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ASSOCIATION OF INFLAMMATORY, ENDOTHELIAL DYSFUNCTION MARKERS AND CARDIOVASCULAR RISK FACTORS IN OVARIECTOMIZED STZ-DIABETIC RATS

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A B S T R A C T

The present study was carried out on eighty female albino rats. They were randomly divided into fourth groups ;the first group involved twenty rats was sham operated control group, the second group was subjected to induction of diabetes type 2 rats were injected with (125 ml/kg nicotinamide) ¼ hour before injection with streptozotocin 60 ml/kg, the third group consist of 20 rats was rendered to bilateral ovariectomy .the fourth group Consists of 20 rats was subject to bilateral ovariectomy and induction of type 2 diabetes. Biochemical investigation involved the measurement of total cholesterol , triacylglycerol , high density lipoprotein (HDL) , low density lipoprotein (LDL) , nitric oxide (NO) , hs-CRP, and TNF-α. The results of the present study indicate that inflammation, unfavorable lipid profile in form of significant increase of total cholesterol, triacylglycerol, and low density lipoprotein (LDL). Meanwhile, the serum nitric oxide in diabetic rats as well as those of ovarictomy were significantly different from those of control. However, serum nitric oxide and, high-density lipoprotein (HDL) concentration in the ovarictomy STZ-Diabetic rats was highly significant decrease compared to those of sham-operated group.

Keywords: inflammation, endothelial dysfunction, cardiovascular risk, diabetes, ovarictomy

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1. INTRODUCTION

The incidence of cardiovascular disease differs significantly between men and women, in part because of differences in risk factors and hormones [1]. Human life was prolonged by 30 years in the past century, with the result that about 40% of a woman's life falls within the postmenopausal period [2]**.** There is now a large body of evidence suggesting that the decline in ovarian function with menopause is associated with spontaneous increases in proinflammatory cytokines. The cytokines that have obtained the most attention are IL-1, IL-6, and TNF- β. The exact mechanisms by which estrogen interferes with cytokine activity are still incompletely known but may potentially include interactions of the ER with other transcription factors, modulation of nitric oxide activity, antioxidative effects, plasma membrane actions, and changes in immune cell function [3]**.** The menopausal consequences, both early and remote, in the form of cardiovascular disease, osteoporosis and neoplastic disease are most pronounced in women suffering from one of the most common diseases, i.e., diabetes mellitus. These patients are problematic for physicians [2]**.**

Many postmenopausal women live with diabetes mellitus; however, little information is available about how the changes that occur around the time of menopause might uniquely affect management of diabetes mellitus in this population [4]**.** postmenopausal diabetic patients encountered the reality of increased atherogenic lipid profile [5], as well as redox imbalance [6], and thereby increased cardiovascular risk factors. It was therefore, worthwhile to investigate the mechanisms that underlie these relationships and to determine how these observations should influence recommendations for the care of postmenopausal women with diabetes. This study was undertaken to evaluate the role of inflammatory markers on endothelial dysfunction hence cardiovascular risk factor of estrogen deficiency in diabetes via determination of some inflammatory markers such as: Serum Tumor Necrosis Factor-alpha.(TNF-α), high sensitive C- Reactive Protein (hs-CRP). Also, determination of serum Nitric oxide as a marker of endothelial dysfunction and serum lipid profile.

2. MATERIAL AND METHODS

2.1. Animals

Eighty Female albino Wistar rats of (200-250) g body weight were used in the study. . Rats were obtained from the laboratory animals research center, Faculty of Veterinary Medicine, Moshtohor, Benha University.

Animals were housed in separate metal cages, fresh and clean drinking water was supplied *adlibtium*. Rats were kept at a constant environmental and nutritional condition throughout the period of experiment. The animals were left for 15 days for acclimatization before the beginning of the experiment.

2.2. Chemicals

Streptozotocin powder supplied by Sigma chemical Co. (USA). All chemical and kits purchased from Sigma (USA).

2.3. Experimental design : Rats were allocated as follows:

Group 1: Sham-operated control rats (Sham): (n =20)

Rats in this group were subjected to all surgical procedures of ovariectomy except for removal of ovaries. 2 weeks later, they studied 2 weeks after STZ injection

Group 2: Sham-operated streptozotocin diabetic rats (STZ): (n =20)

Rats in this group were subjected to induction of type 2 diabetes [7], and all surgical procedures of ovariectomy except for removal of ovaries. They were studied 2 weeks after STZ injection.

Group 3: Ovariectomized rats (OVX): (n =20)

Rats in this group were subjected to bilateral ovariectomy. 20 days after the operation, they received a single i.p. injection of citrate buffer (1 ml/kg) and were studied 2 weeks after buffer injection.

Group 4: Ovariectomized STZ diabetic rats (OVX–STZ): (n =20)

Rats in this group were subjected to bilateral ovariectomy. 20 days after the operation, they renderd to diabetes.

2.4. Ovariectomy:

For the experimentation, animals were either ovariectomized or sham operated [8]. Bilateral ovariectomy [9] was performed under anesthetic condition with a single mid-ventral incision. For sham operation, ovaries were located but were not removed from the body. Following surgery, animals were kept in a resting phase for about 20 days to enable them to recover completely from surgical stress and to allow the circulating sex steroid levels to diminish.

2.5. Blood Sample Collection:

The animals were fasted over night. Blood samples were withdrawn via eye vein using ether as general anesthetic. The samples were centrifuged at 3000 rpm. Serum was separated then divided into 3 fractions and stored at -20 °C until assayed for serum lipid profile (Triglycerides, total cholesterol, LDL-c, HDL-c), Nitric Oxide and inflammatory markers (hs-CRP and TNF-α).

2.6. Statistical analysis:

All data were expressed as mean ± SD and statistical significance was evaluated using One Way ANOVA followed by Tukey's Multiple Comparisons test using Graph Pad Prism Version 6.0 for Windows (Graph Pad Software, San Diego, CA, USA). The mean difference is significant at the 0.05 level

3. RESULTS AND DISCUSSION

In general, the combination of female sex steroid hormone deficiency with insulin hormone deficiency in ovariectomized diabetic rats resulted in worsening of many metabolic aspects as compared to rats exposed to any of them alone. Unfriendly lipid profile persisted and was aggravated following combination of ovariectomy to diabetes where serum triglycerides, total cholesterol and LDL-c showed significant increase as compared to control, ovariectomized and diabetic rats while serum HDL-c was significantly decreased compared to controls, ovariectomized and diabetic. This result is similar to a recent study showed that an increment in lipid profile cannot only lead to increasing insulin resistance and exaggerated type 2 diabetic complications but also predispose PMW and POF/surgical menopause individuals to cardiovascular disorders [10]. The prominent effects of estradiol deficiency on decreasing the number of LDL-c receptors and elevating hepatic lipase activity [11,12], were added to the deleterious effects of insulin deficiency on altering the activity of lipoprotein lipase, increasing VLDL-c, triglycerides and LDL-c due to defective clearance of these particles from circulation together with acceleration of clearance of HDL-c, all of which resulted in a significant elevation of these hazardous triglycerides, total cholesterol and LDL-c and lowering of HDL-c in ovariectomized diabetic rats as compared to controls and even to rats exposed to either ovariectomy or diabetes [13]. In the current work hs-CRP was showed highly significant increase in ovarictomiezed STZ-diabetic group compared to sham operated (P<0.001) and significant increase compared to diabetic and ovarictomized groups (p<0.001) , also serum TNF-α revealed significant increase compared to sham operated group (p<0.001) and significant elevation compared to diabetic and ovarictomized groups (p<0.001) (table 1 figure 1,2). This finding was similar to the results obtained by other study showed that Induced diabetes and ovariectomy significantly increase both TNF-α and IL-1 b levels and it was demonstrated that DM, combined with ovariectomy, augments the levels of oxidant and pro-inflammatory cytokines in the lung, liver, and heart [14]. The recorded results may be also attributed to an insulin resistance state may facilitate hepatic hs-CRP production because insulin has anti-inflammatory effects and resistance to this effect would then lead to increased synthesis of CRP [15]. It is also possible that mildly impaired glucose status with-out clinical diagnosis may elicit oxidative stress and production of free fatty acids that may raise levels of hs-CRP [16], these effects added to the deleterious effects of estrogen deficiency which has also been shown to enhance the sensitivity of cells such as monocytes, osteoblasts, and endothelial cells to these cytokines by up-regulating cytokine receptor expression [3]. The role of hs-CRP in the pathogenesis of atherosclerosis is receiving increased attention because of the effect of hs-CRP on the production of the

Table (1) Show TNF-α and hs-CRP in diabetic , ovarictomized and ovariectomized STZ- diabetic rats versus control group.

		TNF-α (pg/ml)	Hs-CRP (mg/L)	
SH	mean±SD	32.6±4.7	±0.33	0.95
DIA	mean±SD	201.2±16.01		5.52 ±2.8
P1		<0.001	<0.001	
OVX	mean±SD	178.3±17.4		4.3
P2		<0.001	±1.47	<0.01
P3		<0.05	NS	
OVX+DIA	mean±SD	273.2±20.4		8.82 ±3.8
P4	P5	<0.001	<0.001	
P6		<0.001	<0.01	
		<0.001	<0.001	

P1 (DIA × SH), P2 (OVX × SH), P3(DIA ×OVX), P4 (OVX-DIA × SO), P5 (OVX-DIA group × DIA) and P6 (OVX-DIA × OVX), P is statistically significant if ($P \leq 0.05$).

Table (2). Serum nitric oxide in diabetic ovariectomized and ovariectomized STZ- diabetic rats versus control group.

	SH	DIA	OVX	OVX-DIA
NO (µmol/L) Mean ± SD	20.72 ±1.06	17.32 ±0.6	17.63 ±1.27	15.7 ±0.78
P1		P<0.001	P<0.001	P<0.001
P2		P<0.01	P<0.001	
P3		NS		

NO (Nitric Oxide) , p1 (compared to sham operated group) , P2 (compared to ovariectomized STZ-diabetic group) and P3 (DIA ×OVX).

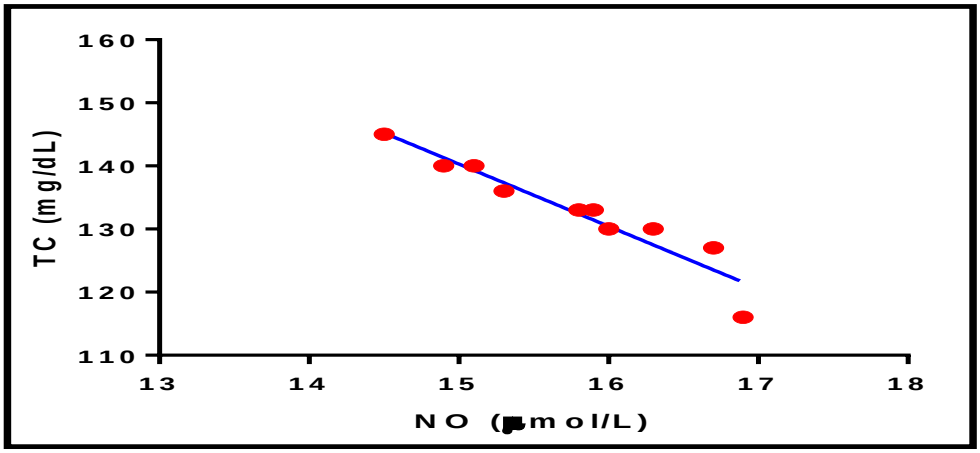

Figure (1). Correlation coefficient (r) between serum nitric oxide and total cholesterol in ovariectomized STZ-diabetic group.

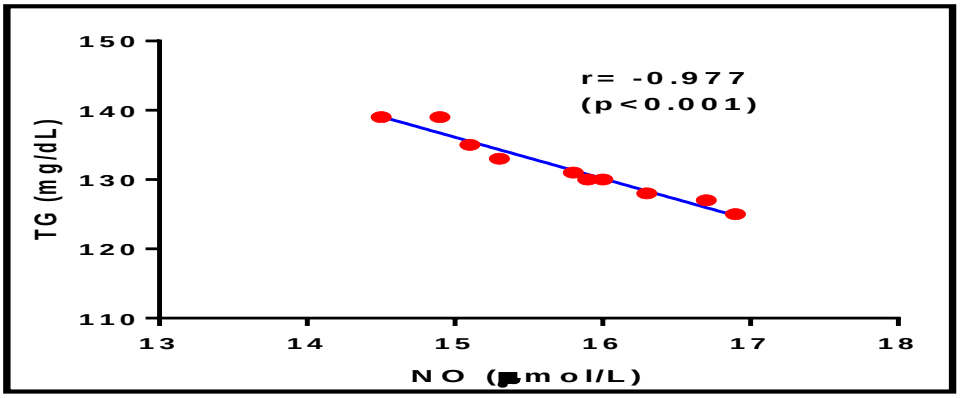

Figure (2). Correlation coefficient (r) between serum nitric oxide and total cholesterol in ovariectomized STZ-diabetic group.

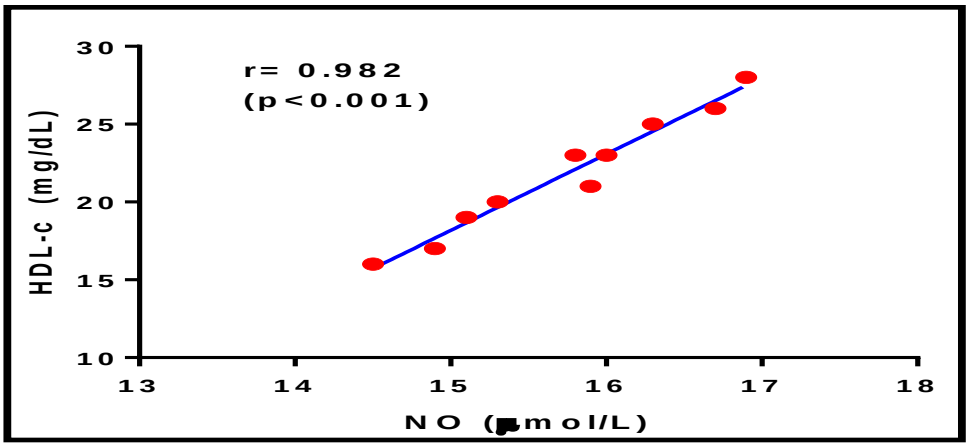

Figure (3). Correlation coefficient (r) between serum nitric oxide and total cholesterol in ovariectomized STZ-diabetic group.

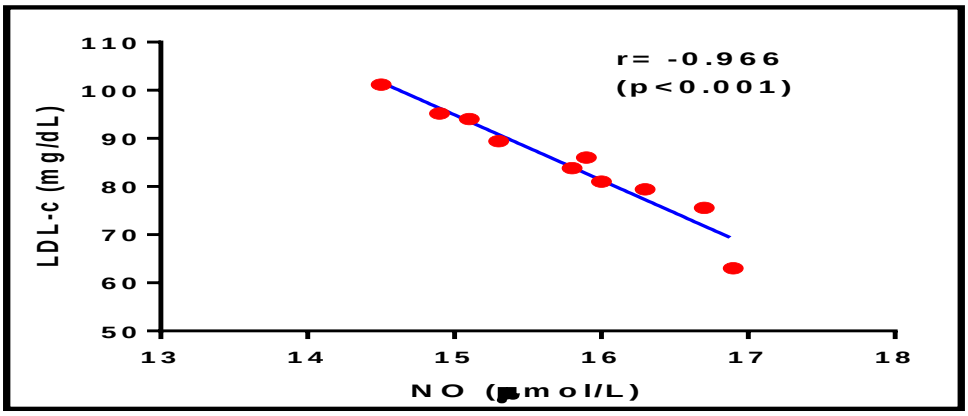

Figure (7). Correlation coefficient (r) between serum nitric oxide and total LDL-c in ovariectomized STZ-diabetic group.

chemokine monocyte chemo-attractant protein-1, which is abolished by fenofibrate but not by aspirin [17], CRP promotes monocyte chemoattractant protein 1–mediated chemotaxis through upregulating CC chemokine receptor 2 expression in human monocytes [18]. Each CRP molecule consists of 5 identical protomers; each protomer has 2 calcium ions that bind to LDL to form a complex. This complex induces the formation of foam cells on the endothelial cell wall, attracting monocytes. Thus, a high level of CRP is both a marker and a cause of atherosclerotic lesions [19]. There are also in (table 2, figure 3) a highly significant decrease in serum nitric oxide in ovarictomized-diabetic rats compared to sham operated control group ($p<0.001$) and significant decline compared to diabetic and ovarictomized groups ($p<0.01$, $p<0.001$) respectively. The results of the present study further support the concept that, the endothelial dysfunction observed in the insulin-resistant states of obesity and type 2 diabetes has been attributed to decreased nitric oxide (NO) availability, likely related to both impaired production and increased consumption. Endothelial function reflects an imbalance of both vasodilating and vasoconstricting factors [20,21]. Endogenous endothelin-1 activity is increased in obesity and type 2 diabetes, and several studies suggest that this factor may itself reduce the bioavailability of NO, through impairment of NO generation by the vascular endothelium as well as via direct vasoconstrictor effects on the vascular endothelium [20], but, other study related it to the positive vascular effects of estrogen which have been attributed primarily to estrogen upregulation of endothelium-derived nitric oxide (NO) [22]. Also, in this group there are negatively significant correlation between serum nitric oxide and total cholesterol, TG and LDL-c but, there was positively correlation between nitric oxide and HDL-c. The recorded correlation may be also attributed to that hypercholesterolemia was reported to impaired endothelial function, manifested as an attenuation of endothelium-dependent relaxation prior to the formation of atherosclerosis [23]. The additive effect of estrogen and insulin deficiencies could explain the significant rise in blood glucose following streptozotocin injection in ovariectomized rats that was even significantly higher than diabetic rats [24]. Not only, but also a highly significant elevation of inflammatory markers, endothelial dysfunction, and dyslipedimia. Ovariectomy and diabetes teamed up for worsening dyslipidemia, where serum triglycerides, total

cholesterol and LDL-c were significantly higher than sham-operated, ovariectomized and diabetic groups and the atherogenic index was significantly higher than control and ovariectomized groups while serum HDL was significantly lower than sham-control group. These data are confirmed by the significant negative correlation between each of plasma estradiol and insulin with triglycerides, total cholesterol, LDL-c and atherogenic index and significant positive correlation with plasma HDL-c [24.] The complications of Diabetes Mellitus include cardiovascular disease (CVD) and it has been found that CVD is due in part to low grade systemic inflammation [25]. In addition, In the Increased triglyceride and LDL levels are risk factors for cardiovascular disease [26]. In general, there is accumulating evidence that inflammation is an important risk factor in cardiovascular disease (CVD). Elevated levels of the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) are associated with increased risk for CVD and diabetes mellitus. Adding hs-CRP to the definition of the metabolic syndrome has been shown to improve the prediction of CVD. Elevated hs-CRP levels may also be predictive of development of the metabolic syndrome [27]. Overall, Inflammation is an important risk factor in cardiovascular disease (CVD), Dyslipidemia together with hypertension and diabetes is major modifiable risk factor for atherosclerotic disease and the subsequent development of cardiovascular events [28,29.] Endothelial dysfunction, which is a condition that has been strongly associated with dyslipidemia, plays a key role in the development and progression of atherosclerosis [30] and it is known to be an independent predictor for cardiovascular events [31]

The reduced availability of nitric oxide (NO) resulting from both a decreased synthesis and/or an enhanced degradation by reactive oxygen species seems to be the major cause of endothelial dysfunction documented in subjects with cardiovascular risk factors including dyslipidemia [32]. It is also well accepted that atherosclerosis can be considered a chronic vascular inflammatory disease [33]. Inflammatory cytokines are responsible for activation of endothelial cells, a condition characterized by the expression of endothelial cell surface adhesion molecules such as vascular cell adhesion molecule-1 (sVCAM-1) and p-Selectin, that favor the attachment of circulating monocytes to the endothelium [34]. Similarly, C-reactive protein (CRP), which is a well-described inflammatory marker, has been shown to be an independent predictors of future cardiovascular events in both high-risk and healthy subjects [35,36]. Moreover, increased circulating cytokines including tumor necrosis factor alpha (TNF α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6) have also been associated with cardiovascular events [37]. In view of the aforementioned data, diabetic rats showed marked hyperglycemia, dyslipidemia, elevated inflammation and significant endothelial dysfunction. Ovariectomized rats showed increased inflammation, unfavorable lipid profile and increased endothelial dysfunction. Combination of these two metabolic threats in ovariectomized diabetic rats was associated with dyslipidemia, inflammation and endothelial dysfunction than did ovariectomy or diabetes alone. In addition, a significant correlation was established between serum nitric oxide with lipid profile and inflammatory markers in this study this is can report that, there are correlation of dislipidemia, inflammatory, endothelial dysfunction markers and cardiovascular risk factor in ovarictomized STZ- diabetic rats.

Conclusion: It can be concluded that estrogen deficiency with diabetes worsen the metabolic consequences of either disorder alone. These data suggest that insulin and estrogen deficiency may act as mixed hazards, and increase cardiovascular risk factors. Therefore it must be careful and

under physician supervision to avoid more risk and guard against its effects.

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تداخلات دلالات الالتهاب والخلل الوظيفي للبطانة الداخلية للأوعية الدموية وعوامل الخطورة المسببة لأمراض القلب في الجرذان مستأصله المبايض والمصابة بمرض البول السكري التجريبي

أميمة أحمد رجب أبو زيد، عاطف جوده، سحر السيد البدوي احمد

قسم الكيمياء الحيوية –كلية الطب البيطري بمشتهر–جامعة بنها.

الملخص العربي

في محاوله لمواكبه العصر ودراسة مشكله بدت في هذه الآونة من أهم المشكلات وأكثرها انتشارا وهي مرض البول السكري في حاله نقص الاستروجين كتلك التي تحدث بصوره طبيعية للسيدات في سن اليأس أو جراحيا كاستئصال المبايض لأي سبب . بالإضافة إلى قله الدارسات التي أجريت أو اتجهت لهذا النحو. لذا تم إجراء هذا البحث لدراسة تأثير النقص في هرمون الاستروجين مع مرض البول السكري على ما يمكن ان يحدث داخل الجسم من التهابات او خلل وظيفي للبطانة الداخلية للأوعية الدموية مما قد يؤدي إلى زيادة عوامل الخطورة على القلب .وقد أجريت هذه الدراسة على عدد (80) ثمانون من إناث الفئران البيضاء والتي تتراوح أعمارها بين شهر وشهر ونصف وأوزانها بين 200–250 جرام، وضعت في أقفاص حديدية مفصولة وتعايشت في نفس الظروف البيئية وظروف التربية والتغذية لمدة أسبوع قبل بدأ التجربة حيث تم تغذيتها على نفس نوع العليقة دون تمييز. قسمت إلى أربع مجموعات: 1. المجموعة الضابطة: تعرضت هذه المجموعة إلى عمليات زائفة لاستئصال المبيضين لمدة أسبوعين ثم تم حقنها بمحلول السترات. 2. مجموعة مستحدث فيها مرض البول السكري: تم حقنها (125 مج/كجم نيكوتين أميد ربع ساعة قبل حقنها ب (60 مج/كجم الاستربتوزوتوسين). 3. مجموعة استئصال المبيضين. 4. مجموعة تم فيها استئصال المبيضين ثم استحداث مرض البول السكري بحقنها بمادة الاستربتوزوتوسين (60 مج/كجم مسبوقة بحقن النيكوتين أميد (125 ملليجرام/كيلوجرام من وزن الجسم) ثم تم دراستها بعد أسبوعين. تم تجميع العينات بعد الأسبوع الخامس من بداية التجربة وقد أوضحت الدراسة ما يلي :أسفر الجمع بين تأثير استئصال المبيضين واستحداث مرض البول السكري عن انخفض استهلاك الأنسجة للسكر وكذلك زادت معدلات قياس دلالات الالتهاب زيادة ملحوظة مقارنه بالمجموعة الضابطة وكذلك مجموعه البول السكري ومجموعه استئصال المبايض. أيضاً ارتفعت الزيادة في الدهون والكولسترول ارتفاعاً ذا دلالة إحصائية بالمقارنة بالمجموعتين السابقتين. كما سجلت هذه المجموعة أيضا انخفاضا واضحا في مستوي النيتريك أكسيد في الدم مما يشير إلى وجود خلل وظيفي في البطانة الداخلية للأوعية الدموية. كما لوحظ وجود علاقة عكسية بين مستوى النيتريك أكسيد وكل من الدهون الثلاثية والكولسترول في الدم وأيضا دلالات الالتهاب مما يشير إلى أن الجمع بين النقص في هرمون الأستروجين ونقص هرمون الأنسولين يرفع من نسبة حدوث أمراض القلب وتصلب الشرايين بصوره أكبر من أي منهما على حدة.

(مجلة بنها للعلوم الطبية البيطرية: عدد 24 (1)، يونيو 2013: 309–319)