International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 12 Issue 8, August 2025

ISSN: 2394-4404

Hypogonadism In Diabetes Mellitus

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I. INTRODUCTION

Hypogonadism in men is a clinical syndrome that results from failure of testes to produce physiological levels of testosterone (androgen deficiency) and in some instances normal number of spermatozoa (infertility) due to disruption of one (or) more levels of the hypothalamic pituitary testicular axis.[1]

Risk factors for male hypogonadism include diabetes, hypertension, heart disease, psychological stress, inflammatory illness, chronic obstructive pulmonary disease (COPD), chronic pain with Opioid use and obesity.[2]

Testosterone is the principal sex hormone in men. It is important not only for normal sexual function but also for maintaining bone and muscle strength, mental and physical energy and overall well being. Low testosterone is associated with diminished libido, erectile dysfunction, increased fat mass, decrease muscle, bone mass and energy, depression and anemia.[3] Mild low testosterone was defined as a total testosterone level of <350ng/dl, and very low testosterone was defined as < 230ng/dl.[4] Statin like simvastatin, pravastatin, and lovastatin and atorvastatin are recommended to treat hyperlipidemia in military personnel. The use of statins and its probable side effect is reported to be lowered testosterone level along with myositis. (Official Air Force Approved Aircrew Medications. Effective: 19 May, 2011).

II. DIABETES

Diabetes mellitus is a chronic endocrine disorder characterized by hyperglycemia resulting from absolute or relative insulin deficiency. The pathophysiology of type I diabetes (T1DM) desires the autoimmune deficiency of insulin secreting pancreatic beta cell, resulting in insulin deficiency and subsequent hyperglycemia. Type I diabetes accounts for about 10-15% of all diabetes.

Type II diabetes (T2DM) is characterized by abnormal insulin secretion due to peripheral resistance and accounts for 85-90% of all diabetes. [5]

The rising epidemic of type II diabetes represents a major public health problem worldwide. The prevalence of diabetes is increasing among all age groups and a significant number are likely to be in prime reproductive years. The fact that one third of men with type II diabetes mellitus have low testosterone creates a substantial public health burden in terms of inadequate sexual function and potential infertility.[3]

PREVALENCE OF HYPOGONADISM IN DIABETES

The prevalence of both hypogonadism and type 2 diabetes mellitus increases with age.[6] Male hypogonadism is strongly associated with metabolic syndrome and may be a risk factor for the development of type II diabetes and coronary artery disease (CAD). In the last decades concepts are developing whether male hypogonadism and testosterone deficiency can lead to the development of insulin resistance and subsequent type II diabetes.

INSULIN RESISTANCE

Insulin resistance is one of the significant features of type II diabetes which features like obesity, hyperglycemia, hypertension and dyslipidemia. Diabetes mellitus is probably due to obesity leading to insulin resistance because of decreased in oxytocin neurons and leptin resistance.

HYPOGONADISM IS MOSTLY HYPOTHALAMIC IN ORIGIN

Hypogonadism / Androgen deficiency may be primary, due to a problem with testes (or) secondary, due to problem with hypothalamic pituitary-gonadal axis (or) combined both primary and secondary.[1] Secondary hypogonadism is observed with Prader-will syndrome (20%) cases in diabetes mellitus. Type II diabetes mellitus may be one of the commonest cause of hypogonadism- a lack of function in testes, which adversely affects testosterone production.

Androgens produced by testis and adrenal glands play a crucial role in the development and maintenance of male

reproductive organs such as the epididymis, vas deferens, seminal vesicle, prostate, penis and also needed for sexual functions to puberty, male fertility, muscle formation, body composition, bone mineralization, fat metabolism and cognitive function.[7]

Testosterone levels decrease as a process of ageing: signs and symptoms caused by this decline can be considered a normal part of ageing. Low levels of circulating androgen can cause disturbances in male sexual development, resulting in congenital abnormalities of the male reproductive tract. Later in life, this may cause reduced fertility, sexual dysfunction, decreased muscle formation and bone mineralization, disturbance of fat metabolism and cognitive dysfunction.[8]

Testosterone affects both the hypothalamus and the pituitary gland, causing the secretion of gonadotrophin - releasing hormone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) to be decreased. Low testosterone due to testicular failure (such as removal of the testicles) leads to high levels of LSH and FSH. This is called 'primary hypogonadism'.[3]

The testosterone in a normal man is predominantly bound to sex hormone binding globulin (SHBG) (44%) and albumin (54%); only around 2% circulates as free testosterone, only this free testosterone can entre body tissues and exerts its effects. Testosterone bound to albumin become free in small vessels and exert a biological effect but that remain bound to SHBG cannot exert its effect.[3]

LIBIDO, ERECTILE DYSFUNCTION AND TESTOSTERONE

The libido and sexual life of a man is initiated and maintained by testosterone and it's inter- action with SHBG. Lower testosterone levels are associated with erectile dysfunction (ED). In men, endogenous sex steroids impart beneficial effects on the heart with proven coronary atherosclerosis; have lower levels of testosterone and SHBG which negatively correlates with VLDL cholesterol, triglyceride (TG), basal metabolic index (BMI) and body fat.[2]

STATINS-HOW THEY ACT?

Statins act by inhibiting HMG CoA reductase, the rate limiting enzyme in cholesterol biosynthesis.

On this basis, statins could potentially decrease serum testosterone levels by reducing the availability of cholesterol for androgen bio synthesis.[4,9,] Statins (or) HMG-CoA reductase inhibitors have been central in the prevention of cardiovascular (CV) events associated with increased lipids and atherosclerotic lesions.[10]

Statins are structural analogues of 3-hydroxy 3-methylglutaryl-Coenzyme A, and competitively inhibit the HMG-CoA reductase enzyme responsible for the first committed sterol biosynthesis. By reducing intracellular levels of cholesterol, the expression of LDL receptors in liver cells is up- regulated, leading to increased clearance of LDL from the blood stream. Thus, their main effect lies in the reduction of LDL cholesterol.[11]

Statins are termed "Pleiotropic"', have numerous other effects unrelated to lowering LDL also includes in decreasing, oxidative Stress and vascular inflammation[12] by increasing the stability of atherosclerotic lesions.[13] Scandinavian Simvastatin Survival study (4s)[10] trial over a decade ago have reported a 30% reduction in the relative risk for all – cause mortality; a 22% reduction in the long term intervention with Pravastatin in Ischemic disease (lipid)[14]; and a 13% reduction in the heart protection study (HPS).[15]

Almost all conventional risk factors for atherosclerosis are associated with endothelial dysfunction, which is characterized by damage due to reactive oxygen species which promote the release of transcription factors, growth factors, proinflammatory cytokines, chemokines and adhesion molecules.[16]

In patients with coronary artery disease and hyperlipidemia, statins improve endothelial function; decrease the plasma concentration of tumor necrosis factor-alpha (TNF- α) and reduce morbidity and mortality.[17] Other cholesterol independent effects of statins include the inhibition of platelet function by decreasing the production of thrombaxane A2 and decreasing the cholesterol contents of platelet membranes, thus lowering their thrombogenic potential.[18]

Statins are also known to reduce C-reactive protein (CRP) which specifically renders oxidized LDL more susceptible to uptake by macrophages, induces the expression of vascular – cell adhesion molecules, stimulates the production of tissue factor and impairs the production of nitric oxide.[19, 20, 21]

Bhatia V, et al[22] in a study of 70 T2DM patients observed mild normocytic normochromic anemia with normal (or) high erythropoietin and raised C-reactive protein (CRP). Because inflammatory mediators interfere with insulin signal transduction, they may result in hypogonadotropic hypogonadism. Because of high CRP level, hypotestosteronemia in anemic patients can produce increased risk of atherogenesis.

STATIN USE AND HYPOGONADISM

The prevalence of hypogonadism among male veterans has been found to be as high as 38.7%.[23] In one study low testosterone was associated with increased mortality in male veterans[24], the percentage of patients was very high who ever on statins.[11] Thus, the evidence suggests that use of statin is a significant contributor to decreased serum testosterone levels.[10, 12, 14, 16]

Statin users are older and have a higher prevalence of DM, CAD and hypertension (HTN) than non-users. Statin use persists as a significant factor when controlling for BMI, DM, CAD, HTN, age, dyslipidemia and Opioid use. Thus in patients with obese and DM high dose statin use may exacerbate the disorder severe hypogonadism.[25]

Statin therapy induce overt primary hypogonadism which should be considered for the evaluation of low testosterone levels in patients with ED.[10, 12, 14, 16] Effects of lipid lowering treatment on steroid synthesis in patients with type II diabetes, 80 mg of atorvastatin decreased gonadal steroids.[26] On contrary another study showed high dose of atorvastatin seemed to be safe in terms of gonadal steroidogenesis.[27]

III. CONCLUSION

The rising epidemic of type 2 diabetes represents a major public health problem worldwide. Statin use in type 2 diabetes mellitus is a significant factor contributing to male hypogonadism. The fact that one third of men with type 2 diabetes have low testosterone creates a substantial public health burden in terms of inadequate sexual function and potential infertility. Testosterone deficiency in men, associated with type 2 diabetes mellitus improved by testosterone replacement therapy. For this, a screen to be done for diabetes mellitus in all cases of hypogonadism and vice versa.

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