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TESTOSTERONE REPLACEMENT THERAPY IN OBESE MALES

TOMASZ DREWA[1,2], DOROTA OLSZEWSKA-SŁONINA[2] and PIOTR CHLOSTA[3]

[1] Department of Urology, Institute of Oncology, Romanowskiej 2, 85-796 Bydgoszcz, Poland

[2] Department of Medical Biology, Nicolaus Copernicus University, Karłowicza 24, 85-092 Bydgoszcz, Poland

[3] Department of Urology, Institute of Oncology, Artwińskiego 3, 25-734 Kielce, Poland

Abstract: Controversy surrounds testosterone replacement therapy in obese ageing due to no generally accepted lower limits of normal testosterone level and high prevalence of hypogonadal symptoms in the ageing male population and the non-specific nature of these symptoms. Late onset hypogonadism is a clinical and biochemical syndrome associated with advancing age, often coexisting with obesity and metabolic syndrome. High fat and carbohydrates (fructose) consumption is responsible for development of obesity and metabolic syndrome which is one of risk factors for hypogonadism in older men. High fructose intake has been shown to cause dyslipidemia and to impair hepatic insulin sensitivity. Obesity and lack of physical activity negatively influence testosterone level. Low testosterone level should be regarded as an effect of obesity, but reverse relationship has not been proved yet. The management of late-onset hypogonadism symptoms has to be treated by a change of a life style and prevented with healthy nutrition and physical activity. The question related to rational indications for testosterone replacement therapy in obese males seems to be still actual.

Keywords: testosterone replacement therapy, late onset hypogonadism, obesity, metabolic syndrome

Controversy surrounds setting a lower limit of normal testosterone. There is also no generally accepted lower limits of normal testosterone level in ageing males. Patients with serum total testosterone levels below 8 nmol/L (230 ng/dL) will usually benefit from testosterone treatment, those with testosterone level above 12 nmol/L (350 ng/dL) not require substitution, but "grey zone" between 8 and 12 nmol/L still exists. It was demonstrated that demographic differences in testosterone level within population of aging males exist (1–3). In healthy adult men, about 44% of the circulating testosterone bound to sex-hormone binding protein (SHBG) is tightly bound and thus biologically inactive, 50% is nonspecifically bound to albumin, and 3.5% is bound to cortisol-binding globulin. Only 2–3% of testosterone is unbound (free) and thus bioactive (4). Concentrations of SHBG are related to variables such as diet, body mass index (BMI), insulin concentrations and age (5). Diet low in protein in elderly men may lead to elevated SHBG levels and decreased testosterone availability and activity. SHBG level influences bioactive testosterone level especially when serum albumin is low (6). SHBG level is not related to total calories, nor fat (animal or vegetable), nor carbohydrate intake. The decrease in bioactive testosterone can result in declines in sexual function, muscle strength, red cell count, and contribute to the loss of bone density (7). The measurement of free (bioavailable) testosterone should be considered when total testosterone can not confirm the symptoms related to hypogonadism, particularly in obese men (1). Men with low total testosterone and low SHBG have an increased risk of diabetes dependent of obesity (8). Bioavailable (free) testosterone positively correlated with muscle strength and bone mineral density, and is known to better reflect clinical symptoms of late onset hypogonadism than total testosterone (9), but it is difficult to found the firm threshold values for bioactive testosterone, depending on the method used and being not generally available (5, 10, 11). Difficulties can be found when one would classify the clinical syndrome related to late onset hypogonadism. It is due to the high prevalence of hypogonadal symptoms in the ageing male population and the non-specific nature of these symptoms. Late onset hypogonadism often coexists with obesity and metabolic

* Corresponding author: Tomasz Drewa, e-mail: tomaszdrewa@wp.pl; phone: 0048525853737; fax: 0048525853742

syndrome (12, 13). The overall prevalence of late onset hypogonadism varies from 6–9% in men aged 40–70 years and rises to 15–30% in diabetic and obese men (14, 15). Late onset hypogonadism will be in the near future a very often treated syndrome due to the fact that obesity is common from childhood (16).

Testosterone secretion is disturbed in obese males

Testosterone secretion is regulated by complicated feedback loops. Many factors influence on testosterone secretion. The most important are gonadotropin release hormone (GnRH) and luteinizing hormone (LH), which are involved in main negative feedback loop. Follicule stimulating hormone (FSH), dihydrotestosterone (DHT), estradiol and prolactin seems to control testosterone level as well. LH secretion is under negative feedback control by gonadal steroids, both testosterone and estradiol. The androgens slow the frequency of LH pulsate release (16). LH pulse modulation remains undisturbed in severely obese men but LH amplitude is significantly attenuated compared to non-obese individuals. Decreased LH levels and LH pulse amplitude were observed in the massively obese men with BMI > 40 kg/m^2 (17). There are also such factors like: inhibin, activin, adrenocorticotropic hormone (ACTH), leptin, neuropeptide Y, semen production, androgen receptor expression and function, liver function and serum protein production, which can influence testosterone secretion (12, 13, 18). FSH acts in the control of spermatogenesis following its binding to the FSH receptor in the basal aspect of the plasma membrane of Sertoli cells. FSH secretion is modulated by activin and inhibin (18). Obesity is associated with increased plasma levels of leptin, the obese gene product secreted from adipocytes. Circulating leptin correlates with total and free testosterone independently of SHBG, LH and estradiol, so it seems that leptin is the best hormonal predictor of lower androgen levels in obese men. Leptin receptors are present in testicular tissue and leptin may play a role in reduced androgen levels in obese men (19).

Obesity leads to metabolic syndrome, which is common in ageing males and often coexists with late onset hypogonadism. Obesity is associated with a reduction in serum total testosterone and SHBG levels (20). Men who were obese, whether measured by BMI or central obesity (waist-hip ratio or waist circumference) had a greater decline of free and total testosterone and SHBG, compared to men who were never classified as obese (21). Visceral adipose tissue correlate independently with free (bioactive) testosterone (22) and is associated with decreased basal cortisol secretion and increased cortisol response to exogenous adrenocorticotropin stimulation, which may contribute to higher insulin levels and decreased SHBG levels (23).

Metabolic syndrome is connected with non-alcoholic fatty liver disease, which can be a consequence of diet (24). Patients with more severe liver disease have lower testosterone and PSA levels than patients less affected (25). Male reproductive system is impaired early in liver dysfunction (26). It seems that, the way from obesity to hypogonadism is logical and empirically proven. Is the reverse relationship possible?

Does testosterone influence obesity?

Several questions are arising, but the most important is: Can simply testosterone replacement therapy rebuilt the balance of its regulation feedback system? It has to be emphasized that we intent to treat mostly men with functional Leydig cells. Complex multiple alternations of the testosterone secretion in older men are linked to modifiable risk factors like obesity, smoking and life style (13, 27). The second important question is: Can testosterone be really responsible for all symptoms and disorders, which occurred during ageing in men? In other words, can testosterone be used to treat obesity, and obesity related disorders like diabetes type 2, hypercholesterolemia, hypertension, ischemic heart disease, and cardiac failure and finally metabolic syndrome? It is worth to point out that obesity is regarded as a trigger factor leading to many mentioned above disorders including metabolic syndrome. On the other hand, it was shown that testosterone treatment can lead to an increase lean mass and decrease obesity in hypogonadic ageing males (12, 13, 27, 28). It is very interesting, how the obesity in ageing males should be interpreted? Does obesity result from a low serum testosterone level or does obesity exert an influence on testosterone level? The answer to this question is crucial for possible treatment decision. It seems that metabolic syndrome is not a consequence of low testosterone level, but low plasma testosterone concentration is only a coincidence with visceral obesity. One can suspect that metabolic syndrome can decrease testosterone level in ageing males. Some data show that lower levels of total testosterone and SHBG are predictive of the development of the metabolic syndrome, particularly in men with BMI < 25 kg/m^2 (29). Others suggest that the metabolic syndrome is an independent factor of hypogonadism in middle-aged men (30) and relative androgen deficiency appears to be a marker for,

rather than a cause of, metabolic syndrome in older men (31). This phenomenon and presented relationships remain unresolved (32).

How should we treat an obese men with hypogonadal symptoms?

Elevated intake of fat and carbohydrates and particularly fructose, which is common sweetener in beverages cause metabolic syndrome (24). Consumption of fructose-sweetened but not glucose-sweetened beverages increases *de novo* lipid synthesis, promotes dyslipidemia, impairs insulin sensitivity, and increases visceral adiposity (33, 34). Replacing sugar-sweetened beverages intake with water is associated with reductions in total calories and weight loss (35, 36).

Obesity is an important risk factor for many common diseases including cardiovascular disease, type 2 diabetes, cancer and erectile dysfunction (16, 37). It has to be emphasized that 100 kcal/day reduction would eliminate 71.2 mln cases of obesity in US, while 5 g/day reduction of fat would eliminate 3.9 mln cases of high cholesterol in US (38). The highest rates of obesity and type 2 diabetes are observed among people with low level of tested parameters, who used energy-dense food as the best way to provide daily calories. Obesity is the toxic consequence of economic insecurity and a failing economic environment, but not the effect of low testosterone (39). Obesity and obesity-related disorders, are epidemic in Western countries, where cheap energy-dense food is available, but not in really poor countries (40).

The link between physical activity and testosterone level can be easily shown. Anabolic hormones such as testosterone and growth hormones are elevated after exercise. Exercise leads to significant increases in testosterone and growth hormones in women and men (41, 42). A large number of trials have demonstrated a positive effect of testosterone treatment on bone mineral density and bone architecture, because it is an anabolic hormone, which takes part in "body building", but there is lack of data to prove that testosterone treatment in ageing males reduces fractures (12, 43–46).

The androgen receptor and several enzymes involved in androgen metabolism are also expressed in adipose tissue. It is true that dihydrotestosterone (DHT) inhibits adipocyte differentiation in subcutaneous and intraabdominal (omental) adipocyte in humans. 5α-DHT inactivation was detected in abdominal adipose tissue in men (47). Testosterone replacement therapy (parenteral testosterone undecanoate) generates physiological levels of DHT (48). On the other hand, it has to be emphasized that the regional depot difference in androgen inactivation rates could be a consequence of obesity. It was found significantly higher 5α-DHT inactivation rates in mature adipocytes compared with preadipocytes in subcutaneous adipose tissue (47, 49). Serum DHT levels do not change markedly with advancing age, but some studies suggest that DHT treatment may be a useful alternative for hormone replacement therapy in older men (50, 51). Based on a large amount of evidence it can be easily proved that testosterone level decreasing is an effect of improper life style, diet and lack of physical activity, which can lead to metabolic syndrome. It is worth to ask; Do we really need a testosterone replacement therapy in obese ageing males, who present a metabolic syndrome and low testosterone level? Most consistent effects of treatment have been on body composition. It was suggested that androgen administration to elderly men should be reserved for the minority of elderly men who have both clear clinical symptoms of hypogonadism and frankly low serum testosterone levels (20). It was proved that therapy including the both elements, i.e., body mass reduction and testosterone treatment can lead to success in obese ageing males with hypogonadism, but this fact did not exclude that body mass reduction alone would exert similar effect (52). One could speculate that preventing late onset hypogonadism through healthy life style and diet is a much better way than testosterone augmentation in obese ageing males. We think that this point of view deserves future studies.

Conclusions

High fat and fructose consumption is responsible for development of obesity and metabolic syndrome, which are characterized by low testosterone level. Obesity and lack of physical activity can negatively influence the testosterone level. Low testosterone level should be regarded as an effect of obesity, but reverse relationship has not been proved yet.

We hypothesized that management of late-onset hypogonadism symptoms has to be treated with a change of a life style and prevented with a program focused on healthy nutrition and physical activity in youth and elderly, as well. The question related to rational indications for testosterone replacement therapy in obese males seems to be still actual.

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