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Central body fat changes in men affected by post-surgical hypogonadotropic hypogonadism undergoing testosterone replacement therapy are modulated by androgen receptor CAG polymorphism

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Abstract *Background and aims:* Little is known about the effect of androgen receptor (AR) gene CAG repeat polymorphism in conditioning body composition changes after testosterone replacement therapy (TRT). In this study, we aimed to clarify this aspect by focussing our attention on male post-surgical hypogonadotropic hypogonadism, a condition often associated with partial or total hypopituitarism.
Methods and results: Fourteen men affected by post-surgical hypogonadotropic hypogonadism and undergoing several replacement hormone therapies were evaluated before and after TRT. Dual-energy X-ray absorptiometry (DEXA)-derived body composition measurements, pituitary-dependent hormones and AR gene CAG repeat polymorphism were considered. While testosterone and insulin-like growth factor-1 (IGF-1) levels increased after TRT, cortisol concentration decreased. No anthropometric or body composition parameters varied significantly, except for abdominal fat decrease. The number of CAG triplets was positively and significantly correlated with this abdominal fat decrease, while the opposite occurred between the latter and Δ-testosterone. No correlation of IGF-1 or cortisol variation (Δ-) with Δ-abdominal fat was found. At multiple linear regression, after correction for Δ-testosterone, the positive association between CAG triplet number and abdominal fat change was confirmed.
Conclusions: In male post-surgical hypogonadotropic hypogonadism, shorter length of AR CAG repeat tract is independently associated with a more marked decrease of abdominal fat after TRT.

Introduction

It is well established that one of the mechanisms by which testosterone influences the metabolic profile is by its effect on body composition [1]. Ageing-related testosterone decline in men is one of the factors which causes abdominal fat accumulation, contributing to a higher risk of metabolic syndrome, type 2 diabetes and coronary heart disease [2–5]. Similarly, in patients affected by hypogonadism, testosterone replacement therapy (TRT) resulted in total and visceral adiposity decrease [6,7] and in fat-free mass increase. [7]

Abbreviations: AR, androgen receptor; TRT, testosterone replacement therapy; DEXA, dual-energy X-ray absorptiometry; IGF-1, insulin-like growth factor-1; GH, growth hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; FT3, free T3; FT4, free T4; PCR, polymerase chain reaction; Δ-, variations.

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Testosterone has an effect on target organs via the androgen receptor (AR), which is also expressed in muscle and adipose tissue [8]. The AR gene (Xq11–q12) contains a polymorphic trinucleotide CAG repeat sequence in exon 1, which encodes a polyglutamine chain in its NH_2-terminal transcriptional activation domain [1]. It is generally believed that the number of CAG repeats (the CAG repeat polymorphism) is inversely correlated to the transcriptional activity of the hormone–receptor complex [1]. The possible underlying mechanisms between transcriptional activity and AR CAG polymorphism can be attributed to variations in the basal activity of the AR, to the functional interaction of the polyglutamine stretch with coactivators such as ARA24 and p160 and to the decreased expression of AR messenger RNA (mRNA) [1]. However, results regarding the association of this polymorphism with body composition are contradictory. In studies analysing healthy, community-dwelling or randomly selected subjects, some authors identified a relationship of CAG repeat number with various measurements of body fat (i.e., total, trunk and thigh fat mass) [1,8,9] and lean mass (total, thigh and trunk amount) [1,8,10], whereas others did not find any association [11,12]. Specifically, no longitudinal studies have been carried out which have evaluated the impact of AR CAG polymorphism in conditioning TRT effects on the amount of body composition in hypogonadal subjects.

Given these premises, the aim of our work is to study the role of CAG repeat polymorphism in body composition variations in hypogonadal subjects undergoing TRT; we focussed on post-surgical hypogonadotropic hypogonadism, a rare condition which is usually associated with partial or total hypopituitarism.

Methods

Subjects

Fourteen men were retrospectively considered. Inclusion criteria were as follows: a) hypogonadotropic hypogonadism [2,13] due to surgical removal of pituitary adenoma; b) lack of hormone imbalance, including hypogonadism, before surgery; and c) availability of follow-up data.

Study protocol

Instrumental and biochemical evaluation at the beginning of TRT (time 0) and in the recovery phase (before the eight undecanoate testosterone injections (74–84 weeks after the first)) was carried out. Undecanoate testosterone (1000 mg intramuscularly) was administered 6 weeks after the first one (loading dose), followed by similar injections after 10–14 weeks depending on the clinical and biochemical profile [14].

Pituitary function deficits were as follows: all patients had a deficit of both somatotropic and gonadotropic functions [2,13,15], six also had thyrotropic function deficit [16], two also corticotropic deficit [17] and three had both thyrotropic and corticotropic deficits. Glucocorticoid (cortisone acetate, 37.5–50 mg daily), somatotropic (recombinant human growth hormone (GH), 0.3–0.6 mg daily) and thyroid (levothyroxine, 75–100 μg daily) replacement therapies were started depending on the specific deficit. Replacement therapies with cortisone acetate and levothyroxine were initiated upon diagnosis of the deficit. Recombinant human GH and testosterone were administered between 6 and 12 months after surgery; in all our subjects, replacement therapy with recombinant human GH was started before TRT. The period between surgery and the beginning of TRT (time 0) was considered as the duration of hypogonadism.

This study is a retrospective one and the data considered were part of the diagnostic work-up, with the exception of genetic and body composition evaluation, which was carried out as part of a research protocol. The study was conducted according to the principles of the Helsinki Declaration and was approved by the institutional ethics committee. Participants gave their written informed consent.

Body composition measurement

Body composition measurement was carried out as previously described [3]. Briefly, a whole-body dual-energy X-ray absorptiometry (DEXA) scanner (Lunar Prodigy, GE Medical Systems, Madison, WI, USA; software enCore 2007 version 11.4.) was used. The entire body was scanned. Scanned images of the whole body were subdivided into head, trunk, left and right arm and legs. The abdominal area, which has been shown to exhibit a relatively high content of visceral fat and a low content of subcutaneous fat on magnetic resonance imaging [18], was also measured by DEXA between vertebrae L2 and L4. All scans were obtained and analysed by the same physician. Body fat and lean mass were expressed in grams.

Hormone evaluation

Blood samples were taken at 8 AM after fasting. The following parameters were considered: follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, free T3 (FT3), free T4 (FT4), cortisol, insulin-like growth factor-1 (IGF-1) and prolactin. All hormone assays were carried out by immunoassay commercial kits. The reference ranges for the hormone parameters studied were: FSH, 1.7–6.9 IU/L; LH, 1.6–10.0 IU/L; total testosterone, 3–8.5 ng/mL; FT3, 2.3–4.2 pg/mL; FT4, 0.8–1.8 ng/dL; serum cortisol (8.00 AM), 7–27.5 mcg/dL; IGF-1, 66–251 ng/mL for males between 40 and 50 years; 57–221 ng/mL for males between 50 and 60 years; 46–211 ng/mL for males between 60 and 70 years; and prolactin, 2–15 ng/mL.

Polymerase chain reaction amplification and sequencing

We carried out a previously described protocol for the amplification of AR CAG tract [19]. DNA was extracted from blood and the AR CAG gene polymorphism was analysed