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The role of the androgen receptor in the pathogenesis of obesity and its utility as a target for obesity treatments

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Summary

Obesity is associated with hypothalamic–pituitary–testicular axis dysregulation in males. Here, we summarize recent evidence derived from clinical trials and studies in preclinical animal models regarding the role of androgen receptor (AR) signaling in the pathophysiology of males with obesity. We also discuss therapeutic strategies targeting the AR for the treatment of obesity and their limitations and provide insight into the future research necessary to advance this field.

KEYWORDS
fat, men, obesity, testosterone

1 | INTRODUCTION

Obesity represents a major global public health problem with a rapidly growing incidence rate that confers a great socioeconomic burden on our society. According to the World Health Organization (WHO), obesity is characterized by abnormal or excessive fat accumulation that presents a health risk.[1] While the WHO defines obesity as a body mass index (BMI) over 30 kg/m^2, this categorical definition does not capture the fact that the risks imparted by increasing body mass follow a continuum and vary considerably between individuals and ethnic groups.[2] In addition, BMI alone is not linearly predictive of mortality[3] and does not capture important aspects of body composition such as distribution of body fat (e.g., visceral adiposity), ectopic fat deposition (e.g., hepatic steatosis), and sarcopenia all of which may modulate cardiometabolic risks in ways not captured by BMI. Importantly, obesity is best understood as a chronic disease of energy imbalance driven by multiple not fully understood pathogenetic mediators (e.g., genetics and dysregulation of satiety factors) driving excess deposition of adipose tissue. The pathologic impact of excess adiposity depends not only on the amount, but also on its distribution and function. Excess adiposity is in turn is associated with multisystem comorbidities (e.g., diabetes,[4] cardiovascular disease,[5,6] obstructive sleep apnea,[7] osteoarthritis,[8] increased risk of certain cancers,[9] in some people, depression,[10] and low self esteem[11]) that confer excess morbidity and mortality, and socioeconomic ramifications.[3] In this context, the American Association of Clinical Endocrinology and the European Association for the Study of Obesity have recently proposed "Adiposity-Based Chronic Disease" as a clinically more appropriate term for obesity.[12]

The Organization for Economic Co-operation and Development (OECD) reported in over 37 member countries that one in five adults have obesity.[13] This high prevalence translates to an enormous economic burden, with the directs costs in Germany alone estimated to be 29.39 billion euros and indirect costs to be a further 33.65 billion euros.[14] Hormonal mediators such as ghrelin and leptin have been well researched in the pathogenesis of obesity,[15] but this has not led to effective therapy. In contrast, the contribution of sex steroids is

Abbreviations: AI, aromatase inhibitor; APs, adipocyte precursors; AR, androgen receptor; ARKO, androgen receptor knock out; BMI, body mass index; BMPCs, bone marrow precursor cells; CHH, congenital hypogonadotropic hypogonadism; DHT, dihydrotestosterone; E2, estradiol; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ESR, estrogen receptor gene; FSH, follicle stimulating hormone; GPCR, g protein coupled receptor; HFD, high fat diet; HPT, hypothalamic–pituitary–testes; LH, luteinizing hormone; MAP, mitogen associated protein; ORX, orchidectomy; PCOS, polycystic ovary syndrome; SARMS, selective androgen receptor modulators; SHBG, sex hormone binding globulin; Tfm, Testicular feminized mouse.

less clear. While it is well established that testosterone negatively regulates fat mass in males, the mechanisms by which this hormone exerts its fat-reducing effects are not well understood. In this review we discuss the evidence from clinical and pre-clinical studies supporting a role for testosterone action in reducing fat mass, both directly via the androgen receptor (AR), as well as following conversion to dihydrotestosterone (DHT) by the enzyme 5-alpha reductase, and through the estrogen receptors α and β (ER) via conversion of testosterone to estradiol (E2) by the enzyme aromatase.

The biologic actions of sex steroids may have sex-specific aspects,[16] and these differing functions may, at least in part, play a role in the sexual dimorphism of body fat distribution.[17,18] In men, circulating androgens have been reported to be negatively associated with body fat mass, and in particular with intra-abdominal fat mass.[19,20] In contrast, in women, although the role of androgens in regulating fat mass is less clear, the evidence suggests that androgens are positively associated with fat mass. Studies have reported that bioavailable testosterone is associated with adiposity in peri-menopausal women.[21,22] Moreover, women with polycystic ovary syndrome (PCOS) often exhibit hyperandrogenism which is correlated with abdominal obesity.[23,24] Transgender males undergoing gender affirming hormone therapy with testosterone, exhibited a loss in fat mass in android, gynoid, leg, and arm regions.[25] A study in postmenopausal women with obesity administered nandrolone decanoate with concomitant calorie restriction for 9 months reported a reduction in total fat mass compared with patients treated with spironolactone or placebo.[26] However, it is important to note that the loss of fat mass was only seen in subcutaneous fat while there was an increase in visceral fat.[26] Overall, these data are suggestive of a possible dose-dependent effect of testosterone whereby increasing serum testosterone into the male reference range (either by treatment of hypogonadal men or transgender men) is associated with reductions in fat mass in both sexes. In contrast, intermediate testosterone concentrations, that is, below the male reference range but above the female reference range (e.g., untreated hypogonadal men and women with PCOS) are associated with accumulation of fat in both sexes.[27] Within this review, we will focus on the role of testosterone in regulating fat mass in males. Furthermore, we discuss the amenability of testosterone signaling via the AR as a therapeutic target to reduce fat mass and the research avenues required to generate novel treatments to target this pathway.

2 | THE ROLE OF SEX STEROID SIGNALING IN REGULATING FAT MASS—A DISCUSSION OF THE CURRENT EVIDENCE

2.1 | Androgen signaling mechanisms

Androgen signaling is complex due to the several endogenous ligands of the AR and numerous molecular pathways by which androgen mediated signaling can occur. Within this review, we focus on the large body of evidence derived from studies investigating the actions of testosterone and DHT; however, it is important to note that there are several other androgens that can exert important biological effects either by direct interaction with the AR or by serving as substrates for local metabolism into testosterone, including 4-androstendione,[28] 11-ketotestosterone,[29] and DHEAS.[30,31] The primary receptor for testosterone and DHT, the AR, is a nuclear transcription factor which can activate both the DNA-binding-dependent (genomic) and non-DNA binding-dependent (non-genomic) signaling pathways. Both mechanisms are reviewed in depth elsewhere by ourselves[32] and others.[33–35] In the circulation, testosterone is plasma-protein bound, tightly to sex hormone binding globulin (SHBG) and loosely to albumin, with only a small percentage circulating as free testosterone. According to the free hormone hypothesis which remains controversial,[36,37] free testosterone is the primary bioactive hormone. However, there is evidence that SHBG bound testosterone may have biologic activity potentially via a SHBG membrane receptor. This is discussed in depth in Section 2.6. DNA-binding-dependent AR signaling occurs when testosterone diffuses through the cell membrane and binds to the AR, or is converted to the more potent agonist DHT by 5-alpha reductase, which also binds to the AR. The androgen/AR complex translocates to the nucleus where it binds to androgen response elements to initiate or repress the transcription of target genes. Testosterone can also be aromatized to E2 by the enzyme aromatase which exerts its actions via the ERs by a similar DNA-binding-dependent mechanism. This transcriptional regulation of the AR may be further modified by coregulators, molecules that can bind to nuclear transcription factors to magnify or reduce the transcriptional activity.[38] Coregulators of the AR are reviewed extensively elsewhere[39–41] and as such are not included in Figure 1. Testosterone can also elicit cellular changes via rapid signaling of non-DNA dependent-pathways which distinguishes them from the DNA-binding-dependent pathways. There are numerous non-DNA binding pathways such as the SHBG receptor[47] and membrane localized calcium channels[48] that have been studied in different tissue types including reproductive, cardiac and skeletal muscles[33,34] with some examples depicted in Figure 1. The role of these non-DNA binding dependent pathways in regulating fat mass, however, has not yet been investigated.

2.2 | Obesity and hypogonadism

2.2.1 | Clinical evidence of the relationship between hypogonadism and obesity

Male hypogonadism (hypoandrogenism) is a clinical syndrome comprising of clinical symptoms and signs of androgen deficiency in combination with a low serum testosterone concentration.[49] Hypogonadism is classified either as organic (i.e., due to anatomical disease of the hypothalamic–pituitary–testes [HPT] axis), or as functional (due to suppression of the HPT axis by extragonadal disease).[50] Organic hypogonadism is either primary (due to testicular pathology, e.g., Klinefelter's syndrome) or secondary (due to hypothalamic–pituitary disease, e.g., pituitary tumor). Primary hypogonadism is

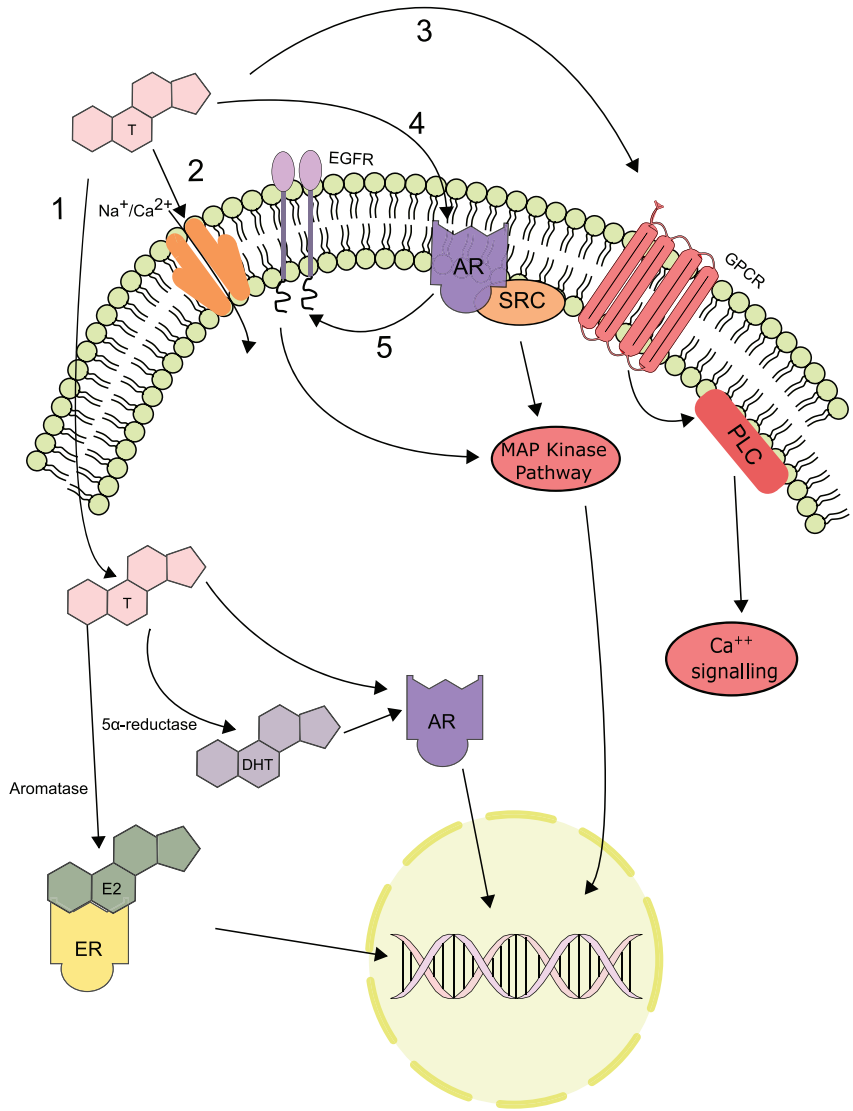

FIGURE 1 Summary of putative testosterone signaling mechanisms. DNA-binding dependent signaling (1) occurs via diffusion of testosterone (T) across the cell membrane where it binds directly to the androgen receptor (AR) or is converted by 5α reductase to dihydrotestosterone (DHT), which also binds to the AR. The androgen/AR complex translocates to the nucleus where it binds to androgen response elements to activate or repress the transcription of target genes. T can also be converted to estradiol (E2) by the enzyme aromatase and mediate its actions following binding to estrogen receptors (ER). Examples of non-DNA binding-dependent AR signaling pathways are depicted: (2) testosterone activation of ionotropic receptors such as transient receptor potential melastatin 8 (TRPM8) to enable influx of calcium or sodium[35,42,43]; (3) testosterone can bind membrane-bound g protein coupled receptors (GPCR) to activate several canonical GPCR signaling pathways including phospholipase C-mediated signaling, which regulates calcium levels[44,48]; (4) testosterone activation of membrane-associated AR which binds to Src and activates the mitogen associated protein (MAP) kinase pathway via transactivation of the epidermal growth factor receptor (EGFR)[45]; and (5) via non-EGFR signaling[46]

caused by dysfunction of the testes and is associated with low testosterone and high levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), while secondary hypogonadism is due to dysfunction of the hypothalamus and/or the pituitary gland and is associated with low testosterone and low to (inappropriately) normal levels of LH and FSH.[50,51] Organic hypogonadism is due to a specific pathology causing dysfunction of the HPT axis, is usually irreversible and requires life-long testosterone replacement (unless fertility is desired). Organic hypogonadism can be congenital (e.g., Klinefelter's syndrome or congenital hypogonadotropic hypogonadism [CHH]) or acquired (e.g., testicular injury or pituitary mass lesion).

There are several congenital disorders that result in hypogonadism which exemplify organic hypogonadism. Klinefelter's syndrome is a genetic condition characterized by an extra X chromosome which results in an XXY genotype; however, 20% of cases have additional aneuploidies.[52] Patients with Klinefelter's syndrome present with primary hypogonadism, and it is typically associated with increased body fat mass, particularly abdominal obesity and consequently with an increased risk of metabolic syndrome.[53] The extent to which the metabolic phenotype is caused by testosterone deficiency or by the additional X chromosome is difficult to ascertain. Of note, in CHH which, depending on the genetic defect can be associated with anosmia (i.e., Kallmann's syndrome), an adverse metabolic phenotype is less dominant.

Functional hypogonadism is usually due to hypothalamic–pituitary suppression by extragonadal disease, and obesity is a very common cause. Functional hypogonadism occurs in the absence of recognizable disease of the HPT and can be reversible by treating the disease causing hypothalamic–pituitary suppression, such as weight loss in obesity.[50,54] While the definition of hypogonadism comprises both clinical and biochemical evidence of androgen deficiency, in some studies, hypogonadism is defined biochemically.[50,54] Of note, clinical features of androgen deficiency are non-specific, and in a patient with a high burden of comorbidities, it is often difficult to determine whether androgen deficiency-like clinical features and low testosterone are causally related or whether they merely reflect

effects of comorbidities.[55] Obesity is often associated with lowered testosterone and low to normal gonadotrophin concentrations; however, whether this reflects causality, reverse causality, or merely in-common risk factors remains unclear.[56,57] The relationship is likely bidirectional because on the one hand weight loss is associated with an increase in serum testosterone, whereas on the other hand testosterone treatment reduces fat mass. However, it is important to note that, in men with obesity, the effect of substantial weight loss (i.e., generally only achievable only through bariatric surgery) on serum testosterone is arguably more marked than the effect of testosterone treatment on fat mass.[58,59] In contrast, the increases in serum testosterone achieved by lifestyle changes are modest around 3 mM,[60,61] and difficult to sustain.[62] While a bidirectional Mendelian randomization study suggested that the effect of an elevated BMI on low testosterone is more important than the effect of low testosterone on an increased BMI, such studies require confirmation in independent samples.[63]

Effects of obesity on testosterone

Modest obesity is predominantly associated with reduced total testosterone due to insulin resistance associated reductions in its carrier protein sex hormone binding globulin (SHBG).[64,65] However, marked obesity (body mass index (BMI) > 35 kg/m^2) may lead to genuine suppression of the HPT axis.[56] There are several postulated mechanisms by which obesity may mediate HPT axis suppression including leptin resistance and/or dysregulated insulin signaling.[66,67] Additional contributing factors include paternal genetics,[68] leptin resistance,[69] and obesity-associated elevations in pro-inflammatory cytokines (reviewed in Grossmann[56]). Other putative mechanisms such as increased E2 production have been not been confirmed by recent studies using LCMS-MS based assay technology to accurately measure E2 concentrations in men.[70,71]

Effects of testosterone treatment on fat mass

Evidence for a role of testosterone in regulating fat mass is provided by numerous studies, of varying quality, that examine the effects of administration of exogenous testosterone on fat mass.[72–74] These studies are heterogenous due to the numerous variables that differ between studies including gonadal state, that is, hypogonadal versus eugonadal, testosterone therapy regimen and selected patient cohorts, thus making comparisons difficult. A systematic review by Huo et al. reporting the effects of testosterone treatment in men with functional hypogonadism[75] showed that of the 25 studies that assessed the effect of testosterone on fat mass, 60% displayed a reduction in fat mass after testosterone treatment.[75] In addition, a meta-analysis performed by Corona et al. demonstrated a modest −0.34 standardized mean difference in fat mass following testosterone treatment.[59] Subsequently, several additional studies investigating the effects of testosterone on fat mass have been reported and are summarized in Table 1. Together, the majority of studies examining the effect of exogenous testosterone therapy report a modest reduction of fat mass. Isidori et al. reported a ∼2 kg reduction of fat mass[83] corroborating evidence from systematic reviews[84]; however, several questions remain relating to the mechanisms by which testosterone reduces fat mass as well as the long-term safety of testosterone therapy. Caution, however, must be taken when interpreting these data as a number of confounding factors exist including differences in baseline BMI and gonadal status of the patient cohorts as well as different formulations of testosterone treatment administered. While no rigorous head-to-head trials exist, it is plausible that the biologic actions imparted by different formulations of testosterone may differ. For example, it has been suggested that intramuscular testosterone injections are more effective than transdermal gels in increasing lean body weight.[85] Whether this is because intramuscular injection, which eliminates compliance and skin absorption issues, achieve higher testosterone doses than topical (or oral) preparations, and/or whether other factors (such as metabolism, tissue distribution) play a role, has not been fully clarified.

Whether the reduction in fat mass following testosterone treatment in men is depot specific remains unclear, with some studies reporting reductions occurring in subcutaneous[76,79] and others, in visceral fat depots.[60,86] The specific fat depot in which reductions are noted following testosterone treatment is an important consideration as only increases in intramuscular[87] and visceral fat[88,89] as well as an increase in visceral to subcutaneous fat ratio[90] have been associated with increased mortality in men.[91] In contrast, subcutaneous fat mass, especially if located in the gluteofemoral region is associated with decreased all-cause mortality.[90] However, subcutaneous fat, especially if located in the abdominal region, may not be innocuous. Of note, testosterone has been shown to downregulate lipoprotein lipase in abdominal subcutaneous tissue, which stimulates release of free fatty acids contributing to systemic insulin resistance.[92] In a controlled study, testosterone deprivation increased in insulin resistance despite the lack of an increase in VAT. In this study the testosterone deprivation-associated increase in insulin resistance was associated with the increase in total fat mass (but not with the decrease in lean mass) collectively suggesting that fat depots other than VAT modulate insulin resistance and that testosterone exerts insulin reducing effects that are, at least in part, independent of changes in VAT.

Reductions in fat mass are among the most consistent effects observed in clinical studies of testosterone treatment in men; however, the amount of fat mass lost differs between studies. This is due to study heterogeneity, with studies including patient with different baseline characteristics (e.g., differing baseline BMI and gonadal states) and differences with respect to treatment length and testosterone formulations used, hence potentially diluting the effect of testosterone treatment. In studies using intramuscular testosterone undecanoate, reductions in fat mass ranged from 3.4 kg[81] to 4.2 kg,[93] In the largest study to date, T4DM, testosterone undecanoate treatment over 2 years, reduced fat mass by 2.7 kg, over and above the effects of a lifestyle program.[74] Skinner et al. reported that intramuscular testosterone injections were more effective than transdermal gels at increasing lean body weight.[85] RCTS to date have been relatively short in duration, with the majority observing testosterone effects over 12 months or less. Observational studies in contrast,[82,94] with longer follow up, suggest that testosterone treatment-associated

TABLE 1 Summary of studies post-2016 demonstrating the effect of testosterone to reduce fat mass

Brief synopsis	Clinical gonadal state of men in study and method of T measurement	Effect of T treatment on fat mass	Reference
DB, PC, RCT. Men with type 2 diabetes aged 30 to 65 years with HH or eugonadal states were treated with 250 mg of testosterone cypionate intramuscularly every 2 weeks for 23 weeks. Of the 94 men recruited, 50 were eugonadal and 44 had HH. Men with HH were allocated equally to T treatment and placebo.	Fasting testosterone was measured initially and 2 weeks after the first visit. HH was defined as a calculated free T level of <6.5 ng/dl. T measured by LCMS.	Decrease in trunk subcutaneous fat mass (−3.3 kg) but not visceral or hepatic fat mass.	76
DB, PC, RCT. Men aged 50–70 years with T2D and low T were given testosterone gel (50 mg T daily) increasing to 100 mg T if T levels did not increase, for 24 weeks.	Men had bioavailable T < 7.3 nM. T measured by LCMS.	Average loss of total fat free mass −1.2 kg measured by DEXA.	77
DB, PC, RCT. Men aged 18–70 with BMI ≥ 30 kg/m^2, were given a low caloric diet for 10 weeks followed by 46 weeks of weight maintenance and were supplemented with either Testosterone undecanoate (Injections of 1000 mg at 0, 6, 16, 26, 36, and 46 weeks) or placebo.	Men had a total T level ≤12 nM. T measured by LCMS.	After initial weight loss, men on T therapy maintained weight loss and at study end had lost more fat (−2.9 kg) than their placebo counterparts. However, in a follow up study, loss of fat free mass was not sustained 82 weeks after treatment.	60,62
DB, PC, RCT. Effect of testosterone on atherosclerosis in 308 community dwelling men ≥60 years age was assessed. Patients were randomized and given placebo or 7.5 g of 1% testosterone gel treatment daily for 3 years. Testosterone was titrated to 10 g if serum testosterone was <17.3 nM or 5 g if testosterone was >31.2 nM.	Total T of 3.47 nM to 13.88 nM. Free T of <173.5 pM considered to be low or low-normal T levels. Immunoassay measurement of T validated against LCMS.	Fat mass was assessed by DEXA. Both groups exhibited increased fat mass, but fat accumulation was significantly less in the T treated group.	78
DB, PC, RCT. 13 men with Klinefelter's syndrome (av. aged 22–56 years, BMI average 26.7 kg/m^2) were given 160 mg (2 doses 80 mg) testosterone undecanoate per day (orally) or placebo for 6 months and compared with 13 age and BMI matched controls.	Gonadal state is unclear as most Klinefelter's patients are supplemented with T. T assessed by LCMS.	Visceral fat mass, total abdominal and intra-abdominal fat increased while T decreased total body fat and subcutaneous fat mass.	79
Men with opioid-induced hypogonadism were randomly assigned to testosterone undecanoate 1000 mg or placebo (injection).	Total bioavailable T average = 2.9 nM. Fasting T levels assessed by LCMS.	T decreased DXA measured total fat mass by 1.2 kg.	80
12-month double-blinded, placebo-controlled trial. 101 men <70 years old with cirrhosis and low testosterone were given either testosterone undecanoate (1000 mg intramuscularly) or placebo at 0, 6, 18, 30, and 42 weeks.	Low T was defined as <12 nM measured by immunoassay or Vermeulen calculated free testosterone <230 pM from 2 separate samples.	Patient body composition was assessed by DXA at baseline 6 months and 12 months, patients treated with T exhibited −4.34 kg reduced fat mass. Total lean mass increased by +4.74 kg	81
Registry-based, observational study of 823 men average age 60.6 years with a baseline serum total testosterone concentration ≤12.1 nM were treated with testosterone undecanoate (n = 474) every 12 weeks (after an initial 6 weeks booster injection) or	All men exhibited symptoms of hypogonadism. Of the 823 trial participants, 474 were obese, 286 overweight, and 63 normal weight.	All patients given testosterone exhibited significant weight loss (normal weight −4.8%, overweight −9.6% and obese −20.6% of body weight), and favorable changes in lipid profiles	82

(Continues)

TABLE 1 (Continued)

Brief synopsis	Clinical gonadal state of men in study and method of T measurement	Effect of T treatment on fat mass	Reference
untreated ($n = 395$) and were assessed 2 times a year for 11 years.			
DB, PC, RCT, multi-center trial. 1007 men aged 50–74 years with an average BMI of 34.7 were randomly assignment to placebo or testosterone undecanoate treatment (1000 mg intramuscularly) at baseline, 6 weeks and subsequently every 3 months for 2 years.	Patients were stratified into low (<8.0 nM), medium (8.0 to <11.0 nM), or high (≥11.0 nM) T levels. Average T at baseline was 13.9 nM (placebo) and 13.4 nM (T group). Fasting T levels were measured by validated LCMS assay.	T treatment resulted in a reduction of total fat mass (−2.71 kg) and abdominal fat mass (−2.34%) assessed by DXA.	

Abbreviations: DB, double blind; DEXA, dual-energy X-ray absorptiometry; DHT, dihydrotestosterone; HH, hypogonadotropic hypogonadism; LCMS, liquid chromatography and mass spectrometry; PC, placebo controlled; RCT, randomized clinical trial; T, testosterone.

fat lass is progressive over time with greater amount of fat loss observed in studies with longer duration (Table 1). Moreover, Haider et al. reported in a prospective registry study over 11 years in 178 men with lowered serum testosterone, that testosterone treatment was associated with type 2 diabetes remission in 34.3% of patients.[95]Collectively, these studies suggest that testosterone-related reductions in fat mass may translate into metabolic benefits. However, it is likely that effects of testosterone treatment on other tissues such as muscle or potentially pancreas may contribute to the metabolic benefits of testosterone.[74]

In summary, the clinical evidence from RCTs shows that testosterone treatment given relatively short term (3 months – 24 months) leads to modest reductions in fat mass with two studies reporting a reduction in the risk of type 2 diabetes. In the T4DM trial, testosterone treatment in high risk men over 2 years, reduced the risk of diabetes relative to placebo by 40%. Furthermore, Haider et al. reported in a prospective registry study over 11 years of 178 men with hypogonadism, that 34.3% of patients administered testosterone resulted in remission of their type 2 diabetes[95] suggesting that at least in part, the testosterone-related reductions in fat mass may translate into metabolic benefits, however, the mechanism by which this occurs remains to be elucidated and is likely not exclusively ascribed to the loss of fat mass.[74] While one of the most consistent effects of testosterone treatment in men is reduction in fat mass and an increase in muscle mass, changes expected to be metabolically favorable, current testosterone treatment guidelines slightly differ in their recommendation regarding indications for testosterone treatment. While all guidelines agree that men with true hypogonadism should (unless they seek fertility) be offered testosterone treatment, metabolic benefits are highlighted in some[96] but not in all guidelines.[49,97] While long term benefits and potential risks of testosterone treatment, especially with respect to cardiovascular outcomes, remain unknown. Of note, an ongoing large RCT, the TRAVERSE trial, seeks to evaluate the effect of testosterone therapy on the risk of major adverse cardiovascular events (ClinicalTrials.gov Identifier: NCT03518034). Until more definitive evidence is available, the only unequivocal clinical indication for testosterone treatment is testosterone replacement for men with organic hypogonadism.[49,98]

2.2.2 | Preclinical orchidectomy models to investigate testosterone actions on fat mass

To mimic hypogonadism in men, castration or orchidectomy (ORX) in rodents has been widely utilized. It is well established that ORX in rodents leads to decreased lean body mass[99–103]; however, there are some discrepancies with regard to changes in fat mass. The majority of studies report an increase in whole body adiposity or in specific adipose depots post-ORX[99,104–108]; however, a handful of studies either report no change[101,102] or, in one case, a reduction.[103] These discrepancies may be due to different ages of the animals studied as well as the differing length of the studies.[102] Together, the data suggest that ORX and subsequent dysregulation of fat mass may be attributed to reductions in testosterone. The mechanism by which this increase of fat mass occurs due to the reduction of testosterone is unclear; however, recent studies do give evidence to possible mechanisms. Baik et al. reported that castrated mice fed a normal diet exhibited increased adiposity and expression of fatty acid synthesis associated genes. Additionally, concomitant castration and a high fat diet (HFD) resulted in increased expression of the fatty acid transporter CD36 in subcutaneous fat.[104] Similarly, Sebo et al. reported that castrated mice fed an HFD have large adipocytes that are reduced in size by testosterone administration.[106] These studies suggest that loss of testosterone may regulate fatty acid uptake or storage; however, other potential mechanisms by which testosterone regulates fat mass are described below.

The relationship between testosterone and fat mass is further informed by studies that treat orchidectomized animals with testosterone. Sebo et al. reported that testosterone treatment in male mice reduces ORX and HFD associated weight gain with decreases observed in visceral and subcutaneous fat mass as well as adipocyte size.[106] The abrogation of weight gain in orchidectomized rodents via

testosterone administration has also been reported by others[100,109] with these pre-clinical data being consistent with the clinical evidence that testosterone treatment reduces fat mass in men.

The mechanisms by which testosterone regulates fat mass remain unclear. Data obtained from in vitro experiments show that testosterone and DHT can inhibit the differentiation of human and BM-mesenchymal pluripotent cells into adipocytes via AR dependent pathway.[110–113] While these data provide evidence for a role of testosterone in the inhibition of adipogenesis in pre-adipocytes, they do not explain the action of testosterone to reduce the mass of pre-existing fat depots in humans and rodents. Other mechanisms by which testosterone may regulate fat mass include modulation of lipid metabolism,[114,115] alteration of muscle metabolism[116] and alteration of mitochondrial function[117]; with these actions being extensively reviewed elsewhere[118] but further validation is required. Studies in utilizing clinical antagonists that target AR signaling pathways and genetically modified mice have provided further insight into the mechanisms of testosterone action to decrease fat mass.

2.3 | The androgen receptor (AR)

2.3.1 | Clinical effects of AR inhibition on fat mass

There are few clinical examples of exclusive AR inhibition to draw from when examining the evidence for AR-mediated regulation of fat mass. One such example is the use of non-steroidal anti-androgen (NSAA) compounds such as bicalutamide or flutamide as a monotherapy in prostate cancer patients. Although these compounds inhibit prostate cancer growth by inhibiting androgen binding to the AR, NSAA monotherapy is no longer recommended in favor of androgen deprivation therapy (ADT), which utilize GnRH agonists or antagonists, to abrogate production of endogenous androgens.

In a 12 month open label trial, Smith et al. reported that patients treated with bicalutamide or leuprolide (a GnRH agonist) monotherapies exhibited an increase in whole body fat mass of 11.2% for leuprolide and 6.4% for bicalutamide.[119] Similar increases in fat mass following bicalutamide[120] and enzalutamide[121,122] monotherapy have also been reported supporting a role for testosterone acting via the AR to regulate fat mass. It is important to note however, that treatment with AR antagonists also disrupts the negative feedback of testosterone on the central HPT axis, resulting in increased circulating E2,[119] which may also effect body fat. Thus, the increase in fat mass reported in these studies cannot conclusively be ascribed to inhibition of the AR.

2.3.2 | The pre-clinical genetically modified androgen receptor models

The AR is widely expressed in most tissues and cell types making understanding its contribution to physiological processes challenging to unravel. In this review we have broadly grouped these pre-clinical models into four subtypes. Global AR knockouts (ARKO), where the AR is inactivated in all tissues and cell types (reviewed in Rana et al.[123]); tissue and/or cell specific ARKOs where the AR is deleted in a specific cell type or tissue while it is expressed normally in all other tissues,[124] AR over-expression transgenic models where the AR is overexpressed in a specific cell/tissue type[125] and AR gene replacement models in which the AR is expressed in a specific cell-type while it is inactivated in all other tissues.[126]

Testicular feminized mouse (Tfm) model

The Tfm mouse was one of the first rodent models of AR insufficiency. Generated in 1970, [127] these mice possess a single base deletion in the AR resulting in a frameshift mutation and a non-functional AR protein.[128] Tfm mice have reduced endogenous testosterone levels[129] and develop hepatic steatosis as well as aortic fatty streaks when fed a HFD.[130–132] More recently, Sebo et al. utilized Tfm mice to investigate whether the fat reducing effect of androgens is mediated via an adipocyte-specific AR dependent mechanism. Following feeding a HFD, Tfm mice displayed an increase in the proliferation of adipocyte precursors (APs) in the subcutaneous but not visceral fat depot compared with control mice as determined by bromodeoxyuridine labelling. This suggests an important role for the AR in regulating subcutaneous fat deposition. However, transplantation of mTomato labelled APs from Tfm mice into subcutaneous fat depots of WT mice fed a HFD did not proliferate at a faster rate compared with WT APs expressing a functional AR,[106] inferring that adipocyte proliferation is not mediated via the AR expressed in APs but may be mediated by another AR dependent mechanism. It is important to note, that the Tfm mouse model has a number of limitations, including potential residual AR activity due to the production of a truncated AR protein.[133–135] The discovery of the Cre/*lox*P system has enabled the generation of alternative Global-ARKO mouse models as well as tissue and/or cell specific knockout models of the AR thereby overcoming the limitations of the Tfm mice and have proved advantageous for investigating the mechanism by which testosterone decreases fat mass.[133]

Global AR knockout mice

There are several ARKO mouse models generated using the Cre/*lox*P system which have been reviewed extensively by ourselves[32,123] and others[124,133,136] and are summarized in Table 2. The adipose tissue phenotype of these ARKO mice differs with regards to both the age of onset and fat depots affected. An obese phenotype of increased subcutaneous and visceral fat mass as well as increased numbers of larger adipocytes have been reported in ARKOs fed a regular chow diet from 9–12 weeks of age.[137,144,147] In contrast, late-onset obesity characterized by increases in epididymal and perirenal fat pad size as well as increased adipocyte size has been observed at 40 weeks of age.[138] In contrast to the majority of ARKO models which exhibit spontaneous obesity,[143] there is a report of an ARKO model which only displays an obese phenotype when challenged with a HFD.[100] The differences in the fat phenotype of these ARKO models may be attributed to the differences in the genetic background of the mice[126]

TABLE 2 Summary of the fat phenotype of male global-ARKO models generated using Cre-loxP technology

Targeted AR region and Cre mouse line	Androgen receptor mutation	Fat phenotype	Reference
Exon 1 CMV-Cre	Recombination results in excision of Exon 1 resulting in a frame shift mutation and no AR protein.	Late onset obesity (12 weeks) with increases in total body adiposity in subcutaneous, infrarenal and intraperitoneal depots but not gonadal.	137–139
Exon 2 Beta actin (ACTB) -Cre	Excision of Exon 2 results in a frameshift mutation and two premature stop codons leading to nonsense mediate decay of mRNA transcript	Late-onset increased fat accumulation in gonadal and perirenal fat pads, increased adipocyte size at 35 weeks.	124,140–142
Exon 2 phosphoglycerate kinase 1 (PGK1)-Cre	Deletion of exon 2 results in a similar frameshift mutation to Yeh et al.[140]	Increased adiposity following feeding a HFD characterized by white adipocyte hypertrophy and increased weight of perigonadal and subcutaneous fat pads.	100,143
Exon 3 CMV-Cre	In-frame deletion of exon 3 which encodes the second zinc finger of the DNA binding domain (DBD). DNA-binding-dependent actions of the AR are abolished, while non-DNA binding activity remains.	Increased adiposity, specifically increased visceral and subcutaneous fat pads mass and adipocyte hypertrophy at 12 weeks	144,145
Exon 2 CAGGCre-ER	Excision of exon 2 of the AR results an AR null allele following treatment with tamoxifen. Generated by breeding the AR floxed mouse generated by De Gendt et al.[143] tamoxifen-inducible CAGGCre-ER mice.	Pre-pubertal inactivation of AR results in increased total fat mass and retroperitoneal fat mass.	146

as well as the region of the AR targeted for deletion which results in either retainment[145] or inactivation[139,140,143] of the non-DNA-dependent actions of the AR in addition to its DNA-binding-dependent actions.[148]

More recently, findings from a tamoxifen-inducible Global-ARKO model suggests that the obesity phenotype observed in the previously published Global-ARKO mouse models is attributed to the loss of AR action pre-pubertally as post-pubertal knockdown of the AR had no effect on fat mass.[146] These data, however, must be interpreted with some caution as AR gene knockdown is not complete (approximately 20% mRNA expression remained) and the induction of knockdown via tamoxifen, despite the short induction time (4 days), may pose some effect of fat mass through ER signaling.[149] Together, these data support an action of testosterone via the AR to regulate fat mass. In order to further elucidate the target tissues and/or cells responsible for mediating this effect, tissue-specific AR knockout and overexpression mouse models have been generated.

2.3.3 | Examples of tissue specific androgen receptor knockout models

To determine whether the action of testosterone to decrease fat mass is mediated directly via the AR in adipocytes, several adipocyte-ARKOs have been generated. Yu et al. and McInnes et al. have both generated adipocyte-specific ARKOs by crossing floxed AR mice with mice expressing Cre recombinase under the control of the adipocyte protein 2 (aP2). Yu et al. reported male aP2-ARKOs exhibited no difference in adiposity or morphology of epididymal white adipose tissue at 20 weeks of age when fed a chow diet.[141] Similarly, aP2-ARKO male mice generated by McInnes et al. displayed no difference in adipose weight of the subcutaneous or mesenteric regions and a statistically significant but biologically small reduction in perigonadal fat mass at 12 weeks of age compared with chow fed wild-type controls. No difference in adipocyte area was observed in either the perigonadal or subcutaneous fat depots. Despite this lack of difference in fat pad mass in aP2-ARKOs fed a standard chow diet, following challenging the mice with a HFD for 24 weeks, mesenteric and omental fat pad mass were increased in aP2-ARKOs compared with wild-type controls.[150] The lack of spontaneous obesity in ap2-ARKO mice suggests that the action of testosterone to decrease fat mass is mediated via the AR in another target tissue. It is important to note that the aP2 promoter is also expressed in several cell types in the brain which may confound these findings as AR action in the brain may indirectly regulate fat mass by regulating voluntary activity.[151]

Evidence from muscle-specific ARKOs suggest that the AR in myocytes may contribute to the fat reducing effects of testosterone. Myocyte-specific deletion of the AR using mice expressing Cre recombinase under the control of the muscle creatine kinase promoter (MCK-Cre) resulted in decreased intra-abdominal fat and lean body mass.[152] In contrast, deletion of the AR specifically in satellite cells using the myoblast determination protein 1 (MyoD-iCre) promoter mice had no effect on fat mass as measured by DXA.[153] This discrepancy may be due to the different activities of the Cre promoters as

the improved Cre with increased Cre expression was used to generate the MyoD-Cre mice. Irrespective, the action of AR via muscle in the regulation of fat mass remains unclear.

2.3.4 | AR expression in bone marrow cells

More recently, bone has been recognized for its importance as an endocrine organ that may regulate numerous metabolic functions through the secretion of osteokines. Once such example is osteocalcin which can regulate several physiological functions including glucose metabolism,[154] energy expenditure,[155] and testosterone levels.[156] Investigation into the potential role of androgen action via the AR in bone marrow cells in negatively regulating fat mass is an exciting research direction, with current papers related to this topic summarized in Table 3.

Utilizing a unique bone marrow transplant model whereby the bone marrow of ARKO mice was grafted into irradiated C57BL/6 J WT mice, Rubinow et al. demonstrated that WT mice receiving ARKO bone marrow exhibited significantly higher visceral and total fat mass than WT mice receiving WT bone marrow when fed a HFD diet.[157] In a subsequent study, the authors narrowed their focus to the specific bone marrow monocyte and macrophage cell type due to their endogenous expression of AR as well as their documented role in energy metabolism.[160] Deletion of the AR specifically in monocytes/macrophages expressing the lysozyme 2 gene did not affect adiposity.[160] Intriguingly, while the loss of the AR in bone marrow cells confers a propensity to obesity, this is not mediated by lysozyme 2 expressing monocytes/macrophages, suggesting that another cell type in the bone marrow may be responsible for mediating the fat reducing effects of testosterone.

Bone marrow precursor cells (BMPCs) are pluripotent cells that can differentiate into osteoprogenitors, osteoblasts, osteocytes, chondrocytes and adipocytes.[163] Given the significant contribution of BMPCs to the various cellular components of the bone and the evidence that bone may act as endocrine organ,[164,165] it stands to reason that these BMPCs may play a role in the regulation of fat mass. One of the first studies investigating the action of the AR via BMPCs utilized the 3.6 kb α_1 1 collagen promoter to overexpress the AR in BMPCs (Col3.6AR-Transgenics [Tg]). Male Col3.6AR-Tg mice displayed reduced visceral fat mass in the gonadal and peri-renal fat depots and smaller adipocyte area in the absence of any changes in serum adipokines.[166] Of significant interest, DHT treatment was able to reverse the increase in fat accumulation that occurs following gonadectomy in both adult male and female Col3.6AR-Tgs but not WT mice.[158] In contrast, overexpression of the AR in mature osteoblasts of male mice utilizing the 2.3-kb α_1(1) collagen promoter (Col2.3AR-Tg) had no effect on fat mass[125] indicating that the decrease in fat mass is mediated at an earlier stage of osteoblast development, that is, in BMPCs and osteoprogenitors.

Recently, we provided evidence for an action of androgens via the AR in bone marrow BMPCs to negatively regulate fat mass and improve metabolic function.[126] Replacement of the AR gene specifically in BMPCs of our Global-ARKOs to generate PC-AR Gene Replacement mice, completely attenuates their increased fat mass.[126] PC-AR gene replacement mice had an increase in the number of smaller adipocytes and a healthier metabolic profile, characterized by normal serum leptin, elevated serum adiponectin and improved whole-body insulin sensitivity, with higher glucose uptake into subcutaneous and visceral fat than Global-ARKOs.[126]

Collectively, these studies utilizing genetically modified mouse models provide evidence to support the notion that the action of

TABLE 3 Reports pertaining to the effects of AR signaling in bone marrow cells on adiposity

Model	AR expressing cell	Fat and metabolic phenotype	Reference
BM transplant (ARKO)	WT or ARKO bone marrow was transplanted into WT mice and fed HFD for 16 weeks.	Visceral fat mass was increased in WT mice that received ARKO bone marrow 8 weeks post-HCD and BM transplantation. No effect was observed at 16 weeks post-HCD and BM transplantation.	157
3.6-kb α_1 1 collagen promoter AR over expression (Col3.6 AR transgenic)	AR overexpression in bone marrow progenitor cells, and their descendants (i.e., osteoblasts and osteocytes)	DHT treatment of Col3.6 AR transgenics reverses ORX-mediated adiposity.	158,159
2.3-kb type 1α1 collagen promoter AR over expression (Col2.3 AR transgenic)	AR overexpression in mature and mineralizing osteoblasts and osteocytes.	No difference in adiposity.	125,141
PC-AR Gene Replacement mice	Expression of the AR in BMPCs$^{Col3.6}$ while it is deleted in all other tissues. Generated by breeding Global-ARKO mice[145] with Col3.6 AR transgenics[159]	Expression of the AR in BMPCs on a global ARKO background results in complete attenuation of the increased fat mass of global ARKOs.	126
Monocyte/macrophage specific ARKO	Deletion of the AR in monocytes and macrophages. Generated by breeding floxed AR and Lyz2-Cre[160] mice.	No effect on adiposity.	160
AR- null BMPCs	Bone marrow progenitor cells isolated from Global-ARKOs[161]	Loss of the AR in BMPCs promoted adipogenesis and inhibited osteogenesis.	162

testosterone to negatively regulate fat mass, is at least in part, mediated directly via the AR. While the current data do not support the adipocyte or myocyte as the target cells for this AR action, BMPCs appear to be a strong candidate for further study.

While our discussion on the metabolic syndrome is focused on AR action, it is important to note that, in men, the presence of the metabolic syndrome is associated with many factors, including but not limited to age, marital status, recent paternity, and lifestyle factors (e.g., sedentary behavior). Of note in men, such factors are also associated with circulating testosterone concentrations,[167] hence intertwining the metabolic syndrome and serum testosterone in complex ways, making the disentanglement of pathogenic links between circulating testosterone and the metabolic syndrome a complex endeavor.

2.4 | 5 α reductase and dihydrotestosterone (DHT)

5 α reductase (5αR) is the enzyme which converts testosterone to DHT, a more potent, non aromatizable, androgen that regulates the formation of the external male genitalia and the prostate.[168] 5αR and DHT are integral to AR signaling but clinical data suggest that 5αR and DHT are not strongly associated with the regulation of fat mass. This is evidenced by the absence of weight gain in patients with prostate cancer treated with the 5αR inhibitor, finasteride.[169] Moreover, in a mechanistic RCT in healthy men, the fat-reducing effects of testosterone treatment were not altered by co-administration of the 5αR inhibitor dutasteride, implying that the testosterone-mediated reduction in fat mass does not require its reduction to DHT with the caveat that the RCT may not have been sufficiently powered to make this conclusion.[170,171] In a separate study, Juang et al. abrogated endogenous sex steroid production through the GnRH agonist acycline, in healthy men and randomized them to three treatment groups or a fourth placebo group. The three treatment arms were testosterone add-back only, testosterone add-back combined with dutasteride (to suppress DHT), and testosterone add-back combined with the aromatase inhibitor (AI) anastrozole (to suppress E2). As expected, patients treated with testosterone exhibited significant reductions in fat mass. Inhibition of aromatase abrogated these effects but consistent with the previous findings of Bhasin et al.,[170] 5αR inhibition did not alter the effects of testosterone.[172] Taken together, this evidence suggests that while DHT does not play role in the fat reducing effects of testosterone, the fat reducing effects of testosterone may require its aromatization to E2 (see Section 2.5). Conversely, some evidence points to a role for DHT in regulating fat mass.[173] Idan et al. reported in a randomized, placebo controlled trial of 114 older men that DHT treatment over 2 years increased lean mass but decreased fat mass, akin to the effects of testosterone.[174] Of note, DHT treatment was associated with reduced circulating E2, implying that there was no confounding effect of increased E2 on fat mass, but rather, the effects were directly related to DHT.

Overall, the evidence suggests that 5αR and by this extension, DHT, is less significant in regulating fat mass than testosterone, and that the fat reducing effects of testosterone may not be exclusively mediated through the AR. One possible alternative mechanism inferred by the work of Juang and Finkelstein could be, at least in men, the conversion of testosterone to E2 (see Section 2.5).

2.4.1 | 5 α reductase KO mice and alternative murine models

There are a handful of studies investigating the role of 5αR and DHT in the regulation of adipose tissue in murine models with largely incongruent results. Sato et al. report a reduction of subcutaneous fat mass in male mice treated with DHT.[139] More recently, Sebo et al. demonstrated a decrease in subcutaneous fat following DHT treatment in orchidectomized mice fed a HFD, although to a lesser extent than observed with testosterone,[106] and Kim et al. reported no effect of DHT on overall fat mass in HFD fed, chemically castrated mice.[175] There have been also several reports of 5αR type 1 KO mice with no reports of altered fat[176] including in gonadal depots.[177] The only piece of data contradictory to this was reported by Movérare-Skrtic et al., who reported in male orchidectomized mice treated with DHT for 5 weeks has been shown to increase gonadal and retroperitoneal fat mass.[178] However, interestingly, the authors report no statistically significant changes in retroperitoneal or gonadal fat mass in ORX only mice. Taken together these data suggest that while DHT may be able to negatively modulate fat mass, its contribution is not as marked as testosterone and may be restricted to subcutaneous depots.

2.5 | Estradiol, aromatase, and the estrogen receptor

There is evidence from both human and pre-clinical studies suggesting that the fat reducing effects of testosterone are, at least in part, dependent on its aromatization to E2. As the role of E2 as a male hormone has been reviewed extensively elsewhere,[71,179] below we summarize here the key role of testosterone derived E2 in regulating fat mass.

2.5.1 | Clinical evidence of the role of estradiol and aromatase mediated reduction of fat mass

An important role for E2 in limiting fat mass in men is supported by observations that men with inactivating mutations in the CYP19 gene which encodes aromatase, and men with inactivating mutations of the ERα have increased BMI and abdominal adipose tissue.[71,180] Mechanistic studies in men where testosterone is administrated concomitantly with an AI,[172,180–183] suggest that the fat reducing effects of testosterone are at least in part dependent on its aromatization to E2.

Upon appraisal of the literature as well as data from other reviews,[71,179] we conclude that aromatization of testosterone to E2 is required to mediate at least some of the fat reducing effects of

testosterone. However, studies using AI have inferred the role of E2 by reducing its serum concentrations, and no study in men to date has assessed the direct effects of E2 in the absence of T.

2.5.2 | Preclinical evidence of estradiol and aromatase regulation of fat mass

Preclinical models are useful for dissecting the role of E2 in mediating the actions of testosterone on fat mass. Male aromatase KO mice have increased adiposity compared with controls despite having elevated circulating levels of testosterone due to the lack of negative feedback of E2 on the HPT axis,[106,184–187] analogous to men with aromatase deficiency. In one report, male aromatase KO mice exhibited increased gonadal adipose tissue which was ameliorated by E2 treatment.[188] Consistent with these findings, treatment of intact mice with the aromatase inhibitor, letrozole, was shown to increase fat mass compared with vehicle-treated mice[106] and the administration of E2 to castrated mice fed a HFD was effective in decreasing diet-induced weight gain.[106] These data support the notion that in addition to the action of testosterone directly via the AR to decrease fat mass, testosterone can also exert these effects following conversion to E2 and action via the ER. Data generated with cell-specific overexpression or deficiency of aromatase is somewhat contradictory. Bone marrow transplantation from aromatase deficient mice into irradiated wild type mice results in a small, but statically significant increase in fat mass at 8 weeks post-transplantation that was no longer evident by 16 weeks.[189] Male mice that overexpress aromatase specifically in white adipose tissue have decreased subcutaneous and gonadal fat mass, but somewhat unexpectedly have increased retroperitoneal fat mass.[190] It is difficult to consolidate the discrepancy between cell-specific and whole body aromatase knockout data; however, we may speculate, due to the wide spread expression of aromatase,[191] that the specific cells salient to modulating the effect of aromatase on fat mass are yet to be discovered.

2.5.3 | Clinical evidence of estrogen receptor mediated signaling regulating fat mass

Estrogen receptors (ER) are expressed broadly in both men and women.[71,192] There are two ER subtypes, ER α and ER β, cytosolically located nuclear transcription factor receptors that signal via DNA-binding-dependent signaling pathways. A third, more recently characterized G-protein coupled ER, which is localized in the membrane and signals via canonical G protein coupled receptor signaling pathways, provides another avenue of ER mediated signaling.[193] The role of estrogens in regulating body fat distribution has been reviewed in detail elsewhere[194,195] but of specific interest to this review is the direct contribution of ER signaling in testosterone-mediated fat loss.

To date, only two men with mutations in the estrogen receptor gene (ESR) 1 which encodes ER α have been reported. One patient had a BMI in the obese range of 30 kg/m^2 and clinical evidence of insulin resistance,[196] although fat mass was not reported. This phenotype resembles that of men with inactivating mutations in the aromatase gene.[180] The second patient had a BMI of 23.7 kg/m^2, but also had low serum testosterone due to cryptorchidism.[197] Overall, the data from these rare case reports are consistent with the notion that the lifelong absence of E2 signaling in men, via ER alpha may limit fat mass accumulation and promote insulin resistance. Of note, men with inactivating mutations in the ESR 2 gene encoding ER β have not been, to our knowledge, reported.

There are currently no definitive mechanistic studies that precisely quantify the contribution of ER signaling in testosterone-mediated fat loss. This may be in part attributed to the lack of appropriate pharmacological compounds available that specifically bind one of the three ER subtypes. In an optimal situation, complete co-administration of a GnRH agonist (to achieve confounding suppression of endogenous testicular sex steroid production) and of an ER receptor specific antagonist would allow the dissection of the role of specific ER receptors in the regulation of fat mass. However, some mechanistic studies have been performed that yield some evidence for a role of estradiol signaling in regulating fat mass by utilizing two classes of compounds; aromatase inhibitors and Selective Estrogen Receptor Modulators (SERMS). Aromatase inhibitors such as anastrozole have been reported to increase fat loss when combined with weight loss programs in men affected by obesity[198] and in a RCT of older men with hypogonadism.[199] Of note, these findings which imply that inhibition of E2 promotes fat loss are contrary to Finkelstein's work[181] reporting that E2 is required to mediate the fat reducing action of testosterone. These differences could be partially explained by the differences in age and baseline body composition of the participants in the three trials. Compounds such as clomiphene and tamoxifen are SERMS and act as mixed agonist-antagonists of the ER depending on the tissue specific expression and subtype specific expression of the ER.[200] It is important to note however, that SERMs and aromatase inhibitors, via diminishing estradiol mediated negative feedback on GnRH and gonadotrophin secretion, can increase serum testosterone concentrations thereby confounding interpretation of data.[201] The few studies investigating the use of clomiphene citrate to treat adult men with overweight/obesity, have reported no[202] to moderate[203] reductions in fat mass. Thus, the clinical evidence to date does not provide a conclusive picture on the role of E2 in the regulation of fat mass. Evidence attempting to decipher the role of ER signaling in testosterone mediated fat reductions has also arisen from pre-clinical models.

2.5.4 | Pre-clinical evidence of estrogen receptor mediated signaling regulating fat mass

There are numerous animal models that modulate the ER signaling pathway. These are predominantly receptor KO models and have provided insight into the role of ER signaling in the regulation of fat mass. Male ERα KO mice have increased fat mass[204–207]; while

in contrast, ER β KO mice exhibit no fat phenotype,[207–209] suggesting that ERα but not ER β regulates fat mass. However, it is important to note, that there is one report of adipocyte-specific knock down of the ERα using siRNA that had no effect on fat mass in male mice.[210] Several additional cell specific ERα KO mice have been generated including osteocytes[211] and hepatocytes[212] that show no change in fat phenotype.

Despite the absence of any reported changes in fat deposition in global ERβ KO mice, agonistic ERβ-selective ligands have been reported to mitigate diet-induced obesity in male mice.[213] Activation of ERβ using 4-(2-(3-5-dimethylisoxazol-4-yl)-1*H*-indol-3yl) phenol (DIP) can alter fat deposition in male mice to a female deposition.[214] In addition, strong interactions between E2 and leptin signaling have been reported in male rats[179] indicating that ER signaling has the potential to also modulate fat mass through indirect mechanisms such as decreasing satiety. In summary, these data suggest that activation of ERα may play a role in the regulation of fat mass in males, but further study is required to ascertain the contribution of the fat reducing effect ERβ activation and the mechanisms by which it exerts these effects. Estradiol has been reported to regulate lipid and glucose metabolism[210,215,216] representing potential mechanisms.

2.6 | Sex hormone binding globulin (SHBG)

Testosterone is present in plasma in a free form and a bound form. Bound testosterone is predominantly bound to the sex hormone binding globulin (SHBG) and albumin. SHBG binds testosterone and DHT with high affinity and E2 with a comparatively lower affinity.[217] Of note, SHBG is inversely associated in men with obesity,[64,218] however, whether SHBG contributes to the pathogenesis of obesity in men is not known.

Androgen binding protein (ABP) is synthesized by Sertoli cells of the testis in rodents and humans and has a similar amino acid structure to SHBG, but differs in carbohydrate composition.[219] While ABP has been shown to regulate the accumulation and bioavailability of testosterone within the seminiferous tubular epithelium,[220,221] there is, to our knowledge, no evidence of association of ABP with obesity or fat mass.

2.6.1 | Clinical evidence of SHBG contribution to testosterone, and regulated fat reduction

Obesity has been reported to be associated with lower circulating levels of SHBG.[64,222] SHBG is increased by resistance training with concomitant increases in lean body mass and reductions in total and trunk fat mass.[223] Additionally, bariatric surgery has been reported to reverse reduced testosterone and SHBG concentrations in men with obesity.[224] In congruence with this, the reduction of visceral and subcutaneous fat mass through the use of lifestyle intervention and metformin has been reported to increase SHBG levels.[225] This infers there is an association between SHBG and obesity, but whether this is causal, due to reverse causality or merely reflects in-common risk factors is not known. Pre-clinical models have provided more evidence in this regard.

2.6.2 | Pre-clinical evidence of a role for SHBGs in testosterone-mediated fat reduction

As hepatic SHBG is not expressed in rodent models,[226] pre-clinical rodent models have utilized genetic expression of human SHBG[227] in order to study its role in mediating the action of testosterone to regulate fat mass. One such example is a mouse model that over-expresses human SHBG on the db/db mouse model of obesity (leptin KO model). db/db mice over-expressing SHBG were less obese than control db/db mice expressing normal levels of SHBG[228] consistent with observations in humans[64] indicating that SHBG is inversely associated with obesity. This same model has been used to demonstrate the importance of SHBG in regulating sex steroid activity[226] and interestingly, may protect against HFD induced obesity through the induction of lipolysis in white adipose tissue,[229] though this finding is contradicted elsewhere.[230] Given these contradictory findings combined with the use of over-expression models with supraphysiological expression of SHBG, it is not possible to ascertain whether SHBG has a direct role in the regulation of fat mass, an indirect role via modulation of circulating sex steroid concentrations, or whether changes in circulating SHBG are simply a marker of adiposity.

3 | AR-REGULATED PATHWAYS MAY BE AMENABLE FOR THERAPEUTIC TARGETING—LIMITATIONS AND FUTURE DIRECTIONS

Obesity is a debilitating disease with numerous co-morbidities that confers a significant socioeconomic burden. Obesity's wide, growing prevalence and recalcitrance to treatment makes finding more effective treatments of immediate importance. There are several novel treatments being developed that are reviewed elsewhere[231] and exhibit promise; however, it is of benefit to generate a suite of anti-obesity compounds that may enable specific obesity therapies. Testosterone has been studied as a potential therapy for hypogonadism related obesity and has been reported to have moderate efficacy.[74]

Understanding how molecular signaling pathways lead to physiological or pathophysiological changes has long been a key way of identifying therapies for diseases including cancer[232,233] and diabetes. Alternative therapies that signal through the AR pathways to reduce fat mass without masculinizing side effects are a promising therapeutic avenue.[234]

3.1 | Current limitations to using the AR as a therapeutic target for obesity

There are several limitations that prevent targeting the AR for obesity. These can be broadly grouped into two categories: (1) understanding of the mechanisms of fat loss and (2) generation of specific targeting compounds.

3.1.1 | Understanding AR signaling mechanisms to reduce fat mass

A mechanistic understanding of how androgens regulate body composition has long been sought after to enable more efficacious therapies.[166] Current evidence suggests that the fat sparing effects of testosterone may be mediated through a variety of cells other than adipocytes,[150] including muscle cells.[152,153,235] In addition, more recent evidence discussed in this review suggests that androgen action via the AR in BMPCs decreases fat mass,[126,166,189] is an exciting avenue of research.

3.1.2 | Undiscovered osteokines, and adipokines released from the bone

One of the unresolved questions is whether AR signaling modulates body composition via direct effects, that is, tissue specific (autocrine or paracrine) AR signaling, and/or via indirect endocrine effects, that is, via stimulating the secretion of yet to be identified circulating effectors. It is well understood that the bone,[165] muscle[236] and adipose tissues[237] secrete numerous cytokines, some of which represent an unexamined source of potential novel therapeutic targets. Additionally BMPCs have also been reported to secrete factors and regulate metabolic function both in a paracrine and endocrine capacity.[238,239] Testosterone has been reported to regulate the secretion of metabolic factors such as adiponectin[240] and leptin.[241] Therefore, it is conceivable that that the AR may regulate the secretion of novel yet to be discovered factors, which in turn may decrease fat mass. Thus, it is possible that some of these novel, or yet to be discovered secreted factors may form the basis of new treatments.

This notion of novel inter-cellular communication molecules forming the basis of novel therapeutics have been previously reported.[242] Hormones were identified and subsequently leveraged for use as therapeutics throughout the 20th century but it is only in more recent times that numerous families of secreted signaling molecules bearing the suffix "-kines" such as myokines,[243] osteokines, adipokines,[244] and hepatokines[245] have been identified.[242] The first identified adipokine that was thought to have value as a therapeutic was leptin,[246] but leptin therapy alone has failed as a therapy for obesity. Since then, numerous other signaling molecules have been identified but have yet to yield results,[242] suggesting there may be other opportunities that remain to be discovered.

3.1.3 | Compounds that leverage unique AR signaling mechanisms

The AR signaling pathway elicits its biological effects through both DNA-binding-dependent and non-DNA-binding-dependent pathways[32] which may be activated by either cytosolically located AR or membrane localized AR[46] as well as other membrane localized receptors.[35] This offers opportunities to generate specific novel compounds that activate desired pathways. One such example of this was the recently developed testosterone loaded monosialoganglioside micelles, which were able to bypass the effects of membrane-initiated signaling to target DNA binding-dependent signaling exclusively by the micelle directly delivering testosterone to the cytoplasm. This represents an exciting avenue for enabling novel therapeutics[247] but also requires a clearer understanding of the contribution of DNA binding- and non-DNA binding- dependent AR signaling to the regulation of fat mass.

A class of compounds termed selective androgen receptor modulators (SARMs)[248] present another potential opportunity to specifically activate the AR pathways responsible for regulating fat mass. A better understanding of the mechanisms by which SARMs exhibit tissue selectivity would greatly benefit the development of novel compounds. Putative mechanisms of SARM selectivity include tissue specific enzymes, modulated recruitment of coregulators and activation of unique subcellular signaling cascades are some of the putative mechanisms of SARM selectivity,[249] but more research is required to understand these mechanisms and then leverage these unique features to generative more efficacious therapeutics. Generating SARMs that exclusively target the AR mediated mechanisms of fat reduction may hold an alternative approach to treating obesity. However, SARMs have a number of potential limitations. Considering the work of Finkelstein et al.[181] demonstrating the importance of the aromatization of testosterone to estradiol and ER signaling in the reduction of testosterone-mediated fat mass, SARMs may be less potent in fat mass reduction compared with testosterone due to their non-aromatizable nature. Furthermore, the utilization of SARMs as therapeutics opens several important questions regarding the effect of SARMs on physiological parameters such as bone health and fertility. However, as highlighted in this review, there are important knowledge gaps with regards to the mechanism by which androgens regulate fat mass and more research is needed in order to inform the utility of targeting the AR signaling pathway as a treatment for obesity.

4 | CONCLUSION

It is apparent that a two-pronged approach is required to enable the targeting of unique AR signaling pathways, that is understanding the signaling mechanisms that traditional AR agonists such as testosterone and DHT utilize to reduce fat mass or elicit other positive effects, as well as developing novel compounds that can target these molecular processes with minimal negative side effects.

Obesity is a multifactorial disease[250] that requires novel therapies in conjunction with current lifestyle and pharmacological interventions in order to be effectively treated. In this review we have discussed the importance of AR signaling in the regulation of fat mass and highlight the lack of research into this molecular pathway. By investigating AR signaling pathways that reduce fat mass and identifying novel therapeutic targets to leverage this pathway, we may ultimately be able to offer new treatments for this debilitating disease and reduce the immense burden placed on society. This review has focused on males, but such novel therapies may also be of value to females affected by obesity. However, as highlighted in this review, there are important knowledge gaps with regards to the mechanism by which androgens regulate fat mass and more research is needed in order to inform the utility of targeting the AR signaling pathway as a treatment for obesity.

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