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Review

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Pentraxin 3 – a potential link between inflammation, obesity and cardiovascular complications in polycystic ovary syndrome

Pentraksyna 3 jako czynnik łączący stan zapalny i otyłość oraz powikłania sercowo-naczyniowe w zespole policystycznych jajników

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Summary

Polycystic ovary syndrome (PCOS) is the most frequently diagnosed endocrine disorder among women in reproductive age. Metabolic disturbances in PCOS include among others increased incidence of insulin resistance and hyperinsulinemia, type 2 diabetes, dyslipidemia, pre-thrombotic state, hypertension, sleep apnea, atherosclerosis and cardiovascular diseases. Adipose tissue disturbances, including inflammation, were shown to play an important role in the development of both endocrine and metabolic disturbances, accelerating the progression of arteriosclerosis, which leads to premature cardiovascular disease development in PCOS.

Pentraxin 3 (PTX3) seems to be one of the factors linking obesity and cardiovascular complications observed in PCOS. PTX3 belongs to a family of long pentraxin proteins. It primarily plays a role in acute immunological response; however, some data suggests that it may also be involved in oocyte maturation. In contrast to the short pentraxin, C-reactive protein, which is primarily produced in the liver, PTX3 is produced locally in the site of the inflammation by several types of cells, for example, adipose tissue during development of inflammation. Increased PTX3 expression was found in visceral fat tissue in obese subjects, and was shown to be under TNF-α control. PTX3 expression has not been tested in PCOS women, yet.

Up to now there are only 5 studies investigating PTX3 in PCOS. Only in one study PTX3 level in PCOS women was increased compared to the control groups, in two other studies – decreased, and in two – similar. Also, the association between PTX3, PCOS and obesity remains uncertain.

Further research, including ones with a greater number of subjects, especially obese and older women, are necessary to assess the role of PTX3 as a potential link between the inflammation, obesity and polycystic ovary syndrome.

Keywords: **pentraxin 3 • inflammation • obesity • PCOS**

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Abbreviations: **AMH** – anti-mullerian hormone, **BMI** – body mass index, **CIMT** – carotid intima-media thickness, **CCL2** – monocyte chemoattractant protein-1, **CRP** – C-reactive protein, **CVD** – cardio-vascular diseases, **eNOS** – endothelial nitric oxide synthase, **GDM** – gestational diabetes mellitus, **HDL-C** – high density lipoprotein cholesterol, **HOMA-IR** – homeostatic model assessment insulin resistance, **ICAM-1** – intercellular adhesion molecule – 1, **IHD** – ischemic heart disease, **IL-1β** – interleukin 1β, **IL-6** – interleukin 6, **IL-10** – interleukin 10, **MCP-1** – monocyte chemoattractant protein-1, **oxLDL** – oxidised low-density lipoproteins, **PCOS** – polycystic ovary syndrome, **PCO** – polycystic ovaries, **Pre-proAVP** – pre-provasopressin, **PTX3** – pentraxin 3, **SAA** – serum amyloid A, **TNF-α** – tumor necrosis factor alpha, **TG** – triglycerides, **TGF-β** – transforming growth factor beta, **TLR** – toll-like receptor, **VCAM-1** – vascular cell adhesion protein-1, **WC** – waist circumference, **WHR** – waist-hip ratio.

INTRODUCTION

Polycystic ovary syndrome (PCOS), the most frequently diagnosed endocrine disorder among women in reproductive age, is characterized by the co-occurrence of ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology [21]. Hyperandrogenism (present in 60-80% of patients), elevated concentrations of free testosterone and an increased index of free androgens are frequent; however, these markers cannot be taken as a single diagnostic criteria because normal values are observed in 20-40% PCOS women. It has been shown that mothers and sisters of PCOS women have increased concentrations of androgens [27]. In addition, there is also an abnormal profile of adipokines expression in PCOS women. An inverse association between serum LH concentration and plasma resistin level hasbeen described as well as lower levels of adiponectin in obese PCOS women [42,43]. Detailed pathogenesis of PCOS remains largely unknown. There are some new markers which are suspected to play an important role in PCOS pathogenesis, among them, pentraxin 3 (PTX3). Therefore, the aim of this manuscript was to present the current state of knowledge about the possible role of PTX3 as a risk marker of metabolic disturbances in PCOS.

Obesity, especially visceral, is an important risk factor of hormonal and metabolic disturbances observed in PCOS women. The metabolic disturbances in PCOS include: insulin resistance and hyperinsulinemia, type 2 diabetes, dyslipidemia, pre-thrombotic state, hypertension, sleep apnea, atherosclerosis and cardiovascular diseases (CVD) [13,45]. Ehrman et al. showed that the prevalence of metabolic syndrome in women with PCOS is higher compared with the general population, especially among women with a higher insulin level and body mass index (BMI) [18]. Meta-analysis conducted by Mayer et al. revealed that women with PCOS have a greater carotid artery intima-media thickness than healthy controls [36], which may predict a high risk of cardiovascular disease [24]. It was observed that hypertension and ischemic heart disease (IHD) occur approximately a decade earlier among women with PCOS than in healthy women [63]. Recently, a 7-fold higher risk for myocardial infarction and 3.3-fold higher risk of cardiovascular death in postmenopausal women with PCOS have been reported [14,34]. This suggests that women with this syndrome have additional risk factors for premature cardiovascular disease development [62].

Atherosclerosis plays the most important role in the pathogenesis of cardiovascular diseases in the general population. There are several factors that could explain the earlier development of atherosclerosis in PCOS, including increased prevalence of obesity, low-grade systemic inflammation, abnormal adipokines secretion, insulin resistance, impaired glucose tolerance, dyslipidemia and hyperandrogenism [25]. It was shown that endothelial dysfunction in PCOS is strictly related to the increased release of several cytokines by adipose tissue. Visceral adipocytes with increased volume release monocyte chemoattractant protein – 1 (MCP-1; also known as CCL2) that stimulates monocytes migration, deposition in fat tissue and transformation to macrophages [49]. Mutual interactions between those two groups of cells increase tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) secretion [49]. Increased production and release of proinflammatory cytokines by the adipose tissue is associated with an increase in their concentrations in the circulation, and,

in a consequence, the development of systemic micro-inflammation and endothelial dysfunction. Endothelial dysfunction is manifested by an increase in the synthesis of adhesion molecules (vascular cell adhesion protein – 1 [VCAM-1], intercellular adhesion molecule – 1 [ICAM-1] and endothelin – 1) and reduced activity of endothelial nitric oxide synthase (eNOS), with decreased nitric oxide production [54].

Chronic low-grade inflammation was proved to play a major role both in insulin resistance and atherosclerosis development [7]. In several epidemiological studies, serum C-reactive protein (CRP) has been shown to independently predict cardiovascular risk [10]. The increased CRP levels have been reported in women with PCOS [20].

Serum amyloid A (SAA), another molecule involved in the inflammatory response, is released from hypertrophic adipocytes and is involved in cholesterol metabolism modulation during inflammatory state [28]. Several studies suggest that its concentration is increased (sometimes even double the concentrations observed in healthy controls) in women with PCOS, and this increase is independent of changes of other inflammatory markers as CRP, myeloperoxidase or neopterin (marker of cellular system activation released by macrophages) [22,28,58]. This increase was observed both in serum as well as in adipose expression of SAA, which suggests that adipose tissue in women with PCOS may be the primary source of increased inflammation markers. It was also shown that SAA concentrations decrease during treatment of insulin resistance with metformin, with a significant link to a decrease in glucose level [58].

Data from the literature suggests that copeptin, anti-mullerian hormone (AMH) and PTX3 can also play a role in PCOS-related metabolic and cardiovascular disturbances development.

Copeptin is a C-terminal part of pre-provasopressin (pre-proAVP). It is a marker of stress and seems to be involved in the pathogenesis of obesity-related complications [19,52]. Karbek et al. observed that copeptin positively correlated with fasting insulin, triglycerides (TG) and free testosterone levels as well as carotid intima-media thickness (CIMT), homeostatic model assessment insulin resistance (HOMA-IR) and hyperandrogenism assessed by Ferriman-Gallwey scoring system in PCOS women [29]. However, Deveer et al. did not confirm these associations [15]. These authors found only a positive correlation between copeptin and BMI and serum cholesterol level.

AMH is a molecule that belongs to transforming growth factor beta (TGF-β) family. Its level is positively associated with androgens levels in PCOS [16] or total testosterone levels [15,48]. However, not all studies demonstrated these associations [23]. Its role and relations with other markers require more detailed analysis in laboratory and clinical studies [61].

PTX3 is an inflammatory marker that is released during fat tissue inflammation development [33]. It belongs to a family of long pentraxin proteins, involved in acute immunological response. In contrast to the short pentraxin – C-reactive protein, which is primarily produced in the liver, PTX3 is produced locally in the site of inflammation. It is expressed by several types of cells, primarily monocytes, macrophages, dendric cells, endothelial cells, smooth muscle cells and fibroblasts [55]. PTX3 expression is modulated by a number of anti-inflammatory molecules such as high-density lipoprotein cholesterol (HDL-C) in endothelial cells (low HDL-C may induce PTX3 expression and release by endothelial cells) [8]. PTX3 production seems to be stimulated by several cytokines, including interleukin 1β (IL-1β), TNFα, interleukin 10 (IL-10) and by toll-like receptor (TLR) agonists and oxidised low-density lipoproteins (oxLDL), but not by IL-6 [17]. Conversely, IL-6 induces CRP secretion [46]. Low PTX3 may enhance insulin resistance through diminished effects on glucose transport proteins, enhance complement mediated inflammation and promote the recruitment of leukocytes to inflamed endothelium [32].

Apart from its anti-inflammatory properties, PTX3 was described to be involved in the regulation of fertility. PTX3 expression increases in cumulus-oocyte complex before successful ovulation. PTX3 belongs to so-called hyaladherins – one of its roles is to stabilize cumulus oophorus hyaluronian-rich extracellular matrix during follicular maturation [3]. Studies on rat models of PCOS showed considerably reduced levels of PTX3 during follicular maturation and ovulation phases [3]. Interestingly, PTX3 levels are markedly elevated in women with preeclampsia [61] and type 1 diabetes during pregnancy [12] and correlates with the degree of glucose intolerance in women with gestational diabetes mellitus (GDM) [59].

PENTRAXIN 3 IN OBESITY AND OBESITY-RELATED DISEASES

Miyaki et al. reported elevated plasma PTX3 levels in obese men [38]. Additionally, higher PTX3 levels were described in subjects with metabolic syndrome [66]. A positive association between PTX3 and visceral obesity in subjects with acute myocardial infarction was also described [56]. In a large cohort study including nearly 2,900 participants aged 45-84, performed by Jenny et al., PTX3 levels were not associated with BMI as a continuous measure; however, increased PTX3 concentrations were observed in subsequent BMI categories [26]. Numerous studies described an inverse relation between body mass and systemic PTX3 concentrations. Bossuti et al. reported an inverse association of PTX3 with fat mass in men under caloric restrictions and bed rest [9]. The similar inverse associations have also been described by Knoflach et al. [30].

PTX3 expression was found both in subcutaneous and visceral fat tissue, and was higher in the visceral tissue of obese than in normal weight subjects [1,44], and

probably was under TNF-α control [44]. Surprisingly, despite upregulation of PTX3 gene in visceral adipose tissue depots, lower plasma concentrations in obese subjects was shown [44], which may suggest low specificity of applied ELISA. Contrary to Shim et al., a study of Barazzoni reported an inverse association between obesity and circulating PTX3 in acute coronary syndrome patients [6]. In this study, PTX3 was inversely associated with BMI and waist circumference [6,51]. Similar results were obtained by Miyaki et al. In addition, a negative correlation between PTX3 levels and arterial stiffness was found [37], as well as an inverse relationship between this inflammatory marker and both fat, body mass and visceral obesity was shown in patients with chronic kidney failure [39]. Furthermore, both Ogawa et al. and Yamasaki et al. showed lower PTX3 in subjects with metabolic syndrome [41,65]. In the second study, such a correlation was reported also for body mass and waist circumference [65]. Other studies confirmed the above-mentioned inverse relation between PTX3 and anthropometric parameters [40,64]. In a large study by Miyazaki et al., participants with higher PTX3 concentrations had a lower prevalence of metabolic syndrome, as well as lower BMI and waist circumference [40].

Previous studies indicated that PTX3 is related to a higher risk of CVD; however, its role is not clear [26,47,57]. Jenny et al. [26] observed that PTX3 was positively associated with age, insulin levels, systolic blood pressure, CRP and CIMT. A higher level of PTX3 was associated with an increased risk of myocardial infarction, combined with CVD events and IHD events but not stroke, CVD-related mortality or any cause of death. In addition, Peri et al. suggested that PTX3 is as early marker of acute IHD in the case of the absence of correlation between PTX3 and CRP concentration [47].

PENTRAXIN 3 AND POLYCYSTIC OVARY SYNDROME

The above-described observations that PTX3 level is related to a higher risk of CVD and that women with PCOS have a higher risk of CVD suggest a role of PTX3 in CVD development in PCOS women.

Similarly to studies describing the relationship between PTX3 and obesity and obesity-related diseases, to our knowledge, there are only 5 studies investigating PTX3 levels in PCOS, and no study assessing its expression in adipose tissue. In a study by Deveer et al. [15], serum PTX3 level was similar in adolescent PCOS group, adult

Table 1. Available data on PTX3 levels among PCOS women compared with healthy controls

	PCOS women				Healthy controls				Kit producer	References
	Group size (*n*)	**Age (*years*)**	**BMI (kg/m^2)**	**PTX3 (*ng/ml*)**	**Group size (*n*)**	**Age (*years*)**	**BMI (kg/m^2)**	**PTX3 (*ng/ml*)**		
	40	24.7 ± 6.2	28.8 (14.0)	**0.65 (1.28)**	40	25.9 ± 4.5	25.0 (15.0)	**0.89 (0.72)**	ELX50; BioTek Instruments, USA	[53]
BMI <25 kg/m^2	20	24.5 ± 3.4	22.0 (2.0)	**0.50 (1.75)**	20	26.7 ± 4.2	20.3 (4.0)	**1.1 (1.52)**		
BMI ≥25 kg/m^2	20	25.8 ± 5.9	35.8 (7.0)	**0.65 (0.99)**	20	25.0 ± 4.7	35.8 (2.0)	**0.86 (0.67)**		
	40	21.3 ± 4.7	24.7± 5.3	**1.0 ± 3.6**	40	21.9 ± 3.5	22.5 ± 2.4	**0.8 ± 0.3**	R&D Systems, Inc, MN, USA	[4]
Adolescent PCOS										
	25	18.0 ± 1.6	23.8 ± 4.2	**1.36 ± 0.56**	25	31.8 ± 8.1	25.4 ± 5.1	**2.0 ± 1.0**	Boster Biological Technology Co., Ltd, CA, USA	[16]
Adult PCOS										
	25	27.2 ± 5.3	25.9 ± 4.6	**1.64 ± 0.72**						
	66	23.0 (19.0-27.0)	28.5 (22.9-33.9)	**0.84 (0.46-1.62)**	51	27.5 (24.0-32.0)	21.0 (19.7-22.5)	**1.15 (0.76-1.88)**	R&D Systems, Inc, MN, USA	[60]
	64	22.9 ± 4.3	30.3 ± 8.7	**5.5 ± 2.8**	46	21.9 ± 4.5	29.7 ± 5.2	**6.8 ± 2.7**	Hycult biotech, Netherlands	[51]
BMI ≤25 kg/m^2	NA	NA	21.2 ± 2.0	**6.7 ± 2.6**	NA	NA	24.0 ± 2.7	**6.9 ± 2.4**		
BMI >25 kg/m^2	NA	NA	35.2 ± 7.0	**4.8 ± 2.8**	NA	NA	32.1 ± 3.8	**6.8 ± 2.8**		

Data presented as means ± SD, or median (IQR), NA – not available

PCOS group and control subjects. Also, Sari et al. [53] found no difference in PTX3 level between PCOS women and the control group (our analysis of the table attached in this paper allows us to conclude that there was a tendency towards statistical significance (p=0.09) for PTX3 to be lower in PCOS subjects than in the control group (Table 1). Data on PTX3 concentrations among women with and without PCOS are inconsistent – Tosi et al. [60] observed decreased and Aydogdu et al. [4] increased PTX3 concentrations in women with PCOS compared with healthy controls. The last study [4] also described increased circulating PTX3 levels as a predictor of insulin resistance (positive correlation between PTX3 and BMI, waist-hip ratio (WHR), high sensitivity CRP and HOMA-IR), which may predict a higher risk of atherosclerosis development later in life. Similar correlations were described in a study by Sari et al. [53]. Also, Sahin et al. observed significantly lower serum PTX3 levels in PCOS women than in the control group [51]. Results obtained in all of the above mentioned studies are presented in Table 1.

Only in the studies by Sari et al. [53] and Sahin et al. [51] the participating women were divided according to BMI values (normal weight and overweight or obesity). Sari et al. [53] observed no difference in PTX3 concentrations between all groups. However, there was a tendency to statistical significance (p=0.05). Women of normal weight with PCOS had the lowest PTX3 levels (0.5 ng/ml, median=1.75) compared to normal weight controls, obese PCOS group and obese controls. Contrary Sahin et al. [51] observed significantly lower serum PTX3 concentrations in obese PCOS women than in normal weight PCOS women, as well as normal weight and obese controls.

The differences are difficult to explain. It should be stressed that none of the commercial ELISA kits for PTX3 was validated against quantitative western-blot method. It seems that the methodology of all the above mentioned studies was similar. It should be noted that all studies included comparable number of patients. The diagnosis of PCOS in four out of five of the studies were carried out according to Rotterdam European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine – sponsored consensus Workshop Group (presence of two out of three of: clinical or biochemical manifestation of hyperandrogenism, oligomenorrhea and polycystic ovaries in ultrasound) [50]. An exception was the study by Deveer et al. [15], who used criteria proposed by Carmina et al. (all three: hypeandrogenism, chronic anovulation and polycystic ovaries must be present) [11]. Measurements of PTX3 levels in all studies were performed with ELISA kit during early follicular phase of menstrual cycle. However, the used kits were produced by different manufacturers.

An almost 10-fold difference in PTX3 concentrations levels between studies of Sari et al. [53] and Sahin et al. [51] (in normal weight PCOS women respectively: 0.50 ng/ml, median=1.75 vs. 6.7±2.6 ng/ml) has to be stressed. PTX3 concentrations obtained in the other three studies were more comparable with the results obtained by Sari et al. [53].

Additionally, the results presented by Sahin et al. are inconsistent [51]. These authors wrote in their abstract that 'serum PTX3 level of PCOS patients were significantly higher than in the control group' and 'PCOS women with obesity had significantly higher serum PTX3 level than normal weight PCOS subjects, normal weight controls and obese controls'. However, according to the main text and attached table, PCOS patients had lower serum PTX3 levels than the control group and obese PCOS women had a significantly lower serum PTX3 concentration than normal weight PCOS women, normal weight controls and obese controls (Table 1).

It is hypothesised that PTX3 secreated by different tissues or the cellular component [55] may play different roles [60]. Different places of PTX3 synthesis can also influence its serum concentrations in PCOS women. Whether PTX3 levels are elevated in PCOS women, and which particular cells or tissues could secreted it, is not known. Conversely, if PTX3 level is decreased in PCOS women, we do not know by which particular factor or factors its secretion is inhibited.

Also, the relationships between PTX3 and obesity in the above five studies are inconclusive. In the study by Aydogdu et al. [4], the level of PTX3 was increased in women with PCOS, and there was also a positive correlation between PTX3 and BMI and WHR. While in the studies by Tosi et al. [60] and Sahin et al. [51], the level of PTX3 was reduced in PCOS women and there was in the first study only a weak relationships between PTX3 and BMI only when PCOS women were analysed separately (data not shown in the paper) and in the second study negative correlation between PTX3 and BMI and waist circumference (WC) was found. Sari et al. [53] observed no differences in PTX3 levels between PCOS women and the control group and have shown a significant positive correlation between plasma levels of PTX3 and body mass and BMI, while Deever et al. [15] did not describe any relation between PTX3 and anthropometric parameters.

The first limitation in the above-described studies is a relatively small sample size. Second, there were significant differences in age, anthropometric and metabolic parameters between PCOS and control women. To overcome this problem, the authors carried out different statistical analyses; however, it is not possible to exclude the influence of all these factors. Third, all the studies were based mostly on the 'classic' phenotype of PCOS (coexistence of hyperandrogenism, oligoanovulation, with or without polycystic ovaries [PCO] morphology). However, the percentage of PCOS patients with and without hyperandrogenism was not described. It is difficult to predict the role of PTX3 in rarer 'normoandro-

genic' phenotype (coexistence of oligoanovulation and PCO morphology) and in 'ovulatory' phenotype (coexistence of hyperandrogenism and PCO morphology). It should be emphasized that the lower levels of PTX3 were described among men, which suggests that androgens may influence PTX3 production [65]. On the other hand, it is also unclear if there are differences between the above "androgenic types" of PCOS and the risk of CVD [31]. Some previously published studies suggested the existence of a protective role of androgens against CVD in men [2,35]. With the use of Androgen Excess Society criteria (presence of hyperandrogenism is necessary to diagnose PCOS) it could probably be possible to explain the observed discrepancies [5]; nevertheless, the exact explanation remains unknown. Fourth, all studies investigating PTX3 in PCOS were based mostly on young women. There was a lack of older women with PCOS. Studies investigating the role of PTX3 in CVD were mostly based on older patients. The PTX3 level seems to increase with age [6,26,38], which indicates the necessity of including older PCOS patients in further studies. Fifth, and probably the most important limitation is the lack of obese PCOS group and obese control group in the studies by Deveer et al. [15], Tosi et al. [60] and Aydogdu et al. [4]. It seems that the construction of the study proposed by Sari et al. [53] and Sahin et al. [51] (four groups: obese PCOS, normal weight PCOS, normal weight controls and obese controls) is the most appropriate. The differences between PTX3 expression in visceral and subcutaneous adipose tissue indicated, by Osorio-Conles et al. [44], showed also the necessity of including the measurement of visceral fat deposit as an additional variable.

CONCLUSION

There is a need for further (enrolling big cohorts of PCOS patients) studies to evaluate the role of PTX3 in PCOS. In two out of five published studies, the level of PTX3 was lower than the values obtained among healthy controls; in one the value was increased and in two other there was no difference. However, in one of last mentioned two studies our analysis of a table attached in this paper allows us to conclude that there was a tendency towards statistical significance for PTX3 to be lower in PCOS subjects than in the controls. In total, three out of five studies suggest that circulating level of PTX3 is decreased. Nevertheless due to inconsistent data, the relations between PTX3, PCOS and obesity should be investigated in a broader way.

Further studies including more subjects, especially more obese and older PCOS women, are necessary to explain the role of PTX3 as a potential link between obesity, inflammation, and CVD development in polycystic ovary syndrome.

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