

Connection of Low Serum Testosterone Levels in Cardiovascular Disease in Metabolic Syndrome Patients with Diagnosis of Critic Iliac Artery Stenosis (TASC II A and B) and Can Exercise Improve those Levels and Primary Potency of Revascularization after Surgical and Endovascular Treatment? (Pilot Study)

Sid Solaković^{1*}, Hajrudin Spahović², Ratko Pavlović³, Anes Jogunčić⁴, Nina Solaković⁵, Mensur Vrcić⁶, Fedja Hajrulahović⁷

¹Special Hospital dr.Solakovic Department for Vascular Surgery and Rehabilitation Sarajevo, The International University of Gorazde (IUG), Medical Faculty, BIH

²Clinic for Urology University of Sarajevo, BIH

³Faculty of Physical Education and Sports, University of East Sarajevo, Bosnia and Herzegovina

⁴School of Science and Technology, Medical Faculty, University of Sarajevo, BIH

⁵Special Hospital dr. Solakovic, Clinic's Dermatology Department, BIH

⁶Faculty of Sports and Physical Education of the University of Sarajevo, Bosnia and Herzegovina

⁷Health Centre, Sarajevo, BIH

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*Corresponding Author: Sid Solaković

Special Hospital dr.Solakovic Department for Vascular Surgery and Rehabilitation Sarajevo, The International University of Gorazde (IUG), Medical Faculty, BIH

Abstract

Introduction: Low concentration of free testosterone and low serum testosterone levels are associated in males patients with metabolic syndrome and cardiovascular disease and in some cases in connection with critic iliac stenosis and also in most cases with lack of physical activity. Exercise can be also important factor to improve primary bypass and endovascular potency and general health benefits after surgical and endovascular treatment in patients with critical ischemia over 75% of lumen obstruction of short iliac artery segment have positive impact on improvement of generally Testosterone Levels. **Subjects and Methods:** 72 selected Patients with Cardiovascular Disease with Metabolic Syndrome and Critic Iliac Artery Stenosis (TASC II A and B) were observed in period 3 years between February 2015 and February 2018. In focus was 1 year potency after invasive and minimalinvasive treatment (45 patients treated with surgical dacron reconstruction and 25 patients with endovascular treatment of short segment critical iliac artery stenosis (TASC II A and B). **Results:** In the total population no difference in changes of CIMT from baseline was observed between the standard exercise group and controls. However, there was no significant interaction between the effect of exercise training and primary bypass potency during 1 year. **Conclusion:** Primary potency of Endovascular procedure and Dacron bypass revascularization after 1 year in exercise training group significantly rise of testosterone levels higher but still not therapy adequate. With potential optimization testosterone therapy levels we can answer of the question. Is any major influence on primary bypass potency and are higher levels of free testosterone are preventing further progressing of cardiovascular disease and general symptomatic and asymptomatic atherosclerosis?

Keywords: Exercise Cardiovascular Disease, metabolic syndrome, Critic Iliac Artery Stenosis (TASC II A and B) Surgical bypass treatment, Endovascular Treatment.

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INTRODUCTION

Atherosclerosis, as a progressive disease of modern and contemporary times, regardless of age, tends to increase in younger, obese and inactive people. In the later state of progression of the pathology itself, endovascular or surgical treatment is the only treatment

option, in addition to conservative therapy [1-4]. Controversial scientific views are that male patients with metabolic syndrome, short claudication symptomatology of critical stenosis of the iliac segment over 75% of the iliac artery lumen (TASC II A and B) are imperceptibly associated with ischemic cardiocerebrovascular diseases, as well as

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atherosclerotic processes on other systems in direct correlation. andropause and less physical activity. Acceleration of the pathology of arteriosclerotic processes on the systems (heart and carotid arteries) which, along with uncontrolled irrational and malnourished caloric intake, as well as lack of physical activity are directly correlated with metabolic syndrome (MS) and peripheral arterial disease (PAB) with a potential background of hormonal deficit and testosterone deficiency in serum (TS) regardless of the level of total testosterone (TT) [1-8]. Critical stenosis of the atherosclerotic altered short iliac segment (TASC II A and B) can cause hemodynamic obstruction, reduce blood flow in the leg, which is manifested by symptoms of claudication or, rarely, pain at rest. This most often requires urgent endovascular and/or surgical intervention, especially in the case of a less developed collateral compensatory system in combination with supra- and infrapopliteal hemodynamic main arterial obstructions, and the time is suitable for endovascular and/or hybrid surgical treatment [9-11].

McDermott, Mehta, Ahn, *et al.*, [13] and many other authors indicate known risk factors for critical obstructive stenosis, as well as for the consequences of peripheral arterial disease. These are mainly smoking and an age limit above 40 years (andropause), progression of type 2 diabetes mellitus, hyperlipidemia, arterial hypertension and hyperhomocysteinemia, which also correspond to risk factors of critical stenosis of the iliac segment. With certain symptomatology or asymptotology, they should be considered as candidates for primary established endovascular therapy or because of the impossibility of the primary choice for the classic surgical bypass method, and secondary antithrombotic prevention after performing the indicated treatment. Multiple scientific studies [11-15] prove the connection between the lack of circulating testosterone (testosterone in the serum) and insulin-like growth factor-I (IGF- I) in old, obese, physically inactive people, as well as in immunocompromised people with a weaker general state of health and deficient immunonutrition. with the unsuccessful possibility of compensating the general condition with additional nutritional supplementation. However, some studies prove the opposite results, leaving large gaps in the target group. Also, the association of a reduced level of testosterone in the serum (TS) leaves open the question of the debate on the connection with steotic-occlusive arterial disease of cardiovascular etiology, as well as the possibility of a simultaneous simultaneous connection of the disease of the peripheral and central (main) arteries of the lower extremities.

Also with hemodynamically critical stenoses of the short iliac segment (TASC II A and B) there are very controversial opinions regarding the impact of testosterone deficiency in the serum in the form of future additional therapeutic applications in cardiovascular diseases. It is even more common in the

case of stenotic-occlusive diseases of the central and peripheral main arteries in the form of a reduction in mortality and an improvement in the success of primary surgical or endovascular treatment of critical stenoses of the central and peripheral arterial segments. Studies suggest [14, 18] with or without adequate implementation of the prescribing dose (synthetic testosterone) as well as with an adequate concept of physical activity in cardiovascular patients with serum testosterone deficiency in symptomatic and asymptomatic coronary disease improve the general condition of the patient while suppressing the symptoms of angina pectoris, and improve general cardiovascular parameters as an objective state of the general state of health [22, 23].

Some authors [19, 21, 31] indicate and focus on accompanying comorbidities of other systems of cardiovascular blood diseases (extracranial vessels with progression of carotid thickening Carotid Intima Media Thickness-CIMT) and the association with mortality in dialysis patients. The results suggest a higher rate of cardiovascular mortality with associated low serum testosterone in all mentioned vascular systems of generalized arteriosclerosis. We could direct a roadmap of scientific facts and studies that indirectly indicate the potential connection and imbalance of testosterone in the serum in critical stenosis of the iliac segment over 75% lumen obstruction with accompanying comorbidities of cardiovascular disease. The authors Maurice & Lesser [32] proved that with the individual controlled therapeutic application of testosterone propionate (TP) in 100 patients with angina pectoris after suffering for up to 5 years, there was a regression of pain symptomatology and paresthesias in 91 patients with a reduction in morbidity, which is a retrograde significant interesting observation. The question arises whether retro-futurative application therapy of synthetic testosterone derivatives or various combined testosterone esters as a cardioprotective secondary or even primary therapy is possible? Would they have a therapeutic benefit in postoperative therapy with remodeling of lifestyle and eating habits as well as the impact of primary patency after endovascular or surgical bypass treatment of critical iliac segment stenosis (TASC II A and B).

Definitely the lack of studies limits and restricts such progress and implementation of applications of synthetic testosterone in different phases of action. Prospective studies have also proven that low total testosterone is directly correlated with cardiovascular risk including metabolic syndrome, obesity, dyslipidemia. Hypertension and even with peripheral arterial disease on different segments of the central and peripheral arteries, thereby potentiating hemodynamic disturbance in critical iliac stenosis of the short iliac segment (TASC II A and B) [7, 21, 30]. Limitation of post-surgical or endovascular studies of vascular treatment of the iliac segment, monitoring and

focus on the quality of a particular concept of physical activity as a selection of one of the advanced concepts of vascular rehabilitation treatment, we can with great potential and the support of conservative therapy influence the very primary patency of vascular bypass or endovascular intervention with the benefits of the piety of the general conditions of vascular treated patients.

The aim of this study is to try to prove whether primary patency bypass (dacron) or endovascular treatment of critical stenosis of the iliac segment over 75% of lumen obstruction can be improved by supervised quality aerobic activity and modification of dietary habits. An attempt will be made to determine the level of serum testosterone (TS) after the procedure in patients with continuity of physical activity as well as in patients with a lack of physical activity.

Is there a connection between physical activity and an increase in serum testosterone at the primary patency of the vascular treatment and is this amount of therapeutic potential that could provide the best possible postoperative (invasive surgical or non-invasive endovascular treatment of the primary patency of the treatment of the short iliac segment of critical stenosis (TASC) and B).

METHODS AND MATERIAL

Participants and Study Design

Given that it is about the postoperative monitoring of patients without modification of the ethical indicative medical treatment, not a single ethical principle of this study was violated or additionally violated. A total of 72 patients who met the criteria for inclusion in the study were included.

The study is planned as a prospective double-blind international study of a 3-year period (February 2015 - February 2018), which includes a follow-up period of one year. In this way, the outcome of the patency treatment medical through physical activity and

the association of testosterone in the serum on the primary effect of the patency of the dacron bypass and Stent (Iliac Self expendable stent) procedure after the treatment of critical stenosis of the iliac segment over 75% would be determined. All patients passed the stress test and were suitable for the implementation of the physical concept. Training programs are planned to be conducted at least 4 to 6 times a week. Patients are given the opportunity to choose the physical activity they will use: fast walking or riding a stationary bike, anaerobic-aerobic gym concept (combination of various devices and treadmills/or various types of combinations) load up to 70% max.

This international trial was conducted at the Clinic for Cardiovascular Surgery of the University Clinical Center in Sarajevo (Bosnia and Herzegovina) where patients were and were not treated, in cooperation with the Wuppertal Hospital in Germany, as well as at the Faculty of Sports and Physical Education in Sarajevo. The best international members of professional international teams (from Germany, Japan, Slovak Republic) were involved with the empirical supervision of ethical, moral and professional principles. Before the start of walking and cycling training, after each month, all patients were examined by the sports medicine team and were also called every 7-21 days to check motivation and health status. All patients underwent cardiac catheterization.

Also, each patient (individual concept) was given detailed instructions on lifestyle (restriction of animal fat in the diet, reduction of low-quality, nutritionally poor diet, modification of the use of sugar according to the diet. Each patient was explained in detail how and how much to exercise, all accompanied by and with the strict supervision of the sports medicine team during the research. Although this study is of a wide range, the emphasis of the study is the influence of physical activity on the outcome of vascular treatment in the form of the best possible outcome of postoperative treatment of patients.

Table 1: Clinical characteristics of all patients before study covered by medicament treatment and before surgical and endovascular intervention

Obesity (Metabolic syndrome)	72
Average BMI 25-35	28 ± 2,53
Average male age	47.32
Hypertension/Prehypertension	68
Smocking	67 ± 2
Apstinent Smocker	16 ± 2
Angina pectoris stabilis	2
Chronic opstructive pulmonary disease (COPD)	12
Dislipidemia	48
Claudicatio intemitens glutealis over 200m	8
Claudicatio intemitens glutealis under 200m	62
Rest pain	0
Total patients	72

Table 2: Types of surgical and endovascular interventions in all 70 patients before study

Endovascular intervention of the iliac segment (TASC II A and B) - iliac Self expendable stent-	27
Aorto-iliaco bypass (dacron) 6-9mm	35
Iliaco- femoral bypass (dacron) 6-9mm	7
Aorto-femoral bypass (dacron) 6-9mm	3

Table 3: Types of surgical and endovascular interventions before study (endovascular approach)

Total patients	27
Lost to follow up (mortality)	0
Average serum testosterone values 91 -579 pmol/L	74 ±9,45
Average total testosterone 5,6 – 29,6 nmol/	10,3 ±1,36
Average Right Carotid Intima-Media Thickness (CIMT)	1,12 ±0.03
Average Right Carotid Intima-Media Thickness (CIMT)	1,12 ±0.03
Application of (Iliac Self expendable stent) in critical iliac stenosis TASC II A and B	15
Application of PTA (Percutaneous Transluminal Angioplasty)	0

Table 4: Transperitoneal approach and retroperitoneal approach

Total patients	45
Average serum testosterone values 91 -579 pmol/L	82 ±7,08
Average total testosterone 5,6 – 29,6 nmol/L	11 ±1,39
Average Right Carotid Intima-Media Thickness (CIMT)	1,12 ±0.03
Average Left Carotid Intima-Media Thickness (CIMT) female	1,08 ±0.05
Aorto-iliaco bypass (dacron) 6-9mm	23
Aorto-femoral bypass (dacron) 6-9mm	25
Iliaco- femoral bypass (dacron) 6-9mm	12

Table 5: Physical concept of variable physical activities after treatment during one year

Strength Training (70% of max.)	70
Standard walking procedure 30 - 60min (70% of max.)	12
Stationary cycling/indoor cycling (70% of max)	47
Combined strength training, walking and cycling (70% of max)	23

RESULTS

Table 6: Testosterone levels and carotid intima-media thickness (CIMT) after one year of study

	After Endovascular Interventions	After Surgical Interventions
Strength Training (70% of max)	19±3	14 ± 3
Average exercise 1-2 time per week	26,784,±110,2 min	12.262,8±10,2 min
Average exercise 3 time per week	34.933±203 min	15,231±10,2 min
Average exercise over time per week	39.237±120,2 min	16,440,8±10,2 min
Standard walking procedure 30- 60min maximal (70% of max.)	22	22
Stationary cycling/indoor cycling maximal (70% of max,)	13±1	13
Combined strength training, walking and cycling (70% of max)	13±5	15 ±4
Average serum testosterone values 91 -579 pmol/L	219 ±6,08	162 ±16,08
Average total testosterone 5,6 – 29,6 nmol/L	23 ±4,36	23 ±4,36
Average Right Carotid Intima-Media Thickness (CIMT)	1,00 ±0.03	1,02 ±0.03
Average Left Carotid Intima-Media Thickness (CIMT)	1,03 ±0.05	1,07 ±0.03
Average BMI 25-30	30 ±2	13
Average BMI under 25	4	10
Claudicatio intemittens simptoms over 200m	1	4
Claudicatio intemittens simptoms under 200m	0	0
No evidence of Claudication symptoms	0	0

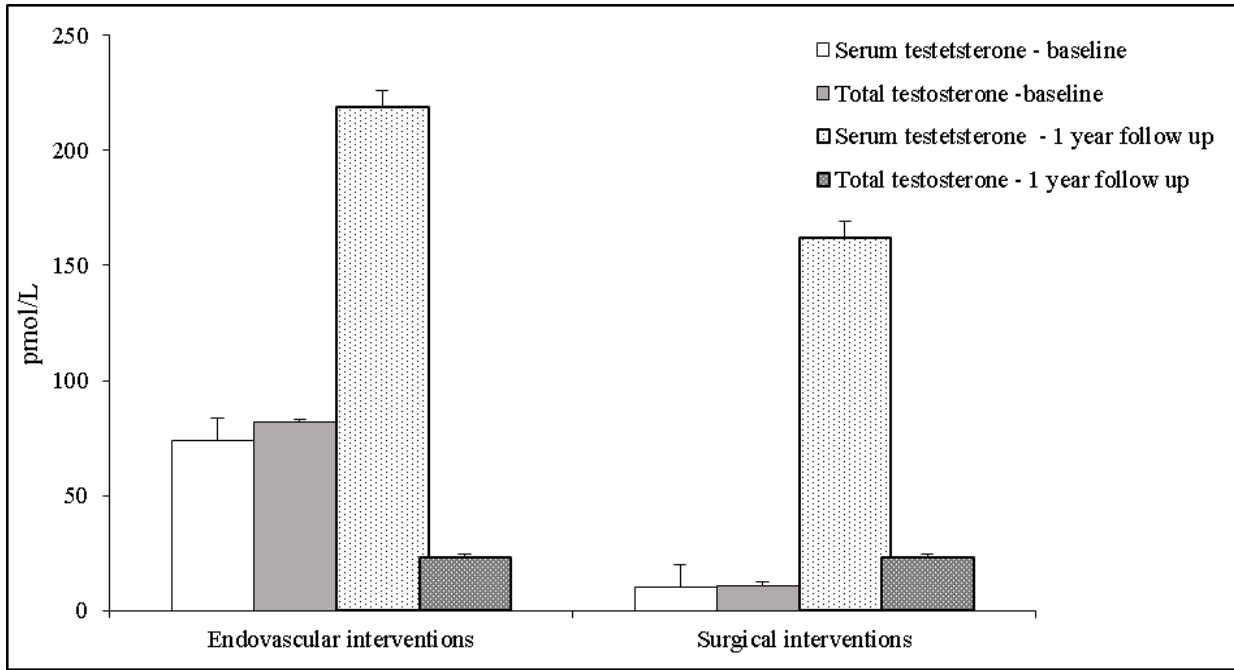


Figure 1: Serum and total testosterone in endovascular and surgical intervention

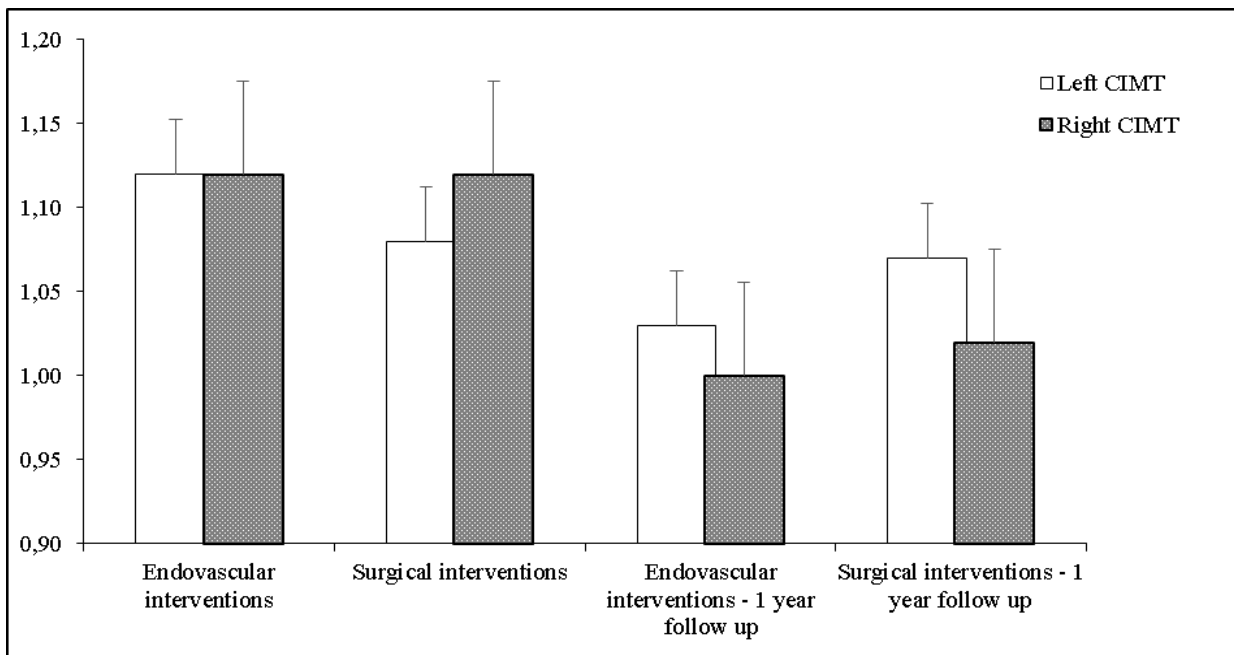


Figure 2: Left and Right Carotid Intima-Media Thickness (CIMT) in group of endovascular and surgical intervention after 1 year of follow up

DISCUSSION

Conflictingly deficient and devastating research data on variable correlations of testosterone deficiency in serum (TS) in cardiovascular patients. This is especially present in patients with critical stenosis over 75% of the iliac artery segment (TASC II A and B) and the connection between the metabolic syndrome of obesity and minor movements on the primary birth rate of surgical or endovascular treatment, post-therapy applications of physical activity that are evident in this study. Whatever, scientific data suggest in some cases a correlation between cardiovascular

diseases of critical stenosis on the iliac as well as on the coronary segment. This indicates a potential connection between arteriosclerosis and serum testosterone deficiency (TS) in other individual vascular systems with the development of claudication symptomatology of peripheral arterial disease (PAD) of the lower extremities on different arterial trunk segments. Although the data are scientifically limited, there is still room for future research on testosterone deficiency in the serum (TS) with the connection of different states of the pathophysiology of atherosclerosis. Thus, further scientific studies on different arterial systems are

emphasized, emphasizing the very intimate connection of obstruction of the hemodynamics of different arterial segments [22, 36, 37].

Regardless of age, serum testosterone (TS) has a positive effect on the regulation of lipid metabolism, especially on the level of the LDL/HDL ratio, as well as on the benefits of modulating the vascular reactivity of the coronary vascular tone, while it has no therapeutic protective effect on the increase of pathological triglyceride levels [33-35].

Although this study is limited by the number of participants, some scientific questions remain open regarding deficiency (TS), arteriosclerosis, coronary, carotid, central and peripheral arterial segments, as an influence and determining the intensity of physical activity. Therefore, further studies are needed to confirm the outcome benefit of primary bypass or stenting of critical iliac artery segment stenosis (TASC II A and B). The deficit itself (TS), in addition to impaired lipid status (dyslipidemia), affects pathophysiological processes with a decrease in physical and social activity, the general cardiological condition and is directly correlated with metabolic syndrome, type II diabetes, increased BMI and central circumferential thickness. All this corresponds to the increased pathophysiological state of acceleration of atherosclerosis and the acceleration of symptoms of stenotic occlusive disease of arteries in different segments, and the primary patency of surgical or endovascular intervention of critical stenosis of the iliac segment [40- 43]. Even more controversial and confusing scientific positions have also been taken on the very cardioprotective effect of estrogen in men. In the further scientific domain of consideration, as well as the confusion of coronary morbidity and mortality between therapeutic and sports doses of different testosterone esters (cypionate, propionate, phenylpropionate, isocaproate, enanthate, undecanoate, etc.) which leads to the confusion of applied therapeutic contrast, as well as anti- ischemic effect TRT (testosterone replacement therapy) or TOP (testosterone optimization therapy) in patients with coronary risk, general arteriosclerosis, as well as dyslipidemia, and the ratio (HDL-a-LDL) [48, 49].

There is scientifically significant and convincing evidence that a deficient level (TS), regardless of a normal level of total testosterone (TT), is an independent risk and predictor of the acceleration of arteriosclerosis in cardiovascular patients, so there is an important connection in the further development of the metabolic syndrome and the progression towards type II diabetes. An increased level of testosterone would have a potential and promising indicative therapeutic, preventive and cardioprotective meaning with the correction of risk factors, adequate application of physical activity, as well as remodeling of the diet itself, and lifestyle guidelines [44-47]. Some studies

[50-52] indicate an increase in the symptomatology of intermittent claudication in elderly patients with increased cardiovascular mortality with deficiency (TS). This indicates the conclusion of androgenopause and an indirect indicator of the occurrence of arteriosclerosis and the future development of symptoms of peripheral arterial disease. To be able to focus attention on a potential additional cardiovascular risk factor and help address barriers to further consideration of therapeutic and preventive cardioprotective options in the future. Other studies [53, 54] show opposite directions with subjective feeling due to deficient testosterone in obese men over 40 years of age with risk factors of abstinence resulting from decade-long nicotineism without subjective feeling, any symptomatology with the assumption of a connection between the causes of symptomatology with comorbidities and risk factors of age, more than TS deficit. Also the authors Price & Leng [55] suggest that there are no great scientific beneficial expectations from short-term treatment with synthetic testosterone in patients with arteriosclerosis of the lower extremities, a more limited number of subjects than the actual effect of the therapy. Given that each testosterone ester has its own therapeutic effect, such as oral and intramuscular applications, they still have a great deficiency in the application itself and in the potential therapeutic outcome of arteriosclerosis in cardiovascular patients, as well as in medicinal anticoagulant support for the post-therapeutic treatment of surgical bypass or endovascular procedures in patients with a recorded deficit testosterone. Hata, *et al.*, [56] point to the therapeutic importance of physical activity, which improves the correction of lipid imbalances in the serum and affects the higher-quality benefits of dietary remodeling (carbohydrate, fat and protein ratio), which leads to better success of preventive and postoperative treatment. For this reason, a more serious attitude should be taken towards impaired lifestyle habits of eating and lack of physical activity, which are one of the important risk factors of further progression of the disease as well as the outcome of surgical and endovascular treatment. Although normal or mildly elevated findings (TS) have benefits on cardiac pump physiology and ischemic heart disease, central and peripheral arterial pathways, a deficient level (TS) still represents a potential therapeutic option with a vasodilating effect to consider supporting anticoagulant therapy in further primary patency surgical and endovascular interventions on the iliac segment. Studies of supplementation (TS) combined with physical activity in patients have been shown to be successful in some patients with angina pectoris and post-myocardial infarction. Supplementation (TS) improves the subjective general condition of patients with loss of central fat, reducing obesity, so it would be logical to apply individually adjusted doses in surgically and endovascularly treated patients suffering from testosterone deficiency [30]. According to the results of studies [23- 28], it is common for physical activity to raise the level of

testosterone under certain loads, especially high- load anaerobic exercises are associated with an increase in testosterone, while prolonged exercises of a lower intensity can affect decreased serum testosterone as well as total testosterone (TT). Our current study showed recognizable benefits of regular exercise on the quality of the primary patency of the graft, and on the primary patency of the endovascular reintervention of the iliac segment (TASC II Ai B) with a crucial asymptomatic effect on the level of testosterone and myocardial ischemia, which is confirmed by other studies of the association between groups [57-59]. Umbreeni, Khan, Khan, *et al.*, [60] suggest that the level of physical activity (continuity and load) is an important predictor for the regression, as well as for the progression of carotid thickening Carotid Intima Media Thickness (CIMT) and that an independent risk factor is a lack of physical activity, which in comparison in our research can lead to reduction of the potential primary patency of surgical and endovascular intervention on the iliac segment. Hentzer & Madsen [61,62] did not prove that the therapeutic application of testosterone without an adequate concept of physical activity leaves no effect on increasing strength and claudication distance in the examined group. With that, they emphasize the weaker effect of the therapeutic benefit of testosterone application in claudication symptomatology of peripheral arterial disease.

The results of our study indicate a greater patency of the bypass procedure and endovascular treatment of the iliac segment (TASC II A and B) with continuous exercise, its own reflection on the level (TS) and reduction of BMI, which represents physical activity as a powerful medicinally supportive postoperative therapeutic goal in the form of cardioprotection and the primary patency of the two procedures with a general improvement of the objective health status. In general, the identifiable risk of cardiovascular patients with metabolic syndrome leaves a trace of deficit (TS) that physical activity can individually correct, but not ideally optimize at the therapeutic level in patients with initial andropause. On the other hand, the patency of the graft as well as the progression of the neointimal hyperplasia itself on the dacron graft should be examined in more detail, and more detailed studies of the influence of free testosterone levels with more subjects are needed to draw a scientific conclusion in the further prevention of arteriosclerosis. In this way, the best possible vascular postoperative or post-interventional rehabilitation outcome and quality of life would be ensured, as well as the primary patency of surgical and endovascular intervention, the influence of optimizing testosterone on the ratio of neointimal thickening of dacron material.

CONCLUSION

We believe that the research showed an interesting correlation of serum testosterone (TS) in cardiovascular patients (age over 40 years) with critical

stenosis of the iliac segment over 75% treated with surgical and endovascular treatment, as primary patency in patients who were physically active. In the examined patients in the group who were the most physically active, a greater increase (TS) was recorded, as well as an improvement in the quality of life, as well as the primary patency of surgical and endovascular intervention. If there was a greater increase (TS), in our opinion, it is not competent for the effect of cardioprotection. In this regard, one of the potential scientifically determined futuristic options would be the introduction of potential therapy in the form of cardioprotection, as a benefit of the general cardiovascular system and general circulation. Further studies are needed to examine the therapeutic benefit, as well as the potential effect of atherosclerosis remission, effectiveness and outcome benefits of TRT or TOT (testosterone optimization therapy) to influence the therapeutic quality of vascular treatment.

Limitation of Study

In conclusion, due to the small number of subjects who recorded the significance of the study objective, additional studies with a larger number of subjects are needed to reach a final scientific answer of the connection in the primary patency of surgical or endovascular intervention of critical iliac segment stenosis (TASC II A and B) with the association of testosterone in serum (TS). His physiological response to further vascular and cardioprotective rehabilitation treatment of medium load with an interval of increased load, as well as the potential (direct or indirect) reflection of the progression of non-intimal hyperplasia on Dacron or Nitinol, would be obtained.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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