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Whether exercises and testosterone replacement therapy support a treatment for cardiovascular and atherosclerotic patients with iliac artery stenosis and low total testosterone and high-density lipoprotein cholesterol after endovascular procedure?

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Serum levels of testosterone (ST) and high-density lipoprotein (HDL) are generally associated with atherosclerosis in male patients over 50 years with critic iliac stenosis (TASC II A and B) and cardiovascular disease with significant changes in HDL and low-density lipoprotein (LDL). In addition to the standard therapy, combined medicamentous therapy and adequate model of exercise are also important factors as medicines can improve HDL levels and primary bypass and endovascular potency impacting positively on improvement of ST or it can be the following testosterone replacement therapy (TRT) comprising cardiovascular disease prevention and vascular treatment as adjunct therapy options after endovascular and vascular surgical procedures.

The aim of the study is to identify the association between HDL and ST after surgical and endovascular intervention on the iliac segment (TASCII A and B), as well as cardiovascular risk factors with modified medium activity (MET) <6 with short interval increase over >6 (MET), with total duration of 30–60 minutes. It also attempts to remodel a patient behavioral pattern, optimize ST levels and link them to outcomes and patency of vascular procedures on the iliac segment.

Materials and methods. 108 selected male patients with cardiovascular disease combined with metabolic syndrome and critical iliac artery stenosis (TASC II A and B) were examined during 2014–2018, 4 years after invasive and minimal invasive treatment (54 patients were treated with surgical Dacron reconstruction and 54 patients – with endovascular treatment on short segment of critical iliac artery stenosis (TASC II A and B).

Results. In the total population, no difference was observed in changes of constraint-induced movement therapy between the standard exercise group and the control one after 4 years from baseline. However, there was no significant interaction between the effect of exercise trainings and primary bypass potency within 4 years.

Conclusions. Primary effects of endovascular procedure and Dacron bypass revascularization raise the risk of elevated testosterone levels after 4 years of group training but does not provide adequate answers to questions as to whether higher levels of ST have any major influence on primary bypass potency preventing further progression of cardiovascular disease and general symptomatic and asymptomatic atherosclerosis. However, exercise and TRT can be potential adjunctive therapeutic options for a future supporting postsurgical and endovascular illiac treatment in cardiovascular patients with low testosterone levels.

Key words: exercise, testosterone replacement therapy, critical iliac stenosis II A and B, serum testosterone.

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Чи підтримують фізичні вправи та замісна терапія тестостероном лікування пацієнтів із серцево-судинними захворюваннями й атеросклерозом зі стенозом клубової артерії після ендоваскулярної процедури з низьким рівнем загального тестостерону та ліпопротеїдів високої щільності?

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Рівень загального тестостерону (ЗТ) і ліпопротеїдів високої щільності (ЛПВЩ) загалом пов'язані з атеросклерозом у пацієнтів-чоловіків віком понад 50 років із критичним клубовим стенозом (TASC II A та B) і серцево-судинними захворюваннями зі значними змінами рівнів ЛПВЩ і ліпопротеїдів низької щільності. Крім стандартної терапії, необхідно поєднувати медикаментозну терапію з адекватною моделлю фізичних вправ, оскільки ліки можуть також бути важливим фактором для підвищення рівня ЛПВЩ, ефективності первинного шунтування та ендоваскулярної терапії, що сприяє підвищенню рівня тестостерону, або це наступний рівень замісної терапії тестостероном (ЗТТ), який передбачає профілактику та лікування серцево-судинних захворювань, і судинної недостатності як варіанти допоміжної терапії після ендоваскулярних і судинних хірургічних процедур.

Ключові слова: фізичні вправи, замісна тестостеронова терапія, критичний стеноз клубової кістки (TASC II A і B), сироватковий тестостерон.

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Мета роботи – виявити асоціацію ЛПВЩ і загального тестостерону (ЗТ) після хірургічного та ендоваскулярного втручання клубового сегмента (TASC II A і B), а також факторів серцево-судинного ризику з модифікованою середньою активністю (MET) <6 з коротким інтервалом, що збільшується понад >6 (MET), загальною тривалістю 30–60 хвилин. Також зроблено спробу змінити модель поведінки пацієнта, оптимізувати рівень ЗТ у сироватці крові та зв'язати їх із результатом і прохідністю судинної процедури клубового сегмента.

Матеріали та методи. 108 пацієнтів чоловічої статі з серцево-судинними захворюваннями, метаболічним синдромом і критичним стенозом клубової артерії (TASC II A і B) перебували під спостереженням протягом 2014–2018 рр., через 4 роки після інвазивного та мінімального інвазивного лікування (54 пацієнти, яким здійснили хірургічну реконструкцію дакроном, і 54 пацієнти з ендоваскулярним лікуванням короткого сегмента критичного стенозу клубової артерії (TASC II A і B)).

Результати. У загальній популяції не виявили різницю за змінами обмежено-індукованої рухової терапії порівняно з вихідним рівнем через 4 роки між групою, де пацієнти виконували стандартні фізичні вправи, і контрольною групою. Втім, протягом 4 років не встановили значущі зв'язки між ефектом фізичних вправ і первинною шунтувальною потенцією.

Висновки. Первинна ефективність ендоваскулярної процедури та реваскуляризації дакронового шунтування після чотирьох років групових тренувань підвищує ризик збільшення рівня тестостерону, але не дає адекватної відповіді на запитання про те, чи має якийсь суттєвий вплив на ефективність первинного шунтування та вищий рівень ЗТ, що запобігає наступному прогресуванню серцево-судинних захворювань і загального симптоматичного, безсимптомного атеросклерозу. Втім, при низьких рівнях ЗТ за допомогою фізичних вправ і ЗТТ може бути потенційним варіантом допоміжної терапії для майбутнього підтримувального післяхірургічного й ендоваскулярного лікування пацієнтів із серцево-судинними захворюваннями із низьким рівнем тестостерону.

Rational optimization of resourceful maintaining adequate physical activity with drug therapy using different synthetic testosterone esters (testosterone replacement therapy – TRT or testosterone optimization therapy – TOT). Scientific therapeutic approaches to conservative and postoperative treatment of generalized atherosclerosis are rather controversial from an ethical perspective. It relates to different main segments as well as the iliac segment, and a therapeutic effect on primary cardioprotection in cardiovascular patients and a primary patency of surgical and endovascular treatment for critical stenosis of the iliac segment are more ambiguous [15,16,29,34,53]. Although many studies present promising effective potential results of applied therapy with various testosterone esters, many scientists, specialists in medicine and endocrinology, as well as anti-aging experts are skeptical about the idea of using such treatment. They are often misled by irrational high dose synthetic testosterone derivatives used in sports as well as abuse of synthetic testosterone esters used to enhance athletic performance. Therefore, the significance of practical therapeutic success remains a reason for a more optimistic assumptions as to this therapy [42,45,46].

On the whole, a decades-long debate will continue to occur in the future over benefits from heart and peripheral artery protection. There is an inevitable scientific discussion to shed light on the specific points of misuse in sports and physiological (therapeutic) doses. Trials provided high-quality evidence for benefits of optimal therapeutic doses of various synthetic testosterone esters to improve angina pectoris symptoms, including subjective improvement of general health in patients with cardiovascular disease [16,29,34].

The focus is still on the impact of both the therapy itself and potential reduction of high-density lipoprotein (HDL) cholesterol due to the therapeutic effect of synthetic serum testosterone (ST) as one of the main reasons for the debate. Low HDL can be successfully modified by adequate supplementation, diet remodeling as well as adequate exercise. Some authors do not even classify it as a high risk factor for cardiovascular and peripheral artery disease, unlike elevated low-density lipoprotein (LDL) and triglycerides, where only after 3 months of transdermal testosterone administration no significant decrease in HDL occurred that could compromise the progression status of atherosclerotic pathology [2,30,40].

Although considerable benefits have been observed in improving atherosclerotic symptomatology of microangiopathy and macroangiopathy in patients with and without type 2 diabetes mellitus, and even more convincing results have been shown by studies on synergy between application frequency and regularity of aerobic physical activity, but some scientific facts regarding the true potential of adequate testosterone administration and physical activity continue to be obscured. Despite the fact that the strong emphasis in atherosclerotic process is primary given to smoking, hypertension, obesity, lack of physical activity, and the effect of diet on HDL and LDL levels, optimal ST levels does not correspond to the degree of HDL reduction. It basically contradicts the development of atherosclerosis, a reduction in systemic inflammation and inflammatory markers, and it is cardioprotective with the benefits of anaerobic and aerobic physical activity following the implementation of surgical or endovascular revascularization of the iliac segment (TASC II A and B) [8–10,17,28,37]. Intensity and individual protocol as key factors remain partially unclear, while frequency and continuity with risk factor reduction and diet modification with appropriate medication support of comorbid conditions are the main pillars of treatment success [3,28].

Some authors of meta-analytic studies [1,6,36] show statistical insignificance between ST levels and cardiovascular disease, while others [7,10], unlike the above-mentioned authors, show the interaction, correlation and synergy between reduced ST and cardiovascular disease. This is evident in patients with generally poor overall condition, indicating the possibility of potential mortality from cardiovascular disease, and the importance of synergy between medicamentous and conservative therapy, the implementation of physical activity with appropriate supplementation and modifications in eating habits, impact on general and cardiovascular status, as well as benefits of hemodynamic patency after surgical and endovascular treatment with risk factor reduction [13,18,19,32].

Furthermore, a meta-analytical study by Haddad et al. [18] has demonstrated a significant association between cardiovascular risk and andropause in men, including obese

ones, who were found with significant changes in ST levels, regardless of a large age difference, in contrast to estrogen deficiency in women, which appears later in menopause. Thus, the etiological importance of administrating various testosterone esters at rationally tailored therapeutic doses remains an uncertain topic for future treatment options for cardiovascular patients with aortoiliac atherosclerotic disease as one of the possible synergistic variants for supportive care.

Aim

The aim of the study is to identify the association between HDL and ST after surgical and endovascular intervention on the iliac segment (TASC II A and B), as well as cardiovascular risk factors with modified medium activity (MET) <6 with short interval increase over >6 (MET), with total duration of 30–60 minutes. It also attempts to remodel a patient behavioral pattern, optimize ST levels and link them to outcomes and patency of vascular procedures on the iliac segment.

As part of the sub-disciplinary improvement of physical activity, experts in the field of sports and/or sports recreation were involved to manage factors of psychological motivations, empirical support and monitoring from Sports and Physical Education Faculties of Sarajevo and East Sarajevo, as well as the Clinic for Cardiovascular Surgery of University of Sarajevo, alongside consultations with others international experts in the field of sports and medical sciences.

Materials and methods

The study was designed as a prospective double-blind international trail with a four-year follow-up period (December 2014 – December 2018). During the four-year period, 108 selected patients (54 patients were treated with surgical Dacron reconstruction and 54 patients – with endovascular treatment on short segment of critical iliac artery stenosis (TASC II A and B)) were enrolled to determine treatment outcomes based on physical activity and correlation between ST levels and primary patency of Dacron bypass and stent (iliac self-expendable stent) procedures after treatment for critical stenosis over 75 % (TASC A I B II) of the iliac segment (*Table 1*).

All the patients passed the load test and were fit to carry out the physical concept. Training programs were planned to be conducted at least 4–6 times per week. The patients were offered the opportunity to choose individual physical activity: brisk walking or stationary cycling, anaerobic-aerobic exercises at a gym (combination of various exercise equipment and treadmills / or various types of combinations using elliptical trainer workloads up to 70 %). A weeklong intensity and time of physical activities were documented within 4 years after endovascular or surgical treatment for steno-occlusive iliac artery disease.

All the patients were examined by a sports medical team before the beginning of walking and cycling and after each month, as well as every 7–21 days to assess the health status and motivation. All the patients underwent cardiac catheterization. Additionally, each patient (individual approach) was given detailed lifestyle instructions (animal fat-restricted diet, correction of improper diet, dietary modification in regard to carbohydrates). Each patient was taught

Table 1. Clinical characteristics of all patients on medicamentous treatment before the study

Indicators	Surgical group	Endovascular group
Mean LDL, mmol/l	4.20 ± 0.23	4.1 ± 0.03
Mean HDL, mmol/l	0.92 ± 0.03	0.97 ± 0.07
Mean ST	57.00 ± 9.45	68 ± 11.34
Mean total testosterone	10.30 ±1.36	10.8 ± 1.36
Patients with obesity	8 ± 2	11 ± 3
Mean BMI	24.70 ± 5.80	26.90 ± 5.34
Age of men	54.30 ± 5.20	49.60 ± 4.20
Risk factors		
Smoking	43	37
Angina pectoris	2	5
COPD	12	15
Dyslipidemia	48	35
Intermittent gluteal and femoral claudication above 200 m	39	37
Chest pain in rest	4	1

to understand how and how much to exercise according to recommendations of sport physicians focusing on the study of physical activity influence on postoperative vascular treatment outcomes to the maximum extent possible. This international study was conducted at the Clinic for Vascular Surgery and partly also at the Clinic for Cardiovascular Surgery at the University Clinical Centre in Sarajevo (Bosnia and Herzegovina), regardless of whether the examined patients were treated or not at these institutions. The study was supervised by professors from the Faculty of Sport and Physical Education in Sarajevo and the Faculty of Sport and Physical Education in East Sarajevo.

Ethical authorization. Informed consent was obtained from all participants in the study. Since this is a postoperative follow-up of patients without modifications of ethical indicative medical treatment, none of the ethical principles of this study has been violated or further compromised.

T-test for large independent samples was used for data processing, and the threshold for statistical significance was set at $P < 0.05$. The statistical package Statistica, version 10.0 (STA999K347150-W), was used for data analysis.

Results

In total, 108 patients were divided into two groups for examinations and follow-up. Training level was analyzed over the four-year period. In the group of surgically treated patients, one year post-surgery, an average duration of trainings was 62.8 ± 10.2 min in 25 individuals who exercised once or twice per week. The duration of exercise training was increased with the increasing number of trainings per week. Nevertheless, exercise trainings averaged longer in patients after endovascular procedures, 79.8 ± 9.4 min. At the same time, the duration of exercise training was 145.00 ± 17.21 min in patients after three or more sessions. Similar results were observed over the next years (*Table 2*). Furthermore, in most cases, the patients who underwent endovascular procedures demonstrated better endurance in training ($P < 0.05$).

Endovascular procedures were less invasive, but even after 2 years, surgical patients were not able to reach training duration. At the same time, cholesterol levels, ST and total testosterone levels were examined and analyzed.

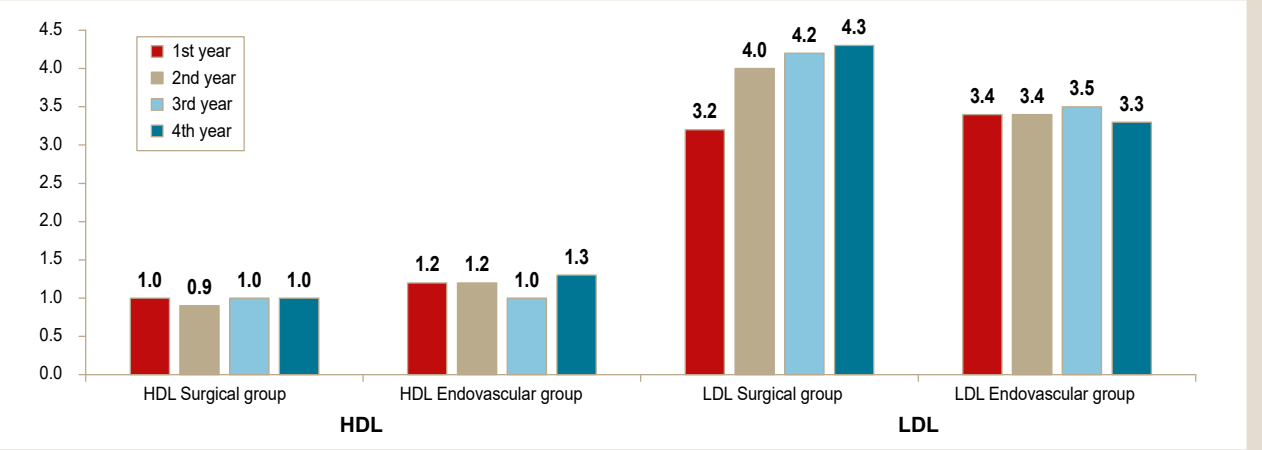

Fig. 1. HDL and LDL during the studied period of 4 years.

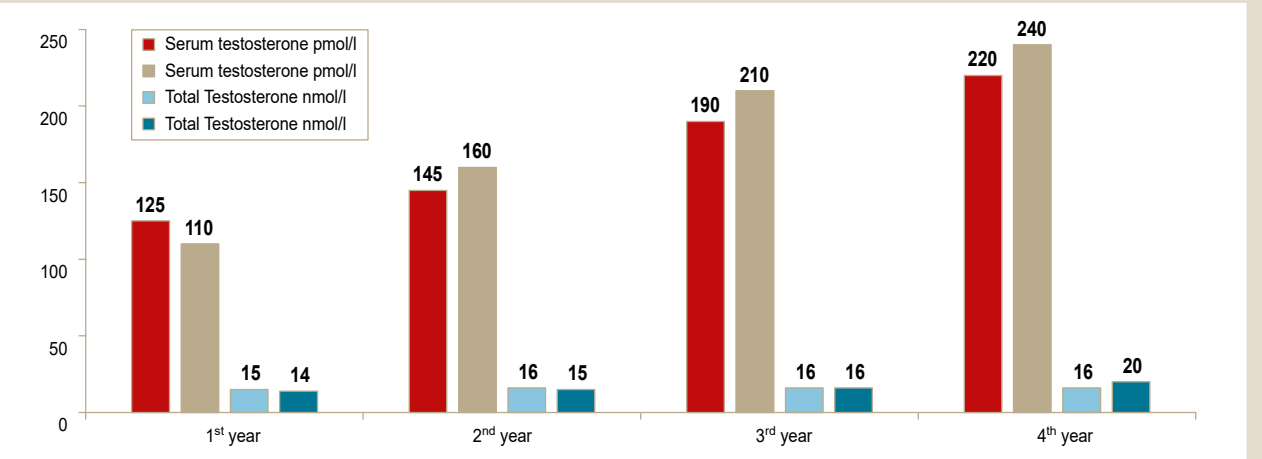

Fig. 2. ST and total testosterone during the studied period of 4 years.

Table 2. Comparison of exercise training duration between groups

Year	Number of exercises	Surgical patients	Endovascular patients	P
I	1–2 exercise trainings	62.8 ± 10.2	79.8 ± 9.4	<0.001
	3 and more exercise trainings	108.2 ± 22.3	145.1 ± 17.2	<0.001
II	1–2 exercise trainings	69.5 ± 18.8	82.7 ± 11.5	0.0086
	3 and more exercise trainings	122.8 ± 11.0	148.2 ± 28.6	<0.001
III	1–2 exercise trainings	73.3 ± 7.9	84.4 ± 17.2	0.0057
	3 and more exercise trainings	128.9 ± 38.4	148.4 ± 37.3	0.052
IV	1–2 exercise trainings	73.5 ± 11.6	91.3 ± 8.9	<0.001
	3 and more exercise trainings	133 ± 24.8	155.4 ± 27.9	0.001
V	1–2 exercise trainings	75.4 ± 27.4	89.3 ± 12.3	0.031
	3 and more exercise trainings	138.7 ± 23.1	152.8 ± 37.8	0.098

Results showing exercise training duration (min) are expressed in mean ± SD, significance – P < 0.05.

In the surgical group, HDL levels were 0.99 ± 0.14 in the first year, while in the endovascular group, it was 1.13 ± 0.18 with a significant difference (P < 0.001). A significant difference was found also in the second year. In the third year, there were not significant differences in HDL levels (P = 0.296). Later on, in the fourth year, subjects after endovascular procedures had significantly higher values of HDL (P = 0.001). LDL levels did not statistically differ in the endovascular treatment group (P = 0.219). After that, the opposite occurred in the results. In the following three years, LDL levels were higher in the group of patients after surgical treatment (*Fig. 1*). ST and total testosterone levels were analyzed over the period of 4 years. In the first year after surgery, the results were surprising, as ST and total testosterone levels were higher in the surgical group, but without any significant difference (P > 0.05) in both cases (*Fig. 2*).

From the second year, both testosterone levels were increased in both groups, but in the endovascular group of patients, that increase were greater: ST – P = 0.048 and total testosterone – P = 0.0132. In the third year, that difference was even greater: ST levels were significantly higher in the patients after endovascular treatment (P = 0.0012). Total testosterone levels were also significantly higher (P = 0.0027). In the fourth year, the mean ST level was 238.00 ± 23.00 in the endovascular group, while in the surgical group, it was 222.00 ± 35.08, with a significant difference at the level of P = 0.006. Furthermore, total testosterone levels were significantly higher in the endovascular group of patients, P < 0.001.

Discussion

A correlation between the patency of bypass procedure and endovascular treatment of the iliac segment (TASC II A and

B) and the physical activity intensity and combined influence of ST variability and HDL indicators remains partly unclear. Further research should therefore focus on the missing link between long-term vascular patency by optimizing ST and lipid levels with a larger group of enrolled patients, as well as the benefits of interventions aimed at cardiovascular protection and vascular patency. In addition to arterial hypertension and smoking, as some of the leading risk factors, physiological key values (LDL and HDL) reflect the regulation of cholesterol balance, where pathological elevation of LDL is one of the main causes of atheromatosis that subsequently results in the development of atherosclerosis with potential surgical risk [31,33,35].

High levels of HDL can result in cardiovascular benefit, reducing low-density lipoprotein deposition in the arterial intima and improving or slowing atherosclerotic pathological processes in the myocardium as well as in the arterial system (carotid, iliac, femoral arteries). However, a progression of intimal thickening can also occur that directly corresponds to ST deficiency in andropause syndromes, regardless of the patients' age. It also has a possible tendency to reflect the success and quality of the performance and patency of surgical or endovascular interventions, as well as the quality of patient mobilization [25,27,41]. HDL cholesterol is a strong inverse predictor of future cardiovascular events and important for preventing endothelial dysfunction in all systems, and its deficit plays a central role in further atherosclerotic pathology and direct onset of intermittent claudication symptomatology [11,12,24,26]. Apart from the cardiovascular benefit from subjective intensity of the exercise (submaximal and maximal), various complex load effects after coronary artery bypass grafting were observed and recommended using a level of 5–7 metabolic equivalents (METs) depending on patient age, general condition and associated comorbidities [52]. Physical activity combined with medicamentous therapy positively impacts the triglyceride profile as well as the LDL/HDL ratio, especially if the process of continuous movement towards accelerating fat and carbohydrate metabolism at shorter intervals, >50 MET weekly, reducing cardiovascular disease risk factors by 26 % [49].

Little weight is attached to patient motivation after vascular surgical and endovascular treatment of the iliac segment with difficulties during the implementation of the continuity of physical activity, lifestyle remodeling, and in understanding the importance of physical activity to further achieve adequate physiological hemodynamics, reduction of atherosclerosis indicators, as well as the benefits of endovascular surgery. Although today some facts about applied intensity of physical activity are quite modernized through studies, clarified and qualitatively examined via meta-analytical studies, high-intensity interval training would have a greater impact on hemodynamics in a risk of cortisol elevation. Unlike high-intensity interval training, moderate- or low-intensity continuous exercises are characterized by a very promising potential to maintain a value of >50 MET per week. After that there are good effects, as well as maintaining continuity and risk factor reduction, controlling a possible increase in blood lactate levels, and regulating comorbidity and supporting the primary patency following vascular interventions [15,21,22,44,47,50]. Patients with endovascularly treated iliac segment are of great advantage over surgical patients treated with a bypass procedure to achieve the initial effect of implementing adequate adaptive physical exercise through a combination of light running, brisk walking, or any other types of aerobic and/or anaerobic activity. According to a study [21], it is possible to achieve significantly increased HDL in middle age by moderate- or low-intensity continuous exercises for an hour or at least at a distance of over 11.265 meters weekly. Vascular interventions in the elderly and andropause remain a matter of great research interest in the field of sports and medicine. Correct and rational dietary modification in combination with medicamentous therapy and sustaining physical activity could reduce a potential supplementation with omega-3 fatty acids for the treatment of HDL-deficient hyperlipidemia [20]. Some studies have shown that physical activity declined the catabolic effect of HDL, which was 7–14 % reduced in patients with biological ageing, while it was 10–15 % increased in patients with normal HDL values. In control groups of patients with atherosclerosis, low HDL values were not changed, showing exponential growth with mono- and polyunsaturated fatty acids due to appropriate drug treatment with statins and acetylsalicylic acid 75–300 mg per day.

The challenge is whether it makes sense and therapeutic supportive benefit to use combined intramuscular injections or separate testosterone and testosterone ester administration [23,55]. There has been much discussion about the potential compensation of synthetic testosterone levels for cardioprotection in testosterone deficiency at the time of andropause, and some researchers were hoping for unexplored advantageous cardioprotective effect of estrogen and estradiol on blood lipid ratios [4]. There is a high rate of atherosclerotic pathology in the coronary, cerebral and peripheral arteries and compensatory systems in patients with low serum testosterone levels. Therefore, a myth about increased cardiovascular disease morbidity and mortality in patients with atherosclerosis and high testosterone levels, contradicting most evidence, should be busted. Patients would benefit substantially from study-based therapeutic reductions in dietary and physical activity risk factors [41]. We believe that compensation for testosterone without reducing the risk factors of dietary and physical activity would bring better therapeutic results. An association between estrogens and cardiovascular disease affects all vascular system components, resulting in progression of pathological atherosclerotic processes in the vascular systems. Therefore, we think that it is an important component in the therapeutic treatment of vascular patients after surgical or endovascular procedures of the iliac segment [14,38,50,51].

Furthermore, an etiological importance of various testosterone ester administrations at individual therapeutic doses as a supportive treatment component remains an uncertain topic for consideration regarding cardiovascular patients with atherosclerotic iliac occlusive disease. While some retrospective meta-analytic studies have not established the ST impact on the morbidity of patients with myocardial infarction, or have decided on a significant association between low ST and risk factors in patients with myocardial ischemia and generalized atherosclerosis of the main arterial segments [1,6], other studies have considered insignificant relationship between testosterone levels and cardiovascular disease [7,9,18]. The patients with individual TRT or TOT could benefit from improved physical concept, adherence to a reasonable diet, risk factors reduction,

especially nicotine use. Although there are no therapeutic guidelines for vascular patients, we think that it should be developed in the future to adjust the therapy according to ST levels. TRT does not increase the incidence of cardiovascular diseases, such as ischemic cerebrovascular disease (stroke), or angina pectoris.

Studies have shown that TRT had little to no effect on elevation of HDL as cardioprotective cholesterol, instead, leading to reduction of triglycerides and LDL levels, which were correlated with endovascular and surgical interventions. The therapeutic procedures resulted in reversion of sarcopenia, myohypertrophy, reduction in bone fragility and bone mineral density loss (which is typical for andropause), as well as alleviation of the need for revascularization of the iliac segment over 4 years with better cardioprotective and life quality results. Therefore, we need longer studies including more patients with intramuscular synthetic testosterone therapy (different types of esters) to develop new treatment guidelines for cardiovascular pathology and generalized atherosclerosis [5,39,43,48,54].

Conclusions

1. The study has shown improved primary vascular patency and serum testosterone levels as well as insignificant increase in HDL associated with proper physical activity in endovascular patients over 50 years with andropause. The most physically active patient group has demonstrated the significant increase in serum testosterone levels and HDL, associated with improvements in the quality of life and better primary vascular patency.

2. Although most authors are skeptical about controversial and varying views on the protective testosterone replacement therapy or testosterone optimization therapy combined with physical activity and risk factor reduction (complete cessation of nicotine), the further testosterone supportive therapy might include testosterone ester administration with dietary modifications and enhanced physical activity. This can be achieved by optimizing cardiovascular activity after conservative and postoperative treatment of atherosclerotic aortoiliac occlusion.

Prospects for further scientific research. The authors suggest studying long-term exercise and TRT effects in patients with cardiovascular disease and atherosclerosis (with low ST and HDL) combined with iliac artery stenosis after endovascular procedures.

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