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ORIGINAL RESEARCH

Comparison of BDNF and NGF Levels in Adenomyotic Tissue, Adjacent Myometrium, and Normal Myometrium and Their Correlation with Pain Severity

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Background: Adenomyosis is a major cause of chronic pelvic pain in women of reproductive age and significantly affects quality of life. Identifying biomarkers associated with pain mechanisms may improve understanding of disease pathophysiology and support the development of targeted therapeutic strategies. The mechanisms underlying adenomyosis-related pain are not fully understood but are thought to involve neurogenic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), which promote nerve fiber proliferation and sensitization. However, evidence regarding the relationship between BDNF, NGF, and pain severity in adenomyosis remains limited.

Objective: To compare BDNF and NGF levels in adenomyotic tissue, adjacent myometrium from patients with adenomyosis, and normal myometrium, and to evaluate their association with pain severity measured using the Visual Analog Scale (VAS).

Methods: This cross-sectional study analyzed BDNF and NGF levels in adenomyotic tissue, adjacent myometrium, and normal myometrium from 120 tissue samples. Neurotrophin levels were compared among tissue groups and evaluated for their association with pain severity using Visual Analogue Scale (VAS) scores.

Results: BDNF levels differed significantly among the three tissue groups ($H = 99.364$; $p < 0.001$), showing a decreasing trend from adenomyotic tissue to adjacent myometrium and then to normal myometrium. Post-hoc analysis confirmed significant differences across all pairwise comparisons ($p < 0.001$). NGF levels also differed significantly among groups ($H = 96.056$; $p < 0.001$), with significant differences in all pairwise comparisons ($p < 0.001$). No significant correlations were found between BDNF and VAS scores ($\rho = -0.038$; $p = 0.817$) or NGF and VAS scores ($\rho = 0.125$; $p = 0.441$).

Conclusion: Although BDNF and NGF levels differed significantly among tissue types, neither neurotrophin was significantly associated with pain severity, suggesting that additional mechanisms (eg, central sensitization or other inflammatory mediators) may underlie adenomyosis-related pain.

Keywords: adenomyosis, BDNF, NGF, neuroinflammation, pelvic pain, VAS

Introduction

Adenomyosis is a gynecological disorder characterized by the presence of ectopic endometrial glands and stroma within the uterine myometrium, resulting in chronic inflammation under estrogenic influence.[1,2] It is increasingly recognized as a significant contributor to gynecologic morbidity among women of reproductive age. The reported annual incidence is approximately 28.9 cases per 10,000 women (1.03%), while global prevalence estimates vary widely from 5% to 70%, largely due to differences in diagnostic criteria, histopathological confirmation, imaging modalities, and population characteristics.[3]

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The pathogenesis of adenomyosis is complex and involves multiple mechanisms. Several hypotheses have been proposed, including invagination of the endometrial basalis into the myometrium, microtrauma at the endometrial–myometrial junctional zone due to repeated tissue injury and repair (TIAR), de novo metaplasia from stem or progenitor cells, and inward invasion associated with retrograde menstruation. Additionally, metaplastic transformation of Müllerian remnants or activation of adult stem cells residing in the endometrial basalis may contribute to the development of ectopic endometrial glands within the myometrium.[4–8]

Pain represents the most debilitating and clinically significant symptom of adenomyosis and is a primary reason for patients seeking medical care. Severe dysmenorrhea, chronic pelvic pain, and dyspareunia are frequently reported and may progressively worsen over time. The mechanisms underlying adenomyosis-associated pain are multifactorial, involving chronic inflammation, local hyperestrogenism, neuroangiogenesis, and hyperinnervation of affected tissues, all of which contribute to enhanced nociceptive signaling. Emerging evidence suggests endometrial tissue in adenomyosis exhibits an increased in production of neurotrophic factors.

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are found in uterine sensory nerves. NGF and BDNF, along with their respective receptors TrkA and TrkB, play essential roles in neuronal survival, neurite growth, and sensitization. They promote neurogenesis and hyperinnervation within adenomyotic lesions, contributing to enhanced nociceptive signaling and persistent pain perception.[9–11]

The Visual Analog Scale (VAS) is a validated and widely used instrument for assessing pain intensity, providing a reliable quantitative measure of subjective pain perception in clinical and research settings. In patients with adenomyosis, VAS serves as an important clinical tool to quantify dysmenorrhea and chronic pelvic pain severity.[12]

Although neurotrophins are increasingly recognized in pain modulation, comparative data on BDNF and NGF expression across adenomyotic tissue, adjacent myometrium, and normal myometrium remain limited, and their relationship with pain severity is not fully understood. Therefore, this study compared BDNF and NGF levels among these tissue types and evaluated their association with pain severity measured by the VAS, aiming to clarify the role of neurotrophins in adenomyosis-associated pain and guide future diagnostic and therapeutic strategies.

Materials and Methods

Study Design and Setting

This study employed an analytic observational design with a cross-sectional approach. It was conducted at Dr. Hasan Sadikin General Hospital Bandung, Limijati Women and Children Hospital, Bandung Kiwari General Hospital, Cibabat General Hospital, and Dustira Hospital, Indonesia, between July and October 2025. Laboratory analyses were performed in accordance with standardized research protocols.

Sample Size Determination

Sample size was calculated for correlation analysis based on the primary study objective of evaluating the association between neurotrophin levels and pain severity. A two-sided significance level of 5% ($\alpha = 0.05$) and statistical power of 80% ($\beta = 0.20$) were applied. In the absence of prior studies specifically evaluating the correlation between BDNF and NGF in adenomyosis, a minimum correlation coefficient of 0.60 was assumed. The estimated minimum sample size was 30 participants per group.

Study Population and Sample Collection

The population included patients with adenomyosis confirmed by transvaginal ultrasonography and histopathological examination who received treatment at the participating hospitals during the study period.

Eligible women aged 20–50 years who met the inclusion criteria and none of the exclusion criteria were enrolled. The adenomyosis group consisted of patients diagnosed by transvaginal ultrasonography according to the Morphological Uterus Sonographic Assessment (MUSA) criteria and confirmed by histopathology at the participating hospitals. The control group included patients with histologically normal myometrium obtained from hysterectomy specimens without

evidence of adenomyosis (control tissue samples were obtained from patients undergoing surgery for non-adenomyosis conditions rather than from completely healthy individuals). Written informed consent was obtained from all participants.

Tissue samples were classified into three groups: adenomyotic tissue, adjacent myometrium from patients with adenomyosis, and normal myometrium. BDNF and NGF levels were subsequently analyzed in all samples.

Exclusion criteria included recent use (within three months) of gonadotropin-releasing hormone agonists, progestins, or systemic steroids; history of pelvic inflammatory disease; immunological, endocrine, or metabolic disorders; pelvic malignancy or prior chemotherapy; refusal to participate; and intensive physical exercise that could affect neurotrophin levels.

Tissue Collection and Neurotrophin Measurement

Specimens were collected intraoperatively and classified into three groups: adenomyotic tissue, adjacent myometrium from patients with adenomyosis, and normal myometrium obtained from control patients undergoing hysterectomy for non-adenomyosis indications. All tissue samples were collected under sterile conditions in accordance with institutional laboratory protocols.

Approximately 1 g of tissue (1 × 1×1 cm) was collected from each specimen and processed for neurotrophin analysis. Tissue levels of BDNF and NGF were measured using enzyme-linked immunosorbent assay (ELISA) in the Clinical Pathology Laboratory at Dr. Hasan Sadikin General Hospital, Bandung. All laboratory procedures were performed according to the manufacturer's instructions and standardized laboratory protocols to ensure accuracy and reproducibility.

Tissue levels of BDNF and NGF were quantified using commercially available ELISA kits (Bioenzyme, China), according to the manufacturer's instructions. The BDNF ELISA kit had a sensitivity of 18.75 pg/mL and a detection range of 31.25–2000 pg/mL, while the NGF ELISA kit had a sensitivity of 14 pg/mL and a detection range of 6.86–5000 pg/mL. Both assays had intra-assay and inter-assay coefficients of variation below 10%.[13]

Tissue samples were rinsed with cold phosphate-buffered saline (PBS, pH 7.4) to remove excess blood, weighed, and homogenized in PBS at a ratio of 1:9 (w/v) under cold conditions. The homogenates were further processed by sonication and centrifuged at 5000 × g for 5–10 minutes at 2–8°C to obtain the supernatant. The supernatant was used for ELISA analysis.[13]

The assays were performed using the sandwich ELISA method, and optical density was measured at 450 nm using a microplate reader. Neurotrophin concentrations were calculated based on standard calibration curves and expressed in pg/mL.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Software (Version 31.0.0). Descriptive statistics were used to summarize the characteristics of the study subjects. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as mean ± standard deviation (SD) or median and range, as appropriate.

Data normality was assessed using the Shapiro–Wilk test. Since the neurotrophin data were not normally distributed, comparisons of BDNF and NGF levels among the three tissue groups (adenomyotic tissue, adjacent myometrium, and normal myometrium) were performed using the Kruskal–Wallis test, followed by Dunn's post-hoc test for pairwise comparisons.

The association between BDNF and NGF levels and pain severity measured by the VAS was evaluated using Spearman's rank correlation test. A p-value of less than 0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia (DP.04.03/D.XIV.6.5/399/2025). All procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Results

Characteristics of Patients with Adenomyosis

A total of 40 patients with adenomyosis were included (Table 1). The mean age was 33.2 ± 5.62 years, mean BMI was 26.4 ± 2.50 kg/m^2, and the median lesion size was 3.6 cm (range 1.50–7.70 cm). The mean VAS score was 7.9 ± 1.32, reflecting moderate to severe pain.

Most lesions were located on the posterior uterine wall (92.5%), and the majority of patients had severe disease (57.5%). Most patients had normal menstrual cycle frequency (87.5%) and regular cycles (92.5%). Prolonged menstrual duration was observed in 40% of patients. Heavy menstrual bleeding was common (92.5%), and intermenstrual bleeding occurred in 55% of patients.

Table 1 Characteristics of Study Populations

	Adenomyosis n = 40	**Control n = 40**	**p-value**
Age, mean (SD)	33.2 (5.62)	41.5 (6.18)	< 0.001*
BMI, kg/m^2 (mean (SD))	26.4 (2.50)	25.8 (2.60)	0.296*
Adenomyosis size (median (min-max)	3.6 (1.50–7.70)		
Pain Score (VAS) mean (SD)	7.9 (1.32)	2.13 (0.99)	< 0.001*
Adenomyosis Location (Frequency (%))			
• Anterior	3 (7.5%)		
• Posterior	37 (92.5%)		
Severity			
• Mild	2 (5%)		
• Moderate	15 (37.5%)		
• Severe	23 (57.5%)		
Menstrual Pattern (FIGO) (Frequency (%))			
Frequency			
• Frequent (<24 hari)	2 (5%)	0 (0%)	0.313**
• Normal (24–38 hari)	35 (87.5%)	38 (95%)	
• Infrequent (>38 hari)	3 (7.5%)	2 (5%)	
Duration			
• Prolonged	16 (40%)	0 (0%)	< 0.001**
• Normal	24 (60%)	40 (100%)	
Regularity			
• Regular (Variations <7–9d)	37 (92.5%)	38 (95%)	1.000**
• Irregular (Variations >8–10d)	3 (7.5%)	2 (5%)	
Menstrual Volume			

(*Continued*)

Table 1 (Continued).

	Adenomyosis n = 40	Control n = 40	p-value
• Heavy	37 (92.5%)	3 (7.5%)	< 0.001**
• Normal	3 (7.5%)	34 (85%)	
• Light	0 (0%)	3 (7.5%)	
Intermenstrual Bleeding			
• None	18 (45%)	40 (100%)	< 0.001**
• Yes	22 (55%)	0 (0%)	

Notes: *Independent *T*-Test. **Chi-square Test.

Characteristics of Control Subjects with Normal Myometrium

A total of 40 control subjects with histologically normal myometrium were included. The mean age was 41.5 ± 6.18 years, mean BMI was 25.8 ± 2.60 kg/m^2, and the mean VAS score was 2.13 ± 0.99, indicating mild pain.

Most controls had normal menstrual cycle frequency (95%), regular cycles (95%), and normal menstrual duration (100%). The majority reported normal menstrual volume (85%), and no cases of intermenstrual bleeding were observed.

Control tissue samples were obtained from hysterectomy specimens performed for non-myometrial indications, including uterine prolapse, suspected ovarian malignancy with normal uterine findings, endometrial hyperplasia, and cervical intraepithelial neoplasia.

Association of BDNF and NGF Levels with Intermenstrual Bleeding and Menstrual Volume

Binary logistic regression showed that BDNF and NGF levels were not significantly associated with intermenstrual bleeding (both $p > 0.05$). However, adenomyosis status was independently associated with an increased risk of intermenstrual bleeding compared with normal myometrium (OR 5.70; 95% CI 1.90–17.10; $p = 0.002$). Subgroup analysis within the adenomyosis group showed no significant associations between neurotrophin levels and intermenstrual bleeding.

Similarly, ordinal logistic regression demonstrated no significant association between BDNF or NGF levels and menstrual volume (both $p > 0.05$). In contrast, adenomyosis status was significantly associated with increased menstrual volume compared with normal myometrium ($p < 0.01$).

Association of VAS Pain Scores with Menstrual Duration and Volume

Pain severity was significantly higher in patients with prolonged menstrual duration compared to those with normal duration (median 9 vs 7; $p = 0.004$). In contrast, no significant difference in VAS scores was observed between patients with normal and heavy menstrual bleeding ($p = 0.565$).

Association of Lesion Location with Pain Severity and Menstrual Duration

Lesion location (anterior vs posterior) was not significantly associated with VAS pain scores ($p = 0.427$) or menstrual duration ($p = 1.000$).

Comparison of BDNF Levels Among Adenomyotic Tissue, Adjacent Myometrium, and Normal Myometrium

Analysis of brain-derived neurotrophic factor (BDNF) levels demonstrated statistically significant differences among the three tissue groups (Kruskal–Wallis test, $p < 0.01$), as shown in Table 2. The adenomyotic tissue group (n = 40) showed the highest BDNF levels, with a mean ± standard deviation (SD) of 40.7 ± 8.16 ng/mL, median of 42.4 ng/mL, and range of 28.2–55.8 ng/

Table 2 Comparison of BDNF Levels Among Adenomyotic Tissue, Adjacent Myometrium (Myo-NA), and Normal Myometrium (Myo-N) Using the Kruskal–Wallis Test

Kruskal–Wallis Test				
	Adenomyosis (n = 40)	**Mio-Na (n = 40)**	**Mio-N (n = 40)**	**p-value**
BDNF (ng/mL)				< 0.01
Mean (SD)	40.7 (8.16)	20.8 (3.65)	16.4 (1.46)	
Median	42.4	19.9	16.9	
Range (Min–Max)	28.2–55.8	15.1–33.1	12.3–18.8	

Table 3 Comparison of NGF Levels Among Adenomyotic Tissue, Adjacent Myometrium (Myo-NA), and Normal Myometrium (Myo-N) Using the Kruskal–Wallis Test

Kruskal–Wallis Test				
	Adenomyosis (n = 40)	**Mio-Na (n = 40)**	**Mio-N (n = 40)**	**p-value**
NGF (ng/mL)				< 0.01
Mean (SD)	212.63 (117.24)	70.6 (11.59)	46.6 (14.28)	
Median	165.05	68.5	44.1	
Range (Min – Max)	101.1–540.1	50.9–96.8	21.4–75.8	

mL. The adjacent myometrium from patients with adenomyosis (n = 40) exhibited lower BDNF levels, with a mean ± SD of 20.8 ± 3.65 ng/mL, median of 19.9 ng/mL, and range of 15.1–33.1 ng/mL. The normal myometrium group (n = 40) showed the lowest BDNF levels, with a mean ± SD of 16.4 ± 1.46 ng/mL, median of 16.9 ng/mL, and range of 12.3–18.8 ng/mL.

Post-hoc pairwise comparisons using Dunn's test revealed that BDNF levels in adenomyotic tissue were significantly higher than those in adjacent myometrium ($p < 0.01$) and normal myometrium ($p < 0.01$).

Comparison of NGF Levels Among Adenomyotic Tissue, Adjacent Myometrium, and Normal Myometrium

Analysis using the Kruskal–Wallis test demonstrated statistically significant differences in nerve growth factor (NGF) levels among the three tissue groups ($p < 0.01$) (Table 3). The adenomyotic tissue group (n = 40) showed the highest NGF levels, with a mean ± standard deviation (SD) of 212.63 ± 117.24 ng/mL, median of 165.1 ng/mL, and range of 101.1–540.1 ng/mL. The adjacent myometrium from patients with adenomyosis (n = 40) exhibited lower NGF levels, with a mean ± SD of 70.6 ± 11.59 ng/mL, median of 68.5 ng/mL, and range of 50.9–96.8 ng/mL. The normal myometrium group (n = 40) demonstrated the lowest NGF levels, with a mean ± SD of 46.6 ± 14.28 ng/mL, median of 44.1 ng/mL, and range of 21.4–75.8 ng/mL.

Post-hoc pairwise comparisons using Dunn's test, with adenomyotic tissue as the reference group, revealed that NGF levels were significantly higher in adenomyotic tissue compared to adjacent myometrium ($p < 0.01$) and normal myometrium ($p < 0.01$).

Correlation Between BDNF, NGF, and Pain Severity in the Adenomyosis Group

Spearman correlation analysis was performed to evaluate the association between BDNF and NGF levels and pain severity measured by the Visual Analog Scale (VAS) in patients with adenomyosis. The results showed no statistically significant correlations between neurotrophin levels and pain severity.

BDNF levels demonstrated a very weak negative correlation with VAS scores (Spearman's rho [r_s] = −0.038; p = 0.817). Similarly, NGF levels showed a very weak negative correlation with VAS scores (r_s = −0.055; p = 0.735). These findings indicate that neither BDNF nor NGF levels were significantly associated with pain severity in patients with adenomyosis.

Neurotrophins as Predictors of Pain Severity

Binary logistic regression analysis showed that neither BDNF nor NGF levels were significantly associated with high pain severity (VAS ≥ 7) in patients with adenomyosis (both p > 0.05). Thus, neither neurotrophin acted as an independent predictor of high pain intensity.

Interaction analyses further demonstrated that the relationship between BDNF or NGF levels and VAS scores did not differ significantly between the adenomyosis and normal myometrium groups (both p > 0.05).

Discussion

Baseline Characteristics of the Study Population

Analysis of baseline characteristics revealed notable demographic and clinical differences between the adenomyosis group (n = 40) and the control group (n = 40). Patients with adenomyosis were younger, with a mean age of 33.2 ± 5.62 years, compared to 41.5 ± 6.18 years in the control group. This finding is consistent with recent advances in diagnostic techniques, which have led to increased detection of adenomyosis in younger women, particularly due to the improved sensitivity of imaging modalities such as transvaginal ultrasonography and magnetic resonance imaging (MRI).[14,15] If we look further, age-related biological changes could also represent a potential confounding factor. Hormonal variations associated with age, including changes in estrogen status and reproductive physiology, may influence neurotrophin expression and pain perception. Therefore, the potential contribution of age-related factors should be considered when interpreting the present findings. Despite this trend, adenomyosis remains closely associated with cumulative lifetime estrogen exposure. The development and progression of adenomyotic lesions are thought to be triggered by repeated myometrial injury, including trauma related to pregnancy and obstetric interventions.[16]

The relationship between obesity and adenomyosis has been proposed due to the role of adipose tissue in converting androgens into estrogen, potentially promoting the proliferation of ectopic endometrial tissue.[17] However, the mean body mass index (BMI) in the adenomyosis group (26.4 ± 2.50 kg/m^2) was comparable to that in the control group (25.8 ± 2.60 kg/m^2), suggesting that BMI was not a primary determinant of adenomyosis in this study population. This finding indicates that other etiological factors, including local hormonal dysregulation, chronic inflammation, and prior uterine injury, may play a more significant role in disease pathogenesis.[16]

Morphologically, the median lesion size in this study was 3.6 cm (range 1.50–7.70 cm), reflecting progressive lesion growth associated with chronic inflammatory processes. The presence of ectopic endometrial tissue within the myometrium induces surrounding myometrial hypertrophy and hyperplasia, contributing to lesion expansion. Increased lesion size and tissue infiltration have been associated with greater symptom severity, particularly pain and abnormal uterine bleeding.[16]

Pain represents the most prominent clinical manifestation of adenomyosis, as reflected by the significantly higher mean Visual Analog Scale (VAS) score in the adenomyosis group compared to controls (7.9 ± 1.32 vs 2.13 ± 0.99; p < 0.001). Adenomyosis-associated pain is thought to result from abnormal uterine contractility triggered by increased production of prostaglandins and inflammatory mediators released by ectopic endometrial tissue. These factors may lead to myometrial ischemia and activation of nociceptive pathways.[16] Furthermore, lesion distribution in this study was predominantly located in the posterior uterine wall (92.5%), which has important clinical implications due to its proximity to the uterosacral ligaments and pelvic nerve plexus. Involvement of these structures may contribute to increased severity of chronic pelvic pain and dyspareunia, thereby contributing to the high pain scores observed in affected patients.[18]

The severity of adenomyosis in this study was predominantly classified as severe (57.5%), indicating a substantial disease burden within the study population. Advanced disease severity is associated with more pronounced clinical

manifestations, including severe pain and abnormal uterine bleeding, and may also impair fertility through disruption of junctional zone function and alterations in myometrial architecture.[18]

Analysis of menstrual patterns showed that most patients with adenomyosis had normal menstrual cycle frequency (87.5%) and regular cycles (92.5%), similar to the control group, with no significant differences between groups. These findings support the concept that adenomyosis is primarily a localized structural disorder that does not directly disrupt systemic hormonal regulation by the hypothalamic–pituitary–ovarian axis.[19] However, significant differences were observed in menstrual bleeding characteristics. Prolonged menstrual duration was significantly more frequent in patients with adenomyosis compared to controls (40% vs 0%; $p < 0.001$), likely due to impaired myometrial contractility caused by lesion infiltration, resulting in ineffective vascular compression and impaired hemostasis.[20] This condition was further exacerbated by increased menstrual volume, which was significantly more common in patients with adenomyosis (92.5% vs 7.5%; $p < 0.001$), and is associated with increased endometrial surface area and abnormal vascularization in adenomyotic tissue.[20]

Brain-Derived Neurotrophic Factor (BDNF) in Adenomyotic Tissue, Adjacent Myometrium, and Normal Myometrium

The results of this study demonstrated statistically significant differences in BDNF levels among adenomyotic tissue, adjacent myometrium from patients with adenomyosis, and normal myometrium. The highest BDNF levels were observed in adenomyotic tissue, followed by adjacent myometrium, while the lowest levels were found in normal myometrium. This pattern suggests that increased BDNF expression is closely associated with the presence and extent of adenomyotic tissue involvement.[11,21]

Biologically, BDNF is a neurotrophin that plays a critical role in neurogenesis, neuronal plasticity, and modulation of pain signaling. In adenomyosis, invasion of endometrial tissue into the myometrium triggers a chronic inflammatory response, which may stimulate increased BDNF expression by stromal cells, immune cells, and myometrial smooth muscle cells. Activation of the BDNF–TrkB signaling pathway may promote nociceptive nerve fiber proliferation and reduce the threshold for pain activation, thereby contributing to peripheral sensitization.[11,21]

The observation of elevated BDNF levels in adjacent myometrium compared to normal myometrium suggests that molecular alterations are not confined to adenomyotic lesions but also involve surrounding myometrial tissue. This finding supports the concept of adenomyosis as a diffuse uterine disorder characterized by widespread microenvironmental changes resulting from sustained exposure to inflammatory and neurotrophic mediators.[11,21] In contrast, the lower BDNF levels observed in normal myometrium reflect physiological uterine conditions without excessive activation of inflammatory and neurogenic pathways.[22]

Overall, the increased BDNF levels in adenomyotic tissue and adjacent myometrium highlight the role of this neurotrophin in the pathophysiology of adenomyosis, particularly in relation to neuroinflammation and nociceptive sensitization. However, these findings likely reflect underlying biological alterations associated with disease processes rather than serving as direct indicators of subjective pain intensity.[11,21]

Nerve Growth Factor (NGF) in Adenomyotic Tissue, Adjacent Myometrium, and Normal Myometrium

NGF is a neurotrophin that plays a critical role in the growth, maintenance, and sensitization of peripheral nerve fibers, particularly nociceptive fibers. In addition to its function in the nervous system, NGF is also involved in regulating inflammatory responses and angiogenesis, contributing to the pathogenesis of various chronic inflammatory conditions, including adenomyosis.[21,23]

In this study, NGF levels differed significantly among adenomyotic tissue, adjacent myometrium from patients with adenomyosis, and normal myometrium, with the highest levels observed in adenomyotic tissue. These findings indicate that adenomyotic lesions represent biologically active environments characterized by increased inflammatory and neurotrophic activity. The invasion of endometrial tissue into the myometrium, accompanied by repeated

microhemorrhage and chronic inflammation, is thought to stimulate NGF production by endometrial stromal cells, immune cells, and myometrial smooth muscle cells.[21,23]

From a pathophysiological perspective, increased NGF expression may promote the growth and maintenance of nociceptive nerve fibers through activation of its high-affinity receptor, TrkA. This signaling pathway contributes to increased nerve fiber density and enhanced neuronal sensitivity within uterine tissue, thereby lowering the pain threshold and facilitating nociceptive sensitization. In addition, NGF plays an important role in promoting angiogenesis and increasing vascular permeability, which may contribute to key clinical manifestations of adenomyosis, particularly abnormal uterine bleeding.[21,23]

The higher NGF levels observed in adjacent myometrium compared to normal myometrium suggest that the biological effects of adenomyosis extend beyond visible lesions and involve the surrounding myometrial tissue. This finding reflects widespread inflammatory activity and tissue remodeling within the uterus, even in areas that appear structurally normal. These changes further support the concept of adenomyosis as a diffuse uterine disorder that affects the uterine microenvironment at a broader level.[21,23]

Overall, the elevated NGF levels observed in adenomyotic tissue and adjacent myometrium support the role of NGF as an important mediator in the pathophysiology of adenomyosis. Increased NGF expression reflects activation of neuroinflammatory pathways and vascular remodeling within the uterine tissue, which may contribute to the characteristic clinical manifestations of adenomyosis, including pain and abnormal uterine bleeding.[21,23]

Correlation Between BDNF, NGF, and Pain Severity in Adenomyosis

In this study, correlation analysis demonstrated that BDNF and NGF levels were not significantly associated with pain intensity measured using the Visual Analog Scale (VAS) in patients with adenomyosis. The observed correlations were weak and not statistically significant, indicating that variations in neurotrophin levels did not directly reflect differences in subjective pain severity. These findings suggest that BDNF and NGF levels are not primary determinants of pain intensity in adenomyosis.

In addition to within-group analysis, comparison of the relationship between neurotrophin levels and pain severity between the adenomyosis and normal myometrium groups also showed no significant differences. Although patients with adenomyosis experienced substantially higher pain levels compared to controls, the relationship between neurotrophin levels and pain intensity did not differ between groups. This finding suggests that increased pain severity in adenomyosis is not accompanied by a differential association between neurotrophin levels and subjective pain perception.

From a biological perspective, BDNF and NGF play important roles in pain modulation through regulation of nerve fiber growth, peripheral nociceptor sensitization, and neuronal plasticity. However, the absence of a significant correlation in this study suggests that circulating neurotrophin levels may reflect underlying chronic biological processes or tissue activity rather than dynamic changes in subjective pain perception. Pain in adenomyosis is a multifactorial phenomenon involving complex interactions among abnormal myometrial contractility, increased production of prostaglandins and inflammatory mediators, structural alterations in the junctional zone, and both peripheral and central sensitization mechanisms.[24]

The lack of a significant association between neurotrophin levels and pain severity may also be explained by central sensitization mechanisms. Central sensitization refers to a state of persistent hyperexcitability within the central nervous system, in which repeated nociceptive input amplifies pain processing and alters pain perception. In chronic pain conditions, these neural adaptations may result in pain experiences that are not directly proportional to local tissue pathology or peripheral biomarker levels. Therefore, although BDNF and NGF may contribute to local neurogenic and inflammatory processes in adenomyosis, subjective pain severity may also be influenced by central nervous system mechanisms beyond tissue-level neurotrophin expression.[24]

Furthermore, circulating levels of BDNF and NGF are influenced by various systemic factors, including psychological stress, physical activity, circadian rhythms, and inflammatory conditions outside the reproductive system.[24] These factors may obscure direct associations between neurotrophin levels and localized pain originating from adenomyotic lesions. In addition, pain assessment using the VAS is inherently subjective and influenced by individual and

psychosocial factors, which may further contribute to the lack of concordance between biological biomarkers and perceived pain intensity.[25]

Overall, these findings indicate that although BDNF and NGF are involved in neurogenic mechanisms of pain, circulating levels of these neurotrophins are not directly associated with pain severity in adenomyosis. This highlights the importance of a multidimensional approach to understanding adenomyosis-related pain, incorporating structural alterations, local inflammatory processes, neural mechanisms, and clinical and psychosocial factors.[24] Further studies evaluating local neurotrophin expression within adenomyotic lesions and their relationship with lesion characteristics and inflammatory mediators may provide additional insight into the biological mechanisms underlying pain in adenomyosis.

This study has several strengths. First, neurotrophin levels were directly measured in tissue samples rather than serum, providing more accurate representation of local biological activity. Second, inclusion of both adjacent myometrium and normal myometrium allowed comprehensive evaluation of neurotrophin distribution across different tissue environments. Meanwhile, this study has several limitations. The cross-sectional design limits causal inference, and pain assessment relied on subjective measures. Menstrual cycle phase at tissue collection was not systematically recorded, while neurotrophin receptor expression (TrkA/TrkB) and other inflammatory mediators were not evaluated. In addition, the control group included patients with non-adenomyosis conditions, which may introduce baseline differences and affect interpretation of the findings.

Conclusion

Significant differences in BDNF and NGF levels were observed among adenomyotic tissue, adjacent myometrium, and normal myometrium, with the highest levels found in adenomyotic lesions. These findings indicate increased neurotrophic activity associated with adenomyosis.

However, neither BDNF nor NGF levels were significantly correlated with pain severity measured by the Visual Analog Scale (VAS), nor did they independently predict high pain intensity. The relationship between neurotrophin levels and pain did not differ between adenomyosis and normal myometrium groups.

Overall, although BDNF and NGF are involved in the biological processes of adenomyosis, their levels do not directly reflect subjective pain severity, underscoring the multifactorial nature of adenomyosis-associated pain. These findings suggest that assessment and management of adenomyosis-related pain may require consideration of multiple biological and clinical factors beyond neurotrophin expression.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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