Androgen dysfunction in non-alcoholic fatty liver disease: Role of sex hormone binding globulin

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Non-alcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease in the world. It is linked mainly to insulin resistance and metabolic syndrome including obesity and dyslipidemia. In addition, various endocrine dysfunctions including polycystic ovary syndrome (PCOS) and hypogonadism are involved in the development and progression of NAFLD. We need to know the disease pathophysiology more accurately due to the heterogeneity of clinical presentation of fatty liver disease. The liver is the major metabolic organ with sexual dimorphism. Sexual dimorphism is associated not only with behavioral differences between men and women, but also with physiological differences reflected in liver metabolism. In men, normal androgen levels prevent hepatic fat accumulation, whereas androgen deficiency induce hepatic steatosis. In women, higher androgens can increase the risk of NAFLD in PCOS. Sex hormone binding globulin (SHBG) is involved in androgen regulation. Recently, SHBG may be reported as a surrogate marker for NAFLD. Therefore, this review will focus on the mechanism of androgen dysfunction in the regulation of hepatic metabolism, the risk of developing NAFLD in PCOS. Sex hormone binding globulin (SHBG) is involved in androgen regulation. Recently, SHBG may be reported as a surrogate marker for NAFLD. Therefore, this review will focus on the mechanism of androgen dysfunction in the regulation of hepatic metabolism, the risk of developing NAFLD in PCOS. Sex hormone binding globulin (SHBG) is involved in androgen regulation. Recently, SHBG may be reported as a surrogate marker for NAFLD. Therefore, this review will focus on the mechanism of androgen dysfunction in the regulation of hepatic metabolism, the risk of developing NAFLD in PCOS. Sex hormone binding globulin (SHBG) is involved in androgen regulation. Recently, SHBG may be reported as a surrogate marker for NAFLD. 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Introduction

Nonalcoholic fatty liver disease (NAFLD) imposes a major public health burden with increasing incidence of comorbidities including obesity and dyslipidemia (1). The main histologic and imaging characteristic of NAFLD is the hepatic accumulation of lipids. Dysregulation of lipid metabolism in liver leads to the accumulation of toxic lipids, which may result in inflammation, hepatocellular injury, and fibrosis (2–4).
Recently, it was suggested that metabolic dysfunction associated fatty liver disease, which is not merely a differential diagnosis for NAFLD could reflect the current knowledge of the disease pathophysiology and aid risk stratification and management of fatty liver disease, which shows a heterogeneous clinical presentation (5).

Obesity and metabolic syndrome lead to the development of NAFLD and may be accompanied by endocrine and hormonal disturbances. The liver is the major metabolic organ related to sexual dimorphism (6, 7). NAFLD prevalence is 2.0-3.5-fold higher in men than in women (8). Epidemiological studies have reported that NAFLD is also more severe in men, indicating a deleterious effect of androgens and, on the other hand, protective effect of estrogens in the pathogenesis of NAFLD (9-11). However, the sex-specific mechanisms underlying the development and progression of NAFLD remain to be elucidated.

Sex-differences in the prevalence, progression, outcomes and comorbidities of fatty liver might be considered as the result of gender differences indicative of the liver phenotype between males and females (8). The sexual dimorphism usually observed in NAFLD is reflected in polycystic ovary syndrome (PCOS) in women and hypogonadism in men. Furthermore, sex hormone binding globulin (SHBG) is related to androgen regulation (12). Recently SHBG is reported as a surrogate marker for NAFLD. Investigating the role of androgens in the development and progression of NAFLD in consideration of the gender differences is necessary. Therefore, this review will focus on the mechanism of androgen dysfunction in the regulation of hepatic metabolism, the risk of developing NAFLD, and the potential role of SHBG in the course of NAFLD.

**Hepatic lipid metabolism in NAFLD**

Hepatic fatty acids (FAs) are derived from two main sources including excess carbohydrates and FAs that are produced by diet and lipolysis in the adipose tissue. Uptake of circulating lipids are facilitated by fatty acid transporters (CD36, FATP2-5) in hepatocyte membrane and is regulated by Peroxisome proliferator-activated receptor-γ (PPAR-γ) (13). Fatty acid binding protein 1 facilitate the transport of hydrophobic FAs with the cytoplasm. De novo lipogenesis (DNL) is regulated by the sterol regulatory element binding proteins 1c (SREBP1c) that induces the expression of genes involved in de novo FA synthesis including acetyl-CoA carboxylase (ACC), fatty acid synthase, the long-chain elongase and stearoyl-CoA desaturase (14). In NAFLD, enhanced SREBP1c-mediated DNL is a key character. FA oxidation is controlled by PPAR-α and reduces intrahepatic fat levels by utilizing FAs as a source of energy in mitochondrial β-oxidation. Mitochondrial dysfunction in NAFLD results in liver injury through increased production of reactive oxygen species. Triglycerides (TGs) are secreted from the hepatocytes in the form of very low density lipoprotein (VLDL) via the fusion of apolipoprotein B-100 (ApoB100). Decreased level of microsomal triglyceride transfer protein (MTP) and ApoB100 may limit VLDL export and facilitate fat accumulation. An imbalance of these processes leads to the progression of steatosis to nonalcoholic steatohepatitis (NASH).

**Hepatic sexual dimorphism according to sex hormone dysfunction**

Sex hormones, including estrogens and androgens play a key regulatory role in lipid metabolism and insulin sensitivity (15-17). Sex hormone dysfunction may contribute to the development of NAFLD, because a reduction in insulin sensitivity increases hepatic gluconeogenesis and lipogenesis, in turn, this may exacerbate hepatic steatosis (18).

Among the sex hormones, estrogens have critical metabolic actions in both women and men. The biologically active form of estrogens is 17β-estradiol (E2). In premenopausal women, the main source of E2 is from cholesterol, while in postmenopausal women and men, it is primarily derived from testosterone aromatization. Estrogen reversibly binds to SHBG and diffuse into liver to exert its functions by binding to estrogen receptors (ERs). Estrogen reduce TG accumulation in the liver via ERα. Estrogens play a key role in protecting against hepatic steatosis, by promoting lipolysis and improving FA oxidation in mitochondria via the induction of ACC (19). Therefore, an imbalance in estrogens may have a marked effect on hepatic lipid metabolism. Menopause, a physiological condition of estrogen deficiency, promotes the risk of development and progression of NAFLD (60% and 32% prevalence rates in menopausal and premenopausal women, respectively) (20). The incidence of NAFLD after menopause increases significantly (to that observed in men) due to the protective effect of estrogens, although gender-differences in the prevalence of NAFLD also depend on age (8). Menopause-related fat redistribution also increases the risk of insulin resistance (IR) and subsequently the risk of NAFLD (21). Accordingly, premature menopausal women are also at risk of severe liver fibrosis (22).

On the contrary, androgens showed different opposite effects by sex differences. The major circulating androgens are dehydroepiandrosterone (DHT), androstenedione, testosterone, and dihydrotestosterone, but only testosterone and DHT can bind to androgen receptors (18, 23). Testosterone plays an important role in lipid, and protein metabolism, and has a major influence on body composition including adipose fat and skeletal muscle in men (18, 24). Androgens are achieved by activation of androgen receptor (AR), followed by binding to androgen response element (ARE) or interacting with cytoplasmic signal transduction pathways, including PKA and MAPK/ERK (18). Overexpression of genes involved in lipid accumulation and down expression of FA oxidation is modulated by 5α reductase inhibition because it does not covert testosterone to DHT. Normal androgen levels
HA itself is the independent risk factor to affect NAFLD, although IR is associated with high androgen levels (34). HA directly affects LDL receptors in the liver, causing an increase in LDL, that renders women with PCOS more likely to develop dyslipidemia and NAFLD (44). Furthermore, androgens may affect the production of adipokines, including leptin, and adiponectin, which could be concerned with the metabolic characteristics of PCOS and the development of NAFLD (45). In PCOS mice model, DHT increased binding of AR to ARE in elevating the SCAP-SREBP1 interaction, resulting in increased hepatic DNL (46, 47). Chronic androgen excess induces IR and hepatic fat accumulation through mitochondrial dysfunction and causing apoptosis, and autophagy imbalance (48). Androgens can induce mitochondria β-oxidation imbalance and DNL and can exacerbate liver inflammatory injury by the overexpression of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), MCP-1, and IL-1β (49). Therefore, HA may be a key contributor to NAFLD development in women with PCOS. The causality of the relationship between NAFLD and PCOS requires further research.

Lifestyle interventions are the most effective treatments for women with PCOS due to improvements in insulin sensitivity. Although metformin has been widely used in women with PCOS, it showed limited efficacy for resolving NASH (50, 51). A randomized clinical trial showed that liraglutide, a glucagon like peptide-1 receptor agonist, achieved body weight loss, of 5.6%, a 66% reduction in NAFLD prevalence, and an 18% reduction in visceral adipose tissue (VAT) when administered to women with PCOS (52). However, the evidence is insufficient to recommend liraglutide as a treatment regimen in women with PCOS. Further research should aim to determine whether novel therapeutics can improve insulin sensitivity and reduce the risk of NAFLD in women with PCOS.

**Hypogonadism in men and NAFLD**

Male hypogonadism is a clinical syndrome characterized by deficient or absent gonadal function that results in insufficient testosterone secretion (53). Obesity is one of the most important risk factors for secondary hypogonadism in men (54). Male obesity secondary hypogonadism (MOSH) impairs fertility, sexual function, bone mineralization, and fat metabolism, also leads to lower muscle mass and altered body composition (54). Although the prevalence of MOSH remains unclear, rates as high as 45.0–57.5% have been reported (54–56). 26% of men with NAFLD have low free testosterone in a study of 159 men randomly selected from the NASH clinical research network cohort (57). Men with low free testosterone were more likely to have NASH and advanced fibrosis than simple steatosis (88% vs. 67%, 27% vs. 14%, respectively) (57).

The mechanism that increases the risk of NAFLD in subjects with hypogonadism has been poorly described. Testosterone plays...
an important role in insulin sensitivity, body composition and lipid metabolism (58). There is a bidirectional relationship exists between low testosterone and IR (59). In preclinical study, low testosterone levels may cause hepatic fat accumulation through increased DNL via upregulation of hepatic SREBP-1 (60, 61). The upregulation of SREBP-2 and ACC-1 is apparently due to reduced AMP-activated protein kinase (AMPK) activity (60). Testosterone may promote the expression of hepatic scavenger receptor class B member 1, which is involved in selective uptake of cholesterol esters from circulating high-density lipoprotein (HDL) and facilitates reverse cholesterol transport. Furthermore, testosterone decreases MTTP expression, thus reducing apolipoprotein B-mediated VLDL secretion and cholesterol 7α-hydroxylase levels, which in turn leads to hepatic steatosis due to increased cholesterol uptake and decreased removal (62, 63). Testosterone also significantly increases the mRNA expression of insulin receptors, resulting in increased insulin binding, and elevated glucose oxidation (64). Serine phosphorylation of insulin receptor substrate 1, which attenuates insulin signaling by inhibiting tyrosine phosphorylation, was improved by testosterone treatment (65, 66). Testosterone deprivation leads to reduced glucose transporter type 4 expression in liver tissue and results in hyperglycemia, low insulin level, and diminished glucose uptake in adipose and skeletal muscle tissue (67).

Low testosterone and SHBG in men are independent predictors of metabolic syndrome (68). Low testosterone is related to the visceral fat distribution and exhibits sexual dimorphism due to the dependency on testosterone and E2 of men and women, respectively. Testosterone levels are inversely proportional to the amount of visceral fat. Testosterone and E2 regulate the expansion of visceral fat by activating ERs (ERα and ERβ) and ARs. ER is activated by E2 derived from testosterone aromatization; thus, testosterone deficiency, which leads to low estradiol levels, is a major cause of visceral fat deposition and IR in men (69–71). Efficient AR activation also lowers body fat and increases insulin activity (69, 72). Thus, testosterone exerts its anti-obesity effect (which inhibits the expansion of visceral fat deposition, as well as insulin and leptin resistance, leading to lipogenesis in liver and adipose tissue) by activating the AR pathway (73–75). In addition, SHBG is associated with the low testosterone levels in men with adult-onset hypogonadism (76). SHBG regulates testicular negative feedback either directly or by modulating the entry of testosterone or estradiol into cells in the hypothalamus and/or pituitary to control gonadotropin synthesis and secretion (76). Low total testosterone and SHBG were strongly associated with increased likelihood of having metabolic syndrome, independent of IR (77). Therefore, Hypogonadism is a risk factor for the development of NAFLD.

Testosterone replacement therapy in hypogonadal men with metabolic syndrome had favorable effects on hepatic steatosis, insulin sensitivity, and glucose control (78, 79). However, evidence is lacking to support the use of testosterone therapy in hypogonadal patients with NAFLD. Furthermore, the biochemical mechanisms of underlying the potential therapeutic benefits of testosterone in NAFLD remain to be elucidated, and further study is needed to understand the liver-specific role of testosterone. Studies with large cohorts are necessary to determine whether men with low androgens levels on long-term testosterone therapy are protected against prostate cancer and have a reduced risk of cardiovascular disease over time.

**Sex hormone binding globulin status in the course of NAFLD**

SHBG is a glycoprotein produced by the liver (80). The primary function of SHBG is to bind and transport circulating testosterone and estradiol to regulate their bioavailability and sequester circulating androgens and estrogens (43, 81). SHBG shows high affinity for testosterone and low affinity for estradiol (81). The free testosterone in plasma is strongly influenced by the SHBG concentration because only 1-2% of testosterone in plasma is free and active; 65% is bound to SHBG and the rest to albumin. Therefore, women with low SHBG levels can have normal total testosterone levels but increased bioavailability thereof, which leads to the progression of PCOS. In addition, IR subsequently results in reproductive dysfunction by diminishing SHGB synthesis. PCOS patients with NAFLD usually have lower SHBG levels and a higher free androgen index compared with those without NAFLD, although differences in circulating androgens are not apparent (26, 34, 82, 83). Furthermore, experimental studies indicated that sex hormones bound to SHBG may directly mediate cell surface signaling, cellular delivery, and the biologic action of sex hormones (84–88). Future research on the association between the biological activity of SHBG binding fractions and risk of NAFLD is warranted.

SHBG also acts as a signal transduction factor. An experimental study showed that thyroid and estrogenic hormones increase SHBG synthesis by upregulating the expression of hepatocyte nuclear factor-4α (HNF-4α), which performs as a key factor in regulating SHBG promoter activity in the liver (89, 90). Conversely, (PPAR-γ competes with HNF-4α for a binding site on the SHGB promoter, such that PPAR-γ inhibits SHBG expression (91). SHBG levels are inversely correlated with hepatic TG and ACC activity (92). SHBG may downregulate the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, which is involved in the development of local and systemic IR (93). Increased hepatic lipogenesis or IR downregulates HNF-4α expression thereby diminishing hepatic SHBG synthesis and production. In addition, inflammatory status affects the expression of SHBG. During chronic inflammation diseases, patients show increased expression of inflammatory cytokines such as IL-1 and TNF-α that affect the production of SHBG. The action of IL-1 is mediated by the NF-kB factor which downregulate HNF-4 α transcription leading to the suppression of SHGB synthesis (94).
Low testosterone is associated with a suboptimal distribution of body fat and adipocyte IR, which impairs suppression of lipolysis, and leads to ectopic fat deposition and "lipotoxicity" [95]. Adipose inflammatory cytokines, such as TNF-α, IL-6, and C-reactive protein, can impair hepatic insulin signaling and promote hepatic fat accumulation, leading to inhibition of HNF-4α mRNA via the activation of NF-κB or activating the Methyl ethyl ketone-1/2 (MET-1/2) and c-Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) pathways [96, 97]. In contrast, adiponectin increases SHBG production by activating AMPK, which increases FA oxidation and HNF-4α levels [98]. Therefore, low circulating SHBG is associated with a high risk of NAFLD in men with hypogonadism.

SHBG may serve as a biomarker of NAFLD. Low testosterone and SHBG concentrations are related with metabolic syndrome and fatty liver. In a recent meta-analysis, low total testosterone was positively associated with NAFLD in men but inversely in women, on the other hand, low SHBG concentration was reportedly associated with a high risk of development of NAFLD in both men and women [99]. Furthermore, SHBG has anti-inflammatory and lipolytic effects on adipocytes and macrophages, which could explain its association with lower incidence rates of metabolic syndrome and its complications [100]. In a biopsy proven NAFLD study, lower SHBG levels were inversely related to the severity of steatosis [101]. Therefore, improving SHBG expression can be a potential therapeutic target for NAFLD.

**Conclusion**

An intricate relationship exists between androgens and NAFLD that may independently affect hepatic homeostasis. Gender differences in the effects of androgen have been observed, with low testosterone levels affecting liver function in men but not in young women, in whom HA presents a risk factor for NAFLD. An apparent bidirectional connection exists between sexual dimorphism of androgens and NAFLD. In addition, SHBGs participate in hormone regulation, acting as a buffer in the context of androgen homeostasis (Figure 1). Therefore, understanding the molecular mechanism of androgens in the liver would aid the development of mechanism-based therapeutic interventions for NAFLD.

**Author contributions**

MJS contributed to the selection and analysis of preview literature, and wrote the original draft for this mini review. JYC supervised the manuscript and contributed to the review and editing for this mini review. All authors contributed to the article and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
39. Dauud A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* (1997) 18:774-800. doi: 10.1210/edrv.18.6.0318
40. Yki-Jarvinen H, Makimattila S, Utriainen T, Rutanen EM. Portal insulin concentrations rather than insulin sensitivity regulate serum sex hormone-binding globulin and insulin like growth factor binding protein 1. *J Clin Endocrinol Metab* (1999) 84:3227-32. doi: 10.1210/jcem.84.11.759340
41. Chang RJ. The reproductive phenotype in polycystic ovary syndrome. *Nat Clin Pract Endocrinol Metab* (2007) 3:688-95. doi: 10.1038/ncpem20637
42. Dapass M, Lin FTJ, nadkarni GN, Sisk R, legro RS, URBANEK M, et al. Distinct subtypes of polycystic ovary syndrome with novel genetic associations: An unsupervised, phenotypic clustering analysis. *PloS Med* (2020) 17:e1003132. doi: 10.1371/journal.pmed.1003132
43. Quo X, Donnelly R. Sex hormone-binding globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome. *Int J Mol Sci* (2020) 21:1-17. doi: 10.3390/ijms2101359
44. Baranova A, Tran TP, Afendy A, Wang L, shamssaddin A, Mehta R, et al. Molecular signature of adipose tissue in women with both non-alcoholic fatty liver disease (NAFLD) and polycystic ovarian syndrome (PCOS). *J Transl Med* (2015) 13:113. doi: 10.1186/1479-5876-11-1133
45. Xu A, Chan KW, Hao RL, Wang Y, Tan KC, Zhang J, et al. Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. *J Biol Chem* (2005) 280:18073-80. doi: 10.1074/jbc.M412312200
46. Wang D, He B. Current perspectives on nonalcoholic fatty liver disease in women with polycystic ovary syndrome. *Diabetes Metab Syndr Obes* (2022) 15:1281-91. doi: 10.2147/dmos.S362424
47. Seidu T, McWhorter P, Myer J, Alamgir R, Eregha N, Bogle D, et al. Differential effects of testosterone via transcriptional regulation of SCDAP in normal weight female mice. *J Endocrinol* (2021) 250:49-65. doi: 10.1530/je.120.11040
48. Cui P, Hu W, Ma T, Hu M, Tong Z, Zhang P, et al. Long-term androgen excess induces insulin resistance and non-alcoholic fatty liver disease in PCOS-like rats. *J Steroid Biochem Mol Biol* (2021) 208:105829. doi: 10.1016/j.jsbmb.2021.105829
49. Zhang Y, Meng F, Sun X, Sun X, Hu M, Cui P, et al. Hyperandrogenism and insulin resistance contribute to hepatic steatosis and inflammation in female rat liver. *Oncotarget* (2018) 9:18108-97. doi: 10.18632/oncotarget.24477
50. Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosen MC, et al. Prevalence of male secondary hypogonadism in men referred for infertility evaluation. *Clin Gastroenterol Hepatol* (2019) 15:83. doi:10.1016/j.cgh.2019.11.053
51. Aguirre V, werner ED, Giraud J, Lee YH, Shoelson SE, White MF. Phosphorylation of Ser97 in insulin receptor substrate-1 blocks interactions with the insulin receptor and inhibits insulin action. *J Biol Chem* (2002) 277:1531-7. doi:10.1074/jbc.M105121200
52. Muthusamy T, Murugesan P, Srinivasan C, Balasubramanian K. Sex steroids influence glucose oxidation through modulation of insulin receptor expression and IRS-1 serine phosphorylation in target tissues of adult male rat. *Mol Cell Biochem* (2011) 352:35-45. doi: 10.1007/s11010-011-0737-1
53. Muthusamy T, Murugesan P, Balasubramanian K. Sex steroids deficiency impairs glucose transporter 4 expression and its translocation through defective Akt phosphorylation in target tissues of adult male rat. *Metabolism* (2009) 58:1581-92. doi: 10.1016/j.metabol.2009.05.010
54. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. *MINER* (2019) 22:1571-25. doi: 10.2337/db10-1510415
55. Bianchi VE, Locatelli V. Testosterone a key factor in gender related metabolic syndrome. *BMJ* (2018) 19:400. doi:10.1136/bmj.j9689
56. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab* (2006) 91:4335-43. doi: 10.1210/jc.2006-0410
57. Zitzmann M, Gromoll J, von Eckardstein A, Nieschlag E. The CAG repeat polymorphism in the androgen receptor gene modulates body fat mass and serum concentrations of leptin and insulin in men. *Diabetologia* (2003) 46:319-32
58. Fan W, Yanase T, Nomura M, Okabe T, Goto K, Sato T, et al. Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipidic activity but show normal insulin sensitivity with high adiponectin secretion. *Diabetes* (2005) 54:1000-8. doi: 10.2337/diabetes.54.4.1000
59. Lin HY, Xu Q, Ye S, Wang RS, Sparks JD, Chang C. Insulin and leptin resistance with hyperleptinemia in mice lacking androgen receptor. *Diabetes* (2005) 54:1717-25. doi: 10.2337/diabetes.54.16.1717
60. Singh R, Artaa JN, Taylor WE, Gonzalez-Cadavid NF, Iliassn S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in CHC12712 pluripotent cells through an androgen receptor-mediated pathway. *Endocrinology* (2003) 144:5081-8. doi: 10.1210/en.2003-0741
61. Winters SJ. SHBG and total testosterone levels in men with adult onset hypogonadism: what are we overlooking? *Clin Diabetes Endocrinol* (2020) 6:17. doi: 10.1007/s40312-020-00116-3
62. Li C, Fodi ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. *Diabetes Care* (2010) 33:1618-24. doi: 10.2337/dc09-1788
63. Traish AM, Haider A, Deros G, Saad F. Long term testosterone therapy in hypogonadal men ameliorates elements of the metabolic syndrome: an observational, long-term registry study. *Int J Clin Pract* (2014) 68:314-29. doi: 10.1111/ijcp.12319
64. Traish AM. Testosterone and weight loss: the evidence. *Curr Opto Endocrinol Diabetes Obes* (2014) 21:213-22. doi: 10.1097/med.0000000000000086
65. Lee IR, Dawson SA, Wetherall JD, Hahnel R. Sex hormone-binding globulin secretion by human hepatocarcinoma cells is increased by both estrogens and androgens. *J Clin Endocrinol Metab* (1987) 64:825-31. doi: 10.1210/jcem.64-4.825
66. Dunn JF, Nisula BC, Rodbard D. Transfer of steroid hormones: binding of 21-dehydrogenases to both testosterone-binding globulin and corticosterone-binding globulin in human plasma. *J Clin Endocrinol Metab* (1981) 53:58-68. doi: 10.1210/jcem-53-1-58
67. Nisula BC, Durand J, Rabinovitch N, DiGirolamo D, Zitzmann M, Hall F. New evidence for the presence of SHBG in human serum. *J Clin Endocrinol Metab* (1991) 72:83-9. doi: 10.1210/jcem-72-1-83
68. Zaitas M, wellons M, cedars MI, Van Wagner L, Gunderson EP, Ajmera V, et al. Testosterone levels in pre-menopausal women are associated with...
nonalcoholic fatty liver disease in midlife. Am J Gastroenterol (2017) 112:755–62. doi: 10.1038/ajg.2017.44

84. Ding EL, Song Y, Manson JE, Hunter DJ, Lee CC, Rifai N, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. N Engl J Med (2009) 361:1152–63. doi: 10.1056/NEJMou0804381

85. Rosner W, Hryb DJ, Khan MS, Nakhla AM, Romas NA. Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. J Steroid Biochem Mol Biol (1999) 69:481–5. doi:10.1016/s0960-0760(99)00070-9

86. Hammes A, Andreassen TK, Spoelgen R, Raila J, Hubner N, Schulz H, et al. Role of endocytosis in cellular uptake of sex steroids. Cell (2005) 122:751–62. doi: 10.1016/j.cell.2005.06.032

87. Fortunati N, Becchis M, Catalano MG, Comba A, Ferrera P, Raineri M, et al. Sex hormone-binding globulin, its membrane receptor, and breast cancer: a new approach to the modulation of estradiol action in neoplastic cells. J Steroid Biochem Mol Biol (1999) 69:473–9. doi:10.1016/s0960-0760(99)00068-0

88. Selva DM, Hammond GL. Thyroid hormones act indirectly to increase sex hormone-binding globulin production by liver via hepatocyte nuclear factor-4alpha. J Mol Endocrinol (2009) 43:19–27. doi: 10.1677/jme.0.090627

89. Jaruvongvanich V, Sanguankeo A, Riangwiwat T, Upala S. Testosterone, sex hormone-binding globulin and nonalcoholic fatty liver disease: a systematic review and meta-analysis. Ann Hepatol (2017) 16:10. doi: 10.5604/16652681.1235481

90. Tanaka H, Tsuchiya S, Hattori M, Tsuchiya Y, Nakatsu Y, et al. Protective effect of sex hormone-binding globulin against metabolic syndrome: In vitro evidence showing anti-inflammatory and lipolytic effects on adipocytes and macrophages. Mediators Inflamm. (2018) 2018:3062319. doi: 10.1155/2018/3062319

91. Mueller NT, Liu T, Mitchel EB, Yates KP, Suzuki A, Behling C, et al. Sex hormone relations to histologic severity of pediatric nonalcoholic fatty liver disease. J Clin Endocrinol Metab (2020) 105:5496–504. doi: 10.1210/clinem/dgaa574