Serum adiponectin concentrations are decreased in women with endometriosis

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Introduction

Endometriosis is an enigmatic disease that deteriorates the health of women of reproductive age (Momoeda et al., 2002; Osuga et al., 2002). A widely believed aetiology is that endometrial debris in retrograde menstruation implants, survives and grows in the peritoneal cavity (Halme et al., 1984). However, it remains unknown why only some women develop endometriosis whereas retrograde menstruation is observed in most women.

It is well known that the development of endometriosis is estrogen dependent. Estrogen also functions as a promoting factor for gynaecological tumours such as breast cancer, endometrial cancer and uterine leiomyoma. Notably, several recent studies demonstrated that circulating adiponectin concentrations are decreased in women with breast cancer (Miyoshi et al., 2003; Mantzoros et al., 2004), endometrial cancer (Dal Maso et al., 2004) and uterine leiomyomas (Chen et al., 2004), suggesting possible roles of adiponectin in these diseases.

Adiponectin is an ~30 kDa polypeptide containing an N-terminal signal sequence, a variable domain, a collagen-like domain, and a C-terminal globular domain. It is highly and specifically expressed in differentiated adipocytes and circulates at high levels in the blood stream (Scherer et al., 1995; Hu et al., 1996; Maeda et al., 1996; Nakano et al., 1996; Kadowaki and Yamauchi, 2005). Both adiponectin concentrations in adipose tissue and in the circulation are reduced in obesity (Hu et al., 1996; Arita et al., 1999). Adiponectin was first discovered as a regulator of insulin sensitivity and metabolism; later studies manifested its pleiotropic activities such as anti-inflammatory, anti-angiogenic and anti-atherosclerotic effects (Yokota et al., 2000; Brakenhielm et al., 2004; Goldstein and Scialla, 2004).

In view of the possible implication of adiponectin in the estrogen-related tumours, we set out to examine whether serum adiponectin concentrations are aberrant in women with endometriosis.

Materials and methods

A total of 78 women of reproductive age with (n = 48) and without (n = 30) endometriosis participated in this study. They underwent laparoscopy for pain, infertility or other benign gynaecological disorders. All the women had regular menstrual cycles. None of the women took medication that affect hormonal or immunological status within 3 months before laparoscopy, or had undergone surgical treatment for endometriosis within 1 year. No woman had a history of diabetes, liver, vascular or neoplastic disorders. Endometriosis was diagnosed both laparoscopically and histologically. The stage of endometriosis was evaluated according to the revised American Society for Reproductive Medicine (r-ASRM) classification (American Society for Reproductive Medicine, 1997). In addition, the scores of endometriosis and of adhesion of r-ASRM classification were used.
The distribution of the stage of endometriosis was as follows: stage I, \( n = 10 \); stage II, \( n = 6 \); stage III, \( n = 10 \); stage IV, \( n = 22 \). The non-endometriosis (control) group consisted of women with infertility (\( n = 13 \)), ovarian dermoid cysts (\( n = 14 \)), and ovarian serous cysts (\( n = 3 \)), and none of these women had uterine leiomyoma. In the non-endometriosis group, 15 women were in the proliferative phase and 15 were in the secretory phase. Eight women were in each phase in stage I/II endometriosis, and 16 were in each phase in stage III/IV endometriosis.

Fasting morning blood samples were taken for measurement of adiponectin before laparoscopy. The blood was immediately separated by centrifugation at 400g for 10 min, and the serum was stored at \(-80^\circ\text{C}\) until use.

Concentrations of adiponectin in the serum were measured using a specific enzyme-linked immunosorbent assay (ELISA; Genzyme/Techne, Minneapolis, MN, USA) according to the manufacturer’s protocol. The sensitivity of the assay was 62.5 pg/ml for adiponectin. The intra- and inter-assay coefficients of variation were 3.2 and 7.4% respectively.

Statistical analysis was conducted using Mann–Whitney \(U\)-test and linear regression analysis. \( P < 0.05 \) was considered significant.

**Results**

The mean age of patients in the endometriosis group (33.6 years, SD 4.8) and the control group (32.8, SD 7.0) was virtually identical (Table I). BMI was also substantially identical between the groups (Table I). The concentrations of adiponectin for all serum samples were above the lower limit of the assay.

As shown in Figure 1, adiponectin concentrations in the serum with endometriosis (median, 13.1 \( \mu \text{g/ml} \); IQR, 10.2–16.7) were significantly lower than those without endometriosis (15.9 \( \mu \text{g/ml} \), 13.5–19.5; \( P = 0.008 \)). The women with endometriosis were then subdivided into those with stage I/II and those with stage III/IV for further analysis. The concentrations of adiponectin in stage III/IV endometriosis (12.8 \( \mu \text{g/ml} \), 10.6–16.6) were significantly lower than those in non-endometriosis (\( P = 0.004 \)), while those in stage I/II endometriosis (15.1 \( \mu \text{g/ml} \), 9.3–17.0) appeared to be intermediate. No remarkable difference was observed between the proliferative phase and the secretory phase in each stage (data not shown).

The correlations between serum adiponectin concentrations and endometriosis scores or adhesion scores are shown in Figure 2. A significant negative correlation was found between serum adiponectin concentrations and both endometriosis scores (\( R = -0.307, P = 0.006 \)) and adhesion scores (\( R = -0.254, P = 0.026 \)). As demonstrated in Figure 3, the women with obliteration of cul-de-sac had significantly lower adiponectin concentrations (12.8 \( \mu \text{g/ml} \), 7.8–16.6) than those without obliteration (14.8 \( \mu \text{g/ml} \), 12.8–18.3; \( P = 0.026 \)).

**Table I.** Characteristics of the subjects

<table>
<thead>
<tr>
<th>No.</th>
<th>Controls</th>
<th>Endometriosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Stage I/II</td>
</tr>
<tr>
<td>No.</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.8 ± 7.0</td>
<td>33.6 ± 4.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.9 ± 3.3</td>
<td>20.8 ± 3.1</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

BMI = body mass index.

**Discussion**

In the present study, we first demonstrated that serum adiponectin concentrations were significantly decreased in women with endometriosis compared to those without the disease. In particular, the decrease was remarkable in women with advanced stages (stages III/IV) of endometriosis. Inverse relationships between serum adiponectin levels and both endometriosis scores and adhesion scores were observed.

It is well known that the circulating levels of adiponectin are inversely related to body mass index (BMI) (Arita et al., 1999; Hotta et al., 2000; Yang et al., 2002). However, BMI is substantially the same in women with endometriosis and in those without the disease in this study. Therefore, the low serum adiponectin concentrations observed in women with endometriosis is not due to the difference of BMI but related to the disease per se.

Estrogen is known to stimulate the development of endometriosis. Together with the findings that circulating adiponectin concentrations are decreased in women with estrogen-related tumours, such as breast cancer (Miyoshi et al., 2003; Mantzoros et al., 2004), endometrial cancer (Dal Maso et al., 2004) and uterine leiomyomas (Chen et al., 2004), it is speculated that the decrease in adiponectin concentrations observed in the present study may facilitate the growth-promoting effect of estrogen on endometriosis. A possibility is that insulin resistance induced by low adiponectin is associated with low SHBG levels (Jayagopal et al., 2004), and may potentiate the effect of estrogen.

Another possible reason why low adiponectin levels may be associated with the development of endometriosis could be explained with an anti-angiogenic property of adiponectin. Adiponectin has been shown to inhibit angiogenesis both in vitro and in vivo (Brakenhielm et al., 2004). Furthermore, adiponectin suppressed tumour growth with decreased neovascularization.
in a mouse model (Brakenhielm et al., 2004). These findings support the notion that low adiponectin concentrations may permit angiogenesis required for the development of endometriosis. Similarly, circulating and peritoneal fluid levels of angiogenic factors, such as angiogenin (Steff et al., 2004; Suzumori et al., 2004), hepatocyte growth factor (Osuga et al., 1999; Zong et al., 2003) and vascular endothelial growth factor (Matalliotakis et al., 2003), are increased in women with endometriosis.

Low circulating adiponectin concentrations have been shown to be associated with increased plasma insulin levels (Yamamoto et al., 2002). Circulating insulin levels are inversely correlated with levels of serum insulin-like growth factor-binding protein 1 (IGFBP-1) (Suikkari et al., 1989), which binds to insulin-like growth factor (IGF-1) and regulates its biological effect. Accordingly, low adiponectin concentrations may enhance effects of IGF-I, which has been shown to stimulate the growth of endometriosis (Giudice et al., 1994).

It is well established that peritoneal inflammation is involved in the pathogenesis of endometriosis. In accordance with the notion, many proinflammatory cytokines are elevated in serum and peritoneal fluid of women with endometriosis (Wu and Ho, 2003; Yang et al., 2004). Adiponectin has been shown to suppress macrophage activities (Yokota et al., 2000). In addition, circulating adiponectin concentrations negatively correlate with C-reactive protein (Krakoff et al., 2003; Ouchi et al., 2003). Given the anti-inflammatory potential of adiponectin, it is feasible that low adiponectin concentrations are related to proinflammatory status associated with endometriosis.

A remarkable finding in the present study is that serum adiponectin concentrations are negatively correlated with adhesion scores as well as endometriosis scores. It is also noted that women with cul-de-sac obliteration had lower adiponectin concentrations than those without the obliteration. Anti-fibrotic characteristics of adiponectin were recently reported with the findings that adiponectin prevents liver fibrosis and suppresses the gene expression of transforming growth factor (TGF) β, an inducer of fibrosis, in hepatic cells (Kamada et al., 2003). Considering that fibrosis often accompanies adhesions in endometriosis, low adiponectin concentrations might also be related to pelvic adhesions associated with endometriosis.

Due to limitations of an observational study, it is difficult to determine whether the present findings are a cause or consequence of the endometriotic condition. Nevertheless, many
biological features of adiponectin fit well for possible causes of the disease. Further studies are needed to settle the issue.

In summary, the present study demonstrated that serum adiponectin concentrations are decreased in women with endometriosis. In view of its pleiotropic functions, adiponectin may be involved in the pathophysiology of endometriosis.

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References


