Review

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Testosterone and Glucose Homeostasis in Adult Males: Current Insights and Future Prospects

Charalampos Milionis[1], Eftychia Koukkou[1], Evangelia Venaki[1], Ioannis Ilias[2,*]

[1]Department of Endocrinology, Diabetes, and Metabolism, Elena Venizelou Hospital, 11521 Athens, Greece
[2]Department of Endocrinology, Hippokration Hospital, 11527 Athens, Greece
*Correspondence: iiliasmd@yahoo.com (Ioannis Ilias)
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Insulin plays a central role in blood glucose regulation, with insulin resistance contributing to the progression of prediabetes to diabetes, underscoring the importance of early intervention. Androgens, primarily synthesized in the testis under pituitary gland influence, impact male reproductive function. Testosterone, crucial for sexual development and secondary male characteristics, declines with age, leading to issues like anemia, sexual dysfunction, and reduced bone density. Sex-specific differences in glucose metabolism highlight males' lower insulin sensitivity and less effective glucose utilization compared to females due to androgenic effects. Testosterone's intricate role extends to potential benefits in glycemic control, fat mass reduction, and muscle strength increase in men with diabetes. However, cautious consideration of testosterone therapy is crucial, especially in the presence of underlying health conditions, warranting further research for clear guidelines in managing hyperglycemia.

Keywords: androgens; diabetes mellitus; insulin; insulin resistance; pancreatic beta-cells; testosterone

Introduction

A body of evidence from studies in human male subjects [1–3] and animal models [4] suggests that low blood testosterone levels may induce insulin resistance and type 2 diabetes mellitus. Possible causality may also go in the opposite direction, since research data also indicate that hyperglycemia may lead to hypogonadism in males [5,6]. From a physiological perspective, this bidirectional relationship between testosterone insufficiency and dysglycemia is complex and largely unknown. It can be attributed in part to effects on body composition, including mainly changes in visceral fat and muscle mass. However, direct actions of androgens on insulin synthesis and action are also possible. Hence, it is reasonable to hypothesize that the administration of testosterone may be able to arrest the exacerbation of metabolic syndrome and prediabetes in obese individuals and improve glycemic management in people with overt diabetes mellitus. Indeed, contemporary research efforts have focused on elucidating the mutual relationship between androgen action and glucose homeostasis and, by extension, the contribution of testosterone to cardiometabolic health [7]. In order to answer these questions, it is appropriate to review and understand the physiology of glycemic regulation, the mechanism of androgenic synthesis and action, as well as their interrelationship within the body's homeostasis.

Physiology of Insulin

The pancreatic beta-cells are located in the islets of Langerhans and produce insulin. The latter consists of two polypeptide chains, namely A (21 amino acids) and B (30 amino acids), joined by disulfide bonds. The c-peptide connects the A and B chains in the precursory molecule of proinsulin. In the fasting state, insulin is secreted in small bursts every few minutes. After meals, the release of insulin follows two consecutive phases. The first phase is rapid and involves the release of molecules that have already been synthesized and stored. The second phase is gradual over a longer period and includes the secretion of both stowed and newly produced insulin [8,9].

The primary regulator of insulin release is blood glucose. The pacemaker of glucose metabolism, which subsequently dictates the insulin secretory response, is the phosphorylation of glucose by glucokinase. Several factors can affect (trigger, amplify, or suppress) the synthesis and secretion of insulin. Besides glucose, other stimuli are amino acids, neural activity, hormones, and medications [9,10]. Once secreted, insulin enters the blood circulation and reaches the peripheral tissues. Fat, muscle, and liver are the main target tissues. Insulin exerts its physiological role through the metabolic and mitogenic pathways. The metabolic actions are crucial in controlling the metabolism of proteins, fats, and carbohydrates, while the mitogenic effects contribute to the promotion of cell division and growth [11].

Insulin action is essential for the cellular uptake of glucose in insulin-dependent tissues. It promotes the use of glucose in hepatocytes for the production and storage of glycogen as well as the conversion of extra glucose into fatty acids. Additionally, it inhibits gluconeogenesis and glycogenolysis in the liver, either directly or indirectly, via paracrine suppression of the secretion of pancreatic glucagon by the alpha-cells. Moreover, skeletal muscle tissue is significantly affected by insulin. In particular, it promotes the synthesis of proteins as well as the production of glycogen from glucose for the coverage of muscle energy expenditure later on. Triglycerides are stored and synthesized in the adipose tissue in response to insulin, serving long-term energy requirements [11,12].

In addition to lowering blood sugar and controlling nutrition metabolism, insulin also directly affects inflammatory mediators and enhances immunocompetence by acting upon immune cells. In this regard, insulin functions as an anti-inflammatory agent, while hyperglycemia promotes inflammation [13,14]. This hormone also plays important, albeit less well-studied, physiological roles in endothelial function, neural plasticity and cognitive processes, renal homeostasis, bone formation, and skin integrity. Yet, the specific mechanisms at play are still unknown.

Glucose Homeostasis and Insulin Resistance

A balance between the amount of carbohydrates obtained from diet and the uptake and use of glucose by peripheral tissues is reflected in glucose homeostasis. The principal regulator of blood sugar is the endocrine release of insulin. Low insulin levels limit glucose absorption in insulin-sensitive tissues (skeletal muscle and fat) and enhance glucose synthesis through hepatic gluconeogenesis and glycogenolysis in order to maintain fasting euglycemia. Pancreatic alpha-cells secrete glucagon when both insulin levels and glucose concentrations are low, or during exercise. Glucagon stimulates glycogenolysis and gluconeogenesis by the liver and, to a lesser degree, by the kidneys. Glucose absorption after meals results in the opposite processes: a rise in insulin and a fall in glucagon. Skeletal muscle uses most of the digested glucose. Insulin is not necessary for the utilization of glucose by certain tissues, primarily the brain [15,16]. The metabolism of glucose is also influenced by other elements, including hormones, metabolic signals, and neural stimulation.

Insulin resistance is a condition in which the tissues' physiologic sensitivity to insulin action is diminished. In the liver, the abundance of fatty acid delivery increases intracellular acetyl-coenzyme A (acetyl-CoA), which in turn activates protein kinase C, while the increased delivery of glycerol further enhances hepatic gluconeogenesis. In addition, the activation of protein kinase C impairs hepatic insulin signaling, thereby constraining the insulin-stimulated synthesis of glycogen. In the skeletal muscle, lipid-mediated activation of protein kinase C impairs insulin signaling and hence, impedes glucose uptake. In the adipose tissue, inflammation and impaired insulin action lead to increased lipolysis, which raises the availability of fatty acids and glycerol delivery to the liver [17].

Pancreatic insulin production rises when islet function is sufficient to maintain blood glucose levels within a normal range. Weight gain from elevated endogenous insulin exacerbates insulin resistance, creating a pathophysiological vicious cycle. A series of problems, such as dyslipidemia, hypertension, obesity, prothrombotic state, endothelial dysfunction, inflammatory diseases, abnormal uric acid metabolism, and sleep apnea, can be associated with an excess of insulin. Moreover, the gradual incapacity of beta-cells to preserve the overproduction of insulin leads to the development of glucose intolerance and type 2 diabetes mellitus [8,11].

The molecular pathways that underlie insulin resistance are complicated, and their causes are not fully understood. If there are no autoimmunities or heritable disorders, being overweight is the main pathogenetic factor causing poor insulin sensitivity. Excessive nutritional intake can cause lipid metabolic problems, altered gut microbiota, and chronic inflammatory diseases, all of which can impair the effects of insulin [18,19]. Furthermore, a variety of pharmaceutical substances, each with its unique mechanism, may be involved in the development of glucose intolerance. Glucocorticoids, antipsychotics, thiazide diuretics, beta-blockers, statins, somatostatin analogs, and some anticancer agents are medications that may negatively impact the metabolism of carbohydrates [20].

Diabetes Mellitus

Hyperglycemia is the prevalent characteristic of a range of metabolic disorders that make up diabetes mellitus. Diabetes mellitus consists of different types, most of which are pathogenically related to the interaction of environmental and hereditary factors. According to the pathophysiological mechanisms that underlie the development of hyperglycemia, two primary types exist. Absolute insulin insufficiency resulting from autoimmunity against components of the pancreatic beta-cell is the cause of type 1 diabetes mellitus. Different levels of insulin resistance, decreased insulin secretion, and elevated hepatic glucose synthesis are the hallmarks of type 2 diabetes mellitus. Additional forms of diabetes mellitus comprise clinical entities resulting from genetic disorders in insulin secretion or activity, anomalies hindering insulin secretion, impairments to the mitochondria, or circumstances compromising glucose tolerance [21].

Chronic hyperglycemia-induced metabolic dysregulation is linked to potentially serious secondary consequences on a number of tissues and organs. Microvasculopathy, which affects the capillary blood vessels in the glomeruli,

retina, heart, skin, and muscle, can certainly be caused by diabetes mellitus. Furthermore, hyperglycemia seems to have a role in the etiology of macrovasculopathy [22]. Complications from diabetes mellitus can seriously impair quality of life [23] and place a heavy strain on the healthcare system [24]. The present epidemiological state of this disease and its future trajectory constitute a significant public health issue. Throughout the previous forty years, the prevalence of diabetes mellitus has increased globally, and in the years to come, this trend is predicted to continue. At present, there are more than 500 million individuals worldwide living with diabetes mellitus, and by 2050, that figure is expected to surpass the number of 1.3 billion people [25].

Prediabetes is characterized by intermediate glucose levels that are above average but below the cutoff points for establishing the diagnosis of diabetes mellitus, such as impaired fasting glucose and/or impaired glucose tolerance. There is a significant risk that prediabetes may eventually lead to overt diabetes mellitus [21,26]. A pathological deficiency in insulin action exists in prediabetes, regardless of the underlying etiology. Reversion of prediabetes to normal glucose homeostasis significantly decreases the risk of future hyperglycemia [27,28]. Therefore, clinical interventions should focus on achieving and maintaining both euglycemia and appropriate insulin sensitivity from the earliest point in time.

Synthesis and Secretion of Androgens

The pituitary gland releases discrete pulses of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in response to the respective secretion of the hypothalamic gonadotropin hormone-releasing hormone. LH in turn stimulates testosterone synthesis by the Leydig cells. The hypothalamus and pituitary are both impacted by the feedback effects of testosterone and estradiol [29,30]. FSH promotes the survival and differentiation of Sertoli cells. It also drives spermatogenesis and the synthesis of products like inhibin B. The latter selectively suppresses pituitary follicle-stimulating hormone [29,31]. Despite these distinct Leydig and Sertoli cell-regulated pathways, there are multiple degrees of integration in male reproductive function. Indeed, the gonadotropin hormone-releasing hormone regulates both gonadotropins. In addition, spermatogenesis necessitates high intra-testicular testosterone levels, while many paracrine interactions between Leydig and Sertoli cells are required for optimal testicular function [29].

The synthesis of testosterone within the Leydig cells follows the classical steps of steroidogenesis. In fact, all steroidogenic organs (the ovary, testis, adrenal cortex, and placenta) use the same pathways for the production of steroid hormones. However, the specific enzymes expressed in each tissue affect the type and quantity of hormones that are produced [32]. A family of steroid 5-alpha-reductase isoenzymes can convert testosterone to the more potent dihydrotestosterone. Aromatase can aromatize testosterone into estradiol [33,34]. Testicular production accounts for 95% of the circulating testosterone in males. An additional 5% is produced by the peripheral conversion of androstenedione to testosterone and the direct production of testosterone by the adrenal gland. The testis secretes only a small amount of dihydrotestosterone. Peripheral conversion of testosterone is the source of most of the circulating dihydrotestosterone.

In the bloodstream, testosterone is mostly attached to sex hormone-binding globulin, albumin, and, to a lesser degree, cortisol-binding globulin and orosomucoid. The percentage of free, physiologically active testosterone in circulation is only 1–4%. Bioavailable testosterone consists of free testosterone and testosterone that is loosely linked to albumin [35]. It is primarily metabolized in the liver, while some degradation takes place in peripheral tissues, especially the skin and prostate.

Actions of Testosterone

Testosterone binds to the androgen receptor directly or after conversion to dihydrotestosterone in order to produce its biological effects. The actions of testosterone on the embryonic Wolffian structures, skeletal muscle, erythropoiesis, and bone do not require conversion to dihydrotestosterone. However, dihydrotestosterone is necessary for the masculinization of the urogenital sinus and genital tubercle. Additional effects of testosterone on bone resorption, epiphyseal closure, sexual desire, vascular endothelium, and fat are mediated by the aromatization of testosterone to estradiol [36]. The androgen receptor is structurally linked to the nuclear receptors for progesterone, estrogen, and glucocorticoids. It is encoded by a gene on the long arm of the X chromosome. Dihydrotestosterone attaches to the androgen receptor with twice the affinity of testosterone and separates from it more slowly [37].

Testosterone drives sexual development, which includes spermatogenesis, testicular descent, penile and testicular growth, and increased libido. Additionally, it is involved in the development of secondary male characteristics, including voice deepening, male hair patterns, and the formation of a masculine body figure. Testosterone also promotes erythropoiesis, which gives men a higher hematocrit than women [36]. Testosterone levels often decline as one age. Specifically, total testosterone decreases gradually from around the age of 20 years old at an estimated rate of 1% per year of life. As a result, some older men may suffer from anemia, impaired bone density, lower libido, decreased muscular mass, and increased fat production [38].

Type 2 diabetes mellitus is often associated with subnormal testosterone levels and inappropriately low concentrations of gonadotropins. The presence of low testosterone may be partly linked to excessive adiposity (Fig. 1, Ref. [39]). In this case, overproduction of estrogen

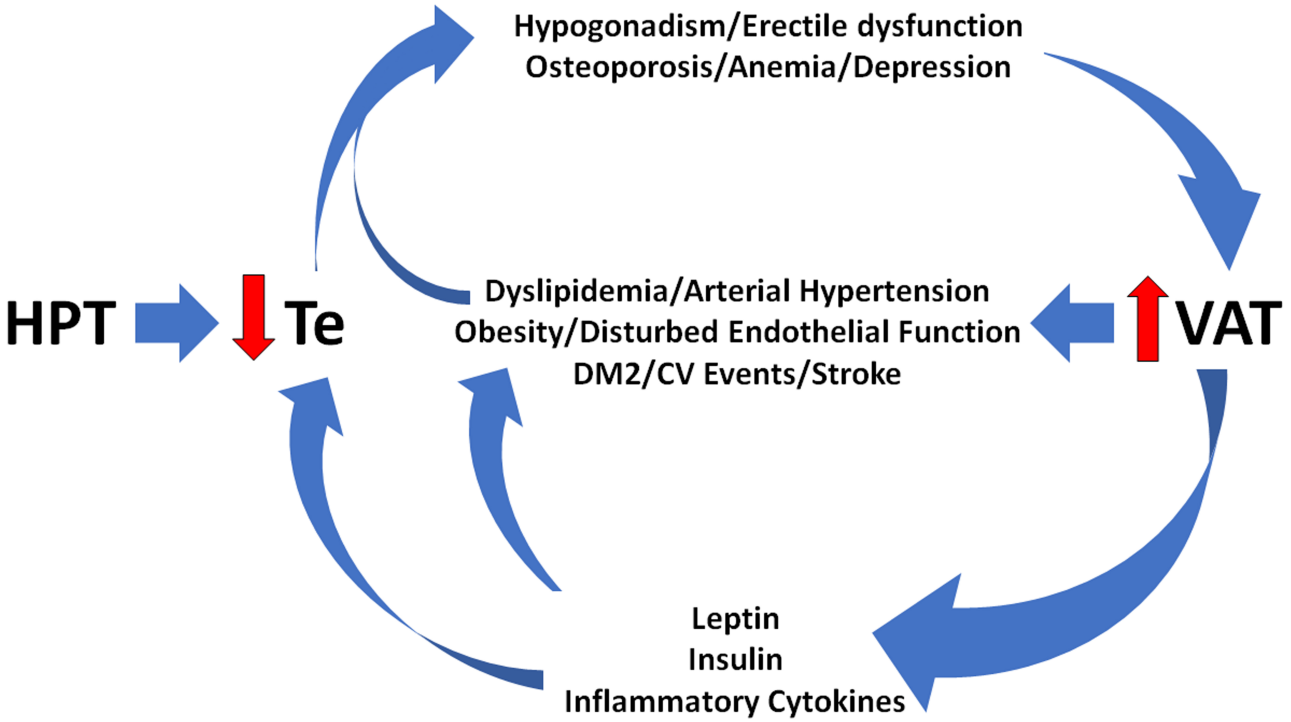

Fig. 1. Auto-fueling of the pathological relationship between hypogonadism and excessive visceral adipose tissue (with information taken from [39]). HPT, hypothalamus-pituitary-testicular axis; Te, Testosterone; DM2, Type 2 Diabetes Mellitus; CV, Cardiovascular; VAT, Visceral adipose tissue; Drawn with Powerpoint [Software]. Microsoft Corporation, 2007, Redmond, WA, USA.

due to aromatase activity in the adipose tissue can potentially suppress the hypothalamic-pituitary-testicular axis [40]. In addition, increased leptin in obese males may impair the responsiveness of Leydig cells to luteinizing hormone [41]. However, chronic hyperglycemia predisposes to hypogonadism, even regardless of the existence of obesity [42]. Hyperglycemia-induced pro-inflammatory factors could possibly hinder the local production of testosterone in the testis [43]. Of course, the duration of diabetes, glycemic control, age, and lifestyle are plausible determining factors of diabetes-related hypogonadism [44]. Nonetheless, many further hitherto unknown biological mechanisms are likely to be involved in the reduction of androgen levels due to diabetes.

Sex-Specific Differences in Glucose Metabolism

Males and females do not have the same regulation of glucose homeostasis. In humans, there is a strong correlation between insulin sensitivity with body composition and fat distribution. Due to the anabolic effects of testicular androgens, adult men have more lean tissue mass than women. Men also exhibit a larger percentage of visceral fat deposition, despite adult women having a higher percentage of total fat mass. As a net result, male subjects are less sensitive to insulin and use glucose with lower effectiveness in comparison with their female counterparts [45,46].

When matched for age, body mass index, and physical fitness, euglycemic women are more responsive to insulin than males due to a variety of potential physiological characteristics. First, women have a higher proportion of type I muscle fibers and a denser capillary network than men do, which promotes increased glucose uptake in skeletal muscle [47]. Second, females have a higher capability for insulin secretion as well as a stronger incretin effect compared to males [48]. Thirdly, the microbiota in the human intestine is significantly influenced by sex, which may have some special causal relationship with glucose intolerance in men [49]. Of course, several other physiological processes, the majority of which are unknown, may also be valid reasons. Broadly speaking, sex-specific features in glucose homeostasis may be important in determining the best strategy for managing and preventing diabetes.

The action of gonadal hormones but also properties of the sex chromosomes may be responsible for the sex-specific differences in glucose metabolism. Independent of the *SRY* gene, gonad type, and circulating sex hormones, XX individuals in animal models show higher fat deposits and food consumption, and thus, a higher risk of insulin resistance from a high-fat diet than their XY counterparts [50]. These sex differences could be caused by holandric genes (apart from the *SRY*) or the number of X chromosomes [51].

Sex-specific particularities of glucose homeostasis could provide an opportunity for personalized anti-diabetic treatment, especially in individuals with type 2 diabetes mellitus under multi-drug diabetes treatment. Apparently, thiazolidinediones are more effective insulin sensitizers in women with obesity. In addition, female sex is associated with greater weight loss from the use of glucagon-like peptide-1 (GLP-1) analogs. In contrast, sulfonylureas and sodium-glucose transporter 2 (SGLT2) inhibitors seem to generate greater responses in men. Metformin may lead to better glycemic control in men, but it can cause greater reductions in body weight in women. Mixed results have been observed for the comparative effectiveness of insulin in the two sexes [52,53]. Nonetheless, the relevant evidence is still nascent.

The Impact of Androgens on Glycemia

The incapacity of circulating insulin to efficiently control the uptake of glucose by target tissues is termed insulin resistance. Initially, compensatory hyperinsulinemia occurs in order to keep normal blood glucose levels. Nonetheless, pancreatic beta-cells may begin to fail following a period of increased insulin demand. This would subsequently result in non-physiological hyperglycemia and, ultimately, diabetes [18]. It is unclear whether endogenous or synthetic testosterone influences the onset of dysglycemia, and the potential underlying mechanisms are also poorly known.

Testosterone may participate in the metabolism of carbohydrates through direct effects on skeletal muscle, liver, adipose tissue, and immune cells, as well as via indirect effects on changes in body musculature and fat mass and distribution [54]. Insulin resistance is linked to several adverse metabolic consequences, in addition to playing a pivotal role in the pathophysiology of type 2 diabetes mellitus. Some examples include hypertension, dyslipidemia, obesity, and atherosclerotic cardiovascular disease, even in those without diabetes [55]. Therefore, knowing whether or not androgens and insulin resistance are linked may help in treating adult males with dysglycemia.

Androgens have a male-specific effect on adipocytes, affecting their hormonal secretion, lipolysis and lipogenesis, microRNA synthesis, and expression of aquaporins. This plays a role in the sex-specific distribution and function of adipose tissue [56]. Furthermore, testosterone uses a multifaceted mechanism to promote muscular tissue growth. First, it increases the synthesis of contractile proteins by enhancing myonuclei's transcriptional activity (and potentially accretion). Secondly, it stimulates satellite cells, which cause new myotubes to develop [57]. In addition, androgens increase the size of type IIb muscle fibers, thereby promoting oxidative metabolism [58]. There is a physiological interrelationship between insulin sensitivity, muscle mass, and body fat. Adipose tissue affects the resistance to insulin through the activity of many mediators, such as adipokines, pro- and anti-inflammatory cytokines, and chemokines [59,60]. Because skeletal muscle uses glucose as an energy source and as a substrate for glycogen synthesis, it promotes insulin sensitivity [61]. Therefore, testosterone may indirectly affect insulin resistance through modifications in skeletal muscle size and body fat mass.

It is unclear if testosterone directly affects insulin resistance. Long-term testosterone therapy may help men with prediabetes or diabetes and hypogonadism improve their glycemic control and other parameters of metabolic syndrome [62,63]. However, little is known about the biological mechanisms involved. Testosterone likely prevents mesenchymal pluripotent stem cells from differentiating into adipocytes while promoting their commitment to the myogenic lineage [64]. Additionally, it may influence insulin receptor and glucose transporter type 4 (GLUT4) expression, as well as the activity of glycolysis-related enzymes, to regulate metabolic processes in adult adipocytes and myocytes. Finally, testosterone may shield pancreatic beta-cells from apoptosis induced by glucotoxicity [65].

Hypogonadal men are at high risk of developing dysglycemia due to the inadequate action of testosterone on various tissues that influence glucose/energy homeostasis. The exact biological mechanisms are not fully known and most evidence derives from studies in animals. Androgen deficiency, regardless of its etiology, promotes the accumulation of visceral fat, thereby reducing insulin sensitivity. Moreover, the lack of testosterone generates an alteration of insulin sensitivity in skeletal muscle because it probably affects the expression of genes that participate in glucose metabolism. The activation of the androgen receptor induces the transcription of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PPARGC1α). The latter is the principal regulator of mitochondrial biogenesis and may be involved in the function of skeletal muscle oxidative fibers. Low testosterone is also associated with decreased expression of peroxisome proliferator-activated receptor alpha (PPARα) in the liver tissue which leads to decelerated fatty acid oxidation and increased lipid synthesis. The possible adverse effects of androgen deficiency on the central nervous system are multiple and may include decreased vitality, reduced thermogenesis, and altered leptin action. Together, these effects lead to an unfavorable imbalance in energy intake/energy expenditure. Finally, hypogonadal male subjects may exhibit hindered glucose-stimulated pancreatic insulin secretion [66].

Interestingly, supraphysiological levels of androgens are also associated with impaired glucose tolerance. For example, the illicit use of androgenic-anabolic steroids to enhance athletic performance or improve body image is associated with higher values of insulin resistance indices, despite the often-greater lean body mass among the users [67]. Perhaps endogenous androgens within a physiological window have a beneficial role in maintaining glucose homeostasis, whereas pharmacological administration at excessive dosages has the opposite effect.

Of course, testosterone also interacts with other hormones, thereby indirectly participating in several other metabolic pathways. For example, research findings indicate possible negative relationships between circulating testosterone and certain stress hormones (cortisol and prolactin) in humans [68–70]. Cortisol raises blood sugar concentrations by upregulating enzymes involved in hepatic gluconeogenesis and by inhibiting the absorption of glucose in peripheral tissues [71]. Moreover, elevated prolactin levels are associated with insulin resistance [72], possibly via effects on insulin receptors and changes in adiponectin and interleukin-6 (IL-6) production in adipose tissue. Therefore, hypogonadism could further enhance insulin resistance through stress-related mechanisms. Unfortunately, research in this area is incomplete.

Treatment of Hyperglycemia with Testosterone

Androgen deficiency, characterized by clinically significant symptoms and signs of markedly low serum testosterone levels, is prevalent among a substantial portion of elderly, obese males due to compromised functionality of the hypothalamic-pituitary-gonadal axis. Androgen therapy for men with glycemic disorders, but without clear-cut classical hypogonadism, is controversial because available information on the relevant benefits and risks is scarce. A fundamental concept relates to making a distinction between replacement and pharmacological treatment. In the former, there is pathological damage to the production of testosterone, while in the latter, there is only maladaptation because of the aging process and age-related comorbidities.

Symptoms of hypogonadism are non-specific, especially in men of advanced age with metabolic disorders. In addition, the reduction in both free and total hypotestosteronemia is often modest in these subjects. Therefore, identifying androgen deficiency in aging men with comorbidities is difficult. The establishment of diagnosis could be based on bone densitometry, hemoglobin values, lean body mass measurements, and self-reports of sexual activity. Unfortunately, no gold standard for the diagnostic criteria currently exists and further research in this direction is desirable.

It is evident that males with a poor metabolic phenotype may have low testosterone levels. Nevertheless, it is still unclear if decreased testosterone is a direct cause of alterations in glucose metabolism. In fact, it is possible that low testosterone is also a consequence of insulin resistance. Metabolic factors, such as leptin, insulin, ghrelin, and kisspeptin may act at the hypothalamus and alter the release of gonadotropin-releasing hormone. Hence, a bidirectional relationship between androgens and dysglycemia possibly exists [65].

Treatment with testosterone has the potential to break the vicious cycle between insulin resistance and excessive adiposity in diabetes-associated hypogonadism. Possible beneficial effects of testosterone therapy include improvement of glycemic control, decrease in fat mass, and increase in skeletal muscle mass and muscle strength, mainly in men with uncontrolled diabetes or grave metabolic syndrome. Therefore, testosterone could be considered as an adjunctive therapy to conventional anti-diabetic medications.

The expected increase in insulin sensitivity from testosterone administration should lead to better glycemic control and a reduction in the frequency of diabetic complications to be clinically significant. The course of metabolically favorable changes could be objectively estimated with various clinical and biochemical tools. Body composition analysis is a relatively satisfactory method of estimating the dynamics of insulin action. The c-peptide-based homeostatic model assessment of insulin resistance (HOMA-IR-CP) gives a good direct approximation of pancreatic beta-cell function. The triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C) and the triglycerides/glucose (TyG) index are also valid markers of insulin resistance. Of course, glycated hemoglobin (HbA1c) can be applied to assess changes in glycemic control, but only in patients with overt hyperglycemia.

Symptomatic hypogonadal men with unequivocal reduction in testosterone levels should, after an appropriate diagnostic investigation, be considered for testosterone therapy, irrespective of its effect on glucose metabolism. However, it appears that testosterone has limited effects on glucose metabolism in relatively healthy men with only mildly reduced testosterone. In summary, the available evidence is inconsistent. Probably the heterogeneity of results stems from differences in the degree of glycemic dysregulation, the duration of hyperglycemia, and the dosage of androgen replacement [73,74]. Thus, whether testosterone treatment can improve health outcomes in men with diabetes or whether it can reduce the risk of developing diabetes in high-risk males requires further research.

Testosterone therapy is contraindicated for men with prostate or breast cancer. It should not be given to males who have a palpable prostate nodule, elevated prostate-specific antigen (PSA) levels, or significant symptoms related to the lower urinary tract without first undergoing an additional urologic assessment. Men who have an elevated baseline hematocrit, severe untreated obstructive sleep apnea, uncontrolled congestive heart failure, or a recent cardiovascular event should also not take testosterone therapy. Assessments of the safety and clinical efficacy of testosterone treatment should be conducted a few months after initiation and every year thereafter. Acne, oiliness of the skin, erythrocytosis, breast enlargement and tenderness, leg edema, and a higher risk of prostatic disorders are possible side effects [75].

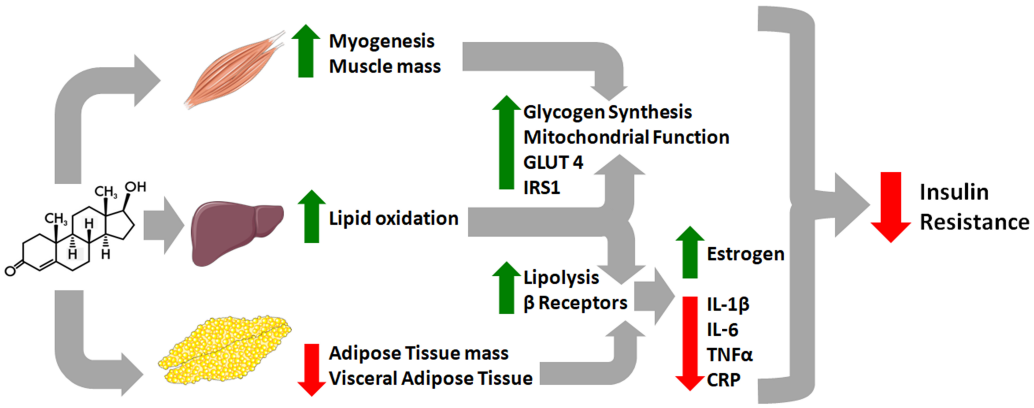

Fig. 2. The diverse impacts of testosterone on insulin resistance (and appearance of type-2 diabetes). Testosterone exerts effects on adipose tissue, diminishing fat mass and visceral fat while promoting estradiol formation and diminishing inflammatory markers such as cytokines (IL-1β, IL-6, and TNFα) and C-reactive protein. In the liver, testosterone enhances lipid oxidation by stimulating β-receptors and lipolysis. In muscles, testosterone stimulates myogenesis, fostering muscle mass development, subsequently enhancing glycogen synthetase, mitochondrial function, GLUT4, and IRS1 activity. Collectively, these mechanisms contribute to the reduction of insulin resistance, improvement of glucose control, and a decreased incidence of type 2 diabetes mellitus. CRP, C-reactive protein; GLUT4, glucose transporter type 4; IL-6, interleukin-6; IL-1β, interleukin-1 beta; IRS1, Insulin receptor substrate 1 (a substrate for the insulin receptor); TNFα, tumor necrosis factor-α. Adapted, amended and redrawn from [76]; partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license; Drawn with Powerpoint [Software]. Microsoft Corporation, 2007, Redmond, WA, USA.

Conclusion

The intricate and multidirectional link between testosterone and glucose homeostasis may entail multiple pathways (Fig. 2, Ref. [76]). The relationship between testosterone and insulin sensitivity—either directly or through effects on inflammation, energy expenditure, and hormone secretion—is a key element. Comorbidities related to aging may increase insulin resistance and lower testosterone levels. Moreover, variations due to age, ethnicity, and lifestyle choices significantly impact androgen synthesis and the risk of developing diabetes, underscoring the importance of these factors in clinical considerations.

The current evidence and recommendations regarding the use of exogenous testosterone in treating dysglycemia are vague. Future research should test the effectiveness and safety of androgens in clinical trials. Optimal glycemic control, lifestyle interventions, and treatment of comorbidities remain the first-line approach to the management of men with hyperglycemia and low testosterone levels. When reliable studies provide favorable evidence regarding the risk-benefit ratio of testosterone therapy, the latter may become an option. Currently, it can be occasionally considered only in men with diabetes and low circulating testosterone when lifestyle measures and anti-diabetic medications fail to achieve satisfying glycemic control. However, what constitutes a sufficient circulating testosterone level is unknown, and thus, prior discussion with the candidate recipient is necessary.

Availability of Data and Materials

Not applicable.

Author Contributions

CM, EK, EV and II performed the literature research; CM, EK, EV and II were involved in drafting the manuscript and revising it critically for important intellectual content. All authors give final approval of the version to be published. All authors have participated sufficiently in the work to take public responsibility for its content and agree to be accountable for all aspects of this work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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