

·Review·

Effects of testosterone replacement and its pharmacogenetics on physical performance and metabolism

Michael Zitzmann

Institute of Reproductive Medicine of the University of Münster, Münster D-48129, Germany

Abstract

In men, testosterone (T) deficiency is associated with decreased physical performance, as defined by adverse traits in body composition, namely increased body fat content and reduced muscle mass. Physical abilities in androgen-deficient men are further attenuated by lower oxygen supply due to decreased hemoglobin concentrations and by poor glucose utilization. Dysthymia and a lack of necessary aggressiveness also contribute to deteriorate physical effectiveness. Substitution of T can improve lipid and insulin metabolism as well as growth of muscle fibers and decreasing fat depots, which consequently will result in changes of body composition. Increment of bone density will further contribute to increase physical fitness. The effects of T replacement therapy (TRT) are strongly influenced by age, training, and also pharmacogenetics: the CAG repeat polymorphism in exon 1 of the androgen receptor (AR) gene modulates androgen effects. *In vitro*, transcription of androgen-dependent target genes is attenuated with increasing length of triplet residues. Clinically, the CAG repeat polymorphism causes significant modulations of androgenicity in healthy eugonadal men as well as efficacy of TRT. Thresholds at which T treatment should be initiated, as well as androgen dosage, could be tailored according to this polymorphism. (*Asian J Androl* 2008 May; 10: 364–372)

Keywords: testosterone; androgens; hypogonadism; pharmacogenetics; androgen receptor; physical performance; metabolism

1 Introduction

Testosterone (T) exerts a widespread pattern of effects on metabolism and body composition. This is most obviously seen in the difference between men and women. Hypogonadal men lacking sufficient T levels show evidence of particular physical and metabolic traits seen as alterations in lipid and glucose metabolism, which further influence fat depots and muscle mass and, ultimately, physical performance. These effects are augmented by adverse effects of androgen deficiency on hemoglobin levels, bone density, and psychological traits.

T replacement therapy (TRT) in hypogonadal men is

able to alter these variables and restore normal male functions. These effects are reviewed here, starting with the impact of androgens on metabolism and various tissues, and concluding with a discussion of the effects on psychological and physical performance. New pharmacogenetic findings are also considered.

2 Pharmacogenetic background

T and its metabolite dihydrotestosterone exert their effects on gene expression and thus affect maleness through the androgen receptor (AR). A diverse range of clinical conditions, starting with complete androgen insensitivity, has been correlated with mutations in the AR. Subtle modulations of the transcriptional activity induced by the AR have also been observed and frequently assigned to a polyglutamine stretch of variable length within the N-terminal domain of the receptor. This stretch is encoded by a variable number of CAG triplets in exon 1 of the AR gene located on the X chromosome.

Correspondence to: Michael Zitzmann, MD, PhD, Institute of Reproductive Medicine of the University of Münster, Münster D-48129, Germany.
 Tel: +49-251-835604 Fax: +49-251-8356093
 E-mail: michael.zitzmann@ukmuenster.de
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Longer triplet residues mitigate binding of AR co-activators and, hence, facilitate decreased androgenicity. A marked relation to androgenic traits can be seen in men with an elongation of more than 37 CAG repeats, but also in those with CAG repeats within the normal range [1, 2]. Extending these findings to pharmacogenetic considerations, a possible modulation of androgen effects during TRT has to be considered (see below).

3 Metabolic aspects and glucose metabolism

Within the last century, life circumstances have changed in developed countries as physical activity has become less frequent and, simultaneously, an oversupply of food is present. This has resulted in an increasing prevalence of overweightness and obesity, particularly over the past two decades. As a consequence, a complex disorder consisting of visceral obesity, dyslipidemia, insulin resistance, and hypertension has emerged with increasing incidence. The so-called “metabolic syndrome” contributes to a symptomatology that progressively leads to the manifestation of type 2 diabetes mellitus and cardiovascular disease. Although the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged as important causative factors [3–6]. Persons affected are twice as likely to die from, and three times as likely to suffer, a heart attack or stroke compared to those free of the metabolic syndrome [7]. They also have a 5-fold greater risk of developing type 2 diabetes mellitus, if not already present [8].

The International Diabetes Federation (IDF) has recently updated the criteria for diagnosis of the metabolic syndrome (Reproduced from http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf with permission from the IDF):

Central obesity, defined as waist circumference (> 102 cm for North American men, > 94 cm for European men, and > 90 cm for Asian men), plus any two of the following four factors:

- Concentrations of fasting triglycerides > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Concentrations of high-density lipoprotein cholesterol < 40 mg/dL (1.0 mmol/L) in males, or specific treatment for this lipid abnormality
- Systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg, or treatment of previously diagnosed hypertension
- Concentrations of fasting plasma glucose > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes mellitus

In men, obesity as the central component of the

metabolic syndrome is associated with low T concentrations [9–12].

3.1 Epidemiological approaches

A cross-sectional study in independently living men examined the association between endogenous T concentrations and the prevalence of the metabolic syndrome as well as relationships between androgen levels and its sub-components. Logistic regression analyses showed an inverse relationship for circulating total T concentrations with the prevalence of the metabolic syndrome. Within the cohort of men, each increase of one standard deviation of total T (5.3 nmol/L) was associated with a 57% reduced risk of having the metabolic syndrome. In agreement, higher T levels were associated with higher insulin sensitivity. In addition, the more factors of the metabolic syndrome that were present, the lower the total T concentrations that were measured [13].

These findings are corroborated by longitudinal epidemiological approaches. In a cohort of 700 healthy middle-aged Finnish men without metabolic syndrome, concentrations of total T and factors related to insulin resistance were determined at baseline and after 11 years. During that time, 147 men had developed the metabolic syndrome. Men with total T in the lower fourth quartile had an increased risk of developing the disorder and subsequent type 2 diabetes mellitus. Adjustment for potential confounders such as cardiovascular disease, smoking, alcohol intake, and socioeconomic status did not alter the associations [14]. A similar approach was taken in 950 healthy, aging men during the Massachusetts Male Aging Study. The incidence of the metabolic syndrome was strongly related to lower T concentrations, especially in men with a body mass index (BMI) lower than 25 kg/m². This points to the specific, adverse role of central adiposity in combination with androgen deficiency, especially in those men with slender extremities compared to generally overweight persons. The latter develop the metabolic syndrome more independently from androgen deficiency [15].

Summarizing these non-interventional findings, there are strong indications that a T deficiency in men might contribute to the prevalence of the metabolic syndrome. This applies especially to elderly persons with an age-related decline of hypothalamic–pituitary–testicular functionality, referred to as late-onset hypogonadism [16, 17]. Nevertheless, non-interventional studies cannot fully elucidate cause and effect in this regard: the metabolic syndrome leading to vascular and endocrine disturbances might initiate hypogonadism as well, an effect known from other chronic disorders [18]. There are indications that such an effect exists, as a Finnish cohort study involving 651 men indicated. After 11 years of surveillance, the odds ratio was 3 to be diagnosed with

total T concentrations below 11 nmol/L for men with the metabolic syndrome compared to non-affected persons [19].

3.2 Interventional studies

Interventional approaches altering T concentrations are able to further illuminate these questions. Pharmacological deprivation of T is a treatment option in men with prostate cancer. A study in such patients assessed the effects of short-term gonadotropin-releasing hormone (GnRH) agonist treatment on insulin sensitivity within the setting of a prospective 12-week study involving 25 men without evidence of diabetes mellitus at baseline. Leuprolide depot and bicalutamide were used for T ablation. The mean percentage of body fat mass as well as mean hemoglobin type A1c (HbA1c) increased significantly, whereas insulin sensitivity decreased markedly [20].

The results are corroborated by a cross-sectional study in 53 men, including 18 men with prostate carcinoma, who received androgen ablation for at least 12 months prior to the onset of the study, 17 age-matched men with non-metastatic prostate carcinoma who had undergone prostatectomy and/or received radiotherapy and who were not receiving androgen ablation therapy, and 18 age-matched controls. None of the men had a known history of diabetes mellitus. Men in the treatment group had a higher BMI compared with the other groups as well as higher fasting levels of glucose, insulin, and leptin. The homeostatic model assessment for insulin resistance showed markedly higher values for men with decreased T concentrations [21].

Consistently, a placebo-controlled study in healthy men receiving short-term T deprivation by a GnRH-receptor antagonist showed incremental effects on concentrations of insulin and leptin after 3 weeks within a condition of marked hypogonadism [22].

Correspondingly, androgen substitution in hypogonadal men has marked beneficial effects on these metabolic markers. In a well designed double-blind study, 30 middle-aged men with abdominal obesity were treated with transdermal preparations of T, dihydrotestosterone, or placebo. In the group treated with T, visceral fat mass decreased (measured by computerized tomography) without significant changes in other depot fat regions. In addition, the glucose disposal rate, measured with a euglycemic hyperinsulinemic clamp, was markedly augmented. Plasma triglycerides, cholesterol, and fasting blood glucose concentrations, as well as diastolic blood pressure, decreased [23].

Corresponding effects were seen in 24 hypogonadal men with type 2 diabetes mellitus involved in a double-blind placebo-controlled crossover study. The men received an intramuscular T preparation or placebo for

3 months in random order, followed by a washout period of 1 month before the alternate treatment phase. T therapy improved fasting insulin sensitivity. HbA1c levels were reduced correspondingly, as were fasting blood glucose levels. T treatment resulted in a reduction in visceral adiposity as assessed by waist circumference. Total cholesterol decreased with T therapy but no effect on blood pressure was observed [24].

These studies are supported by a larger, cross-sectional observation in elderly men. The subjects were either untreated hypogonadal men ($n = 24$), treated hypogonadal men ($n = 61$), or healthy eugonadal men ($n = 60$). In eugonadal men, serum T levels decreased with advancing age while BMI, total body fat content, and leptin increased significantly. In untreated hypogonadal patients, an increase in BMI and total fat mass was also observed with advancing age. However, in substituted hypogonadal patients, no age-dependent change in BMI, body fat content, or serum leptin was found [25]. The decreasing effects of T treatment on visceral adipose tissue are most likely dose-dependent, as shown by a study in men receiving various doses of intramuscular T [26].

3.3 Pathophysiological considerations

Visceral fat tissue plays a central role within the metabolic syndrome, acting as a source of inflammatory, anti-insulinergic, and atherogenically relevant cytokines such as tumor necrosis factor- α and interleukin-6 [27, 28]. Fat tissue also functions as an endocrine organ, its product adiponectin plays an important role in metabolism and is related to cardiovascular risk factors. It is produced by fat cells in large quantities, yet its levels are inversely associated with total body fat mass, most likely caused by auto/paracrine downregulation through inflammatory cytokines. Improvement of insulin sensitivity and inhibition of various atherogenic processes within the vessel wall are direct effects of adiponectin [29]. Leptin is another hormone secreted by fat cells. Hypophagia to reduce fat mass is supported by leptin signals, but adipose tissue fosters further food intake by facilitating leptin resistance at the hypothalamic level by way of afferent nerve signals [30]. A vicious circle is thus induced as leptin resistance increases further adipocyte-related production of this hormone. There are indications that high levels of leptin can mitigate T secretion [31, 32].

T seems to have various effects on fat cells and insulin resistance. A study in mouse pluripotent stem cells indicates that T regulates body composition by promoting the commitment of these mesenchymal cells into the myogenic lineage and inhibiting their differentiation into the adipogenic lineage. This provides a unifying explanation for the reciprocal effects of androgens on muscle

and fat mass in men [33]. An inhibiting effect of T has also been described concerning the differentiation of pre-adipocytes. In 3T3-L1 cells that differentiate to form fat cells in adipogenic medium, T inhibits adipocyte differentiation *in vitro* through an AR-mediated nuclear translocation of β -catenin and activation of downstream Wnt signaling (such Wnt signals direct distinct fates of differentiation in precursor cell types) [34]. In addition, T increases lipolysis and the number of adrenoreceptors in male rat adipocytes [35].

T might facilitate insulin sensitivity both in fat and muscle cells by upregulating the expression of insulin-induced downstream protein expression. Respective dose-dependent effects of T on insulin receptor substrate-1 and glucose transporter 4 expression were seen in cell models [36]. Recent models of insulin resistance also suggest a pivotal role of mitochondrial function with the decreased transcription of oxidative phosphorylation genes in skeletal muscle of insulin-resistant subjects. This leads to decreased oxidative phosphorylation, decreased lipid oxidation, intracellular accumulation of triglycerides in skeletal muscle, and ultimately insulin resistance [37]. A study in 60 men showed T levels to correlate positively with mitochondrial capacity assessed by measuring maximal aerobic capacity and also expression of oxidative phosphorylation genes [38].

As discussed, leptin resistance and consequently upregulated adipocyte leptin secretion play a pivotal role in obesity. T substitution in hypogonadal men is able to reduce leptin secretion of fat cells, probably by an AR-mediated pathway [12], thus breaking the described vicious circle of leptin resistance and obesity [25, 39–41].

3.4 Role of AR in metabolism

T effects are mediated by the AR [42]. It is therefore not surprising that an AR knock-out model in mice shows evidence of effects in agreement with T deficiency. Progressively reduced insulin sensitivity and impaired glucose tolerance are seen these mice with advancing age. Aging AR knock-out mice have accelerated weight gain, hyperinsulinemia, and hyperglycemia. The loss of the AR contributes to increased triglyceride content in skeletal muscle and liver in these animals and leptin concentrations are elevated in serum [43].

Apart from complete dysfunctionality of the AR, modulations of its activity have been observed and can be assigned to a polymorphic polyglutamine stretch of variable length within the N-terminal domain of the receptor protein. This stretch is encoded by a variable number of CAG triplets in exon 1 of the AR gene, located on the X chromosome. The length of the polymorphism is inversely associated with androgen-induced gene transcription [41]. Pathological CAG triplet elongations (> 36) are observed in spinobulbar muscular

atrophy, the so-called “Kennedy syndrome”. Long before the AR polymorphism was recognized as a cause for the disease [44], an association of the disorder with diabetes mellitus had been suspected [45]. As confirmed recently, markedly reduced androgen function indeed leads to pathological glucose metabolism in approximately 50% of these patients [46]. Also within the normal range of CAG triplet length (13–36 repeats), modulatory effects on androgenic activity are reflected by metabolic parameters. Concentrations of insulin and leptin as well as body composition in men are associated with this polymorphism [12, 47].

3.5 Metabolic perspectives for men

Hypogonadal men, especially Klinefelter patients, have an increased prevalence of the metabolic syndrome [48]. Special efforts to detect this under-diagnosed chromosome disorder and mitigate the increased mortality of these men due to complications of diabetes mellitus and cardiovascular events [49] are necessary. Although approaches examining the effects of T on sub-parameters of the metabolic syndrome have been made (see above), prospective studies investigating its incidence in hypogonadal men receiving T substitution therapy are needed. Such studies should take the modulatory effect of the AR into account to fully elucidate the putative potential of T to attenuate or prevent the metabolic syndrome in men.

4 Erythropoiesis

T treatment for anemia in patients with renal failure was a common medication before synthetic erythropoietin was available [50]. T probably acts directly on bone marrow at the level of polychromatophylic erythroblasts and enhances the synthesis of ribosomal RNA or its precursors and stimulates a nuclear ribonuclease. It was postulated that erythropoietin and T act synergistically to create the biochemical machinery for hemoglobin synthesis [51]. In agreement, hypogonadal men often present with anemia. Elevation of T levels, irrespective of the preparation used, will increase hemoglobin levels in these patients [52–54]. Substitution effects will reach a plateau after approximately 6–9 months [56]. The above-mentioned studies show a marked variability in responsiveness of the hematopoietic system to T and strengthen the necessity for surveillance. In some men, unacceptably high levels of hemoglobin concentration and hematocrit can develop, so that the dosage has to be adjusted in order to prevent adverse vascular events [52]. It has been shown that pharmacogenetic effects of the CAG repeat polymorphism are visible during TRT and have to be considered for evaluating erythropoiesis and hematocrit [57].

5 Body composition

5.1 Body fat content

Cross-sectional investigations in healthy, eugonadal men have indicated a negative relationship between body fat content and levels of total T [58, 59], this applies in particular to abdominal fat tissue [9, 11]. In healthy obese men, the issue is complicated by simultaneously decreasing levels of sex hormone binding globulin, thus levels of free or bioavailable T are often maintained [60].

In hypogonadal men, an increased total BMI is regularly observed as well as a reduced lean body mass, measured with dual photon absorptiometry (DEXA) or bioimpedance, is found when compared to age-matched healthy controls, suggesting higher body weight due to increased fat mass in the presence of lower muscle mass [61, 62]. T treatment can significantly reduce body fat content in hypogonadal men and, vice versa, it can increase lean body mass, an observation that is not only due to shifts in proportions but also to growth of muscle tissue (see below) [25, 52, 53, 63–67]. This is exerted through a redistribution of body fat during which mainly visceral and intermuscular fat depots are affected, but subcutaneous tissue seems to be spared [68]; it is likely that fat cell size itself is modulated by androgens [69]. The process seems to follow a linear dose–response relationship to T [68], but the exact mechanism by which fat cells are subject to androgen influence is not known. It can be speculated that this is mediated through increased insulin sensitivity and improved glucose utilization, resulting in lower insulin levels and, thus, less lipid storage.

5.2 Muscle tissue

In addition to the effects of T deficiency on body fat content, a loss of fat-free mass and decrease in muscle protein synthesis is observed in hypogonadal men [70]. In agreement with these findings, when androgens are substituted in such patients, fat-free mass increases significantly, an effect attributable to muscle growth [65, 71]. The growth of muscle tissue seems to follow a linear dose–response relationship over a wide range of T levels, as was indicated in healthy young men receiving androgen ablation by a GnRH agonist and subsequent T treatment in various doses to achieve low to supraphysiological levels. As fat-free mass increased with the increasing T dose, so did volumes of thigh muscles [72]. Muscle biopsies in these men indicated a homogenous increase in cross-sectional areas of both type I and II muscle fibers, which maintained their proportion. As muscle fiber hypertrophy involves the addition of newly formed myonuclei through the fusion of myogenic cells, the myonuclear number increased in direct relation to the increase in muscle fiber diameter. Muscle cell hyperplasia did not play a significant role [73].

5.3 Bone tissue

In conditions of T deficiency, bone mineral density is decreased and markers of bone turnover are usually elevated [74–77]. Especially in hypogonadal men, whose trabecular bone density is decreased, T substitution is effective in regard to significant increase in bone density, particularly in those patients with a marked baseline deficit [78–82]. The type of hormone substitution as well as the disease causing low androgen levels do not influence the effectiveness of T substitution on bone density. Nevertheless, there is a tendency of higher T substitution levels to contribute to higher bone density, albeit marginally, as androgen influence on bone tissue seems to be non-linear. The effect is much stronger in alterations within the low range than in the high range and is influenced by the CAG repeat polymorphism [83].

The underlying mechanisms depend on both T and estradiol, as they contribute to higher bone density. These effects are probably exerted through different pathways: T inhibits osteoclastic activity, whereas estradiol seems to activate osteoblasts [84, 85]. As an interactive, paracrine positive feedback exists between both types of cells [86], both hormones take effect on both types of cells. The mediators of these effects are still unclear. Indications are that androgens act mainly through inhibition of secretion of the cytokine interleukin-6, thus downregulating osteoclastic activity [87, 88], but also through the insulin-like growth factor system of osteoblasts [89]. T treatment given externally leads to reduction of markers of bone turnover [87]. It is possible that increased muscle strength during T substitution contributes to the gain of bone tissue by enhancing traction forces, a positive stimulus for osteoblasts [90].

6 Mental issues

Physical performance is strongly influenced by mental status. Mood changes in terms of depression and aggression are especially likely to modulate physical abilities. Both parameters are subject to androgen influence and an interdependence of physical performance with both hormone levels and mood is likely to exist [91].

6.1 Depressiveness

A relation between T levels and depressive mood disorders has been shown by investigations in patients treated for major depression [92, 93]. Viewing the aspect from the angle of hypogonadism, clinical consensus exists that this condition in men is related to depressive symptoms. Low T levels seem to be associated with depressive symptoms and late-life dysthymia [94]. When T levels and depressive symptoms were collected in a large sample of elderly men ($n = 856$; mean age 70.2 ± 9.2 years), Beck

Depression Inventory scores and free T levels were inversely correlated with high significance [95].

In a large sample of healthy older men, T levels and modulation of androgen activity by the CAG repeat polymorphism of the AR gene are associated with depressed mood [96]. Therefore, it is no surprise that hypogonadal men profit largely from T substitution in regard of mood improvement, an effect that seems to be independent from substitution modalities [52, 97, 98].

6.2 Aggression

Indications are strong that there is an interdependent feedback mechanism between T and aggression that is modified by experiences of victory and defeat, as well as by education, cultural, and socioeconomic background [99]. The immense variety of individual response patterns to androgens was shown by a controlled trial in which exceptionally high doses of 600 mg T-cypionate/week were given. Aggressive effects were reported in 16% of the men. The psychological behavior of the others remained unremarkable [100]. The effects of T treatment, given externally, on aggressive behaviour in eugonadal men are seen as controversial [101–103].

In hypogonadal men, several sub-parameters associated with aggression such as tension, anger, and fatigue can be reduced by T substitution and, simultaneously, vigor can increase. There is obviously a level of negative affect experienced by hypogonadal men that can be reduced by elevation of androgen levels [104].

7 Physical performance

As outlined above, hypogonadism is associated with increased body fat content, reduced muscle mass, unfavorable parameters of glucose metabolism, anemia, and mood disorders. One can therefore assume that actual physical performance is reduced in these patients and can possibly be restored by elevation of T levels. Nevertheless, it is important to distinguish between various kinds of physical effort.

7.1 Strength

Physical strength, as determined by the one-repetitive maximum in bench press and seated leg press exercises (this assesses the maximal force-generating capacity of the muscles used to perform the test), can improve in hypogonadal men when T levels are artificially elevated [52, 66]. Such results are dependent on the muscle. Larger thigh muscles in particular show a measurable response, whereas the effects in smaller shoulder muscles are not significant [54, 55]. Variation in results can also be explained by different settings (training or no training) and the age of patients. It seems that gain of strength by T substitution is possible without training

in younger men [72] but this is not achievable to a significant degree in older persons, despite an increase in muscle mass [105]. A significant dose–response relationship of gained strength and the amount of substituted T seems to exist, reaching a putative plateau at the supraphysiological range of T concentrations, despite a further growth of muscle tissue [72].

7.2 Endurance, gait, balance and mobility

One could expect an overall improvement of the above-named variables when T levels are elevated in hypogonadal men, as these parameters depend on muscle mass, body composition in general, hemoglobin content as oxygen provider, as well as mood, all being improved by androgen substitution. Nevertheless, data strengthening such hypotheses are scarce. An increased number of red blood cells improving oxygen supply is likely to improve endurance capacities, as has been seen in trials with rats treated with nandrolone [106] or reports concerning athletes using uncontrolled doping [107].

In hypogonadal men, the fractional velocity of muscle glycogen synthetase can be increased by T treatment [108]. Along with improved oxygen supply, this could infer increased performance in efforts requiring endurance rather than strength.

Gait, balance and mobility under treatment with a dihydrotestosterone gel were tested in a controlled setting involving 31 older men with low to low-normal T levels. Despite significant positive changes in lean body mass, strength, and hemoglobin content, the complex variables assessed by maximal reach, standing balance, fast walk, or chair rise were not altered by treatment [55].

8 Conclusion

Hypogonadism in men is a state associated with decreased physical abilities, especially strength and endurance. These endpoints are based on significantly measurable adverse traits in body composition, namely increased fat content and reduced muscle mass. Physical abilities are further hampered by lower oxygen supply due to decreased hemoglobin levels and poor glucose utilization. In addition, dysthymia and lack of necessary aggressiveness contribute to further deteriorate physical performance.

Substitution of T can improve lipid and insulin metabolism, which consequently results in changes of body composition, such as decreasing fat depots and growing muscle fibers. Stabilization by increased bone density will further contribute to performance. This is ultimately reflected by increased strength, although this parameter is subject to various other influences, such as age and training. The reviewed issues strongly support treatment of hypogonadal men under regular monitoring.

The effects of T are most likely modulated by the CAG repeat AR polymorphism. An individually tailored approach to T treatment is a future option.

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