Correlation between Elevated Nerve Growth Factor mRNA Expression with Pain Intensity or Disease Severity in Endometriosis

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Abstract
Objective: To analyze the relationship between NGF mRNA expression in both blood plasma and endometriotic lesion tissue with pain intensity and disease severity in women with endometriosis.
Methods: This descriptive case series involved 30 patients undergoing surgery for endometriosis at a tertiary referral center from November 2024 to April 2025. NGF mRNA expression levels were quantified via qRT-PCR in blood plasma and lesion tissue. Pain intensity was retrospectively assessed using the Visual Analog Scale (VAS), and disease severity was staged intraoperatively using the revised ASRM classification. Statistical correlations were analyzed using Spearman's test and Mann–Whitney U test.
Results: NGF mRNA expression was significantly higher in endometriotic lesion tissue (17.319-fold) compared to blood plasma (6.943-fold) ($p < 0.0001$). However, no significant correlation was observed between NGF mRNA expression and pain intensity (plasma: $p = 0.692$; tissue: $p = 0.845$) or disease severity (plasma: $p = 0.982$; tissue: $p = 0.510$). Pain severity was also not significantly associated with disease stage ($p = 1.000$).
Conclusion: Although NGF mRNA expression was significantly elevated in endometriotic lesions compared to plasma, it was not associated with pain intensity or disease severity. These findings suggest that while NGF is upregulated in endometriosis, its expression alone may not predict clinical manifestations, indicating the need for multifactorial diagnostic approaches.

Keywords: Biomarker; Endometriosis, mRNA, NGF, Pain, Severity

Korelasi antara Ekspresi mRNA Nerve Growth Factor (NGF) yang Meningkat dan Intensitas Nyeri atau Derajat Keparahan Endometriosis

Abstrak
Tujuan: Penelitian ini bertujuan menganalisis hubungan antara ekspresi mRNA NGF pada plasma darah dan jaringan lesi endometriosis dengan intensitas nyeri dan derajat keparahan penyakit pada pasien endometriosis.
Metode: Penelitian deskriptif ini menggunakan desain serial kasus dan melibatkan 30 pasien yang menjalani pembedahan endometriosis di rumah sakit rujukan tersier dari November 2024 hingga April 2025. Ekspresi mRNA NGF diukur dengan teknik qRT-PCR pada sampel plasma darah dan jaringan lesi. Intensitas nyeri dinilai secara retrospektif menggunakan Visual Analog Scale (VAS), sementara stadium penyakit ditentukan secara intraoperatif berdasarkan klasifikasi revised ASRM. Analisis statistik dilakukan menggunakan uji Spearman dan uji Mann–Whitney U.
Hasil: Hasil penelitian menunjukkan bahwa ekspresi mRNA NGF secara signifikan lebih tinggi pada jaringan lesi endometriosis (17,319 kali lipat) dibandingkan plasma darah (6,943 kali lipat) ($p < 0,0001$). Namun demikian, tidak ditemukan korelasi bermakna antara ekspresi mRNA NGF dengan intensitas nyeri (plasma: $p = 0,692$; jaringan: $p = 0,845$) maupun dengan derajat keparahan penyakit (plasma: $p = 0,982$; jaringan: $p = 0,510$). Selain itu, intensitas nyeri tidak berhubungan secara signifikan dengan stadium penyakit ($p = 1,000$).
Kesimpulan: Simpulan penelitian ini adalah bahwa meskipun ekspresi mRNA NGF meningkat secara signifikan pada jaringan lesi dibandingkan plasma, peningkatan ini tidak berkorelasi dengan intensitas nyeri atau derajat keparahan endometriosis. Temuan ini menunjukkan bahwa meskipun NGF mengalami regulasi naik pada endometriosis, ekspresinya saja tidak cukup untuk memprediksi manifestasi klinis, sehingga dibutuhkan pendekatan diagnostik multifaktorial.

Kata Kunci: Biomarker; Endometriosis; Ekspresi mRNA; NGF; Nyeri; Tingkat Keparahan

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Introduction

Endometriosis is a chronic gynecological disease characterized by the growth of tissue resembling endometrial glands and stroma outside the uterine cavity.[1,2] The prevalence of endometriosis is estimated to affect approximately 5–10% of women of reproductive or premenopausal age worldwide. A study conducted at Dr. Mohammad Hoesin Central General Hospital reported an incidence rate of endometriosis at 10.3%.[3]

Menstrual pain and infertility are the most common complaints among endometriosis patients.[4] An epidemiological study conducted in Cyprus from January 2018 to February 2020, which assessed pain related to endometriosis, found that 52.9% of patients experienced pain, with 90.8% reporting dysmenorrhea, 11.5% dyspareunia, and 24.4% experiencing non-cyclical pelvic pain. Data from the Dr. Cipto Mangukusumo National Referral Hospital (RSCM) indicate that 82.5% of endometriosis patients reported pelvic pain, 81% dysmenorrhea, and 33.7% infertility.[5] Chronic pelvic pain is not directly correlated with lesion size or disease severity.[6] In some cases, pain persists even after the surgical removal of endometrial lesions, with chronic pain recurring within 12 months.[7] One study highlighted the increased need for care among endometriosis patients and women with chronic pelvic pain due to late diagnosis and decreased quality of life, resulting in a higher economic burden due to suboptimal pain management.[6]

Various theories have explained the mechanisms of pain in endometriosis, with two widely accepted causes: inflammatory cytokine activity in the peritoneum and irritation or infiltration of nerves near endometriotic lesions. Endometriotic lesions secrete proinflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α, which activate macrophages and T cells in the peritoneum, facilitating an inflammatory response. Immune cells such as mast cells and macrophages, growth factors, NGF, and proinflammatory cytokines contribute to persistent pain.[7] Immune system dysfunction leads to the failure of clearing ectopic endometrial tissue, triggering chronic inflammatory responses. However, increased expression of the anti-inflammatory cytokine IL-10 suggests a compensatory mechanism to local inflammation in endometriotic lesions. Systemically, elevated mRNA levels of IL-10 and TGF-β without corresponding increases in IL-2 indicate that immune regulation is more active at the local tissue level than systemically.[7]

In addition to cytokines, NGF is a key modulator of pain in endometriosis, acting as a pro-inflammatory neuroactive agent that sensitizes sensory nerve terminals.[8] Increased NGF mRNA expression in endometriotic lesions has been demonstrated in several studies on endometriosis-associated pain.[9] Genetic-based pain response studies have identified key genes expressed by nerve fibers involved in nociceptor detection. Levels of mRNA for pain-related neurotrophic factors such as NGF, GDNF, IL-6, and their receptors are increased in neuropathic conditions.[10] One study stated that IL-1β directly stimulates NGF expression in endometriosis and is associated with local neurogenesis near lesions and severe dyspareunia.[11]

A study on the expression levels of neurotrophic factors—BDNF and NGF—in serum and endometriotic lesions revealed higher BDNF expression in endometriotic tissue and increased BDNF levels in the serum of endometriosis patients. Similar findings were observed for NGF, although data were much more limited.[12]

Based on this background, the researcher is interested in further analyzing the relationship between NGF mRNA expression in blood as a non-invasive biomarker in endometriosis patients, in relation to pain and

disease severity at Dr. Mohammad Hoesin General Hospital, Palembang.

Methods

This descriptive case series was conducted at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, from November 2024 to April 2025. The study aimed to evaluate the association between Nerve Growth Factor (NGF) mRNA expression in plasma and endometriotic lesion tissue with pain intensity and disease severity in patients diagnosed with endometriosis.

Eligible participants were women of reproductive age (18–45 years) undergoing laparoscopic or open surgery with intraoperative findings of endometriosis, confirmed by histopathological examination. Inclusion criteria comprised patients who had not received hormonal therapy within the preceding three months, were not pregnant, and were free of systemic inflammatory or autoimmune diseases. Exclusion criteria included women with endometrial cancer, ovarian cancer, endometritis, endometrial hyperplasia, other malignancies, hydatidiform mole, pregnancy, current hormonal therapy, and those with osteoarthritis. A total of 30 patients met the inclusion criteria and were enrolled in the study through consecutive sampling. Written informed consent was obtained from all participants prior to enrollment. Prior to surgery, 3–5 mL of venous blood was collected from each participant and processed to isolate plasma. During surgery, endometriotic lesion tissue was excised and immediately preserved in RNA later solution for molecular analysis. Pain intensity was assessed retrospectively based on patient records using the Visual Analog Scale (VAS), while disease severity was staged intraoperatively using the revised American Society for Reproductive Medicine (r-ASRM) classification.

Total RNA was extracted from both plasma and tissue samples using a validated commercial RNA extraction kit. Complementary DNA (cDNA) was synthesized, and NGF mRNA expression was quantified using quantitative real-time polymerase chain reaction (qRT-PCR) with SYBR Green. Specific primers for NGF and the reference gene β-actin were employed. Relative gene expression was calculated using the ΔΔCt method and expressed as fold change.

All statistical analyses were performed using SPSS version 26.0. Data normality was assessed using the Kolmogorov–Smirnov test. As the data were not normally distributed, results were presented as median and interquartile range (IQR). Comparisons between groups were analyzed using the Mann–Whitney U test, and correlations were assessed using Spearman's rank correlation coefficient. A p-value of <0.05 was considered statistically significant.

This study received ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya / Dr. Mohammad Hoesin General Hospital, Palembang (DP.04.03/D. XVIII.06.08/ETIK/241/2024).

Results

A total of 30 patients diagnosed with endometriosis were included in this study with a mean age of 33.57 years, ranging from 21 - 45 years. Most patients were in the 20–35-year age range (60%), followed by 36–45 years (40%). The majority had a normal body mass index (56.7%). The most common type of endometriosis was endometrioma combined with deep infiltrating endometriosis (DIE), found in 46.7% of patients. Severe pain (VAS > 6) was reported by 63.3%, and 90% were classified as having severe endometriosis (rASRM stage III–IV). The demographic and clinical characteristics are summarized in Table 1.

NGF mRNA expression was successfully quantified in both plasma and endometriotic lesion tissue. As illustrated in Figure 1, the expression of NGF mRNA was significantly higher in lesion tissue (median fold change: 17.319; IQR: 11.283–21.507) compared to plasma samples (median fold change: 6.943; IQR: 3.707–11.579), with a statistically significant difference ($p < 0.0001$) based on Fisher's Exact Test.

In order to assess whether NGF expression correlated with pain intensity, Spearman's rank correlation test was applied. No significant correlation was found between NGF mRNA expression and Visual Analog Scale (VAS) pain scores, both in plasma ($r = 0.085$, $p = 0.692$) and tissue ($r = –0.037$, $p = 0.845$), as shown in Figure 2. Similarly, comparison of NGF expression based on disease severity also revealed no significant differences between early-stage (I–II) and advanced-stage (III–IV) endometriosis, in either plasma ($p = 0.982$) or tissue ($p = 0.510$), as shown in Figure 3.

Discussion

The subjects of this study consisted of 30 women of reproductive age diagnosed with endometriosis through laparoscopy

Table 1 Characteristics of Endometriosis Patients

Characteristics	n	%	$\bar{x} \pm sd$ (min-max)
Age			33,57 ±7,20 (21-45)
20-35	18	60,0	
36-45	12	40,0	
Body mass index			
Underweight	1	3,3	
Normoweight	17	56,7	-
Overweight	4	13,3	
Obese	8	26,7	
Parity			
Unmarried	3	10.0	
Primary infertility	16	53.33	
One	6	20.0	
Two	5	16.67	
Endometriosis type			
Endometrioma	10	33,3	
DIE	5	16,7	
Endometrioma + DIE	14	46,7	-
Endometrioma+DIE + Superficial Endometriosis	1	3,3	
Level of pain			6,47±1,52 (4-8)
Mild-Moderate (≤5)	11	36,7	
Severe (>6)	19	63,3	
Level of severity			
Mild (I, II)	3	10,0	-
Severe (III, IV)	27	90,0	

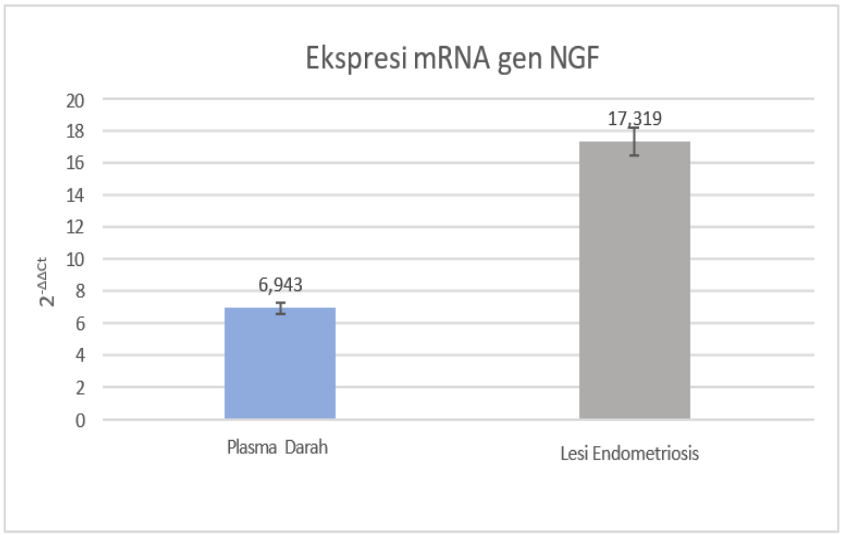

Figure 1 Comparison of NGF mRNA Expression in Plasma and Endometriotic Lesion Tissue.

Bar graph illustrating the fold change of Nerve Growth Factor (NGF) mRNA expression measured by qRT-PCR in plasma and lesion tissue of patients with endometriosis (N = 30). NGF mRNA expression was significantly higher in lesion tissue compared to plasma ($p < 0.0001$).

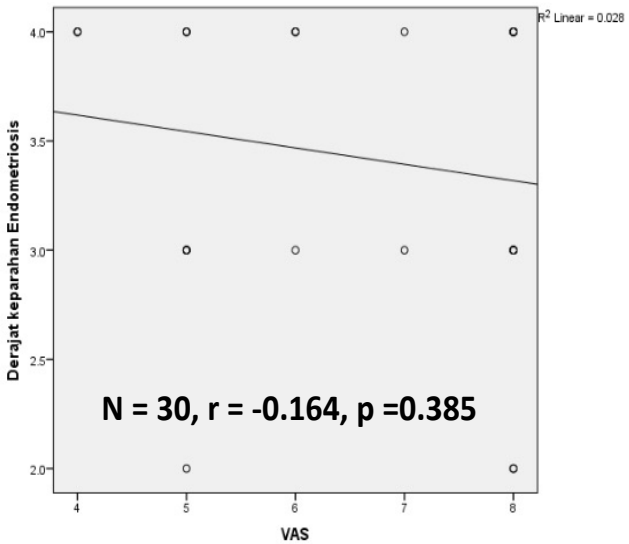

Figure 2 Correlation Between Pain Intensity and Endometriosis Severity

Scatter plot displaying the correlation between VAS pain score and r-ASRM disease stage in patients with endometriosis (N = 30). No significant correlation was observed ($r = –0.164$, $p = 0.385$), suggesting that pain intensity does not correspond with lesion severity.

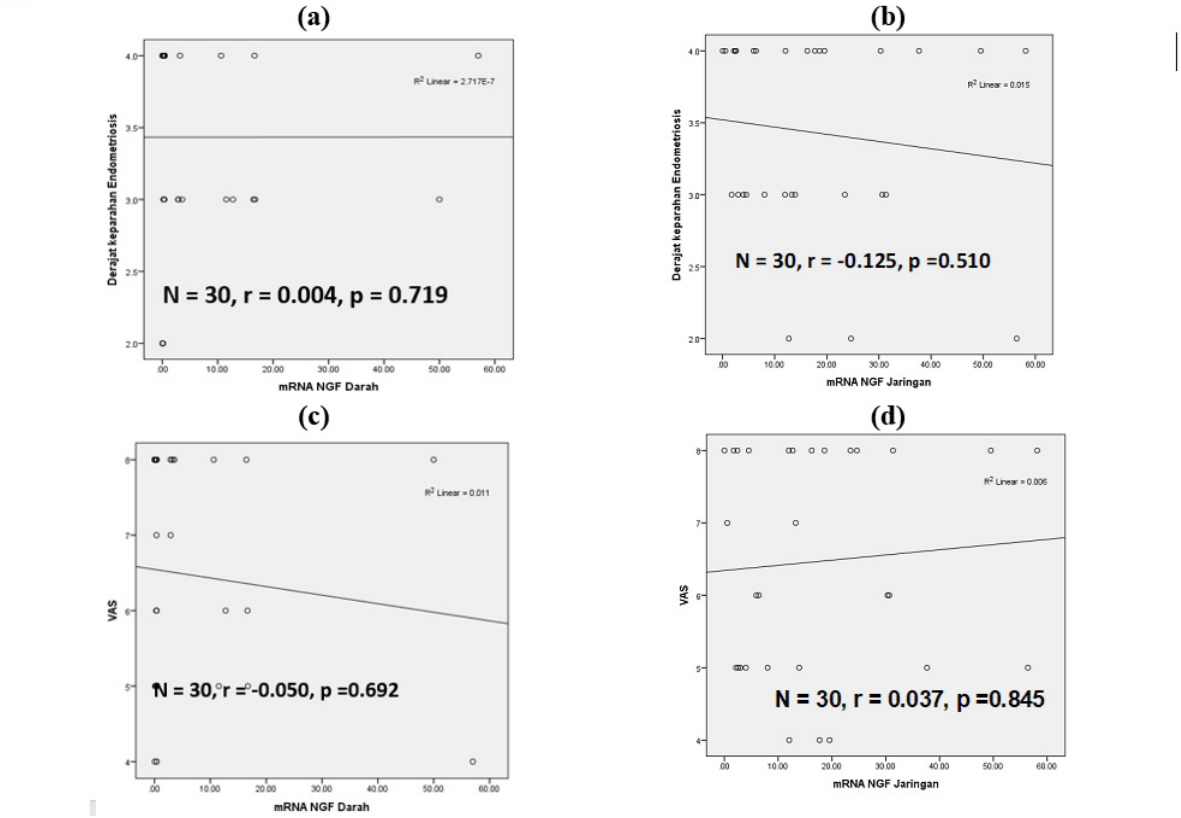

Figure 3. Correlation Between NGF mRNA Expression and Disease Severity or Pain Intensity.

Scatter plots showing the correlation between NGF mRNA expression and clinical parameters in patients with endometriosis (N = 30). (a) NGF mRNA expression in plasma versus endometriosis severity (r = 0.004, p = 0.719); (b) NGF mRNA expression in lesion tissue versus endometriosis severity (r = –0.125, p = 0.510); (c) NGF mRNA expression in plasma versus VAS pain score (r = –0.050, p = 0.692); (d) NGF mRNA expression in lesion tissue versus VAS pain score (r = 0.037, p = 0.845). No statistically significant correlations were found.

or laparotomy. Characteristics observed included age, Body Mass Index (BMI), parity, pain level, and disease severity. Sample collection was conducted based on inclusion and exclusion criteria to minimize confounding factors. Most subjects (60%) were aged between 20–35 years, with a mean age of 33 years. This age range aligns with the peak prevalence of endometriosis, typically between 25 and 35 years. Several population studies report an endometriosis prevalence of around 10–15% among women of reproductive age.[13-15] More than half of the subjects (56.7%) had a normal BMI. The proportions of overweight and obese subjects were relatively small. This finding supports previous studies indicating that endometriosis is less common among obese women, although the association between BMI and endometriosis remains inconsistent.[16,17] A relatively high rate of infertility (53.3%) was found in this study, consistent with literature describing endometriosis as a risk factor for infertility. Endometriosis-related infertility is multifactorial, involving immunological, genetic, and structural disruptions such as tubal damage, embryo transport disturbances, and endometrial dysfunction.[14,15] Endometrioma and Deep Infiltrating Endometriosis (DIE) were the most common types, found in

46.7% of cases. This contrasts with some studies where peritoneal endometriosis is more common. Differences may be due to study population, diagnostic methods, or classification criteria.[15,16]

The most frequently reported symptoms were chronic pelvic pain, dysmenorrhea, dyspareunia, and painful defecation-common manifestations of endometriosis and reasons for seeking medical help.[17] Pain in endometriosis arises from inflammation at lesion sites and in the peritoneal cavity, leading to sensory nerve transduction influenced by inflammatory mediators like NGF.[23,24] NGF is a key neurotrophin involved in pain perception, acting as a pronociceptive mediator. Tissue damage can cause the nociceptive system to shift from a protective function to aiding tissue repair.

This study found no significant correlation between pain intensity and endometriosis severity, suggesting that pain severity does not always correlate with lesion extent. Some patients with mild disease experience severe pain, while others with severe disease report few or no symptoms. This aligns with Yong et al., who concluded that disease stage and pain intensity are not always correlated in endometriosis.[16] Other studies suggest that pain is more influenced by neuroproliferation and lesion location than stage. Deep lesions (>5 mm invasion) are associated with severe dysmenorrhea, while dyspareunia is often due to uterosacral ligament or sacrovaginal septum involvement. DIE and bowel wall lesions are highly innervated, leading to more severe pain.[16,17] An epidemiological study in Cyprus (2018–2020) showed 52.9% of endometriosis patients experienced pain, including dysmenorrhea (90.8%), dyspareunia (11.5%), and non-cyclic pelvic pain (24.4%). Canadian data also showed higher pain prevalence among endometriosis patients compared to the general population. Three main pain mechanisms in endometriosis include peritoneal cytokine activity, local lesion bleeding, and nerve irritation. Other factors like hormones, peripheral nerves, and the central nervous system also contribute. Jones et al. noted a genetic role in dysmenorrhea, with NGF as a key pain mediator.[17]

This study found no significant correlation between NGF gene mRNA expression in either blood plasma or endometriotic lesion tissue and the severity of endometriosis. This was evidenced by p-values of 0.982 ($r = 0.004$) for plasma and 0.510 ($r = –0.125$) for lesion tissue. Although previous studies have demonstrated increased NGF expression in endometriotic lesions, its expression is influenced by various factors. Moreover, endometriosis severity is not determined solely by NGF levels, suggesting that NGF expression may not directly correlate with disease stage. A study by Björk et al. revealed increased mRNA expression of IL-10 and IL-2, particularly in endometriotic lesions, associated with regulatory T cell (Treg) activation and reduced cytotoxic function of NK and T cells. Additionally, the expression of pro-inflammatory cytokines such as IL-6, IL-8, IL-1β, and TNF-α was elevated, supporting the notion that endometriosis is an inflammatory disease.[18] Kajitani et al. reported that NGF mRNA expression was higher in ovarian endometriomas and peritoneal endometriosis compared to intrauterine endometrium without endometriosis. NGF expression was more dominant in peritoneal lesions, possibly via the PGE2-cAMP signaling pathway, which is involved in lesion growth and inflammation.[19] Apart from the pronociceptive environment caused by endometriotic lesions, degraded tissue products like ROS, PGE2, and acidic conditions increase the sensitivity of sensory nerve fibers. This is exacerbated by neurogenic inflammation, where nerve excitation triggers the release of pro-inflammatory neuropeptides such as SP and CGRP, often found near lesions in patients

with pain. Nerve activation recruits mast cells and induces the release of inflammatory cytokines like TNF-α, NGF, PGE2, and IL-1β, perpetuating chronic inflammation.[20] Giudice explained that adhesions and pelvic scarring in endometriosis result from cytokines and prostaglandins released into the peritoneal fluid. Microenvironmental variability (e.g., inflammation and hypoxia) in endometriotic tissues may affect NGF expression without necessarily reflecting disease severity. Other factors such as angiogenesis, fibrosis, and local immune responses may also influence the progression of endometriosis, meaning NGF levels in the blood may not serve as a specific marker for disease severity.[20]

Gene expression is the process by which genetic information is used to synthesize proteins, and it varies depending on tissue type. In this study, NGF gene mRNA expression was measured using qRT-PCR, a sensitive and specific method for assessing gene expression. This technique uses RNA as a template, which is then converted into cDNA before amplification by PCR, with relative expression analyzed using the Livak method.[21] This study found no significant correlation between NGF mRNA expression in either blood plasma or endometriotic lesion tissue and the pain intensity reported by patients. These findings are consistent with the study by Barcena de Arellano et al., which found moderate NGF expression in the peritoneal fluid of endometriosis patients, without significant differences between pain groups. Coelho et al. also reported that NGF and BDNF expression did not correlate with pain, while Liu D et al. found that only BDNF showed high expression in both endometriotic lesions and serum—not NGF.[21] However, there was a trend observed in this study suggesting that higher NGF mRNA expression in endometriotic lesion tissue may be associated with higher pain levels. This is supported by Peng et al., who demonstrated that IL-1β stimulates NGF expression, promoting local neurogenesis and contributing to dyspareunia. The NGF–TrkA signaling pathway plays a more dominant role in mediating endometriosis-related pain compared to BDNF–TrkB or VEGF–VEGFR1 pathways.[21,22]

Other studies have produced conflicting results. Tokushige et al. observed increased NGF expression around endometriotic lesions, linking it to pain due to inflammation-induced growth of nociceptors in the pelvic cavity. Gori et al. also demonstrated that NGF expression is higher in ovarian endometriosis and DIE compared to eutopic endometrium. McMahon highlighted that C-fiber nociceptors express the TrkA receptor, which responds to NGF, while Kobayashi et al. reported that even though nerve cells are absent in endometriotic lesions, NGF and BDNF can enhance nerve formation and are associated with pain.[23] NGF is known to promote sensory neuron growth and is linked to persistent inflammatory hyperalgesia. Increased NGF and TrkA expression have been observed in endometriosis patients, with NGF immunoreactivity in the stroma correlating with local nerve fiber density and severity of dyspareunia.

Pain is a key symptom of endometriosis, but its mechanisms remain poorly understood. Pain manifestation varies significantly between patients—some experience severe pain, others none at all. Pain depends on lesion type and location, with different mechanisms for peritoneal endometriosis and DIE. Pain assessment using the Visual Analogue Scale (VAS) has limitations due to its subjective nature. In this study, data were collected when patients were stable and hospitalized preoperatively, which may have affected results. Additionally, patients with endometriosis may experience altered pain thresholds due to nociceptor sensitization, leading to chronic hypersensitivity even after inflammation resolves. This could explain why some patients with severe endometriosis

report high pain tolerance, complicating the identification of a clear relationship between NGF expression and pain intensity.[24]

The average NGF mRNA expression was found to be elevated in both blood plasma and endometriotic lesion tissue, based on the Livak formula and normalized using two non-endometriosis patients as controls. Expression was 6.943-fold higher in plasma and 17.319-fold higher in lesion tissue. This may be due to the increased number of macrophages and inflammatory products—such as NGF—in endometriotic lesions, which contribute not only to the associated pain and infertility but also to the progression of the lesions themselves.[1]

This study confirmed a significant difference in NGF mRNA expression levels between blood plasma and lesion tissue. These results are consistent with Orellana et al., who reported significantly higher NGF gene expression in invasive compared to non-invasive endometriotic lesions.[23] NGF and its receptor TrkA showed sharply increased immunoreactivity in the epithelial and stromal components of endometriotic lesions in women with deep infiltrating endometriosis (DIE). The intensity of NGF immunoreactivity in the stroma was also significantly associated with the density of local nerve fiber bundles and the severity of deep dyspareunia.[25]

This study offers several strengths. It is one of the few to evaluate and compare NGF mRNA expression in both plasma and lesion tissue in women with endometriosis, providing insight into systemic versus localized molecular activity. The use of quantitative real-time PCR (qRT-PCR) ensures high sensitivity and specificity in gene expression analysis. Moreover, clinical parameters such as pain intensity and disease severity were objectively measured using validated tools, including the VAS and revised ASRM classification. However, this study also has limitations. The small sample size (N = 30) may limit the statistical power to detect subtle associations. Its cross-sectional design prevents assessment of temporal or causal relationships. Additionally, pain assessment was retrospective and based on chart review, which may introduce reporting bias. Finally, as a single-center study, the findings may not be generalizable to broader populations, and confounding variables such as hormonal status, lesion phenotype, and nerve fiber density were not evaluated.

Conclusion

NGF mRNA expression was significantly higher in endometriotic lesion tissue than in plasma, but it showed no correlation with pain intensity or disease severity. This suggests that NGF alone may not be a reliable clinical marker in endometriosis.

Recommendations

Future research should involve larger, multicenter cohorts to validate these findings and increase generalizability. Longitudinal studies are recommended to explore dynamic changes in NGF expression over time and in response to therapy. In addition, combination with other molecular mediators—such as proinflammatory cytokines, neuropeptides, and hormonal modulators—may provide a more comprehensive understanding of pain mechanisms and disease progression in endometriosis. Combining molecular profiling with imaging and clinical data may enhance the development of personalized diagnostic and therapeutic approaches.

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