Clinica Chimica Acta 499 (2019) 142–148

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Sex hormone-binding globulin and polycystic ovary syndrome

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ARTICLE INFO

Keywords:
Sex hormone-binding globulin (SHBG)
Hepatocyte nuclear factor-4α (HNF-4α)
Polycystic ovary syndrome (PCOS)
Androgen
Insulin resistance (IR)

ABSTRACT

Polycystic ovary syndrome (PCOS), one of the most common endocrine diseases that causes infertility in reproductive women, is characterized by hyperandrogenemia, chronic anovulation, and polycystic ovary morphology (PCOM), and most women with PCOS have metabolic abnormalities. A reduction in plasma sex hormone-binding globulin (SHBG), a transport carrier that binds estrogen and androgens and regulates their biological activities, is often used as an indicator of hyperandrogenism in women with PCOS. Low serum SHBG levels are considered a biomarker of abnormal metabolism and are related to insulin resistance (IR), compensatory hyperinsulinemia and abnormalities in glucose and lipid metabolism in PCOS patients. SHBG is also associated with the long-term prognosis of PCOS. SHBG gene polymorphism is correlated with the risk of PCOS. As SHBG plays a vital role in the occurrence and development of PCOS, knowledge regarding its role in PCOS is helpful for further understanding the molecular mechanism of SHBG in PCOS development and providing new ideas for the treatment of female infertility. Hepatocyte nuclear factor-4α (HNF-4α) is a vital transcription factor in the SHBG synthesis process. HNF-4α binds to the cis-type element DR1 in the SHBG promoter to initiate transcription and regulates hepatic SHBG levels by modulating glucose and lipid metabolism and inflammatory factors. However, it remains unclear whether HNF-4α is indirectly involved in the pathogenesis of PCOS via regulation of hepatic SHBG synthesis. Therefore, this review discusses the interaction between SHBG and the various complications of PCOS as well as the regulatory effect of HNF-4α on SHBG expression.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder that causes infertility in women of childbearing age. PCOS is mainly caused by excess androgens, and it affects 6% to 10% of women worldwide [1]. Furthermore, PCOS is a powerful risk factor for type 2 diabetes (T2D), cardiovascular disease, gestational diabetes, pregnancy-induced hypertension, and endometrial cancer. The clinical manifestations of PCOS are highly heterogeneous, the etiology is still unknown, and the pathological mechanism is very complex and is generally believed to be associated with hypothalamic-pituitary-ovarian axis dysfunction, adrenal dysfunction, heredity, metabolism and other factors. The most widely used diagnostic criteria are those proposed by members of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine in 2003, known as the Rotterdam standard [2]. These criteria propose that PCOS can be diagnosed by meeting two of the following three conditions and excluding other diseases caused by excess androgens: rare ovulation or long-term anovulation, clinical hyperandrogenic signs or biochemical hyperandrogenism, and polycystic ovary morphology (PCOM).

Hyperandrogenism is a key characteristic of PCOS. Clinically, assessment of an excess of female biochemical androgen generally includes detection of total testosterone (TT), free testosterone (FT), and sex hormone-binding globulin (SHBG) or calculation of the free androgen index [3]. As a transporter of sex hormones, SHBG is produced by the liver and binds to circulating sex steroids with high affinity, regulating the concentration of bioactive sex hormones in the blood and affecting their bioavailability [4]. As SHBG exhibits high affinity for testosterone and a low affinity for estradiol, it is an effective auxiliary indicator for the determination of androgen levels [5]. The binding of testosterone by SHBG does not result in biological effects, and only approximately 1–2% of unbound free testosterone has biological

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https://doi.org/10.1016/j.cca.2019.09.010
Received 14 May 2019; Received in revised form 11 September 2019; Accepted 12 September 2019
Available online 13 September 2019
0009-8981/

activity. Therefore, SHBG can be used to judge the severity of hyperandrogenism and evaluate the therapeutic efficacy of treatment. Previous studies have found that insulin affects SHBG, with hyperinsulinism inhibiting its synthesis and secretion [6]. Compared with levels in healthy individuals, serum SHBG levels are significantly decreased in patients with hyperinsulinemia [7], and low serum SHBG levels may be a risk factor for abnormal glucose metabolism. In general, both hormone levels and serum SHBG levels should be considered in PCOS patients, as they play important roles in the development and prognosis of PCOS in clinical practice.

Hepatocyte nuclear factor-4α (HNF-4α), an orphan receptor, is a member of the nuclear receptor superfamily that is mainly expressed in the liver, intestines, pancreas and kidneys [8]. HNF-4α has an important function in SHBG expression and synthesis, and it is a major transcription factor regulating SHBG gene expression in the liver [9]. Overexpression of SHBG significantly increases HNF-4α mRNA and protein levels and reduces those of PPAR-γ [10], and the positive correlation between SHBG mRNA and HNF-4α mRNA levels has been confirmed in human liver biopsies [10]. Although activation of HNF-4α does not require exogenous ligands, long-chain fatty acids (including palmitate) have been identified as endogenous ligands that may affect the transcriptional activity of HNF-4α [11]. Activated HNF-4α regulates lipid metabolism in the liver, and its target genes are apolipoproteins, including apoA-I, apoB, and apoC-III [12]. Therefore, expression of HNF-4α is related to lipid metabolism disorders, with greater severity with weaker HNF-4α expression. Lipid accumulation reduces hepatic SHBG expression [13], and HNF-4α not only regulates lipid metabolism but also maintains glucose homeostasis by regulating insulin secretion and glycosylation. Nonetheless, it remains unknown whether HNF-4α is involved in PCOS development and long-term prognosis by regulating circulating SHBG levels. Understanding the effects of HNF-4α on SHBG regulation and PCOS development may provide a new perspective regarding the pathogenesis of PCOS. Overall, more research and verification on this topic is needed.

2. Structure of SHBG and regulation of the SHBG promoter by HNF-4α

The SHBG gene, which contains eight exons and seven introns, is located on chromosome 17p12—p13 [14,15]. Exons 2–8 encode two contiguous laminin G–like (LG) domains [14]. The steroid-binding sites of SHBG are located in the amino-terminal LG domain encoded by exons 2–5 [16]. The SHBG protein is a homologous dimer composed of two identical noncovalently bound subunits [15]. As each SHBG subunit has a steroid-binding site, mature SHBG homodimers have two distinct steroid-binding sites [17].

HNF-4α is the most significant transcription factor that activates SHBG expression in the liver [9,18–21] and functions by binding to the cis-element DR1-binding site located upstream of the transcription initiation site. This binding site is the region where TATA-binding protein (TBP) normally binds in numerous gene promoters. However, the liver-specific SHBG promoter lacks the traditional TATA box; instead, HNF-4α actively recruits the transcriptional machinery to this binding site [9,16], which is important for expression of SHBG in the liver. Chicken OVA upstream promoter–transcription factor 1 (COUP-TF1) competes with HNF-4α for binding at this site. When lipogenesis increases, obesity, fatty liver or metabolism changes occur, HNF-4α levels are reduced, COUP-TF1 is bound at the site, and SHBG transcription is blocked [9]. Additionally, peroxisome proliferator-activated receptor-γ(PPAR-γ) competes with HNF-4α for binding at the third site of the SHBG promoter, and SHBG production can thus be increased by lowering the levels of PPAR-γ [22]. PPAR-γ acts as an inhibitor of SHBG expression [23]. However, it has been shown that thiazolidinediones, PPAR-γ agonists, increase plasma SHBG levels [24]. In fact, the effect is often attributed to improved insulin resistance (IR) and glycemia [10].

3. Roles of SHBG in PCOS-related manifestations

3.1. The association between low serum SHBG levels and obesity in women with PCOS

Obesity is considered to be one of the most important factors leading to the development of PCOS. Indeed, it is reported that 35–80% of women with PCOS are overweight or obese [25]. The metabolic phenotype of PCOS is exacerbated by obesity, and the incidence of PCOS is higher in overweight and obese patients [6]. With the improvement in living standards, obesity is not only common in adults but has also greatly increased in teenagers and children. In addition to effects of reproductive disorders in adults, obesity impacts the development of girls during puberty. Overweight or obese women with PCOS have lower serum SHBG levels than do normal-weight women with PCOS, and low serum SHBG levels are found in overweight and obese women of all ages [26]. However, whether low serum SHBG levels are significant factors causing PCOS in patients who are obese is not well understood, and in general, it is critical to understand the impact of obesity as a risk factor for serum SHBG levels in women with PCOS.

Low plasma SHBG levels have been shown to be associated with obesity, especially abdominal obesity [27]. Some studies have shown that weight, especially the relative amount of adipose tissue and lean muscle, is one of the most important determinants of plasma SHBG levels [27]. Compared to normal-weight women with PCOS, women with PCOS who are obese have lower SHBG and higher TT, free androgen index (FAI), HOMA-IR, fasting insulin, and fasting glucose levels [6]. This suggests that obesity may be one of the important causes of insulin resistance (IR) and hyperandrogenism in women with PCOS. However, a low serum SHBG level is a possible factor resulting in an increase in TT and IR, which can be observed in adolescent girls who are obese compared with those of normal weight [28]. Body mass index (BMI) is considered a major determinant of SHBG plasma concentration, with a negative correlation [29] that may be due to the decreasing insulin sensitivity and hyperinsulinemia caused by obesity. Moreover, a high BMI directly increases the degree of IR in PCOS patients [30], and recent evidence confirms that women with PCOS who are obese have higher IR and lower insulin sensitivity [31]. Insulin decreases circulating SHBG levels by inhibiting the synthesis of hepatic SHBG [6,32], thereby increasing bioactive free testosterone (FT) levels. This elevated serum FT level further reduces the insulin clearance rate and aggravates IR (IR), ultimately producing a vicious circle. Obesity-induced hyperinsulinemia also directly stimulates the ovaries and adrenal glands to produce excess androgens in women with PCOS [32]. Accordingly, a change in living habits is particularly important for obese PCOS patients, and reducing weight through diet restriction and physical exercise can significantly alleviate hyperandrogenemia, improve menstruation, and restore ovulation. Weight loss surgery has been used clinically to ameliorate IR, reduce androgen production, improve SHBG levels, and restore ovulation in PCOS patients [33].

3.2. The negative correlation between serum SHBG levels and hyperandrogenemia in women with PCOS

Excess androgen is a major feature of PCOS, and it is also a crucial cause of infertility in women with PCOS. In these women, excess androgens are produced mainly by the ovaries and the adrenal gland, inhibiting the selective growth of follicles, leading to a large amount of follicular atresia and ultimately causing ovulation disorders [34]. This is the direct reason for anovulation in PCOS patients with hyperandrogenism. In a study of adolescent girls with PCOS, serum androgen levels were shown to be an independent risk factor for metabolic syndrome [35]; androgen levels also correlate positively with IR in PCOS patients [36] because hyperandrogenism induces IR by reducing insulin clearance and increasing lipoprotein lipase activity and triacylglycerol release [37]. Compensatory hyperinsulinemia in turn further

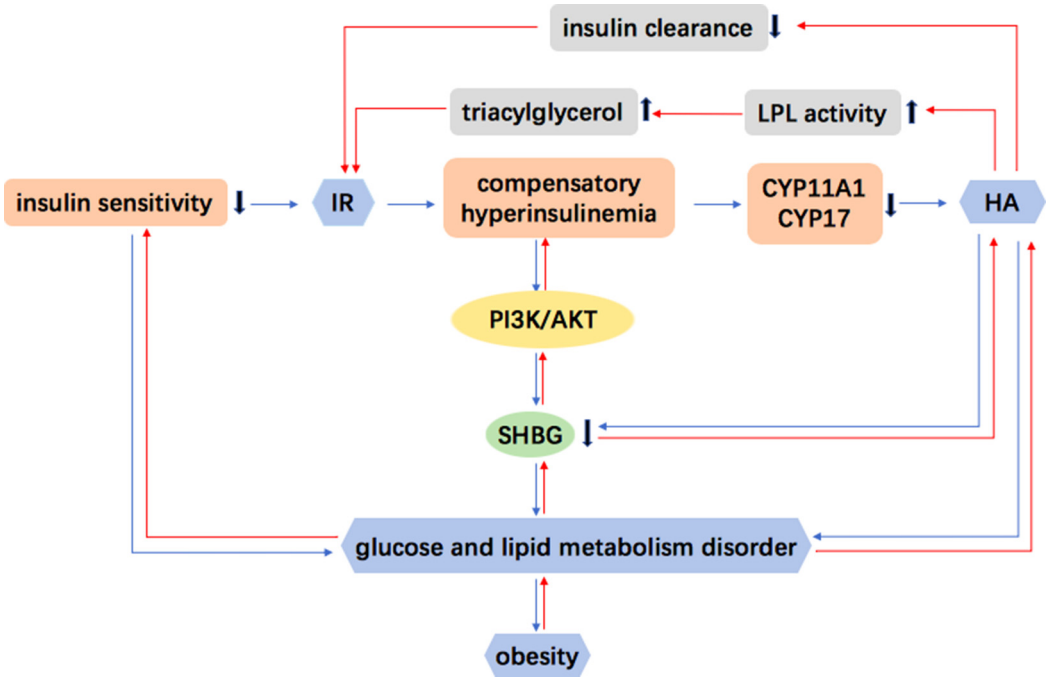

Fig. 1. The correlation between PCOS-related manifestations and SHBG.
IR, HA and obesity are PCOS-related manifestations. IR, HA and obesity can reduce serum SHBG levels. Low serum SHBG in turn aggravates IR, HA and glucose and lipid metabolism disorder, causing a vicious circle. Blue arrows indicate the effect of these processes on SHBG, and red arrows indicate the effect of SHBG on these characterizations. IR: insulin resistance; CYP: cytochrome P450; HA: hyperandrogenemia; LPL: lipoprotein lipase; SHBG: sex hormone-binding globulin.

aggravates hyperandrogenism [38]. SHBG lowers free androgen levels by binding free androgens to alleviate hyperandrogenism and IR.

Compared with the levels in healthy individuals, testosterone is significantly increased in PCOS patients, and SHBG levels correlate negatively with those of testosterone [16]. The study showed that SHBG production was inhibited by testosterone in HepG2 cells [39], though the mechanism was not elucidated. As boys enter puberty, serum SHBG levels decrease with increasing testosterone levels [40], and other studies have reported that exogenous androgens, even at low doses, can inhibit SHBG [41]. It can be concluded that hyperandrogenemia is one of the reasons for the low serum level of SHBG in PCOS patients. Regardless, as the human SHBG promoter does not contain androgen-binding elements [42], the androgen signaling pathway may influence SHBG expression via regulation of other factors. HNF-4α binds to the SHBG promoter to stimulate transcription of the gene [9,16]. Androgens may reduce HNF-4α levels by inhibiting lipid synthesis, thereby decreasing the production of SHBG. However, the effect of androgens on HNF-4α expression has not been demonstrated, and it remains to be further studied whether HNF-4α is involved in the regulation of SHBG expression in the hyperandrogenic environment.

In contrast to the effect of testosterone on SHBG, estradiol (E2) increases hepatic SHBG levels, which may be due to the upregulation of HNF-4α gene expression mediated by estrogen receptor-α (ER-α) [16,27]. Oral E2 in women very effectively increases SHBG content, whereas the effect of topical administration is small [43]. Therefore, by directly increasing plasma E2 levels, oral contraceptives are used to treat PCOS. Clinically, oral contraceptive pills are an important treatment to regulate menstruation and improve hyperandrogenemia in PCOS patients. Similarly, tamoxifen, a synthetic antiestrogenic drug structurally similar to estrogen, competes with E2 for binding to estrogen receptors, increasing free E2 and plasma SHBG levels [27].

3.3. The association between serum SHBG levels and hyperinsulinemia in women with PCOS

Approximately 75% of PCOS patients have IR, which is a prominent feature of PCOS [30]. IR and the resulting hyperinsulinemia are considered potential causes of the relationship between metabolic disorders and reproductive dysfunction in PCOS [44]. Serum SHBG levels correlate negatively with IR and HOMA-IR and are an independent predictor of impaired glucose tolerance (IGT) [45]. Therefore, it is absolutely critical to understand the correlation between SHBG and insulin resistance for explaining the etiology of PCOS and treatment of PCOS complications. Some data show that serum SHBG levels can predict the severity of IR [46]. Moreover, low SHBG levels are not only associated with IR but can also serve as a diagnostic indicator of gestational diabetes and an independent risk factor for the development of type 2 diabetes (T2D) [47]. Therefore, SHBG can be employed as an important method to evaluate glycometabolism and IR in patients with PCOS. Although the mechanism by which SHBG affects insulin resistance is still unclear, it has been reported that SHBG regulates the PI3K/AKT signaling pathway and plays a role in insulin resistance [48]. Activation of PI3K results in phosphorylation of downstream mTOR, leading to insulin resistance.

Currently, insulin is believed to be an important regulator of SHBG metabolism, and insulin can inhibit the production of SHBG in the liver [6]. When insulin sensitivity decreases and insulin compensatory secretion increases, the synthesis of hepatic SHBG is reduced [45]. However, it has been reported that insulin does not directly regulate SHBG gene transcription but rather that monosaccharides control expression of this gene by modulating HNF-4α levels [49]. The mechanism by which monosaccharides reduce SHBG production involves competition between HNF-4α and COUP-TF1 for binding sites in the SHBG promoter [49]. High dietary intake of monosaccharides, especially fructose, can reduce serum SHBG levels in nondiabetic patients by approximately 80% and in diabetic patients by approximately 40–50% [49]. In addition, it is possible that insulin indirectly reduces SHBG synthesis by inhibiting de novo lipogenesis in the liver. This may explain why SHBG tends to be higher in lean patients with type 1 diabetes (T1D) and lower in those with obesity and IR [46]. It has also been reported that hyperinsulinemia reduces HNF-4α mRNA and protein levels by upregulating sterol regulatory element-binding protein

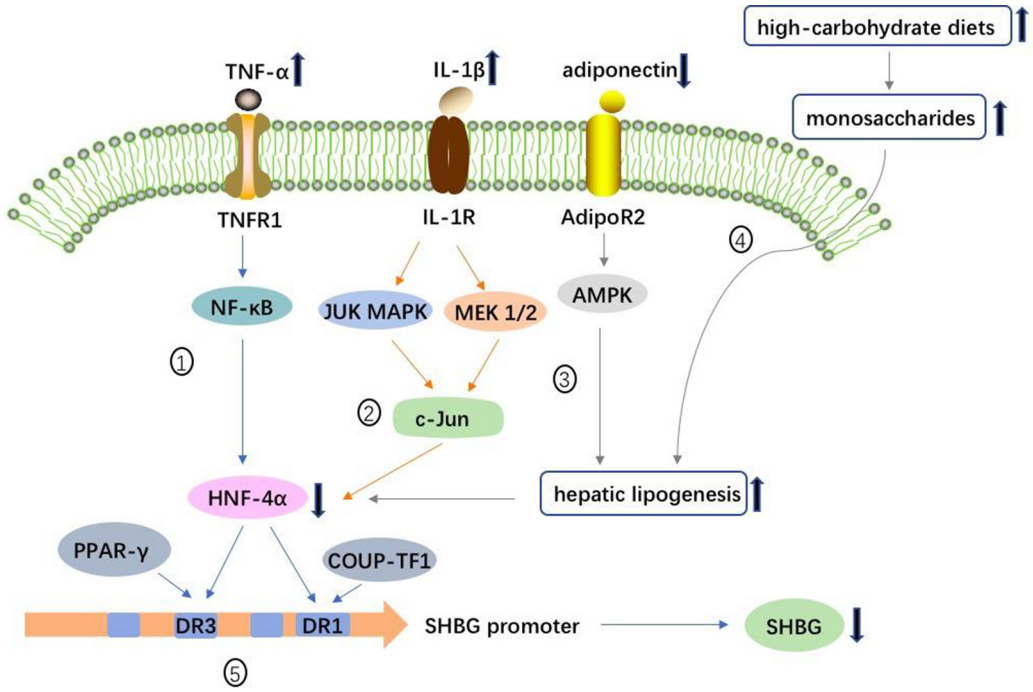

Fig. 2. The molecular mechanism of various factors regulating SHBG through HNF-4α.
1) TNF-α downregulates HNF-4α expression through NF-κB activation. 2) IL-1β decreases HNF-4α expression through the MEK-1/2 and JNK MAPK pathways. 3) Adiponectin increases HNF-4α levels through AMPK activation. Expression of adiponectin in obesity is reduced, decreasing hepatic lipogenesis and thereby leading to downregulation of HNF-4α. 4) A high-carbohydrate diet increases monosaccharide levels in the body, and monosaccharide-induced lipogenesis reduces hepatic HNF-4α levels. 5) HNF-4α increases SHBG transcriptional activity by binding to the cis-elements DR1 and DR3 in the SHBG promoter. COUP-TF1 and PPAR-γ compete with HNF-4α for binding to DR1 and DR3, respectively, and inhibit SHBG transcriptional activity, which attenuates SHBG expression. TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; COUP-TF1: chicken OVA upstream promoter–transcription factor 1; PPAR-γ: peroxisome proliferator-activated receptor-γ.

(SREBP) in the liver [50]. Therefore, insulin may downregulate HNF-4α expression through this pathway, thereby reducing hepatic SHBG levels. Regardless, the mechanism for the interaction between SHBG and IR is not fully clear, and more research is needed (Fig.1).

3.4. The influence of SHBG on lipid metabolism in women with PCOS

PCOS with lipid metabolism disorder is attracting increasing attention. Abnormal lipid metabolism is considered to be an independent risk factor for cardiovascular diseases and one of the most dangerous long-term complications of PCOS. Dyslipidemia in PCOS patients mainly includes high levels of low-density lipoprotein (LDL) and triglyceride (TG) and low levels of high-density lipoprotein (HDL). Furthermore, lipid abnormalities are closely associated with obesity, insulin resistance and hyperandrogenemia in PCOS patients. Obesity promotes abnormal lipid metabolism by inhibiting lipoprotein lipase activity, increasing TG levels and reducing HDL levels. PCOS patients with abdominal obesity experience visceral fat accumulation, and lipolysis of visceral fat mobilizes large amounts of free fatty acids to the liver. A recent study found that SHBG correlate positively with HDL and negatively with HOMA, LDL levels, triglyceride levels and the waist-hip ratio [51]. In addition, knockout of the HNF-4α gene in liver cells has been shown to inhibit lipogenesis, cholesterol biosynthesis, and fatty acid uptake [52]. Hyperandrogenism and hyperinsulinemia reduce serum SHBG levels, and low levels of SHBG promote lipid disorders in PCOS patients. Obesity in turn promotes lipid accumulation in the liver, which reduces SHBG expression by decreasing HNF-4α levels, thus elevating androgen activity.

Adipose tissue is an important endocrine tissue that secretes a variety of active adipokines and inflammatory factors, including leptin, adiponectin, resistin, visfatin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6). These factors may lead to local or systemic inflammation and are also associated with diabetes and IR [53]. A case-control study found that obese subjects have reduced serum adiponectin levels [54]. Adiponectin can increase oxidation of fatty acids, enhance insulin sensitivity, and regulate glucose and lipid metabolism. Adiponectin also significantly decreases triglyceride and LDL levels and increases those of HDL. Studies have confirmed that adiponectin correlates positively with SHBG [55], with both being negatively correlated with BMI [56]. The mechanism by which adiponectin reduces liver lipid content occurs through the AMPK pathway, reducing HNF-4α levels and ultimately SHBG production in the liver [13].

4. The regulatory effect of thyroid hormone on SHBG

In utero, fetuses have a low level of SHBG, though the level starts to rise after birth [57]. There is evidence that the increase in plasma SHBG after birth is caused by the production and maturation of thyroid hormone [58]. Moreover, patients with hyperthyroidism usually have elevated plasma SHBG levels [59]. In vitro studies have shown that thyroid hormone therapy increases the production of hepatic SHBG, as well as levels of SHBG mRNA [60]. However, the SHBG promoter lacks response elements for thyroid hormone. Thyroid hormone increases liver SHBG production by inducing fatty acid oxidation and reducing the liver lipid content, and the decrease in lipid accumulation enhances HNF-4α levels [18]. Therefore, thyroid hormone indirectly upregulates the expression of the SHBG gene through increased HNF-4α levels.

Compared with the incidence in the general population, the incidence of subclinical hypothyroidism is significantly higher in women with PCOS. Hypothyroidism also has similar manifestations as PCOS, such as IGT, dyslipidemia and low serum SHBG levels. The presence of subclinical hypothyroidism can aggravate obesity, glucose and lipid metabolism disorder and insulin resistance in PCOS patients [61]. These findings suggest that abnormal thyroid hormone levels may be involved in the pathogenesis of PCOS and that SHBG plays an important role. Accordingly, thyroid function detection is of great significance for PCOS patients in clinical applications.

5. Inflammatory cytokines associated with HNF-4α-mediated regulation of SHBG

Chronic low-grade inflammation is common in PCOS patients, and it

is associated with excess androgens, IR, obesity and atherosclerosis [62]. Obesity-induced chronic low-grade inflammation is an important factor leading to insulin resistance. Common markers include c-reactive protein (CRP), interleukin (IL), tumor necrosis factor-α (TNF-α) and adipokines. Circulating levels of CRP, TNF-α, IL-1 and IL-6 are elevated in PCOS patients [63], and low serum SHBG levels are observed in chronic low-grade inflammatory diseases, such as obesity and diabetes [51]. This suggests that these inflammatory cytokines may regulate SHBG expression. One study found a negative correlation between SHBG levels and inflammatory cytokines, such as CRP and IL-6, but the mechanism has not been clarified [64].

HNF-4α is inhibited by inflammatory cytokines, as shown in Fig. 2. TNF-α inhibits HNF-4α gene expression and reduces HNF-4α protein levels. TNF-α decreases the activity of the HNF-4α P1 promoter by promoting the binding of NF-κB [19]. IL-1 downregulates expression of HNF-4α through the MAPK kinase (MEK)-1/2 and c-Jun N-terminal kinase (JNK) MAPK pathways [21]. Androgens also induce production of inflammatory cytokines such as TNF-α, IL-1, which activate the ROS system and the NF-κB inflammatory pathway by specifically binding to androgen receptors and promoting production of other inflammatory factors [65]. The adipokine adiponectin has an important anti-inflammatory role and increases insulin sensitivity [13]. Adiponectin inhibits the synthesis of androstenedione, and this decreased expression promotes the occurrence of hyperandrogenemia. Adiponectin reduces the hepatic lipid content and increases HNF-4α levels by activating AMPK [13]. As this increase in HNF-4α levels directly promotes SHBG synthesis in the liver, low expression of adiponectin may be one of the reasons for hyperandrogenemia in PCOS patients. These chronic inflammatory factors indirectly reduce SHBG production by lowering HNF-4α levels. In general, early identification and intervention of chronic low-grade inflammation may provide new ideas for research into the etiology and treatment of PCOS.

6. The correlation between SHBG gene polymorphism and PCOS

The correlation between SHBG gene polymorphism and serum SHBG levels is attracting increasing attention and research [14,66]. SHBG polymorphisms have been regarded as important predictors of hyperandrogenism in women with PCOS [66]. The motif (TAAAA)n is present in the upstream region of the SHBG promoter, and it has been shown to influence transcriptional activity in vitro [67]. In addition, (TAAAA)n polymorphism affects SHBG mRNA and further affects SHBG levels [68]. Longer repeat sequences of (TAAAA)n are associated with lower SHBG expression, and long SHBG (TAAAA)n alleles (> 8 repeats) exhibit a positive correlation with PCOS [68]. For example, a study in Croatia showed that the SHBG (TAAAA)n repeat polymorphism influences serum SHBG levels in women with PCOS [69]. However, other studies have reported insufficient evidence to indicate a correlation between the SHBG TAAAA polymorphism and the risk of PCOS [70,71].

Single-nucleotide polymorphisms (SNPs) are the most common type of human heritable variation, and SHBG SNPs affect the levels of serum SHBG. Moreover, SHBG genetic polymorphisms may lead to differences in the incidence and clinical phenotype of diseases among different races and regions. SHBG SNPs rs727428 and rs6259 are associated with PCOS in the Mediterranean region, whereas SNPs rs1799941 and rs6257 are not associated with PCOS; in addition, no correlation between SHBG SNPs and serum SHBG concentrations was found in this study [72]. Similar findings of no correlation between rs6259 and SHBG levels have been reported [73]. Interestingly, other studies found that four SHBG SNPs (rs1779941, rs6297, rs6259 and rs727428) were not associated with PCOS but that rs1799941 and rs727428 were associated with serum SHBG levels [74–76]. In addition, SHBG SNPs affect the outcome of in vitro fertilization-embryo transfer (IVF-ET) for PCOS patients and the development of T2D [47,66]. Regardless, there is at present no unanimous conclusion with regard to whether SHBG polymorphisms are related to the incidence of PCOS, and the reasons for these controversies may be racial differences among the study groups or the different phenotypes of PCOS (such as BMI and IR).

Thus far, there is no study on the correlation between HNF-4α SNPs and PCOS susceptibility. However, the HNF-4α rs745975 SNP is associated with fasting insulin, HOMA-IR and 2-h glucose levels [77]. Furthermore, in a study of aging men, HNF-4α SNPs rs1884613 and rs2144908 were associated with levels of serum total testosterone [78]. Nonetheless, there is no literature on the relationship between HNF-4α SNPs and androgen levels in women.

Overall, research on susceptibility genes in PCOS is still in the exploratory stage, though we will obtain a deeper understanding of the mechanism of PCOS with further research.

7. Conclusion and prospects

PCOS is one of the most common diseases affecting infertility in women of childbearing age, and it remains a difficult condition to manage due to a lack of knowledge regarding the pathophysiological mechanisms. Obesity, IR, and abnormal glucose and lipid metabolism show a significant correlation with PCOS. A low serum SHBG level in PCOS patients is not only an important influencing factor for hyperandrogenemia but is also an important predictor of insulin resistance, as well as a risk factor for glucose and lipid metabolism disorders. Serum SHBG is associated with complications and long-term prognosis in PCOS, and it plays an important role in the pathogenesis of PCOS. The SHBG promoter contains a binding site for HNF-4α, which binds to this site to enhance the transcriptional activity of the gene. Intracellular palmitate is an endogenous ligand of HNF-4α, and HNF-4α expression is affected by abnormal glucose and lipid metabolism. Obesity [24,25], excess androgen [34], IR, hyperinsulinemia [30,44,46] and hyperlipidemia [51] are risk factors for PCOS, reducing serum SHBG levels by downregulating expression of HNF-4α. Moreover, HNF-4α may participate in regulating follicular metabolism [79], providing energy for ovarian metabolism to ensure the completion of fertilization and embryo development [80]. Although there are no data regarding whether HNF-4α plays a role in the pathogenesis of PCOS, it is certain that HNF-4α indirectly participates in PCOS by regulating SHBG expression. In summary, the pathogenesis of PCOS is extremely complicated and cannot be entirely explained at this stage. SHBG plays a unique role in the screening, early diagnosis and prognosis of PCOS, and detection of serum SHBG levels can provide a certain reference value for clinical treatment and early intervention in complications of PCOS. Nonetheless, there are many issues that have not been resolved, including the effect of HNF-4α on the pathogenesis and long-term prognosis of PCOS and the mutual influencing mechanism between SHBG and insulin. Current studies on the effect of SHBG in PCOS mostly focus on phenomena, and the mechanism needs to be further investigated.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by grants from the Horizontal Cooperation project with Yueyang Maternal & Child Health-Care Hospital (2018KHX41), the College Students' Research Learning and Innovative Experiment Plan in University of South China (NO. 2017XJYZ049, 2018XJXZ163), the Key Lab for Clinical Anatomy & Reproductive Medicine of Hengyang City (2017KJ182), and the Chuanshan Talents Project in University of South China.

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