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Review

The Role of Physiological Androgen Receptor Signaling in Female Glucose Metabolism: Potential as a Protective Factor

Takahiro Tsutsumi[1,†], Kyoichiro Tsuchiya[1,*,†]

[1]Department of Diabetes and Endocrinology, Graduate School of Interdisciplinary Research, Faculty of Medicine, University of Yamanashi, 409-3898 Chuo-shi, Yamanashi, Japan

*Correspondence: tsuchiyak@yamanashi.ac.jp (Kyoichiro Tsuchiya)

[†]These authors contributed equally.

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Abstract

The androgen receptor (AR), beyond its classical roles in male sexual function and muscle maintenance, has emerged as a pivotal regulator of metabolic health. In men, age- or hypogonadism-related androgen decline is strongly associated with an increased risk of type 2 diabetes and impaired glucose tolerance, underscoring the protective role of AR signaling in glucose homeostasis. Conversely, its physiological significance in women remains largely unexplored, as clinical and basic research has predominantly focused on pathological hyperandrogenism, such as polycystic ovary syndrome (PCOS). This review delineates the genomic and non-genomic molecular mechanisms of AR action and synthesizes evidence from male genetically modified mouse models and cellular studies to clarify its role across key metabolic tissues, including skeletal muscle, liver, pancreatic β-cells, adipose tissue, and the central nervous system. Based on these insights, we hypothesize that physiological AR signaling exerts beneficial metabolic effects in women, whereas adverse metabolic outcomes are primarily associated with supraphysiological AR activation. Finally, we highlight key knowledge gaps and propose future directions to validate this hypothesis, with the goal of establishing a novel conceptual framework for understanding female metabolic homeostasis and informing sex-specific therapeutic strategies.

Keywords: androgen receptor (AR); AR signaling; glucose metabolism; women's health; physiological androgen

1. Introduction

The androgen receptor (AR) has gained increasing attention as a molecular target in the pathophysiology of metabolic diseases, which represent a major global health challenge, extending beyond its classical role as a nuclear receptor that regulates male sexual function and muscle mass maintenance [1].

In men, both hypogonadism and age-related declines in androgen levels exhibit a strong association with visceral fat accumulation, hepatic steatosis, impaired glucose tolerance, and an elevated risk of type 2 diabetes (T2D). Importantly, evidence indicates a bidirectional relationship between androgens and glucose metabolism: prolonged hyperglycemia and severe insulin resistance can impair the synthesis and secretion of testosterone [2,3], whereas testosterone levels are believed to exacerbate insulin resistance and may even contribute to the development of diabetes [4]. Collectively, these findings suggest that AR signaling plays a protective role in systemic glucose metabolism [5].

In women, the role of AR signaling in glucose metabolism remains controversial, as most evidence derives from hyperandrogenic contexts rather than physiological conditions. Most available clinical data originate from cohorts with androgen excess, such as women with polycystic ovary syndrome (PCOS) or severe obesity, which consistently demonstrate adverse metabolic effects [6,7]. This pathological state should be clearly distinguished from healthy women with physiological androgen levels, where evidence remains limited [6,7]. Conversely, studies in male animal models and *in vitro* experiments have demonstrated that physiological androgen concentrations, acting through AR signaling, confer beneficial effects on glucose metabolism [8,9,10]. These effects include suppression of adipogenesis, enhancement of insulin sensitivity, and preservation of pancreatic β-cell function [8,10,11]. This disparity underscores the urgent need to elucidate the physiological role of AR signaling in female glucose metabolism [12].

It is crucial to consider that, similar to thyroid hormones, the metabolic effects of androgens may be concentration-dependent, differing significantly between physiological and supraphysiological levels [13,14]. Furthermore, given that androgen levels decline with age in women and that the prevalence of impaired glucose tolerance and T2D concomitantly rises with aging [12,15], it is biologically plausible that not excessive, but physiological AR signaling may also serve a protective function against metabolic dysfunction in women.

This review aims to provide a comprehensive and novel perspective on the molecular mechanisms underlying AR-mediated metabolic regulation. We first delineate

Table 1. Androgen production pathways in women.

Source/Tissue	Contribution to serum testosterone	Primary hormones produced
Ovaries	~25%	Testosterone, Androstenedione
Adrenal glands	~25%	DHEA/DHEA-S, Androstenedione
Peripheral tissues	~50%	Testosterone, DHT

Abbreviations: DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone.

the distinct molecular mechanisms of classical genomic and rapid non-genomic signaling. Subsequently, we will synthesize evidence from genetically modified animal models and cellular studies, focusing on AR actions across key metabolic organs—skeletal muscle, liver, pancreatic β-cells, adipose tissue, and the nervous system—that are intricately involved in glucose metabolism. Finally, we integrate these insights to reassess the physiological role of AR signaling in female glucose metabolism and highlight essential future research directions, offering novel, evidence-based insights relevant to the potential clinical application of testosterone replacement therapy in women and to the development of strategies for preventing metabolic diseases in the aging female population.

2. Endogenous Androgens and Their Physiological Levels in Women

Before discussing the molecular pathways, it is essential to define the endogenous androgens and their physiological context in females. The primary circulating androgens include testosterone, dihydrotestosterone (DHT), and their precursors, dehydroepiandrosterone (DHEA) and androstenedione. In reproductive-aged women, approximately 50% of circulating testosterone is secreted directly by the ovaries and adrenal glands, while the remaining 50% is derived from the peripheral conversion of these precursors [12]. DHT, the most potent androgen, is primarily generated in target tissues through the action of 5α-reductase on testosterone [16] (Table 1).

In this review, we define "physiological" androgen concentrations as the normal endogenous range observed in healthy women across different life stages. Typical physiological levels of total testosterone range from 0.5 to 2.4 nmol/L in premenopausal women, declining significantly with age to approximately 0.2–1.4 nmol/L after natural menopause [17,18]. In contrast, "supraphysiological" concentrations indicate levels exceeding these ranges, typically resulting from exogenous administration or pathological conditions such as PCOS.

Physiological androgen concentrations in women are significantly lower than in men, being approximately one-tenth to one-twentieth of male levels, and exhibit a distinct lifelong trajectory. Peak levels are typically reached during the 20s, followed by a steady age-related decline [12]. Importantly, this decline begins well before the onset of menopause; by the time a woman reaches her 50s, circulating testosterone levels are approximately half of those observed in her 20s [17,18]. Crucially, the total amount of testosterone remains the most abundant sex steroid in women, with circulating testosterone levels being 5 to 50 times higher than those of estradiol (E2) throughout their lifespan [12].

The menopause transition itself is characterized by a dramatic drop in estrogen due to follicular depletion; however, ovarian androgen production can persist into the postmenopausal years, albeit at reduced levels. Nevertheless, the cumulative effect of aging and the loss of adrenal precursors leads to a state of relative androgen deficiency in many elderly women [17]. This age-related decline coincides with a rising incidence of metabolic syndrome and type 2 diabetes [12,15], providing a clinical rationale for investigating the protective role of AR signaling within these declining physiological ranges.

It is essential to distinguish "physiological" concentrations—the endogenous range found in healthy women—from "supraphysiological" levels, which surpass these baseline values due to exogenous treatment or underlying conditions such as PCOS.

3. Molecular Basis of Androgen Action Mechanisms: Genomic and Non-Genomic Signaling

AR plays a central role in regulating cellular functions within metabolically relevant organs, including skeletal muscle, adipose tissue, and the liver [1,8]. Although AR has long been characterized as a classical nuclear receptor mediating genomic actions, androgens also trigger rapid non-genomic signaling through membrane-associated mechanisms, which are increasingly recognized as physiologically relevant [19,20,21]. This section delineates the molecular mechanisms underlying the two principal modes of androgen action at the cellular level: genomic and non-genomic signaling (Fig. 1).

3.1 The Genomic Signaling Pathway

AR is a nuclear receptor belonging to the steroid hormone receptor superfamily, activated upon binding to androgens such as testosterone and DHT. Upon activation, AR dimerizes and translocates to the nucleus, where it acts as a transcription factor [16].

(1) DNA Binding: The AR dimer recognizes and binds to specific DNA sequences, known as Androgen Re-

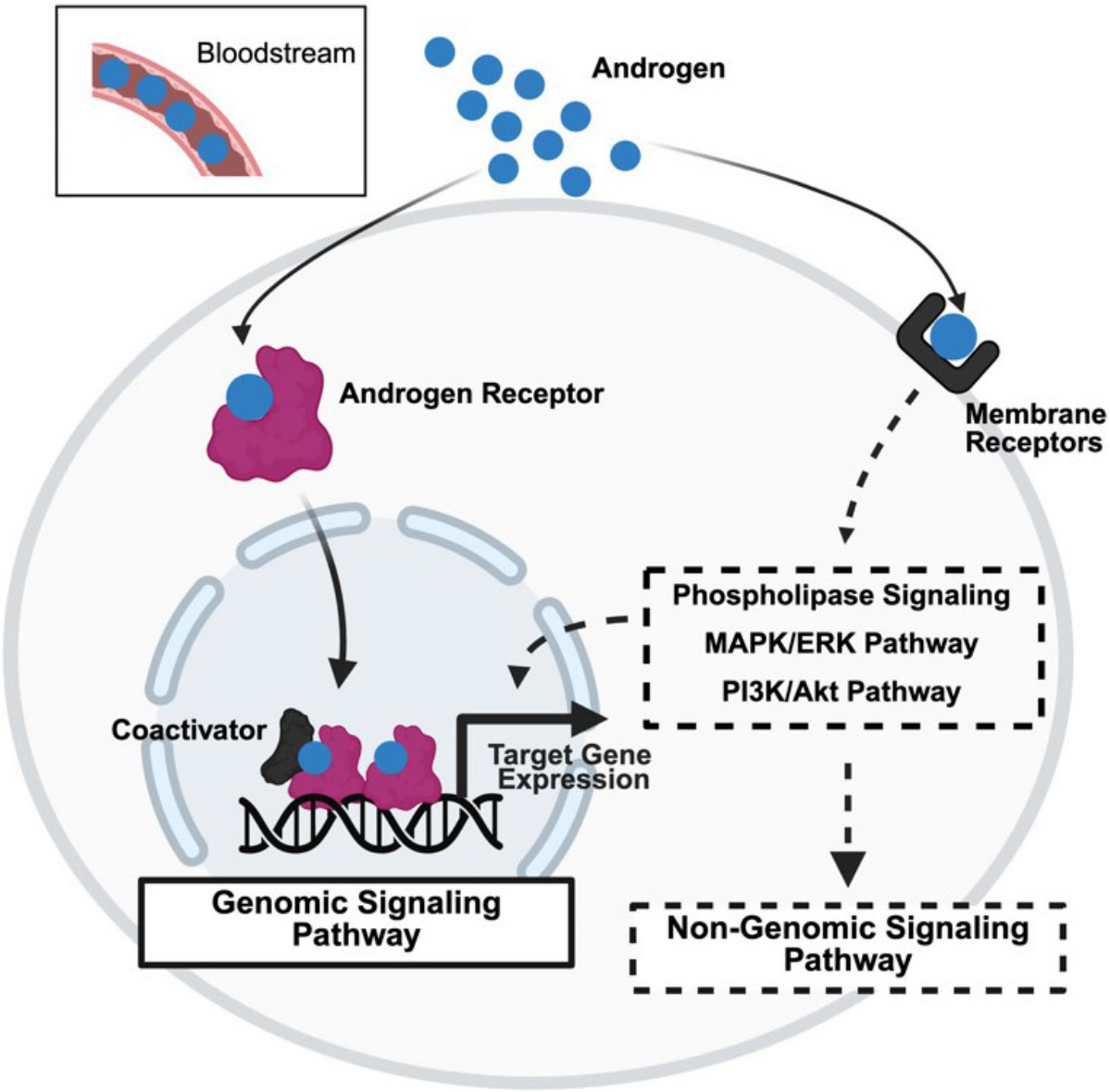

Fig. 1. Molecular mechanisms of androgen receptor signaling: genomic and non-genomic signaling pathways. This figure illustrates the two principal mechanisms of androgen receptor (AR) signaling. In the genomic pathway, androgens bind to AR, which translocates to the nucleus, recruits coactivators, and regulates target gene expression. In contrast, the non-genomic pathway involves membrane-associated receptors that rapidly activate intracellular signaling cascades, including phospholipase signaling, MAPK/ERK, and PI3K/Akt pathways. These rapid actions occur independently of direct DNA binding and contribute to diverse physiological processes such as glucose metabolism, cell survival, and muscle contraction. Abbreviations: AR, Androgen Receptor; MAPK, Mitogen-Activated Protein Kinase; ERK, Extracellular Signal-Regulated Kinase; PI3K, Phosphoinositide 3-Kinase; Akt, Protein Kinase B. Created in BioRender. TSUTSUMI, T. (2026) https://BioRender.com/xzsz4pq.

sponse Elements (AREs), located within the promoter regions of target genes [16,22,23,24].

(2) Transcription Complex Formation: Upon binding to the response element, co-regulators (coactivators and corepressors) are recruited, forming the AR complex. These co-regulators modulate chromatin structure through histone-modifying enzymes, including histone acetyltransferases and methyltransferases [22].

(3) Transcriptional Regulation: Epigenetic modifications, particularly the acetylation and methylation of histone H3 lysine residues, precisely control the transcriptional activity of target genes by adjusting the accessibility of the AR complex (i.e., chromatin occupancy and looping) to the target gene [22,24].

Recent genomic studies have revealed that AR can also bind to non-ARE or non-classical DNA sequences, ex-

hibiting tissue- or disease-specific transcriptional activity that is strongly dependent on other transcription factors and the genomic environment [25,26]. Thus, while ARE binding provides the foundation, AR utilizes complex formation with other factors for flexible and diverse mechanisms of action.

3.2 The Non-Genomic Signaling Pathway via Membrane Receptors

In addition to its classical genomic actions, androgens can trigger rapid non-genomic signaling within seconds to minutes through membrane-associated mechanisms, without direct DNA binding [16,19]. Several molecules located at or near the cell membrane have been identified that bind to androgens and exert physiological actions through rapid signaling pathways. Although the precise molecular identity and relative contribution of these mechanisms remain under investigation, the following pathways have been reported.

(1) The conventional nuclear AR is localized and functional at the membrane due to lipid modifications such as palmitoylation [20,27].

(2) Androgens can activate membrane signaling through GPCRs such as GPR133 (ADGRD1), which function independently of the classical AR [28].

(3) Beyond the classical nuclear AR, non-genomic signaling can be rapidly initiated by androgens binding to alternative membrane targets, including the transporter ZIP9 and the ion channel TRPM8 [29,30].

These membrane-associated androgen-binding proteins rapidly activate key intracellular signaling pathways. Reported pathways include Mitogen-Activated Protein Kinase (MAPK)/Extracellular Signal-Regulated Kinase (ERK) (cell proliferation and differentiation), Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (Akt) (cell survival and glucose metabolism), and cyclic adenosine monophosphate (cAMP)/Protein Kinase A (PKA) and Ca^{2+} signaling (metabolic regulation, muscle contraction, and secretory responses) [27,28,30,31].

4. Androgen Receptor Action in Individual Organs

4.1 Skeletal Muscle

Skeletal muscle is the principal insulin-sensitive tissue responsible for whole-body glucose uptake, and its maintenance is essential for systemic glucose homeostasis. Loss of skeletal muscle mass directly induces insulin resistance and is recognized as a major pathophysiological factor that increases the risk of developing and worsening T2D [32].

In adult males, androgens exert potent anabolic effects, consistently reported to increase skeletal muscle mass (lean body mass) and enhance maximal muscle strength primarily by promoting muscle protein synthesis [33,34]. Consequently, skeletal muscle has long been a major subject in the study of AR action. This section will summarize recent research focusing on elucidating the molecular mechanisms of AR action in skeletal muscle.

4.1.1 Investigating the Site of AR Action Using Animal Models in Males

Studies on global AR knockout (ARKO) mice have demonstrated reduced muscle weight and decreased contractility in males, indicating that AR signaling is essential for maintaining skeletal muscle [35,36]. The effects of androgens in skeletal muscle are thought to be exerted by the cooperation of multiple cell types within the muscle tissue, rather than a single cell type. To evaluate this, studies using skeletal muscle-specific AR-deficient mice have been conducted across several cell lineages.

4.1.2 Satellite Cells

Satellite cells are quiescent mononuclear cells located between the basal lamina and the sarcolemma of muscle fibers. They activate upon muscle injury, differentiate into myoblasts, and fuse with existing muscle fibers to contribute to muscle regeneration and hypertrophy. A study employing satellite cell-specific ARKO mice found no significant difference in muscle regeneration compared with controls, suggesting that satellite cells are not a critical site of AR action in muscle regeneration [37].

4.1.3 Mesenchymal Progenitor Cells (MPCs)

Research using specific ARKO mice targeting MPCs within skeletal muscle tissue confirmed that androgens promote the myogenic lineage differentiation of MPCs while simultaneously suppressing their differentiation into adipocytes (adipogenesis). The AR signaling here was suggested to contribute to increased or maintained skeletal muscle mass by acting on neighboring muscle fibers and satellite cells in an autocrine or paracrine manner via *Igf1*, thereby promoting protein synthesis and supporting the proliferation and differentiation of satellite cells [38].

4.1.4 Muscle Fibers

Initial studies using ARKO mice in both myoblasts and mature muscle fibers showed that while changes in the expression patterns of *c-myc*, *Fzd4*, and *Igf2* were observed, there was little change in the muscle mass of major limb muscles at physiological androgen concentrations. This finding was pivotal in establishing subsequent research directions, suggesting that the systemic increase in muscle mass mediated by androgens might primarily be mediated by cells outside the muscle fiber (e.g., mesenchymal progenitor cells or neural tissue) or by non-genomic AR signaling that is independent of the genomic signaling pathway [39].

A separate study administering DHT to muscle fiber-specific ARKO model mice found that while the increase in muscle mass was similar in both groups, the increase in muscle strength (grip strength) was observed only in the

control group and was absent in the ARKO group. Transcriptome analysis identified myosin light-chain kinase 4 (*Mylk4*) as a novel AR target gene. *Mylk4* was found to enhance muscle strength by phosphorylating the myofibrillar structural protein Myomesin1, thereby increasing muscle fiber stiffness and contraction efficiency [40].

Furthermore, focusing on the association between sarcopenia (age-related muscle mass and strength loss) and muscle fiber type shifting, a study using fast-twitch fiber-specific ARKO mice was reported [41]. In this model, a type shift from fast-twitch to slow-twitch fibers was observed in the soleus muscle with aging, and a decrease in hindlimb muscle mass was confirmed after middle age. Microarray and gene ontology analyses suggested that AR in fast-twitch fibers acts on gene clusters related to polyamine biosynthesis, which is crucial for cell proliferation and metabolism. This insight suggests that targeting fiber type-specific AR signaling pathways (especially polyamine biosynthesis) may be effective in developing therapeutic agents for sarcopenia. However, since this sarcopenia-like phenotype was only confirmed in male mice, the necessity for further clarification of the sex-specific mechanisms was highlighted. Another study using a different muscle fiber-specific ARKO mouse model revealed a broader role for AR, demonstrating that it coordinates the regulation of muscle energy metabolism and contraction function, not just muscle mass and strength [8]. Specifically, the male ARKO model exhibited altered expression of gene clusters related to muscle contraction (*Myh7*, *Acta1*, *Tnnt2*, *Tnni1*), glucose metabolism (*Pfkp*, *Pdk1*), fatty acid catabolism (*Cpt2*, *Acadvl*, *Bckdha*), polyamine biosynthesis (*Srm*), and antioxidation (*Nos2*). This led to the confirmation of myofibrillar structural defects, reduced glycolytic activity, insulin resistance, intracellular fatty acid accumulation, decreased polyamine synthesis, and increased ammonia and H_2O_2. This result suggests that AR action in muscle fibers is essential for maintaining not only muscle mass and strength but also overall muscle metabolic homeostasis, and is deeply involved in the pathology of metabolic diseases such as T2D.

4.1.5 Elucidating AR Action Pathways Through In Vitro Experiments

In vitro studies using L6 myoblasts and C2C12 cells have indicated that one of the major mechanisms of androgen-induced muscle hypertrophy involves the AR-mediated increase in Insulin-like Growth Factor-1 (IGF1) expression and the subsequent activation of its downstream signal, ERK1/2 activity [42]. This research also suggests that AR action is influenced by environmental factors such as mechanical stimuli (stretching) and physical load (exercise).

Another study showed that the addition of testosterone to C2C12 cells increased the nuclear localization of Nuclear Respiratory Factor-1 (NRF-1), a key transcription factor regulating mitochondrial biogenesis. This suggests that testosterone not only promotes protein synthesis (anabolic effect) but may also enhance mitochondrial function itself within muscle cells, improving muscle endurance and metabolic capacity. This finding supports the importance of AR action in treating sarcopenia and metabolic diseases [43].

4.1.6 Involvement of AR Non-Genomic Signaling Action

The non-genomic signaling actions of AR in skeletal muscle are hypothesized to include the suppression of muscle atrophy via the promotion of cell proliferation and the immediate promotion of muscle contraction mediated across the cell membrane. Analysis of human muscle biopsy samples showed increased phosphorylation of cytoskeleton proteins (filamin and paxillin) related to non-genomic signaling in samples from older individuals. This suggests an involvement in the activation of Focal Adhesion Kinase (FAK)-mediated survival/proliferation signals (Mitogen-Activated Protein Kinase (MAPK)/Extracellular Signal-Regulated Kinase (ERK)) and has been linked to the pathology of age-related muscle atrophy [44,45].

Furthermore, mechanisms have been shown where androgens rapidly increase intracellular calcium concentration and promote muscle contraction via a membrane receptor, through the activation of L-type calcium channels and release from the sarcoplasmic reticulum via the IP3 pathway [46,47,48]. However, to clarify the physiological and clinical significance of these non-genomic actions *in vivo*, it is essential to elucidate the molecules and signaling mechanisms through which AR acts on the skeletal muscle cell membrane and to validate these findings using corresponding knockout animal models.

4.1.7 Androgen Action and Skeletal Muscle in Females

Regarding androgen action and skeletal muscle in females, multiple studies have suggested that AR action may differ between sexes. Research using muscle fiber-specific ARKO mice showed that inhibition of AR signaling reduced *in vivo* glycolytic activity and accelerated T2D onset in male mice, but this effect was not observed in female mice [8]. Additionally, DHT-treated female skeletal muscle-specific ARKO mice exhibited a phenotype equivalent to that of wild-type mice [49]. This suggests the possibility that AR action is attenuated in women or is compensated for by factors such as estrogen. Given the current bias in reports towards males, detailed analysis of glucose metabolism using female skeletal muscle-specific ARKO mice (in muscle fibers, satellite cells, and MPCs) is critically important for understanding the physiological role in women.

Although data are limited, some indirect evidence has been reported in women. In females with androgen deficiency (due to hypopituitarism, oophorectomy, or natural menopause), testosterone therapy at doses restoring phys-

Table 2. Investigation of androgen receptor (AR) action sites in skeletal muscle.

Cell type	Model/Androgen	Androgen context	Phenotype	Mechanism/Role	Sex	Reference/Year
Satellite cells	Satellite cell-specific ARKO/KO	KO (AR deletion)	No difference in regeneration	AR is not essential for regeneration	Male	[37]/2020
MPCs	MPC-specific ARKO	KO (AR deletion)	Promotes myogenesis, inhibits adipogenesis	AR contributes to increased skeletal muscle mass by autocrine/paracrine via IGF1	Male	[38]/2024
Muscle fibers	Fiber-specific ARKO	KO (AR deletion)	Little change in muscle mass	Muscle gain may be mediated primarily by non-fiber or non-genomic AR actions	Male	[39]/2016
Muscle fibers	Fiber-specific ARKO + DHT	KO + Supraphysiological androgen	Strength loss	AR regulates Mylk4 and increases muscle fiber stiffness	Male	[40]/2021
Muscle fibers (fast-twitch fibers)	Fast-twitch fiber ARKO	KO (AR deletion)	Fiber type shift, mass loss	AR regulates polyamine biosynthesis AR signaling may be a therapeutic target for sarcopenia	Male	[41]/2023
Muscle fibers (female)	Fiber-specific ARKO	KO (AR deletion)	No difference	AR action may differ between sexes	Female	[8,49]/2023, 2022

Abbreviations: ARKO, androgen receptor knockout; MPC, mesenchymal progenitor cell; IGF1, Insulin-like Growth Factor-1; DHT, dihydrotestosterone; Mylk4, myosin light-chain kinase 4.

iological female concentrations increased lean body mass, including muscle mass [50,51,52]. In another study, postmenopausal women with chronic heart failure showed improvements in aerobic capacity, muscle strength, and exercise tolerance following testosterone therapy [53]. While these findings are indirect, they suggest that testosterone at physiological concentrations may exert beneficial effects on glucose metabolism in women.

4.1.8 Conclusion and Future Outlook

Collectively, studies using various ARKO male mouse models suggest that muscle fibers are likely the primary site of AR action in regulating muscle mass, strength, and metabolism. These findings imply that supraphysiological androgen levels may be required to maximize AR-mediated muscle mass gains, whereas physiological AR signaling may suffice to maintain muscle metabolic function. In particular, AR-mediated metabolic homeostasis in muscle fibers may play a protective role in systemic glucose metabolism [8,33]. Moving forward, analysis of glucose metabolism using female skeletal muscle-specific ARKO mice is strongly needed to understand the physiological role in women (Table 2, Ref. [8,37,38,39,40,41,49]).

4.2 Pancreas (β Cells)

Studies, primarily involving pancreatic β-cell-specific ARKO (βARKO) mice, have reported contrasting findings: mechanisms by which AR signaling contributes to metabolic protection in males and detrimental effects caused by hyperandrogenism in female polycystic ovary syndrome (PCOS) models.

4.2.1 Animal Experiments: Functional Analysis via Cell-Specific Male ARKO

Whole transcriptome sequencing (RNA-Seq) performed on pancreatic heads from male βARKO mice and controls identified 214 gene related to cytokine-cytokine receptor interaction, insulin signaling, and T2D [54]. The gene changes resulting from AR signaling deletion were categorized into two main groups: reduced insulin secretory capacity and decreased anti-inflammatory action.

Reduced Insulin Secretory Capacity: Increased expression of *Kcnq1* (which inhibits insulin secretion), *Nr0b2* (which impairs insulin gene transcription), and *Sostdc1* (which induces β-cell dysfunction) were confirmed upon AR deletion. These findings imply that β-cell insulin secretory capacity is reduced upon AR deletion.

Decreased Anti-inflammatory Action: Increased expression of *Fgf21*, *Il1rn*, and several guanylate-binding proteins (GBPs) that activate the inflammasome were observed, suggesting a propensity for increased inflammation upon AR deletion.

These findings suggest that male AR signaling in pancreatic β-cells is functionally important through genomic

mechanisms, regulating insulin secretion-related genes and maintaining an anti-inflammatory environment. However, identification of direct genomic binding sites remains a future challenge.

4.2.2 Maintenance of β-Cell Mass by AR Action (Male Rats)

Studies using castrated male rats suggest that AR action contributes to the maintenance of β-cell mass [55]. Castrated male mice, with cessation of testosterone supply, exhibited a reduction in total β-cell mass and impaired glucose tolerance. *In vitro* experiments using a β-cell line (INS-1 cells) showed that testosterone directly acts on cells via AR to promote cell viability. Conversely, an inverse finding also suggested that hyperglycemia promotes AR degradation. This indicates the potential for androgen to maintain β-cell mass in a healthy state and, consequently, suppress the risk of diabetes in males.

4.2.3 Non-Genomic AR Action Mechanisms

A protective mechanism where androgens amplify Glucagon-like Peptide-1 (GLP-1) action and promote insulin secretion via non-genomic effects on pancreatic β-cells has been clearly demonstrated using genetic models and molecular biological techniques [9,10]. DHT activates AR near the pancreatic β-cell membrane, forming a complex with the GLP-1 receptor (GLP-1R). This complex activates transmembrane adenylyl cyclase (tmAC), promoting the production of intracellular cAMP. Furthermore, DHT enhances mitochondrial metabolism, and the generated carbon dioxide (CO_2) activates the cytoplasmic soluble adenylyl cyclase (sAC), further stimulating cAMP production. The increased cAMP enhances glucose-stimulated insulin secretion (GSIS) via Protein Kinase A (PKA). It promotes the exocytosis of insulin granules involving actin remodeling via the FAK/SRC/PI3K/mTORC2 pathway.

4.2.4 Androgen Excess and β-Cell Dysfunction in Females

In females, particularly in the context of PCOS pathophysiology, high concentrations of androgens have been reported to exert detrimental effects on glucose metabolism [56,57,58].

A study using β-cell and mediobasal hypothalamus (MBH) neuron-specific ARKO mice demonstrated that chronic high-dose administration of DHT combined with a high-fat diet to female mice induced a T2D-like state (hyperinsulinemia, insulin resistance, pancreatic β-cell dysfunction). This abnormality was not observed in β-cell and MBH neuron-specific ARKO mice, indicating that androgen excess induces the pathology through a dual mechanism.

Activation of β-Cell AR: Leads to β-cell dysfunction via insulin hypersecretion, increased mitochondrial respiration, and damage due to oxidative stress.

Activation of Hypothalamic Neuron AR: Causes insulin resistance in peripheral tissues. This finding elucidates the mechanism by which androgen excess impairs glucose metabolism via AR signaling in female PCOS models. However, these results should not be generalized to healthy women.

4.2.5 Beneficial Effects of Testosterone on Pancreatic β-Cells in Human Females

One significant example illustrating the physiological role of testosterone in female metabolism is its intracrine conversion into active steroids within pancreatic islet β-cells [59]. Both mouse and human female β-cells express aromatase, which converts circulating testosterone into 17β-estradiol (E2), and 5α-reductase (5α-R), which converts it into DHT. This enzymatic conversion of T to E2 or DHT has been directly observed in human female islets. Importantly, this intracrine activity has been shown to enhance GSIS, suggesting a potential contribution to maintaining glucose homeostasis in women [59].

4.2.6 Conclusion and Future Outlook

The animal study results demonstrate distinct concentration-dependent effects that appear to manifest as sex-specific phenotypes. AR signaling in pancreatic β-cells exhibits a dual nature, functioning as a protective factor at physiological levels while becoming detrimental when excessive. Findings from male ARKO models—characterized by impaired insulin secretion and increased inflammation—underscore the necessity of baseline AR signaling for maintaining β-cell integrity in males. In contrast, female PCOS models demonstrate that supraphysiological androgen levels trigger oxidative stress and β-cell exhaustion. These collective findings suggest that AR signaling operates within a specific "physiological window" to optimize GSIS.

However, it is crucial to exercise caution before extrapolating these findings across sexes, as the protective role of AR signaling in the female pancreas remains only indirectly inferred. A lack of data regarding the impact of physiological androgen concentrations in females significantly limits current research. Given that the incidence of T2D increases as women age [60]—coinciding with a decline in androgen levels [12]—and considering the clinical association between low androgen levels and metabolic syndrome in women [61], it is reasonable to speculate, albeit indirectly, that a similar protective mechanism might exist in females. Nevertheless, this remains a hypothesis that lacks direct experimental evidence. Therefore, future research must urgently prioritize the use of female-specific pancreatic β-cell ARKO models without exogenous androgen administration. Such studies are essential to verify whether physiological androgens indeed exert a protective effect in women and to elucidate the underlying molecular mechanisms in a sex-specific context (Table 3, Ref. [9,10,54,56,57,58]).

Table 3. Investigation of androgen receptor (AR) action in pancreatic β-cells.

AR action	Model	Androgen context	Phenotype	Mechanism/Role	Sex	Reference/Year
Genomic	βARKO	KO (AR deletion)	↓Insulin secretion, ↑Inflammation	AR maintains β-cell function	Male	[54], 2017
Non-genomic	βARKO INS-1 832/13 cells Human islets cells C57BL/6 mouse islet cells	KO (AR deletion) Physiological androgen	↑GLP-1 action, ↑GSIS	AR-GLP-1R complex promotes insulin exocytosis	Male	[9,10]/2016, 2023
Androgen excess	DHT-treated PCOS model	Supraphysiological androgen	Hyperinsulinemia, β-cell dysfunction	Androgen excess leads to β-cell dysfunction	Female	[56,57,58]/2010, 2018

Abbreviations: βARKO, pancreatic β-cell-specific androgen receptor knockout; GLP-1, Glucagon-Like Peptide-1; GSIS, glucose-stimulated insulin secretion; GLP-1R, GLP-1 Receptor; DHT, dihydrotestosterone; PCOS, polycystic ovary syndrome; ↑, increased; ↓, decreased.

Table 4. Investigation of androgen receptor (AR) action in the liver.

AR action	Model	Androgen context	Phenotype	Mechanism/Role	Sex	Reference/Year
Genomic	Liver ARKO	KO (AR deletion)	Fatty liver, insulin resistance	AR prevents fatty acid accumulation	Male	[65]/2008
Non-canonical	AR antagonist	Pharmacological AR blockade	Lipolysis via glucagon signaling	AR-PGC-1α/ERRα complex enhances lipid breakdown in response to glucagon stimulation	Female	[67]/2025
Androgen excess	DHT-treated PCOS model	Supraphysiological androgen	DHT-induced glucose intolerance suppressed by liver AR deletion	Androgen excess induces insulin resistance	Female	[69]/2021

Abbreviations: ARKO, androgen receptor knockout; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ERRα, estrogen-related receptor alpha; DHT, dihydrotestosterone; PCOS, polycystic ovary syndrome.

4.3 Liver

The liver is a central organ regulated by insulin and glucagon, essential for maintaining systemic glucose homeostasis. Its function involves precisely regulating glucose storage and release to prevent hyperglycemia after meals and avoid hypoglycemia during fasting. Clinically, liver metabolic dysfunction is a crucial factor in the pathophysiology of T2D, profoundly impacting the overall metabolic balance [62].

Clinical evidence strongly indicates that male hypogonadism is associated with an increased prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), a term recently adopted to replace non-alcoholic fatty liver disease (NAFLD) [63]. This suggests that AR signaling in the liver may play a crucial role in maintaining glucose and lipid metabolic homeostasis, thus preventing T2D onset. This section provides a comprehensive review of the fundamental data regarding the influence of AR signaling on glucose metabolism, mediated through hepatic function.

4.3.1 Impact of Androgen Decline on Hepatic Metabolism

A decline in androgens (due to aging, hypogonadism, etc.) is clinically associated with an increased incidence of glucose metabolism disorders, often accompanied by fatty liver [63]. Evidence from castrated male mice, a model of hypogonadism, validates these clinical findings [64]. A comprehensive analysis of the liver in castrated male mice revealed an increase in hepatic inflammation despite a significant decrease in food intake. Transcriptome analysis showed increased transcription of fatty acid synthesis and fatty acid oxidation-related genes. Mass spectrometry confirmed a reduction in specific fatty acids, such as arachidonic acid, involved in inflammation and signaling. This suggests that androgen decline leads to inflammatory changes and abnormal fatty acid composition in the liver, necessitating further detailed analysis of the mechanism by which decreased AR action leads to inflammatory hepatitis.

4.3.2 AR Signaling Action: Regulation of Lipid Metabolism in Males

Studies using liver-specific ARKO male mice have been reported for many years [65]. Analysis of liver-specific ARKO male mice fed a high-fat diet confirmed the development of hepatic steatosis and insulin resistance compared with controls. Relevant genetic changes included decreased expression of PPARα, crucial for fatty acid β-oxidation, and increased expression of SREBP-1c, a key regulator of lipid synthesis. This led to the hypothesis that the increase in fatty liver was induced by reduced fatty acid β-oxidation due to decreased PPARα and increased de novo lipid synthesis, subsequently leading to insulin resistance. Thus, a major role of AR signaling action is presumed to be preventing fatty acid accumulation and maintaining normal lipid metabolism.

Furthermore, a study using liver-specific AR transgenic mice observed that AR transgenesis in male mice led to decreased hepatic gluconeogenesis, reduced blood glucose, and decreased hepatic triglyceride levels [66]. The proposed mechanism suggested that AR signaling regulates cytosolic glycerol-3-phosphate dehydrogenase (cGPDH), a key component of the glycerol phosphate shuttle, thereby reducing gluconeogenesis from glycerol.

4.3.3 Non-Canonical AR Signaling Actions and Glucagon Signaling

Non-canonical actions of hepatic AR have been shown to mediate glucagon signaling, promoting gluconeogenesis and lipid catabolism. In female mice, pharmacological inhibition of physiological AR action by enzalutamide revealed that AR interacts with the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/estrogen-related receptor alpha (ERRα) complex to enhance glucagon-stimulated lipid breakdown [67]. The energy derived from lipid catabolism was then utilized for hepatic glucose production. Interestingly, female mice exhibited approximately threefold higher hepatic AR expression compared to males, and a stronger lipolytic response to glucagon. This may be related to the higher prevalence of MASLD in males and underscores the importance of considering sex differences in AR actions [68].

4.3.4 AR Signaling and Hepatic Insulin Resistance in Females

Conversely, in female mouse hyperandrogenism models (PCOS models), DHT administration induced glucose intolerance, impaired gluconeogenesis, and insulin resistance, but these abnormalities were suppressed in liver ARKO females [69]. Similarly, in a high-fat diet model, wild-type females developed glucose intolerance, whereas its onset was suppressed in ARKO females [70]. However, the finding that ARKO females did not gain weight on the high-fat diet may influence the interpretation of these results, warranting future investigation.

4.3.5 Conclusion and Future Outlook

The liver is a key organ for precise blood glucose regulation through glycogenolysis and gluconeogenesis, and its dysfunction—particularly hepatic insulin resistance—is central to the pathophysiology of T2D. Clinical evidence strongly links hepatic lipid accumulation to insulin resistance, suggesting that AR signaling-mediated suppression of fatty liver may play an important role in T2D prevention. Findings from male ARKO models indicate that physiological testosterone levels exert a protective effect on glucose and lipid metabolism, helping to prevent hepatic steatosis and maintain insulin sensitivity. In contrast, studies using female PCOS models clearly demonstrate that excessive testosterone acts as a detrimental factor, promoting hepatic insulin resistance and metabolic dysfunction. Therefore, it is critical to distinguish between the effects of physiological androgen concentrations and hyperandrogenism on hepatic metabolism. These observations imply that while supraphysiological androgen levels are harmful, testosterone within the physiological range likely exerts protective effects in women as well. However, definitive evidence regarding the role of physiological testosterone in female hepatic metabolism remains critically lacking. Future research is urgently needed to clarify this role by employing female ARKO models under normal androgen conditions and excluding confounding factors such as obesity. Additionally, further studies should elucidate genome-wide transcriptional mechanisms, particularly investigating whether genes that promote lipid catabolism—such as PPARα—are direct AR targets (Table 4, Ref. [65,67,69]).

4.4 Adipose Tissue

Obesity, particularly excessive visceral fat accumulation, drives adipose tissue dysfunction and constitutes a major pathophysiological contributor to T2D through adipose tissue insulin resistance. When adipose tissue insulin resistance occurs, the insulin-mediated suppression of hormone-sensitive lipase fails, leading to the excessive breakdown of triglycerides (TG) and the release of free fatty acids (FFAs) into the circulation, even during fasting or between meals. These FFAs are taken up by the liver and skeletal muscle, accumulating as diacylglycerols and ceramides, which directly inhibit insulin signaling [71,72].

Furthermore, dysfunctional adipose tissue excessively secretes pro-inflammatory cytokines such as TNF-α and IL-6, while reducing the secretion of the anti-inflammatory and insulin-sensitizing adipokine, adiponectin. Immune cells, like macrophages, infiltrate the adipose tissue, initiating chronic low-grade inflammation [71]. This inflammatory signal spreads systemically, further amplifying insulin resistance in distant organs. Clinically, male hypogonadism is strongly associated with an increased risk of metabolic syndrome, characterized by increased visceral fat and systemic insulin resistance [73,74]. This section will summarize the molecular mechanisms of androgen and AR action in adipocytes and their impact on metabolism.

4.4.1 AR-Mediated Regulation of Adipocyte Differentiation

The role of AR action in adipocytes has long been investigated through cell-based experiments. Studies using C3H 10T1/2 cells demonstrated that testosterone and DHT inhibit adipocyte differentiation (adipogenesis), reducing adipocyte number and downregulating adipogenic transcription factors PPARγ and C/EBPα [75]. Furthermore, research using 3T3L1 cells reported a mechanism where the androgen-bound AR forms a complex with β-catenin and translocates to the nucleus, suppressing adipogenesis via a pathway distinct from Wnt signaling [11].

Studies using human subcutaneous fat-derived stem cells also indicated that testosterone and DHT act via AR to suppress the commitment of adipose stem cells to preadipocytes and the early stages of differentiation, thereby limiting adipocyte numbers and fat storage in subcutaneous fat [76]. These cellular findings suggest the existence of an anti-obesity effect by AR signaling, which prevents excessive expansion of adipose tissue by limiting the number of adipocytes.

4.4.2 Fat Accumulation and Insulin Resistance in AR Deficiency Models in Males

In castrated male mice and global ARKO mice, increased fat accumulation and worsening insulin resistance were observed, along with a decrease in lean mass (skeletal muscle), consistent with findings in human hypogonadism [77]. This clearly demonstrates that AR signaling acts protectively on metabolic homeostasis at a systemic level.

In adipocyte-specific ARKO male mice subjected to a high-fat diet, visceral fat mass significantly increased and systemic insulin resistance developed compared to wild-type controls. The mechanism was shown to be the suppression of retinol binding protein 4 (RBP4) mRNA expression [78]. Interestingly, no changes in total body weight or subcutaneous fat mass were observed in this model, a finding consistent with observations in other adipocyte-specific ARKO models [79]. This suggests that AR is not necessarily directly linked to systemic obesity (weight gain).

A model mouse where AR was expressed only in bone marrow mesenchymal progenitor cells showed reduced adipose tissue expansion, suggesting that AR action might be mediated by signaling at the progenitor cell stage rather than directly within the mature adipocyte [80]. This model confirmed an increase in small adipocytes, hyperadiponectinemia, and an increased glucose infusion rate during euglycemic-hyperinsulinemic clamp studies, suggesting that AR action enhances insulin sensitivity. Furthermore, rats overexpressing AR in skeletal muscle exhibited decreased gonadal fat mass compared to wild-type animals [81].

4.4.3 Androgen Excess and Adipose Tissue Changes in Females

In female mice, evidence on the effects of physiological androgen concentrations is limited, with most studies focusing on the metabolic impact of androgen excess. Research using a PCOS model showed that the transplantation of AR-unresponsive ($AR^{-/-}$) white and brown adipose tissue, in addition to DHT administration, had a protective effect against metabolic PCOS traits such as weight gain, fat accumulation, and adipocyte hypertrophy [49]. This result aligns with the clinical pathology of PCOS, where excessive androgens are implicated in metabolic dysfunction in females.

4.4.4 Conclusion and Future Outlook

Evidence from male models demonstrates that physiological testosterone exerts a protective effect on glucose metabolism by reducing fat accumulation and improving insulin sensitivity. In contrast, studies using female PCOS models clearly show that excessive testosterone acts as a detrimental factor, worsening glucose metabolism and promoting insulin resistance. These findings indirectly suggest that while supraphysiological androgen levels are harmful, testosterone within the physiological range may provide metabolic protection in women.

Cell-based experiments have confirmed that AR signaling directly inhibits adipocyte differentiation and fat accumulation. However, the absence of adipocyte-specific AR action in knockout models did not lead to increased body weight or subcutaneous fat in males. This indicates that the anti-obesity effect of AR signaling *in vivo* may not be solely attributable to direct actions on adipocytes. Instead, AR-mediated suppression of visceral fat accumulation likely involves significant indirect contributions from other organs, such as skeletal muscle, and signaling at the progenitor cell stage.

In women, physiological factors—including the synthesis of approximately 50% of circulating testosterone in peripheral tissues like adipose tissue and the observed correlation between increased fat cell mass and elevated circulating testosterone levels [12]—make it difficult for clinical studies to establish a clear causal relationship between body fat accumulation and androgen action. Definitive evidence regarding the role of physiological testosterone in female adipose tissue and systemic metabolism remains critically lacking. Future research using global and adipocyte-specific ARKO female models under normal androgen conditions is urgently needed to clarify this role (Table 5, Ref. [49,77,78,80]).

4.5 Nervous System: Metabolic Control via Activity and Feeding Regulation

Physical activity and feeding behavior are critical physiological determinants in the development of obesity and subsequent glucose metabolism disorders [82]. Clini-

Table 5. Investigation of androgen receptor (AR) action in adipose tissue.

AR action	Model	Androgen context	Phenotype	Mechanism/Role	Sex	Reference/Year
General	Systemic ARKO	KO (AR deletion)	↑Fat, ↓Lean mass	AR protects metabolic homeostasis	Male	[77]/2016
Visceral	Adipocyte ARKO	KO (AR deletion)	↑Visceral fat, insulin resistance, no change in total weight or subcutaneous fat	AR suppresses RBP4 expression and enhances insulin sensitivity	Male	[78]/2012
Precursor	AR in progenitor cells	Physiological androgen	↑Small adipocytes, ↑Adiponectin	AR enhances insulin sensitivity	Male	[80]/2018
Androgen excess	DHT-treated PCOS model	Supraphysiological androgen	↓Fat accumulation with $AR^{-/-}$ transplant	AR mediates PCOS pathology	Female	[49]/2022

Abbreviations: ARKO, androgen receptor knockout; RBP4, retinol binding protein 4; DHT, dihydrotestosterone; PCOS, polycystic ovary syndrome; ↑, increased; ↓, decreased.

cal studies have reported that testosterone replacement therapy reduces post-exercise fatigue and elevates circulating levels of the appetite-promoting hormone ghrelin, underscoring a potential link between androgens, behavior, and metabolism [83,84]. However, limitations in the detailed analysis of human neural function necessitate the use of animal models [83,84]. This section will summarize the influence of androgen signaling on activity and appetite, primarily based on studies using neuron-specific ARKO mice.

4.5.1 AR Action on Activity and Feeding in Males

In male mouse models with neuron-specific ARKO targeting the cortex, forebrain, hypothalamus, and olfactory bulb, both spontaneous and non-spontaneous physical activity decreased by up to 60%. This reduction in energy expenditure consequently promoted body fat accumulation [85]. This data provide evidence for a role of androgens via the AR in neurons to positively regulate f physical activity in male mice. A separate study demonstrated that AR signaling deficiency induces insulin resistance by upregulating hypothalamic protein tyrosine phosphatase 1b (PTP1B) expression through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [86]. This result indicates that AR action in the hypothalamus is involved in regulating energy balance (feeding and energy expenditure) and plays a role in suppressing visceral fat accumulation. Regarding short-term feeding regulation, reduced glucose utilization is known to promote feeding behavior through the activation of orexin A neurons and NPY neurons located in the lateral hypothalamus and perifornical area. Studies in castrated male rats revealed enhanced hypoglycemia-induced feeding, suggesting that endogenous androgens suppress this response and inhibit orexin A neuron activation [87]. These findings support the possibility that physiological androgen action in males controls feeding behavior via the central nervous system.

4.5.2 Androgen Excess and Hypothalamic Function in Females

Similar to other organs, studies in female neuron-specific ARKO mice have focused on the state of androgen excess (PCOS models). In DHT-administered PCOS model mice, hypothalamic inflammatory markers (NF-κB, IBA1) and food intake were markedly increased [88]. Conversely, in neuron-specific ARKO females, both inflammatory activation and hyperphagia were partially suppressed, indicating that hypothalamic dysfunction induced by androgen excess is AR-dependent.

4.5.3 Conclusion and Future Outlook

In males, AR signaling mediated by physiological testosterone concentrations appears to support glucose metabolism by reducing obesity risk through enhanced physical activity and suppressed feeding behavior. In contrast, studies in female PCOS models demonstrate that androgen excess promotes hyperphagia and induces metabolic dysfunction via hypothalamic inflammation. These findings highlight the importance of distinguishing the effects of physiological AR action from those of pathological hyperandrogenism. To clarify the role of physiological androgens in regulating activity and appetite in females, studies using hypothalamus-specific ARKO models are essential. Furthermore, investigating the relationship between circulating androgen levels, physical activity, and appetite in healthy women—and integrating these clinical observations with mechanistic research—will be critical for advancing translational insights (Table 6, Ref. [85,86,88]).

5. Conclusion and Future Research Directions

This review synthesizes findings on AR action derived from cellular experiments and ARKO mouse models and delineates directions for future research. The concept that a decline in AR signaling (androgen deficiency) in men increases the risk of metabolic syndrome—characterized

Table 6. Investigation of androgen receptor (AR) action in the nervous system.

AR action	Model	Androgen context	Phenotype	Mechanism/Role	Sex	Reference/Year
Activity	Neuron ARKO	KO (AR deletion)	↓Muscle mass and physical activity, ↑Fat	AR in neurons promotes physical activity	Male	[85]/2017
Insulin resistance	Neuron ARKO	KO (AR deletion)	↑PTP1B via NF-κB	AR suppresses hypothalamic inflammation	Male	[86]/2013
Androgen excess	DHT-treated PCOS model	Supraphysiological androgen	↑Feeding, ↑Inflammation	AR-dependent hypothalamic dysfunction	Female	[88]/2023

Abbreviations: ARKO, androgen receptor knockout; Drd1a, dopamine receptor D1 subtype; Maob, monoamine oxidase B; PTP1B, protein tyrosine phosphatase 1b; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; DHT, dihydrotestosterone; PCOS, polycystic ovary syndrome; ↑, increased; ↓, decreased.

Table 7. Impact of androgen receptor (AR) signaling on organ-specific glucose metabolism across different androgen levels (low, physiological, and high) in males and females.

Androgen level	Male	Female
Low	↓Muscle mass, ↑Insulin resistance, ↑T2D risk	Data are lacking
Physiological	Maintenance of muscle mass & strength, ↑Insulin sensitivity, ↓Hepatic Gluconeogenesis, ↓Visceral fat	Data are lacking
High	↑Muscle strength	β-cell Dysfunction, ↑Hepatic Insulin Resistance, ↑Adipocyte Hypertrophy, ↑Hypothalamic Dysregulation

This table integrates key concepts presented in this review: AR signaling exerts well-established protective effects on glucose metabolism in men, particularly under physiological androgen concentrations, by maintaining muscle mass, improving insulin sensitivity, and suppressing hepatic gluconeogenesis. In contrast, the impact of physiological or low androgen levels on female glucose metabolism remains largely unknown, as most available data derive from hyperandrogenic states such as PCOS. The table highlights concentration-dependent and sex-specific differences, emphasizing the urgent need for research to clarify AR's role in women under normal androgen conditions. Abbreviations: PCOS, polycystic ovary syndrome; T2D, type 2 diabetes; ↑, increased; ↓, decreased.

by skeletal muscle loss, visceral obesity, hepatic steatosis, and worsening insulin resistance—is now well established. However, the available data concerning women remain heavily skewed toward models of androgen excess (e.g., polycystic ovary syndrome, PCOS), preventing a complete elucidation of the AR's physiological role. Consequently, it remains challenging to define the precise effects of physiological AR signaling on glucose metabolism in women.

Building on this status, this chapter critically discusses the potential effects of female physiological AR signaling on glucose metabolism from a molecular mechanism perspective and emphasizes the research imperatives needed to resolve this crucial issue.

5.1 Distinguishing Hormonal Effects by Concentration and the Need for Female ARKO Models

5.1.1 Differential Effects of Hormone Concentrations

The phenomenon where a hormone's effects on glucose metabolism differ significantly between the physiological and supraphysiological range is clearly documented for thyroid hormones. While thyroid hormone at physiological concentrations appropriately maintains basal metabolism and insulin sensitivity [14], excess levels dramatically stimulate hepatic glucose production (gluconeogenesis), severely impairing systemic glucose homeostasis [13,14].

Similarly, AR action requires careful consideration of concentration-dependent differences. To clarify these differential effects on glucose metabolism, comparative studies administering both physiological and supraphysiological androgen concentrations to sex-specific mouse models are required.

5.1.2 Research Imperatives for Elucidating Physiological AR Action in Females

Testosterone is present at higher concentrations than estradiol throughout a woman's life and is believed to play important physiological roles [12]. In reproductive-age women, approximately 50% of circulating testosterone is derived from peripheral conversion of androstenedione,

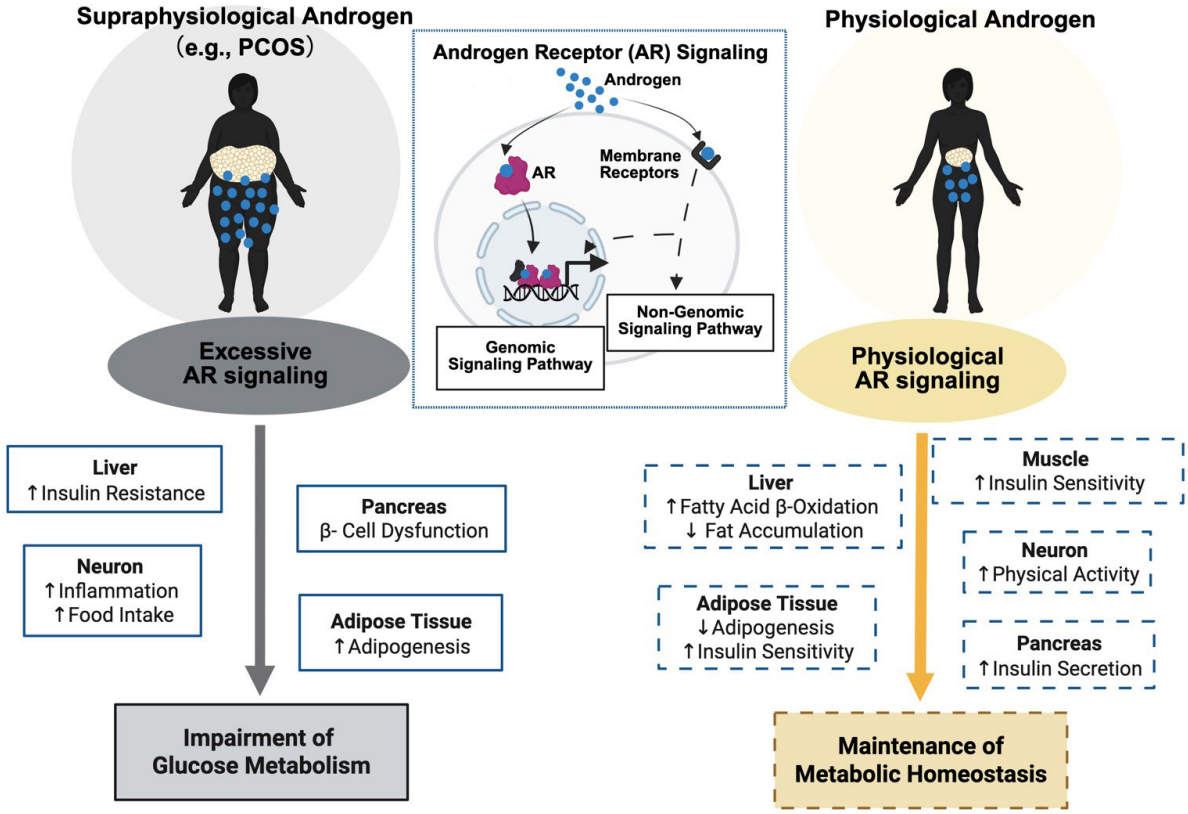

Fig. 2. The detrimental effects of androgen receptor signaling on glucose metabolism in women under pathological androgen excess (hyperandrogenism), and the potential protective role of physiological androgen levels, as inferred from male models and limited reports in women. Detrimental actions are associated with supraphysiological AR signaling (e.g., PCOS), whereas a potential protective role is hypothesized for physiological AR signaling, based on evidence from male models and emerging clinical data in women. Solid lines indicate established findings, while dashed lines represent hypothesized or inferred relationships. Abbreviations: PCOS, polycystic ovary syndrome. Created in BioRender. TSUTSUMI, T. (2026) https://BioRender.com/gv9av6h.

particularly in adipose tissue [12]. Therefore, it is essential to distinguish between the effects of obesity-induced hyperandrogenism and those of physiological AR signaling.

While clinical studies have suggested a positive correlation between elevated androgen concentration and impaired glucose tolerance in obese women [89,90], recent investigations, including those with non obese participants, have reported an inverse correlation between the incidence of metabolic syndrome and serum testosterone levels [61]. This finding strongly suggests the possibility that physiological AR signaling, similar to that in men, exerts a protective metabolic effect, particularly in non obese women.

To validate this protective hypothesis, accumulating data from models where endogenous AR action is inhibited under physiological androgen secretion, specifically, female ARKO mice, is essential, rather than relying solely on models of androgen administration. Urgently required research includes analyses using tissue-specific ARKO female mice to clearly delineate the physiological role of AR in key organs such as the liver, adipose tissue, and skeletal muscle.

Furthermore, clinical research focusing on the relationship between serum androgen concentrations and glucose metabolism markers (HbA1c, fasting glucose, insulin levels) in healthy, non obese women, differentiating by obesity status, is anticipated to advance translational research.

5.2 The Importance of Assessing AR Action and the Role of Diverse Ligands

5.2.1 Differentiating Androgen Concentration from AR Action

While some clinical studies have reported a positive correlation between increased circulating androgen levels and T2D risk in women [91], it is important to recognize a fundamental interpretative issue: previous research often equates androgen concentration with the “action” mediated by AR signaling. However, these are distinct concepts. For example, elevated insulin levels in insulin-resistant individuals do not indicate enhanced insulin action; similarly, higher androgen levels do not necessarily reflect increased AR signaling. In obese women, elevated androgen levels may represent a compensatory response to reduced AR signaling, potentially due to epigenetic changes. Indeed,

AR gene methylation has been positively correlated with impaired fasting glucose, suggesting that increased testosterone levels may be a compensatory phenomenon [92].

5.2.2 The Need for Biomarker Development to Assess AR Action

Currently, there are no established biomarkers or indices in humans to objectively quantify AR action in specific tissues, such as skeletal muscle, liver, adipose tissue, pancreas, or neurons. Similar to the necessity of assessing insulin action in diabetes care, accurate evaluation of AR signaling is essential for determining the appropriateness and efficacy of testosterone replacement therapy in both men and women. Future research must focus on developing reliable methods to quantitatively assess AR activity in humans.

5.2.3 The Involvement of Ligands Beyond Testosterone

AR signaling is mediated not only by the primary androgens, testosterone and DHT, but also by multiple steroid hormones, commonly referred to as androgen metabolites, such as DHEA and androstenedione [16]. Further molecular elucidation is required to understand the differences in binding affinity and action that these diverse ligands confer on AR, particularly their involvement in non-genomic actions.

5.3 Conclusion: The Metabolic Protective Role of Physiological AR Signaling and the Importance of Female Research

Reduced AR signaling—commonly observed in male hypogonadism and age-related decline—is closely associated with an increased risk of sarcopenia, visceral obesity, osteoporosis, MASLD, and T2D. Although this spectrum of metabolic disorders exhibits a pronounced sexual dimorphism, it represents a significant health challenge that intensifies with aging in both sexes. In this review, primarily based on findings from male models and *in vitro* studies, we have reaffirmed that physiological levels of androgen-mediated AR signaling play an indispensable role in maintaining insulin sensitivity and regulating fatty acid metabolism across key metabolic organs, including skeletal muscle, the liver, and adipose tissue.

This protective effect of physiological AR signaling on glucose metabolism may also be shared by females. However, reports directly investigating the impact of physiological androgens on female metabolism are extremely scarce, and their physiological significance remains largely elusive. To date, research on androgens in females has predominantly focused on the pathophysiology of hyperandrogenism, as exemplified by PCOS. While this research bias has advanced our understanding of PCOS, it has inadvertently fostered a paradigm that female androgens are deleterious to glucose metabolism regardless of their concentration (Table 7).

To validate this prevailing view, it is necessary to conduct comparative analyses of the effects of physiological versus pathologically high androgen concentrations on glucose metabolism. However, as female androgens are synthesized not only in the ovaries but also locally within peripheral tissues, particularly adipose tissue, clinical studies face inherent limitations in distinguishing between "hyperandrogenism associated with obesity" and "metabolic deterioration caused by obesity itself". To overcome these challenges, rigorous cross-sectional and interventional studies targeting non-obese women would be highly valuable.

Alternatively, animal models such as ARKO mice allow for the elucidation of pure molecular mechanisms that are often difficult to isolate in human studies due to confounding variables. Nevertheless, existing research using female ARKO models has been largely restricted to conditions of "pathological androgen excess". There is an urgent need for studies focusing on the impact of physiological androgen concentrations to address this critical knowledge gap. Furthermore, it must be acknowledged that rodent models often fail to capture the complex dynamic fluctuations inherent to human female physiology, such as the rhythmic hormonal shifts of the menstrual cycle and the profound endocrine transitions during menopause. Because animal models cannot accurately simulate these lifelong and cyclic variations, any insights derived from them must be clinically re-validated in humans to ensure their applicability to female metabolic homeostasis. Consequently, future efforts to elucidate the physiological role of AR signaling using female tissue-specific ARKO mice must be complemented by robust clinical evidence.

In conclusion, this review is not intended to provide clinical recommendations; rather, it seeks to offer molecular mechanistic insights and highlight the potential protective role of physiological androgen signaling in female glucose metabolism. Given the growing use of androgen replacement therapy for female sexual dysfunction and psychological symptoms [93], elucidating the impact of physiological AR signaling on female metabolic homeostasis is an urgent priority in contemporary medicine. However, evidence supporting the therapeutic use of testosterone for metabolic indications in women remains insufficient. Furthermore, safety concerns persist due to the lack of long-term data. Advancing our understanding of these molecular mechanisms will be pivotal for developing next-generation, sex-specific strategies to prevent and treat metabolic diseases (Fig. 2).

Author Contributions

TT: Conceptualization, Writing, Reviewing, and Editing; KT developed the overall concept and critical review of the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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During the preparation of this work, the authors used Google Gemini for spell-checking, identifying relevant literature from an objective perspective, clarifying sentence structure, and English language editing. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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