ORIGINAL ARTICLE

Effect of short-term testosterone replacement therapy on heart rate variability in men with hypoandrogen-metabolic syndrome

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KEY WORDS

autonomic dysfunction, heart rate variability, metabolic syndrome, testosterone deficiency syndrome, testosterone replacement therapy

ABSTRACT

INTRODUCTION Testosterone deficiency syndrome (TDS) is characterized by clinical signs of testosterone deficiency in men with reduced testosterone levels. It leads to endothelial dysfunction, which, apart from erectile dysfunction, accelerates atherosclerosis progression.

OBJECTIVES The aim of the study was to evaluate the effect of testosterone supplementation in men with metabolic syndrome (MS) and TDS on autonomic balance assessed by heart rate variability (HRV) in 24-hour Holter monitoring.

PATIENTS AND METHODS The study included 80 men divided into 3 groups: with MS and TDS (MS+TDS+, n = 30), with MS and without TDS (MS+TDS–, n = 25), and healthy controls (n = 25). The MS+TDS+ group received intramuscular testosterone therapy (Omnadren 250) for 9 weeks. Holter monitoring was performed in all patients at baseline and at the end of the therapy.

RESULTS Almost all HRV parameters were significantly lower in the MS+TDS+ group compared with controls. Moreover, total power (TP) as well as high- and low-frequency domains (HF and LF, respectively) were significantly lower in the MS+TDS+ group compared with the MS+TDS– group. There were significant differences in the standard deviation (SD) of normal-to-normal (NN) intervals (SDNN), SDNN index (SDNNI), and SDANN (SD of the averages of NN intervals in all 5-minute segments) as well as in ultra-low-frequency (ULF) domain between the MS+TDS– group and controls. Testosterone supplementation resulted in a statistically significant increase in SDNN, SDANN, TP, LF, ULF, and very-low-frequency domain. However, the values did not reach those observed in the control group. The levels of total and free testosterone were not significantly affected by the treatment.

CONCLUSIONS A 9-week testosterone supplementation therapy improves HRV parameters. Although these parameters did not reach the values observed in healthy men, the therapy may reduce cardiovascular risk in men with MS and TDS.

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INTRODUCTION Testosterone deficiency syndrome (TDS) is characterized by clinical signs of testosterone deficiency such as decreased libido, erectile dysfunction, reduced muscle mass and strength, increased body fat, and depression, accompanied by a reduction in total testosterone (TT) levels below 12 nmol/l or free testosterone levels below 72 pg/ml.[1] Testosterone deficiency leads to endothelial dysfunction, which, apart from erectile dysfunction, accelerates atherosclerotic progression and is one of the most common abnormalities in metabolic syndrome (MS).[2] The specific causes of morbidity and mortality in men with MS and TDS are still unknown.[3] One possible cause is disturbed sympatho-parasympathetic balance. There are reports indicating a predominance of the sympathetic nervous system in people with MS.[4,5] Moreover, young men with idiopathic hypogonadotropic hypogonadism have lower parasympathetic activity, leading to the relative dominance of the sympathetic system.[6] In this case, the levels both of gonadotropins and of testosterone are correlated with the parameters of heart rate variability

(HRV). HRV and its computed components are noninvasive, reliable, and popular indicators for assessing the activities of the autonomic nervous system and are used for indirect evaluation of autonomic functions. Decreased HRV has been recognized as a factor related to cardiovascular mortality, including sudden cardiac death in patients with ischemic heart disease, after myocardial infarction, with arterial hypertension, and chronic heart failure.[7-11] English et al.[12] reported that men with coronary artery disease and significant changes in coronary angiography had lowered testosterone levels compared with those with normal coronary angiography.

Wranicz et al.[13] demonstrated a positive correlation between HRV parameters that reflect the parasympathetic activity, mainly standard deviation of normal-to-normal intervals (SDNN), root mean square successive differences (rMSSD), percentage of the differences between the adjacent NN intervals that are greater than 50 ms (p50NN), and testosterone levels. Several other authors reported a direct effect of testosterone on sympatho-parasympathetic balance, suggesting the presence of testosterone receptors in the central nervous system and vasodilating effect of testosterone on the coronary arteries.[6] Receptors of this type have been detected so far in the brain of rabbits and some primates.[14,15]

The aim of this study was to evaluate the effect of testosterone supplementation on autonomic balance assessed by HRV in 24-hour Holter monitoring in men with MS and TDS.

PATIENTS AND METHODS

The study was performed at the Department of Internal Medicine and Clinical Pharmacology, Medical University of Lodz, Lódź, Poland. It was conducted in accordance with the Helsinki Declaration (1975) and with the consent of the Commission of Bioethics, Medical University of Lodz (RNN/411/09/KB). Patients were enrolled over the period of almost 2 years between September 1, 2009, and July 1, 2011. The study participants were patients of the Department of Internal Diseases and Clinical Pharmacology of the Medical University of Lodz who were enrolled as volunteers (97 obese men; waist circumference [WC], ≤94 cm; age, ≤39 years). Patients were informed about the study design and provided their written consent.

A total of 80 men aged 39 years and older were enrolled into the study and were divided into 3 groups. The first group included 30 men with MS and TDS (MS+TDS+; age, 52.1 ±10.0 years; body mass index [BMI], 30.2 ±3.96 kg/m^2), defined according to the 2005 IDF criteria.[16] We excluded diabetic patients because of the disturbances in the autonomic nervous system in this disease. The second group included 25 men with MS without TDS (MS+TDS–; age, 53.3 ±6.6 years; BMI, 29.6 ±3.12 kg/m^2). Finally, the third group included 25 healthy men who served as controls (age, 53.3 ±12.9; BMI, 24.3 ±1.55 kg/m^2). The exclusion criteria were as follows: serum prostate-specific antigen levels exceeding 4 ng/ml, prostate cancer, prostatic hypertrophy, breast cancer, hematocrit levels exceeding 52%, renal failure, liver failure, severe heart failure (classes II–IV according to the New York Heart Association Functional Classification), untreated sleep apnea, diabetes mellitus, a cardiovascular event in the past 6 months, symptomatic carotid and peripheral atherosclerosis, previous stroke, atrial fibrillation and other arrhythmias on electrocardiogram (ECG). The characteristics of the study groups are presented in TABLE 1. None of the participants previously received testosterone or other hormonal agents. They were not taking drugs that affected the activity of the autonomic nervous system, including β-adrenolytics.

The MS+TDS+ group underwent testosterone therapy. They received Omnadren 250 (a mixture of testosterone esters) intramuscularly every 21 ±3 days for 9 weeks. The indication for supplementation, according to the International Society for the Study of the Aging Male, International Society of Andrology, the European Association of Urology, European Academy of Andrology, and American Society of Andrology recommendations, was the diagnosis of hypogonadism suitable for testosterone treatment given the presence of the signs and symptoms suggestive of testosterone deficiency (level 3, grade A).[1] Symptoms associated with hypogonadism included low libido, erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and depressed mood. One or more of these symptoms must be correlated with a low serum testosterone level (level 3, grade A).[17] In the study, erectile dysfunction was evaluated on the basis of the International Index of Erectile Function survey. Testosterone replacement treatment is indicated in patients with serum TT levels below 8 nmol/l and in those with serum TT levels between 8 and 12 nmol/l and any of the hypogonadism symptoms.[18]

Holter monitoring was performed at baseline and at the end of testosterone supplementation. To exclude the effect of testosterone injections and blood sampling (HRV disturbing factor), 24-hour ECG recordings were performed in patients during normal activities: 1) 24 hours after blood sampling and 2) 21 ±3 days after the last testosterone injection. Serum testosterone levels were measured before and after treatment. Samples for TT determination were obtained during fasting between 8 a.m. and 9 a.m., considering the circadian pattern of testosterone excretion with the highest levels being excreted in the morning.

Holter monitoring

Holter monitoring was performed using the Aspect 702 recorder with a data sampling rate of 128 Hz (Aspel Zabierzów, Poland). Data were analyzed using an automatic computer system (HolCARD 24W, Aspel

TABLE 1 Baseline characteristics of the patients with metabolic syndrome and testosterone deficiency syndrome (MS+TDS+) and those with metabolic syndrome and without testosterone deficiency syndrome (MS+TDS–)

Variable	MS+TDS+		MS+TDS–	P^a	P^b
	before treatment	after treatment			
age, y	50	50	52	NS	NS
body weight, kg	98	96	87.5	NS	NS
BMI, kg/m^2	29.53	29.27	29.13	NS	NS
WC, cm	107	103.3	103.5	NS	NS
SBP, mmHg	140	136.78	139.15	NS	NS
DBP, mmHg	88.3	83.6	86.7	NS	NS
IIEF-5, points	17	20.5	22	<0.01	<0.01
FBG, mmol/l	5.607	5.218	5.384	NS	NS
TC, mmol/l	5.508	5.327	5.392	NS	NS
LDL-C, mmol/l	3.068	3.198	3.224	NS	NS
HDL-C, mmol/l	1.243	1.162	1.045	NS	NS
TG, mmol/l	2.394	2.280	1.967	NS	NS
CRP, mg/l	1.8	1.85	1.4	NS	NS
HbA_{1c}, %	5.335	5.64	5.27	NS	NS
NT-proBNP, pg/dl	41.505	26.21	42.3	NS	NS
Fb, g/l	3.05	2.995	3.090	NS	NS
Ht, %	44.8	46.49	44.95	NS	NS

Data are presented as median.

a MS+TDS+ before treatment vs. MS+TDS+ after treatment
b MS+TDS+ before treatment vs. MS+TDS– after treatment

Abbreviations: BMI – body mass index, CRP – C-reactive protein, DBP – diastolic blood pressure, Fb – fibrinogen, FBG – fasting blood glucose, IIEF-5 – International Index of Erectile Function, HbA_{1c} – hemoglobin A_{1c}, Ht – hematocrit, HDL-C – high-density lipoprotein cholesterol, LDL-C – low-density lipoprotein cholesterol, NT-proBNP – N-terminal pro-B-type natriuretic peptide, SBP – systolic blood pressure, TC – total cholesterol, TG – triglycerides, WC – waist circumference

Zabierzów). Automatic detection of QRS complexes was performed. Data of insufficient quality were rejected, and electrocardiography was repeated. Automatic detection of QRS complexes was used. The HolCARD system allowed to calculate the basic parameters of HRV both in time and frequency domains. The results were verified by a cardiologist experienced in reading 24-hour ECG recordings. All subjects achieved satisfactory results. The parameters of HRV were analyzed according to the guidelines of the European Society of Cardiology.[7] Calculations were performed using fast Fourier transform. HRV parameters were determined during the entire 24-hour recording. The analysis included the following parameters:

1 time domain: SDNN (ms); SD of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN; ms); SDNN index (SDNNI; mean of the SD of all NN intervals for all 5-minute segments; ms); rMSSD (ms); and p50NN

2 frequency domain: total power (TP) of frequency domain (ms^2); high-frequency (HF) domain (ms^2; 0.15–0.4 Hz); low-frequency (LF) domain (ms^2; 0.04–0.15 Hz); very-low-frequency (VLF) domain (ms^2; 0.003–0.04 Hz); ultra-low-frequency (ULF) domain (ms^2; <0.003 Hz); and LF/HF ratio.

Of the time domain parameters, SDANN was considered the most suitable to assess the activity of the sympathetic nervous system, while p50NN and rMSSD were selected for the assessment of parasympathetic activity.[18] Low SDNN is associated with a high risk of hypertension and progression of atherosclerotic lesions in the coronary arteries after coronary artery bypass grafting.[19] This simple relationship has not been associated with any of the frequency domain parameters yet. However, there are data indicating the relationship between HF and the activity of the vagus nerve, LF and the activity of sympathetic and parasympathetic systems, while the ratio of LF to HF reflects the sympatho-parasympathetic balance.[20,21]

Statistical analysis A statistical analysis was performed using STATISTICA 8 PL (Stat Soft Inc.). Variable distribution was assessed by the Shapiro–Wilk test. Continuous variables were non-normally distributed. We used the nonparametric Mann–Whitney *U* test for the independent variable and the Wilcoxon signed-rank test for dependent paired variables. To calculate the correlation between the variables in the two groups, we used the Spearman's rank correlation test. A *P* value of less than 0.05 was considered statistically significant. The results were presented as the median and minimum/maximum value.

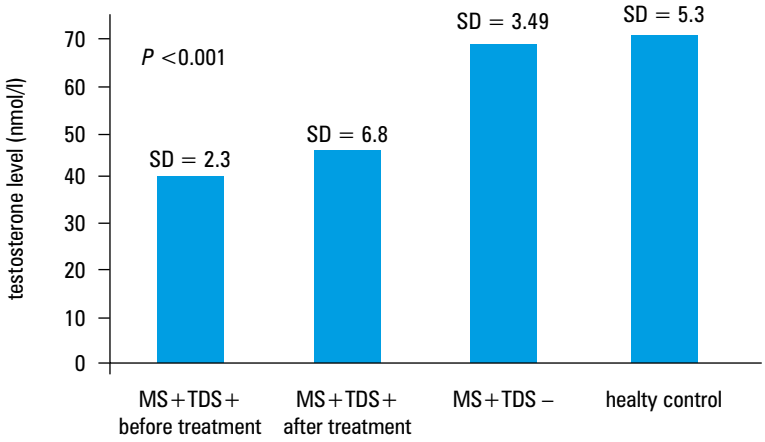

FIGURE Testosterone levels in patients with metabolic syndrome and testosterone deficiency syndrome (MS+TDS+), patients with metabolic syndrome and without testosterone deficiency syndrome (MS+TDS–), and controls; P <0.001 for MS+TDS+ before and after treatment vs. MS+TDS– and controls Abbreviations: SD – standard deviation

RESULTS There were no differences between the MS+TDS+ and MS+TDS– groups in terms of the mean age, body mass, BMI, WC, systolic and diastolic blood pressures, fasting blood glucose, lipids, blood cell count, and creatinine, both at baseline and after treatment. Serum TT levels are presented in the FIGURE.

All time domain parameters were lower in the MS+ TDS+ group compared with the control group (TABLE 2).

There were significant differences between the MS+TDS– group and controls in SDNN, SDNNI, and SDANN (TABLE 2). Except for the LF/HF ratio, there were significant differences in frequency domain parameters between the MS+TDS– group and healthy controls, and the parameters were lower in the MS+TDS+ group compared with controls.

TP, HF, and LF were lower in the MS+TDS+ group compared with the MS+TDS– group (P = 0.009, P = 0.007, and P = 0.019, respectively). There were no differences between the MS+TDS– group and controls except for ULF, which was lower in the MS+TDS– group (TABLE 2).

Testosterone supplementation resulted in increased SDNN and SDANN as well as TP, LF, VLF, and ULF although the values were not different from those observed in the MS+TDS– group. SDNN, SDNNI, SDANN, p50NN, VLF, and ULF were still lower compared with the control group. No such difference was observed for r-MSSD, TP, HF, and LF (TABLE 2).

There were no correlations between testosterone levels and the parameters of HRV, either in the time or frequency domains. During follow-up, no serious side effects were observed, including cardiovascular events or arrhythmia. Only a higher hematocrit level was reported (44.8% vs. 46.49%; P <0.05). None of the patients reached the upper limit of the reference range for prostate-specific antigen. No cases of prostate cancer were observed within 1 year after the end of testosterone replacement therapy.

DISCUSSION There have been few studies on the effects of testosterone on ECG parameters, especially those observed in 24-hour Holter monitoring. Most of these studies focused on the QT interval and changes depending on the concentration of testosterone in various disease states.[22-24] They demonstrated a significant effect of testosterone on the QT-interval shortening and changes in QT-interval dispersion. In this paper, we focused on the assessment of HRV that reflects the autonomic balance.

MS is a group of disorders that significantly increase the risk of cardiovascular diseases and their complications. One of the most common

TABLE 2 Comparison of heart rate variability in time and frequency domains between patients with metabolic syndrome and testosterone deficiency syndrome (MS+TDS+), patients with metabolic syndrome and without testosterone deficiency syndrome (MS+TDS–), and controls during a 24-hour period

Parameters	MS+TDS+			MS+TDS–	Controls
	before treatment n = 30	after treatment n = 30	P[a]	n = 25	n = 25
time domain					
SDNN, ms	117 (70–179)[b]	138.5 (67–185)[c]	0.020	141.0 (55–220)[c]	164.0 (116–220)
SDNNI, ms	38.5 (21–98)[b]	40.0 (20–113)[c]	0.059	44.0 (29–79)[e]	53.0 (38–99)
SDANN, ms	111.0 (63–175)[b]	121.5 (62–177)[c]	0.001	125.0 (47–223)[e]	150 (102–223)
rMSSD, ms	24.0 (11–134)[c]	28.5 (13–188)	0.056	36.0 (18–126)	36.0 (18–126)
p50NN, %	4.2 (0.23–33.27)[c]	5.3 (0.42–39.96)[e]	0.112	10.4 (1.37–45.04)	10.4 (1.37–45.04)
frequency domain					
TP, ms^2	9655.5 (6322–32 207)[b]	11 351.5 (5893–37 174)	0.017	11 965.0 (7337–23 808)	12 960.0 (9011–27 196)
HF, ms^2	2144.5 (1167–13 422)[c]	2797.0 (960–19 085)	0.054	3236.0 (1424–9385)	3479.0 (1524–10 655)
LF, ms^2	2784.0 (1070–7250)[b]	2898.0 (878–8823)	0.022	3193.0 (1307–5558)	3402.0 (1820–6801)
VLF, ms^2	2896.5 (1606–4151)[b]	2939.0 (1175–10 458)[e]	0.005	3257.0(1538–5104)	3774.0 (2553–5719)
ULF, ms^2	755.0 (486–1189)[b]	814.5 (427–1583)[c]	0.021	761.0 (445–1258)[c]	981.0 (702–1369)
LF/HF	1.06 (0.45–2.29)	0.98 (0.3–2.25)	0.6	1.07 (0.51–1.83)	1.17 (0.36–1.82)

a before vs. after treatment, **b** P <0.001 compared with controls, **c** P <0.01 compared with controls, **d** P <0.05 compared with patients before treatment, **e** P <0.05 compared with controls

abnormalities affecting men with MS is further deficiency of testosterone. TDS itself is an independent risk factor for cardiovascular diseases.[2,25] Abnormal regulation of the autonomic nervous system in both disorders has been reported.[5,13] This is one of the mechanisms of increased risk for dangerous arrhythmias and overall cardiovascular morbidity and mortality. Our results confirmed that HRV parameters are significantly lower in patients with MS compared with healthy men, especially SDNN, SDNNI, SDAN, and ULF.[26,27] This was observed despite the fact that we excluded patients with diabetes and included patients with prediabetes (impaired fasting glucose or impaired glucose tolerance or both). Diabetes is known to be the major cause of autonomic dysfunction associated with abnormal HRV parameters. In our study, significantly lower values of HRV parameters were obtained in men with TDS, both in time and frequency domains. This is consistent with the study by Wranicz et al.,[13] who reported lower values of time domain parameters (SDNN, SDNNI, SDANN, rMSSD, and p50NN) in patients after myocardial infarction and with low testosterone levels. Moreover, testosterone levels correlated positively with the above parameters of HRV. Similarly, Doğru et al.[28] reported a reduction in HRV parameters related to the parasympathetic system (HF, p50NN, rMSSD) along with a decrease in testosterone levels. Our study also demonstrated lower values of those parameters in men with MS and TDS, but we have not identified correlations between testosterone levels and HRV parameters. An increased risk of cardiovascular and coronary heart disease in men with MS and TDS is also indicated by lower SDNN, TP, and HF values. This is in line with the findings of the ARIC study, in which the reduced value of SDNN was correlated with a higher incidence of ischemic heart disease in patients with arterial hypertension (one of the components of MS).[19] Lower values of TP and HF correlated with a higher incidence of other cardiovascular risk factors such as fibrinogen or elevated norepinephrine, as well as with high incidence of diabetes.[29] This was particularly true for men with reduced testosterone levels. All the above findings were confirmed in our study. Regarding the LF/HF ratio, we did not find any significant differences between the study groups, which might result from a small number of the patients. The issue requires additional research on a larger study group.

Testosterone supplementation in men with MS and TDS did not result in increased incidence of arrhythmias, including ventricular arrhythmia, which supports the findings of Wranicz et al.[13] The improvement of the majority of HRV parameters in patients with MS and TDS (although not all parameters reached the levels observed in controls) might suggest a reduction in cardiovascular risk in those individuals. However, the risk may still remain higher than in healthy individuals. The improvement of the function and regulation of the autonomic system, including increased parasympathetic activity, may significantly contribute to the reduction of mortality, especially from severe arrhythmias and sudden cardiac death. It is assumed that testosterone supplementation may also have a positive effect on other cardiovascular risk factors associated with the predominance of the sympathetic nervous system and numerous other metabolic disorders, although it does not completely reduce associated risks. Further studies are necessary to establish the optimal duration of testosterone supplementation and to assess its long-term safety. During testosterone replacement therapy it is particularly important to monitor the safety of treatment. However, there is no evidence indicating that it may increase a risk of prostate cancer or its hypertrophy, or that it may enhance the transformation ofsubclinical prostate cancer into clinically evident forms. Nonetheless, it was confirmed that testosterone may stimulate the progression of existing, locally advanced cancer or metastatic prostate cancer.[1] A statistically significant increase in hematocrit levels was noted in treated patients. However, it did not result in significant polycythemia. In the group of treated men, there was no case of prostate cancer or an increase in prostate-specific antigen levels above the upper limit of the reference range. Therefore, testosterone replacement therapy appears to be safe and potentially beneficial in reducing cardiovascular risk in men with MS and TDS.

In conclusion, the present study confirmed that patients with MS and TDS have significantly lower HRV parameters compared with healthy subjects. A 9-week testosterone supplementation therapy can improve disturbed HRV parameters and restore their levels to those observed in healthy men. Our study suggests that testosterone supplementation therapy, with its beneficial effect on HRV, might reduce the cardiovascular risk in men with hypoandrogen-metabolic syndrome.

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Wpływ krótkookresowej testosteronowej terapii zastępczej na zmienność rytmu serca u mężczyzn z zespołem niedoboru testosteronu i zespołem metabolicznym

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dysfunkcja autonomiczna, testosteronowa terapia zastępcza, zespół metaboliczny, zespół niedoboru testosteronu, zmienność rytmu serca

STRESZCZENIE

WPROWADZENIE Zespołem niedoboru testosteronu (ZNT) określa się obecność objawów niedoboru testosteronu u mężczyzn z obniżonym poziomem testosteronu. Prowadzi on do dysfunkcji śródbłonka, który poza zaburzeniami erekcji powoduje przyspieszenie powstawania zmian miażdżycowych.

CELE Celem badania była ocena wpływu suplementacji testosteronu u mężczyzn z ZNT i zespołem metabolicznym (ZM) na równowagę autonomiczną z wykorzystaniem parametrów zmienności rytmu serca (*heart rate variability* – HRV) w 24-godzinnym monitorowaniu EKG metodą Holtera.

PACJENCI I METODY Do badania włączono 80 mężczyzn podzielonych na 3 grupy: z ZM i ZNT (ZM+ZNT+, n = 30), z ZM i bez ZNT (ZM+ZNT–, n = 25), oraz grupę kontrolną (n = 25). Grupę ZM+ZNT+ poddano 9-tygodniowej terapii zastępczej domięśniowymi iniekcjami z testosteronu (Omnadren 250). U wszystkich pacejntów wykonano zapis 24-godzinnego EKG metodą Holtera przed i po zakończeniu terapii.

WYNIKI Prawie wszystkie parametry HRV były znamiennie niższe w grupie ZM+ZNT+ w porównaniu do grupy kontrolnej. Ponadto całkowita moc widma (*total power* – TP), pasmo wysokich częstotliwości (*high frequency* – HF) i pasmo niskich częstotliwości (*low frequency* – LF) były znamiennie niższe w grupie ZM+ZNT+ w porównaniu z grupą ZM+ZNT–. Wystąpiły także istotne różnice w wartościach SDNN, SDNNI i SDANN oraz pasma ultra niskich częstotliwości (*ultra-low frequency* – ULF) pomiędzy ZM+ZNT– a grupą kontrolną. W wyniku suplementacji testosteronem wystąpił wzrost wartości SDNN, SDANN, TP, LF, ULF oraz pasma bardzo niskich częstotliwości. Nie osiągnęły one jednak wartości obserwowanych w grupie kontrolnej. Leczenie nie wpłynęło istotnie na stężenie całkowitego i wolnego testosteronu.

WNIOSKI Dziewięciotygodniowa testosteronowa terapia zastępcza poprawia wartości parametrów HRV. Chociaż nie osiągnieto wartości obserwowanych u zdrowych mężczyzn, taka terapia może zmniejszyć ryzyko sercowo-naczyniowego u mężczyzn z ZM i ZNT.

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