

The interplay between androgens and adipocytes: the foundation of comorbidities of polycystic ovary syndrome

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ABSTRACT

This review updates current knowledge of the relationship between androgens and adipocytes in women with polycystic ovary syndrome. Relevant studies published between 1983 and 2021 were examined. Adipocytes take up androgens, convert weak androgens into potent ones, and modulate the ovarian production of testosterone and androstenedione through the actions of various adipocytokines. Androgens also modulate adipocyte proliferation and differentiation, stimulate adipocytokine production, and promote visceral adipose tissue accumulation. Androgens induce hypertrophy and insulin resistance in adipocytes. Finally, androgens stimulate β -cell production and insulin release. Insulin, in turn, amplifies androgen production by ovarian theca cells and favors visceral fat deposition. Altogether, these conditions favor the development of future comorbidities such as type 2 diabetes mellitus, dyslipidemia, non-alcoholic fatty liver disease, metabolic syndrome, arterial hypertension, low-grade chronic inflammation, and cardiovascular disease..

KEYWORDS

Polycystic ovary syndrome, hyperandrogenism, adiposity, adipokines, insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by oligo-anovulation, hyperandrogenism, and polycystic ovaries on ultrasound. Frequently, PCOS is accompanied by carbohydrate and lipid metabolism disturbances and inflammatory abnormalities that lead to an increased risk of development of cardiovascular disease (CVD) [1-3]. Higher levels of circulating androgens occur in 70-80% of women with PCOS; overweight/obesity and insulin resistance are also found in about 70% of women with this condition [4-7]. The amount and distribution of adipose tissue and the preferential visceral adipocyte deposition seen in normal-weight and overweight/obese women with PCOS are currently not completely understood [8]. Despite the understanding that high levels of androgens help determine visceral adipocyte accumulation in women with PCOS, many knowledge gaps need to be filled [9].

Material and methods

This comprehensive review aimed to summarize the current knowledge regarding the implications of the intimate relationship between androgens and adipocytes, favoring the development of comorbidities in women with PCOS. The review entailed a detailed analysis of publications on the interrelationship

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between hyperandrogenism and adipocyte dysfunction in women with PCOS. We searched Scopus, Google Scholar, Medline, and PubMed to identify the most relevant publications between 2000 and 2021. The search was expanded by the retrieval of bibliographic citations from the identified articles.

When providing crucial basic knowledge, studies published before 2000 were also included. Keywords used in the search were as follows: polycystic ovary syndrome, hyperandrogenism, obesity, adiposity, dysfunctional adipocyte, insulin resistance, adipose tissue distribution, and various combinations of these terms.

Adipocyte steroid uptake, production, and metabolism

Adipocytes, directly and indirectly, participate in androgen production [10]. In addition to ovarian and adrenal sources, conversion of the weak androgen dehydroepiandrosterone (DHEA)

into androstenedione (A4), of A4 into testosterone (T), and of T into dihydrotestosterone (DHT) in adipose tissue are also essential sources of circulating androgens. Adipocytes express several steroidogenic enzymes, and they locally modulate steroid levels [11]. The steroidogenic enzyme activity of adipocytes appears to be relevant in the development of hyperandrogenism in PCOS, particularly because weak androgens such as A4 are rapidly taken up, sequestered from circulation by mature adipocytes, and converted into strong androgens [10-12]. For this reason, the amount of androgens in adipocytes, which differs in omental and subcutaneous depots, is even more significant than the amount in circulation [13]. Furthermore, enhanced adipocyte steroidogenesis in women with PCOS may explain the association between hyperandrogenism and obesity [14, 15].

Regarding the direct participation of adipocytes in steroidogenesis, levels of type 5 17 β -hydroxysteroid dehydrogenase (17 β -HSD), the enzyme that converts A4 into T, are increased in subcutaneous adipose tissue of obese women [16]. The activity of 5 α -reductase, the enzyme that converts T into DHT, is increased in PCOS with or without obesity [17].

Of note, 17 α -hydroxylase (CYP17A1) activity positively correlates with the waist/height ratio and negatively correlates with the conicity index in women with PCOS [18]. Furthermore, 17,20 lyase activity correlates with various biomarkers of adiposity in PCOS [18]. Levels of 11 β -hydroxylase are slightly decreased in hyperandrogenic women with PCOS [19]. These findings suggest that clinical biomarkers of body fat mass and distribution correlate with the activities of various steroidogenic enzymes within adipose tissue.

Indirect participation of adipocytes in the production of androgens may be modulated by the action of adipocytokines on adrenal and ovarian steroidogenic cells. The effects of adipocytokines on steroidogenesis have recently been reviewed [20]. In women with PCOS, there is increased secretion of harmful adipocytokines such as leptin and tumor necrosis factor- α (TNF- α), and lower secretion of beneficial adipocytokines such as adiponectin and omentin-1. The effects of adipocytokines on adrenal cell steroidogenesis depend on their amounts and types. In humans, leptin decreased adrenocorticotrophic hormone-induced secretion of DHEA by decreasing the expression of CYP17A1 [21], while adiponectin stimulates cortisol production and the expression of a steroidogenic acute regulatory protein (StAR) and a cholesterol side-chain cleavage enzyme (CYP11A1) [22]. In ovarian cells, there is a bidirectional relationship between theca cells, granulosa cells, and adipocytes [20].

In women with PCOS, leptin levels are positively correlated with T, body fat mass, body mass index, waist-hip ratio, and metabolic abnormalities [23]. Adiponectin has lower levels and is negatively correlated with androgen levels in women with or without PCOS [24]. Resistin levels positively correlate with T through the higher activity of CYP17A1 [25]. In obese PCOS, chemerin and RBP-4 levels are positively associated with T concentrations [26, 27].

Overall, androgens are produced and interconverted by adipocytes, and these phenomena could account for a third source of androgen production, mainly in conditions of adiposity [28]. Regional differences in steroidogenic enzyme

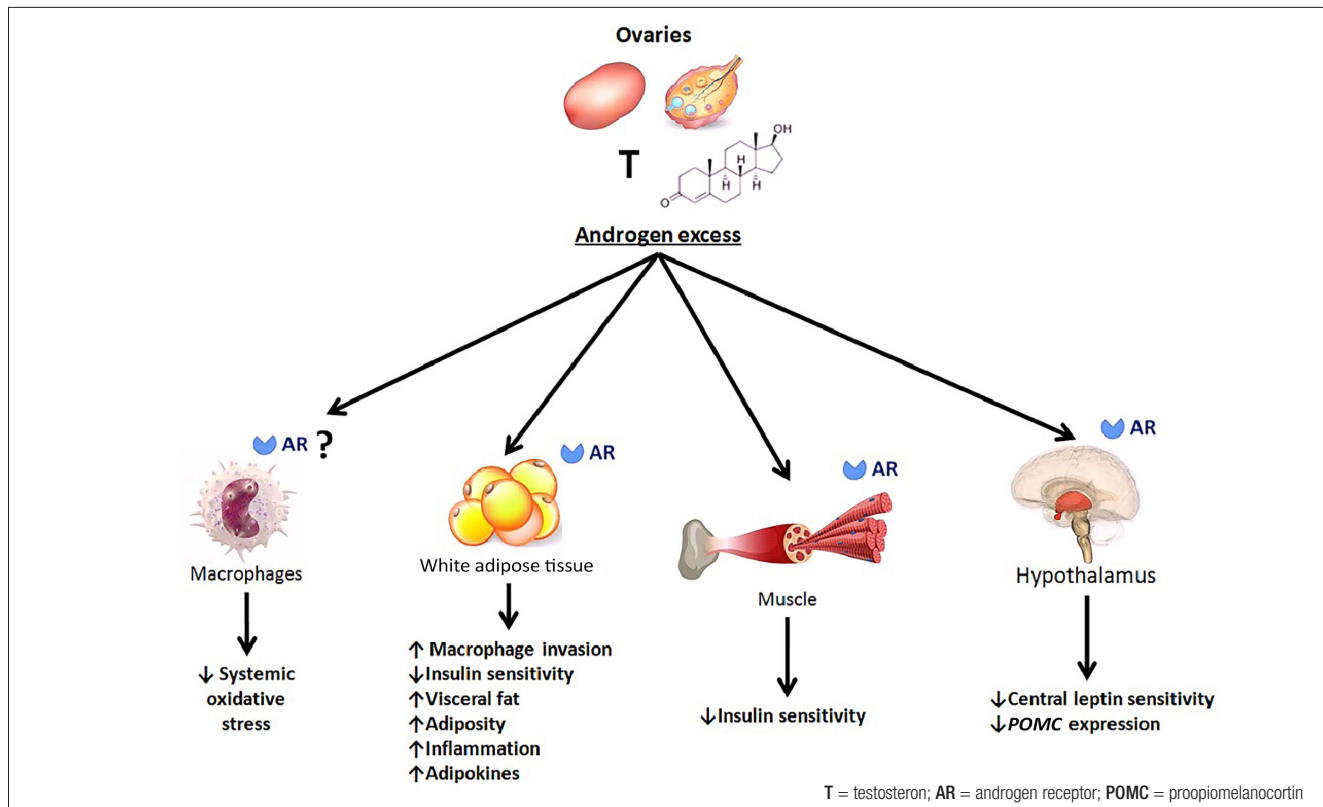
activities may exist. The net amount of excessive androgen production, particularly of potent androgens, by adipocytes in women with PCOS has not yet been determined.

The role of androgens on adipocyte function

The effect of androgens on adipose tissue function depends on circulating androgen levels, androgen receptor (AR) density and affinity, and local steroidogenic enzyme activities. There are androgen receptors both on preadipocytes and on mature adipocytes [29]. In these cells, androgens may influence gene expression, cell proliferation, cell differentiation, and carbohydrate and lipid metabolism. Androgens increase the transcription of their receptors in mononuclear cells, favoring the release of adipocytokines [30]. Furthermore, T also increases the transcription of the chemokine (C-C motif) ligand 2 (CCL2) in omental adipose tissue, triggering macrophage invasion [31].

As regards gene expression, androgens bound to AR function as transcription factors that regulate the expression of various genes. Gene expression regulation is controlled through several factors [32] that may modulate the transcription of peroxisome proliferator-activated receptor-gamma (PPAR γ) and the mitogen-activated protein kinase (MAPK) cascade involved in adipocyte differentiation, proliferation, adipogenesis, and lipid metabolism [33, 34]. T also promotes visceral adipose tissue (VAT) distribution and chronic low-grade inflammation (Fig. 1).

The androgen DHT may not inhibit the proliferation of preadipocytes *in vitro* [35]; however, in general, androgens suppress adipocyte differentiation into mature adipocytes by epigenetic control through decreased PPAR γ transcription [36]. Thus, T and DHT inhibit preadipocyte differentiation and late-stage adipocyte maturation in both subcutaneous adipose tissue (SAT) and VAT compartments [37]. By contrast, DHEA has a more complex role [37]. It does not affect subcutaneous preadipocyte differentiation; instead, DHEA decreases adipogenesis in omental preadipocytes [37, 38]. In addition to modulating adipocyte proliferation and differentiation, T at higher levels promotes adipocyte hypertrophy [39] and overproduction of adipokines [40] through AR stimulation [30]. Furthermore, T enhances the infiltration of macrophages of adipocytes and promotes expansion and lipid accumulation in VAT [41]. The distribution and capacity of androgen receptors on adipocytes vary by region, with a higher binding capacity observed in VAT. As regards lipid metabolism, T is a potent regulator of lipolysis and its action varies across species [42]. T modulates adipogenesis and lipolysis. Androgens may increase abdominal lipolysis without altering lipolysis in the gluteal-femoral compartment, by decreasing lipid uptake and synthesis [43, 44]. T diminishes lipolysis in SAT by decreasing expression of β 2-adrenergic receptors and hormone-sensitive lipase (HSL), while cyclic adenosine monophosphate stimulates adenylate cyclase activities [35]. At high levels, T diminishes lipolysis in VAT of nonhuman primates [45] and stimulates lipogenesis in women with or without PCOS [2, 46]. Nevertheless, even in nonobese PCOS, T increases the ability of catecholamines to activate hydrolysis of triglycerides into free fatty acids (FFAs) [47]. This primary lipolytic defect in PCOS is an exception.

Figure 1 Proposed mechanism of excess androgen receptor activation in various system in hyperandrogenic woman.

Adipocyte size in PCOS

The size of adipocytes is closely associated with their function; hypertrophic adipocytes are dysfunctional^[48]. In hyperandrogenic obese women with PCOS, adipocytes are even larger than those taken from obese controls^[39], and they produce many adipocytokines^[49]. In nonobese hyperandrogenic women with PCOS, adipocytes may also be enlarged and dysfunctional^[50]. The hypertrophy of adipocytes in PCOS may be due to imbalanced abilities of adipocyte storage or adipocyte lipolytic activities^[51]. Adipocyte size is related to insulin growth factor-1, phosphoinositide 3-kinase, and protein kinase B gene expression^[52]. Of note, these genes combine external signals such as insulin and T^[52,53].

In PCOS, hyperandrogenism has an essential role in the development of adipocyte hypertrophy in SAT and fat expansion^[40, 51, 54]. In obesity, adipocytes are hypertrophic, possessing a propensity to pro-inflammatory gene expression. They are also dysregulated in their expression of cytokines and are characterized by an increased proportion of macrophage invasion^[10,55]. Hypertrophic adiposity driven by T is highly correlated with insulin resistance^[39,50]. Hypertrophic adipocytes produce and secrete various paracrine growth factors that stimulate increases in the number and size of preadipocytes^[56]. In general, because of the higher production of adipocytokines and cytokines, hypertrophic adipocytes are associated with abnormal lipid metabolism, metabolic syndrome, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and CVD^[39,57]. In summary, hypertrophic adipocytes are associated with PCOS and various comorbid conditions^[25, 50, 51].

Adipose tissue distribution in PCOS

In normally-cycling women, various genetic, ethnic, social, and hormone factors influence body adipose tissue distribution. Typically, women with a higher percentage of body fat tend to show distribution of adipose tissue in the hips and thighs^[58]. In abnormal conditions such as obesity and PCOS, the capacity of subcutaneous adipose tissue to safely store fat is exceeded, and excess fat is deposited in abnormal locations such as the retroperitoneum, omentum, liver, and muscle^[48, 59]. Also, impaired adipocyte proliferation or differentiation capacity leads to the redistribution of fat tissue from subcutaneous areas to visceral depots^[51]. In this manner, androgens may drive adipose tissue mass in a depot-specific way through site-specific modulation of preadipocyte proliferation and differentiation or by lipid synthesis (lipogenesis) or lipolysis in mature adipocytes^[60].

In women with PCOS, hyperandrogenism modifies body fat distribution, causing adipocytes to accumulate in the abdominal wall, and to surround or infiltrate intra-abdominal organs^[46, 61]. Androgens are associated with increased fat mass and an increased amount of fat localized on the trunk^[62, 63]. Thus, women with PCOS have more central obesity than weight- and body mass index-matched controls^[64]. Total intra-abdominal fat appears to be increased even in normal-weight PCOS^[65, 66]. Additionally, even when not increased, the abdominal fat of normal-weight women with PCOS is comprised of a more significant proportion of small dysfunctional adipocytes (hyperplasia), compared with what is found in controls^[8]. In overweight/obese women with PCOS, visceral adipocytes are enlarged (hypertrophic), expanded, and dysfunctional^[39, 50, 67], and they

positively correlate with T, free testosterone, and A4 levels [8]. Conversely, some studies did not show more significant visceral fat accumulation in either obese or nonobese PCOS [68, 69]; nevertheless, there is a global excess of fat mass in PCOS [68, 70]. Despite persistent debate regarding the presence of increased visceral fat in women with PCOS, these women have decreased gluteal-femoral gynaecoid adiposity.

Subcutaneous adipose tissue in PCOS

Adipocytes from various regions produce different signaling molecules that influence insulin secretion and glucose and lipid metabolism in muscle and liver [71]. *In vitro*, T reduces early-stage adipocyte differentiation, limiting adipocyte number and fat storage in abdominal subcutaneous adipose tissue of lean women with PCOS [72]. When pronounced, abdominal subcutaneous adipose tissue is associated with hyperandrogenemia and a higher risk of comorbidities [73-75]. In PCOS, subcutaneous adipocytes may also be enlarged or hyperplastic with limited capacity to store fat, thus favoring increased release of FFAs with uptake in lean non-PCOS cells and omentum. This lipotoxicity explains insulin resistance in lean, non-PCOS individuals [66, 76]. Furthermore, SAT increased conversion of the weak androgen (A4) into the potent androgen (T), and enhanced local adipogenesis within adipocytes predisposes to fatty acid overspill into the systemic circulation in non-PCOS and normal-weight PCOS [77]. Abnormal subcutaneous adipocytes (hyperplastic or hypertrophic) decrease insulin-mediated glucose utilization, reduce glucose transporter type 4 expression (GLUT-4), and stimulate lipolysis through β 2-adrenergic receptors, decreasing the HSL and protein kinase A (PKA) regulatory components [50].

In obese or nonobese PCOS, adipocytes of SAT are equally insulin-resistant in regard to glucose metabolism and antilipolytic activity [78]. In preadipocytes of SAT of nonobese PCOS, T decreases the number of β -adrenergic receptors and diminishes HSL activity with a lower catecholamine lipolytic effect [47, 50]. The reduced lipolysis in SAT may explain adipocyte hypertrophy and dysfunction in this depot. Of note, even in normal concentrations, T amplifies the ability of catecholamines to activate hydroxylation of triglycerides in FFAs and glycerol [30].

Visceral adipose tissue in PCOS

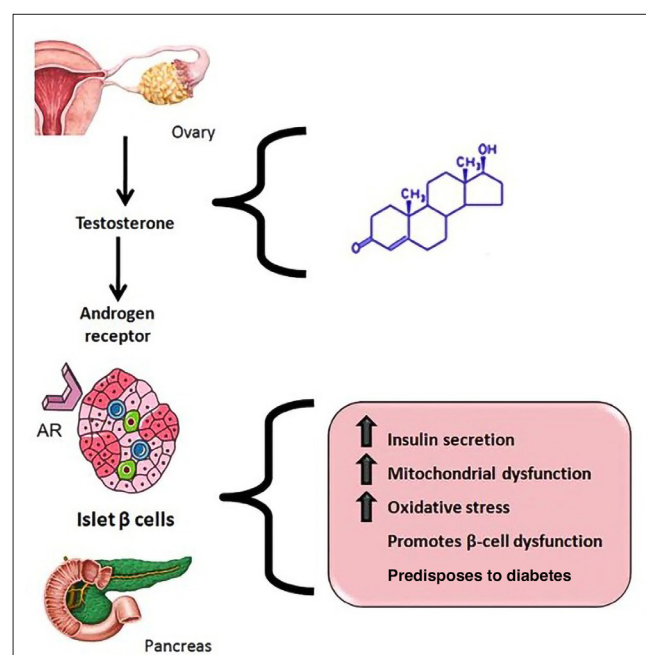
Among the relevant comorbidities of women with PCOS, about 70% are overweight or obese [78]. Androgen binding capacity is more significant in VAT [30]. Hyperandrogenemic states such as obese PCOS may favor visceral deposition even when compared with obese non-PCOS [65, 79, 80]. Despite previous reports of women with PCOS having global adiposity rather than visceral adiposity, most studies showed that adipose tissue has a preferentially visceral distribution in this syndrome [81]. The preferential VAT distribution in nonobese PCOS is accompanied by an increased number of small subcutaneous adipocytes [8]. The increased visceral adiposity in nonobese and obese PCOS is associated with metabolic dysfunctions such as dyslipidemia, abnormal carbohydrate metabolism, insulin resistance, arterial hypertension, low-grade chronic inflammation, and a pro-thrombotic state, resulting in a higher risk of T2DM and CVD [18, 51, 82-84]. Of note, preferential central obesity distribution in women with PCOS was not found [85].

VAT releases more FFAs than SAT [86], suggesting that there are regional variations in adipocyte lipolysis. Thus, VAT has higher catecholamine-stimulated lipolysis, lower lipoprotein lipase activity, and lower glucose uptake than SAT [71, 87]. Because VAT is linked to the liver via the portal vein, alterations in visceral adipocytes directly affect liver function. VAT lipolysis is enhanced in PCOS, while the lipolysis in abdominal SAT is diminished by T in this syndrome [47, 51]. The increased rate of VAT lipolysis in PCOS, even in nonobese women, is due to β 2-adrenoceptor catecholamine-induced adipocyte lipolysis mediated by a unique stoichiometric change in the properties of the PKA-HSL enzyme complex [47]. Additionally, in *in vitro* studies, T was shown to be a positive contributory factor to catecholamine lipolytic capacity. In summary, human and animal data strongly suggest unique upregulation in visceral fat cells due to selective increases in the function of the PKA-HSL complex [88]. The altered lipolysis in both SAT and VAT in women with PCOS has an important pathophysiological role.

Hyperandrogenism, obesity, and insulin resistance in PCOS

In women with PCOS, an increase in luteinizing hormone pulsatility is associated with a decrease in follicle-stimulating hormone levels, and this combined effect on ovarian theca and granulosa cells results in increased production and release of T and A4. Higher testosterone levels directly stimulate the secretion of insulin by pancreatic β -cells [89-93] (Fig. 2). Additionally, higher circulating insulin levels amplify the effects of luteinizing hormone (LH) on theca cells and on T production, which is increased by LH. Furthermore, the increase in T promotes not only pancreatic β -cell dysfunction, but also the expression and accumulation of adipose tissue in the omentum and intra-abdominal organs [94].

Figure 2 The role of androgen modulation of pancreatic B-cell function and insulin secretion.



As previously stated, in visceral adiposity, adipocytes are enlarged, and insulin resistance and increased lipolysis occur [95]. More significant release of FFAs in the portal vein affects liver function [47,50]. Although hypertrophic adipocytes are markers of metabolic derangements, dysregulated metabolism in PCOS can be related to either larger or numerous small adipocytes of abdominal subcutaneous adipose tissue [66]. In clinical studies, androgens strongly correlated with markers of central adiposity [7,18,96].

Androgens can induce insulin resistance by directly affecting skeletal muscle and adipocytes through increased adipocytokine secretion and increased visceral adiposity in experimental studies [97-99]. Even normal-weight women with PCOS exhibited increased fasting insulin levels and greater pancreatic β -cell response than body mass index-matched controls [8]. Of note, visceral fat deposition is primarily driven by insulin resistance, and VAT distribution exacerbates insulin resistance. This bidirectional vicious cycle is present in PCOS [79]. The hypertrophic insulin-resistant adipocyte appears to be a consequence of diminished insulin-dependent autophosphorylation [100], reduced IRS-2 tyrosine phosphorylation, or reduced GLUT-4 within the adipocyte [101,102]. In summary, higher androgen levels can impair the insulin effect directly or through various changes in different tissues [103]. To overcome peripheral insulin resistance, more insulin is produced by β -cells, resulting in hyperinsulinemia. This hyperinsulinemia, acting on theca cells, increases testosterone synthesis. Furthermore, chronic androgen excess predisposes to T2DM secondary to pancreatic β -cell failure [93,104,105].

Conclusions

There is a close interrelationship between androgens and adipocytes in women with PCOS. Adipocytes produce potent androgens, and androgens modulate adipocyte proliferation, hypertrophy, macrophage invasion, and overproduction of various adipocytokines that stimulate steroidogenic cell secretion. There is a role for hyperandrogenism in adipose tissue distribution, favoring subcutaneous abdominal wall and visceral adiposity instead of fat distribution to the hips and thighs. In nonobese women with PCOS, adipocytes can be hyperplastic, enlarged, and dysfunctional in subcutaneous adipose tissue, and this finding may explain the insulin resistance and abnormal lipid metabolism with lipid toxicity in this group. The intra-abdominal deposition also appears to be increased in lean PCOS.

Overweight/obese women with PCOS have a global excess fat mass. When pronounced, abnormal subcutaneous adipose tissue is also associated with hyperandrogenism and a higher risk of comorbidities. However, in obese PCOS, obesity is preferentially centralized, even when compared with body mass index-matched controls. In PCOS with obesity, the hypertrophic adipocytes are also associated with dyslipidemia, abnormal carbohydrate metabolism, insulin resistance, type 2 diabetes mellitus, low-grade chronic inflammation, the pro-thrombotic state, and cardiovascular disease. Taken together, these findings reinforce the notion that lowering fat mass is an essential therapeutic measure in the management of women with PCOS, particularly when overweight or obese.

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Conflict of interest

The authors declare there are either no financial or other conflicts of interest that could be perceived as prejudicing the impartiality of this study.