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Serum paraoxonase-1 activity in women with endometriosis and its relationship with the stage of the disease

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BACKGROUND: There is increasing evidence that oxidative stress may play a role in the pathophysiology of endometriosis. Serum paraoxonase-1 (PON-1) is a high-density lipoprotein (HDL) associated enzyme that prevents oxidative modification of low-density lipoprotein (LDL). The aims of the study were to (i) compare the serum PON-1 activity in women with endometriosis versus controls and (ii) assess whether PON-1 activity can be used as a diagnostic test for endometriosis. METHODS: A total of 87 women who underwent laparoscopy or laparotomy were divided into groups by visual diagnosis at surgery: control patients ($n = 40$) with no pathologic findings; endometriosis sufferers with minimal to mild ($n = 24$) and moderate to severe ($n = 23$) stage. Serum PON-1 activity was measured spectrophotometrically. Lipid hydroperoxide (LOOH) levels were measured by iodometric assay. Serum triglyceride (TG), total cholesterol (TC), HDL and LDL levels were also determined. RESULTS: PON-1 activity was significantly lower whereas LOOH levels were significantly higher in women with moderate to severe endometriosis than in women with minimal to mild endometriosis and controls, and in women with minimal to mild endometriosis compared with control groups ($P < 0.0001$, for all). A significant negative correlation was found between PON-1 activity and stage of the disease ($r = -0.74$, $P < 0.0001$). PON-1 activity and HDL levels were decreased whereas LOOH, TG, TC and LDL levels increased in all women with endometriosis versus controls (all $P < 0.0001$). CONCLUSIONS: Reduced serum PON-1 activity and increased LOOH might contribute to the increased susceptibility for the development of atherosclerosis. PON-1 activity can be used as a diagnostic test to detect endometriosis.

Keywords: endometriosis; oxidative stress; paraoxonase-1; atherosclerosis; lipid hydroperoxide

Introduction

Endometriosis is characterized by the implantation and growth of endometrial tissue outside the uterine cavity. Little is known about the etiology of endometriosis; however, it has been suggested that oxidative stress may play an important role in the pathogenesis (Van Langendonckt *et al*., 2002; Szczepanska *et al*., 2003; Jackson *et al*., 2005). Elevated levels of the marker of lipid peroxidation lysophophatidyl choline, a potent chemotactic factor for monocytes/T-lymphocytes, were seen in the peritoneal fluid of women with endometriosis (Shanti *et al*., 1999). Studies have also reported that reactive oxygen species (ROS) may increase growth and adhesion of endometrial cells in the peritoneal cavity that promotes endometriosis and infertility (Jackson *et al*., 2005).

Oxidative stress has also been shown to play a role in the development and progression of atherosclerosis (Stocker and Keaney, 2004; Singh and Jialal, 2006). Oxidized low-density lipoprotein (LDL) promotes vascular dysfunction by exerting direct cytotoxicity to endothelial cells, by increasing chemotactic properties of monocytes, by transforming macrophages to foam cells and by enhancing the proliferation of endothelial cells, monocytes and muscle cells that all contribute to cardiovascular diseases (Girotti, 1998). It has been reported that both atherosclerotic lesions and peritoneal fluid of women with endometriosis are characterized by the presence of macrophages, cytokines derived from macrophages, lipoproteins [LDL, high-density lipoprotein (HDL)], T cells and cytokines derived from T cells, chemotactic factors for T cells plus growth factors and oxidized LDL (Santanam *et al*., 2002).

Paraoxonase-1 (PON-1) is a HDL-associated antioxidant enzyme with paraoxonase, arylesterase and dyazoxonase activities (Aslan *et al*., 2007). PON-1 prevents LDL and HDL oxidation and stimulates cholesterol efflux, the first step in reverse cholesterol transport (Mackness *et al*., 1993). It is also responsible for the antioxidant effect of HDL (Durrington *et al*., 2001). There is strong evidence suggesting that human serum PON-1 is a predictor of coronary artery disease (CAD) (Jarvik *et al*., 2000). Low serum PON-1 activity was present in patients with CAD and in enhanced atherogenesis, such as hypercholesterolemia and diabetes (Sarandol *et al*., 2006).

PON-1 activity was lower in CAD than in normal disease-free controls (Ayub *et al*., 1999). Serum PON-1 was reduced in survivors of myocardial infarction within a few hours of the onset of cardiac ischemic chest pain (Ayub *et al*., 1999). In the case of diabetes, the serum PON-1 activity is decreased even before the onset of clinical CAD (Durrington *et al*., 2001).

Lipid peroxidation leads to the generation of lipid hydroperoxides (LOOHs). LOOHs derived from unsaturated phospholipids, glycolipids and cholesterol are prominent intermediates of peroxidative reactions that are generally more long-lived than any free radical precursors, making intermembrane translocation within a cell, between cells or between lipoproteins and cells possible (Girotti, 1998). LOOHs could actively contribute to the progression of atherosclerotic lesions and their resulting complications (Leitinger, 2003).

The aims of the present study were to (i) compare the serum levels of PON-1 activity in women with endometriosis versus controls and (ii) assess whether PON-1 activity can be used as a diagnostic test to detect endometriosis.

Materials and Methods

The patients in this study were 87 consecutive women undergoing laparoscopy or laparotomy between November 2006 and May 2007 for evaluation of infertility, pelvic pain, pelvic mass, tubal ligation or endometriosis. The presence or absence of endometriosis, the stage of endometriosis according to revised American Fertility Society (rAFS) and other gynecologic pathologies were noted. Forty-seven women had visually confirmed endometriosis and 40 did not have endometriosis. Of these 47 women, 24 had minimal to mild (rAFS Stages I–II) and 23 had moderate to severe (rAFS Stages III–IV) endometriosis. All procedures were performed by the same surgeon. The study has been approved by institutional review board and has therefore been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

All subjects were of premenopausal women aged between 18 and 35 years with regular menstrual cycles of between 21 and 35 days. The exclusion criteria were age older than 35 years, pregnancy, hormonal therapy (i.e. oral contraceptives, GnRH agonists, progestins, estrogens and danazol), smoking alcohol drinking, CAD, unstable angina, myocardial infarction, any operation or cardiovascular intervention within the previous 3 months, hypertension, hyperlipidemia, rheumatological or endocrine conditions such as diabetes, polycystic ovarian disease, acute-chronic liver diseases, renal dysfunction, anemia, obesity, parasitic diseases, systemic or local infection, any history of cancer in the past 5 year and therapeutic interventions known to influence antioxidants such as supplemental vitamins.

Hyperlipidemia was defined as follows: serum LDL cholesterol $\geq$160 mg/dl or total cholesterol (TC) $\geq$240 mg/dl or triglyceride (TG) $\geq$200 mg/dl or HDL cholesterol $<$40 mg/dl (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). A patient was considered as diabetic with a fasting plasma glucose level $\geq$126 mg/dl. Obesity was defined as body mass index (BMI) $\geq$30 kg/m^2.

Blood sample collection

Blood samples were collected at the follicular phase of the menstrual cycle between 9:00 and 11:00 a.m. after an overnight fast. The samples were centrifuged within 2 h after withdrawal and stored at -20°C until assayed.

Measurement of PON-1 activity

PON-1 activity was determined by using paraoxon as a substrate and measured by increases in the absorbance at 412 nm due to the formation of 4-nitrophenol as already described (Isik *et al*., 2007). Briefly, the activity was measured at 25°C by adding 50 μl of serum to 1 ml Tris–HCl buffer (100 mM at pH 8.0) containing 2 mM of $CaCl_2$ and 5.5 mM of paraoxon. The rate of generation of 4-nitrophenol was determined at 412 nm. Enzymatic activity was calculated using the molar extinction coefficient 17 100 M^{-1} cm^{-1}. The intra and interassay coefficients of variation (CV) for PON-1 activity were $<$3%.

Measurement of LOOH levels

Triiodide complex formed as a result of the reaction between LOOH and iodine was evaluated by spectrophotometry at 365 nm wavelength. The results were calculated using the extinction coefficient of triiodide ($\varepsilon = 2.46 \times 10^4$ M^{-1} cm^{-1}) (Gorog *et al*., 1991). The intra and interassay CV for LOOH were $<$5%.

Other parameters

The levels of TG, TC, HDL and LDL were determined using commercially available assay kits (Abbott) with an autoanalyzer (Aeroset, Abbott).

Statistics

Results were expressed as mean $\pm$ SD for all continuous variables. Demographic characteristics were defined by descriptive statistics. Differences among the study and control groups were assessed using Student's *t*-test. Differences between moderate to severe and minimal to mild endometriosis and the control groups were assessed using analysis of variance test followed by Tukey test. Correlation between PON-1 activity and the clinical severity of the disease was performed by Spearman's rank test. The area under the receiver operating characteristic curve (ROC) was used to assess the discriminative ability of PON-1 activity in endometriosis and its subgroups.

Results

There was no significant difference in mean age between women with endometriosis (24.4 $\pm$ 4.0 years) and controls (24.8 $\pm$ 3.8 years). Moreover, no significant difference was seen in BMI among the above groups (21.5$-$21.7 kg/m^2). All of the participants underwent laparoscopy (81.6%) or laparotomy (18.4%) (Table I). In addition, preoperative indications were listed in Table I. The proportion of minimal to mild endometriosis was 27.6%, and 26.4% for moderate to severe endometriosis, among all cases. Table II summarizes

Table I. Descriptive statistics of the women included in the study.

Parameters	Distribution among total subjects ($n = 87$)
Surgical approach	
Laparoscopy	71 (81.6%)
Laparotomy	16 (18.4%)
Preoperative indications	
Infertility	50 (57.5%)
Pelvic pain	9 (10.3%)
Pelvic mass	16 (18.4%)
Tubal ligation	12 (13.8%)

Table II. Serum PON-1 and LOOH activities and lipid profiles in women with endometriosis and controls.

Characteristic	Women with endometriosis ($n = 47$) (mean ± SD)	Controls ($n = 40$) (mean ± SD)
TG (mg/dl)	172.8 ± 27.7[a]	135.0 ± 24.0
TC (mg/dl)	206.7 ± 29.0[a]	162.6 ± 22.4
HDL (mg/dl)	48.0 ± 8.4[a]	62.1 ± 8.0
LDL (mg/dl)	140.5 ± 14.5[a]	113.9 ± 11.7
PON-1 (U/l)	106.5 ± 37.4[a]	183.7 ± 22.3
LOOH (μmol/l)	16.9 ± 2.9[a]	11.5 ± 2.3

[a]$P < 0.0001$ versus controls.

the serum PON-1 and LOOH activities and lipid profiles in women with endometriosis and controls.

Women with endometriosis displayed significantly lower levels of PON-1 activity and HDL and higher levels of LOOH, TG, TC and LDL than controls ($P < 0.0001$, for all).

Serum PON-1 and LOOH activities and lipid profiles in subgroups of endometriosis and control groups were shown in Table III. LOOH, TG, TC and LDL were significantly higher whereas PON-1 activity and HDL were significantly lower in women with moderate to severe endometriosis than in women with minimal to mild endometriosis and in control groups. There were also significant differences in PON-1 and LOOH activities, TG, TC, HDL and LDL in women with minimal to mild endometriosis compared with control groups.

A significant negative correlation was found between PON-1 activity and stage of the disease ($r = -0.74$, $P < 0.0001$).

To analyze the diagnostic accuracy of PON-1 activity in women with endometriosis, the ROC curve was analyzed. Area under ROC curve was 0.96 with 95% confidence interval (CI) = 0.93–0.99, a threshold value 141.5 U/l and sensitivity = 97% and specificity = 81% to distinguish women with and without endometriosis.

Area under ROC curves, sensitivities and specificities and threshold values for PON-1 activity in subtypes of endometriosis were also calculated. Area under ROC curve was 0.98 with 95% CI = 0.97–1.00, a threshold value 102.5 U/l and sensitivity = 98% and specificity = 83% in moderate to severe endometriosis.

Area under ROC curve for PON-1 activity was 0.60, with 95% CI = 0.48–0.71, and sensitivity = 63% and specificity = 59% in women with minimal to mild endometriosis. The threshold value in that group was 136.5 U/l.

Discussion

In this study, it was found that serum PON-1 activity and HDL were decreased whereas LOOH, TG, TC and LDL levels were increased in women with endometriosis when compared with the controls. We have also shown that PON-1 activity was lower in women with moderate to severe endometriosis than those with minimal to mild stage disease. In addition, there was a strong relationship between PON-1 activity and stage of disease. ROC analysis showed that PON-1 activity could be a good marker for women with endometriosis with a sensitivity = 97% and specificity = 81%. Endometriosis is associated with general inflammatory response. Oxidative stress has been suggested as a potential factor involved in the pathophysiology of the disease (Van Langendonckt *et al*., 2002; Szczepanska *et al*., 2003; Jackson *et al*., 2005). Women with endometriosis had significantly lower levels of superoxide dismutase and glutathione peroxidase in peritoneal fluid compared with fertile control women, both of which play an important role in break down of free radicals and ROS (Jackson *et al*., 2005). Furthermore, women with endometriosis had significantly lower levels antioxidants than women without endometriosis and significantly higher LOOH (Jackson *et al*., 2005). Shanti *et al*. (1999) found similar results in a study comparing women with endometriosis to women having tubal ligation, in which endometriosis was associated with significantly higher serum levels of lipid peroxide-modified rabbit serum albumin, malondialdehyde-modified LDL and oxidized LDL compared with tubal ligation; but no differences were detected in the peritoneal fluid. Although there were also some conflicting studies that suggested no association between oxidative stress markers and endometriosis (Ho *et al*., 1997; Wang *et al*., 1997), Jackson *et al*. (2005) found a relationship between oxidative stress and endometriosis after adjusting for age, BMI, current smoking, hormone use in the past 12 months, gravidity, serum vitamin E, serum estradiol and total serum lipids. We also demonstrated that LOOH was increased in women with endometriosis in the study.

PON-1 is highly effective in preventing lipid peroxidation of LDL (Mackness *et al*., 1993). PON-1 is principally responsible for the breakdown of lipid peroxides before they accumulate on LDL (Mackness *et al*., 1993). PON-1 can also destroy hydrogen peroxide, a major ROS produced under oxidative stress during atherogenesis (Aviram *et al*., 1998), and increase the LDL clearance (Shih *et al*., 2000).

Table III. Serum PON-1 and LOOH activities and lipid profiles in subgroups of endometriosis and control groups.

	Women with moderate to severe endometriosis ($n = 23$) (mean ± SD)	Women with minimal to mild endometriosis ($n = 24$) (mean ± SD)	Controls ($n = 40$) (mean ± SD)
TG (mg/dl)	189.0 ± 23.6[a,b]	157.3 ± 22.0[c]	135.0 ± 24.0
TC (mg/dl)	227.5 ± 19.7[a,b]	186.7 ± 21.5[b]	162.6 ± 22.4
HDL (mg/dl)	43.1 ± 6.0[a,b]	52.7 ± 7.7[b]	62.1 ± 8.0
LDL (mg/dl)	150.1 ± 12.1[a,b]	131.4 ± 10.1[b]	113.9 ± 11.7
PON-1 (U/l)	75.9 ± 23.3[a,b]	135.9 ± 21.1[b]	183.7 ± 22.3
LOOH (μmol/l)	18.5 ± 2.3[a,b]	15.3 ± 2.6[b]	11.5 ± 2.3

[a]$P < 0.001$ versus women with minimal to mild endometriosis.
[b]$P < 0.0001$ versus controls.
[c]$P = 0.001$ versus controls.

There is a close relationship between arterial macrophages and oxidative stress in early atherogenesis (Rozenberg *et al*., 2003a). PON-1 directly inhibits macrophage oxidative stress, therefore decreasing the ability of macrophages to release superoxide anions and to oxidize LDL (Rozenberg *et al*., 2003b). In addition, PON-1 inhibits macrophage cholesterol biosynthesis (Rozenberg *et al*., 2003b).

PON-1 protects HDL against lipid peroxidation (Mackness *et al*., 1993; Aviram *et al*., 1998; Rozenberg *et al*., 2003a). Inhibition of HDL oxidation by PON-1 preserves the anti-atherogenic effects of HDL in reverse cholesterol transport (Aviram *et al*., 1998). The antioxidant effect of HDL is also assumed to be mediated by PON-1 (Aviram and Rosenblat, 2004). It has been reported that PON-1 activity was decreased in women with endometriosis as we found in our study (Jackson *et al*., 2005). We also showed that PON-1 activity was significantly lower in women with moderate to severe endometriosis compared with women with minimal to mild endometriosis. PON-1 activity had a strong correlation with the stage of the disease. ROC analysis showed that PON-1 had especially a good ability to discriminate moderate to severe endometriosis from minimal endometriosis and women without endometriosis. It has been reported that the levels of inflammatory mediators, such as monocyte chemotactic protein, interleukin-6 and interleukin-8, correlate with the severity of the disease and inflammation and oxidative stress share a common role in the etiology of a variety of chronic diseases (Mahutte *et al*., 2003). The increased inflammation and oxidative stress in advanced disease may be the possible explanation for decreased PON-1 activity in the moderate to severe endometriosis group shown here.

Endometriosis and atherosclerosis have some pathologic similarities. Both endometriosis (Murphy *et al*., 1998) and atherosclerosis (De Villiers and Smart, 1999; Linton and Fazio, 2001) have tissue macrophages that express scavenger receptors and these macrophages are exposed to lipoproteins. Both atherosclerotic lesions and peritoneal fluid of women with endometriosis are characterized by the presence of macrophages, cytokines derived from macrophages, lipoproteins (LDL, HDL), T cells and cytokines derived from T cells, chemotactic factors for T cells as well as growth factors and oxidized LDL (Santanam *et al*., 2002). Moreover, these factors are suggested to play important roles in recruitment of monocytes, growth promotion and generation of localized inflammation at these sites. In addition, PON-1 activity has been found to be decreased in atherosclerosis, and also in women with endometriosis as we demonstrated in our study.

However, there was a limitation of the study. The diagnosis of endometriosis was based on visual examination. Although some studies relied on visual examination (Hemmings *et al*., 2004; Steff *et al*., 2004; Jackson *et al*., 2005; Louis *et al*., 2005), it has been reported that a correct diagnosis of endometriosis should need histologic confirmation (Marchino *et al*., 2005). We suggest future studies that use histologically confirmed the diagnosis criteria are required and may enhance the value of our findings.

In conclusion, we found significantly lower mean serum PON-1 activity in patients with endometriosis correlating with disease severity. Our findings suggest that decreased levels of PON-1 activity may reflect the progression of endometriosis. We also hypothesize that reduced serum PON-1 activity and HDL and increased LOOH, TG, TC and LDL levels might contribute to the increased susceptibility for the development of atherosclerosis. Further studies with larger groups are needed to investigate that possible relationship between atherosclerosis and endometriosis.

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