



What is the link between endometriosis and adiposity?

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Endometriosis is defined by the presence of extrauterine endometrial tissue and presents with symptoms of dysmenorrhea, chronic pelvic pain, and impaired fertility. This condition often follows a chronic progressive course with favorable recurrence, even after surgical or medical treatment. The etiology or exact pathophysiology of endometriosis remains to be clarified, although it is thought to be a complex and multifactorial disease. Prior epidemiological or population-based studies have reported several risk factors related to endometriosis, such as environmental, menstrual, habitual, and lifestyle factors. Moreover, anthropometry has been found to be significantly associated with the diagnosis of endometriosis, as a lower body mass index is associated with an elevated risk of endometriosis. Here, we review studies that have examined the association between body size and the risk of endometriosis and discuss the clinical and biological significance of the relationship between adiposity and endometriosis.

Keywords: Endometriosis; Adiposity; Anthropometry; Obesity; Adipokines

Introduction

Endometriosis is defined as the ectopic implantation of endometrial cells outside the uterus [1]. The prevalence of endometriosis is estimated to be approximately 10% in reproductive-aged women, and 30-50% in symptomatic women [2-5]. Endometriosis often presents with symptoms, such as dysmenorrhea, pelvic pain, and infertility, which may result in profuse morbidity in chronic conditions and reduced quality of life.

The natural history and exact pathogenesis of endometriosis are not fully understood, but the most cited theory is that endometrial cells in retrograde menstruation into the pelvic cavity are implanted and grown by the complex effects of immune, angiogenic, and growth factors [6,7]. Other pathogenic theories, such as lymphatic, hematogenous, and mechanical spread of endometrial fragments, have been suggested for extrapelvic endometriosis [8,9].

Worldwide epidemiological studies have focused on the risk factors for endometriosis and identified that race, ethnicity, lifestyle, and habitual factors such as diet, exercise, caffeine consumption, and smoking are associated with endometriosis diagnosis. However, some of these associations have shown conflicting results [10-13]. Menstrual and reproductive risk factors have less controversial associations with endometriosis. Moreover, lower parity, earlier age at menarche,

shorter menstrual cycle, heavier menstrual volume, and longtime tampon use increase the risk of endometriosis [13-15].

Many studies have addressed the significant association between anthropometric parameters and the incidence of endometriosis. Here, we review the studies that have examined the association between the risk of endometriosis and body size as well as discuss the clinical and biological relevance of the findings and proposed mechanisms involved in adiposity and endometriosis.

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Body size and the risk of endometriosis in population-based studies

1. Body mass index (BMI) is associated with the diagnosis of endometriosis

Many epidemiological and population studies on risk factors for endometriosis have used anthropometric indices to estimate body size; these studies have shown that endometriosis is associated with lower BMI and less obesity, suggesting an inverse relationship between BMI and the risk of endometriosis [11,13,16-19]. A hospital-based case-control study with 50 women with endometriosis and 89 controls found that the risk of endometriosis was positively associated with height (odds ratio [OR], 2.8 per 10 cm increase; 95% confidence interval [CI], 1.4-5.6) and inversely associated with weight (OR, 0.7 per 10 kg increase; 95% CI, 0.5-1.0) and BMI (OR, 0.7 per 5 kg/m² increase; 95% CI, 0.4-1.1) [16]. Another case-control study analyzed the relationship between diet and risk of endometriosis and found an inverse relationship between BMI and the risk of endometriosis [19]. Similarly, a study of 366 Italian women laparoscopically diagnosed with endometriosis and 248 controls showed that women with endometriosis had a lower BMI than controls and were less frequently obese and more frequently thin [17]. Consistent findings have been observed in two case-control studies of Iranian women [20,21].

A recent meta-analysis including a quantitative investigation of 11 studies (two cohort and nine case-control studies) reported that a higher BMI correlates with a lower risk of endometriosis. The overall analysis showed a 33% reduction in the risk of endometriosis for each 5 kg/m² increase in BMI [22]. Compared with those with normal weight, the pooled relative risk for obese women was 0.89 (95% CI, 0.83-0.96). They suggest that several issues need to be considered in their findings, as BMI is a widely utilized indirect marker for estimating body size and obesity, but it may not provide enough etiological information to reflect the nature of obesity. In addition, the inverse relationship between obesity and endometriosis may be attributed to diagnostic bias, where obese women with pelvic pain may be less likely to be provided with an operative intervention, which may subsequently lower the possibility of a laparoscopic diagnosis of endometriosis [22].

Several studies have explored the historical relationship between obesity and endometriosis by analyzing the personal

characteristics of body size in adolescence or early adult life, thereby underscoring obesity as a preceding factor involved in the subsequent development of endometriosis. In their case-control analysis, Nagle et al. [23] reported that being overweight during late childhood (10 to 16 years old) is associated with a higher risk of endometriosis. Similar study designs have demonstrated an inverse relationship between the risk of endometriosis and BMI, both at diagnosis and during adolescence or early adulthood [18,24,25]. These findings provide further evidence that historical body shape and size during early life are closely associated with the subsequent diagnosis of endometriosis. Several possible explanations can be offered: for example, insulin resistance and hyperinsulinemia have been reported in obese adolescent girls, which is associated with increased production of adrenal androgens and decreased plasma levels of sex hormone-binding globulin [26,27]. Using the same biological pathway as androgens, insulin-like growth factor (IGF) has been shown to prevent apoptosis of ectopic endometrial cells, and higher plasma and peritoneal fluid IGF-I levels have been reported in women with endometriosis [28,29].

In a study analyzing 5,504 cases of endometriosis that were collected from a large cohort, both BMI at 18 years and current BMI were significantly inversely associated with endometriosis ($P < 0.0001$) [18]. Obese infertile women with current BMIs of 35-39.9 kg/m² and ≥ 40 kg/m² had a 55% (95% CI, 0.30-0.67) and a 62% (95% CI, 0.23-0.62) lower risk of endometriosis, compared with the low to normal BMI referent (18.5-22.4 kg/m²). This negative association between current high BMI and endometriosis is largely driven by a woman's BMI at 18 years of age, suggesting that there is an etiologically relevant 'early window of exposure', during which higher body size reduces an individual's subsequent risk of developing endometriosis [18]. However, the authors mentioned that it is difficult to confirm that the impact of body size on endometriosis truly precedes the onset of disease, given the inherent impossibility of identifying the precise time point at which endometriosis first appears.

Several possible explanations for the inverse association between BMI and the diagnosis of endometriosis have been reported. It is well-established that increased body size or obesity is often associated with anovulation and/or oligomenorrhea. Therefore, the chance of menstrual regurgitation in the pelvic cavity can be decreased in women with obesity [18,30]. However, epidemiological data have shown that

BMI is an independent factor associated with the frequency of endometriosis by adjusting for menstrual factors in their analyses. Another explanation is that chronic pain symptoms accompanied by endometriosis induce gastrointestinal symptoms or emotional stress that lead to reduced appetite and food intake, which results in lower body size in women with endometriosis [31,32].

In contrast, some studies assessed various predisposing risk factors relevant to endometriosis, but failed to observe a significant relationship between anthropometry and endometriosis [15,33,34].

Body fat distribution and endometriosis

In addition to BMI parameters for body size, the effect of body fat distribution on the risk of endometriosis has been investigated. In a study of 45 women with laparoscopically confirmed endometriosis and 46 controls, the waist-to-hip and waist-to-thigh ratios were found to be inversely correlated with the risk of endometriosis in women under 30 years of age, but this correlation disappeared in women aged 30 years or older [35]. They suggested that a specific somatotype with a predominance of peripheral body fat is related to the disease; more peripheral fat has higher estrogen levels in the case group. A recent systematic review analyzed 21 publications and found that lean body habitus, particularly low amounts of adipose tissue and adipose tissue below the waist, are associated with endometriosis [36]. Considering that endometriosis is an estrogen-dependent disease, this finding was consistent with the proposed hypothesis that estrogen influences the distribution and amount of adipose tissue [37,38].

Relationship between body size and disease severity or typology

A few studies have investigated the relationship between obesity and disease severity in endometriosis but have shown conflicting results. We previously demonstrated that women with advanced stages of endometriosis had lower BMIs than those with mild disease in women who had surgically confirmed endometriosis, denoting that BMI was significantly inversely associated with disease severity even after adjusting

for age, menstrual history, parity, and marital status [39]. Interestingly, such a relationship was found to be significant in later reproductive-aged women (aged 27-36 years and 37-45 years) but not in the younger group (18-27 years). Although the explanation of this finding is limited, the age-related association between obesity and the severity of endometriosis suggests that the growth of endometrial lesions is influenced by the progressive change in the amount or distribution of body fat that occurs with aging. In contrast, another case-control study with 506 women surgically diagnosed with endometriosis showed that lean body mass was associated with a high prevalence of endometriosis, which is consistent with previous studies [31]. However, obesity is associated with a more advanced stage of endometriosis and a reduced frequency of stage I endometriosis.

A case-control study classified different types of endometriosis and found that patients with the lowest BMI (<18.5) had a high risk of deep infiltrating endometriosis (DIE) [40]. Byun et al. [41] assessed the relationships between diverse adiposity measures and the severity and typology of endometriosis; stage IV, ovarian endometrioma, and DIE were associated with the lowest anthropometric and body composition indicators, although they could not determine the causal relationship. They concluded that the association between adiposity and endometriosis severity and typology might be more complicated than a simple correlation.

Biological and *in vivo* studies on adiposity and risk of endometriosis

Mediating mechanisms that can explain the inverse relationship between obesity and the risk of endometriosis are poorly understood, but several hypotheses and pathways have been suggested in published research areas.

One potential pathway suggests that adipose tissue macrophages are differently expressed by body size or fat amount. M2 macrophages have anti-inflammatory properties and promote tissue regeneration in injured tissue, while M1 macrophages promote inflammation and inhibit angiogenesis and tissue remodeling [36,42]. Research has shown that M2 macrophages may be involved in the development of endometriosis, potentially through the actions of M2, including angiogenesis and tissue remodeling [43-45]. Interestingly, leanness is associated with a predominance of M2 macro-

phages, whereas being larger is associated with a predominance of M1 macrophages [36,46].

Adipocytokine (or adipokine), a cytokine family mainly secreted from adipocytes, might be one of the biomolecules that can mediate the adiposity and establishment or progression of endometriosis. Adipokines play various biological roles as immune mediators, regulation of cell survival, inflammation, and angiogenesis, which are also critical functions in the establishment or development of endometriosis [47-51]. In addition, many adipokine levels in circulation are known to correlate with adiposity, such as an increase or decrease in those who are overweight or obese. Considering the anatomical proximity of visceral fat to the pelvic organs where endometriosis commonly occurs, there could be certain paracrine effects of adipokines secreted from visceral fat into the pelvic cavity, which may influence the establishment or progression of endometriosis [52]. Therefore, determining the adipokine levels in the peritoneal cavity with a correlation between an endometriotic condition and visceral fat amount and to study the biological or molecular effects of adipokines on endometriosis would be important to determine the underlying mechanism for biological connections between adiposity and endometriosis. Indeed, some studies have demonstrated aberrant expression of various adipokines in endometriotic peritoneal fluid (PF) and endometriosis lesions [53-57]. We previously reported that resistin concentration is increased in endometriotic PF, and its expression is upregulated in ectopic endometrial tissues compared to that in normal eutopic endometrium [52,53]. Adiponectin is an adipokine with anti-inflammatory and anti-angiogenic properties, and its circulating levels are negatively correlated with obesity [49,50,58]. One study found that adiponectin levels in the PF of women with endometriosis were significantly lower than those of controls, suggesting that this molecule may be an anti-endometriotic factor due to its anti-inflammatory and anti-angiogenic properties [54]. In contrast, our study did not find a significant difference in PF adiponectin levels between the endometriosis and control groups [53]. Despite the findings of aberrant expression of adipokines in various biosamples in patients with endometriosis, the explanation for the causal effect of adiposity on endometriosis is still limited because most studies did not assess the anthropometric indices or did not measure the amount of total or visceral fat or fat distribution in their study subjects. In addition, the correlation between visceral fat mass and the concentrations of

adipokines in the peritoneal cavity is not well understood.

An experimental study in mice with induced endometriosis revealed differentially regulated 26 genes in the liver. Among them, six genes were found to be involved in metabolism [59]. Four of the six genes, *Cyp2r1*, *Fabp4*, *Mrc1*, and *Rock2*, were upregulated and were related to weight loss, whereas two genes, *Igf1* and *Mmd2*, were downregulated and linked to obesity. Altered metabolism mediated by the liver contributes to the clinically observed low BMI that is characteristic of women with endometriosis, suggesting the systemic and multiorgan nature of endometriosis [59].

Conclusion

Obesity and endometriosis are common entities characterized by systemic inflammation [32]. Thus, the finding of an inverse association between these two conditions is interesting but not yet clear. The direction of studies for elucidating this finding can be approached in terms of genetic traits, immune system, and hormonal factors linked to both conditions. Endometriosis is believed to be inherited as a complex genetic trait by which multiple genes confer disease susceptibility and interact with one another and the environment to produce the phenotype [17,39,60]. Therefore, genetic factors involved in endometriosis susceptibility might also be associated with those involved in the physiology of adiposity or obesity [17,61].

Although the etiology of endometriosis remains unclear, endometriosis has historically been regarded as a focal disease primarily within the pelvic and peritoneal cavities [62]. However, recent evidence highlights the multiple links between endometriosis and systemic diseases with immunologic and metabolic changes and has identified comorbidities associated with endometriosis, such as autoimmune diseases, cancers, and cardiovascular disease [63,64]. The factors that transmit systemic signaling beyond the peritoneal cavity remain unclear; thus, research on extracellular signaling pathways such as exosomes, microRNAs, and stem cell biology in terms of the pathophysiology of endometriosis would provide more information on the systemic nature and complexity of endometriosis [62]. In addition, studies targeting biological substances that specifically function in both adipose tissue metabolism and endometriosis could help better understand the observed relationship between adiposity

and the establishment or behavior of endometriosis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The study is not applicable to Institutional Review Board.

Patient consent

There is no need for patient consent in this review article.

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