Medicina (Kaunas) 2013;49(2):71-7

The Effect of Physiotherapy in Addition to Testosterone Replacement Therapy on the Efficiency of the Motor System in Men With Hypogonadism

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Key Words: *male hypogonadism; testosterone replacement therapy; physiotherapy.*

Summary. *Background and Objective. The aim of this study was to analyze whether the addition of physiotherapy to testosterone replacement therapy provides added benefit in improving functional capacity of the motor system in men with hypogonadism.*

Material and Methods. The study involved 3 groups of subjects: group 1, healthy men (n=20); group 2, men with hypogonadism who underwent testosterone replacement therapy with physiotherapy (TRT+PT) (n=8); and group 3, men with hypogonadism who underwent testosterone replacement therapy alone (TRT) (n=10). Physical activity (International Physical Activity Questionnaire [IPAQ]) and body composition (X-SCAN analysis) were analyzed; the vertical jump test (Leonardo Mechanography®) was applied.

Results. The application of testosterone replacement therapy together with physiotherapy for 6 months significantly increased the maximum and relative power of jump in the subjects in the TRT+PT group; however, in the TRT group, no statistically significant difference was observed. The maximum jump height for the subjects in the TRT+PT group significantly increased 6 months after the intervention; however, in the TRT group, this index remained unaltered. The lean body mass of the subjects in the TRT+PT group increased (P<0.05); however, in the TRT group, it did not change. The relative fat body mass in the TRT+PT group decreased significantly (P<0.05), but, in the TRT group, it had a tendency to increase, though insignificantly.

Conclusions. Our results suggest that the application of testosterone replacement therapy together with physiotherapy (1 hour twice weekly) in men with hypogonadism may lead to earlier and better results in comparison with testosterone replacement therapy applied alone.

Introduction

Hypogonadism in men is a clinical syndrome resulting from the deficiency of the production of androgens (1–5) and is linked to the emergence of sarcopenia (4, 6) not only among the middle-aged and elderly men (1, 2, 4, 6). Besides, with the fall of testosterone below the physiological range, there is an increased incidence of visceral obesity, metabolic syndrome, early atherosclerosis, type 2 diabetes mellitus (7), osteoporosis (8), muscle mass reduction (4), and deterioration in physical qualities (2, 4, 6). The prevalence of the syndrome is increasing among young men (1), resulting in the problems related to sexual function (5) and fertility (9).

Testosterone is the main steroid hormone produced in the testicles (2, 5, 6), secretion of which is characterized by a circadian rhythm (3, 10). Its concentration in the blood serum gradually and slowly decreases with age and, as it has also been proven, due to constant tension and stress (11, 12). A biologically significant decline in the levels of testosterone may be due to age (andropause) or failure in the cascade of hormone-producing endocrine glands (2, 5, 11, 13). Depending on the level of impairment, primary (testicular) and secondary, or hypogonadotropic (pituitary or hypothalamic), hypogonadism is distinguished.

For more than 60 years, hypogonadism has been treated by administering various forms of testosterone for medicinal purposes (5, 6, 13, 14) or as strength-enhancing agents (15). Young men who are diagnosed with hypogonadism commonly use testosterone replacement therapy life-long, as this helps prevent adverse health effects (1, 6, 11, 14, 15). With the treatment goal to achieve the mid-range value of serum testosterone levels in young men, an average weekly dose of 125 mg of testosterone (16) or 75–100 mg of long-acting testosterone undecanoate is usually required. Testosterone replacement therapy helps maintain bone mineral density (1, 5, 6), body muscle mass and strength (4,

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12, 17), erythropoiesis, sexual desire and capacity, as well as mood and overall well-being (2, 6, 9, 14, 16).

The prevalence of hypogonadism is increasing due to growing numbers of metabolic diseases, especially diabetes (18). Many studies in elderly men use different methods to analyze the testosterone-and-muscle strength ratio as well as to register muscle strength (e.g., 1 repetition maximum [RM] or dynamometry) (4). It has been established that dynamometry indices depend on the efforts and the efficiency of motivation, mood, and fatigue (19); thus, dynamometry is characterized by a large number of variables, which can distort the registered changes in strength after testosterone therapy and exercise in smaller groups of subjects (4).

It has been established that even in physically active men, muscle mass decreases by about 1% per year (4), which is linked to the decline in testosterone levels with aging (4). However, it has not been adequately studied yet how testosterone levels in healthy men change with age and how this relates to the changes in muscle mass (4); effects of testosterone are still questioned (20). There are studies suggesting that the use of testosterone replacement therapy improves physical function and increases strength in healthy older men (4); however, some studies have shown decreased strength after the application of testosterone therapy (12, 21).

It has been established that testosterone levels in healthy humans correlate well with muscle strength (22), but it is not clear how muscle strength correlates with testosterone levels in young men with hypogonadism. In young men with hypogonadism, testosterone replacement therapy is applied with great caution due to the possible side effects (9), and the efficacy of the treatment is observed in the functional improvement in the quality of life as well as other organs and systems (1). However, it is still not clear how physical exercises alter the functional indices of muscle performance and how testosterone levels change in such patients. We expect that the application of physiotherapy in addition to testosterone replacement therapy (by prescribing physiological doses of testosterone) will provide greater benefit for the functional capacity of the motor system and body composition in men with hypogonadism.

Thus, the aim of the study was to analyze whether the addition of physiotherapy to testosterone replacement therapy provided added benefit in improving the functional capacity of the motor system in men with hypogonadism.

Material and Methods

Subjects. The study involved 3 groups of subjects: group 1, healthy men (HM) (n=20); group 2, men with hypogonadism who underwent testosterone replacement therapy with physiotherapy (TRT+PT) (n=8); and group 2, men with hypogonadism who underwent testosterone replacement therapy alone (TRT) (n=10). The subjects in the group 1 and group 3 were patients of the Department of Endocrinology, Hospital of Lithuanian University of Health Sciences Kaunas Clinics, who had been diagnosed with hypogonadism: the baseline total testosterone levels were 4.13 nmol/L (SD, 1.31) in the patients who received TRT and 4.19 nmol/L (SD, 1.7) in those who received TRT+PT; thus, the groups were homogenous. The characteristics of the subjects are provided in Table 1.

Table 1. Baseline Characteristics of Participants

Index	HM (n=20)	MH TRT+PT (n=8)	MH TRT (n=10)
Age, years	26.00 (4.71)	26.50 (4.99)	26.00 (5.50)
Height, m	1.80 (0.06)	1.80 (0.04)	1.80 (0.06)
Weight, kg	78.67 (9.14)	74.40 (7.78)	74.71 (12.35)
BMI, kg/m^2	24.28 (2.62)	22.98 (1.89)	23.06 (2.95)
Fat body mass, %	20.03 (6.76)	24.92 (5.19)	23.39 (6.07)
Fat body mass, kg	16.03 (6.26)	18.81 (5.16)	18.12 (7.20)
Lean body mass, kg	58.08 (6.36)	50.19 (4.45)*	51.50 (5.67)*

HM, healthy men; MH TRT+PT, men with hypogonadism who underwent testosterone replacement therapy with physiotherapy; MH TRT, men with hypogonadism who underwent testosterone replacement therapy alone.
*$P<0.001$, compared with HM.

Methods. Body composition analysis was carried out using the X-SCAN equipment and the BIA tetrapolar electrode method, measuring the resistance of the body with 8 tactile electrodes (on feet and palms) and using 4–6 different frequencies of the measurement signal (1, 5, 50, 250, 500, 1000 kHz) because different cells are characterized by different resonant frequency.

Having recorded the subjects' age into the X-SCAN analyzer connected to a computer, with the patients standing barefoot on a special platform, the device registered their height. The body composition of the subjects was established using the bioelectrical impedance measuring method, i.e., the body composition was measured emitting low and safe electrical current through the body. The analysis took several minutes; it was noninvasive and had no impact on the subject's health. The device immediately calculated and produced body composition indices such as height (m), body weight (kg), body mass index (BMI, kg/m^2), fat body mass (%), fat body mass (kg), lean body mass (kg), and waist-hip ratio (WHR).

The changes in body mass index, percentage fat body mass, and waist-hip ratio before and after the study were estimated following the estimation standards proposed by the X-SCAN manufacturer Interlux.

Vertical jump test is the test evaluating the indices of subjects' physical abilities when they perform a standing high jump with both legs. The study employed the Leonardo Mechanography® Ground Reaction Force Platform (NOVOTEC Medical GmbH, Germany), which was connected to the computer.

Before the test, the subjects had a 5-minute warm-up, after which they performed a jump with a squat amortized over the knee joints, from a static position, with arms swinging up. At the beginning of the study, the subjects were asked to jump as high as possible from the initial vertical neutral body position with their feet at the width of shoulders and hands down and relaxed. After a jump, they had to land on their feet with their knees at an angle of about 180 degrees. Each subject performed 3 jumps, and the most successful attempt was used for the analysis. The subjects had a 30-second break between the jumps. The registered signals were analyzed using the computer software, which automatically registered the dynamogram of a standing high jump and calculated its dynamic indices.

The following indices, which were developed in a jump, were assessed: maximum power, P_{max} (kW); maximum height, h_{max} (m); and relative power, $P_{max/kg}$ (W/kg).

Study Design. The research was started after the permission of the Bioethics Centre at the Medical Academy, Lithuanian University of Health Sciences (MA, LUHS), had been received. The study was carried out without any violation of the norms of ethics, the voluntary participation in the study was discussed with the subjects, and the confidentiality of the research data and details was guaranteed. The researchers obtained written informed consent of the research participants. The subjects were informed that they could discontinue participation in the study whenever they wished.

All the subjects were tested in the laboratory of the Clinic of Endocrinology, Hospital of Lithuanian University of Health Sciences. At baseline, physical activity of the healthy men and the men with hypogonadism during the previous week was assessed using the International Physical Activity Questionnaire (IPAQ), developed for the observation of physical activity in the population and for clinical studies (23). The IPAQ is a measure assessing physical activity and is used in the epidemiological research for the population aged 18–69 years. The assessment involved the following activity components: leisure, work, housework, and transportation. The questionnaire allows determining 3 physical activity levels, which are evaluated by calculating the average metabolic equivalent of task (MET) minutes per week. It has been established that testosterone has no effect on physical activity, but men not engaged in sports have increased estrogen levels in the blood serum (24) as well as estradiol concentration, and their physical activity decreases with age.

The group of the healthy men underwent a single analysis. The men with hypogonadism were randomly assigned into 1 of the 2 subgroups: the men who underwent TRT+PT for 6 months and the men who underwent TRT alone. After 6 months at the end of the study, the analysis of the subjects was repeated. The research protocol is shown in Fig. 1.

Individual physiotherapy (PT) sessions were conducted in the gym of the Department of Kinesiology and Sports Medicine, MA LUHS, for 6 months, 60 minutes in duration 2 times a week. The exercises were meant to strengthen leg, arm, and back muscles, i.e., 3 sets of 6–8 repetitions were devoted to each group of muscles, at 80% of 1 RM with a 1-minute break between the exercises. Jumps were not included into the exercise program.

Application of Testosterone Replacement Therapy. Due to their disease, men with hypogonadism underwent testosterone replacement therapy. Every 10–14 weeks, depending on the testosterone levels in the blood, a solution of injectable testosterone undecanoate (1000 mg/4 mL) was injected into the gluteal muscles. In fact, 1 mL of the solution contained 250 mg of testosterone undecanoate, corresponding to 157.9 mg of testosterone. Testosterone replace-

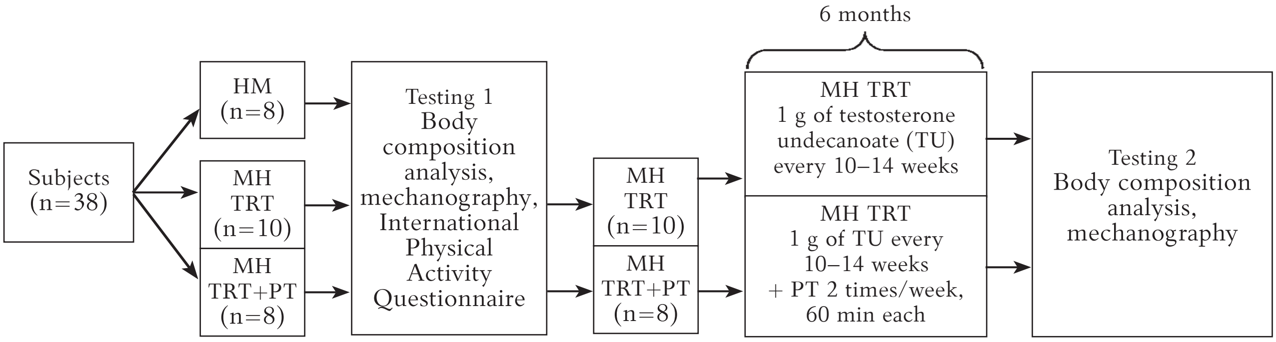

Fig. 1. Research Protocol
HM, healthy men; MH TRT, men with hypogonadism who underwent testosterone replacement therapy; MH TRT+PT, men with hypogonadism who underwent testosterone replacement therapy and physiotherapy.

ment therapy was controlled and applied by an endocrinologist of the Clinic of Endocrinology, LUHS.

Statistical Analysis. The data obtained were processed using the statistical package IBM SPSS 19.0. We applied nonparametric criteria to check the hypotheses about the equality of averages: the Mann-Whitney test for 2 independent samples and the exact Wilcoxon test for 2 related samples. The differences were considered statistically significant at $P<0.05$.

Results

Moderately physically active men according to the results of the International Physical Activity Questionnaire were enrolled into the study (Fig. 2). Physical activity of the healthy men was significantly higher ($P<0.001$) compared with that in the groups of PT or TRT+PT.

No significant changes in BMI throughout the intervention were observed in any of the groups. The lean body mass increased in the TRT+PT group ($P<0.05$); however, it did not change in the TRT group. The fat body mass and the percentage fat body mass decreased significantly in the TRT+PT group ($P<0.05$) and had a tendency to increase in the TRT group, though the change was not significant. The results are presented in Table 2.

In the TRT+PT group, the maximum jump power (P_{max}) at baseline was 2.56 kW (SD, 1.04); however, after the intervention, it increased significantly to 3.32 kW (SD, 0.79) ($P<0.05$) (Fig. 3). Meanwhile, P_{max} in the men with hypogonadism who received TRT alone did not significantly differ before and after the study (2.60 kW [SD, 1.21] and 2.64 kW [SD, 1.16], respectively; $P>0.05$). P_{max} in the men with hypogonadism who underwent testosterone replacement therapy and physiotherapy at baseline was significantly lower than in the healthy men ($P<0.05$), but after the intervention, there was no significant difference between the 2 groups ($P>0.05$).

The changes in the maximum jump height (h_{max}) are shown in Fig. 4. In the men with hypogonadism, h_{max} was 0.29 m (SD, 0.11) before TRT+PT and significantly ($P\leqslant0.05$) increased to 0.37 m (SD, 0.07) after TRT+PT. In the men with hypogonadism who received TRT alone, h_{max} did not significantly differ before and after the study (0.30 m [SD, 0.15] and 0.34 m [0.15], respectively; $P>0.05$). h_{max} in the men with hypogonadism who underwent testoster-

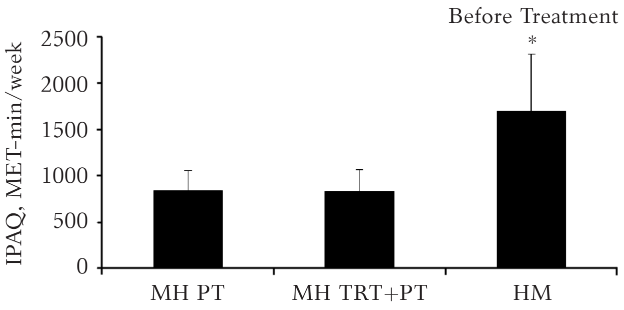

Fig. 2. International physical activity data at baseline

IPAQ, international physical activity.
*$P<0.001$, compared with Mh PT and MH TRT+PT groups.

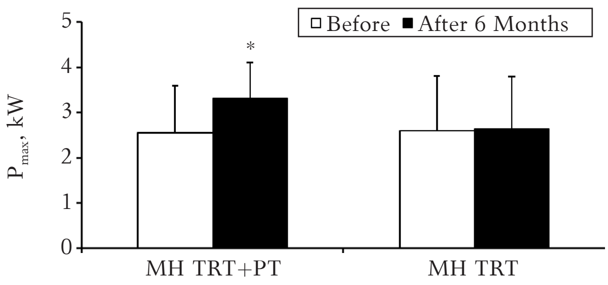

Fig. 3. Maximum power of jump

P_{max}, maximum power of jump.
*$P\leqslant0.05$, compared with the baseline value.

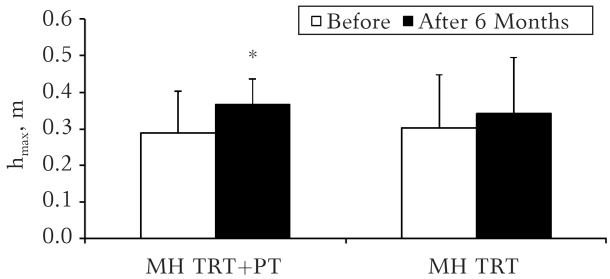

Fig. 4. Maximum jump height

h_{max}, maximum jump height.
*$P\leqslant0.05$, compared with the baseline value.

Table 2. Changes in Characteristics of Body Composition

Index	Group of Subjects			
	MH TRT+PT (n=8)		MH TRT (n=10)	
	Before	After 6 Months	Before	After 6 Months
BMI, kg/m^2	22.98 (1.89)	22.79 (1.89)	23.06 (2.95)	22.60 (3.26)
Fat body mass, %	24.92 (5.19)	20.23 (3.98)*	23.39 (6.07)	23.17 (6.78)
Fat body mass, kg	18.81 (5.16)	14.95 (3.57)*	18.12 (7.20)	17.57 (7.39)
Lean body mass, kg	50.19 (4.45)	54.55 (3.16)*	51.50 (5.67)	51.53 (6.20)

Values are mean (standard deviation). MH TRT+PT, men with hypogonadism who underwent testosterone replacement therapy with physiotherapy; MH TRT, men with hypogonadism who underwent testosterone replacement therapy alone.
*$P<0.05$, as compared with the baseline values.

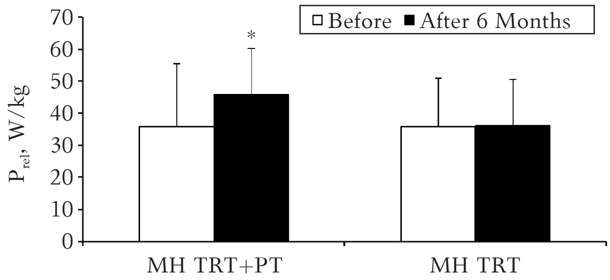

Fig. 5. Relative power of jump
P_{rel}, relative power of jump.
*$P \leqslant 0.05$, compared with the baseline value.

one replacement therapy and physiotherapy at baseline was significantly lower than in the healthy men ($P<0.05$); however, no significant difference was observed after the intervention ($P>0.05$).

The changes in the relative jump power (P_{rel}) within the subgroups are shown in Fig. 5. In the men with hypogonadism, P_{rel} was 35.86 W/kg (SD, 19.63) before TRT+PT, and it increased significantly to 45.77 W/kg (SD, 14.50) after TRT+PT ($P<0.05$). In the men with hypogonadism who received TRT alone, P_{rel} did not change significantly throughout the study (35.77 W/kg [SD, 15.12] at baseline and 36.34 W/kg [SD, 14.23] at the end of the study).

The relative jump power (P_{rel}) in the men with hypogonadism who underwent testosterone replacement therapy and physiotherapy at baseline was significantly lower than in the healthy men ($P<0.05$), but there was no significant difference at the end of the study ($P>0.05$).

The muscle mass in the men with hypogonadism who underwent TRT+PT increased by 9.1% (SD, 3.7%) ($P<0.05$), but no significant changes were observed in the men with hypogonadism who underwent TRT (0.1% [SD, 1.8%], $P>0.05$). Additionally, the relative fat body mass in the TRT+PT group decreased by 17.5% (SD, 6.5%), and an increase by 1.1% (SD, 2.1%) in the TRT group was not significant.

Discussion

Our study showed the following: a) the application of testosterone replacement therapy together with physiotherapy for 6 months significantly increased the maximum and relative jump power in the subjects in the TRT+PT group, but no significant differences were observed in the TRT group; b) the maximum jump height in the subjects in the TRT+PT group increased significantly, while this index remained unaltered in the TRT group; c) the lean body mass increased in the TRT+PT group ($P<0.05$), while it did not change in the TRT group. The relative fat body mass significantly decreased in the TRT+PT group ($P<0.05$), while it had a tendency to increase in the TRT group, although this change was not significant.

Effect of Testosterone on Working Capacity of the Motor System. Researchers (13) have previously shown that with therapeutic doses of testosterone (as was in our case), lean body mass increased and fat body mass decreased in men with low testosterone levels. Our study showed that during 6 months of the treatment, this effect was observed only in the men who had resistance exercise with testosterone replacement therapy; testosterone replacement therapy alone did not have a significant effect on the lean body mass and the fat body mass. This could be due to a rather short duration of the study as Depo-Testosterone was used. It should be noted that no research addressing working capacity of their muscle motor system has been carried out in young men with hypogonadism because more emphasis is given to the quality of life indicators of those young patients (1, 9).

It has been found that testosterone replacement therapy in elderly men with hypogonadism increases their power due to muscle hypertrophy and decreases fat body mass as a response to higher testosterone doses (5, 6, 11). However, the relation between testosterone and power is largely unknown because the research data are rather controversial (4). No studies have analyzed changes in the jump height and power of older men with hypogonadism.

It is also not clear how exercise together with testosterone replacement therapy affects the working capacity of the motor system in young men with hypogonadism. It has been previously established that testosterone therapy not only increases strength, but also power in young men with hypogonadism (12); however, in this study, Australian researchers did not apply physical load. The novelty of our research is that we found an increase in the maximum and relative jump power as well as a significant increase in the maximum jump height when young men with hypogonadism underwent physical exercise in addition to testosterone replacement therapy.

It is well known that resistance exercise causes the hypertrophy of skeletal muscles, thus, resulting in changes in free testosterone (17, 25), but the basic level of testosterone does not change (26). Other indices of the functional systems related to physical exercises and changes in testosterone levels have also been previously investigated (13, 27); however, this has been done in healthy men only, so it is still not clear how the analyzed indices differ in men with hypogonadism.

It has been established that in men with hypogonadism, low serum testosterone levels are associated with reduced physical activity due to a reduced hemoglobin concentration, which in turn results in reduced oxygen uptake, deterioration of glucose product utilization, faster onset of fatigue resulting in body composition changes: an increase in fat body mass and a decrease in muscular body mass (2, 4–6, 28) as well as muscle weakness; however, this does not affect physical capacity (6, 11). According to the IPAQ, men with hypogonadism demonstrate the moderate levels of physical activity (600–3000 MET minutes per week).

Resistance Exercise and Muscle Hypertrophy. It has been established that physical loads adapted for the development of strength increase protein synthesis in muscle fibers (11, 17, 22), which leads to an increase in muscle mass. The activity of protein synthesis is affected by the growth factor, which depends on insulin (1, 11, 20, 29) and testosterone secretion (19, 25, 26, 28). However, the metabolic mechanisms of muscle hypertrophy do not trigger cell hyperplasia if there is no mechanical activity of muscles (29). This means that muscle hyperplasia and hypertrophy mostly depend on muscle training (17, 20, 29). For this reason, we suppose that submaximum resistance exercise is a significant factor leading to an increase in lean body mass and changes in muscle functions in men with hypogonadism, even more so because there is evidence that muscle strength did not increase after applying 6-mg testosterone injections once a day for 36 months (5, 14). Muscle strength in men with hypogonadism increased when testosterone doses exceeded 125 mg per week (11, 22). On the other hand, some researchers do not recommend continuous high-dose testosterone replacement (16) because, with gradually increasing testosterone doses, muscle strength will not increase at the same pace (11, 28) and even higher testosterone doses will not affect the increase in muscle strength (6). Higher testosterone doses may have significantly greater side effects, in particular prostate hyperplasia and elevated hematocrit.

Muscle strength increases due to muscle fiber hypertrophy (25, 28, 29) as well as due to higher numbers of contractile elements and the enhanced recruitment and impulsion of motor units. These processes are a response to strength-developing physical exercises (6, 17, 26). However, an increase in muscle strength in men with hypogonadism has only been observed after performing resistance exercises for a longer time and taking higher doses of testosterone. An increase in circulating testosterone levels by as much as 30% caused little or no increase in strength (6, 10). Brill and coauthors applied testosterone at a dosage of 5 mg/day and reported that subjects could climb stairs faster, but their strength did not increase. It is worth noting that the effect was observed only with the treatment duration of at least 1 year to 36 months.

It has been established that the physical exercise of higher intensity has a greater effect on changes in strength when compared with the exercise of lower intensity (17). However, a significant increase in strength can only be observed when higher than moderate testosterone doses are applied in the course of the treatment (28). Researchers found that 200-mg testosterone injections twice weekly lasting for 36 months improved arm and leg strength (6) in men with hypogonadism.

The power and height of jump increase with increasing strength. External resistance determines the power of muscle contraction, which results in jump height (29). The more the muscle contracts, the more power it develops, but the speed can decrease due to external resistance (29). With an increase in lean body mass rather than fat body mass with the same BMI, the muscles engaged in the jump experience lower external resistance, which leads to an increasing jump height. Gabriel et al. suggest that higher external resistance results in the development of greater strength, but lower speed (30). Contraction force depends on speed changes due to the length of muscle contraction (29); in our case, due to the technique of jump performance during testing.

Conclusion

Our results suggest that the application of testosterone replacement therapy with physiotherapy (1 hour twice weekly) in men with hypogonadism may lead to earlier and better results in comparison with testosterone replacement therapy applied alone.

Statement of Conflict of Interest

The authors state no conflict of interest.

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Received 21 August 2012, accepted 25 April 2013