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Multiple Mechanisms Linking Type 2 Diabetes and Alzheimer's Disease: Testosterone as a Modifier

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Abstract

Evidence in support of links between type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) has increased considerably in recent years. AD pathological hallmarks include the accumulation of extracellular amyloid- β (A β) and intracellular hyperphosphorylated tau in the brain, which are hypothesized to promote inflammation, oxidative stress, and neuronal loss. T2DM exhibits many AD pathological features, including reduced brain insulin uptake, lipid dysregulation, inflammation, oxidative stress, and depression; T2DM has also been shown to increase AD risk, and with increasing age, the prevalence of both conditions increases. In addition, amylin deposition in the pancreas is more common in AD than in normal aging, and although there is no significant increase in cerebral A β deposition in T2DM, the extent of A β accumulation in AD correlates with T2DM duration. Given these similarities and correlations, there may be

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common underlying mechanism(s) that predispose to both T2DM and AD. In other studies, an age-related gradual loss of testosterone and an increase in testosterone resistance has been shown in men; low testosterone levels can also occur in women. In this review, we focus on the evidence for low testosterone levels contributing to an increased risk of T2DM and AD, and the potential of testosterone treatment in reducing this risk in both men and women. However, such testosterone treatment may need to be long-term, and would need regular monitoring to maintain testosterone at physiological levels. It is possible that a combination of testosterone therapy together with a healthy lifestyle approach, including improved diet and exercise, may significantly reduce AD risk.

Keywords

Alzheimer's disease; men; testosterone; type-2 diabetes; women

INTRODUCTION

The prevalence of type 2 diabetes (T2DM) and Alzheimer's disease (AD) both increase with age. There is also an age-related gradual loss of testosterone levels in men and women, together with increasing testosterone resistance due to factors such as rising sex hormone-binding globulin (SHBG) levels and hypothalamic-pituitary-gonadal axis insensitivity. Mounting evidence, originally from epidemiological studies and now also from pre-clinical and clinical studies, indicates that people with T2DM are at increased risk of developing AD and that hallmarks of T2DM such as insulin resistance and hyperinsulinemia can lead to cognitive impairment [1]. A recent animal study that crossed two well-established mouse models of T2DM and AD showed that diabetes exacerbates memory impairment [2]. T2DM and AD also have similar pathological features of amyloid accumulation, indicating common pathogenic mechanisms; in the brain in AD (amyloid- β ($A\beta$) peptide) and in islets of the pancreas in T2DM (islet amyloid peptide, or amylin). Other similarities include the fact that they can both be degraded by the same protease, insulin degrading enzyme (IDE), the fact that they can both bind to the amylin receptor, and the common β -sheet secondary structures of these two amyloid proteins [3]. $A\beta$ has no established physiological functions, yet amylin, which is co-secreted with insulin from the pancreas, can readily cross the blood-brain barrier and mediate improvements in glucose metabolism and reduce inflammation. Furthermore, amylin and its analogs have been shown to reduce $A\beta$ pathology in an AD animal model [4], and the deposition of amylin in the pancreas has been found to be more common in AD compared with healthy controls. Despite no significant increase in $A\beta$ amyloid in the brains of T2DM individuals versus controls, for those with amyloid plaques, the extent of plaque accumulation correlates with the duration of T2DM [5]. Furthermore, impairments in insulin signaling, glucose metabolism, lipid metabolism, and inflammation have all been observed in both conditions [6]. Given these similarities, there may be common underlying mechanism(s) via testosterone that predispose susceptible individuals to T2DM and AD. In this review, we focus on the age-related changes in circulating testosterone levels in men and women and discuss how these changes may increase the risk of both T2DM and AD. We also evaluate the potential of testosterone therapy as a modifier of both conditions.

TESTOSTERONE AND DIABETES

Total testosterone circulating in the plasma comprises ~2% free testosterone, ~20–40% albumin-bound testosterone, and ~60–80% SHBG-bound testosterone [7]. The levels of total and free testosterone are significantly lower in men with T2DM [8]. Mounting evidence from animal models, epidemiological studies and human clinical trials have indicated a strong association between low testosterone levels, which result from the age-related gradual decline in testosterone levels and insulin resistance, one of the hallmarks of T2DM [8, 9]. Testosterone levels in men appear to influence glycemic status, and to be inversely proportional to the risk of having T2DM [10]. It has been shown that men with T2DM and low testosterone can benefit significantly from testosterone treatment [11–13]. Furthermore, testosterone therapy for the treatment of androgen deficiency has been shown to reduce features of T2DM such as insulin resistance, adiposity, inflammation, and hypercholesterolemia while improving glucose levels [14, 15]. In contrast, a reduction in testosterone levels due to androgen deprivation therapy [16] in the treatment of prostate cancer magnifies the incidence and prevalence of T2DM by increasing blood insulin levels and lowering insulin sensitivity and glycemic control [17–20]. Moreover, ADT has been associated with increased insulin resistance [21, 22]. In summary, the above findings indicate that low testosterone increases the prevalence of insulin resistance and T2DM in men.

In contrast to men, increased testosterone levels (excess testosterone levels) induces insulin resistance in pre-menopausal women [23], thus increasing the risk of T2DM [10]. This is exemplified by excessive testosterone in women with polycystic ovary syndrome, which is associated with insulin resistance, predisposing these women to higher risk of T2DM [24]. However, in healthy women, testosterone administration is associated with increased insulin resistance [25]. Compared to men, women generally tend to have all the factors that would be predicted to promote insulin resistance such as having more adipose mass, abrupt loss of estrogen and persistent lower testosterone levels post-menopause, while having only two thirds the skeletal muscle mass of men. Some studies report that women are equally as sensitive to insulin as men [25, 26], whereas one study found women to be more insulin sensitive than men; however this study was done in a young, healthy population (average age of 34 years) in which the levels of sex hormones would have fluctuated according to the reproductive cycle, thus the contribution of sex hormones toward insulin sensitivity cannot be determined from these latter studies [25, 26].

There is no doubt that the actions of sex hormones (testosterone and estrogen) on metabolic homeostasis are implicated in diabetes both in males and females (extensively reviewed in [27]). Interestingly, the sex difference in the prevalence of diabetes is reversed based on the stage of reproductive life, that is, there are more males with T2DM before puberty whereas more females with T2DM post-menopause, based on a survey of global diabetic populations [28]. Furthermore, there are conflicting reports about the effects of hormone replacement therapy on insulin sensitivity. For instance, estrogen replacement therapy has been reported to have no effect on insulin sensitivity in post-menopausal women [29, 30], but it increased insulin sensitivity when administered in post-menopausal women with diabetes [31]. In

addition, the association of sex hormones (testosterone and estrogen) with insulin resistance differs depending on the estrogen status [32].

Testosterone replacement therapy in postmenopausal women has shown the potential to increase insulin sensitivity through indirect effects on lipid metabolism and body fat distribution (reviewed in [33]). Furthermore, a small but significant reduction in insulin resistance was observed in post-menopausal women treated with the testosterone replacement therapy, as well as with a combination of testosterone and estrogen treatment, but not with only estrogen treatment [34]. Despite the potential value of the metabolic effects of testosterone treatment in women, research is significantly lacking in this area.

The literature on animal studies (mostly rodent) that addresses sex hormone effects on activity has demonstrated that female rodents are not only more active than male rodents [35], but also protected against high fat diet induced metabolic syndrome [36]. For example, the prevalence of T2DM has been found to be significantly higher in male compared to female transgenic mice overexpressing human amylin; however, in cell culture studies aimed at determining whether the hormones testosterone and estrogen themselves influenced the amylin-induced cytotoxicity, it was found that the sex steroids were not able to reduce the cytotoxicity caused by amylin in any of the three cell culture models tested [37]. In other studies, amylin deficiency was shown to modify bone development during growth, and this effect was found to be gender-dependent [38], suggesting that sex steroid levels (testosterone in particular) can influence amylin metabolism. In summary, further investigation is required to elucidate the influence of sex hormones on glucose metabolism and insulin resistance, and to clarify to what extent risk factors and treatment guidelines should be gender-specific. There is a need for both animal studies and human clinical trials to be designed specifically to evaluate gender differences when determining efficacy and outcomes of the available treatments.

TESTOSTERONE AND AD

Modest changes in testosterone levels can be detected in many men during mid-life, and yet with age, testosterone levels decrease further, and the incidence of such changes also increases with advancing age. Furthermore, it should be noted that decreases in testosterone levels are even more significant in men who are overweight or obese, conditions which are linked to development of diabetes, and which result in turn in a higher risk of AD. The gradual decline in testosterone levels begins in early adult life in both men and women. This decline occurs many decades before the accumulation of cerebral A β begins. Therefore, testosterone replacement therapy aimed at restoring normal physiological levels of testosterone in both men and women should be considered as an important prevention strategy for T2DM and AD. Furthermore, relatively low dose testosterone treatment close to age and gender appropriate physiological testosterone levels should be sufficient, obviating the need for higher testosterone doses and thus avoiding the associated side-effects.

Experiments using numerous animal and cellular models have demonstrated a variety of neuroprotective effects of testosterone, which include improving cognitive performance and synaptic plasticity [39, 40], improving synapse density on hippocampal dendritic spines [41–

43], maintaining hippocampal function during aging [39, 44], improving cerebral blood flow and glucose metabolism in specific brain regions [45], reducing the aggregation of A β and its associated neurotoxicity [46, 47], and reducing tau hyperphosphorylation [47]. We were the first to report that low testosterone levels in elderly men are associated with increased plasma levels of A β [48], the peptide that aggregates and deposits in the brain as amyloid in AD.

Low testosterone levels have been linked to a reduction in cognitive skills [49]. In both rodents and humans, the depletion of testosterone has been shown to reduce cognitive performance, and it has been found that this effect can be reversed by testosterone supplementation [50]. Research from several groups including our own have shown that men with low testosterone in their brain and blood are at increased risk of AD [51, 52]. Similarly, low testosterone levels have been shown to precede the cognitive impairment and neuropathological outcomes of AD [53, 54], suggesting that low testosterone may partially be a cause rather than a consequence of AD. Recently, a large retrospective cohort study which utilized data from hospital medical records indicated that long term androgen deprivation treatment [16] for prostate cancer is associated with an increased risk of AD, and that this increased risk correlated with the duration of ADT [55]. This risk of AD may also be influenced by apolipoprotein E (*APOE*) ϵ 4 allele status, the strongest genetic risk factor for AD, to our knowledge this has not yet been examined, and it should be incorporated in future analyses [56].

Testosterone treatment has been trialed as an approach to prevent cognitive decline and the development of AD, and although clinical trials have shown some promise in improving cognition in men with low testosterone [57], clinical efficacy has shown mixed outcomes [58]. However, it is important to bear in mind that there is a paucity of data on the relationship between testosterone and AD in older men, such as whether it is reduced total or free (bioavailable) testosterone that might predispose men to AD. Based on two recent meta-analyses and a review of the significance of low testosterone as a risk factor for AD, it is clear that this concept needs further research. The review, which is similar to ours, looked at mechanisms that link AD and T2DM and highlighted the evidence that age-related endocrine changes, particularly low testosterone levels, precede the cognitive and neuropathological changes seen in AD, and increase the risk of both T2DM and AD [59]. One meta-analysis that supports the concept that testosterone levels influence the risk of AD takes into account all forms of testosterone [60], whereas another meta-analysis opposes it: this review only takes into account total testosterone levels, yet also considers estrogen and SHBG [61], and comes to the conclusion that SHBG levels are higher in AD, thus influencing bioavailable testosterone. This leads back to the same concept that bioavailable testosterone is the key factor influencing AD risk, though indicating SHBG levels are also relevant and should be measured in future studies. Thus, as proof of concept, testosterone trials need to not only utilize an accurate testosterone (free and total) measurement assay by mass-spectrometry, but also require correction for SHBG levels as SHBG increases with aging and the majority of testosterone is SHBG-bound. As mentioned above, consideration of the *APOE* genotype is also of the utmost importance.

The prevalence of AD is significantly higher in women compared to men (almost two-thirds of people with AD are women), which cannot be attributed simply to the higher longevity of women compared to men. There must be other factors, biological explanations, that account for this gender difference; factors that may include genetics and in particular, differences in sex hormones [62].

Unlike andropause in men, testosterone levels are largely unaffected by natural menopause in women. However, circulating levels of testosterone produced by the ovaries and the adrenal glands decline gradually with age starting from late reproductive years [63, 64]; a decline which persists during and after menopause [65]. This may result in decreased libido, diminished well-being, and lowered mood [65]. Despite the fact that men produce more testosterone than women, testosterone is actually the most abundant sex steroid in women, circulating in the micro and nanomolar range, compared with a picomolar concentration range of estrogen [66]. Estrogen is made from testosterone and other adrenal hormones in women, thus women can experience disease-related symptoms due to lack of testosterone. However, gender-specific clinical studies in AD research have not been a major focus, including assessments of gender-specific effects of testosterone replacement therapy in men and women. The role of testosterone is much more clearly defined in men than it is in women, and the diagnosis of testosterone deficiency in women at present is lacking because there are no defined levels of testosterone below which a woman can be diagnosed as androgen deficient [67]. Despite the fact that low doses of testosterone have been widely used in women for the symptomatic treatment of sexual dysfunction and premenstrual syndrome, clinical trials addressing the effect on cognition are still lacking. Testosterone administration in women with low testosterone levels has resulted in small but statistically significant improvements on verbal learning and memory [68], yet other studies found neither an improvement or worsening of cognitive performance [69, 70]. However, most of these studies were done over a short term (26 weeks) thus it is not known whether the effects of testosterone replacement on cognition are long-lasting; and furthermore, little is known about the long term safety of testosterone use in women.

MECHANISMS PROPOSED TO LINK T2DM AND AD: TESTOSTERONE TREATMENT AS A MODIFIER

Cell culture and animal model studies indicate several mechanisms may potentially link T2DM and AD. Impairments in insulin signaling, inadequate A β clearance by IDE, neprilysin (NEP), and ApoE, disrupted glucose metabolism, inflammation, and altered lipid metabolism are all thought to contribute to both T2DM and AD. The possible role of testosterone in mediating changes to these potential mechanisms will be discussed in this section.

Impaired insulin receptor signaling and testosterone action

Insulin resistance is characterized by the inability to respond to insulin, which results in reduced downstream signaling following insulin stimulation, and eventually an increase in production of insulin (hyperinsulinemia) by the islet beta cells of the pancreas, in compensation. The insulin receptors [34] are tyrosine kinases that facilitate several signaling

pathways, including glucose transport and are expressed not only in the peripheral insulin-sensitive organs such as the liver and muscles, but also in the central nervous system (CNS), such as in the hippocampus and cortex [71]. Brain insulin, however, is thought to originate mostly from endogenous production [72], and the high levels of insulin in the brain are reported to be independent of peripheral insulin, since circulating plasma insulin levels do not influence the levels in the brain [73,74]. In the brain, insulin binds to IRs, then auto-phosphorylation occurs on multiple substrates including insulin receptor substrate-1 (IRS-1) and IRS-2. Phosphorylated IRS activates downstream signaling pathways linked to phosphatidylinositol 3-kinase (PI3K), which is important for synaptic plasticity, learning, and memory [75]. The activation of PI3K converts membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), leading to the activation of Akt which phosphorylates glycogen synthase kinase (GSK)3 β [76]. It has been known for a long time that GSK3 β regulates tau phosphorylation in AD [77], and recent evidence has shown that the enzyme similarly regulates tau phosphorylation in the T2DM brain, thereby leading to neurofibrillary tangle formation [78].

There is evidence that impairments in insulin signaling and function in the brain are linked to AD. However, the underlying mechanisms are not clear. Cell culture and animal model studies have demonstrated that insulin plays a role in A β and tau metabolism. For example, insulin has been shown to affect both the production and degradation of A β in neurons as well as tau hyperphosphorylation [79]. Furthermore, IR knockout mice exhibit a significant reduction in both Akt and GSK3p phosphorylation, which in turn can lead to the hyperphosphorylation of tau. However, there were no changes observed in memory or glucose metabolism in these mice, suggesting that either there are other mechanisms involved, or increased tau phosphorylation *per se* is not sufficient to explain the link between T2DM and AD [80]. Other links between insulin signaling dysfunction and AD involve vascular remodeling, at least partly via increased RAGE (receptor for advanced glycation endproducts) expression, which increases reactive oxygen species levels and vascular inflammation [81].

Testosterone levels have also been linked to insulin signaling and downstream events; for example, cell culture and animal experimental data have shown that testosterone depletion via castration reduces IR expression and increases IRS-1 serine phosphorylation [82]. Conversely, testosterone treatment has been shown to increase the expression of IR in both liver and skeletal muscle, but not adipose tissue; the three major insulin responsive target organs which also express androgen receptors (AR) [83–85]. It is important to remember that peripheral testosterone can also reach the brain via the blood brain barrier using a receptor-mediated transport system [86, 87], and it has been shown that testosterone treatment prevents the heat-shock induced over-activation of GSK3 β and subsequently diminishes tau hyperphosphorylation in female rats [88, 89], which may be effected via aromatization of testosterone to estrogen [47]. In other studies, male mice bred with pancreatic cells lacking AR (β ARKO) fed a high fat diet have been shown to secrete less insulin and to develop glucose intolerance [90]. Further work by this same group, demonstrated that testosterone enhanced glucose-stimulated insulin secretion via AR in human pancreatic β cells and male mouse islet, an effect that is eliminated in β ARKO(–/y) islets as well as human islets treated with an AR antagonist, suggesting that AR is a novel

receptor that enhances pancreatic β cells function. The mechanism of this testosterone activated AR-enhancing insulin secretion is through the interaction between extranuclear AR and the glucagon-like peptide 1, which in turn increases islet cAMP and activates protein kinase A [90].

Clinical trials have shown that anti-androgen treatment decreases insulin resistance in women with excessive testosterone [91, 92]. However, most studies investigating the effect of testosterone on peripheral insulin sensitivity have been done in an excessive testosterone (hyperandrogenic) setting, and concerned with reducing testosterone levels. Studies of testosterone administration that investigate peripheral insulin sensitivity have been restricted to men, and there are no clinical trials examining brain insulin sensitivity to date. Nevertheless, these findings concerning testosterone's potential effects on insulin signaling pathways support the concept that testosterone therapy may be valuable in the prevention and treatment of T2DM and AD.

Impaired A β clearance via insulin degrading enzyme and testosterone

Cell culture and animal model studies have demonstrated that insulin and related proteins affect both the production and degradation of A β [93, 94]. For example, there are several A β degrading enzymes, one of which is IDE. This enzyme plays a major role in the degradation of both insulin and A β [95], yet IDE has a preferential affinity for insulin such that it can inhibit IDE-mediated degradation of A β . This is likely to be one of the reasons that higher levels of A β have been found in the brains of diabetic patients and animals, in a brain region-dependent manner [96–99]. Furthermore, IDE defects are linked to the development of T2DM [100] and IDE has been identified as a T2DM and AD susceptibility gene [101].

Testosterone levels are likely to influence A β degradation, as testosterone has been shown to be an endogenous regulator of several A β -degrading enzymes, including IDE and NEP. For example, the new generation selective androgen receptor modulators (SARMs) exhibit potential therapeutic value by reducing A β levels in the brain via increased levels and activity of IDE in AD animal models [102]. While SARMs are efficacious in the treatment of osteoporosis and sarcopenia, a recent study found that one SARM—NEP28—increased the activity of NEP which may reduce brain A β levels [103]. Similarly, other studies have shown that testosterone strongly elevates neuronal expression of NEP through an AR-dependent mechanism which in turn decreases A β , demonstrated in both castrated rats treated with DHT, and APP23 mice crossed with aromatase knockout mice [104, 105]. Furthermore, testosterone supplementation has been shown to elevate IDE levels in hyperinsulinemic castrated rats [106]. The upregulation of IDE and NEP may also have a beneficial effect on the levels, toxicity or fibrillization of amylin [107, 108]. Thus, the effect of testosterone in modulating IDE and NEP expression and activity in both T2DM and AD may improve these conditions.

Impaired glucose metabolism and testosterone

Defective insulin secretion or action results in reduced insulin-stimulated glucose uptake. This eventually leads to persistently elevated blood glucose levels, thereby predisposing to serious complications that contribute to AD pathology [109,110]. There is now also

accumulating evidence that testosterone has a significant direct effect in modulating glucose metabolism [111]. For example, many studies have demonstrated that testosterone may improve glucose metabolism by modification of the glucose transporter GLUT4 and increased expression of insulin receptor protein (reviewed in [112]). Testosterone also mediates sex-specific activation of the AR in the brain, skeletal muscle, liver, adipose tissue, and pancreatic islet β -cells for maintenance in glucose homeostasis (reviewed in [27]).

However, recent studies have also shown that glucose uptake and GLUT4 translocation is stimulated by testosterone via liver kinase B1/AMP-activated protein kinase (LKB1/AMPK) signaling in adipocytes, a mechanism that is independent of AR [113]. AMPK plays a key role in glucose metabolism and is a master regulator of cellular energy homeostasis for gonadal function as well as the biogenesis of GLUT4 and mitochondria in adipose tissue, skeletal muscle, and liver [114, 115]. It is activated by LKB1 and in response to metabolic stresses, exercise, sex hormones, and insulin sensitizing agents such as Metformin [116–118]. In T2DM, dysregulation of AMPK has been observed in both animals and humans and AMPK activation improves glucose uptake [119]. AMPK activation has also been shown to decrease mTOR signaling activity which facilitates autophagy and promotes lysosomal degradation of Ap. However, LKB1/AMPK signaling can also lead to greater A β generation and tau phosphorylation [116]. Thus the potential of AMPK activation in AD in reducing development of AD is still unclear, as both beneficial and detrimental effects have been observed [116]. Nevertheless, the LKB1/AMPK pathway, and the influence of testosterone on this pathway, are worth investigating further as a potential treatment avenue for T2DM and AD.

Testosterone deprivation has been shown to increase blood glucose levels, an effect accompanied by the inhibition of Akt phosphorylation, GLUT4 protein expression, and glucose uptake. The inhibition of these parameters was found to be reversed following testosterone treatment [83]. In young men with idiopathic hypogonadotropic hypogonadism, acute testosterone withdrawal reduced insulin sensitivity in the blood [120]. Long-term effects may also occur, however, as there is also much evidence that insulin sensitivity is indirectly influenced by testosterone via its effects on body composition (reviewed in [121, 122]). Interestingly, a reciprocal relationship also exists in which acute and chronic hyperglycemia can lower testosterone levels, suggesting that low testosterone is a consequence of impaired glucose metabolism [123, 124]. Thus, a bi-directional relationship exists between testosterone and glucose control, at least mediated in part by increased visceral fat [125]. This suggests that the normalization of testosterone levels, either by testosterone treatment or a weight loss approach (by diet, exercise, or surgery) has therapeutic potential in the prevention and treatment of T2DM and thus possibly also AD.

Studies of the effects of testosterone supplementation in hypogonadal men on glucose homeostasis have so far produced mixed results [126]; though interestingly, positive outcomes of testosterone replacement therapy on glucose uptake have been measured by FDG-PET scans in elderly patients with AD [127]. Testosterone replacement in hypogonadal men with T2DM improved glycemic control in some studies [13, 14] but no improvements were found in other studies [15, 128, 129]. Thereasons for these discrepancies were in part related to the cut-off value to measure insulin resistance, HOMA-IR1 or 2, indicating that

participants need to be selected to have insulin resistance at baseline to be able to assess the effect of testosterone on this parameter. Another likely reason for discrepancies in the results is the difference in duration of these studies; those of long term duration (~6 years) resulted in improvements in insulin resistance, whereas shorter term studies (~1 year) resulted in no improvements [130]. Consideration should also have been given to the forms of testosterone supplementation used in these studies; a recently published retrospective cohort study reported significant variation in metabolic outcomes that were dependent on the administration method [131]. In accordance, only one (testosterone implant) had significantly beneficial effects on glucose levels after 12 months, despite almost unanimously beneficial effects on lipid profile.

Both rodent and human data has shown that there are gender-specific differences in peripheral glucose metabolism; that is, healthy females have higher glucose effectiveness compared to males [132]. In the CNS, similar gender differences exist in the hypothalamic circuitry controlling brain glucose homeostasis [133]. These differences are clearly attributed to the sex hormones. However, once low levels of testosterone manifest due to aging, the resulting impairment in glucose metabolism does not differ significantly between men and women. Thus, it is believed that testosterone therapy can improve glucose metabolism in elderly men and women [45, 127, 134], despite findings from randomized clinical trials so far being inconsistent [125].

Impaired lipid homeostasis and testosterone

Another feature that links T2DM and AD is lipid dysregulation both in the brain and circulation. Commonly seen in both conditions are hypercholesterolemia and perturbations of the high-density lipoprotein (HDL) and low-density lipoprotein (LDL) ratio, as well as elevated very low density lipoproteins (VLDL), triglycerides, and free fatty acids [135–137]. These factors may contribute to the development of insulin resistance and cardiovascular disease, but also AD-related pathology [138, 139]. Testosterone depletion has been shown to induce dyslipidemia in men [140, 141], while studies of testosterone replacement demonstrate favorable outcomes on lipid parameters such as decreasing total and LDL cholesterol, and reductions in triglyceride levels, although not all studies report changes in LDL levels [131, 142]. Conversely, testosterone replacement also appears to reduce levels of HDL cholesterol which could be deleterious due to increased cardiovascular disease risk. However, testosterone replacement does not lower levels below the normal range (if at all), when testosterone levels are maintained at a eugonadal level [131]. In addition, differences in the length of the CAG repeat polymorphism in the *AR* gene which is known to influence AR sensitivity, may mediate the effect on HDL cholesterol or other parameters [141]. Dietary and lifestyle factors could also be relevant. Despite the mixed findings, most studies indicate that testosterone elicits beneficial effects on blood lipid profiles.

In humans, gender-specific differences are associated with distinct body fat distribution and energy substrate utilization patterns; that is women store more lipids and have higher whole-body insulin sensitivity than men, whereas men tend to oxidize lipids more than women. These conditions are influenced by the menstrual phase in females, and by nutritional status and exercise intensity in both genders (reviewed in [132]). In contrast to the vast amount of

evidence regarding the effect of estrogen on lipid metabolism, randomized clinical trials, investigating testosterone therapy-induced changes to lipid parameters in women with low testosterone, are still lacking. One study showed that a low dose of testosterone caused a modest increase in plasma HDL and VLDL levels [143]. However, a meta-analysis concerning peri- and post-menopausal women found that adding testosterone to hormone therapy caused a reduction in HDL [144]. There is a need for more randomized clinical trials of testosterone therapy in both men and women to elucidate gender-specific differences that may occur in lipid homeostasis.

Impaired A β clearance via ApoE and testosterone

Apolipoprotein E (ApoE) is another important agent involved in A β clearance. The *APOE* $\epsilon 4$ allele is the strongest genetic risk factor for AD, and interestingly, the ApoE $\epsilon 4$ protein is less efficient than ApoE $\epsilon 2$ and ApoE $\epsilon 3$ in promoting A β clearance [145]. Furthermore, differences in lipidation status between the ApoE isoforms influence the ability of ApoE to promote A β degradation, and the lipidation of ApoE is influenced by its lipid transporter ABCA1, whereby higher lipidation increases the clearance of A β [146]. It has also been found that ApoE in *APOE* $\epsilon 4$ carriers has a lower level of lipidation, an effect that is worsened by a high fat diet [147], and possession of *APOE* $\epsilon 4$ alleles has been reported to be associated with T2DM [148] whereas *APOE* $\epsilon 2$ confers a moderate risk for T2DM [149]. ApoE facilitates A β proteolysis by IDE, and another *APOE* characteristic that provides a link to both AD and T2DM is its negative correlation with IDE expression and activity in the brain; for example, it has been shown that AD patients have lower hippocampal IDE levels if carrying an *APOE* $\epsilon 4$ allele [97] and similarly, *APOE* $\epsilon 4$ mice which are known to have increased A β deposition exhibit lower IDE levels [150, 151]. Clinical trials have shown that AD patients exhibit impaired insulin metabolism, as shown by elevated plasma insulin levels, lower CSF insulin levels, and a reduced CSF to plasma ratio when compared to healthy aged controls; however, in *APOE* $\epsilon 4$ allele homozygotes, plasma insulin levels and the CSF- to-plasma insulin ratios have been found to be in the normal range, indicating metabolic differences in *APOE* $\epsilon 4$ allele carriers [152, 153]. Other studies have shown that *APOE* $\epsilon 4$ allele carriers with AD are less likely to benefit from insulin-related therapeutics [151] and that gender as well as *APOE* $\epsilon 4$ status influence insulin resistance and therapeutic responses [154].

Less is known about the interaction between ApoE and tau pathology in AD; however, one study has shown that although *APOE* allele status does show a correlation with A β amyloid deposition levels, it does not appear to predict tau pathology in a cognitively normal elderly cohort [155].

In men, it has been found that both low serum testosterone and the interaction between testosterone and *APOE* $\epsilon 4$ are associated with AD [156]. Moreover, there is compelling evidence of a significant interaction between testosterone levels and *APOE* genotype, with respect to brain function. For example, in people with *APOE* $\epsilon 4$ alleles, brain structure and cognition appear to be particularly sensitive to circulating testosterone levels. Furthermore, free testosterone levels have been found to be positively correlated with verbal episodic memory performance in *APOE* $\epsilon 4$ carriers but not in non-*APOE* $\epsilon 4$ individuals.

Testosterone levels have also been found to influence hippocampal volume in *APOE ε4* allele carriers, in the Vietnam Era Twin Study of Aging, such that those with low testosterone and who are also *APOE ε4* carriers have the smallest hippocampal volumes [157]. In other studies, the depletion of testosterone following castration in *APOE ε4* mice resulted in behavioral deficits in some tasks, which were not apparent in *APOE ε3* or *APOE* knockout mice [158]; furthermore, testosterone treatment appeared to reverse these behavioral deficits by stimulating AR-dependent pathways [159]. Interestingly, a study by Raber et al. showed that female *APOE ε4* mice responded to testosterone treatment with improved memory compared to male mice [159].

Inflammation and testosterone

Insulin resistance, which is recognized as a major T2DM hallmark, is associated with inflammation, which can be stimulated by increased levels of inflammatory mediators such as interleukin-6 (IL-6) and C-reactive protein (CRP) [160]. AD has also been shown to be associated with inflammation. For example inflammatory molecules, including acute-phase inflammatory reactants and pro-inflammatory cytokines, have been found in the CSF and amyloid plaques of AD patient brains [161–164], and increased levels of IL-6 have been found in the lumbar and ventricular CSF of patients with AD [165]. There is also evidence that circulating levels of inflammatory markers, particularly IL-6, are raised before dementia symptoms appear [166]. Although higher levels of these inflammatory mediators alone are not sufficient to serve as a diagnostic marker of AD, it should be noted that the levels of these inflammatory markers are highly variable when compared to cognitively healthy people. For example, elevated CRP levels have been shown to indicate an increased risk of AD in a subset of Japanese American people and also in a European cohort [167, 168], but not in Mexican Americans [169].

Many features of the peripheral and CNS inflammation that can be detected in both T2DM and AD are worsened in people with low testosterone levels. For example, many males with T2DM have low testosterone levels, and it has been found that this subgroup of patients also have high CRP levels. Furthermore, it has now been found that these low-testosterone T2DM males also have a low hematocrit, which correlates inversely with the CRP concentration [170]. Some studies suggest that elevated CRP levels can predict increased severity of AD, although findings have been inconsistent [171–173]. Increased IL-6 together with low testosterone has also been observed in older men with T2DM [174] and AD [175, 176] and evidence from experimental studies indicates that testosterone secretion is inhibited by IL-6 [177]. Interestingly, testosterone treatment appears to be able to reduce some of these inflammatory signs: testosterone has been found to lower the inflammatory state through decreased CRP levels in a study of hypogonadal aging men who were treated with testosterone supplementation for at least 15 months [178]. However, the effect was not found in hypogonadal men with T2DM, although this may be due to the short treatment duration [11]. In *in vitro* and *in vivo* studies, it has been shown that testosterone treatment can downregulate IL-6 production [179]. However, in some clinical studies the effect of testosterone on IL-6 have produced conflicting results; for example, testosterone has been found to partially reverse the increasing IL-6 levels caused by anti-androgen treatment, but

two clinical studies did not find any changes in IL-6 levels post-testosterone treatment [180, 181].

Closely linked to inflammation is oxidative stress, which again is associated with both T2DM and AD pathology [182–185]. Testosterone treatment has been shown to reduce indices of oxidative stress and improve cognition in the SAMP8 mouse model of aging, potentially via upregulating expression of the class III protein deacetylase, SIRT1 [184]. This appears to occur partly by induction of antioxidants and reduced release of reactive oxygen species [186]. However, testosterone may also be pro-oxidant in some circumstances, suggesting a role in redox balance [187]. In naturally-aging rats, testosterone produces positive effects on oxidative markers in the kidney [188]. However, a recent human study in the Texas Alzheimer's Research & Care Consortium (TARCC) cohort showed that the effects of testosterone may be beneficial on cognition in men with low oxidative stress, but detrimental for those with high oxidative stress as determined by homocysteine levels $<12 \mu\text{M}$ [189]. It is also possible these differences may only occur in some ethnic groups.

Less is known about the effects of testosterone on redox processes in T2DM; however, the beneficial effects seen in generalized models and the link between oxidative stress and insulin resistance suggests testosterone may also be able to reduce T2DM-related oxidative stress [190]. Supporting this, testosterone has been observed to reduce oxidative stress in human aortic endothelial cells via AR-mediated activation of PI3K/signaling, leading to activation of endothelial nitric oxide synthase (eNOS) and increased nitric oxide (NO) production [191]. While direct evidence is lacking, eNOS activation and NO upregulation have also been demonstrated to reduce oxidative stress indices in diabetic mice [192]. Conversely, in humans, supra-physiological doses of testosterone have been observed to downregulate expression of eNOS and NO production, as well as reducing antioxidant capacity [193], highlighting the importance of dosage. Overall, these studies indicate that testosterone and changes in inflammatory and oxidative markers are causally linked; however more longitudinal and interventional studies are needed.

TESTOSTERONE REGULATES BACE 1 ACTION IN AD AND T2DM

Accumulating evidence shows that T2DM causes brain insulin resistance, which increases the risk of AD (reviewed in [194]). Moreover, the extent of A β accumulation in the brains of people with T2DM correlates with the duration of T2DM [5]. Interestingly, it has been shown that people with T2DM are more likely to develop neurofibrillary tangles in their brain, irrespective of whether they have AD or cognitive impairment [195]. In fact, AD has been termed “type 3 diabetes”, which represents the chronic insulin resistance and insulin deficiency in the brain. An early piece of evidence for the links to T2DM came from a postmortem study that showed striking reductions in gene expression for insulin, insulin growth factor (IGF)-1 and IGF-II as well as its receptors in the AD CNS, that resembled but was distinct from changes seen in T2DM [196]. While these studies linked T2DM with the risk of developing AD, recent studies showed that this link may also work in the reverse order, such that people with AD may be more likely to develop T2DM. In an animal study that investigated mice expressing human β -site amyloid precursor protein cleaving enzyme 1 (BACE1), the knock-in mice showed signs of systemic poor glucose control compared to

control, such as increased glucose levels and reduced glucose metabolism in the brains of animals, commencing at 4 months of age; the mice also showed systemic changes, including a fatty liver phenotype and impaired liver glycogen storage [197]. BACE1 is a novel aspartic protease that is highly expressed in neuronal cells; it initiates A β formation by cleaving amyloid- β protein precursor (A β PP), with the second cleavage being carried out by γ -secretase [198]. BACE1 activity increases with age and to an even greater extent (two to five-fold) in sporadic AD [199]. Besides the brain, high mRNA levels of BACE1 are also found in the pancreatic β -cells, although the β -secretase activity in these cells is comparatively low due to alternative splicing [200]. This pancreatic isoform of BACE1 may not cleave A β PP, but other newly identified substrates such as enteropeptidase [200]. Some studies have demonstrated that the lack of BACE1 is able to prevent A β synthesis [201–203], and may also protect against obesity and T2DM [204]. Further evidence of links between AD and T2DM come from the findings that the BACE1 gene is present in a region associated with a high risk of diabetes in Pima Indians, which led to the finding (in a Caucasian population) of the T2DM-linked functionally relevant rs535860 SNP [205]. This study also showed that a reduction in BACE1 expression (in a cell culture model) results in much lower insulin mRNA expression, and that Bace1(–/–) mice have lower plasma insulin concentrations, lower body weight, though normal glucose tolerance and insulin sensitivity [205].

The first study to indicate that endogenous testosterone can downregulate BACE1 activities, via a mechanism independent from estrogen, was done by Li and colleagues by genetically targeting aromatase in male APP23 transgenic mice (ArKO $\times$ APP23). The authors found that the brains of aromatase-deficient AD mice had reduced pathology and improved cognitive function than the brains of control AD mice. The aromatase-deficient AD mice had lower levels of BACE1 activity, indicating that testosterone may prevent the production of A β by inhibiting BACE1 activity [104]. On the other hand, in female APP23 mice with a genetic deficiency of aromatase (APP/Ar^{+/–}), in which the brain contains non-detectable levels of estrogen, the administration of estrogen caused the downregulation of BACE1 [206], suggesting that estrogen, but not testosterone, may prevent the A β production by inhibiting BACE1 activity in female mice. Taken together, these studies highlight BACE1 as a major driver of the impaired glucose and insulin regulation, and suggest that BACE1 inhibition is an attractive therapeutic strategy for AD and T2DM. However, caution about potential mechanism-based toxicities resulting from complete BACE1 inhibition should be considered, as data generated from BACE1 deficient mouse models (BACE1^{–/–}) have revealed abnormalities in specific cognitive functions such as spatial and reference memories [207]. In addition, BACE1 is known to cleave a large number of substrates, so it is not surprising complete BACE1 ablation has been associated with a higher mortality shortly after birth, whereas surviving mice are smaller and display hyperactive behavior [203]. However, partial reduction in a BACE1 and AD mouse model (BACE1^{+/–}) resulted in normal spatial memory function, alongside improvements in AD neuropathology [208]. The degree to which BACE1 inhibition may provide beneficial A β -lowering effects and improvements in insulin resistance remains to be determined in preclinical studies, not only in animal models of AD and T2DM, but also in wild-type animals. More research is also needed to investigate the BACE1-lowering effects of testosterone.

COMBINATION OF TESTOSTERONE REPLACEMENT THERAPY AND EXERCISE AS PREVENTION AND TREATMENT FOR T2DM AND AD

Biologically, the sex hormones, in particular testosterone, play a substantial role in regulating various physiological parameters in both males and females and therefore would be the natural target for investigations into a possible involvement in regulating the effects of physical activity. This section describes the beneficial effect of exercise either on its own or in combination with testosterone supplementation in terms of prevention and management of T2DM and AD.

Beneficial effects of exercise alone in the prevention and management of T2DM and AD

With respect to T2DM, few studies have compared the efficacy of exercise interventions in men versus women [209]. Women with T2DM have been shown to have a greater risk of cardiovascular disease than men, and greater difficulties in physical activity adherence may exist for women compared to men in the context of T2DM [210]. However, intensive exercise intervention has been shown to be equally effective in preventing T2DM in both men and women [211]. Thus, exercise is important to reduce morbidity and mortality in individuals with T2DM, regardless of gender. Furthermore, given that increased intensity could determine the effect of exercise in the prevention and management of T2DM, studies have shown that endurance (aerobic) and strength (resistance) exercise trainings are most effective in improving insulin action and reducing blood glucose rapidly [212], however, the mechanistic difference between the two training types are unclear [213, 214]. Whether testosterone promotes peripheral and brain insulin sensitivity via exercise is less well studied. In mice, testosterone has been shown to increase metabolic rate via an AR-dependent action on skeletal muscle [215], and *AR* knockout mice exhibit decreased physical activity [216]. Unfortunately, clinical trials of T2DM that measure changes in physical activity in a careful and comprehensive manner are still lacking [125].

With respect to AD, few studies have compared the efficacy of exercise in men versus women, and there are clear differences between men and women regarding cognitive improvement in association with exercise [217, 218]. The biological explanation for this is partly related to the abrupt loss of the neuroprotective sex hormone estrogen and the decline of testosterone in postmenopausal women [219]. Animal studies and clinical trials have shown the benefit of exercise as a non-pharmacological option in reducing A β amyloid pathology, maintaining cognition, as well as preventing and postponing cognitive decline in the aging brain (extensively reviewed in [220–222]). More recent studies have expanded the research question by investigating exercise mediated effects on hippocampal neurogenesis [220, 223] and anti-inflammatory effects [224, 225]. Of particular interest with the link to T2DM, exercise not only improves peripheral insulin sensitivity, but also brain insulin signaling in rodents [226–228] as well as increased cerebral blood flow in men [229]. It has also been shown that depending on the intensity of the exercise, brain glucose uptake is altered [230]. A single bout of exercise has also been shown to reduced cortical BACE1 expression and activity, independent of changes in adiposity, and which is accompanied by the reductions in AMPK, Akt, and MAPK signaling in the cortex of mice fed a high fat diet [231].

The efficacy of testosterone replacement therapy is enhanced by exercise in T2DM and AD: the role of the muscle-brain axis

Whether exercise may provide benefits to testosterone replacement therapy alone still needs to be validated in studies of longer duration and larger sample size. Interestingly, recent studies have shown that exercise accentuates testosterone replacement therapy in men with low testosterone levels [232] and that these elevated testosterone levels persist, even after cessation of therapy [233]. In fact, different intensities of exercise may change the response of circulating testosterone levels both in animal models and in humans [234]. For example, acute exercise elevated testosterone in rodents, and resistance training induced elevated muscular dihydrotestosterone (DHT) thereby improving glucose metabolism in T2DM rats [235]. Clinical studies have shown that high intensity exercise (strength training), as opposed to low to moderate intensity, increases testosterone levels in older T2DM patients which may help to reduce the risk of AD (reviewed in [234, 236]). The molecular mechanism(s) underlying the effect of exercise on improving testosterone levels may be mediated by one of the most prominent trophic factors in the brain, brain-derived neurotrophic factor (BDNF) involved in neurogenesis and synaptogenesis. BDNF is expressed not only throughout the CNS, but also in skeletal muscle [237]. The link between BDNF and testosterone levels has been demonstrated in the development of the adolescent brain and in the pathogenesis of neurological disorders, with a role in cell proliferation. For instance, castration and testosterone administration in C57BL/6 mice during adolescence results in an AR-dependent effect on BDNF-tyrosine kinase (Trk) B signaling in the hippocampal and forebrain regions of the brain [238] and similarly in macaque monkeys and rats [239]. Previous studies suggest that neurotrophins such as BDNF act as mediators of testosterone action in the survival of new neurons in adult brain [240, 241]. Moreover, testosterone regulates BDNF levels in the skeletal muscle, and in turn androgenic action at the muscle regulates BDNF levels in motoneurons [242, 243]. In humans, plasma BDNF has been shown to be positively correlated with circulating testosterone in the plasma of older men [244]. In both animal models and patients of T2DM and AD, BDNF has been shown to be depleted and these low levels of BDNF may be one of the pathogenic factors that cluster T2DM and AD together [245].

Exercise increases BDNF levels as a stimulus for the induction of neurogenesis to improve synaptic plasticity [246, 247], possibly in a testosterone dependent manner as explained above. However, acute endurance exercise can only transiently increase BDNF in the blood, while strength training does not alter BDNF levels [246].

Another mechanism of an exercise-mediated effect on neurogenesis via testosterone is through interaction with IGF-1. IGF-1 levels are reduced in the aging brain, and testosterone has been shown to increase IGF-1 levels *in vitro* [248] and in both hypogonadal and healthy men [249]. In addition, testosterone interacts with IGF-1 to control IGF-1-binding protein in androgen-responsive skeletal muscle fibroblasts [250]. Exercise has been shown to enhance IGF-1 expression in the brain [223] as well as induce uptake of blood IGF-1 by specific groups of neurons in the rat brain [251], which could possibly be attributed to the involvement of testosterone levels. Thus, on activation by exercise, skeletal muscles may

release growth factors such as BDNF and IGF-1 into the circulation to communicate with the brain, an effect possibly mediated by testosterone.

CONCLUSION

The relationship between low testosterone, T2DM, and AD is complex, and appears to involve a number of mechanisms such as insulin resistance, glucose metabolism, lipid regulation, A β clearance, inflammation, oxidative stress, and increased BACE1 activity. Even though these relationships are complex in nature, and our understanding of these relationships is currently incomplete, the evidence so far suggests that testosterone-based therapy has the potential to affect some of the metabolic pathways common to both T2DM and AD in a favorable manner, as well as modify interactions between some of these pathways (Fig. 1). Testosterone may reduce insulin resistance, improve glucose metabolism, improve several indices of dyslipidemia, increase A β clearance by increasing IDE and NEP expression and activity, and reduce inflammation (with many of these changes influenced by *APOE* allele status and also potentially by *AR*-CAG repeat polymorphism length). Therefore, testosterone may serve as a modifier of several metabolic pathways, disruptions of which have been linked to both T2DM and AD. However, testosterone treatment-induced improvements in the metabolic disturbances that occur in one or both of these conditions can also be achieved to some extent by adopting a healthy lifestyle, involving a better diet, exercise, and weight loss. It may eventuate that lifestyle changes combined with testosterone treatment will provide optimum benefits. Further basic research and adequately designed clinical trials need to be carried out to determine the value and efficacy of testosterone treatment on the metabolic disruptions and pathological changes common to T2DM, AD and related metabolic conditions. In addition, since gender-specific (and reproductive stage-dependent) differences related to T2DM and AD have been demonstrated in humans and animal models, both genders need to be studied in order to elucidate these fundamental differences so that gender-appropriate testosterone treatment regimens can be established.

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Fig. 1.

Common pathogenic mechanisms linking T2DM and AD under low testosterone conditions, showing points (green arrows) at which testosterone treatment modifies this relationship. 1) T2DM patient have insulin resistance which downregulates the expression of phosphorylated IRS and downstream signaling of PI3K activation in the brain. As a result, GSK3 β activity increases, and leads to A β and NFT deposition. 2) Hyperinsulinemia and IDE defects in T2DM patients lead to decreased clearance of A β in the brain. 3) Impairment in insulin-stimulated glucose uptake in the skeletal muscle of T2DM correlates with downregulated expression of GLUT-4 which in turn affects the glycolysis pathway. Although glucose is transported from skeletal muscle to the brain via GLUT-1, the role of testosterone in this pathway is not known. Testosterone also promotes GLUT4 translocation via LKB1/AMPK signaling and stimulates glucose transport in adipocytes, in which dysregulation of AMPK occurs in T2DM and AD. 4) Hypercholesterolemia and perturbations to the HDL:LDL ratio, as well as elevated VLDL, triglycerides and free fatty acids in T2DM contribute to the development of AD-related pathology and testosterone treatment has been shown to reduce all these parameters. 5) Possession of *APOE* $\epsilon 4$ genes causes impairments in lipoproteins and A β clearance, which confers a greater risk of T2DM and AD. 6) Peripheral and brain inflammation is associated with T2DM and AD and can exacerbate the underlying

pathologies through increasing pro-inflammatory mediators. Inflammation is also closely linked to oxidative stress that causes reduction of eNOS and NO. T2DM, type 2 diabetes; AD, Alzheimer's disease; IRS, insulin receptors; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; GSK3 β , glycogen synthase kinase 3p; PI3K, phosphatidylinositol 3-kinase; Ap, amyloid- β ; NFT, neurofibrillary tangles; ApoE e4, apolipoprotein E4; GLUT4, glucose transporter 4.

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