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Are Androgens Valuable in Management of Diabetes?

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Abstract

The Influence of androgens on diabetes mellitus is a subject of extensive discussion. Testosterone effect in clinical trials commonly is evaluated in patients with diabetes type 2. In addition, the studies conducted on experimental models of diabetes (alloxan- and streptozotocin-induced diabetes) also showed positive effects of androgen. Considering that experimental diabetes is more in line with diabetes type 1, it can be assumed that male sex hormone positively effects both types of diabetes. However, its influence may be realized by different pathways. Therefore, research of the opportunity of treatment of the various forms of diabetes with androgens, represents the active scientific and practical feature, which is waiting for the final verdict.

Keywords: Diabetes mellitus; Testosterone; Experimental diabetes

Introduction

It is established, that the testosterone deficiency promotes the development of the metabolic syndrome, insulin resistance, type 2 diabetes mellitus, hyperglycemia, as well as dyslipidemia and arterial hypertension, which, in turn, increases the risk of vascular diseases [1-7]. Conversely, in the case of high level of testosterone, insulin resistance decreases and the risk of development of diabetes is significantly reduced [8,9]. In addition, the decrease in the index of insulin resistance is in higher correlation with free testosterone than with the total testosterone [5,10,11]. Supplementation of testosterone in males with diabetes mellitus reduces the level of glucose in fasting and after eating, as well as level of glycosylated hemoglobin [12,13] and allows to reduce the dose of the insulin in insulin-dependent patients [3,14].

In this background, it is interesting to note that the results of several studies deny the statistically significant difference between the patients with metabolic syndrome and type 2 diabetes, treated with testosterone and without it. This indicates the need to continue research in this direction [15,16].

Discussion

It is confirmed that obesity and associated with it hyperinsulinemia stimulates the formation of testosterone, but suppresses the synthesis of sex hormone binding globulin (SHBG) and thus reduces the number of circulating testosterone [17,18]. Low levels of testosterone and SHBG are considered as a predictors of the development of metabolic syndrome and diabetes mellitus type 2 [19,20] and vice versa [21]. Insulin resistance in the condition of the androgen deficiency is likely to be associated with the changes of sensitivity of the skeletal muscle to insulin. Castration of rats causes the expressed insulin resistance in skeletal muscles, which is completely restored by treatment with physiologic doses of testosterone [22]. Testosterone, except the effect of sensitivity to insulin, can directly influence on pancreatic β-cells [23]. Following the androgen suppression therapy expressed hyperglycemia and β-cells function failure are revealed [24], while streptozotocin-induced early apoptotic damage of β-cells in castrated animals is prevented by testosterone replacement therapy [25].

Testosterone acts through the androgen receptor (AR), which represents a ligand-activated transcription factor. It was shown, that in male mice with reduced number of AR in β-cells, as well as on human cultures, these receptors play an important role in testosterone potentiation of glucose-stimulated insulin secretion (GSIS). The pathway is based on the icrease of the cAMP concentration in the β-cells and the activation of protein kinase A (PKA), which, in turn, increases the GLP-1 (glucagon-like peptide-1) effect. This finding may have important clinical and pharmacological value for the prevention of type 2 diabetes in elderly men [26]. Glucose homeostasis was studied in 12 weeks male mice lacking AR in β cells (βARKO). This is the age, which is followed by the development of the delayed obesity and insulin resistance in mice, backed by the total (or partial) deficit of AR. During 9 weeks, in the conditions of metabolic stress caused by the western diet, the βARKO-/y mice showed reduced insulin concentration and hyperglycemia both, after fasting as well as after feeding, unlike the control group mice. Thus, it has been confirmed that in the mice with a deficiency of AR in β-cells, the tendency to insulin deficiency is revealed,while western diet is followed by GSIS reduction and development of tolerance to glucose, despite the fact that the number of β-cellsdoes not change [26].

It is important that insulinotropic function of the AR is revealed in the human Langerhans islets in case of the physiological concentration of testosterone. It proves that testosterone is important for normal GSIS in males. Lack of androgen causes GSIS deficiency and creates favorable conditions (disposition) for the development of the type 2 diabetes mellitus. Decreasing of glucose concentration after testosterone supplementation also can be explained by the fact, that testosterone acting through the AR of liver cells promotes the synthesis of m-RNA of insulin receptors in hepatocytes, which leads to increased sensitivity of hepatocytes toward Insulin. In this condition the minimal concentration of insulin is enough to stimulate the glucose utilization by the liver cells [3, 27, 28]. In contrast to males, the lower number of AR in the β-cells of females does not change GSIS [29]. The reason is that, apparently, androgen concentrations in serum and tissues of female rats is less than needed to activate the androgen receptors [30]. As it was noted, high levels of testosterone in male are correlated with increased sensitivity to insulin. In addition, aromatization of testosterone 17b to/into estrodiol (E2) is important for energetic homeostasis in males. In the castrated male rodents, treated with pure androgen-DHT, which is not transfered into E2, is developed obesity, unlike the rodents treated with testosterone. This indicates that restoration of fat after the castration is caused by the transformation of testosterone into E2, which influences estrogen receptors (ER). This observation is confirmed by the data in which the marked increase in E2 concentration paralleled the decrease in the testosterone concentration in alloxan diabetes model [28,31,32]. Following the 200 mg/kg intraperitoneal injection of Alloxan toWistar male rats [33, 34], just like after 50 ml/l intraperitoneal injection Streptozotocin (STZ) to Sprague-Dawley female rats, there were found necrotic β-cells in Langerhans islets. The degenerative changes with lower intensity were found in epithelial cells of the liver and kidney tubules. The alloxan or STZ injection in adult rats promotes the development of severe and irreversible diabetes, which is very similar to type 1 diabetes [28, 35-37]. β-cell death is the last phase of its damage in experimental diabetes and can be expressed with the necrosis or caspase dependent apoptosis [37].

Insuline and glucagone have opposite effects on glucose homeostasis in the liver. Low level of insulin and high level of glucagon in the state of hunger promotes gluconogenesis and glycogenolysis in the liver that prevents the development of hypoglycemia. Thus, the fasting glucose level is determined by liver generated glucose level. After eating, glucose is the major factor which promotes insulin synthesis in β-cells and causes its secretion. Synthesized insulin interacts with insulin receptor in peripheral tissues (in skeletal muscles and fatty tissues), causing a number of intracellular reactions that promote glucose absorption and utilization of postprane glucose, thus maintaining glucose homeostasis [38,39]. In case of type 2 diabetes mellitus, β-cells lose their ability to respond adequately to peripheral insulin-resistance and demand for increase of insulin secretion. The increased amount of glucose in the blood promotes the secretion of pro-inflammatory cytokines from β-cells, which leads to the activation of mononuclear cells and the increased production of local cytokines. These pathological inflammation results in the progression of β-cells dysfunction and leads to their death. Male patients with type 2 diabetes mellitus, who demonstrate low levels of testosterone, can improve their health by treatment with testosterone. Such a conclusion has been taken as a result of randomized, double-blind, placebo-controlled study [40].

It should be noted that the majority of clinical trials study estrogen effect in diabetes type 2. In addition, studies conducted on experimental models of diabetes (alloxan- and STZ-induced diabetes), also confirms the positive effects of androgen. Considering that experimental diabetes is more in line with diabetes type 1, it can be assumed that male sex hormone positively affects not only diabetes type 2, but also diabetes type 1. The first positive clinical observations in this regard, which confirm the necessity to continue studies, have appeared [41].

Conclusion

Analysis of those studies, which examine the general mechanism of the action of androgens in "patho- and sanogenesis" of type 1 and type 2 diabetes, gives the basis to conclude that adding androgens may influence in various ways on the different disorders caused by diabetes. Therefore, research of the possibility of treatment of the various forms of diabetes with androgens, represents the active scientific and practical feature, which is waiting for the final verdict.

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