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REVIEW ARTICLE

Diabetes Mellitus and Male Aging: Pharmacotherapeutics and Clinical Implications

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Abstract: Andropause or male menopause is defined as androgen decline and onset of hypogonadism in the aging male. Testosterone deficiency in adult male is associated with diabetes mellitus, coronary artery disease, and heart failure. Type 2 diabetic male patients aged above 30 years showed low testosterone levels which is common in diabetic men and had symptoms of hypogonadism. Male sexual dysfunction among diabetic patients can include disorders of libido, ejaculatory problems, and erectile dysfunctions are common among people with diabetes, particularly in older men who had diabetes for years. Older diabetics tend to have both impaired insulin release as well as insulin resistance. There is growing evidence indicating the pathophysiological connections among the mechanisms of oxidative damage by disruption of the oxidative balance, increased levels of enzymatic glycation products in testicular region and glucose transporters, obesity and proinflammatory cytokines in male infertile patients with diabetes. Epidemiological studies suggest that many clinical findings in diabetics are linked to low testosterone levels. This article reviews pathophysiological mechanisms, observational studies, and clinical implications of testosterone therapy in type 2 diabetes mellitus.

Keywords: Testosterone, andropause, hypogonadism, insulin, diabetes mellitus.

1. INTRODUCTION

Diabetes mellitus (DM) is a worldwide problem and is primarily associated with other endocrinal and metabolic disturbances. The metabolism was found to be varied in different age groups. During ageing process characterized by several changes in human being by accumulation of physical, psychological, and social changes over time and ultimately led to death. After the age of 45 years the most vulnerable endocrine glands might be affected with diabetes [1]. The prevalence and incidence of diabetes were found to be more in adult population in many countries. The older age and family history of diabetes in male are key demographic risk factors for diabetes.

The low testosterone levels are an important factor to predict the occurrence of diabetes mellitus as demonstrated in several studies from last few years [2]. Men with type 2 diabetes are three times more likely to develop erectile dysfunction due to low testosterone levels than non-diabetic men. The decline in testosterone in diabetic men is due to both hypothalamic pituitary dysfunction as well as a testicular defect [3]. But the conditions are more extensive during ageing progress. The majority of healthy men complain of hypogonadal manifestations after the age of 55 years, a state termed andropause. The low testosterone concentrations are associated with poor sleep quality, insulin resistance, and increased risk for diabetes mellitus, obesity and metabolic syndrome as reported in recent studies [4].

Diabetes mellitus has an additive pathophysiological effect to aging in the progression of andropause (age of onset, progression, and morbidity) and testicular hypogonadism, neuropathy, vasculo-

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pathy, and endothelial dysfunction [5]. The decline in testosterone in diabetic men is due to both hypothalamic pituitary dysfunction as well as a testicular defect [6]. Diabetes accelerates age-related hypogonadal dysfunction in male with additive defects in hypothalamic-pituitary gonadal and sex hormone binding globulin (SHBG) regulations, which increases the severity of andropause in diabetics.

1.1. Andropause

Andropause is associated with low testosterone levels results in dysfunction in sexual satisfaction or in sexual desire in older man and total androgen deficiency does not occur only after surgery, accident, and diseases. Testosterone is a hormone responsible for the secondary sex characteristics that appear at puberty which is associated with enhanced metabolic processes in muscles, bones, bone marrow (erythropoiesis), the immune system, and the brain (cognition and mood) [7]. Older men are commonly experienced with hypogonadism symptoms with weakness, fatigue, obesity, osteopenia, lethargy, insomnia, mood disorders, flushes, sexual dysfunction, difficulty in erection, low volume of semen, alopecia, lack of energy, loss of muscle mass, obesity and decrease in bone mass [8, 9].

1.2. Testosterone Deficiency

Epidemiological data show that both serum free and total testosterone levels also fall with normal aging, which is termed as biochemical testosterone deficiency [10, 11]. The prevalence of testosterone deficiency increases with age due to slowing of metabolic clearance reported in several studies. This is partly due to falling of serum free and total testosterone levels with normal ageing and also decreased testosterone levels associated with illness or debility [12, 13]. Traditionally, hypogonadism has been characterized as testicular failure with elevated luteinizing hormone (LH) called primary hypothalamic-pituitary failure with low LH called as secondary hypogonadism.

According to the International Society for Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), and European Association for Urology (EAU) define that the total testosterone level < 8 nmol/l requires testosterone replacement therapy, whereas a level > 12 nmol/l does not require replacement therapy in ageing male [14]. Testosterone in men is synthesized and secreted by the Leydig cells of the testes into the circulation. It is mostly bound to plasma proteins. Total serum testosterone is found in 0.5-3.0% of free testosterone unbound to plasma proteins, 30-44% SHBG-bound testosterone and 54-68% albumin-bound testosterone [15, 16]. The 33-50% of type 2 diabetes mellitus patients have low plasma testosterone in association with low gonadotropins (borderline and overt hypogonadism) causes 10-20% decrease in hemoglobin concentration [17]. Testosterone treatment in elderly hypogonadism men has been shown to improve insulin sensitivity, assessed by HbA1c and homeostatic model assessment (HOMA) [18].

Long-term complications, such as metabolic syndrome (MetS), insulin resistance (IR), type 2 diabetes (T2D) [19], vascular disease [20], erectile dysfunction (ED), hypertension [21, 22], dyslipidemia [23, 24], osteoporosis [25], Alzheimer's disease [26], frailty [27], cardiac failure [28] and ischemic heart disease [29], are associated with low testosterone levels. Additionally, it is also associated with increases in SHBG levels due to reduction in free and bioavailable testosterone levels [30].

2. TESTOSTERONE DEFICIENCY TO DIABETES MELLITUS

Clinically testosterone deficiency was more commonly seen in the diabetic groups characterized by symptoms and signs of decreased androgen activity and senescence in both diabetics and non-diabetics and the prevalence and severity were almost similar in elderly (60-70 yrs.) and middle age (45-55 yrs.) diabetic patients. Age related decreases in growth hormone, androgens, testosterone (especially in men), and dehydroepiandrosterone levels may contribute to diabetes, if any reduction in these hormones may lead to loss of lean tissue, accumulation of fat and reduced physical performance. Unaltered hepatic glucose sensitivity to insulin and β-cell sensitivity was reported during ageing [31, 32].

The prevalence of both hypogonadism and diabetes increases with age in men. Lower testosterone levels are predicted with greater risk of developing diabetes mellitus [33, 34]. Men with diabetes have lower testosterone levels compared to men without a history of diabetes (Fig. **1**) [35]. The plasma testosterone levels were found to be varied in between type 1 (who have normal levels) and type 2 diabetes mellitus (who have subnormal levels) due to the differences in circulating levels of insulin (low in type 1 diabetes mellitus and high in type 2 diabetes mellitus) [36]. Decrease in testosterone, decreased muscle mass and increased abdominal mass is associated with ageing, it leads to the increased triglyceride levels which are associated with incidence of diabetes [37].

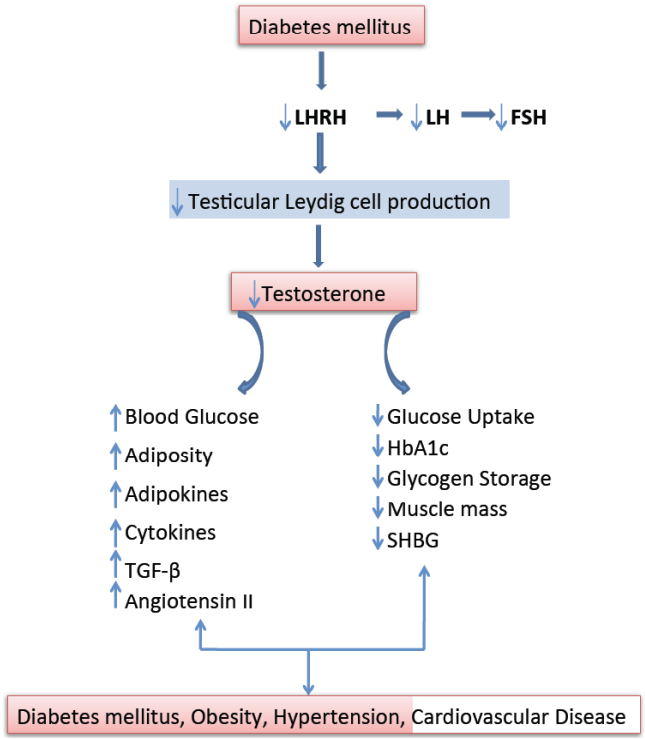

Fig. (1). Leading consequences of diabetes related Hypogonadism.

It contributes to the development of type 1 diabetes mellitus- or type 2 diabetes mellitus-associated hypogonadism. Additionally, both conditions occur with age related factors, such as increased fat mass which lead to the development of insulin resistance in adult male [38].

Leydig cells secrete testosterone and it also contains insulin receptors. Development of insulin resistance led to impair testosterone secretion by the Leydig cells [39]. Several studies reported to show that lower testosterone levels in patients also have the metabolic syndrome [40] or diabetes [41]. Reduced levels of total (48%) and free (26%) testosterone concentration with inappropriately low levels of LH and FSH were observed in type 2 diabetes mellitus cases. During andropause, low total testosterone concentrations and low SHBG were significantly associated with increased risk of obesity with increased glucose levels [42, 43] and that low SHBG levels are associated with a higher risk of type 2 diabetes in men

and high levels of SHBG are associated with lower risk of diabetes [44]. The development of insulin resistance was inhibited in the liver by signaling the hepatic androgen receptor in mice [45]. Endogenous reproductive hormones suppression was due to sequential stimulation of GnRH and human chorionic gonadotropin (hCG) in the pituitary gland and in the testes, leads to control over the testosterone and insulin levels mediated via HPG axis. Diabetes mellitus-associated andropause may affect male reproductive endocrine control over spermatogenesis, impairing penile erection, and ejaculation [46]. In testes, maintenance of spermatogenesis depends upon glucose metabolism [47]. During diabetes, multiple molecular mechanisms and pathways are involved in important consequences of male reproductive function in ageing male. The present review describes the molecular consequences of andropause during diabetes in ageing male and the current evidence on low serum testosterone level in patients with type 2 diabetes, and its clinical implications and adverse clinical outcomes. Leading consequences of diabetes related hypogonadism are clearly described in Fig. **1**.

2.1. Oxidative Stress

The spermatozoa are highly sensitive to oxidative stress. Increased cellular oxidative stress led to the development of diabetes mellitus due to the overproduction of reactive oxygen species (ROS) and decreased antioxidant efficiency (Fig. **2**) [48]. The glucose metabolism is very active to produce lactate, expected increased levels of oxidative stress particularly in Sertoli cells of testicular region. In fact, hyperglycemia was reported to induce important alterations in sperm concentration and motility by inducing free radical production and by altering energy production [49]. Compromising the fertility potential in the diabetic patients due to oxidative stress induced sperm plasma membrane and nuclear or mitochondrial DNA fragmentation [50].

2.2. Obesity

Diabetes mellitus is known to alter the lipid metabolism and is essential for a normal spermatogenesis might be due inactivation of genes involved in lipid metabolism [51]. Altered lipid metabolism leads to the development of obesity. Free testosterone levels have been reported to inversely with the degree of obesity with increased visceral adipose tissue in hypogonadal men, which further reduce the testosterone concentrations [52]. Studies reported that low serum total or free testosterone levels were reported in 20-64% of obese men and 33-50% type 2 diabetes mellitus patients have low plasma testosterone [53]. Visceral adiposity correlates positively with the degree of insulin resistance due to decreased uptake of triglycerides in abdominal tissue by the inhibition of lipoprotein lipase activity leading to improved insulin resistance, which lowers free fatty acids and reduction in adipocytes results in increased aromatase conversion. Aromatase is involved in metabolism of estradiol and has high activity in adipocytes. The breakdown of testosterone depends on the number and volume of adiposities. Testosterone inhibits the enzyme lipoprotein lipase. Lower testosterone levels would enhance the enzyme activity in aging male leading to improved insulin sensitivity and beta cell function. Because of greater uptake of triglyceride into the adipocytes, increasing fat storage stimulates the formation of new fat cells from preadipocytes in aging male. This converts testosterone to estradiol, which inhibits lipoprotein lipase results to more fat deposition might cause lower testosterone level with greater degree of hypogonadism [54]. Hence, low testosterone levels are associated with elevated levels of total serum cholesterol, triglycerides, low-density lipoprotein cholesterol, and lower high-density lipoprotein cholesterol in male with hypogonadism [55, 56].

In common men with obesity, type 2 diabetes mellitus and metabolic syndrome have been associated with low total and free

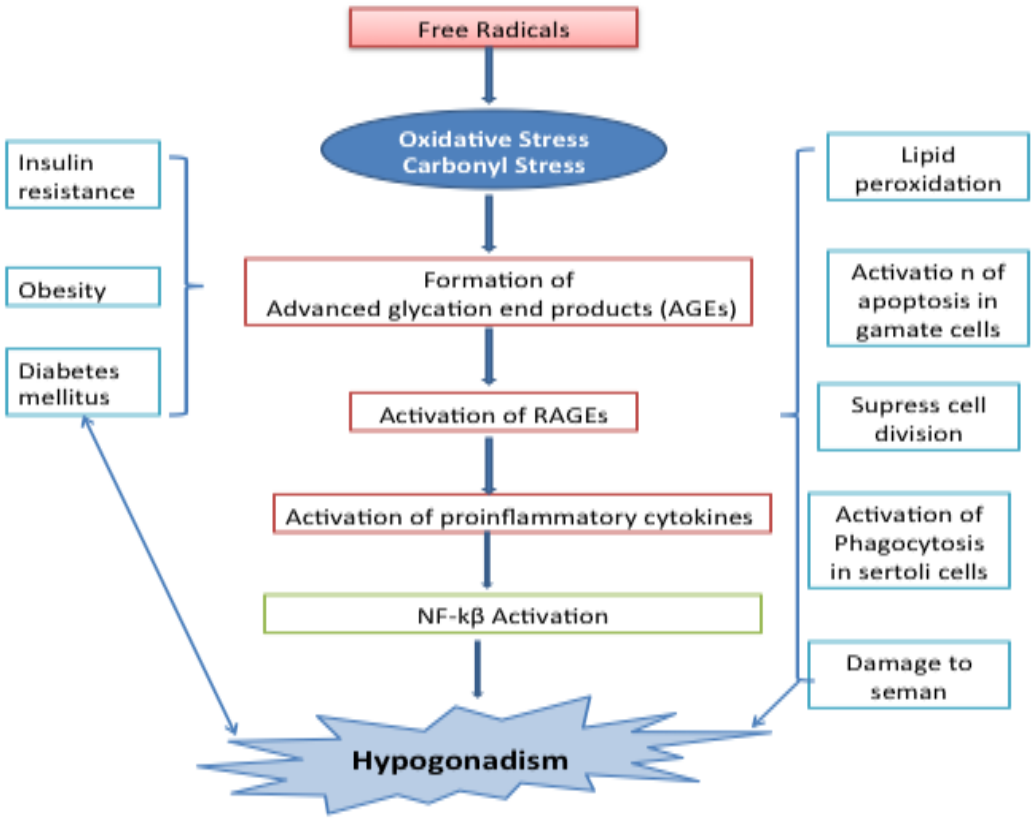

Fig. (2). Molecular pathways leading to hypogonadsim.

testosterone and SHBG levels. But in some cases, obesity is not associated with decreased testosterone and SHBG levels and increase in estrogen level in ageing men. Higher insulin expression may have suppressed SHBG in liver with insulin resistance condition and it may link with obesity. Strain *et al*. [57] reported that with significant weight loss, SHBG and male hormones usually become normal.

Increased amount of testosterone converted to estrogen under the action of the enzyme aromatase may also contribute to hypogonadism. The symptoms of fat mass gain and lose bone mass, muscle mass and strength are common in hypogonadal men. Obesity might also alter the metabolism of testosterone. In obese men, the peripheral conversion from testosterone to estrogen could attenuate the amplitude of luteinizing hormone pulses and inhibit testosterone production to exacerbate the vicious cycle of obesity and low serum testosterone level. Leptin may be a factor associated between adiposity and lowering of testosterone levels. Leptin receptors are present on the Leydig cell and inhibit the testosterone generated by administration of hCG chorionic gonadotropin. To this end, leptin, an adipokine, has been shown to be inversely correlated with serum testosterone level in men [58]. Leydig cells express leptin receptors and it has been shown to inhibit testosterone secretion in rodent models, suggesting the role leptin in obesity and in the pathogenesis of low testosterone [59].

Sex steroid hormones carry out their function in adipose tissues by both genomic and nongenomic mechanisms. Activation of the cAMP cascade by sex steroid hormones would activate hormone-sensitive lipase leading to lipolysis in adipose tissues. Testosterone replacement therapy has been shown to reduce insulin resistance in obese men and to decrease total cholesterol in hypogonadal men with coronary artery disease, along with statins treatment. Study in type 2 diabetic men showed improvement in glycemic control also [60]. There was a functional change in the production of LH, which led to decreased LH pulse frequency and amplitude as well as LH secretion and have a role in the age0related decline in testosterone [61, 62].

2.3. Increased Advanced Glycation end Products (AGEs) in Testicular Region

AGEs are the leading causes of age-related decline in the function of cells and tissues. There was accumulation of AGEs in tissues due to imbalance of the formation and clearance of AGEs [63]. Oxidative stress-induced hyperglycemia leads to the formation and accumulation of AGEs in testicular Leydig cells and affects testosterone secretion being the main causes of erectile dysfunction. High levels of circulating and tissue levels of carboxymethyl lysine (CML), and its receptor for advanced glycation end products (RAGE) were found in the testis, epididymis and sperm of diabetic men [64, 65, 66]. CML and expression of RAGEs cause cellular dysfunction, oxidative stress, and DNA damage in various organs and in a variety of conditions, such as diabetes [67]. Preclinical investigation supports that AGEs can significantly inhibit the secretion of testosterone in primarily cultured rat Leydig cells and increased expression of RAGE exists in rat Leydig cells [68].

2.4. Pro Inflammatory Cytokines

Testosterone biosynthesis is mostly regulated by secretion of LH in Leydig cells of testis, and Leydig cell steroidogenesis is modulated by circulating hormones, growth factors, and cytokines [69]. Testosterone has effect on the immune system through its immunosuppressive effect. As a result of inflammation, infection and trauma can reduce testosterone levels, which show suppressive action of inflammatory cytokines on the hypothalamic-pituitary testis axis. Androgens have been shown to inhibit the expression and release of cytokines and chemokines [70]. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), suppress the production of gonadotropin-releasing hormone from hypothalamus, which leads to decreased release of luteinizing hormone and follicle-stimulating hormone from the pituitary, hence leading to decreased gonadal stimulation in ageing male. This in turn leads to decreased testosterone release. Diabetes is associated with elevated serum levels of inflammatory proteins which include C-reactive protein (CRP), IL-1, IL-6, and TNF-α. In testosterone-deficient men suffering from type 2 diabetes mellitus, testosterone levels are inversely proportional to CRP and IL-6. The testosterone replacement has been shown to reduce TNFα, IL-6, serum leptin, and adiponectin levels [71, 72].

3. CLINICAL IMPLICATIONS OF TESTOSTERONE THERAPY:

According to the study of Clinical Practice Guidelines of Endocrine Society's in 2010, within the context of testosterone replacement therapy in ageing male with andropause showed high prevalence of a low serum testosterone level type 2 diabetic patients. Testosterone replacement in an interventional trial reported that the effect of clinical outcomes has mostly been carried out in men with symptomatic androgen deficiency [73, 74].

The patients with testosterone substitution along with conventional treatment had shown improved survival rate with low levels of testosterone (10.4 nmol/L) in comparison with patients without testosterone substitution and had a positive action on erectile dysfunction in type 2 diabetes. Testosterone substitution is an emerging treatment for the management of hypogonadism, and different testosterone preparations are available to achieve effective treatment. Naturally, testosterone should be used as a substitution therapy in hypogonadism. But the action is effective in the body when the testosterone is aromatized to estradiol reduced to dihydrotestosterone (DHT).

Androgen deficiency is associated with type 2 diabetes mellitus, insulin resistance, metabolic syndrome and obesity, which lead to the stimulation of the production of proinflammatory cytokines. In ageing male with andropause, the testosterone replacement therapy improves insulin sensitivity, fasting glucose, HbA1c levels, visceral obesity, insulin resistance, glycemic control, and lipid profile after short-term therapy with testosterone (Fig. **3**) [75, 76].

Testosterone replacement therapy affects physiologic testosterone levels and reduces the symptoms of hypogonadism. Several forms of injectable, oral, buccal, and transdermal preparations of testosterone replacement therapy are available in the United States [77].

Low testosterone concentration could be an important biochemical risk factor for diabetes in men. The meta-analysis studies indicate that men with high plasma total testosterone (≥15.5 nmol/L) and SHBG concentrations (≥28.3 nmol/L) have up to 50% reduced risk of diabetes compared with men in lower dichotomized groups [78].

A non-blinded study in hypogonadal diabetic has shown that testosterone replacement also improves glycemic control [79]. There was a control over weight gain and fat deposition in visceral adipose tissue in non-obese aging men and reduction in production of proinflammatory cytokines during testosterone therapy [80]. It is therefore proven that testosterone therapy attenuates adipogenesis as well as production of inflammatory mediators.

The sildenafil therapy was insufficient to cure erectile dysfunction in diabetic patients with hypogonadism alone, but in combination with testosterone therapy reverses erectile dysfunction in these patients. Testosterone replacement improves the low testosterone levels in men who fail to respond to phosphodiesterase type 5 inhibitors. The study suggested that long-term treatment with testosterone replacement therapy is not only safe to reduce the mortality rate but it may also improve survival rate in men with type 2 diabetes mellitus and hypogonadism.

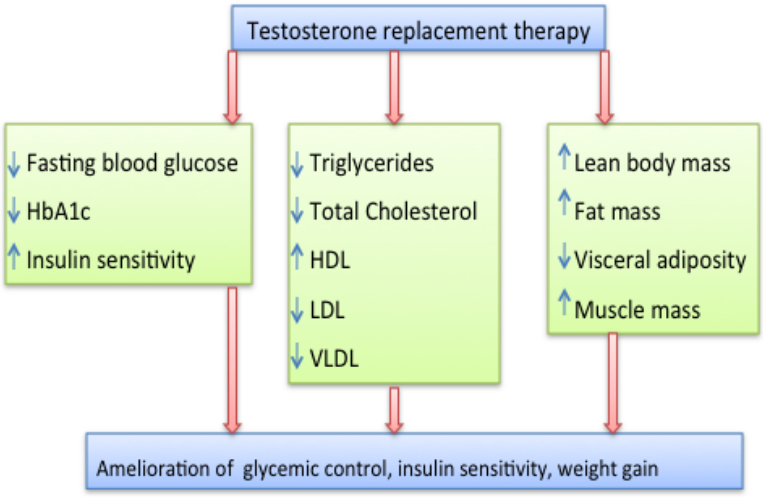

Fig. (3). Testosterone replacement therapy ameliorates glycemic control, insulin sensitivity, and weight gain by modulating various lipid and other mediators.

But even the long-term testosterone therapy showed severe adverse reactions that are reported cardiovascular disease, erythrocytosis, benign prostaticnhyperplasia, prostate cancer, hepatotoxicity, sleep apnea, gynecomastia, testicular atrophy or infertility and fluid retention [81, 82]. Since, health care providers put attention in continuous monitoring of patients in long-term testosterone therapy to avoid untoward effects of testosterone therapy.

4. OBSERVATIONAL STUDIES:

According to the Massachusetts male aging study, the low levels of testosterone and SHBG are the causes of type 2 diabetes mellitus by developing the insulin resistance [83]. In a large number of men with erectile dysfunction showed elevated HbA1c levels [84] and laboratory abnormalities in 3, 547 men with erectile dysfunction was assessed during the study of Kalinchenko *et al.* [85] reported that diabetic erectile dysfunction patients showed different baseline testosterone levels and in these patients experienced a differential response to sildenafil. Malkin *et al.* [86] conducted a randomized, single-blind, placebo-controlled cross-over study in testosterone deficient 27 Caucasian men (mean age 62 yrs.) in which testosterone treatment resulted in improved lipid profile and reduced inflammation due to balanced cytokine production. In 519 diabetic patients with tadalafil treatment, a significant glycemic control and a substantial benefit in all HbA1c ranges were observed [87].

Park *et al.* [88] reported that 162 elderly erectile dysfunction patients at mean age of 64.1 years showed poor response to sildenafil due to uncontrolled diabetes. A hormonal and metabolic evaluation was conducted by Nelly *et al.* [89] in 60 men. Out of that total of 45% of subjects had normal glucose tolerance, 20% had impaired glucose tolerance, and 35% had type 2 diabetes. Testosterone levels were positively correlated with insulin sensitivity, and low serum testosterone levels were associated with impaired mitochondrial function and promotion insulin resistance in men. Ponholzer *et al.* [90] conducted a survey in 2, 869 men and found that diabetics are more prone to increase the risk for developing erectile dysfunction compare with other conditions, such as hyperlipidemia, hypertension and psychologic stress. To assess the relationship between low testosterone and mitochondrial dysfunction, total testosterone levels were correlated with insulin sensitivity and were measured by hyperinsulinemic-euglycemic clamp studies in 60 men of mean age 60.5 years [91].

A double-blind, placebo-controlled, crossover study conducted on 30 patients with type 2 diabetes and hypogonadism by Kapoor *et al.* [92]. Testosterone therapy in all patients has been shown to reduce their homeostatic model assessment index, fasting plasma glucose and glycated hemoglobin. A study in 858 male veterans during andropause, medical comorbidity and other clinical conditions has shown fall in serum total and free testosterone levels was associated with increased mortality [93]. Corona *et al.* [94] conducted survey in 1, 200 men with erectile dysfunction reported to have 24.5% hypogonadism among diabetics than 12.6% among non-diabetic men. A cross-sectional meta-analysis study conducted by Ding *et al.* [95] reported that testosterone level was significantly lower in men with type 2 diabetes mellitus. Prospective studies indicated that men with higher testosterone levels had a 42% lower risk of type 2 diabetes Testosterone replacement therapy in 24 hypogonadal men with type 2 diabetes mellitus showed improvement in fasting insulin sensitivity, decreased HbA1c, fasting plasma glucose, waist hip ratio with no significant changes in lipid parameters and blood pressure [92]. Clinical studies including 6, 427 men reported that higher plasma testosterone levels were associated with lower risk of type 2 diabetes mellitus [95]. Testosterone levels have significant negative correlation with waist circumference, body mass index (BMI), insulin, and homeostatic model assessment of insulin resistance. Ageing males with low testosterone levels were more prone to diabetes because these findings indicate that testosterone may have a protective function against diabetes in men [96]. Treatment with testosterone undecanoate (200 mg) in 24 patients for a period of every two weeks during 12-week period significantly improved insulin resistance in terms of homeostasis model assessment-insulin resistance, total cholesterol, but not measured by blood pressure [97].

Fukui *et al.* [98] reported that testosterone replacement therapy could be associated with decreased insulin resistance and atherosclerosis in a large number of type 2 diabetic Japanese patients with low serum testosterone levels compared to healthy men. A cohort study was conducted in 1, 413 adult men with 101 diabetics. According to the study results, highest rate of free testosterone was associated with diabetes than man with lowest free testosterone in a four-fold change. [99]. A multi-center, randomized, double-blind, placebo-controlled study conducted by Khaw *et al.* [100] in hypogonadal men with type 2 diabetes mellitus showed significant results in insulin resistance and improvement in testosterone levels following testosterone replacement therapy. Long-term treatment in 700 men with testosterone undecanoate treatment showed 5 cm reduction in waist circumference, improvement in energy levels, sexual pleasure, concentration, libido and erectile function. The rate of erectile dysfunction controlled from 61-25% and phosphodiesterase V inhibitors responding rate was improved 37-60% [101].

Parenteral testosterone replacement therapy in 184 ageing male and metabolic syndrome showed significant reduction in weight, waist circumference, insulin levels and CRP levels after 30 weeks of randomization [102].

For a period of 6 months transdermal testosterone replacement therapy is associated with positive effects on insulin resistance, total and LDL-cholesterol, lipoprotein and uncompromised sexual health in ageing male with type 2 diabetes mellitus [103]. Brand *et al*. [104] conducted a cross-sectional study in 1, 292 men and reported that diabetic men had lower testosterone along with lower levels of SHBG when compared with non-diabetic men. Intramuscular testosterone undecanoate gel was assessed retrospectively within the low testosterone group during testosterone replacement therapy.

A study in 581 men with type 2 diabetes subjected to 6 years of testosterone replacement therapy indicates improved conditions and quality of life in hypogonadal diabetic men [105]. Testosterone replacement therapy in 351 late onset hypogonadic men for a period of 6.5 months during five randomized controlled trials showed reduction in fasting blood glucose, fasting serum insulin and triglyceride levels [106]. The BLAST study conducted by Hackett *et al*. [107] showed reductions in total cholesterol (TC), LDL, BMI, weight and waist circumference along with improvements in sexual function and quality of life during testosterone therapy in diabetics.

A study conducted in 255 men between 36 and 69 years for 5 years with long-acting testosterone undecanoate treatment has shown significant waist circumference reductions, weight reduction, reduction in HDL, and triglycerides [108]. A cross-sectional study conducted on 300 males with type 2 diabetes mellitus in ageing male reported significant proportion of diabetic men with low serum testosterone levels and a highly significant inverse relationship with BMI and LH. Rendong *et al*. [109] conducted a clinical study on a total of 213 patients with type 2 diabetes with a low total testosterone and normal total testosterone. The diabetic risk factors were significantly high in ageing male with hypogonadism like body mass index, fasting insulin, and homeostatic model assessment index levels, but lower LH levels were found. Varkonyi *et al*. [110] reported that low levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels could lead to low serum testosterone levels and diabetic neuropathy in 35-75% in erectile dysfunction population [110].

CONCLUSION

The prevalence of diabetes mellitus was found to be high across the world. The co-morbidity of both diabetes and hypogonadism has become more common with aging male. Several molecular pathogenic events are involved in diabetes-induced hypogonadism, besides oxidative stress, obesity, inflammation and accumulation of advance glycation end products on long lived tissues. The diagnosis of hypogonadism in the aging male requires a combination of symptoms and low serum testosterone levels. Indeed, several clinical trials reported that testosterone replacement therapy will improve the testosterone levels and increased sexual ability in aging male and also have potentiality in several aspects of aging male include diabetes mellitus, obesity and cardiovascular complications. Several classes of drugs are used in testosterone replacement therapy, such as selective androgen receptor modulators and phosphodiesterase type 5 inhibitors. Since most of the studies proved that these drugs have beneficial activity in ageing male. Since it needs further studies to examine the risk associated with the low testosterone in type 2 diabetes to assess the benefits, drug interactions and risk factors of suggested antidiabetic and testosterone combinational therapy. Diabetic male can play attention in screening for low testosterone levels. Healthcare providers need to provide information and raise awareness regarding the testosterone replacement therapy with low testosterone levels during ageing in the patients for the effective management of diabetes with healthy sexual life.

LIST OF ABBREVIATIONS

AGEs	=	advanced glycation end products
BMI	=	body mass index
CML	=	N3 -carboxymethyl-lysine
CRP	=	C-reactive protein
EAU	=	European Association for Urology
ED	=	erectile dysfunction
FSH	=	follicle stimulating hormone
hCG	=	human chorionic gonadotropin
HDL	=	high density lipoproteins
HOMA	=	homeostatic model assessment
IL-	=	interleukin-
IR	=	insulin resistance
ISA	=	International Society for Andrology
ISSAM Male	=	International Society for the Study of the Aging
LDL	=	low density lipoproteins
LH	=	luteinizing hormone
MetS	=	metabolic syndrome
RAGE	=	receptor for advanced glycation end products
ROS	=	reactive oxygen species
SHBG	=	sex hormone binding globulin
T2D	=	type 2 diabetes
TC	=	total cholesterol
TNF-α	=	tumor necrosis factor- α

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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