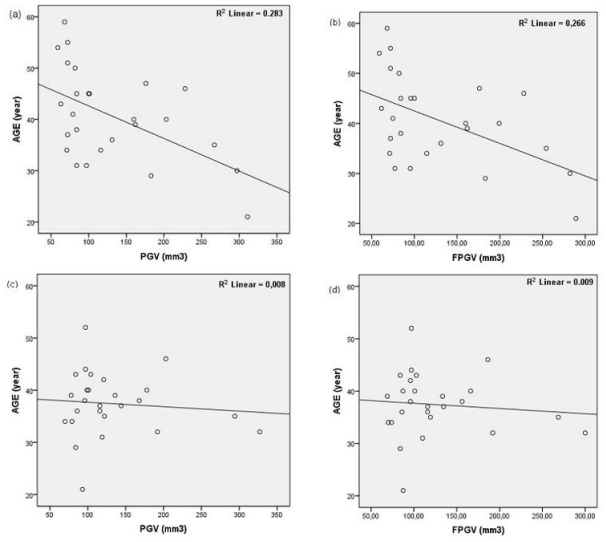
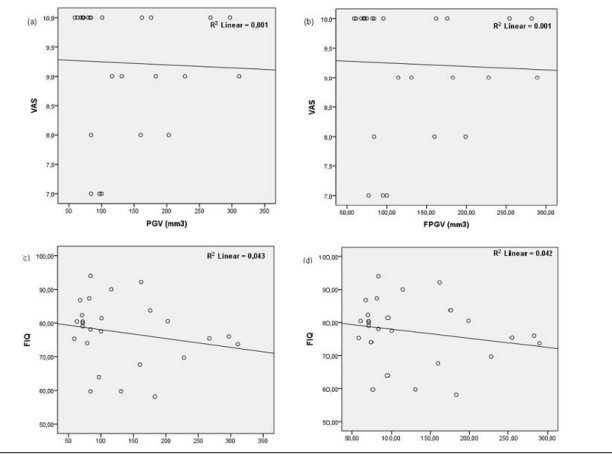



Figure 2. a and b, correlation between age, PGV and FPGV in FM patients; c and d, correlation between age, PGV and FPGV in healthy controls




## DISCUSSION

To the best of our knowledge, this is the first study assessing PGV in patients with FM and healthy controls using MR imaging. In the study, the major finding is that there were no significant differences in PGV and FPGV between FM patients and healthy controls. However, age was negatively correlated with PGV and FPGV in the FM group while no correlation was detected in the control group.

Melatonin is a hormone secreted in lower concentrations during daytime and higher concentrations during nighttime by the suprachiasmatic nucleus (13). PGV is positively correlated with the number of pinealocytes responsible for melatonin secretion and is highly variable among healthy individuals. The reduction in PGV affects pinealocyte count, resulting in low melatonin level. In previous studies, a correlation was detected between PGV and melatonin level (14). Thus, it is thought that PGV may affect etiopathogenesis in chronic diseases that cause sleep/wake cycle and lead affective disorders (2, 14, 15). In a study by Bumb et al. (3), PGV was assessed in patients with primary insomnia and healthy volunteers using MR imaging. It was found that PGV was significantly lower in patients with primary insomnia compared to healthy volunteers. In a study by Fındıklı et al. (16), PGV was found to be lower in patients with schizophrenia when compared to healthy volunteers. However, in the same study, no significant difference was detected in PGV when patients with unipolar depression and bipolar disorder were compared with healthy controls. In a study by Takahashi et al. (17), no significant differences were detected in both total pineal volume and pineal parenchymal volume (excluding pineal cyst volume) between patients with major depression and bipolar disorders and healthy controls. In our study, no significant difference was detected between the FM group and health controls regarding PGV and FPGV.

In a study performing Micro-structural analysis of the pineal gland using the trueFISP imaging technique, both parenchymal volume and volume of cystic structure in the pineal gland were analyzed. In the study, pineal parenchymal volume was obtained by subtracting cystic volume from total PGV. In conclusion, it was found that both PGV and pineal parenchymal volume were reduced by advancing age. However, another striking finding was that total cystic volume or number of cysts had no correlation with age in the study (18). In our study, we found that there was no correlation between age and pineal cystic volume or number of pineal cysts in both FM patients and controls in agreement with the literature.

In the above-mentioned study by Bumb et al. (3), it was also found that there was a negative correlation between PGV and age in patients with primary insomnia but not in healthy controls. In our study, a negative correlation was found between age and PGV in FM patients but no such relationship was detected in healthy controls. It is known that sleep quality is an important age-related change. Older individuals have shorter and more inefficient sleep (19). In a postmortem study on 80 cadavers, effects of age, height, and weight were investigated on PGV and suggested that effects of age on PGV can be negligible (20).

Table 1: Demographic and clinical characteristics of the participants

| | Fibromyalgia (n=26) | Healthy Control (n=26) | p |
|---|---|---|---|
| Age (years), mean ± SD | 40.62 ± 9.02 | 37.42 ± 6.06 | 0.140 |
| Gender (F/M), n (%) | 23/3 (88.5/11.5) | 23/3 (88.5/11.5) | 1.00 |
| BMI (kg/m2), mean ± SD | 28.54 ± 4.06 | 26.78 ± 5.00 | 0.169 |
| Duration of symptoms (month), median (IQR 25-75) | 36 (12 -60) | | |
| VAS pain score, mean ± SD | 9.23 ± 1.07 | | |
| FIQ score, mean ± SD | 77.20 ± 9.63 | | |

FIQ: Fibromyalgia Impact Questionnaire; VAS: Visual Analog Scale; BMI: Body Mass Index; F: female; M: male; SD: standard deviation; IQR: interquartile range; (P < 0.05 considered statistically significant)

**Table 2:** Pineal gland volume and functional pineal gland volume in the control group and fibromyalgia group

| | Fibromyalgia (n=26) | Healthy Control (n=26) | p |
|---|---|---|---|
| PGV, median (IQR 25-75 | 98.5 (72 - 177.75) | 110 (91.25 - 150) | 0.374 |
| FGPV, median (IQR 25-75) | 95.5 (72 - 177.75) | 101.91 (86.93 - 139.99) | 0.421 |
| Cyst volume, median (IQR 25-75) | 0.0 (0.0 - 4.44) | 1.89 (0.0 - 9.99) | 0.291 |
| Number of cysts (yes/no), n (%) | 11/15 (42.3/57.7) | 14/12 (53.8/46.2) | 0.579 |

PGV: Pineal Gland Volume; FGPV: Functional Pineal Gland Volume; SD: standard deviation; IQR: interquartile range; (p<0.05 considered statistically significant).

Table 3: Spearman correlation analysis among age, body mass index, PGV, and FGPV in fibromyalgia and healthy control groups and correlation analysis among Duration of symptoms, VAS, FIQ, PGV, and FPGV in the fibromyalgia group

| | Fibromyalgia Group | | | | Healthy Group | | | |
|---|---|---|---|---|---|---|---|---|
| | PGV | | FPGV | | PGV | | FPGV | |
| | $r_s$ | p-value | $r_s$ | p-value | $r_s$ | p-value | $r_s$ | p-value |
| Age | -0.496** | 0.010 | -0.477** | 0.014 | 0.022 | 0.916 | -0.019 | 0.925 |
| BMI | -0.253 | 0.213 | -0.236 | 0.245 | 0.154 | 0.453 | 0.127 | 0.536 |
| Duration of symptoms | -0.112 | 0.587 | -0.106 | 0.606 | | | | |
| VAS | -0.352 | 0.078 | -0.344 | 0.085 | | | | |
| FIQ | -0.261 | 0.199 | -0.239 | 0.240 | | | | |

Pineal Gland Volume; FGPV: Functional Pineal Gland Volume; BMI: Body Mass Index; VAS: Visual Analog Scale; FIQ: Fibromyalgia Impact Questionnaire; $r_s$: Spearman's correlation coefficients. (p < 0.05 considered statistically significant).

In our study, we failed to find a correlation between age and PGV in healthy controls; thus, we think that such a relationship can be neglected in healthy controls. However, a negative correlation was detected between age and PGV in the FM group in our study. We think the correlation between age and PGV in the FM group is relevant in fibromyalgia syndrome in which sleep quality and efficient are decreased.

This study has some limitations. Firstly, we did not assessed melatonin levels when assessing PGV. However, in previous studies, nocturnal melatonin level was assessed in FM and found to be normal or low (7, 21).We designed this study without melatonin assessment due to concerns regarding cost as there is no previous study investigating correlation between FM and PGV. In PGV, it is known that pineal calcifications and pineal cysts are hormonally inactive part (17). In our study, volume caused by pineal calcifications was neglected although pineal cyst volume was taken into account. Computed tomography (CT) is required for precise assessment of pineal calcifications (22). We did not obtained CT scans due to additional cost and complications caused by ionizing radiation.

## CONCLUSION

This is the first study assessing PGV in FM patients and healthy controls using MR imaging. Based on results, there is no significant difference in PGV and FPGV between FM and control groups.

However, age has an impact on PGV and FPGV in the FM group. However, we concluded that age has negligible effect on PGV and FPGV in healthy controls. There is a need for further studies with larger sample size, which simultaneously evaluate melatonin level, in order to assess PGV in patients with FM.

**Compliance with Ethical Standards:** The study was approved by the local University Ethics Committee (Approval No: 2019/564-24.07).

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

**Conflict of Interest:** The author has no conflicts of interest to declare.

**Financial Disclosure:** The author declared that this study has received no financial support.

## REFERENCES

1. Karakurt P, Hacıhasanoğlu Aşılar R, Yıldırım A, Sevinç H. Knowledge levels and attitudes of diabetic patients about their disease. Eur J Ther 2017; 23: 165-72. [Crossref]
2. Duymaz T. Effects of nutrition and exercise habits in patients with Type 2 diabetes. Eur J Ther 2018; 24(4): 220-3. [Crossref]
3. Teymoori F, Farhadnejad H, Mirmiran P, Nazarzadeh M, Azizi F. The association between dietary glycemic and insulin indices with incidence of cardiovascular disease: Tehran lipid and glucose study. BMC Public Health 2020; 20: 1496. [Crossref]
4. Nimptsch K, Brand-Miller JC, Franz M, Sampson L, Willett WC, Giovannucci E. Dietary insulin index and insulin load in relation to biomarkers of glycemic control, plasma lipids, and inflammation markers. Am J Clin Nutr 2011; 94: 182-90. [Crossref]
5. Bao J, de Jong V, Atkinson F, Petocz P, Brand-Miller JC. Food insulin index: physiologic basis for predicting insulin demand evoked by composite meals. Am J Clin Nutr 2009; 90:986-92. [Crossref]
6. Joslowski G, Goletzke J, Cheng G, Günther AL, Bao J, Brand-Miller JC, Buyken AE. Prospective associations of dietary insulin demand, glycemic index, and glycemic load during puberty with body composition in young adulthood. Int J Obes (Lond) 2012; 36: 1463-71. [Crossref]
7. Mirmiran P, Esfandiari S, Bahadoran Z, Tohidi M, Azizi F. Dietary insulin load and insulin index are associated with the risk of insulin resistance: a prospective approach in Tehran lipid and glucose study. J Diabetes Metab Disord 2015; 15: 23. [Crossref]
8. Anjom-Shoae J, Keshteli AH, Sadeghi O, Pouraram H, Afshar H, Esmaillzadeh A, Adibi P. Association between dietary insulin index and load with obesity in adults. Eur J Nutr 2020; 59: 1563-75. [Crossref]
9. Ghorbaninejad P, Imani H, Sheikhhossein F, Tijani Jibril A, Mohammadpour S, Shab-Bidar S. Higher dietary insulin load and index are not associated with the risk of metabolic syndrome and obesity in Iranian adults. Int J Clin Pract 2021; 75: e14229. [Crossref]
10. Mozaffari H, Namazi N, Larijani B, Surkan PJ, Azadbakht L. Associations between dietary insulin load with cardiovascular risk factors and inflammatory parameters in elderly men: a cross-sectional study. Br J Nutr 2019; 121: 773-81. [Crossref]
11. Bell KJ, Gray R, Munns D, Petocz P, Howard G, Colagiuri S, Brand-Miller JC. Estimating insulin demand for protein-containing foods using the food insulin index. Eur J Clin Nutr 2014; 68: 1055-59. [Crossref]
12. Ostman EM, Liljeberg Elmstahl HGM, Bjorck IME. Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. Am J Clin Nutr 2001; 74: 96-100. [Crossref]
13. Brand-Miller J, Holt SH, de Jong V, Petocz P. Cocoa powder increases postprandial insulinemia in lean young adults. J Nutr 2003; 133: 3149-52. [Crossref]
14. Dugan CE, Fernandez ML. Effects of dairy on metabolic syndrome parameters: a review. Yale J Biol Med 2014; 87: 135-47. [Crossref]
15. Leary M, Tanaka H. Role of fluid milk in attenuating postprandial hyperglycemia and hypertriglyceridemia. Nutrients 2020; 12: 3806. [Crossref]
16. Jargin SV. Management of type 2 diabetes mellitus with overweight: Focus on SGLT-2 inhibitors and GLP-1 receptor agonists. Eur J Ther 2019; 25: 93-96. [Crossref]