Accepted: 4 December 2017

DOI: 10.1111/and.12967

ORIGINAL ARTICLE

WILEY ANDROLOGIA

Health-related physical fitness and quality of life in men with congenital hypogonadotropic hypogonadism

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Funding information
Conselho Nacional de Desenvolvimento Científico e Tecnológico, Grant/Award Number: 135096/2011-1; Fundação de Apoio à Pesquisa do Distrito Federal, Grant/Award Number: 193.000.407/2010

Summary

Congenital hypogonadotropic hypogonadism is a rare disorder characterised by impaired testosterone secretion since birth, and represents a valuable model for studying the effects of testosterone replacement therapy (TRT) in humans. This cross-sectional study aimed to investigate all health-related physical fitness (HRPF) components and quality of life in a series of eight men with hypogonadotropic hypogonadism under regular TRT. The study group was compared to a control group of 16 healthy subjects paired for age, body mass index and physical activity. Body composition, aerobic capacity, muscular strength and endurance, and joint flexibility were evaluated in two different 7-day interval time points, based on the pharmacokinetics of testosterone in the hypogonadal group. Quality of life was assessed by the WHOQOL-brief questionnaire. Both groups had similar performances in all HRPF components evaluated, independently of plasma testosterone levels ($p > .05$). Quality of life was also similar in the four domains analysed ($p > .05$). The results of this pilot study suggest that regular testosterone replacement was efficient in providing HRPF and quality of life in a series of congenitally hypogonadal men to levels like those observed in healthy men. In addition, acute fluctuations in plasma testosterone did not correlate with changes in muscle strength and endurance.

KEYWORDS
hypogonadotropic hypogonadism, muscle strength, physical fitness, quality of life, testosterone

1 | INTRODUCTION

Male congenital hypogonadotropic hypogonadism is a rare endocrine disorder, characterised by absent or incomplete pubertal development due to impaired testosterone secretion by the testis since pre-pubertal life (Bhasin et al., 2010). It arises from inherited hypothalamic defects which result in inappropriately low gonadotrophins' secretion and, consequently, severe testosterone deficiency which can be lifelong unless adequately treated (Harvey et al., 2015). It is generally assumed that chronic testosterone deficiency negatively affects physical fitness, with an impact in general health and quality of life in men. Testosterone replacement therapy (TRT) is effective in increasing plasma testosterone levels and relieving undesirable symptoms, such as decreased libido, erectile dysfunction, weakness, fatigue and psychological distress, therefore improving quality of life in affected individuals (Aydogan, Aydogdu et al., 2012; Bhasin et al., 2010; Blute et al., 2009; Lašaitė, Čeponis, Preikša, & Žilaitienė, 2014). Nevertheless, a complete restoration of the global and system-specific functional capacity is still pursued, and physical and psychological outcomes in testosterone-deficient men remain insufficiently characterised.

Quality of life (QOL) is a multidimensional attribute, which comprises multiple physical and psychological aspects that are not limited to disease indicators. Health-related physical fitness (HRPF) refers to a "set of attributes that people have or obtain, which are related to the ability to perform physical activities" (Garber, Blissmer, & Deschenes, 2011). It classically aggregates the following components: body composition, cardiorespiratory fitness, muscular strength and endurance,

and joint flexibility (Caspersen, Powell, & Christenson, 1985). Recently, it has been proposed that some HRPF components may independently influence cardiovascular risks and improve quality of life (Lee, Artero, Sui, & Blair, 2010; Ståhle, Mattsson, Ryden, Unden, & Nordlander, 1999).

We then hypothesised that many signs and symptoms of testosterone deficiency may be associated with independently impaired HRPF components and may be differently restored by TRT. However, the efficacy of testosterone replacement in the retrieval of health-related physical fitness in hypogonadal men remains elusive (Aydogan, Eroglu et al., 2012; Bhasin et al., 1997). In this context, congenital hypogonadotropic hypogonadism (CHH) represents a valuable model for studying the effects of testosterone on different health parameters in men, as it allows for the investigation of the effects of exogenous testosterone replacement exclusively, without a significant interference of endogenous secretion (Trabado, Lamothe, Maione, & Bouvattier, 2014). We therefore aimed to evaluate the health-related physical fitness components and quality of life in a series of men with CHH under TRT, in comparison with a control group of healthy men.

2 | SUBJECTS AND METHODS

2.1 | Participants

A cross-sectional study was performed in a series of men who had been diagnosed with CHH and were under regular TRT. For comparison analysis, a control group consisting of clinically healthy men was studied.

The hypogonadal group (HG) was composed of eight men (17–45 years.). Participants were selected among those with a diagnosis of CHH from a single reference outpatient Endocrinology Clinic. Diagnosis was based on absent or incomplete pubertal development associated with low plasmatic total testosterone levels and low or inappropriately normal LH and FSH levels, without any other hormonal deficiency before TRT initiation (Harvey et al., 2015). Testosterone replacement dosing protocols was adjusted individually according to hormonal parameters (Aversa & Morgentaler, 2015; Bhasin et al., 2010). Therefore, each patient followed an individualised optimal dosing regimen, with intervals between testosterone injections of testosterone cypionate—200 mg: 15 days (n = 4 subjects) or 21 days (n = 4 subjects). Patients were evaluated with no interference in their clinical assessment and medical routine. They initiated the treatment at the median age of 17.5 years (14–38) with a median TRT duration of 5.5 years (2–10) at the time of the study. Only individuals who were regularly taking intramuscular short-acting testosterone ester for at least 1 year in a full dose regimen and who thereafter had completed pubertal development were included (Marshall & Tanner, 1970). CHH patients who presented any additional disease or comorbidity, or who were taking any other medications were not included. Of note, two patients had gynaecomastia and two patients had cryptorchidism, which are both physical signals associated with the condition of congenital hypogonadism that have been surgically corrected before the study.

For comparison analysis, a control group (CG) was composed of 16 of clinically healthy men recruited from the community with no restrictions for physical activity practice. The CG was selected by convenience among men who were invited to volunteer in the study after data collection in the hypogonadal group. For inclusion in the control group, volunteers were supposed to match the age, body mass index (BMI) and prior physical activity levels of men in the hypogonadal group. This strategy provided the same proportion of physically active (50%) and physically inactive (50%) men in both groups.

All subjects read and signed the informed consent agreement before participating in the study. The research was approved by the Ethics Committee on Human Research of the Faculty of Health Sciences, University of Brasilia—Brazil (Approval number 129/11).

2.2 | Study design

The study protocol comprised two evaluation time points within a 7-day interval, referred as day 1 (D1) and day 2 (D2). The parameters analysed in both groups were plasmatic total testosterone levels (TT), quality of life, body composition, cardiorespiratory fitness, muscle strength and endurance, and flexibility. All data were collected twice, that is in both evaluation moments, except those corresponding to cardiorespiratory fitness and body composition. In the hypogonadal group, the definition of the evaluation time points was based on the pharmacokinetics of testosterone cypionate. Accordingly, D1 corresponded to the predicted peak of circulating testosterone levels, that is 7 days after testosterone administration, while D2 corresponded to the drop/nadir phase, 7 days after D1 (Aversa & Morgentaler, 2015; Srinivas-Shankar & Wu, 2006). In the control group, the first evaluation day was determined by the volunteer availability, conditioned to the 7-day interval between them.

2.3 | Testosterone Levels

In both evaluation time points (D1 and D2), blood samples for T measurements were obtained in the morning, after at least 12 hours of overnight fasting (Bhasin et al., 2010). Plasma samples were immediately separated and stored at −20°C until assayed. Samples were analysed in a reference laboratory by method of chemiluminescence.

2.4 | Procedures

Anthropometrical measures, as well as resting cardiorespiratory parameters (blood pressure, heart rate and respiratory rate), were assessed on D1. Body composition was estimated by the body adiposity index [BAI= hip circumference/((height × 1.5)-18)] (Bergman et al., 2011). On D2, cardiorespiratory fitness was estimated by the Polar Fitness Test (RS 800 model, Polar Electro Oy, Kempele, Finland), which is based on the records of the resting heart rate and heart rate variability (R-R interval acquisition) during a nonexercise testing period, and analysed according to gender, height, weight, age and self-reported physical activity level (Laukkanen, Kinnunen, & Virtanen, 2002).

Thereafter, HRPF tests followed a specific order defined to prevent muscle fatigue and avoid possible adversely effect on test performance. Firstly, the handgrip dynamometer Jamar® (Sammons Preston Rolyan, IL, USA) was used to assess muscle strength in the upper limbs. Secondly, joint flexibility was evaluated by the sit-and-reach test using the Wells bench (ACSM, 2010). Thirdly, strength and endurance of the lower limb were evaluated using isokinetic dynamometer Biodex System 3® (Biodex Medical System, NY, USA). Knee extension peak torque on the dominant side was used as a measure of muscle strength in the lower limbs. One set of ten submaximal repetitions were performed at 180°/s for participants warming and familiarisation, followed by two sets of four maximum repetitions of knee extension at 60°/s, with 1-minute resting between sets. The highest peak torque was recorded. Total work and fatigue index were used to access muscle endurance of the lower limb. All subjects performed 30 maximum repeats at a speed of 180°/s. The total work was calculated as the sum of peak torques in all repeats. The fatigue index was calculated using the percentage difference between the mean peak torque of the first five repetitions, except the first, and the mean peak torque of the final five, in a 30 repeats test.

2.5 | Physical activity level and quality of life questionnaires

Participants were classified as physically active or insufficiently active, according to the recommendations of the American College of Sports Medicine (Garber et al., 2011). Quality of life (QOL) was assessed through the questionnaire proposed by the World Health Organization (WHOQOL-brief) in four domains: physical, psychological, social and environmental (Rocha & Fleck, 2009). A validated algorithm was used to indicate scores ranging from 0 (worst) to 100 (better value) for each of the four domains of QOL.

2.6 | Statistical analyses

Due to the nonparametric distribution of some variables verified with the Shapiro–Wilk test, data were presented as median and extreme values. The differences between groups were considered statistically significant when $p \leq .05$. Wilcoxon test was used for intragroup comparison of dependent samples (D1:HG versus D2:HG, and D1:CG versus D2:CG). Mann–Whitney test was used for intergroup comparison of all single-measure variables (body composition, cardiorespiratory fitness, quality of life) and repeated measures (lower limb muscular strength and muscle endurance, upper limb muscle strength and flexibility), in the two time points, in each group (D1:HG versus D1:CG, D2:HG versus D2:CG). Data analysis and graphic compositions were generated using the statistical software IBM SPSS 17® and Graph Pad Prism® five respectively.

3 | RESULTS

All men in the HG met the diagnostic criteria of congenital isolated hypogonadotropic hypogonadism (median [extremes]; normal range): total testosterone 3.71 nmol/L (<0.69–4.37), NR: (8.33–28.7); LH All <0.1 IU/L, NR: (1.5–9.3); and FSH 1.67 IU/L (<0.03–10.44), NR: (1.4–18.1). Prolactin levels were all normal (<69.4 nmol/L), and no other hormonal deficiency was noted.

The subjects' characteristics and comparative analysis between the two groups are shown in Table 1. The median age, anthropometrical measures and resting cardiorespiratory parameters were similar between the two study groups ($p > .05$). Moreover, both the HG and the CG comprised 50% of physically active men, which is in accordance with the paired sample selection protocol.

In the intergroup comparison on D1, total plasma testosterone levels were similar between HG and CG ($p = .07$), as well as in D2

TABLE 1 Sample characteristics of individuals with congenital hypogonadotropic hypogonadism (HG, $n = 8$) and the control group (CG, $n = 16$), with regard to age, anthropometric measures and resting cardiorespiratory parameters

	HG ($n = 8$)	CG ($n = 16$)	p-value[a]
Age (years)	22.5 (17.1–45.8)	24.3 (18.5–33.8)	.83
Body mass (kg)	75.6 (53.9–107.5)	73.2 (61.5–123.1)	.65
Height (m)	182.3 (164.0–190.4)	177.1 (165.4–188.2)	.25
BMI (kg/m^2)	22.8 (20.0–29.6)	23.6 (21.0–34.7)	.60
Waist Circumference (cm)	79.6 (72.0–102.2)	80.0 (72.7–104.6)	.62
Abdominal Circumference (cm)	83.8 (75.0–106.0)	84.3 (76.0–119.0)	1.00
Hip Circumference (cm)	98.3 (85.3–110.1)	95.3 (87.0–120.0)	.31
Waist/hip ratio	0.84 (0.70–0.96)	0.86 (0.79–0.96)	.26
Systolic BP (mmHg)	115.0 (100.0–124.0)	112.0 (90.0–124.0)	.23
Diastolic BP (mmHg)	77.0 (60.0–84.0)	70.0 (50.0–86.0)	.27
Heart Rate (bpm)	57.5 (44.0–66.0)	65.0 (52.0–87.0)	.07
Respiratory Rate (cpm)	18.0 (9.0–24.0)	15.5 (9.0–24.0)	.62

[a]p-value determined by Mann–Whitney test for the comparison between the hypogonadism group and the control group.

BMI, body mass index; BP, blood pressure; CG, control group; HG, hypogonadism group.

(p = .08). Moreover, the intragroup comparison showed that within the hypogonadal group, the total testosterone was significantly higher in D1, during the peak phase of circulating testosterone levels (p < .01). On the other hand, men in the control group showed no significant differences in total plasma testosterone levels between the two evaluation days (p = .66) (Figure 1). Additionally, the median testosterone levels were statistically similar in both evaluation days, for both men under 15 (n = 4) or 21 days (n = 4) of TRT regimens respectively: (i) D1-peak: 20.81 nmol/L (8.74–27.65) versus 18.63 (5.03–27.14) (p = .74) and (ii) D2-nadir: 7.83 nmol/L (4.16–13.73) versus 8.24 (4.72–9.85) (p = .80).

The HG and CG had similar cardiorespiratory fitness, muscle strength and endurance, body composition and joint flexibility. These similarities were maintained independently of the protocol time points (D1 or D2) and the corresponding testosterone dose-related timing in the HG. Similarly, the intragroup comparison between the two different time points (D1 and D2) revealed that the HG and CG had no significant differences (Table 2). Of note, no correlation was found between each strength variables and the patients' age at TRT initiation.

The quality of life among men in the HG and the CG was also equivalent. Absolute median values were above 60% for both groups regarding the four domains analysed, as shown in Table 3.

4 | DISCUSSION

The present study investigated HRPF components and QOL in a series of eight men with congenital hypogonadotropic hypogonadism, in comparison with healthy men. In this experimental protocol, hypogonadal men who were regularly receiving a short-acting injectable testosterone formulation showed a similar physical performance in all HRPF components, as compared to the control group. These results

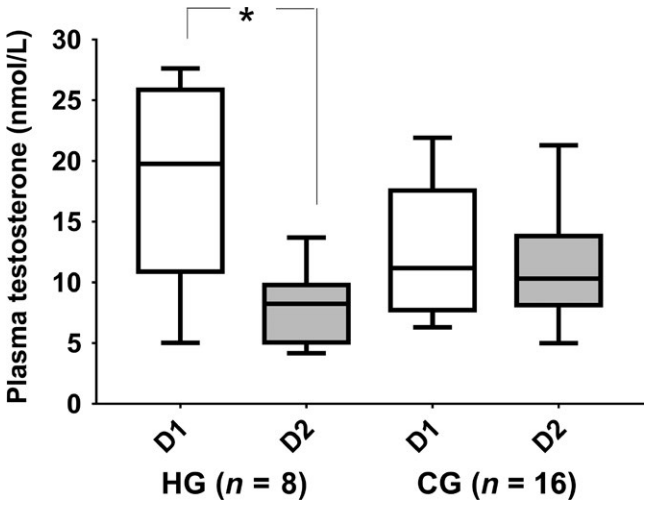

FIGURE 1 Comparison of plasma total testosterone levels between congenital hypogonadism group (HG) and control group (CG). D1: 7 days after exogenous testosterone administration in the hypogonadal group, or first evaluation day in the control group. D2: 7 days after D1 in both groups. *p < .01 (D1:HG > D2:HG)

TABLE 2 Intragroup and intergroup comparisons of lower limb muscle strength and endurance, upper limb muscle strength, joint flexibility, body composition and cardiorespiratory fitness between the hypogonadal group (HG, n = 8) and control group (CG, n = 16), at two evaluation time points (D1 and D2)[a]

	D1		D2					
	HG	CG	HG	CG	p-value HG	p-value CG	p-value D1	p-value D2
PT 60°/s (N m)	263 (175–318)	226 (183–290)	251 (151–309)	234 (200–315)	.20	.16	.31	.73
Total work (J)	3871 (2335–5050)	3717 (3061–4524)	3953 (2150–5118)	3642 (3056–4809)	.94	.45	.48	.60
Fatigue (%)	42.1 (29.5–52.0)	39.9 (6.3–57.0)	41.4 (33.3–53.7)	44.6 (12.4–58.6)	.38	.45	.98	.74
Handgrip d (kgf)	54 (33–77)	50 (39–63)	54 (36–76)	49 (42–76)	.40	.81	.73	.56
Handgrip n (kgf)	51 (34–71)	50 (35–61)	54 (35–72)	50 (39–67)	.14	.34	.60	.67
SRT (cm)	29.7 (20.2–40.0)	22.6 (2.5–39.6)	29.4 (14.3–40.6)	23.4 (1.3–38.7)	.16	.92	.06	.08
BAI (kg/m^2)[b]	22.8 (21.5–24.9)	23.0 (19.1–28.5)	–	–	–	–	.62	–
VO_2 (ml kg min^{-1})[b]	41.0 (32.0–57.0)	42.5 (30.0–57.0)	–	–	–	–	.85	–

[a]HG, hypogonadism group; CG, control group. D1 (evaluation day 1) and D2 (evaluation day 2) were randomly assigned in the control group and were determined according to the testosterone dose-related timing in the hypogonadism group, such as D1 was 7 days after the last testosterone dose injection and D2 was 7 days after D1.

[b]BAI and VO2 were evaluated only in D1 for intergroup comparison using Mann–Whitney test.

PT, peak torque; d, dominant hand; n, nondominant hand; SRT, Sit-and-reach test; BAI, body adiposity index; VO2, maximum oxygen uptake; D1, the peak stabilisation phase of total plasma testosterone in HG or first evaluation day of the CG; D2, drop phase of total plasma testosterone in HG or second evaluation day in the CG; p-value HG, value of "p" for Wilcoxon test between D1 and D2 in hypogonadism group; p-value CG, value of "p" for Wilcoxon test between D1 and D2 in the control group; p-value D1, value of "p" for Mann–Whitney test between D1HG and D1CG; p-value D2, value of "p" for Mann–Whitney test between D2HG and D2CG.

TABLE 3 Comparison of the quality of life scores in the four domains of the WHOQOL questionnaire between the hypogonadism group (HG, *n* = 8) and control group (CG, *n* = 16)[a]

QOL Domain	HG (*n* = 8)	CG (*n* = 16)	*p*-value
Physical	73.2 (53.6–89.3)	75.0 (60.7–85.7)	.40
Psychological	77.1 (45.8–95.8)	70.8 (50.0–91.7)	.23
Social	75.0 (66.7–100.0)	75.0 (50.0–100.0)	.41
Environmental	65.6 (46.9–87.5)	64.1 (34.4–81.3)	.81

[a]values expressed as medians (extremes).
CG: control group; HG: hypogonadism group.
p-value determined by the Mann–Whitney test to the comparison between the hypogonadism group and the control group.

were verified both during the peak phase of circulating testosterone levels (7 days after testosterone cypionate injection—D1), as well as in the dropping/nadir phase (D2), and were independent of the expected difference in plasma testosterone levels between D1 versus D2 in those men (Figure 1). Furthermore, QOL was also similar between the two groups.

Although restricted to a small series of CHH cases, data of this pilot study suggest that TRT was efficient, from a health perspective, in providing physical fitness levels in CHH similar to those found in nonhypogonadal men. These findings are remarkable in face of the uncertainties regarding TRT in men with hypogonadism, who frequently report weakness, fatigue and lack of energy despite optimal treatment protocols (Harvey et al., 2015). Most of the studies that have evaluated physical performance components and QOL assessed male late-onset hypogonadism (LOH), that is a condition in which men have acquired testosterone deficiency anytime during adulthood or senescence. The inherent heterogeneity of men with LOH implicates in different durations and intensities of testosterone deficiency, which may have influenced physical fitness before the initiation of testosterone supplementation (Bhasin et al., 1997; Lašaitė et al., 2014; Maggio et al., 2011). On the other hand, CHH is a lifelong condition, in which specific testosterone-related physical performance turns to be mostly dependent on exogenous testosterone replacement, unfolding critical aspects of testosterone replacement on a global health and physical fitness perspective.

To our knowledge, only one previous study has systematically evaluated the effects of TRT in HRPF in men with congenital hypogonadism, with results comparable to ours, especially regarding muscle performance. Aydogan, Eroglu et al., 2012; using a longitudinal experimental design, showed that a short-acting intramuscular testosterone formulation significantly improved the isokinetic peak torque of knee extension in men with congenital hypogonadism to values similar to controls (Aydogan, Eroglu et al., 2012). In a cross-sectional study, Maggio et al. described elderly men with severe hypogonadism have a lower grip strength and physical performance than paired controls (Maggio et al., 2011). Those studies suggest that only severe and persistent testosterone deficiency is associated with significant impairment of muscle strength.

In this case series, we found that testosterone-treated hypogonadal men had a body composition comparable to men without hypogonadism, irrespective of the evaluation parameter. Of note, BAI is an alternative index that estimates the percentage of body fat with a high correlation with dual-energy X-ray absorptiometry (DEXA) (Bergman et al., 2011). Our results corroborate the evidence that testosterone replacement is effective in reducing the deposits of abdominal fat (Andrade, Clapauch, & Buksman, 2009). Accordingly, we demonstrated that the odds of having metabolic syndrome were enhanced by 23% for each BMI unit increase in a series of men with metabolic syndrome, which might represent an additional health benefit of testosterone replacement in hypogonadal men by preventing an unfavourable body composition (Mileski, Leitao, Lofrano-Porto, & Grossi-Porto, 2015).

Additionally, Tong et al. evaluated the influence of a long-acting testosterone formulation in hypogonadal men QOL and observed a significant improvement in mental health after 30 weeks of treatment (Tong, Ng, Lee, & Lee, 2012). Although the QOL findings presented in Table 3 do not allow the establishment of a link between TRT and QOL, which involves a range of interfering factors, they agree with Tong and collaborators' conclusions. On the other hand, other studies found no significant benefits in the QOL related to TRT. Interestingly, Katznelson et al. showed improvements in QOL only when treatment interacted with physical activity (Katznelson, Robinson, Coyle, & Lee, 2006).

The overall analysis of HRPF components and QOL was performed considering the total testosterone levels between the two groups. As shown in Figure 1, the intragroup comparison showed similar median values of total plasma testosterone in the two testing days in the control group, as expected for healthy young men with normal endogenous testosterone production. Notwithstanding, in the hypogonadal group, the testosterone peak at the stabilisation phase (D1:HG) was 58% higher than at the testosterone drop phase (D2:HG). This pattern is attributable to the pharmacokinetic profile of the short-acting testosterone formulation used, which may occasionally result in supra- or subphysiological levels along time (Shoskes, Wilson, & Spinner, 2016). Overall, it may be speculated that, to achieve the expected health-related physical fitness benefits, the average concentration of total testosterone could be more important than the actual variation.

Although the small sample size limits the extrapolation of our results and may have overestimated the effect of TRT, this should be evaluated considering the nature of the study object. CHH is a rare disorder and has been selected based on strict inclusion and exclusion criteria. Through this approach, the internal validity of our analysis was prioritised. No interference was induced in the individual treatment regimens, which could have accounted for any dose-related effect. Furthermore, subjects were carefully selected to match for physical activity level, age and BMI, thereby restraining confounding variables that could potentially affect both plasma total testosterone levels and HRPF components (Travison, Araujo, Kupelian, O'Donnell, & McKinlay, 2007). All tests show appropriate scientific validity and were performed in both groups equally, thus standardising any inaccuracies of indirect tests. The scarcity and heterogeneity of studies analysing

physical fitness parameters in individuals with congenital hypogonadism, possibly reflecting its low prevalence, limited a broader comparative analysis.

In conclusion, regular use of short-acting testosterone, individually prescribed in clinical routine aiming physiological levels of plasmatic testosterone, seems to be effective in preventing physical fitness impairment in this case series analysis. CHH men had similar HRPF and QOL as compared to their clinically healthy peers, even when evaluated at two different time points, and independently of the expected fluctuations in total plasma testosterone concentrations. Acute fluctuations in TT levels did not correlate with changes in any HRPF component, including muscle strength and endurance, neither in men with CHH nor in healthy individuals. This suggests that chronic levels of T could be more relevant for physical performance than transient fluctuations of this hormone. The relevance of these findings requires further analysis in a larger number of subjects, with a longitudinal design, to evaluate the effects of testosterone replacement on HRPF, as well as the responsiveness to exercise training.

ACKNOWLEDGEMENTS

We thank the medical residents and staff of the Adrenal and Gonadal Diseases Clinics of the University Hospital of Brasília for sample selection; *Nucleo de Apoio a pesquisa do Laboratorio Sabin, Brasilia, DF* (Sabin Laboratory), for gently performing the hormonal assays; students and technicians of the Laboratory of Strength Training (Faculty of Physical Education—University of Brasilia) for support in protocol selection and training. This work was partially supported by *Conselho Nacional de Desenvolvimento Cientifico e Tecnologico*—CNPq—Brazil (scholarship number 135096/2011-1 to KM) and *Fundacao de Apoio a Pesquisa do Distrito Federal*—FAP-DF (research grant number 193.000.407/2010 to ALP).

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How to cite this article: Mileski KSL, Bottaro M, Grossi-Porto LG, Lofrano-Porto A. Health-related physical fitness and quality of life in men with congenital hypogonadotropic hypogonadism. *Andrologia*. 2018;e12967. https://doi.org/10.1111/and.12967