

Effects of growth hormone and testosterone therapy on aerobic and anaerobic fitness, body composition and lipoprotein profile in middle-aged men

Adam Zajac¹, Michał Wilk², Teresa Socha³, Adam Maszczyk⁴, Jakub Chycki²

¹ Department of Sports Theory, Academy of Physical Education, Katowice, Poland

² Department of Sports Training, Academy of Physical Education, Katowice, Poland

³ Department of Individual Sports, Academy of Physical Education, Katowice, Poland

⁴ Department of Methodology, Statistics and Informatics Systems, Academy of Physical Education, Katowice, Poland

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Abstract

Introduction. Andropause and aging are associated with neuroendocrine dysfunctions. Growth hormone and testosterone play a significant role in several processes affecting adaptation and thereby also everyday functioning. The aim of this research project was to evaluate the effects of recombinant human growth hormone and testosterone enanthate injections on body mass and body composition, aerobic and anaerobic fitness and lipid profile in middle-aged men.

Materials and method. The research group was comprised of 14 men aged 45–60 years. Two series of laboratory analyses were performed. Independent tests were carried out at baseline and after 12 weeks of the experiment. The data were analyzed using Statistica 9.1 software.

Results. A two-way repeated measures ANOVA revealed a statistically significant effect of the intervention programme on fat-free mass ($\eta^2=0.34$), total body fat ($\eta^2=0.79$), total cholesterol ($\eta^2=0.30$), high-density lipoprotein cholesterol ($\eta^2=0.31$), low-density lipoprotein cholesterol ($\eta^2=0.42$), triglyceride ($\eta^2=0.28$), testosterone ($\eta^2=0.52$), insulin-like growth factor 1 ($\eta^2=0.47$) and growth hormone ($\eta^2=0.63$). Furthermore, ANOVA revealed a statistically significant effect of the rhGH and T treatment on maximal oxygen uptake ($\eta^2=0.63$), anaerobic threshold ($\eta^2=0.61$) and maximal work rate ($\eta^2=0.53$).

Conclusion. It should be emphasized that the lipid profile was affected not only by rhGH+T replacement therapy, but also by the prescribed physical activity programme. The strength and endurance fitness programme alone did not cause significant changes in body mass and composition, nor the anaerobic and aerobic capacity. On the other hand, the rhGH+T treatment stimulated these changes significantly.

Key words

Physical fitness, growth hormone, testosterone, body composition

INTRODUCTION

Andropause, sarcopenia and aging are associated with neuroendocrine dysfunctions. Age-related endocrine deficiencies and changes in endocrine function decrease the quality of life, which is associated with a decrease in skeletal muscle mass and strength. Growth hormone (GH) and testosterone (T) play a significant role in several processes affecting adaptation and thereby also everyday functioning. The anabolic and lipolytic effects of GH have been well documented among healthy and GH-deficient subjects (GHD) [1]. Testosterone is the principal male sex hormone from the androgen group. It is produced by interstitial cells of Leydig in the testes in the presence of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Testosterone is an anabolic hormone directly affecting increases in muscle mass and strength [2]. A relationship has been found between testosterone concentration and muscle satellite cell increase. Testosterone regulates body composition by promoting the

commitment of mesenchymal pluripotent cells into myogenic lineage and inhibiting the differentiation into adipogenic lineage via an androgen receptor-mediated pathway [3].

Apart from the decline in GH and T secretion with increasing age, hormonal response to physical exercise is also lowered, resulting in partial or complete loss of training-induced physiological adaptations [4, 5]. It has been shown that the acute GH response is somewhat limited in older individuals [4]. Hakkinen & Pakarinen [5] demonstrated that a heavy resistance training session caused an increase in testosterone concentration in 30 and 50 year old men, but not in elderly subjects. Adults with GH deficiency and testosterone dysfunction exhibited a significantly reduced quadriceps muscle strength, compared to a group with physiological levels of GH and T. Since muscle strength reduction among individuals with GHD is most commonly due to a decreased cross-sectional area of a muscle resulting from GH and T decline, the maintenance of FFM seems to play a key role in preventing the consequences of aging. A relationship was also revealed between GHD and a significant decrease in VO_{2max} and muscle strength [6]. Compared to individuals with normal ranges of GH, 40–50% of GH-deficient individuals exhibited changes in exercise capacity and a slight increase in LDL and total cholesterol concentrations [7]. Such abnormalities

Address for correspondence: Adam Maszczyk, Department of Methodology, Statistics and Informatics Systems, Academy of Physical Education in Katowice, Mikołowska 72A, 40-065 Katowice, Poland
e-mail: a.maszczyk@awf.katowice.pl

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underlie sarcopenia, insulin resistance, type 2 diabetes and cardiovascular disease. Prevention of age-related GH and T decline considerably slows down the aging process. As effort-related stimulation of GH or T secretion appears to be insufficient in elderly men, it is necessary to employ other methods of increasing GH and T concentrations. In healthy men, a 6-week testosterone therapy resulted in a body mass increase of 3–5 kg [8]. Testosterone inhibits triglyceride uptake and lipoprotein lipase activity. Similar to other androgens, testosterone has been shown to prevent or delay age-related cognitive impairment. Testosterone replacement for 12–24 weeks increased fat-free mass and muscle size in hypogonadal men by increasing protein synthesis and accretion [9]. Recombinant human growth hormone (rhGH) has also been shown to have noticeable effects. Salomon et al. [10] demonstrated that 6 months of growth hormone replacement (0.07 U per kilogram of body mass) caused mean lean body mass increase of 5.5 kg and fat mass decrease of 5.7 kg. Cuneo et al. [11] documented a rhGH-induced increase in lean tissue and skeletal muscle mass/strength in adults with human GH deficiency. Although GH administration to GH-deficient adults increases fat-free mass and decreases fat mass [11], earlier studies employing GH as a lipolytic agent in the treatment of obesity have been disappointing [12]. Both GH and T have been used in the treatment of andropause and to reduce changes associated with aging.

The aim of this research project was to evaluate the effects of recombinant human growth hormone and testosterone enanthate injections on body mass and body composition, aerobic and anaerobic fitness and lipid profile in middle-aged men.

MATERIALS AND METHOD

The research group comprised 14 men aged 45 – 60 years. Inclusion criteria were: age (45–60 yrs.), BMI (25–33), TBF (23–30%), diagnosed andropause and no contraindications to the procedures in this study. The participants were randomly allocated to 2 groups, ie., experimental and control group (Tab. 1). The experimental group was subjected to rhGH and testosterone oenanthate injections over a period of 12 weeks. RhGH was administered daily in progressive doses of up to 30 µg/kg of body mass. T was given once a week at a dose of 100 mg. The control group were given a placebo during the entire study period. Prior to the study and during the investigations the participants were placed on a isocaloric mixed diet (55% carbohydrates, 20% proteins, 25% fats).

Table 1. Characteristics of the tested subjects

Variables	Experimental group ^a (n=7)	Control group ^a (n=7)
Age [years]	48.36 ± 2.50	49.21 ± 3.50
Body height [cm]	184.0 ± 4.00	187.0 ± 4.00
Body mass [kg]	99.03 ± 14.02	99.54 ± 7.24
BMI [kg/m ²]	30.50 ± 2.61	28.28 ± 2.97
TBF [kg]	26.08 ± 8.63	20.82 ± 5.86
FFM [kg]	72.90 ± 6.84	75.84 ± 8.78

^a – mean value and standard deviation (SD), BMI – body mass index; TBF – Total body fat; FFM – fat-free mass; TBW – total body water

Two series of laboratory analyses were performed. Independent tests were carried out at baseline and after 12 weeks of the experiment.

Body mass and composition were determined between 08.00 – 09.00 using bioelectrical impedance analysis (InBody 220). Body mass index (BMI), body mass (BM), total body fat (TBF), fat-free mass (FFM) and total body water (TBW) were registered. 10-ml blood samples were collected for biochemical determinations of growth hormone (GH), testosterone (T) and insulin-like growth factor 1 (IGF-1). Triglyceride (TAG), total cholesterol (T-Ch), high-density lipoprotein cholesterol (HDL-Ch) and low-density lipoprotein cholesterol (LDL-Ch) were also determined. Capillary blood samples were drawn to evaluate resting and post-exercise lactate concentrations (LA). GH concentrations were assayed by the radioimmune method with a DSL-1900 IRMA diagnostic kit (Diagnostic System Laboratories, Webster, TX, USA). Serum IGF-1 concentrations were also determined utilizing an immunoradiometric assay (IRMA) kit (DSL-2800 Active IGF-1, Diagnostic System Laboratories, Webster, TX, USA). Serum testosterone concentrations were evaluated using the immunoradiometric method with a DSL-1900 kit.

Test protocols. The exercise test used in evaluation of anaerobic fitness was the 30-second Wingate protocol performed on a cycle ergometer, with resistance of 0.08 Nm/kg body mass. Prior to the test, all participants had a 5-minute warm-up at 100 W and a pedal cadence of approximately 70–80 revolutions per minute.

Following the warm-up, the 30-second test started, in which the objective was to reach the highest number of revolutions per minute in the shortest possible time, and to maintain the cadence as long as possible. After completion of the Wingate test, the cool-down resistance was set at 50W for 4 minutes. In order to determine lactate concentrations during rest and the 4th minute of the recovery, 1ml capillary blood samples were collected from fingertips.

The variables of maximal power – P_{max} (W/kg) and total work performed – Wt (J/kg) were registered by the Lode Ergometry Manager (LEM) software package.

In order to determine aerobic fitness, each participant performed a ramp ergocycle test (T_{20x1}) (20W/1min) with the work load increasing linearly (0.33W per 1s). Each test started at a resistance of 40 W and individually adjusted pedal cadence and lasted until volitional exhaustion and VO_{2max} determination. Heart rate (HR), minute ventilation (VE), oxygen uptake (VO₂), expired carbon dioxide (CO₂), respiratory ratio (RER) and breath frequency (BF) were constantly monitored (MetaLyzer 3B- 2R, Cortex).

Maximal oxygen uptake (VO_{2max}) and maximal work rate (Wr_{max} – W) were registered using the Lode Ergometry Manager (LEM) software package. The anaerobic threshold (AT) was determined by the V-slope method. All tests were performed on an electromagnetically braked ergocycle Excalibur Sport (Lode).

Training programme. All subjects taking part in the research participated in a 12-week fitness programme. The 4-day-a-week training regimen included 2 days of strength training and 2 days of aerobic endurance exercise. The initial aerobic sessions consisted of 30-minute continuous pedaling on a stationary ergocycle at 70–75% HR_{max}. Every

2 weeks, the volume of work was increased by 5 minutes, thereby reaching 60 minutes during the last 2 weeks of the experiment. The muscular endurance training was focused on a holistic approach and consisted of multijoint exercises, such as the bench press, lat pulldown, dumbbell biceps curl, barbell squats, barbell upright row, and military press. The training loads were progressively increased from 3 sets of each exercise to 4 and 5 sets in the successive months of the experiment.

Statistical analysis. The data were analyzed using Statistica 9.1 software. The assumption of normality was verified using the Kolmogorov-Smirnov test. Comparison of the analyzed values before and after introduction of the experimental factor, was carried out with a two-way repeated measures ANOVA. When significant differences were found, Tukey's HSD *post-hoc* tests were used. The effect size (η^2) of each test was calculated for all analyses and classified according to Hopkins [13]. Statistical significance was set at $p < 0.05$.

RESULTS

Table 2 presents the pre- and post-intervention values of body composition and body mass variables. A two-way repeated measures ANOVA revealed a statistically significant effect of the intervention on FFM ($\eta^2=0.344$) and TBF ($\eta^2=0.791$). No significant post-intervention differences were observed in BM ($\eta^2=0.151$), TBW ($\eta^2=0.094$) and BMI ($\eta^2=0.114$). Thus, FFM significantly increased while TBF decreased in comparison to the pre-intervention levels.

Table 2. Pre- to post-intervention changes in body composition and body mass, and results of a two-way repeated measures ANOVA

Variables	Group	Before (rhGH and T) X \pm SD	After (rhGH and T) X \pm SD	F	p
BM (kg)	I exp	99.03 \pm 14.02	97.40 \pm 13.72	1.151	0.121
	II cont	99.54 \pm 7.24	99.38 \pm 3.57		
TBF (kg)	I exp	26.08 \pm 8.63	23.40 \pm 8.74	79.941	0.015
	II cont	20.82 \pm 5.86	20.22 \pm 5.93		
FFM (kg)	I exp	72.90 \pm 6.84	74.92 \pm 5.46	9.481	0.008
	II cont	85.84 \pm 8.78	84.77 \pm 8.26		
TBW (kg)	I exp	53.65 \pm 4.96	54.62 \pm 4.09	0.073	0.790
	II cont	62.74 \pm 6.16	61.71 \pm 14.39		
BMI	I exp	30.50 \pm 3.54	27.80 \pm 2.61	1.250	0.270
	II cont	28.28 \pm 3.07	27.64 \pm 3.14		

Table 3 presents pre- and post-intervention values of the biochemical variables under analysis. A two-way repeated measures ANOVA revealed statistically significant effect of the intervention programme on the following variables: T-Ch ($\eta^2=0.301$), HDL-Ch ($\eta^2=0.314$), LDL-Ch ($\eta^2=0.415$), TAG ($\eta^2=0.284$), T ($\eta^2=0.521$), IGF-1 ($\eta^2=0.474$), GH ($\eta^2=0.631$).

The Tukey's HSD *post-hoc* test revealed a statistically significant decrease of T-Ch ($p=0.028$) and increases in HDL-Ch ($p=0.001$), LDL-Ch ($p=0.001$), TAG ($p=0.041$), T ($p=0.001$), IGF-1 ($p=0.006$) and GH ($p=0.001$).

Table 4 presents pre- and post-intervention values of physical fitness related variables. A two-way repeated measures ANOVA revealed a statistically significant effect of

Table 3. Lipoprotein profile and hormone concentrations before and after rhGH and T treatment with results of a two-way repeated measures ANOVA

Variables	Group	Before (rhGH and T) X \pm SD	After (rhGH and T) X \pm SD	F	p
T-Ch (mg/dl)	I exp	216.46 \pm 26.92	184.41 \pm 21.25	5.927	0.025
	II cont	196.42 \pm 26.85	192.36 \pm 15.89		
HDL-Ch (mg/dl)	I exp	74.52 \pm 16.43	84.15 \pm 19.78	7.169	0.015
	II cont	68.90 \pm 4.33	65.57 \pm 4.30		
LDL-Ch (mg/dl)	I exp	114.82 \pm 29.05	101.65 \pm 27.06	12.231	0.021
	II cont	127.63 \pm 11.35	128.78 \pm 8.75		
TAG (mg/dl)	I exp	136.03 \pm 58.20	122.12 \pm 50.64	3.729	0.043
	II cont	113.38 \pm 27.82	115.91 \pm 26.84		
GH (ng/ml)	I exp	0.49 \pm 0.16	2.05 \pm 0.86	23.261	0.001
	II cont	0.58 \pm 0.14	0.57 \pm 0.12		
IGF-1 (ng/ml)	I exp	184.45 \pm 38.57	219.25 \pm 27.23	13.25	0.001
	II cont	191.98 \pm 25.87	191.57 \pm 23.85		
T (nmol/l)	I exp	13.80 \pm 3.81	26.47 \pm 7.96	18.510	0.002
	II cont	17.88 \pm 5.14	17.64 \pm 4.01		

Table 4. Aerobic and anaerobic fitness before and after the rhGH and T treatment and results of a two-way repeated measures ANOVA

Variables	Group	Before (rhGH and T) X \pm SD	After (rhGH and T) X \pm SD	F	p	
Changes in aerobic fitness	VO _{2max} (ml/min/kg)	I exp	35.88 \pm 5.45	40.27 \pm 6.09	32.60	0.002
		II cont	35.10 \pm 6.65	35.84 \pm 6.23		
	AT (W)	I exp	172.33 \pm 23.23	190.67 \pm 30.02	22.60	0.005
		II cont	161.00 \pm 23.13	162.14 \pm 21.59		
WRmax (W)	I exp	290.50 \pm 32.79	308.55 \pm 25.74	18.44	0.021	
	II cont	275.56 \pm 27.75	275.11 \pm 29.27			
Changes in anaerobic fitness	Wt (J/kg)	I exp	200.85 \pm 31.79	210.27 \pm 33.09	1.99	0.061
		II cont	198.44 \pm 27.75	198.48 \pm 26.77		
	Pmax (W/kg)	I exp	16.22 \pm 3.85	17.23 \pm 3.70	1.73	0.068
		II cont	15.02 \pm 1.62	15.37 \pm 1.68		
LA 4min (mmol)	I exp	7.61 \pm 0.81	8.17 \pm 1.17	1.68	0.072	
	II cont	7.39 \pm 0.72	7.40 \pm 0.80			

the rhGH and T treatment on VO_{2max} ($\eta^2=0.631$), AT ($\eta^2=0.611$) and WRmax ($\eta^2=0.531$) while no statistically significant post-intervention differences were observed in Wt ($\eta^2=0.128$), Pmax ($\eta^2=0.108$) and LA ($\eta^2=0.105$). The Tukey's HSD *post-hoc* test revealed a statistically significant increase in VO_{2max} ($p=0.002$), AT ($p=0.005$) and WRmax ($p=0.013$).

DISCUSSION

Both GH and T stimulate protein synthesis and may exert an anabolic effect, thus potentially limiting muscle atrophy and other unfavourable changes in older individuals. Changes in BM, FFM and TBF resulting from rhGH alone, testosterone alone and combined rhGH+T have been mentioned in numerous reports [11, 14, 15, 16]. Rudman et al. [17] used rhGH for 6 months and revealed an 8.8% increase in lean body mass, yet most likely the noticeable gain in FFM resulted from rhGH-induced water-sodium retention rather than actual FFM increase [18].

In order to eliminate data misinterpretation in the presented study, not only BM, FFM and TBF were analysed, but also TBW. The experimental group receiving rhGH and T exhibited a significant increase of FFM and a decrease in TBF. No significant changes were observed regarding BM and TBW. TBF and FFM changes related to hormone replacement therapy usually occur during the first 6 months. The rhGH alone, T alone, and, a more effective combination of rhGH+T lead to changes in body composition [11], as confirmed by a number of investigations in which several very advantageous changes in FFM and TBF were found. Following a long-term rhGH replacement therapy, Chihara et al. [16] revealed a 8.9% decrease in TBF in men compared to a placebo group. It might be of interest that after 24 and 48 weeks of rhGH treatment, overall changes in LBM, BFM and IGF-1 SD score were small, with no significant differences compared to the placebo participants. These results indicate that following a period during which rhGH replacement therapy does exert its metabolic effects, GH activity stabilizes and therapy outcome becomes reduced.

The presented study did not reveal any significant change in BM, which is consistent with the results of Jorgensen et al. [19], who did not observe significant post-rhGH changes in body mass, but did report significant alterations in body composition. The fact of this result having been reached on rhGH replacement alone may suggest that a TBF decrease found in the presented study may also have resulted from the rhGH treatment. There are reports indicating that T or GH replacement alone may cause changes in both body mass and body composition [15]. Testosterone and its therapeutic concentrations seem to exert a particularly noticeable effect on BM. Similar to our findings, Friedl et al. [14] did not find body mass changes in middle-aged men who received testosterone enanthate (TE) at a dose of 100mg/wk. Significant increases were observed only for men receiving a dose of 300mg/wk. Contrary results were presented by Griggs et al. [9], who showed no significant increase in muscle fibre diameter after 6 weeks of testosterone enanthate treatment.

The presented findings regarding the effects of combined rhGH+T therapy are consistent with the findings of Blackman et al. [20] who noted a decrease in TBF and an increase of FFM. Most of the effects of rhGH on FFM are mediated by increased production of IGF-1, which was previously observed by Yarasheski et al. [21]. An IGF-1 increase during rhGH replacement was also found in the current study. IGF-1 enhances amino acid uptake, promotes mRNA transcription and translation, possibly inhibits proteolysis, increases the number of muscle cell nuclei and stimulates muscle hypertrophy [22]. Both rhGH replacement as well as combined rhGH+T treatment result in a significant elevation of IGF-1 levels; thus, the role of this factor in fat-free mass increase cannot be unequivocally determined. A 4-week testosterone therapy administered to elderly men produced serum concentrations equal to those of younger men, increased mRNA concentrations of IGF-1 and decreased mRNA concentrations of insulin-like growth factor binding protein-4 [15]. These findings seem to confirm that increasing testosterone concentrations in elderly men increases skeletal muscle protein synthesis and strength, and that this increase may be mediated by stimulation of the intramuscular IGF-1 system.

The subjects from the experimental group received rhGH and T injections, while all subjects taking part in the research

project participated in a specifically designed physical fitness programme. Enhanced GH and T secretions in response to resistance training suggests that the latter might promote beneficial changes in body mass and composition. The subjects selected for this experiment were regularly engaged in different forms of physical exercise prior to enrolment; thus, the physical activity programme used in the study was a continuation of their healthy lifestyle. Yarasheski et al. [21] hypothesized that heavy-resistance exercise training in older men combined with rhGH replacement would enhance muscle protein anabolism. However, increments in the rate of muscle protein synthesis were similar in the rhGH and placebo groups. These observations suggest that resistance exercise alone is capable of improving muscle strength and anabolism which seems consistent with the presented findings since only rhGH+T participants exhibited significant changes in body mass composition including FFM. In the study of Bhasin et al. [2], increases in lean body mass were 6.1 and 3.2 kg in the steroid-treated groups with and without resistance exercise, respectively. In the current study, the experimental group with rhGH+T treatment combined with resistance training showed significant increases in aerobic and anaerobic fitness, i.e., both VO_{2max} and WR_{max} were increased. It seems that the improvement of aerobic fitness variables in the presented study (group I) was mainly due to testosterone therapy and the physical fitness programme. This seems consistent with the findings of Rodriguez-Arnan et al. [23], whose data support the concept that GH therapy alone, in the absence of an exercise programme, may increase the amount of lean tissue, but not the quality or functional capacity of this tissue. Similar results were reported by Blackman et al. [20], who compared the effects of growth hormone and sex steroids alone to those of rhGH+T. The authors suggested that an increase in aerobic fitness resulting from rhGH+T injections might be associated with a relationship between VO_{2max} and FFM. They concluded that an increase in VO_{2max} was caused by an FFM gain and not by cardiac output. Observations in the presented study seem to confirm these findings since significant FFM and VO_{2max} increases were only found in rhGH+T participants engaged in the resistance and endurance training programme.

Numerous researchers reported that rhGH treatment resulted in the improvement of both aerobic and anaerobic capacities [6]. The current investigations demonstrated a significant increase in anaerobic capacity ($Wt - J/Kg$), while no significant differences were found between in the anaerobic power (P_{max}) of the experimental and control groups. The improvement in anaerobic fitness might have resulted from enhanced glycolysis and a statistically significant increase in FFM. Several research projects investigating the effects of androgen administration on muscular strength and power reported a beneficial influence of GH and T [2]. Muscle strength gain, and, in particular, a significant increase in FFM observed in the presented study, should have resulted in a increased P_{max} . This, however, was not found due to the lack of exercises enhancing muscle power production. As an anaerobic fitness variable, P_{max} is significantly correlated with muscular and neural adaptations, which become compromised in the aging process [24].

The aging process is inevitably associated with unfavourable changes in the lipid profile, which increase the risk of coronary heart disease. Unbalanced concentrations of total and LDL-cholesterol, triglycerides and apolipoprotein B are

caused by metabolic impairment, inappropriate eating habits and insufficient physical activity. The results presented here demonstrate positive changes in the majority of lipidogram components in the group receiving rhGH+T therapy. The experimental group exhibited a T-Ch decrease, HDL-Ch increase, and a significantly lowered LDL-Ch and TAG concentrations. Since both the experimental and control groups participated in the same training programme, it may be assumed that the changes were associated with the rhGH+T treatment. Testosterone decreases LDL-Ch concentrations; additional effects on lipidogram components depend on its doses and forms of administration. After 6-months administration of rhGH, Munzer et al. [25] noted a decrease in LDL-Ch but not in T-Ch, whereas rhGH+T decreased both LDL-Ch and T-Ch. He hypothesized that the post-rhGH+T decrease in TBF was caused by lowered T-Ch and LDL-Ch concentrations and not hormonal actions. Rodriguez-Arnao et al. [23] believed that rhGH+T treatment was particularly effective in the regulation of the lipid profile in overweight individuals, which was confirmed in the presented study. It should be emphasized that the lipid profile is affected not only by rhGH+T replacement therapy but also by physical activity. As opposed to other research projects, the presented study participants had been engaged in physical activity prior to recruitment. Thus, it may be suggested that changes in their lipid profiles were mostly due to the hormone replacement therapy.

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