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Sex Hormone-Binding Globulin and Type 2 Diabetes Mellitus

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Abstract

Sex hormone-binding globulin (SHBG) has emerged as one of the multiple genetic and environmental factors that potentially contribute to the pathophysiology of Type 2 diabetes mellitus (T2DM). In addition to epidemiologic studies demonstrating a consistent relationship between decreased levels of serum SHBG and incident T2DM, recent genetic studies also reveal that transmission of specific polymorphisms in the *SHBG* gene influence risk of T2DM. On the molecular level, elucidation of the multiple interactions between SHBG and its receptors in various target tissues, suggest physiologic roles for SHBG that are more complex than the simple transport of sex hormones in serum. Taken together, these data provide support for an expanded role of SHBG in the pathophysiology of insulin resistance and T2DM.

Keywords

genetic polymorphisms; sex hormone binding globulin; type 2 diabetes mellitus

Altered SHBG Physiology and T2DM

The number of people worldwide affected by diabetes is projected to be 366 million by the year 2030, with the vast majority of these cases being type 2 diabetes mellitus (T2DM) [1]. Significant resources continue to be devoted to unraveling the complex pathophysiology of this disorder. On the most basic level, two metabolic defects must be present in order for an individual to develop T2DM: insulin resistance and impaired pancreatic β -cell function [2]. However, it is now evident that a number of factors, including genetic predisposition, contribute collectively to the primary physiologic derangements responsible for T2DM. Of note, conditions of hyperandrogenism in women, such as in polycystic ovarian syndrome (PCOS), and hypoandrogenism in men have been linked to insulin resistance [3,4],

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suggesting that alterations in normal sex steroid physiology could play a role in the pathogenesis of T2DM.

Sex hormone-binding globulin (SHBG) is a glycosylated homodimeric plasma transport protein synthesized mainly in the liver that binds the androgens testosterone and dihydrotestosterone (DHT), with higher affinity than estradiol [5,6]. In the past, the “free hormone hypothesis” has been the predominant paradigm for describing the physiologic role of SHBG. In this model, SHBG regulates free sex hormone bioavailability to target tissues, through differential binding and transport of sex steroids [7]. A growing body of experimental evidence suggests that SHBG also exerts direct effects on sex steroid cellular uptake and cell proliferation in hormone-responsive tissues via activation of a specific, high-affinity receptor present in the plasma membrane [8–11]. An emerging understanding of the complexity of SHBG synthesis and physiology has led to renewed interest in the protein’s potential role in a wide range of clinical disorders, including T2DM.

Hepatic SHBG production is affected by the interaction of several hormonal and metabolic factors [12–15], and results of several *in vitro* [16] and *in vivo* [14] studies have implicated insulin as a suppressor of hepatic SHBG production. Other observations suggest that excess carbohydrate consumption and levels of fasting glycemia, rather than hyperinsulinemia, are the actual determinants of liver SHBG production [15,17]. Although the controversies regarding specific mechanistic relationship between SHBG and abnormalities in glucose homeostasis are unresolved, low levels of SHBG are frequently observed in states of insulin resistance and have been studied as a potential predictor of the development of T2DM in overweight populations [18–20]. The associations between low SHBG levels and increased risk of T2DM may be explained by the hypothesis that SHBG represents a biomarker of elevated insulin or glucose levels. In addition to hormonal and metabolic factors, plasma SHBG levels are also affected by genetic heterogeneity [21–23], and recent findings demonstrate inheriting single nucleotide polymorphisms (SNPs) in the *SHBG* gene confer risk for the development of T2DM [24,25]. Such findings support a role for altered SHBG physiology in T2DM that may also apply to other disorders associated with insulin resistance.

Associations of Sex Hormones, Circulating Levels of SHBG, and Type 2 Diabetes Mellitus

A number of studies demonstrate relationships between levels of endogenous sex hormones and T2DM. In a large systemic review and meta-analysis involving 6,974 women and 6,427 men, Ding and colleagues describe a sexually-dimorphic relationship between testosterone and risk of development of T2DM: lower testosterone levels are associated with diabetes in men, while higher testosterone levels correlated with increased diabetes risk in women [26]. Animal studies not only support the sexual dimorphism observed in humans but also suggest sex-specific mechanisms between testosterone and the development of diabetes. For example, testosterone treatment in oophorectomized female rats resulted in greater decreases in both glycogen synthase expression and insulin-mediated glucose uptake, compared with oophorectomized rats not receiving testosterone [27]. Furthermore, female androgen receptor knockout mice developed progressive reductions in insulin sensitivity and impaired glucose tolerance with advancing age, when compared with wild-type controls [27,28].

Despite congruent, albeit sexually dimorphic data in humans and animals regarding testosterone and T2DM, the results of studies investigating the relationship between estradiol and T2DM are less clear. In at least two animal studies, estradiol appears to increase pancreatic islet cell survival [29,30]. Moreover, estrogen receptor activation in both cultured rodent and human islet cells inhibits the synthesis and accumulation of intracellular

lipids that may contribute to β -cell failure [31]. Although the meta-analysis by Ding et al. revealed a positive association between endogenous estradiol levels and the risk of T2DM, independent of body mass index (BMI), in both men and post-menopausal women [26], human studies involving exogenous hormone administration have suggested a protective role of estrogen on T2DM, at least in women [32,33]. For example, a trial of 2,029 women randomized to either placebo or 0.625mg of conjugated estrogen with 2.5mg medroxyprogesterone acetate, revealed a 6.2% incidence of diabetes in the hormone-treated group over 4 years of follow-up, compared with an incidence of 9.5% in the placebo group [32]. Similarly, in a subsequent analysis of a large prospective study involving 63,624 postmenopausal French women published by de Lauzon-Guillain and colleagues, estrogen replacement was associated with a reduction in diabetes risk compared with women never treated with replacement therapy (hazard ratio [HR] 0.82; 95% CI, 0.72–0.93) [33]. Moreover, oral estrogen replacement was associated with larger reductions in the risk of T2DM (HR 0.68; 95% CI, 0.55–0.85) than transdermal estrogen (HR 0.87; 95% CI, 0.75–1.00) [33], suggesting that the method of exogenous estrogen exposure may modulate the hormone's potential anti-diabetic effects. In fact, in a randomized crossover trial of 25 women treated with oral conjugated equine estrogen and transdermal estradiol for 12 weeks each, oral estrogen induced a robust (112.9%) increase in serum SHBG levels from baseline, compared with a marginal change (2.6%) following transdermal estrogen therapy [34]. Thus, the differential reduction in the risk of T2DM according to the route of estrogen replacement may be indirectly mediated through associated alterations in circulating SHBG levels.

Cross-sectional studies also support a relationship between serum levels of SHBG and T2DM [26]. A combined analysis of 23 cross-sectional studies found that women with T2DM had significantly lower SHBG levels compared with controls [26]. In the same analysis, men with T2DM appeared to have slightly lower SHBG levels compared with non-diabetic subjects, although the difference between groups did not reach statistical significance [26]. However, in a cross-sectional study of non-diabetic men, SHBG levels were inversely associated with glycated hemoglobin (HgbA1C) levels, suggesting a relationship between SHBG and glucose homeostasis among individuals without diabetes [35]. Similar findings were observed in a cross-sectional study of non-diabetic postmenopausal women who were not receiving hormone replacement therapy, and the inverse relationship between SHBG and HgbA1C persisted after adjusting for BMI [36]. Thus, alterations in circulating levels of SHBG appear to be associated with subtle changes in glucose homeostasis in men and women, even before the development of overt T2DM.

In fact, prospective studies indicate a pronounced relationship between SHBG and risk of T2DM [26,37–39]. Specifically, the meta-analysis conducted by Ding and colleagues included data from 10 prospective studies and demonstrated that women with serum SHBG levels greater than 60 nmol/L had an 80% reduction in the risk of T2DM, compared with women with lower SHBG values [26]. Among men, serum SHBG greater than 28.3 nmol/L was associated with 52% reduction in diabetes risk [26]. These findings have been replicated by others, indicating that low serum levels of SHBG are strongly correlated with the risk of T2DM in both women and men [24,25], and the low SHBG levels may precede the development of impaired glucose metabolism [19,20,25,40]. Table 1 summarizes the results of prospective studies investigating the associations between serum SHBG levels and incident diabetes in both sexes.

Although the apparent relationship between SHBG and diabetes risk may result from the indirect influence of alterations in SHBG on sex-hormone bioavailability, studies suggest that the SHBG-T2DM relationship is independent of the potential impact of sex hormones levels in both men and women [37–39,41]. The associations of circulating levels of SHBG

with T2DM risk remain significant after adjustment for total or free testosterone, again implicating SHBG levels as a predictor of T2DM independent of serum androgen levels [37–39]. Additional evidence in support of an effect of SHBG on T2DM risk independent of sex steroids is provided in a study of glucose metabolism in 55 testosterone-deficient elderly men who were randomized to either 2 years of treatment with testosterone or placebo [42]. When compared with placebo, the testosterone-treated patients showed no improvement in the expected age-related decline in glucose tolerance, as measured by mixed meal and glucose tolerance testing [42].

Increasing evidence suggesting that alterations in SHBG levels precede clinically evident abnormalities in glucose homeostasis imply that the measurement of SHBG may have a role in the early identification of individuals at high risk of T2DM. The metabolic syndrome (MetS) is a constellation of risk factors including central obesity, dyslipidemia, elevated blood pressure, and glucose intolerance, that are driven by insulin-resistance [43]. The presence of MetS is a strong predictor of future risk of both cardiovascular disease and T2DM [44,45]. A cross-sectional study of children with and without MetS aged 14–18 years conducted by Agirbasli et al. found that SHBG levels were significantly lower in both adolescent boys and girls with MetS compared with normal controls (males - 34 nmol/L in control subjects versus 21 nmol/L in MetS group, $p<0.01$; females - 57 nmol/L in control subjects versus 35 nmol/L in MetS, $p<0.01$) [46]. Moreover, in multivariate analysis controlling for the impact of sex-steroids and age, SHBG was the only significant predictor of MetS in these youth [46]. Similarly, in a recent prospective study of girls aged 14 years at study initiation, logistic regression analysis revealed that SHBG levels in the race-specific bottom decile were an independent predictor for the development of MetS by the age of 24 years (odds ratio [OR] 4.28, 95% CI, 1.52–12.6) even after adjustment for age, race, BMI, waist circumference, insulin and sex hormone levels [47]. Finally, in a sample of 1,226 adult men participating in the Third National Health and Nutrition Examination (NHANES) survey, an increase in serum SHBG by one, log-transformed, standard deviation (SD) was associated with a striking 43% decrease in the prevalence of MetS after adjustment for age, while a SD increase in total serum testosterone was associated with a 17% decrease in the prevalence of MetS [48].

SHBG genotype and risk of T2DM

One potential hypothesis for the observed associations between low levels of SHBG and incident diabetes may be that alterations in SHBG are secondary to excessive carbohydrate consumption and increasing insulin resistance long before the development of clinical disease. However, two recent studies demonstrating a direct association between *SHBG* SNP genotypes, circulating SHBG levels, and the risk of T2DM, suggest that altered SHBG physiology may be a primary defect in the pathogenesis of disease which is subsequently followed by clinical derangements of glucose metabolism [24,25].

In a pooled analysis of the effect of *SHBG* genotype on T2DM risk conducted by Perry and colleagues that included 15 studies containing 27,657 T2DM cases and 58,481 controls, the SHBG-raising allele, reference sequence (rs) 1799941, was associated with a lower risk of T2DM development in both men (OR 0.95; 95% CI, 0.91–0.99) and women (OR 0.93; 95% CI, 0.89–0.98) [24]. Moreover, the association between rs1799941 transmission and T2DM persisted even after controlling for the influence of BMI [24]. However, no associations were found between rs1799941 and estimates of insulin resistance or secretion assessed by various techniques, including homeostasis model of assessment – insulin resistance (HOMA-IR), oral glucose tolerance testing, or hyperinsulinemic-euglycemic clamp methods. Importantly, the magnitude of the association between rs1799941 genotype and incident T2DM observed by Perry et al. was consistent with the effect that, based on

previous epidemiologic studies, would be anticipated by the observed differences in serum SHBG levels among genotypes [24]. In a recent analysis of a nested case-control study involving 718 postmenopausal women from the prospective Women's Health Study and a replication study including 280 men from the Physicians' Health Study conducted by Ding and colleagues, elevated SHBG levels at baseline were confirmed to have an inverse association with the risk of developing T2DM [25]. Moreover, genotype analysis for two *SHBG* SNPs of interest, rs6257 and rs6259, in both cohorts revealed that carriers of rs6257 variant allele (CC or CT) demonstrated a 10% decrease in plasma SHBG compared with wild-type homozygotes (TT), which translated to an increased risk of T2DM. Conversely, rs6259 variant allele carriers (AA or AG) had a 10% increase in plasma SHBG, corresponding to a reduction in the risk of T2DM. These specific SHBG polymorphisms were found to be unrelated to subject BMI, suggesting that the SNPs affect T2DM risk independently of adiposity [25]. Furthermore, the impact of various allelic combinations for both SNPs in *SHBG* was considered, and rs6257 and rs6259 genotypes appeared to have independent and additive effects on serum SHBG levels and subsequent risk of T2DM [25]. In fact, based on the results of Mendelian randomization analyses, each standard-deviation increase in plasma SHBG was associated with predicted odds ratios for the development of T2DM of 0.29 (95% CI 0.15–0.58) and 0.28 (95% CI 0.13–0.58) in men and women respectively [25].

Although the results of family-based, twin- and sib-pair heritability studies suggest that genetic variation may account for 50–70% of inter-individual variations in SHBG [21,49,50], the impact of a single *SHBG* SNP or polymorphism on circulating SHBG levels is modest [25,51]. According to the analysis conducted by Ding and colleagues, rs6257 and rs6259 variants accounted for 2.2% of the observed variance in SHBG levels across the study cohort [25]. In an analysis involving 4,720 men participating in the National Cancer Institute's Breast and Prostate Cancer Cohort Consortium (NCI-BPC3), rs1799941 was more strongly associated with SHBG levels than rs6259 (rs6257 was not examined); however, 1799941 genotype still only accounted for approximately 2% of the variance in log-transformed circulating SHBG levels among the men studied [51]. Thus, although studies support the influence of genetic variation on circulating SHBG levels, additional factors beyond the isolated impact of specific polymorphisms in *SHBG* genotype remain important in determining circulating levels of the protein for a given individual.

SHBG Structure and Function

Insights into the biochemical structure of SHBG provide a framework for understanding the relationship between the protein and T2DM risk. Human SHBG is a glycoprotein consisting of two identical, noncovalently-bound 40.5kDa subunits that are encoded by a gene located on the short arm of chromosome 17 [52,53]. The un-dimerized SHBG subunit is comprised of 373 amino acids, with three oligosaccharide side chains and two disulfide bonds [5]. The SHBG homodimer has two distinct, and equally active, steroid binding sites capable of binding DHT, testosterone, or estradiol [54]. Each monomer also contains two β -sheets, linked by eight hydrogen bonds, which are essential for formation of the two continuous 14-stranded β -sheets of the mature homodimer [54,55] (Figure 1).

Mature SHBG, similar to cortisol-binding globulin or thyroxine-binding globulin, contains oligosaccharide side chains which confer a unique structural organization [56]. Specifically, each SHBG homodimer subunit contains an O-linked glycosylation site at Thr7 and two N-linked sites at Asn 351 and Asn 357 [57–59]. These oligosaccharide side chains have not been shown to be essential for the steroid-binding activity of SHBG [59]; however, glycosylation of SHBG may be necessary for the interaction of the complete SHBG-steroid complex with plasma membrane receptors in target tissues [60]. Glycosylation prolongs

serum SHBG half-life, thereby providing another putative regulatory mechanism for duration of biological activity or interaction with other macromolecules [61].

At the target tissue level, the dimerized SHBG complex also functions as a ligand for a specific, plasma membrane high-affinity receptor (R_{SHBG}) [8]. Unoccupied SHBG (i.e., not bound to sex steroids) has the ability to bind to R_{SHBG} [8]. Following the binding of unoccupied SHBG to the cell surface receptor, sex steroids of variable biologic potency can activate the anchored SHBG- R_{SHBG} complex [8]. Additionally, the activated sex steroid-SHBG- R_{SHBG} complex can have either an agonist or antagonist effect, depending upon both the specific sex steroid and the nature of the R_{SHBG} -containing target tissue [8]. For example, DHT may function as either an agonist or antagonist for the system, depending on the specific target cell type [8,62]. SHBG- R_{SHBG} complex activation also appears to affect cell proliferation, as studied in prostate and breast cancer cells, and to modulate the transcriptional activity of classic intracellular steroid hormone receptors; however, the specific effects of the SHBG- R_{SHBG} complex on cAMP-mediated second messenger systems are yet to be elucidated [8].

In addition to the actions of the SHBG- R_{SHBG} complex, SHBG may interact with megalin, an endocytic receptor found in reproductive tissues, and stimulate endocytosis of SHBG-bound androgens and estrogens [9]. This potential interaction provides an additional mechanism by which SHBG may modulate the intracellular effects of sex steroids aside from the protein's role in simple free hormone diffusion into cells of target tissues [9]. Although megalin-mediated endocytosis of SHBG-sex steroid complexes remains controversial [63], such findings suggest roles of SHBG in sex steroid physiology that are both more numerous and more complex than previously thought.

Structure and Transcriptional Regulation of the *SHBG* Gene

Human SHBG is encoded by the 4-kb *SHBG* gene on the chromosome 17p12→p13 which is comprised of eight exons and seven intervening introns (Figure 2) [5,52,64]. Exon 1 encodes a 29 amino acid secretion signal [5], and exons 2–8 encode two contiguous laminin G-like (LG) domains [64]. The amino-terminal LG domain, which is encoded by exons 2–4, contains the sites for the sex steroid and cation binding domains in addition to the dimer interface [65]. Residues 48–57 within exon 3 contain the putative ten amino acid sequence of the R_{SHBG} -binding domain [66].

The majority of plasma SHBG is of hepatic origin [67], although testis, prostate, ovary, endometrium, breast, placenta, and hypothalamus have also been shown to express *SHBG* mRNA in humans [12,53,68–72]. There are recent data to support differential tissue-specific regulation of *SHBG* transcription by at least three distinct promoters (P_L , P_T , and P_N) [73]. The predominant *SHBG* mRNA transcript, exon 1L-8, is activated by the downstream promoter P_L ; exon 1L-8 encodes all eight *SHBG* exons and is abundant in hepatocytes, although it is also found in human prostate, breast, and brain [73]. P_L activation in the testis results in an eight-exon mRNA identical to that produced by P_L activation in the liver; however, through distinct post-translational modifications, testicular 1L-8 results in the production of androgen binding protein (ABP) rather than mature SHBG [53,74]. Additionally, in the testes, activation of a second *SHBG* promoter (P_T), located 1.9 kb upstream of P_L , produces a second major mRNA transcript, exon 1T, which is characterized by a distinct 5' end amino acid sequence and the absence of exon 7 [53,73]. A recently described third *SHBG* gene promoter (P_N), found within intron 1 of the adjacent *FXR2* gene also contains a unique first exon (1N) [73]. P_L -, P_T -, and P_N - derived transcripts of *SHBG* are most abundantly expressed in the liver, testis, and prostate, respectively [73]. Differential activation of these three promoters in a tissue-specific manner allows for

alternative splicing of *SHBG* exons, resulting in the expression of as many as 19 unique *SHBG* transcripts; the biologic roles of these variant *SHBG* transcripts are unknown [73].

The locations of specific T2DM-associated SNPs within the *SHBG* gene imply potential mechanisms by which the polymorphisms impact the protein's synthesis and function (Figure 2). The rs1799941 SNP (G>A in the 5' untranslated region) is located within the promoter sequence, 8 nucleotides upstream of the transcription start site [64]. This location, in conjunction with the observed relationship between rs179994 genotype and serum SHBG, suggests a central role for this primarily liver-derived splice variant in the determination of circulating SHBG levels. The rs6259 *SHBG* polymorphism (G>A) encodes for a non-synonymous amino acid change (D327N) within exon 8, resulting in an additional N-glycosylation site in the mature protein [75]. Although this alternative glycosylation pattern does not appear to impact sex steroid binding capacity [75], the rs6259 SNP likely results in a modest increase in circulating levels of SHBG by reducing plasma clearance of the protein [76]. Lastly, the rs6257 SNP (T>C) is located 17 bp upstream of exon 2 [77]. Despite the associations between rs6257 genotype, circulating levels of SHBG and risk of T2DM, the exact mechanisms underlying these relationships are unknown.

An additional polymorphism, the (TAAAA)_n pentanucleotide repeat (rs35785886), is located in the upstream portion of the *SHBG* promoter and also appears influence circulating SHBG concentrations [64,78]. The number of (TAAAA) repeats in a given individual is highly variable, ranging from six to 11 copies among various populations [64]; and, although the data on the effect of the six-repeat (TAAAA)_n allele on SHBG are conflicting, longer repeats appear to be associated with lower SHBG concentrations [64]. However, despite the potential impact of (TAAAA)_n genotype on SHBG levels, associations between this specific polymorphism and T2DM are currently unknown.

Insulin and Carbohydrate Regulation of SHBG Expression

SHBG synthesis in the liver is influenced by multiple metabolic and hormonal factors including sex steroids, thyroxine, prolactin, and insulin [16,79,80]. *In vitro* experiments in the human hepatoma (HepG2) cell line suggest that insulin suppresses SHBG production [13], in concordance with observed associations between hyperinsulinemia, hyperglycemia and alterations in SHBG [81]. Alternatively, other investigators have suggested that insulin suppression of SHBG is nonspecific and likely reflects global reduction in hepatic protein secretion under nonphysiologic experimental conditions [82]. A series of investigations performed with both transgenic mice and HepG2 cells by Selva et al. have shown that hepatic *SHBG* transcription is reduced in response to monosaccharides, but not insulin, in a dose-dependent manner [15]. Treatment of HepG2 cells with either glucose, or particularly fructose, stimulated hepatic lipogenesis and subsequently reduced SHBG production via downregulation of hepatocyte nuclear factor-4α (HNF-4α), a transcription factor that plays a critical role in controlling the SHBG promoter [15]. Furthermore, in a human study involving 225 subjects conducted by Peter and colleagues, serum SHBG concentrations negatively correlated with fasting glucose levels but were unrelated to insulin secretion during both oral and intravenous glucose tolerance tests [17]. However, the lack of insulin-associated suppression of SHBG in these experiments is in contradistinction to the results of other *in vivo* human experiments demonstrating that administration of diazoxide, which results in acute suppression of pancreatic insulin secretion, is followed by a significant increase in circulating levels of SHBG [14]. In the latter study performed by Nestler and colleagues, increases in SHBG were observed among women with PCOS treated with diazoxide despite concurrent deteriorations in glucose homeostasis during the treatment period [14]. In this study, women were pre-treated with a long-acting gonadotropin-releasing hormone (GnRH) agonist to control for the potential confounding effects of sex steroids on

SHBG levels [14]. Although controversies regarding the direct role of insulin in SHBG suppression persist, available evidence highlights a complex relationship between circulating levels of SHBG and the development of insulin resistance leading to glucose intolerance and T2DM (Figure 3), whereby perturbations in insulin and/or carbohydrate metabolism not only regulate hepatic SHBG synthesis, but primary changes in circulating levels of the protein, resulting from variations in the *SHBG* gene, also contribute to abnormal glucose homeostasis.

Further investigation of the relationship between insulin and hepatic SHBG production could clarify the mechanisms through which plasma SHBG levels are linked to metabolic disturbances, thereby providing physiologic constructs for other disorders of insulin resistance including gestational diabetes mellitus (GDM), PCOS, and non-alcoholic fatty liver disease (NAFLD). For example, serum SHBG levels are decreased in association with GDM, and use of SHBG as adjunctive screening tool for gestational diabetes as early as 11–13 weeks gestational age, a critical period for organogenesis, was recently investigated, with promising results [83].

Furthermore, women with PCOS, a condition of anovulation and hyperandrogenism characterized by insulin resistance, are at increased risk of glucose intolerance and T2DM [84], and levels of SHBG are decreased in women with PCOS [14]. In fact, given the protein's potential contributions to both hyperandrogenemia and insulin resistance, *SHBG* has also been proposed as a candidate gene for PCOS [85]. However, in a study involving 248 women with PCOS and 109 healthy control women conducted by Bendlová and colleagues, the frequency of rs6259 mutations were not statistically different between groups [86]. Similarly, in a study involving 430 families with a PCOS proband, PCOS status was not associated with any of the previously-described diabetes-associated SNPs (rs1799941, rs6257, or rs6259) [85]. Of note, the sample sizes in both studies [85,86] were relatively small, and neither study group conducted an exhaustive interrogation of the *SHBG* gene. Thus, the possibility remains that other distinct loci in *SHBG* are associated with PCOS. Although the prevalence of previously described (TAAAA)_n repeat polymorphism in *SHBG* has not been investigated in T2DM, a case-control study by Xita and colleagues implicates an association between this specific polymorphism and PCOS [87].

NAFLD represents a spectrum of liver pathology resulting from abnormal fat accumulation in hepatocytes that may be driven, at least in part, by insulin resistance [88]. In a prospective study involving pre-menopausal women with PCOS and age- and weight-matched controls, decreased SHBG levels were associated with higher rates of NAFLD in both PCOS patients and controls [89]. Moreover, this association remained significant even after adjustment for BMI and weight circumference. In the study conducted by Peter et al. investigating relationships between changes in regional adiposity following lifestyle modification and circulating levels of SHBG among subjects at high-risk of T2DM, change in liver fat (quantified by magnetic resonance tomography) demonstrated stronger correlations with serum SHBG change than did total body or visceral fat mass [17].

Conclusion

Over the past several years, the biologic role of SHBG has expanded from a simple transport protein for sex steroid to include multiple and complex physiologic interactions with various target tissues. Interestingly, SHBG action appears to influence glucose homeostasis. In fact, epidemiologic evidence regarding the association between decreased SHBG levels and the risk of development of T2DM continues to grow, along with identification of specific genetic polymorphisms in *SHBG* that confer variable risk for the development of T2DM, presumably by influencing the protein's synthesis, degradation, or interaction with target

tissues. Moreover, factors such as insulin and monosaccharides have been implicated as regulators of *SHBG* transcription. As additional details of SHBG structure and function are elucidated, areas that continue to merit investigation include specific downstream effects of the SHBG- receptor complex in intracellular signaling and the roles of numerous alternative *SHBG* mRNA transcripts. Delineation of SHBG physiology could provide valuable venues for future research, including potential risk stratification strategies or novel therapeutic agents for prevention or treatment of T2DM or other disorders of insulin resistance.

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Figure 1.

Crystal structure of SHBG protein. (A) Ribbon representation demonstrating the interaction of the N-terminal domains (residues 13–188) of each SHBG subunit to form the homodimer. The two SHBG N-terminal laminin G-like (LG)-domains, each containing a steroid-binding site, are shown in red and blue. (B) Representation of the domain composition of dimeric full-length SHBG. The steroids bound to the N-terminal LG-domains are depicted as yellow ellipses. The twofold symmetry axis that relates the two monomers in dimeric SHBG is indicated as a vertical line at the center of the sketch. Adapted from Avvakumov et al. [61].

Figure 2.

Schematic of the *SHBG* gene and location of single nucleotide polymorphisms associated with Type 2 diabetes mellitus: rs179994 (in the 5' untranslated region), rs6257 SNP, and rs6259 [64]. Shaded boxes represent exons 1–8. P_N , P_T , and P_L are promoters which are differentially activated in liver, testis, and prostate, resulting in alternative splicing of *SHBG* exons [73].

Figure 3.

Potential mechanisms for the relationship between sex hormone binding globulin (SHBG) and type 2 diabetes mellitus. Multiple nutritional, metabolic, and hormonal factors influence hepatic SHBG production, including insulin and monosaccharides. In addition, SHBG levels are determined in part by genetic variation. Regardless of etiology, alterations in SHBG may contribute to derangements in glucose homeostasis through modulation of sex hormone bioavailability. Recent findings also support a specific receptor for SHBG (R_{SHBG}), implying a more direct role of the protein in certain intracellular signaling pathways. Compensatory hyperinsulinemia, resulting from insulin resistance, may further suppress hepatic SHBG production. However, some studies implicate a direct effect of monosaccharides in regulating SHBG synthesis via reduction of hepatocyte nuclear factor 4- α as opposed to an effect from insulin. Aside from influencing sex-steroid bioavailability, decreases in SHBG, either directly or via R_{SHBG} activation, may have hypothetical effects (represented by dotted lines) that increase insulin resistance and reduce beta cell function defects leading to glucose intolerance and ultimately overt diabetes.

Table 1
Summary of Prospective Studies of Sex Hormone-Binding Globulin and Development of Type 2 Diabetes Mellitus

Location of Study Population	Subject Sex	Duration of follow up (years)	Total number of subjects	Cases of T2DM	Mean age (years)	Mean BMI (kg/m ²)	Mean SHBG in T2DM Cases (nmol/L)	Mean SHBG in Controls (nmol/L)	P	Reference
Sweden	F	12	1424	43	46.8	NR	55	88	<0.001	19*
United States	M	5	352	176	44.8	29.4	37.0±14.8	41.5±18.3	0.08	20*
Massachusetts, United States	M	13	1128	90	53.7(8.3)	27.0(4.1)	26.0±1.6	32.5±0.5	<0.001	37
Norway	M	9.1	1454	76	59.4(10.3)	26.0(3.4)	42.0	53.3	<0.001	38
United States	F	4.7	1612	116	63.1	28.6	35.75	54.45	<0.001	41
Finland	M	11	702	57	51.3(6.7)	26.2(2.9)	26.2	35.6	<0.01	90*
Massachusetts, United States	M	8.9	1030	54	53.9(8.3)	27.1(4.1)	24.4±1.4	32.3±0.5	<0.001	91*
United States (Japanese Americans)	M	3	203	20	68.3(0.6)	23.7(0.2)	45.7±4.2	45.1±1.4	NS	92*
	F	3	280	23	65.4(0.5)	23.0(0.2)	56.5±6.9	69.7±2.7	<0.05	92*
Sweden	M	13	446	35	67	25.4(0.12)	39.9±1.97	51.5±1.38	0.053	93*
Texas, United States	M	8	56	20	48.4	29.0	42.8±4.9	38.6±6.5	NS	94*
	F [†]	8	61	19	52.7	29.5	66.4±15.9	78.5±10.5	NS	94*
	F [‡]	8	48	19	38.5	25.9	41.6±12.4	74.4±10.0	<0.001	94*

Abbreviations: BMI body mass index; F – female; M – male; NR – not reported; NS – not significant; SHBG- sex hormone-binding globulin; T2DM – type 2 diabetes mellitus.

Standard deviations for mean age and BMI are shown where available.

Standard error for SHBG measurements are shown where available.

To convert SHBG (nmol/L) to µg/dl, multiply by 0.025.

* Study included in Ding et al, 2006 meta-analysis.

[†] Postmenopausal.

[‡] Premenopausal.