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RESEARCH ARTICLE

Sex Hormone-Binding Globulin as more than a Biomarker of Metabolic Diseases and Reproductive Disorders: What Physicians Should Know?

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Abstract

Until recent years, Sex Hormone-Binding Globulin (SHBG) has been considered of less a priority in the management of metabolic and chronic inflammatory states. However, emerging research highlights the remarkable role of SHBG in the screening and follow-up of patients not only with metabolic disorders but also in influencing reproductive outcomes. The present review aims to consolidate current knowledge on the involvement of SHBG in various clinical conditions. The search was performed using multiple databases to identify original studies measuring SHBG levels in conditions such as type-2 diabetes, metabolic syndrome (MetS), male obesity secondary hypogonadism, Polycystic Ovarian Syndrome (PCOS), male equivalent of PCOS, Nonalcoholic Fatty Liver Disease (NAFLD), infantile obesity, and early puberty. Among a total of 93,735 studies, 62 met the inclusion criteria, encompassing data from 127,771 subjects comprising both patients and controls. Studies were predominantly cross-sectional and observational cohorts, with MetS and NAFLD being the most extensively investigated conditions. Across all clinical conditions, significantly lower SHBG levels were consistently observed among patients compared to matched controls. The decrease in SHBG was found to be significantly associated with adverse reproductive, metabolic, and cardiovascular outcomes. These findings underscore the importance of considering SHBG as a valuable marker in routine clinical practice. Clinicians are encouraged to recognize the potential of SHBG as a useful marker in the assessment and management of various health conditions within their routine practice.

Abbreviations

BMI: Body Mass Index; CVD: Cardiovascular Disease; DHT: Dihydrotestosterone; E2: Estradiol; FSH: Follicle-Stimulating Hormone; FT: Free Testosterone; GDM: Gestational Diabetes; HDL-C: High-Density Lipoprotein Cholesterol; HNF-4α: Hepatic Nuclear Factor 4-Alpha;

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HOMA-IR: Homeostasis Model Assessment-Insulin Resistance; IL-1: Interleukin-1 Beta; LH: Luteinizing Hormone; IR: Insulin Resistance; MetS: Metabolic Syndrome; MOSH: Obesity-Associated Male Hypogonadism; NAFLD: Nonalcoholic Fatty Liver Disease; PCOS: Polycystic Ovarian Syndrome; SHBG : Sex Hormone-Binding Globulin; T: Testosterone; T2D: Type-2 Diabetes; TG: Triglycerides; TNFα: Tumor Necrosis Factor Alpha; TT: Total Testosterone.

Introduction

Sex Hormone-Binding Globulin (SHBG) serves as the primary carrier for sex steroids like Testosterone (T) and Estradiol (E2), playing crucial roles in their transport and serum level regulation. Beyond these transport functions, SHBG may also act as a hormone or signal transduction factor, implicating it in a range of physiological and pathological conditions [1,2]. The affinity of SHBG for different sex steroids decreases in the order of Dihydrotestosterone (DHT), T, androstenediol, E2, and estrone, with its binding affinity for DHT being 5x greater than for testosterone and 20 x greater than for estradiol [3]. Recent studies have identified low levels of SHBG as a common factor in various human developmental, metabolic, and fertility-related conditions. These include Nonalcoholic Fat Liver Disease (NAFLD) [4], obesity, Metabolic Syndrome (MetS) across all ages [5-7], polycystic ovary syndrome (PCOS) [8,9], Obesity-Associated Male Hypogonadism (MOSH) [10], Gestational Diabetes (GDM) [11], Type-2 Diabetes (T2D) [12,13], and cardiovascular disease [14]. Moreover, diminished SHBG levels have been linked with additional pathologies including several types of cancer [15].

These clinical findings are supported by in vitro and in vivo studies revealing SHBG's potential anti-inflammatory and lipid regulation roles. SHBG can inhibit inflammation and lipid accumulation in macrophages and adipocytes [16], protecting target tissue exposure from the disrupting potential of toxic compounds [17], inhibiting metabolic pathways associated with Insulin Resistance (IR) [17,18], and exerting a protective effect against MetS and related conditions [16,19].

The advancements in SHBG understanding highlight its crucial role beyond merely a biomarker, identifying it as a pivotal factor in onset and disease progression across age groups and a potential target for therapeutic interventions. Thus, the aim of this review is to synthesize the current knowledge regarding the clinical relevance of SHBG monitoring in daily healthcare practices, focusing on MetS, T2D, PCOS, MOSH, NAFLD, GDM, infantile obesity and puberty timing, conditions classically associated to high cardiovascular risk and infertility.

Methods

We conducted a comprehensive search across PubMed/MEDLINE, Cochrane Clinical Trials, Web of Science, Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS), and EMBASE databases. This search spanned from February to June 2021, with an update in May 2023. The search terms "sex hormone-binding globulin" OR "SHBG" were combined with “type-2 diabetes", “metabolic syndrome", "polycystic ovary syndrome”, “male obesity-secondary hypogonadism”, “infertility”, and “gestational diabetes” using Boolean operators to identify potentially eligible articles. The initial selection of articles was based on the relevance of their titles and abstracts to our research criteria. Furthermore, we conducted a manual search through the reference lists of included studies to uncover additional relevant papers. Only in vivo original studies assessing SHBG, published in English, were considered. Experimental studies may be cited but their discussion is outside the scope of this review.

Results

Study selection and main findings

A total of 93,735 articles were identified through the databases. After duplicate exclusion, 62 studies were selected by the reading of titles and abstracts and then were full text read (Figure 1). Studies were predominantly cross-sectional and observational cohorts, with MetS and NAFLD being the most extensively investigated conditions. Collectively, the selected studies encompassed a total of 127,771 subjects comprising both patients and controls. The distribution of the selected studies is detailed in figure 2, where they are categorized by disease, gender, age, and study design.

Virtually all analyzed studies demonstrated a unanimous decrease in SHBG levels in patients with the listed conditions compared to matched controls, highlighting a significant association between SHBG levels and the conditions under review. This paper reviews relevant information indicating that SHBG is a key player involved in several metabolic disturbances, leading to adverse effects on the reproductive system and an increased risk of cardiovascular disease.

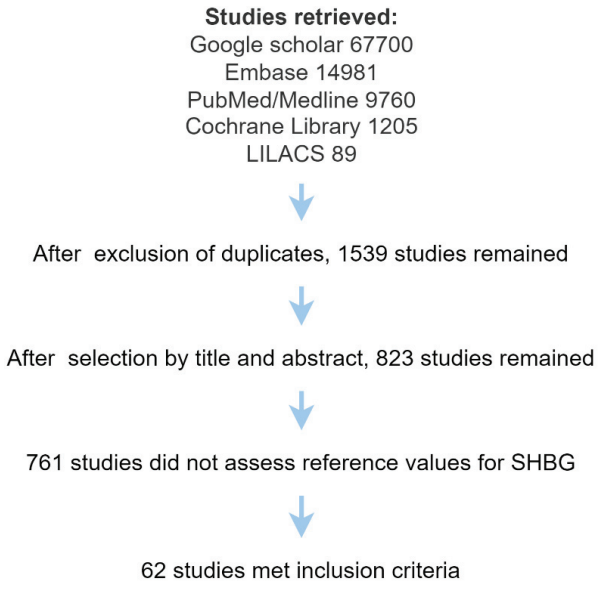

Figure 1 Databases results and process of studies selection.

SHBG: dynamics and influencing factors

SHBG is found in equal levels in fetal circulation and cord blood across genders, low at birth but increases within the first months. Its levels usually remain high until puberty, when they decrease in both sexes, more pronounced in males [20]. In adults, women have higher SHBG levels than men, with levels increasing up to 10 x until 24 weeks of gestation and then stabilizing [21]. Normally, SHBG levels in men start to rise from 40 to 50 years onwards, while in women, they decrease at the end of reproductive life (45 to 65 years old), followed by a gradual increase [22].

SHBG production primarily occurs in the liver, regulated by Hepatic Nuclear Factor 4-Alpha (HNF-4α), and influenced by hormonal, metabolic, and nutritional factors (Figure 3) [23]. Adiponectin, thyroid, and estrogenic hormones increase SHBG production. Conversely, growth hormone, corticosteroids, insulin, and non-aromatizable androgens decrease its production [24]. Dietary elements like excessive monosaccharides that induce inflammatory cytokines and Insulin Resistance (IR) also reduce SHBG levels [24,25]. SHBG levels are inversely correlated with Body Mass Index (BMI) [26], with liver fat influencing these levels more than total body or visceral fat [27]. In addition, individual variation in SHBG levels is noticeable and can be attributed to hereditary factors [28].

SHBG thresholds

Accurately defining "normal" SHBG seems to be challenging. A study published in 2021 with 1477 North American subjects suggested low SHBG thresholds as follows: men < 50 years at < 12.3 nmol/L, men ≥ 50 years at < 23.5 nmol/L, women < 30 years at< 14.5 nmol/L, and women ≥ 30 years at <21.9 nmol/L [29]. These were proposed as 'criteria definition'; however, our review found such thresholds common in patients with chronic metabolic disorders.

Likewise, a study with a healthy Italian population suggested SHBG should be above 41.2 nmol/L for men and 62.6 nmol/L for women, with slight flexibility for men aged 20 to 40 [30]. Reference ranges for SHBG levels should also account for childhood [31], pregnancy [32], and aging [33].

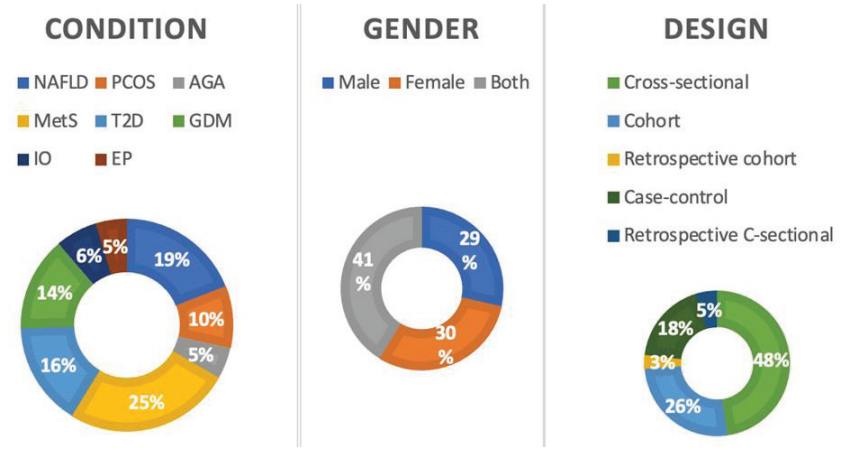

Figure 2 Distributions of the studies included according to clinical condition, sex and study design. AGA: Androgenetic Alopecia; EP: Early Puberty; GDM: Gestational Diabetes; IO: Infantile Obesity; MetS: Metabolic Syndrome; NAFLD: Nonalcoholic Fat Liver Disease; PCOS: Polycystic Ovary Syndrome and T2D: Type-2 Diabetes.

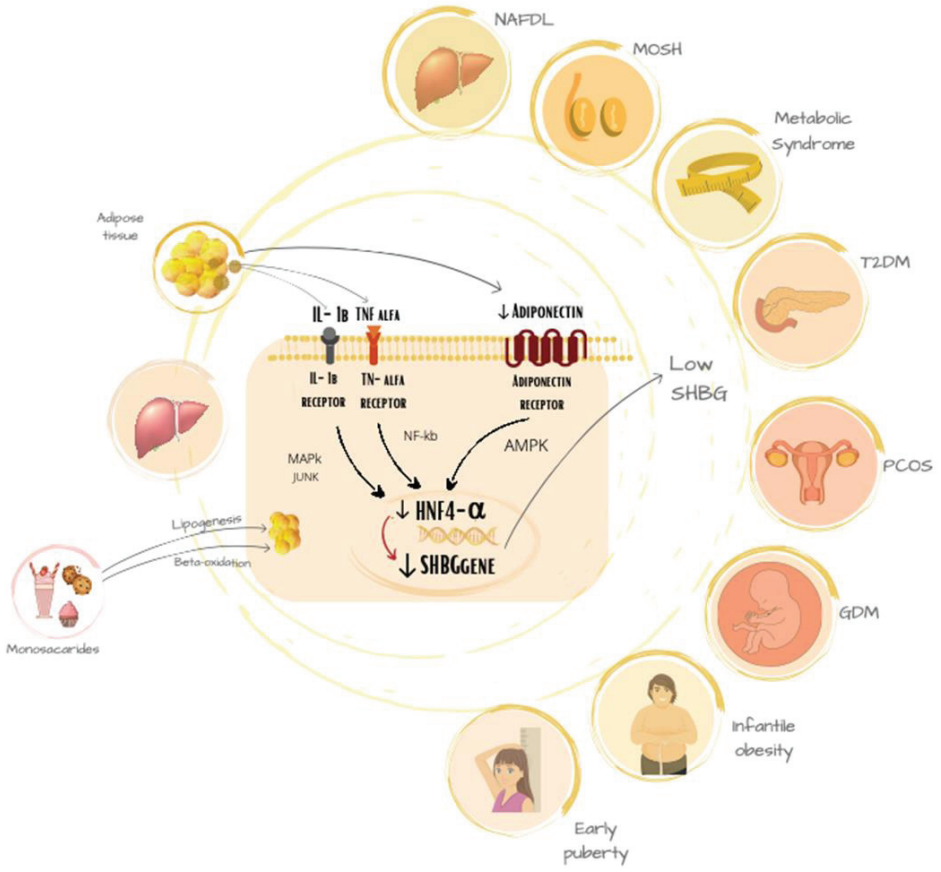

Figure 3 Physiology of SHBG production and pathological mechanisms.

Nonalcoholic fat liver disease

In males, normal androgen levels prevent the development of hepatic steatosis by decreasing lipogenesis and enhancing fatty acid oxidation and lipidic mobilization, whereas testosterone deficiency induces hepatic steatosis [34]. In females, E2 acts protectively against hepatic steatosis, inflammation, and gluconeogenesis [35]. Moreover, there is an obvious association between SHBG and the free androgen index, which is calculated from the ratio of Total Testosterone (TT) to SHBG. Female hyperandrogenism is a key contributor to the development of NAFLD, promoting hepatic steatosis, inflammation, and gluconeogenesis [4].

Additionally, low levels of SHBG are indicative of IR [36] and have been proposed as an early biomarker for the onset of NAFLD [4,37]. Studies suggest that increasing levels of TT and SHBG are associated with reduced risk of hepatic steatosis. NAFLD not only contributes to but also is influenced by other metabolic comorbidities such as Type 2 Diabetes (T2D) and obesity, which may suppress the gonadotropic axis, leading to altered levels of sex steroids. Thus, in men, reduced sex steroid levels might be more a consequence of hepatic steatosis rather than its cause [38,39].

Male obesity secondary hypogonadism

Obesity is linked to an elevated risk of developing MOSH, which in turn is associated with an increased risk of MetS, T2D, and mortality from Cardiovascular Diseases (CVD). Obesity contributes to the reduction of SHBG levels through multiple mechanisms. A decrease in SHBG is correlated with higher levels of leptin and lower levels of adiponectin, as well as with MetS, independently of T levels [40]. Considerable evidence exists to support the notion that insulin plays a regulatory role in the expression of HNF4-α and SHBG [41]. Research using HepG2 hepatoma cells has proposed mechanisms through which inflammation impacts SHBG production. Specifically, it has been suggested that Tumor Necrosis Factor-Alpha (TNF-α) suppresses SHBG production by diminishing the hepatic expression of HNF-4α, facilitated through nuclear factor-kappa B activation.

In a parallel mechanism, Interleukin-1 Beta (IL-1β) is believed to reduce HNF-4α levels via the MEK-1/2 and JNK MAPK pathways [42]. Additionally, these studies have demonstrated that persistently high plasma concentrations of TNF-α or IL-1β are factors involved in the downregulation of SHBG production [43].

SHBG modulates T production through a negative feedback mechanism, influencing T or E2 cellular entry in the hypothalamus and/or pituitary. Low SHBG increases unbound T and E2, suppressing Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) secretion and leading to their 'inappropriately low' levels in men with reduced testosterone and SHBG [44,45]. In MOSH, it is speculated that low SHBG may enhance T metabolism, exacerbating T deficiency. Given the importance of SHBG in controlling serum levels and the cellular T actions, it is suggested that measuring SHBG is helpful for understanding and managing acquired hypogonadism in men [45].

Metabolic syndrome

The correlation of low levels of SHBG and MetS spans various ages [6,46,47], genders [5,47], and includes subjects regardless of obesity status [7,48]. Over 90% of 12-16-year-old children and adolescents with abdominal obesity had low to medium SHBG terciles, which were even lower in those with MetS [6]. In children, low SHBG significantly predicts insulin resistance, low High-Density Lipoprotein Cholesterol (HDL-C), and MetS, emerging as the strongest MetS predictor [49,50]. Thus, SHBG levels may indicate future cardiovascular risk in either overweight or obese children [51]. SHBG levels are inversely correlated with age, BMI, atherogenic index, and Triglycerides [TG], and directly with HDL-C in children and adolescents [51]. Notably, children with one MetS-affected parent had 24% lower SHBG levels, increasing to 55% with two affected parents [52]. This study also found SHBG and waist circumference as predictors of weight gain over a year in children [52].

While low Testosterone (T) levels in men have been linked to a higher MetS risk in some studies [48,53], the causal relationship between T levels and disease remains unclear [54]. Conversely, low SHBG is more closely associated with incident MetS, independently of T and diabetes, after adjusting for age, adiposity, and comorbidities [55-59], and inversely related to severity and criteria number of MetS in men [60]. A study by Fenske, et al. [61] on a large female cohort found SHBG levels inversely associated with MetS and T2DM, suggesting low SHBG as a potential cardiometabolic risk marker, especially in postmenopausal women. Other studies link SHBG with metabolic profiles, particularly in assessing PCOS.

Polycystic ovary syndrome

A meta-analysis have shown that women with PCOS exhibit significantly lower SHBG levels, about 50% less than healthy counterparts, associating low SHBG with PCOS risk [62]. A study of 733 PCOS patients and 469 matched controls identified the lower normal limits of SHBG as 51.90 nM (25th percentile) [63]. Levels below 42 nmol/L in patients with PCOS correlated with fatty liver and prediabetes [64]. Low SHBG has been found to disrupt the PI3K/AKT pathway's regulation, contributing to Insulin Resistance (IR) and exacerbating hyperandrogenism and IR cycles [9,18].

Insulin significantly influences ovarian testosterone production, exacerbating PCOS's hyperandrogenism through increased androgen levels and reduced SHBG [65]. The inverse correlation between SHBG and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was demonstrated in a recent study evaluating newly diagnosed patients with PCOS, suggesting SHBG as a predictor for IR risk [66]. Furthermore, SHBG correlated with several metabolic parameters, including BMI, blood pressure, TG, HDL-C, glycemia, and HOMA-IR pointing to its potential as a metabolic syndrome predictor in PCOS patients [67].

Male equivalent of PCOS

Men with PCOS-like symptoms, referred to as male equivalent of PCOS, often have a family history of classic PCOS [68] and exhibit Insulin Resistance (IR) and early androgenetic alopecia before the age of 35 years [69]. Studies on male first-degree relatives of PCOS patients show elevated TG, IR, glucose, reduced SHBG levels, and more signs of hyperandrogenism. Siblings also display hormonal abnormalities, including lower dehydroepiandrosterone sulfate levels though basal T remains unchanged [70]. Notably, adult male relatives exhibit increased anti-Müllerian hormone, Luteinizing Hormone (LH), and follicle-stimulating hormone (FSH) levels.

Type-2 Diabetes

Multiple studies have suggested that both SHBG and estradiol independently contribute to the T2D risk in women [12,71,72], with high SHBG levels

linked to an 80% lower risk of diabetes [73,74]. Additionally, this inverse SHBG-T2D correlation is more pronounced in women [74,75]. Among men, individuals with high E2 and low SHBG had a 20x higher T2D risk [76]. A prospective analysis involving 1377 young adults over 6 years showed low SHBG predicted future IR and T2D risk [77]. Analysis of over 57,941 individuals highlighted T2D's increased risk with SHBG levels below 40 nmol/L for men and 50 nmol/L for women [12]. A study of 8876 women over 8 years found low SHBG and high free and total T levels significantly linked to T2D [72]. Those in the lowest SHBG quartile had a tenfold higher T2D risk compared to the highest quartile. Also, patients in the lowest SHBG quartile (5.8-24.7 nmol/L) had an approximately 10x higher T2D risk compared to the highest quartile (44.4-122.0 nmol/L) [75]. Taken together, these findings underscore low SHBG as a strong predictor of T2D risk, emphasizing its role in IR and T2D pathophysiology.

Gestational diabetes

Recent evidences suggests that SHBG is a highly promising marker for early GDM diagnosis [78,79] and for identifying high-risk pregnancies [11]. Low SHBG levels, both before and during pregnancy, are associated with increased GDM risk, even in low-risk [80] and normal weight-women with no previous history of GDM [11,78,79]. Zhang, et al. [79] showed that women with SHBG levels below 64.5 nmol/L had a 2.6 x increased GDM risk, which rose to 5.3x in the presence of obesity. Very interestingly, low SHBG levels years before pregnancy are also associated with a higher risk of GDM [79]. The association between lower SHBG levels and the risk of GDM was also reported in women with PCOS [81]. In the second trimester of pregnancy, studies suggest a SHBG threshold under 50 nmol/L predicts GDM with high sensitivity and specificity [82]. Meta-analyses show significantly lower SHBG levels in GDM, with every 50 nmol/L increase in SHBG reducing GDM risk by 15%, regardless of adiposity. Of note, SHBG levels are also lower in neonates from GDM pregnancies [83].

Children with obesity and puberty timing

Pinkney, et al. [84] conducted a longitudinal study on 347 children aged 5 to 15 years old, showing that SHBG levels peak at age 5, and then decrease over time. Initially, boys had higher SHBG levels than girls, but by age 15, this reversed. SHBG negatively correlated with adiposity, insulin, insulin-like growth factor 1, C-reactive protein, and leptin, and positively with adiponectin. Lower SHBG levels at age 5 in girls were linked to earlier puberty markers, while in boys, reduced SHBG was associated with early puberty signs but not with LH secretion or peak height velocity onset [84]. The authors postulated that adiposity-related endocrine mechanisms and chronic inflammation contribute to early SHBG decline and puberty onset [84], reflecting the trend towards earlier puberty in recent decades. Sorensen, et al. [85] found girls with precocious puberty had lower SHBG levels, which did not normalize during gonadal suppression with gonadotropin-releasing hormone analog treatment, indicating persistent hormonal/metabolic changes. Additionally, children with premature adrenarche also exhibited lower SHBG levels when compared with healthy controls [86].

Childhood obesity is an important contributor to the early onset of puberty, and this association is notably stronger in girls than in boys [87]. However, the underlying mechanism of this association remains elusive. Hur, et al. [88] reported a 120% increase in risk of advanced bone age per HOMA-IR unit increase, with a positive correlation between bone age, IR, and an inverse correlation with SHBG, suggesting obesity-induced hyperinsulinemia and IR reduce SHBG, accelerating puberty [89]. Comparing SHBG levels in children with and without obesity by age 6-9 years, lower SHBG was found in both sexes of these ones with obesity, inversely correlated to insulin levels [90]. In a large group of children with overweight and obesity, SHBG level was positively correlated with HDL-C and negatively correlated with TG and BMI [91]. Overall, prepubertal children with obesity had lower SHBG levels compared to normal-weight peers in all studies analyzed [31].

In conclusion, the evidence compellingly suggests that SHBG has a direct impact on metabolic and inflammatory diseases, indicating its significance beyond merely serving as an adjunct biomarker. Although there are some limitations and discrepancies in the literature concerning the recommended cut-off values for SHBG levels, improvements in SHBG levels could be considered as an indicator of therapeutic efficacy. The insights presented in this paper advocate for a re-assessment of the currently adopted threshold range and encourage clinicians to carefully consider this information with the aim of enhancing the prevention, diagnosis, and treatment of various metabolic diseases across all age groups.

Competing Interests

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Author contributions

ACR: Study conception, online search, manuscript writing.

SB: Online search, manuscript writing.

EBT: Manuscript writing and review.

EFC: Manuscript review.

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