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DIABETES AND CARDIOVASCULAR DISEASE (S MALIK, SECTION EDITOR)

Endogenous Sex Hormones, Metabolic Syndrome, and Diabetes in Men and Women

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Abstract Endogenous sex hormones predict impairments of glucose regulation. Cross-sectional studies suggest that lower levels of testosterone in men and higher levels in women increase risk of metabolic syndrome and diabetes, whereas lower levels of sex hormone binding globulin in both men and women increase risk of metabolic syndrome and diabetes. In a systematic review, we summarize existing longitudinal studies, which suggest similar patterns. However, these studies are often limited to a single sex steroid measure. Whether these associations are primarily a marker of adiposity, and whether these associations differ between younger eugonadal vs older hypogonadal adults is also uncertain. The impact of exogenous sex steroid therapy may not reflect relationships between sex hormones and impaired glucose regulation that occur without supplementation. Therefore, examination of endogenous sex steroid trajectories and obesity trajectories within individuals might aid our understanding of how sex steroids contribute to glucose regulation.

Keywords Estradiol · Testosterone · Androgens · Sex hormone binding globulin · Metabolic syndrome · Diabetes · Endogenous sex hormones · Men · Women

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Introduction

Diabetes is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or often, both [1]. Metabolic syndrome (MetS) refers to the common clustering of other metabolic characteristics with hyperglycemia, ie, abdominal obesity, dyslipidemia, and hypertension [2]. Since MetS increases risk for diabetes and cardiovascular disease (CVD) [3], and diabetes is a major risk factor for CVD [4], understanding determinants of MetS and diabetes is important for the prevention of CVD.

In this review, we summarize the evidence for endogenous sex steroid levels as risk factors for MetS and diabetes. Therefore, we begin by providing the definitions of these 2 conditions. Next, we describe briefly the methodologies used to assess circulating sex steroid levels and the distinction between endogenous steroid levels vs effects of exogenous sex steroid administration. We summarize the cross-sectional relationships among endogenous sex steroids, MetS, and diabetes and perform a literature review of prospective studies. We conclude with implications for future research.

Definitions of Diabetes and MetS

The diagnosis of diabetes requires the presence of elevated glucose with cutpoints as defined in Table 1. Prior to 1999, the World Health Organization (WHO) fasting plasma glucose (FPG) cutpoint for diabetes was 140 mg/dL, and studies conducted prior to this year commonly used this cutpoint instead of the current 126 mg/dL (Table 1) [5]. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are intermediate states of impaired glucose regulation that are defined by elevations in FPG or post-challenge glucose during a 75-gram 2 hour oral glucose tolerance test (Table 1); the presence of either of these conditions is now called

Table 1 Definitions of diabetes, impaired fasting glucose, impaired glucose tolerance, and metabolic syndrome

Impaired fasting glucose and impaired glucose tolerance ("Prediabetes")		Type 2 Diabetes	
American Diabetes Association [72]	Former World Health Organization [5]	American Diabetes Association [72]	Former World Health Organization [5]
Hemoglobin A1c 5.7-6.4 OR	Fasting plasma glucose <140 mg/dl AND	Hemoglobin A1c ≥6.5 %, OR	Fasting plasma glucose ≥140 mg/dL, OR
Fasting plasma glucose 100-125 mg/dl	2-hour plasma glucose 140-199 mg/dl	Fasting plasma glucose ≥126 mg/dL, OR	2-hr plasma glucose ≥200 mg/dL, OR
OR2-hr plasma glucose 140-199 mg/dl		2-hr plasma glucose ≥200 mg/dL, OR	Random plasma glucose ≥200 mg/dL, in the presence of symptoms of hyperglycemia
		Random plasma glucose ≥200 mg/dL, in the presence of symptoms of hyperglycemia	
Metabolic Syndrome			
Modified ATP III [2]	World Health Organization [6]	International Diabetes Federation [7]	Harmonized definition [73]
≥3 of the following:	Elevated glucose, and 2 other criteria:	Increased adiposity, and 2 other criteria:	≥3 of the following:
Elevated glucose	Elevated glucose	Elevated glucose	Elevated glucose
Fasting glucose ≥100 mg/dL, OR	Fasting glucose ≥110 mg/dL, OR	Fasting glucose ≥100 mg/dL, OR	Fasting glucose ≥100 mg/dL, OR
Hypoglycemic therapy	Hypoglycemic therapy, OR	Hypoglycemic therapy	Hypoglycemic therapy
	Elevated postprandial glucose		
Increased adiposity	Increased adiposity	Increased adiposity	Increased adiposity
>102 cm waist circumference in men	BMI ≥30 kg/m^2 OR	≥94 cm waist circumference in men	Elevated waist circumference,
>88 cm waist circumference in women	Waist hip ratio >0.9 in men	≥80 cm waist circumference in women	Using population-specific definitions
	Waist: hip ratio >0.85 in women	(these are cut points for Europeans)	
Decreased HDL	Decreased HDL	Decreased HDL	Decreased HDL
< 40 mg/dL in men	<35 mg/dL in men	<40 mg/dL in men	<40 mg/dL in men
< 50 mg/dL in women	<39 mg/dL in women	<50 mg/dL in women, OR drug therapy	<50 mg/dL in women, OR drug therapy
Triglycerides ≥150 mg/dL	Triglycerides ≥150 mg/dL	Triglycerides ≥150 mg/dL, OR drug therapy	Triglycerides ≥150 mg/dL
Elevated blood pressure	Elevated blood pressure	Elevated blood pressure	Elevated blood pressure
≥130 mm Hg, systolic, OR	≥140 mm Hg, systolic, OR	≥130 mm Hg, systolic, OR	≥130 mm Hg, systolic, OR
≥85 mm Hg, diastolic, OR	≥90 mm Hg, diastolic, OR	≥85 mm Hg, diastolic, OR	≥85 mm Hg, diastolic, OR
anti-hypertensive treatment	anti-hypertensive treatment	anti-hypertensive treatment	anti-hypertensive treatment
	Renal insufficiency: Urinary albumin excretion rate ≥20 ug/min OR albumin: creatinine ratio ≥30 mg/g		

"prediabetes" by the American Diabetes Association and other medical groups. More recently, hemoglobin A1c level has also been used to diagnose diabetes. However, studies examining the relationship between sex steroids and glucose levels have preceded the use of hemoglobin A1c. Therefore, the studies in this review rely on blood glucose values.

Several definitions of MetS exist (Table 1). These definitions differ in that the WHO [6] required elevated glucose levels, the International Diabetes Federation (IDF) [7] formerly required the presence of abdominal obesity, and the modified Adult Treatment Panel (ATP) III [2] requires only 3 components as listed in Table 1 but does not mandate that hyperglycemia or obesity be present. Therefore, hyperglycemia can be, but is not necessarily, present in individuals with MetS. These differences in definitions reflected varying philosophies about the underlying defect present in this clustering of risk factors. Comparison of the ATP III, IDF, and harmonized definitions have shown that these are equally predictive of incident CVD [8••].

IFG, IGT, and type 2 diabetes are categories of a group of heterogeneous disorders of glucose regulation, which often include some degree of insulin resistance or impaired insulin

action [1]. Subsequently, adults with MetS are often presumed to have some degree of insulin resistance, although insulin resistance is not an explicit criterion of MetS. Measurement of insulin sensitivity is optimally performed with the hyperinsulinemic euglycemic glucose clamp or with minimal model analysis of frequently sampled intravenous glucose tolerance [9], but there is no accepted measure of insulin sensitivity for clinical use. Furthermore, existing measures are difficult to conduct in epidemiologic studies due to complex logistics and costs if measurements in a large number of participants are required [9]. Surrogate measures utilize glucose and insulin levels obtained from an oral glucose tolerance test or fasting levels alone. The most common measures in epidemiologic studies due to ease of measurement include the inverse of fasting insulin and the homeostasis model of resistance (HOMA-IR), which relies on fasting plasma insulin and glucose measurements only [10]. This proxy measure has been used in several studies of endogenous sex hormones, as it does not require the performance of a 2-hour glucose measurement.

Sex Steroid Terminology

Sex steroids that have been most frequently examined in relation to hyperglycemia include the androgens dehydroepiandrosterone (DHEA) and testosterone (T) and the estrogen estradiol (E2). DHEA (and its sulfated form, DHEAS), is secreted primarily by the adrenal gland and is the most abundant sex steroid [11]. Metabolites of DHEA include androstenedione, which subsequently may be metabolized to T or estrone, which is an E2 precursor. T and E2 are directly produced primarily by gonadal organs. In both men and women, T is aromatized to E2, particularly in adipose tissue.

Interpretation of circulating levels of sex steroids is complex. Both T and E2 are transported in blood by proteins, primarily sex hormone binding globulin (SHBG), and albumin. Total T and E2 levels include both the amounts bound to proteins and unbound or true amounts. The "free" concentration of these steroids is the proportion not bound to any protein, whereas the "bioavailable" concentration is the free amount and the amount bound to albumin, due to the weak binding of albumin with T and E2. Bioavailable E2 is 50 % of total E2 and free E2 is about 3 % of total E2. Bioavailable T is about 30 % of total T and free T is about 3 % of total T.

Levels of DHEAS, T, and E2 decline with age [12], although T levels may actually increase slightly in relation to perimenopause among women [13–15]. Therefore, investigators have hypothesized that the ratio, rather than the absolute level, of androgen to estrogen, affects glucose regulation [16]. However, few studies report the association between T:E2 and glucose. In a related hypothesis, lower levels of SHBG imply a more androgenic environment (since SHBG binds more tightly to T than to E2). Therefore, it has been postulated that associations between SHBG and glycemia reflect this steroid balance rather than any intrinsic properties of SHBG [16].

Currently, there is no single measurement standard of sex steroids, although there is a consensus that such harmonization is needed [17•, 18]. Older adults have low levels of sex steroids and SHBG, but are at highest risk of hyperglycemia. The detection limit of the particular sex steroid assay used may also be a crucial factor, eg, T levels in older women are very low. Direct assays, that is, assays performed without an extraction step, are considered unreliable, and thus, measurement is generally done after extraction and chromatography [17•, 18]. Direct measurement of unbound or free T and E2 can be done using dialysis or ultrafiltration. These methods require relatively large sample volume and are expensive. Therefore, equations that estimate free or bioavailable T and E2 are often substituted for direct measurement [19, 20]. These equations incorporate total T and E2 measurements using mass spectrometry or radioimmunoassay, SHBG measurements, and albumin measurements or estimations. In this review, the majority of the studies examining relationships between sex steroids and MetS and diabetes use indirect assays of sex steroids and equations estimating free or bioavailable sex steroids.

Exogenous Estrogen Therapy

The reported relationships between sex steroid levels and carbohydrate metabolism differ by estrogen use. Randomized trials of estrogen therapy in postmenopausal women have reported favorable effects of oral estrogen upon FPG, which implied that the elevations in E2 and SHBG that result from oral estrogen favorably impacted insulin sensitivity and/or insulin secretion [21, 22]. Furthermore, the decreases in FPG persisted after adjustment for adiposity [21, 22]. Subsequently, it had been hypothesized that estrogen therapy could increase postprandial glucose through reductions in whole-body insulin sensitivity via serum E2 levels [23], even though at least 1 other study showed no association between exogenous estrogen and insulin sensitivity [24].

We examined whether E2 and SHBG levels among oral estrogen users and nonusers were associated with differences in fasting or post-challenge glucose among overweight postmenopausal women with glucose intolerance [25]. Women had been randomized to lifestyle interventions targeting weight loss in order to reduce diabetes risk, and both oral estrogen users and nonusers randomized to lifestyle changes had reductions in fasting and postchallenge glucose. Among women who used oral estrogen, the actual levels of SHBG and E2 were not related to lifestyle intervention-induced changes in fasting or post-challenge glucose. In contrast, among women who did not use any estrogen, increases in SHBG and decreases in E2 were associated with reductions in FPG, and

increases in SHBG were also associated with reductions in postchallenge glucose, before and after consideration of visceral adiposity (estimated by waist circumference) and insulin resistance (estimated by the inverse of fasting insulin levels) [26••]. Therefore, the favorable changes in glucose levels associated with estrogen therapy would seem not to be mediated by actual changes in E2 and SHBG levels. We have also reported that estrogen use, despite altering serum sex steroid levels, does not alter the impact of lifestyle intervention or metformin intervention upon blood pressure changes [27], whereas the impact lifestyle and metformin interventions upon lipid levels differs by oral estrogen use and is only partially mediated by E2 and T changes [28].

The different relationships between sex steroid/SHBG levels with components of MetS in estrogen users and nonusers suggest that the results from randomized trials of estrogen therapy cannot necessarily be extrapolated to persons not using estrogen [21, 22, 29–32]. Randomized studies of estrogen have tested oral formulations [21, 22, 33], and it is possible that levels of E2, SHBG, and MetS components would be different among transdermal estrogen users. However, there is a lack of studies of the impact of transdermal estrogen upon glucose, insulin, and other MetS components.

Exogenous Testosterone Therapy

With the caveat that randomized trials of exogenous sex steroid therapy may not necessarily reflect natural physiology, randomized studies of T therapy conflict [34]. Among veterans with low T who underwent coronary angiography, men who received T had increased risk of CVD events or mortality compared with men who did not [35]. In 1 study of hypogonadal elderly men [36], replacement with transdermal T did not improve insulin sensitivity, secretion, or clearance compared with placebo. However, combined with exercise, T supplementation did reduce fat mass, suggesting that T levels could potentially have a modifying role upon carbohydrate metabolism [37]. This contrast suggests that exogenous T may increase risk of CVD events through pathways other than insulin sensitivity. In contrast, among healthy young men, androgen deprivation using the antagonist acyline led to decreased insulin sensitivity, and replacement with T protected against such declines [38]. In men with glucose intolerance, T therapy led to improvements in glycemic control and insulin sensitivity compared with placebo [39]. Similarly, exogenous DHEAS administration may not reflect endogenous DHEA relationships with carbohydrate metabolism. However, randomized studies of exogenous DHEAS generally demonstrate minimal benefit in men or women regarding insulin sensitivity [40], although such replacement may benefit women who have low levels of DHEAS [41].

Cross-Sectional Relationships Between Androgens and Estrogens with MetS and Diabetes

Cross-sectional relationships between endogenous androgens, SHBG, and MetS were summarized in a 2011 meta-analysis [42]. Men who were highest tertile of total T had lower risk of incident MetS than men in the lowest tertile (RR 0.38, 95 % CI 0.28–0.50) [42]. In contrast, women who were in the highest tertile of total T had an increased risk of incident MetS compared with women in the lowest tertile (RR 1.68, 95 % CI 1.15, 2.45) [42]. Risk was weaker in the longitudinal studies in men (RR estimate highest vs lowest total T tertile 0.64, 95 % CI 0.53–0.79) compared with the overall estimate, which included cross-sectional studies. In both men (RR for the highest vs lowest SHBG tertile 0.29, 95 % CI 0.21, 0.41) and women (RR 0.30, 95 % CI 0.21, 0.42), higher levels of SHBG were associated with lower risk of MetS. Associations between free T and MetS varied between studies, perhaps contributing to the weaker relationship observed between free T and MetS compared with that between total T and MetS.

Similar cross-sectional relationships between androgens, SHBG, and diabetes were summarized in a 2006 meta-analysis [43]. In the cross-sectional studies, levels of T were lower in men with diabetes and higher in women with diabetes compared with controls, whereas levels of E2 were higher in men and women with diabetes compared with controls. In both men and women, higher levels of SHBG were associated with lower risk of diabetes, particularly in women. These patterns were weaker but generally persisted after adjustment for body mass index (BMI) as well as waist-hip ratio, although the majority of studies only adjusted for BMI and not proxies of visceral adiposity. A more recent meta-analysis in 2010 of the relationship between T and incident diabetes in men noted similar results, again with a preponderance of cross-sectional studies compared with only 5 longitudinal studies [44]. Men with diabetes had lower T levels than men without diabetes, but the difference was present primarily in obese men, suggesting that adiposity could modify the relationship between T and incident diabetes [44].

Longitudinal Studies of Sex Steroids, SHBG, MetS, and Diabetes

In June 2013, we performed a systematic PubMed review using the following key words, limited to the English language: sex hormones AND (longitudinal OR prospective) AND (diabetes OR metabolic syndrome OR insulin resistance), which yielded 653 articles. The publications retained for inclusion assessed endogenous serum levels of estrogens, androgens, and/or sex hormone binding globulin (SHBG) in relation to these conditions among men or women not using exogenous sex steroids (DHEA, T, or E2) (n=26). We focused

upon prospective relationships between sex steroids and SHBG upon incident diabetes and MetS after adjustment for measures of adiposity, when performed.

Results

The results of this review are presented in Table 2. When studies adjusted for measures of adiposity such as BMI or waist circumference, these estimates are reported. There were few longitudinal studies in women.

Diabetes; Men

Diabetes was identified primarily by self-report [45–48] with confirmation by additional testing or record review [45], or by FPG levels and medication use [49–52]; several studies used 2-hour glucose levels as well [53–57]. It is possible that this variety in definitions contributed to inconsistent associations.

One study in men examined DHEAS and found no association, although lower levels of DHEAS were associated with increased risk of diabetes [54]. Five studies found an association between lower total T and incident diabetes [47, 49, 55, 57, 58], whereas 3 studies reported no association [46, 48, 59]. Two studies found an association between lower bioavailable or free T and incident diabetes [49, 57], whereas 3 studies reported no association [46, 51, 59]. One study examined total E2 and found an association [48], whereas another examined total and bioavailable E2 in men and diabetes and found no association [55]. Five studies examining SHBG found an association between lower SHBG and incident diabetes [46, 49, 51, 57, 58]; 4 did not [48, 53, 56, 59], particularly after adjustment for waist measures. Tibblin et al [57] examined IGT as well as diabetes as an outcome and also reported that lower total T was associated with incident IGT.

Diabetes; Women

Few longitudinal studies in women exist. Three studies examined DHEAS and found no association [45, 50, 54]. One study found an association between higher total T and incident diabetes [45], whereas another reported no association [55]. Two studies found an association between higher bioavailable or free T and incident diabetes [45, 55], whereas another study reported no association [50]. One study found an association between higher total E2 and incident diabetes [45], whereas another reported no association [55]. Two studies found an association between higher bioavailable E2 and incident diabetes [45, 50], whereas 1 study reported no association [55]. Four studies examining SHBG found an association between lower SHBG and incident diabetes [45, 50, 52, 53], and 2 did not [56, 59], particularly after adjustment for waist measurements.

MetS; Men

With 1 exception [60], studies of incident MetS in men used the modified ATP III definition. Six studies found an association between lower total T and incident MetS [51, 59, 61–63], whereas 2 studies reported no association [60, 64]; however, one of the studies that noted no association did report that declines in total T were associated with incident MetS [60]. One study found an association between lower bioavailable or free T and incident MetS [59], whereas 4 studies reported no association [51, 60, 62, 64]. All studies examining SHBG found an association between lower SHBG and incident MetS [51, 59, 60, 62–64]. Two studies examined DHEAS and MetS and found no association [61, 63].

Two studies examined incident elevations in HOMA-IR as an outcome among men, and the results conflict. Oh et al [55] reported that men with lower total T are more resistant (as represented by HOMA-IR and also by fasting insulin), whereas Soriguer et al [59] found that total T was not associated with HOMA-IR. Although Oh et al found that bioavailable T and HOMA-IR were not associated, Soriguer et al reported a significant association. In addition, Oh et al [55] noted no association with total E2; Soriguer et al did not examine E2. Soriguer et al [59] examined SHBG, reporting that higher SHBG was associated with decreased HOMA-IR in men; Oh et al did not report upon SHBG.

MetS; Women

Only 3 prospective studies in women examined MetS as an outcome. Both used the modified ATP III definition. Janssen et al [65] and Soriguer et al [59] reported that total T was not associated with incident MetS. Janssen et al also noted that higher bioavailable T and increase in T were associated with incident MetS, whereas Soriguer reported no association with incident MetS. Both studies noted that lower SHBG was associated with incident MetS [59, 65], and Janssen et al noted that decrease in SHBG was also associated with incident MetS [65]. The study by Torrens et al [16] overlapped with that of Janssen et al [65] in study population, but Torrens et al also examined the ratio of T:E2 and found that higher levels of T:E2 at baseline as well as changes in the ratio predicted incident MetS [16].

Two studies examined incident HOMA-IR as an outcome in women. Oh et al [55] and Soriguer [59] reported that total T was not associated with incident HOMA-IR in women. Both Oh et al and Soriguer et al reported that higher bioavailable T was associated with higher insulin resistance. Soriguer et al also reported that higher SHBG was associated with decreased insulin resistance.

Table 2 Longitudinal studies examining endogenous sex steroid and SHBG levels with risk of diabetes and metabolic syndrome

Type 2 diabetes				
Reference	Study population-men	Study population-women	Outcome definition	Results
Ding et al, 2007 [45]		Nested case-control study of 359 incident diabetes cases and 359 controls in Women's Health Study (mean age 60 yr)	Self-reported incident diabetes; diabetes confirmed in cases but lack of diabetes not confirmed in controls	• Higher total E2 associated with diabetes in highest vs lowest quintile (RR 12.6, 95 % CI, 2.83, 56.3) • Higher free E2 associated with diabetes in highest vs lowest quintile (RR 13.1, 95 % CI, 4.18, 40.8) • Higher total T associated with diabetes in highest vs lowest quintile (RR 4.15, 95 % CI, 1.21–14.2) • Higher free T associated with diabetes in highest vs lowest quintile (RR 14.8, 95 % CI, 4.44, 49.2) • DHEAS not associated with diabetes, ratio of total T:E2 not associated with diabetes
Haffner et al, 1993 [53]	Nested case-control study of 20 incident diabetes cases and 36 controls in San Antonio Heart Study (mean age 48 yr)	Nested case-control study of 38 incident diabetes cases and 61 controls in San Antonio Heart Study (age range 37–53 yr)	Diabetes, by fasting or 2-hr post-challenge glucose levels or by medication use	• Lower SHBG associated with diabetes in women (OR 0.20, 95 % CI, 0.05, 0.75) • No association between SHBG and diabetes in men
Haffner et al, 1996 [49]	Nested case-control study of 176 incident diabetes cases, 176 "loose" controls (not matched for weight) and 176 "tight" controls (matched for weight) in the MRFIT trial		Diabetes, by fasting glucose levels or by medication use	• Lower quintile of total T associated with diabetes ($P<0.01$ in test for trend) • Lower quintile of free T associated with diabetes ($P=0.02$ in test for trend) • Lower quintile of SHBG associated with diabetes ($P<0.01$ in test for trend)
Kalyani et al, 2009 [50]		Cohort study of 1612 postmenopausal women (ages 45–84 y) in MESA	Diabetes, by fasting glucose levels or by medication use	• Lowest quartile of SHBG associated with incidence of diabetes, after adjustment for BMI and HOMA-IR ($P<0.01$ in test for trend) • Bioavailable T and DHEA did not correspond with diabetes risk, after adjustment for BMI and HOMA-IR. • Higher quartile of bioavailable E2 associated with incident diabetes, after adjustment for BMI and HOMA-IR ($P<0.05$ in test for trend).
Kameda et al, 2005 [54]	Cohort study of 711 Japanese men in the Fungata Study	Cohort study of 911 Japanese women in the Fungata Study	Diabetes, by fasting or post-challenge glucose levels	• Declines in DHEAS associated with diabetes in men (OR per log unit 1.4, 95 % CI, 1.01, 1.95) • Baseline DHEAS and declines in DHEAS not associated with diabetes among women.
Laaksonen et al, 2005 [51]	Cohort study of 702 Finnish men in the Kuopio Ischemic Heart Disease Risk Factor Study (mean age 51 yr)		Diabetes, by fasting glucose levels or self-reported treatment (medications or lifestyle)	• Lower total T associated with diabetes after adjustment for waist/hip ratio and log-transformed insulin (OR 1.97,95 % CI, 1.07, 2.70) • Free T not associated with diabetes • Lower SHBG (<28.3 nmol/l) associated with diabetes after adjustment for waist/hip ratio and log-transformed insulin (OR 2.74, 95 % CI, 1.42, 5.29)
Lakshman et al, 2010 [46]	Cohort study of 1128 men in the Massachusetts Male Aging Study (mean age 54 yr), who were predominantly white		Diabetes by self-report or use of diabetes medications	• Lower SHBG associated with diabetes after adjustment for BMI (hazard ratio 1.93, 95 % CI, 1.38, 2.70) • Total T and free T not associated with diabetes
Lindstedt et al, 1991 [52]		Cohort study of 1462 Swedish women (ages 38–60 yr)	Fasting glucose and self-report	• Lower SHBG associated with diabetes after adjustment for waist-hip ratio and fasting insulin (estimates not given)
Oh et al, 2002 [55]	Cohort study of 294 men in the Rancho Bernardo Study	Cohort study of 233 women in the Rancho Bernardo Study	Diabetes by fasting or post-challenge glucose	• Lowest quartile of total T associated with diabetes in men after adjustment for BMI (OR 2.7, 95 % CI, 1.1, 6.6)

Table 2 (continued)

				• Total T not associated with diabetes after adjustment for BMI in women • Highest quartile of bioavailable T associated with diabetes in women (OR 2.9, 95 % CI, 1.1, 8.4) • Total and bioavailable E2 not associated with diabetes in men or women
Okubo et al, 2000 [56]	Cohort study of 203 Japanese men (mean age 63 yr)	Cohort study of 280 Japanese women (mean age 65 yr)	Diabetes by fasting or post-challenge glucose	• SHBG not associated with diabetes in men or women after adjustment for BMI and WHR
Schipf et al, 2011 [47]	Cohort study of 1339 German men (mean age 50 yr)		Diabetes by self-report or medication use	• Lowest decile of total T associated with diabetes after adjustment for waist circumference (OR 3.0, 95 % CI, 1.6, 5.7)
Soriguer et al, 2012 [59]	Cohort study of 227 Spanish men (mean age 46 y at baseline)	Cohort study of 473 Spanish women (mean age 43 y at baseline)	Diabetes by fasting or 2-hr glucose levels	• Total T and bioavailable T not associated with diabetes after adjustment for BMI in men • Total T and bioavailable T not associated with diabetes after adjustment for BMI in women • SHBG not associated with diabetes in men after adjustment for waist circumference • SHBG not associated with diabetes in women after adjustment for waist circumference
Stellato et al, 2000 [58]	Cohort study of 1156 men in the Massachusetts Male Aging Study (mean age 54 yr)		Diabetes by self-report or medication use	• Lower free testosterone (per SD) associated with diabetes after adjustment for BMI (OR 1.58, 95 % CI, 1.08, 2.29) • Lower SHBG (per SD) associated with diabetes after adjustment for BMI (OR 1.89, 95 % CI, 1.14, 3.14)
Tibblin et al, 1996 [57]	Cohort of 659 Swedish men (mean age 67 yr)		Diabetes by fasting or 2-hr glucose	• Lower total T associated with diabetes • Free T not associated with diabetes • Lower SHBG associated with diabetes
Vikan et al, 2010 [48]	Cohort of 1454 Norwegian men (mean age 59 yr)		Diabetes by self-report, administrative data	• Total T and free T not associated with diabetes after adjustment for waist circumference • SHBG not associated with diabetes after adjustment for waist circumference • Lower quartiles of E2 associated with diabetes after adjustment for waist circumference
Metabolic syndrome				
Reference	Study population-men	Study population-women	Outcome definition	Results
Bhasin et al, 2011 [64]	Cohort study of 618 Framingham Health Study generation 2 men (mean age 59 yr)		modified ATP III	• Lower SHBG associated with MetS after adjustment for BMI and HOMA-IR (RR 1.53, 95 % CI, 1.15, 2.04) • Total T and free T not associated with MetS after adjustment for BMI and HOMA-IR
Haring et al, 2009 [61]	Cohort study of 1004 German men (age 20–79 yr)		modified ATP III	• Lower total T associated with MetS after adjustment for waist circumference (RR for lowest quartile vs highest quartile 2.06, 95 % CI, 1.29–3.29) • DHEAS not associated with MetS, before or after adjustment for waist circumference
Haring et al, 2012 [60]	Cohort study of 956 German men (age 20–79 yr)		harmonized	• Baseline total T and free T not associated with MetS after adjustment for BMI • Declines in T associated with MetS after adjustment for SHBG and BMI (RR 1.19, 95 % CI, 1.02, 1.40)

Table 2 (continued)

				• Lower SHBG associated with MetS after adjustment for BMI (RR 1.30, 95 % CI, 1.03, 1.65)
Janssen et al, 2008 [65]		Cohort study of 949 peri-menopausal women	modified ATP III, with ethnicity-specific cut points for Asians	• Higher baseline bioavailable T (OR 1.34, 95 % CI, 1.11, 1.62) and increase in T (OR 1.10, 95 % CI, 1.01, 1.20) associated with MetS after adjustment for BMI
				• Lower baseline SHBG (OR 0.87, 95 % CI, 0.81, 0.93) and decrease in SHBG (OR 0.87, 95 % CI, 0.81, 0.93) associated with MetS after adjustment for BMI (lower SHBG is referent).
				• E2 and total T not associated with MetS after adjustment for BMI.
Kupelian et al, 2006 [62]	Cohort study of 950 men in the Massachusetts Male Aging Study (mean age 53 yr)		modified ATP III, although components by self-report	• Lower total T associated with MetS after adjustment for BMI (RR per 1 SD 1.41, 95 % CI, 1.06, 1.87) among men with BMI<25 kg/m^2
				• Lower SHBG associated with MetS after adjustment for BMI (RR per 1 SD 1.65, 95 % CI, 1.12, 2.42) among men with BMI<25 kg/m^2
				• Free T not associated with MetS
Laaksonen et al, 2005 [51]	Cohort study of 702 Finnish men in the Kuopio Ischemic Heart Disease Risk Factor Study (mean age 51 yr)		modified ATP III	• Lower total T associated with MetS after adjustment for waist circumference and log-transformed insulin (OR 2.24, 95 % CI, 1.05, 4.74)
				• Lower free T not associated with MetS
				• Lower SHBG (<28.3 nmol/l) associated with MetS after adjustment for waist circumference and log-transformed insulin (OR 1.67, 95 % CI, 1.05, 2.65)
Rodriguez et al, 2007 [63]	Cohort of 417 men in the Baltimore Longitudinal Study of Aging (age 23–94 yr)		modified ATP III	• Lower total T associated with MetS after adjustment for BMI (HR 0.70, 95 % CI, 0.53, 0.92) (lower T is the referent)
				• Lower SHBG associated with MetS after adjustment for BMI (HR 0.58, 95 % CI, 0.44, 0.78) (lower SHBG is the referent)
				• DHEAS not associated with MetS
Soriguer et al, 2012 [59]	Cohort study of 227 Spanish men (mean age 46 y at baseline)	Cohort study of 473 Spanish women (mean age 43 y at baseline)	Upper quartile of HOMA-IR; modified ATP III	• Total T not associated with HOMA-IR in men but lower T associated with MetS in men (OR 0.19, 95 % CI, 0.06, 0.63) (lower T is the referent)
				• Total T not associated with HOMA-IR or MetS in women
				• Lower bioavailable T associated with insulin resistance in men (OR 0.72, 95 % CI, 0.53, 0.97) and MetS in men (OR 0.61, 95 % CI, 0.42, 0.89) (lower T is the referent)
				• Higher bioavailable T associated with increased insulin resistance in women after adjustment for BMI (OR 2.02, 95 % CI, 1.20, 3.39) but not MetS in women
				• Lower SHBG associated with insulin resistance in men (OR 0.34, 95 % CI, 0.18, 0.65) and decreased MetS in men (OR 0.36, 95 % CI, 0.17, 0.87) (lower SHBG is the referent)
				• Lower SHBG associated with insulin resistance in women (0.61, 95 % CI, 0.42, 0.88) and MetS in women (OR 0.62, 95 % CI, 0.36, 0.94) (lower SHBG is the referent)
Torrens et al, 2009 [16]		Cohort study of 1862 women peri-menopausal women		Overlap noted with study by Janssen et al, 2008 [65] noted above findings similar, with addition of baseline T:E2 ratio (1.24, 95 % CI, 1.17, 1.69) and rate of change (1.41, 95 % CI, 1.01, 1.52)

The Role of Adiposity

The results of this review underline the importance of adiposity in the consideration of endogenous sex hormone relationships with carbohydrate metabolism. This relationship is almost certainly bidirectional, as noted in several types of studies. First, observations of women during the menopausal transition suggest that changes in central adiposity, as represented by waist circumference, precede changes in SHBG and total T [66••]. In contrast, changes in E2 can precede changes in adiposity in the early menopausal transition [66••]. Second, Laaksonen et al found that MetS was associated with lower odds of hypogonadism (defined by levels of total T) after adjustment for BMI (RR 2.24, 95 % CI 1.05, 4.74) [67] whereas lower total T and SHBG also predicted incident MetS (Table 2) [51]. In the latter study, the levels of T were in the low-normal range, ie, men were not overtly T deficient. Third, hepatic adiposity may decrease SHBG production [68], which then increases the amount of bioavailable T.

Excess adipose tissue may also minimize any independent effect of sex steroids upon carbohydrate metabolism. In the Massachusetts Male Aging Study, lower levels of T and SHBG were associated with incident MetS, but only in men with a BMI <25 kg/m^2, leading the authors to hypothesize that relationships between androgens/SHBG with MetS were less impactful when excess adiposity was present [62]. In other words, the insulin resistance associated with adiposity overwhelmed any insulin resistance introduced by lower androgen or SHBG levels.

We have reported that among postmenopausal women who were overweight and glucose intolerant, lifestyle intervention-induced changes in endogenous sex steroids were relatively small compared with weight and waist circumference changes [69]. Our results suggest that in this population, the potential role of sex steroids as a mediator of weight-induced declines in glucose is small, although a role for sex steroids and SHBG upon glucose apart from weight was not excluded. We have also reported that sex steroid levels do not modify the amount of weight loss in this same population and that this lack of modification did not differ by estrogen use [69], suggesting that sex steroid levels had little impact upon weight changes among older women who were obese and already glucose-intolerant. In contrast, changes in weight and SHBG were more closely associated [26••], and increases in SHBG were independently related to increases in fasting and 2-hour post-challenge glucose apart from changes in waist circumference [25], suggesting that SHBG might be a mediator of weight-induced glucose improvements as well as an independent determinant of glucose levels.

There is a lack of studies in younger menstruating women with incident MetS or diabetes. With the exception of the report by Janssen et al [65], studies in menstruating women focus upon women with polycystic ovarian syndrome, who may have different pathophysiology of glucose intolerance than women without hyperandrogenicity [70]. As younger women have higher sex steroid levels and tend to be leaner than older women, sex steroids may have different relationships with carbohydrate metabolism as women age. A similar modification by age has been reported in men; levels of T decline with age in men, and thus, relationships between T and carbohydrate metabolism in older adults may differ than that in younger adults. In the Study of Health in Pomerania cohort, lower total T was associated with incident MetS among men aged 20–39 years, but not among men in older age groups [61]. Of note, re-examination of these relationships adjusting for SHBG did not find that baseline levels of total T were related to incident diabetes [60], but change in total T was, suggesting decline within individuals may be more important than absolute levels of T at a given point in time. We have reported a lack of association between sex steroid levels, SHBG, and glucose in premenopausal women who were overweight and glucose-intolerant [71]. The lack of association may also be due to adiposity and insulin resistance, or also be due to the lack of timing of the sampling to the menstrual cycle.

Conclusions and Future Directions

In summary, we report that the majority of prospective studies suggest that lower levels of T and possibly lower androgen relative to estrogen are associated with dysglycemia in men. Conversely, higher levels of T and possibly higher androgen relative to estrogen are associated with hyperglycemia, although the relationship in women was much weaker. Relationships are stronger between total levels of sex steroid and glucose than with free or bioavailable levels in men. Lower levels of SHBG are associated with both sets of adverse outcomes in men and women and have the most consistent relationships with adverse outcomes. Studies conflicted regarding E2. All associations were significantly attenuated by adiposity.

There is great interest in exploring sex steroid supplementation as a means to improve carbohydrate metabolism and other outcomes, which may provide a valuable means of treating glucose intolerance. However, based on the example of the large estrogen replacement trials, such supplementation studies may not reflect naturally occurring physiology. An exploration of endogenous sex hormone levels may better provide insight on the influence of disorders of glucose regulation and sex hormone levels. These examinations should be longitudinal, enabling examination of the impact of change. Although examination of metformin in populations with low sex steroid levels have not shown major changes in sex steroids to date [26••], the impact of metformin in populations with higher sex steroid levels should be explored. Given the

lack of standardization of sex steroid methods and lack of agreement on what constitutes normal levels, individual changes in sex hormone milieu over time may provide better clues to their effects on glucose regulation than between-individual comparisons. These examinations should also account for adiposity and ideally trajectories of adiposity. Examinations of how these risk factors modify each other to affect future glycemia in younger persons with elevations with higher sex steroid levels, as well as lean vs obese individuals, can provide additional insight into how individuals age healthily.

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Compliance with Ethics Guidelines

Conflict of Interest Catherine Kim declares that she has no conflict of interest. Jeffrey B. Halter has received honoraria from Takeda Global Research and Development Center (as a Chair, Safety Monitoring Board for studies of new drug for diabetes; ended in 2012), he was on the 2013 advisory board for Janssen Pharmaceuticals, Inc., and he has received royalties from McGraw Hill as a textbook editor. He also has received payment for development of educational presentations including service on speakers' bureaus from the American Diabetes Association; he has received travel/accommodations expenses covered or reimbursed from the American Diabetes Association, Association of Specialty Professors for teaching activities and a grant he is a co-PI for (ASP).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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