Metformin's therapeutic potential in adenomyosis: insights from interleukin 8 level

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ABSTRACT

Adenomyosis is a gynecological disorder characterized by the invasion of endometrial tissue into the myometrium, leading to chronic inflammation and pelvic pain. Interleukin 8 (IL-8) plays a key role in inflammation and pain sensitization in adenomyosis. Metformin, an antidiabetic agent, exerts anti-inflammatory effects by activating adenosine monophosphate-activated protein kinase, inhibiting IL-8 production, and reducing inflammatory cell infiltration. This cohort-prospective study evaluates the effects of metformin on IL-8 levels and pain in adenomyosis patients. This cohort-prospective study in Makassar, Indonesia, included 40 women diagnosed with adenomyosis *via* physical examination and ultrasound examination in a polyclinic at Hasanuddin University Teaching Hospital. Participants were divided into two groups: 20 received metformin 500 mg and ibuprofen 400 mg every 8 hours for 30 days, while 20 only received ibuprofen. All statistical analyses were conducted using the Statistical Program for Social Sciences (IBM, Chicago, IL, USA). IL-8 levels increased in both groups (p=0.45). Visual Analog Scale (VAS) significantly decreased in the metformin group (p<0.001) but was not significant in the control group (p=0.06). Comparison of changes in IL-8 (p=0.13) and VAS (p=0.09) levels between the metformin and control groups was not statistically significant. This study suggests that the anti-diabetic drug metformin can also be used as an anti-inflammatory drug in adenomyosis patients as an adjunctive therapy. Further clinical trials need to be done on metformin drugs.

Introduction

Adenomyosis is a gynecological disorder characterized by the invasion of endometrial tissue into the myometrium, leading to chronic inflammation and significant pelvic pain.[1,2] Major risk factors for adenomyosis include age, multiparity, and a history of uterine surgery, all of which contribute to hormonal dysfunction and inflammation.[3,4] Pain in adenomyosis is driven by excessive prostaglandin production, activation of inflammatory pathways, and increased expression of cytokines such as interleukin 8 (IL-8), which trigger leukocyte infiltration and neuroinflammation.[5] Additionally, insulin resistance, frequently observed in adenomyosis, exacerbates inflammation by increasing oxidative stress and disrupting glucose metabolism.[6,7]

Pain in adenomyosis is closely linked to systemic inflammation, where IL-8 serves as a key mediator in recruiting inflammatory cells to the myometrial tissue.[8,9] Studies have shown that IL-8 not only plays a role in local inflammation but also contributes to hyperalgesia by activating chemokine receptors.[3,10] In chronic inflammatory conditions like adenomyosis, elevated IL-8 levels contribute to persistent pain sensitivity and influence the response to analgesic therapy.[11,12] Therefore, targeting IL-8 as part of a therapeutic strategy presents a promising approach to reducing pain and inflammation in adenomyosis patients.[9,13]

Metformin, an antidiabetic agent, has been shown to exert anti-inflammatory effects by activating the adenosine monophosphate-activated protein kinase (AMPK) pathway, thereby inhibiting IL-8 production and reducing inflammatory cell infiltration.[14,15] Additionally, metformin has been found to reduce neuropathic and inflammatory pain by suppressing nuclear factor-κ B (NF-κB) pathways and modulating the expression of proinflammatory cytokines.[16,17] Previous studies have indicated that metformin not only decreases IL-8 levels but also improves insulin sensitivity, which plays a role in the inflammatory mechanisms of adenomyosis.[18,19]

This study aims to evaluate the effects of metformin on IL-8 levels and pain in adenomyosis patients in a cohort-prospective study. This research contributes to the understanding of how metformin alleviates adenomyosis-related pain by inhibiting IL-8 and regulating inflammation. The novelty of this study lies in the specific analysis of IL-8 as a therapeutic target in adenomyosis, which has not been extensively explored in previous research. Therefore, this study is expected to provide new insights into non-hormonal therapeutic strategies for adenomyosis.

Materials and Methods

This cohort-prospective study was performed in Makassar, South Sulawesi, Indonesia. The inclusion criterion requires that participants be women diagnosed with adenomyosis through ultrasound examination. Meanwhile, the exclusion criteria consist of several conditions that could confound the study results. Women who are pregnant are excluded to prevent any pregnancy-related physiological changes from affecting the study outcomes. Additionally, individuals with diabetes mellitus are excluded, as metabolic disturbances associated with the disease could influence inflammatory markers and pain perception. A total of 40 women diagnosed with adenomyosis at the Hasanuddin University Teaching Hospital, Makassar, Indonesia, were included in this study. Participants were divided into two groups: 20 women received metformin 500 mg and ibuprofen 400 mg per 8 hours for 30 days, while 20 women in the control group received only ibuprofen 400 mg per 8 hours for 30 days. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (No: 838/UN4.6.4.5.31/PP36/202).

Statistical analysis

Data analysis was conducted using descriptive statistics. Age, body mass index (BMI), parity, and age at menarche were analyzed descriptively and presented as percentages. IL-8 levels and Visual Analog Scale (VAS) scores in the metformin and control groups were analyzed using a paired *t*-test for normally distributed data and the Wilcoxon test for non-normally distributed data. The differences in IL-8 levels and VAS scores between groups were compared using an unpaired t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. All statistical analyses were conducted using the Statistical Program for Social Sciences (IBM, Chicago, IL, USA), with a significance level set at $p<0.05$.

Results

This study included 40 women diagnosed with adenomyosis. The collected women were divided into two groups: 20 women were treated with metformin 500 mg/8 hours and ibuprofen 400 mg/8 hours for 30 days, and 20 women were only given ibuprofen 400 mg/8 hours for 30 days as control. The majority of subjects in the metformin group were over 35 years old (90.00%). Most subjects in both groups had a BMI≤23.9 kg/m^2, with a proportion of 90.00% in the metformin group and 80.00% in the control group. In terms of parity, the metformin group had more nulliparous subjects (40.00%) than the control group (25.00%). The majority of subjects in the metformin (60.00%) and control (70.00%) groups experienced menarche before the age of 12 years. A comparison of the characteristics of the study subjects in both groups is presented in Table 1.

Table 1. Clinical demography of subjects.

Variable	Metformin n=20, %	Control n=20, %
Age (years)		
>35	18 (90.00)	20 (100.00)
≤35	2 (10.00)	0 (0.00)
Body mass index (kg/m^2)		
>23.9	2 (10.00)	4 (20.00)
≤23.9	18 (90.00)	16 (80.00)
Parity		
Nullipara	8 (40.00)	5 (25.00
Para	12 (60.00)	15 (75.00)
Age at menarche (years)		
<12	12 (60.00)	14 (70.00)
≥12	8 (40.00)	6 (30.00)

IL-8 levels showed that the metformin group and the control group had increased, but the p-value in the metformin group was 0.05 and in the control group it was 0.45, which is statistically not significant. Evaluation of pain using VAS showed that before the intervention, the median VAS in both groups was 7 (range 5-8). After the intervention, the metformin group experienced a decrease in median VAS to 6 (range 5-8) with a significant p<0.001, which was statistically significant. Comparison of changes in IL-8 and VAS levels between the metformin and control groups showed p=0.13, which was not significant. VAS changes with p=0.09, which was also not significant. A comparison of the characteristics of the study subjects in both groups is presented in Tables 2-4.

Discussion

Adenomyosis is characterized by the ectopic growth of endometrial tissue into the myometrium, contributing to chronic inflammation and increased levels of pro-inflammatory cytokines, including IL-8.[3] Studies have shown that IL-8 plays a role in the pathogenesis of adenomyosis by increasing leukocyte infiltration into uterine tissue, exacerbating inflammation, and intensifying pain, as measured by the VAS.[20,21] Additionally, with aging, increased oxidative stress and hormonal dysregulation can lead to higher IL-8 expression, further worsening inflammation and chronic pain in adenomyosis patients.[22-24] This condition is further aggravated by an imbalance in estrogen and progesterone receptor expression with age, which increases uterine tissue sensitivity to IL-8 and exacerbates pain.[25,26]

BMI is also associated with IL-8 levels and the degree of inflammation in adenomyosis, where obesity can increase systemic inflammation and upregulate IL-8 expression, contributing to more severe pain.[27,28] Patients with higher BMI also tend to have elevated levels of inflammatory cytokines, which contribute to heightened pain perception.[29] Other studies indicate that obesity can worsen the inflammatory response in adenomyosis, increasing IL-8 production and aggravating pain experienced by patients.[30,31] In this study, most subjects had a BMI≤23.9 kg/m^2, suggesting that BMI may not play a major role in influencing IL-8 levels and pain in the study population.

Parity may also affect pain levels in adenomyosis, as multiparous women are at higher risk of experiencing microstructural changes in the uterus that increase IL-8 expression and local inflammation.[3] Research has shown that multiparous women have higher inflammatory activity than nulliparous women, which is associated with increased IL-8 expression.[9,21] This study shows that the control group had more multiparous individuals compared to the metformin group, which may contribute to variations in pain levels experienced by patients.[22,23]

The results of this study indicate that IL-8 levels increased after the intervention in both the metformin and control groups. In the metformin group, the median IL-8 level increased from 63.56 pg/mL to 69.78 pg/mL, with p=0.05, whereas in the control group, the increase was more significant, from 53.08 pg/mL to 101.59 pg/mL, with non-significant p=0.45. These findings align with previous studies suggesting that metformin can influence IL-8 levels through inflammatory pathways and immune system regulation.[12,16] Other studies on adenomyosis patients have also shown that anti-inflammatory therapy can significantly reduce IL-8 levels, contributing to pain relief.[7,9] The difference in IL-8 level changes between the metformin and control groups may be

Table 2. Interleukin 8 level among metformin and control, pre- and post-intervention.

	Interleukin 8 (pg/mL)		p
	Pre Med (min-max)	Post Med (min-max)	
Metformin	63.56 (1.75-377.91)	69.78 (1.44-255.11)	0.05
Control	53.08 (1.23-249.24	101.59 (1.71-214.99)	0.45

Wilcoxon test, med (median), min (minimum), max (maximum).

Table 3. Visual Analog Scale among metformin and control, pre- and post-intervention.

	Visual Analog Scale (point)		p
	Pre Med (min-max)	Post Med (min-max)	
Metformin	7 (5-8)	6 (5-8)	<0.001
Control	7 (5-8)	6 (5-8)	0.06

Wilcoxon test, med (median), min (minimum), max (maximum).

Table 4. Metformin *vs.* control in changes of interleukin 8 and Visual Analog Scale.

	Metformin Med (min-max)	Control Med (min-max)	p
δIL-8 (pg/mL)	A8.08(-219.42-97.32)	1.05 (-136.14-171.39)	0.13
δVAS (point)	0 (-3-0)	0 (-3-0)	0.09

Mann Whitney test, ted (median), min (minimum), max (maximum). L, interleukin; VAS, Visual Analog Scale.

attributed to the immunomodulatory effects of metformin on the immune and inflammatory systems.

Metformin acts as an anti-inflammatory agent by suppressing the NF-κB pathway and reducing the expression of pro-inflammatory cytokines, including IL-8.[11,32] Studies have demonstrated that metformin can inhibit IL-8 production in various inflammatory conditions, including in patients with polycystic ovary syndrome and colorectal cancer.[33,34] This effect is mediated by the AMPK pathway, which inhibits the activation of pro-inflammatory macrophages and reduces the production of cytokines involved in pain perception.[14,35] Therefore, metformin may help alleviate pain by suppressing both systemic and local inflammation.

In addition to its anti-inflammatory properties, metformin also improves insulin sensitivity and enhances pain-signaling pathways affected by inflammation in adenomyosis. Insulin resistance is often associated with increased systemic inflammation and elevated IL-8 production, which exacerbates chronic pain.[15,36] Other studies have shown that metformin can downregulate the expression of cellular adhesion molecules involved in neuropathic pain responses.[17,37]

The results of this study indicate that metformin therapy significantly contributes to pain reduction in adenomyosis patients, as measured by the VAS. Before the intervention, the median VAS score in both groups was 7, ranging from 5 to 8. After therapy, the metformin group experienced a decrease in median VAS to 6, which was statistically significant ($p<0.001$), while the control group also showed a decrease to 6, but it was not statistically significant ($p=0.06$). These findings align with previous studies demonstrating that metformin has analgesic effects by reducing pain sensitivity through the inhibition of inflammatory pathways.[13,38] Other studies also support that metformin can alleviate pain in chronic inflammatory conditions such as osteoarthritis and diabetic neuropathy, suggesting that similar mechanisms may be involved in adenomyosis.[39,40]

Metformin reduces pain by suppressing inflammatory pathways through the activation of AMPK, which plays a role in inhibiting the production of pro-inflammatory cytokines such as IL-8, IL-6, and tumor necrosis factor-α.[41,42] Studies have shown that metformin decreases macrophage activation and inhibits the NF-κB pathway, a key regulator of chronic inflammation in adenomyosis.[43,44] AMPK activation by metformin also enhances cellular autophagy and reduces free radical production, which collectively lowers pain perception due to inflammation in adenomyosis patients.[45,46]

In addition to its anti-inflammatory effects, metformin also improves insulin sensitivity, which may contribute to pain reduction in adenomyosis. Increased insulin resistance is associated with systemic inflammation, leading to hyperactivation of pain pathways.[6,47] Metformin helps regulate insulin signaling pathways and reduces the expression of pro-inflammatory cytokines in uterine tissue, thereby contributing to reduced pain perception.[18,48] Thus, the effects of metformin extend beyond inflammation reduction to improved metabolic regulation, which may influence the pain threshold in adenomyosis patients.[8,19]

One of the key strengths of this study is its novel approach to exploring metformin as a potential non-hormonal therapeutic option for adenomyosis. By targeting IL-8, a cytokine involved in inflammation and pain, the study adds valuable insights into the pathophysiology of adenomyosis and the broader role of metformin beyond its traditional use in diabetes. The study's design, which involves a cohort-prospective comparison of metformin combined with ibuprofen to a control group receiving only ibuprofen, provides a robust framework for evaluating the combined effects of these treatments on pain reduction.

A significant weakness of this study is the lack of a placebo control group. In the absence of a placebo, it is challenging to conclusively determine whether the noted decrease in pain is directly due to metformin or if it may be from a placebo effect. Furthermore, the study's dependence on a singular 500 mg dose of metformin complicates the ability to establish definitive conclusions on the appropriate dosage and the medication's actual effectiveness in alleviating adenomyosis-related pain and inflammation. The absence of a placebo comparison and restricted dose may undermine the reliability and generalizability of the findings. A significant limitation is the brief duration of the intervention (30 days), which may be inadequate to detect substantial changes in IL-8 levels or to comprehensively evaluate the long-term effects of metformin on inflammation and pain in adenomyosis. This is evidenced by the observation that, although metformin substantially alleviated pain, it did not result in a significant reduction in IL-8 levels, indicating that alterations in inflammation may necessitate an extended treatment duration to manifest. The limited sample size of 40 individuals constrains the statistical power of the results, perhaps hindering the generalizability of the findings to a wider population. The absence of patients with diabetes mellitus impairs interpretation, as metformin's effects may be more significant in this population due to its proven role in enhancing insulin sensitivity.

Conclusions

This study suggests that the anti-diabetic drug metformin can also be used as an anti-inflammatory drug in adenomyosis patients as an adjunctive therapy. Further research needs to be done. Metformin therapy for 30 days in adenomyosis patients effectively reduces pain but does not significantly decrease IL-8 levels. This is because adenomyosis-related pain is neuropathic, and metformin exerts its analgesic effects through AMPK activation and phosphorylation. The lack of IL-8 reduction may be due to an insufficient treatment duration.

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