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Letters to the editor

PCSK7 levels in women with and without PCOS

Dear Editor,

Polycystic Ovary Syndrome (PCOS) is a hormonal disorder marked by a complex interaction involving issues like insulin resistance, dyslipidemia and chronic low-grade inflammation [1]. One significant aspect of PCOS is insulin resistance that significantly influences the development of this condition [2]. When insulin sensitivity is impaired in the body leading to levels of insulin (hyperinsulinemia), it triggers an excess production of androgens by the ovaries. This process contributes to the emergence of hyperandrogenism which is a crucial factor in the pathogenesis of PCOS [1]. The metabolic abnormalities linked to PCOS involve dyslipidemia characterized by elevated triglyceride levels and reduced high density lipoprotein-cholesterol (HDL-C). Additionally observed are elevated small dense low-density lipoprotein (LDL) particle levels [3]. These lipid irregularities are closely associated with insulin resistance and can enhance the risk of cardiovascular problems in individuals with PCOS. Additionally, PCOS is accompanied by raised circulating levels of inflammatory mediators such as C-reactive protein and cytokines (e.g., interleukin-6, and tumor necrosis factor-alpha) [2]. Such a chronic pro-inflammatory state not only accelerates the development and progression of PCOS but also contributes to comorbidities like metabolic disorders and cardiovascular disease [2]. The intricate associations among insulin resistance, inflammation and dyslipidemia in PCOS mirrors the complex pathophysiology of this disorder and underscores the importance of a holistic approach to its management via targeting these interrelated metabolic and inflammatory pathways.

As a less known member of the proprotein convertase (PC) family, PCSK7 is a transmembrane protease that is expressed widely throughout the body and shares substrates with other PCs, particularly furin [4]. According to a recent genome-wide association study, there is a strong association between a locus near PCSK7 (*rs236918*) and indices of body iron stores [5]. Consistently, PCSK7′s impact on hepcidin expression and soluble hemojuvelin levels have been documented which support its role in iron homeostasis [5]. Moreover, PCSK7 might play a role in adipocyte differentiation and potentially impact obesity and metabolic deregulations like insulin resistance [5]. However, while there is evidence suggesting that PCSK7 gene variants can influence dietary carbohydrate intake and insulin sensitivity, the association between PCSK7 genotypes and insulin resistance or type 2 diabetes risk is still far from clear (5). Hepatic PCSK7 is a major regulator of apoB and its absence leads to reduced apoB secretion and increased ubiquitination and degradation by the proteasome, ultimately decreasing hepatic lipid accumulation [6]. GalNac-ASOs targeted against hepatocyte PCSK7 have been demonstrated to reduce apoB and mitigate non-alcoholic fatty liver disease (NAFLD) [6]. Variation in the PCSK7 gene is associated with dyslipidemia and more severe liver disease in high-risk individuals, likely due to modulation of PCSK7 expression/activity [7]. A study found that the PCSK7 gain-of-function SNP *rs236918*, associated with higher protein levels, is linked to increased circulating apoB and partially increased plasma triglyceride (TG) levels[6]. Conversely, individuals with the loss-of-function SNP *rs201598301*, encoding a P777L variant of PCSK7, have lower plasma TG, apoB, and LDLc levels, supporting the hypothesis of PCSK7′s role in lipid metabolism, steatosis/steatohepatitis, and liver-associated complications (6). PCSK7 deletion in HepG2 cells resulted in reduced lipogenesis, fat accumulation, inflammation, transforming growth factor β pathway activation, and fibrogenesis[7]. The minor PCSK7 *rs236918* C allele has been linked to higher triglycerides, aminotransferases, and hepatic inflammation [7]. With respect to PCOS, PCSK7 is found in the ovary but it is the PCSK5 variant found in the theca cells of the follicles that is hormonally responsive[8]; the role of PCSK7 in the ovary is unclear nor is it known if it contributes to ovarian dysfunction in PCOS, and there is no evidence that PCSK7 contributes to the changes in androgen levels.

Given the emerging role of PCSK7 in metabolic regulation, including insulin resistance, dyslipidemia, and inflammation, we set out to examine the link between PCSK7 and PCOS through a case-control study. To assess this relationship, we measured and compared plasma levels of PCSK7 in women with PCOS ($n = 147$) and those without PCOS ($n = 97$). Samples from women with PCOS were sourced from a biobank dedicated to the condition, where all participants had given informed consent [9]. The study participants were of Caucasian descent and had been diagnosed with PCOS according to the Rotterdam criteria [9]. The control group included women with regular menstrual cycles, normal physical examination results, and no evidence of polycystic ovaries as confirmed by ultrasound. Additionally, those with and without PCOS were not on any medication [9]. Plasma levels of PCSK7 were analyzed using the slow off-rate modified aptamer (SOMA)-scan platform, as outlined in a previous study [10].

The groups were matched in age but the PCOS group had higher mean BMI, HOMA-IR, testosterone, insulin and CRP levels, as expected (Table 1). Between-group comparison showed that PCSK7 levels were higher in the PCOS group compared to the control group, and this difference was marginally statistically significant ($p = 0.054$) (Table 1). When BMI, HOMA-IR were accounted for by linear regression analysis, this did not affect the PCSK7 levels. There were no correlations between PCSK7 and the inflammatory markers CRP (control $r = 0.07 p > 0.6$; PCOS $r = 0.13$, $p > 0.2$, respectively) or IL6 (control $r = 0.20 p > 0.05$; PCOS $r = 0.04$, $p > 0.96$, respectively), suggesting that the PCSK7 levels were independent of inflammation. Testosterone did not correlate with PCSK7 (control $r = 0.19 p > 0.09$; PCOS $r = 0.1$, $p > 0.28$, respectively), indicative that PCSK7 levels are not related to androgen levels.

To the best of author's knowledge, this is the first report on the alterations in circulating levels of PCSK7 in women with PCOS. The observed elevation of plasma PCSK7 concentrations in subjects with PCOS may suggest a potential association considering the involvement

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Table 1
Comparison of biochemical indices between PCOS and control groups.

Variable	PCOS (n = 147)	Control (n = 97)	p-Value
Age (years)	27.9 ± 6.1	29.3 ± 6.6	0.102
BMI (kg/m2)	34.1 ± 7.5	26.7 ± 6.5	<0.001
Glucose (mmol/L)	4.9 ± 1.0	4.7 ± 0.7	0.079
HOMA-IR	3.8 ± 5.9	1.6 ± 1.6	0.001
Testosterone (nmol/L)	1.6 ± 1.0	1.1 ± 0.5	<0.001
Insulin (IU/mL)	10.6 ± 6.4	6.3 ± 3.2	0.001
CRP (mg/L)	4.6 ± 4.3	2.4 ± 3.8	<0.001
PCSK7 (RFU)	1097.7 ± 365.8	1017.4 ± 279.7	0.054

Variables are expressed as mean ± SD.

of PCSK7 in metabolic and inflammatory processes, which are integral to PCOS pathophysiology. While the current findings suggest a hypothesis on the identification of a new player in PCOS pathogenesis, the relatively small sample size of this case-control study precludes a definitive conclusion until supporting evidence from large-scale cohorts are available; in addition, this was restricted to a Caucasian population and ethnicity needs to be addressed in future studies. Finally, molecular studies are warranted to look at the mechanisms underpinning this potential association and the therapeutic implication of targeting PCSK7 in PCOS.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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