The Influence of L-Carnitine in the Complex Treatment of Patients with Renal Dysfunction Who Have Synchronous Chronic Coronary Artery Disease and Prostate Adenocarcinoma

Eş Zamanlı Kronik Koroner Arter Hastalığı ve Prostat Adenokarsinoması Olan Renal Disfonksiyonlu Hastaların Kompleks Tedavisinde L-Karnitinin Etkisi

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ABSTRACT Objective: The aim of the study is to evaluate the effect of L-Carnitine on the dynamics of inflammation, insulin resistance (IR), functional status of kidneys in the complex therapy of patients with coronary heart disease (CHD) in combination with prostate adenocarcinoma and renal dysfunction. **Material and Methods:** Forty two men with prostate adenocarcinoma and coronary heart disease were enrolled. The patients were randomly and blindly divided into 2 groups: Group I patients were treated with L-Carnitine in addition to standard treatment; Group II patients received only conventional treatment. Standard laboratory blood tests, lipid profile, glucose, renal and liver function tests, serum C-reactive protein (CRP), insulin, testosterone levels, echocardiographic examination were performed for all patients at baseline and after 10 days of treatment. **Results:** Median level of HOMA index was 3.1 [1.9; 4.8] mg/ml. Insulin resistance was established in 54.8% patients of Group I and 40% patients of control group (p<0.05). In Group I, the mean insulin index and HOMA index decreased by 15.4% (p=0.001) and 19.2% (p=0.003), respectively. The supplementation of L-Carnitine in standard therapy contributed to a significant decrease in serum creatinine level and an increase in the level of glomerular filtration rate (GFR) in Group I patients (p<0.05). **Conclusion:** The supplementation of L-Carnitine in the complex therapy of patients with coronary artery disease in combination with prostate adenocarcinoma contributes to a significant decrease in insulin resistance, improves the functional state of kidneys.

Keywords: Insulin resistance; carnitine; coronary disease; prostatic neoplasms

ÖZET Amaç: Bu çalışmanın amacı koroner kalp hastalığı (KKH) olan hastalarda prostat adeno karsinomu ve böbrek fonksiyon bozukluğu bulunması durumunda tedavide böbreklerin fonksiyonel durumu, inflamasyon dinamikleri ve insülin direnci (IR) üzerinde L-Karnitinin etkisini değerlendirmektir. **Gereç ve Yöntemler:** Prostat adenokarsinomu ve koroner kalp hastalığı olan 42 erkek alındı. Hastalar randomize ve kör olarak 2 gruba ayrıldı: Grup I hastaları standart tedaviye ek olarak L-Karnitin ile tedavi edildi; Grup II hastalar sadece geleneksel tedavi aldı. Bütün hastalar için standart laboratuvar kan testleri, lipid profili, glukoz, böbrek ve karaciğer fonksiyon testleri, serum C-reaktif protein (CRP), insülin, testosteron düzeyleri, ekokardiyografik inceleme bazal olarak ve 10 günlük tedavi sonrasında yapıldı. **Bulgular:** Ortanca HOMA indeksi seviyesi 3,1 [1,9; 4,8] mg/ml. İnsülin rezistansı açılımı Grup I'de %54,8, kontrol grubunda% 40 hastada saptandı (p<0,05). Grup I'de ortanca insülin indeksi ve HOMA indeksi sırasıyla% 15,4 (p=0,001) ve %19,2 (p=0,003) azaldı. L-Karnitinin standart tedaviye eklenmesi, Grup I hastalarında serum kreatinin seviyesinde anlamlı bir düşüşe ve glomerül filtrasyon hızında bir artışa neden oldu (p<0,05). **Sonuç:** Koroner arter hastalığı olan hastaların prostat adenokarsinomu ile kombinasyon halinde kompleks tedavisinde L-Karnitin takviyesi, insülin direncinde önemli bir düşüşe neden olur, böbreklerin fonksiyonel durumunu iyileştirir.

Anahtar Kelimeler: İnsülin direnci; karnitin; koroner hastalığı; prostatik neoplazmalar

Prostate cancer is the most common cancer among men worldwide.[1] Moreover prostate adenocarcinoma is the most common noncutaneous cancer diagnosed in men in the United States and the second leading cause of cancer deaths.[2] Despite the advances in the treatment of these patients in recent years, the rate of cardiovascular diseases among prostate can-

cer cases is growing and leading to mortality. This may be due to both the influence of the cancer itself and the cancer treatment received. Nevertheless, androgen deprivation therapy (ADT) reduces the risk of mortality from prostate cancer, however, it's associated with the development of numerous adverse metabolic effects and an increased risk of fatal and/or nonfatal cardiovascular events.[3-5] Given the high clinical relevance, the European Society of Cardiology (ESC) has issued a 2016 Position Paper on Cancer Treatments and Cardiovascular Toxicity. This document covers aspects of cardiovascular toxicity of anticancer treatment, providing expert opinion for management and summarizing the most important recommendations.[6] But currently, there are no recommendations for screening and primary prophylaxis in patients with prostate cancer, who have pre-existing cardiovascular diseases or those who have a potential risk of cardiovascular morbidity and mortality. Thus, the issues of early diagnosis and primary prevention of coronary artery disease is topic subject in patients with prostate adenocarcinoma.

The heart-kidney axis is the focus of particular attention in cardiac patients, even minimal renal dysfunction is an important predictor of poor prognosis in patients with chronic heart failure and coronary artery disease.[7] On the other hand, a decrease in GFR is an important prognostic factor in oncology, particularily in patients with prostate adenocarcinoma.[8] Thus, this group of patients need complex therapy to overcome cardiovascular risk factors.

In the literature of recent years, more attention is paid to drugs of metabolic correction in the treatment of CAD, in particular L-Carnitine. L-Carnitine plays an important role in the metabolism of fatty acids, and its deficiency is common among cancer patients receiving chemotherapy. Chemotherapy inhibits specific membrane transport systems in renal tubules with a consequent increase in the excretion of L-Carnitine and amino acids.[9]

Consequently, studies have shown that the administration of L-Carnitine led to a significant reduction in both overall mortality and mortality due to ventricular arrhythmia and/or acute myocardial infarction (MI). In addition, there is evidence that L-Carnitine can reduce the level of insulin-like growth factor in diabetes mellitus and improve endothelial function.[10] It should be noted that there is an evidence base for the clinical use of L-Carnitine in chronic kidney disease patients receiving dialysis therapy, in patients with cardiovascular, neurological diseases, etc.[11-13] Particularly the recent meta-analysis has demonstrated that L-Carnitine treatment is effective for improving clinical symptoms and cardiac functions, decreasing serum levels of B-type natriuretic peptide (BNP) and N-terminal-pro-BNP in chronic heart failure (CHF) patients.[14]

Thus, the recommendations of the American Association of Cardiologists for the management of patients with CHF note that the pharmacological treatment of CHF can be supplemented with L-Carnitine.[15] On the other hand, recent studies have shown that supplemental administration of L-Carnitine at a daily dose of 3 grams for 8 weeks is effective in preventing the side effects of chemotherapy for neoplastic diseases, which gives prospects for the use of this drug in patients with combined cardio-oncological pathology.

The purpose of the study was to evaluate the effect of L-Carnitine on the dynamics of inflammation, insulin resistance, renal functional status as part of the integrated therapy of patients with CAD in combination with prostate adenocarcinoma and renal dysfunction.

MATERIAL AND METHODS

The present study was conducted with approval from the Ethics Committee according to the principles outlined in the Helsinki declaration. All participants of the research gave informed, written consent. Dynamic observation and treatment were performed in 42 men with prostate adenocarcinoma and coronary artery disease (CAD) at the age of 45 to 75 years (main group). The control group consisted of 20 men with coronary artery disease and prostatic hyperplasia, comparable in age, cardiovascular risk profile, received treatment for coronary artery disease and didn't get L-Carnitine

infusion. Baseline characteristics of the study patients have been demonstrated in Table 1.

All patients had CAD according to the classification of the the European Society of Cardiology, the diagnosis of prostate adenocarcinoma was verified. Among the forms of CAD, stable angina prevailed in 25 patients (59.5%), the remaining 17 patients (40.5%) had post-infarction cardiosclerosis.

During follow-up, all patients received CAD and prostate cancer treatment which did not change during the whole observation period.

Inclusion criteria were: being aged 45-75 years, the presence of a verified diagnosis of prostate adenocarcinoma, consistently selected anticancer therapy for 6 months, the presence of a verified diagnosis of coronary artery disease, consistently selected cardiac therapy for the last 3 months, voluntary informed consent to participate in the study.

Exclusion criteria included age over 75 years, the presence of metastatic lesions, chronic heart failure with low ejection fraction (EF), arrhythmias that cause hemodynamic disturbances and require

TABLE 1: Baseline characteristics of the study patients.		
Characteristic	Main group (n=42)	Control group (n=20)
Median of age, years	65 [59; 73]	63.6 [57; 71.5]
Median duration of CAD, years	10.3 [7.4; 18.4]	10.1 [7.1; 18.2]
Median duration of prostate cancer, years	5.8 [2.5; 7.8]	5.5 [2.4; 7.5]
Glomerular filtration rate (GFR), ml / (min • 1.73 m2)	74 [61; 79]	77 [63; 82]
Patients with GFR <60 ml / min. / 1.73 m2, %	31	15
Patients with GFR <90 ml / min. / 1.73 m2, %	100	90
Median testosterone level, ng / ml	1.4 [0.8; 2.5]	1.6 [0.9; 2.7]
Patients with decreased testosterone level, %	45.2	20
Patients with hypertension, %	83.3	80
Patients with CHF (%): I functional class (FC) II functional class	54.8	50
	16.7	20
	83.3	80
Median of ejection fraction, %	64.4 [52.4; 69.3]	66.2 [53.8; 70.8]
Patients with reduced ejection fraction, %	14.3	10
Patients, received cardiology treatment (%): ACE inhibitors ACE receptors blockers β-blockers calcium antagonists statins antiplatelet agents	81	80
	16	15
	81	75
	73.8	70
	69	60
	57.1	50
Patients, received oncology treatment (%): ADT surgical treatment combined treatment	61.9	-
	57.1	-
	47.6	-

correction with antiarrhythmic agents (including high gradations of ventricular arrhythmias, atrial flutter, paroxysmal tachycardias, sinus node weakness syndrome, atrio-ventricular (AV) blockade 2-3 degrees), acute myocardial infarction (MI), acute cerebrovascular accident, diabetes, hyper- and hypothyroidism with TTG levels> 10 mU/l, chronic renal insufficiency [glomerular filtration rate (GFR) <30 ml/ min./1.73 m^2], acute cardiac and renal failure, obesity with grade 4, cachexia.

Patients were blindly divided into two groups: Group I (n=20)-CAD patients in combination with prostate adenocarcinoma and renal dysfunction, who received L-Carnitine (Metakartin, World Medicine, MefarIlac San. A.S.) intravenously with 100 ml of 0.9% NaCl once daily for 10 days in addition to standard therapy. Group II (n=22)-patients who were treated with standard regimen without L-Carnitine prescription.

In the initial state, the patients of both groups were comparable in terms of the main disease, indicators of gender, age, duration of the disease, level of GFR, systolic and diastolic blood pressure, heart rate.

In order to determine the effectiveness and safety of exposure to L-Carnitine depending on the hormone sensitivity of prostate adenocarcinoma, patients of Group I are divided into subgroups: Ia (n=11)-CAD patients in combination with hormone-sensitive prostate adenocarcinoma and Ib (n=9)-patients with CAD in combination with hormone-insensitive prostate adenocarcinoma, which were comparable in the main indicators.

To solve the problems of the study, all patients were determined by objective and subjective signs inherent in CAD, they conducted anamnestic data collection, physical examination and laboratory and instrumental methods at the beginning and at the end of the study. The duration of observation in the hospital was 10 days, then the patients were observed at outpatient setting. The survey included: standard clinical and biochemical laboratory tests (clinical study of blood, urine, daily proteinuria level; biochemical blood test: creatinine, urea, ALT, AST, blood lipid spectrum), immunoassay for blood tests for insulin, C-reactive protein (CRP), radioisotope blood test with determination of testosterone levels; electrocardiography (ECG), Doppler echocardiography. Glomerular filtration rate was determined by the formula CKD-EPI, insulin resistance (IR)-by the formula HOMA.[16] Tolerability of the drug was determined on the basis of an assessment of laboratory parameters (serum ALT, AST levels), the level of GFR, the incidence of adverse reactions.

Statistical processing of the obtained results was performed using the licensed program STATISTICS. Non-parametric statistics were used. The data was presented in the form of a median (Me) and the interquartile segment [25%; 75%]. For comparison of indicators in two independent groups, the Mann-Whitney U-test, the two-sided Fisher exact test, and the Wilcoxon test (W) were used to compare two dependent groups. Statistically significant differences in research results were determined at a level of p<0.05.

RESULTS

The level of insulin in patients with coronary heart disease on the background of prostate adenocarcinoma ranged from 8.6 to 22.2 MO/ml baseline, the median was 10.7 [6.9; 15.7] MO/ml, in the control group 8.2 [4.8; 11.0] MO/ml respectively (p=0.003). Insulin resistance was established in 23 (54.8%) patients of main group and 8 (40%) of controls (p<0.05). It was found that patients in the main group had a significantly higher level of HOMA index compared with the control group (p <0.05), with the highest level of IR observed in patients with a hormone-sensitive form of the prostate adenocarcinoma (Table 2). Correlation relations between the HOMA index in patients with the main group and age, GFR, body mass index (BMI) were determined-R=-0.48 (p <0.05), R=-0.62 (p<0.05), R=0, 66 (p<0.05) respectively.

Analysis of the dynamics of the insulin level and insulin resistance on the background of treatment revealed significant differences in these indicators in patients of the Group I and Group II (Figure 1). In the group of patients to whom L-Car-

	TABLE 2: Level of insulin, insulin resistance in patients with coronary heart disease in prostate adrenocarcinoma depending on hormone sensitivity.			
Indicators	**All patients (CAD + prostate adenocarcinoma) (n=42)**	**Group I (CAD + hormone-sensitive prostate adenocarcinoma) (n=20)**	**Group II (CAD + hormone-insensitive prostate adenocarcinoma) (n=22)**	**Control group (CAD+ prostatic hyperplasia) (n=20)**
Insulin, OD/ml	10.7 [6.9; 15.7]	12.4 [8.2; 17.2]#	10.1 [6.2; 12.1]*	7.7 [2.9; 9.3]
HOMA	3.1 [1.9; 4.8]	3.4 [1.8; 5.2]#	2.8 [2.1; 3.3]*	1.8 [1.0; 2.5]

Notes: * - Significance of the differences between the Ia and the Ib subgroups; # - Significance of the differences with the control group.
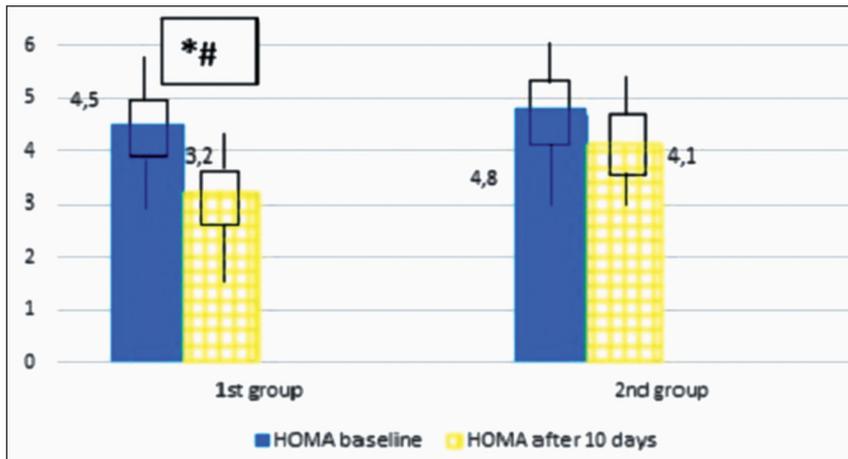
FIGURE 1: Dynamics of insulin resistance in patients depending of L-Carnitine supplementation. Notes; * Significance of differences at the beginning and end of observation, p <0.05 (according to the Wilcoxon test). # Significance of differences compared with group 2, p <0.05 (according to Man-Whitney test).
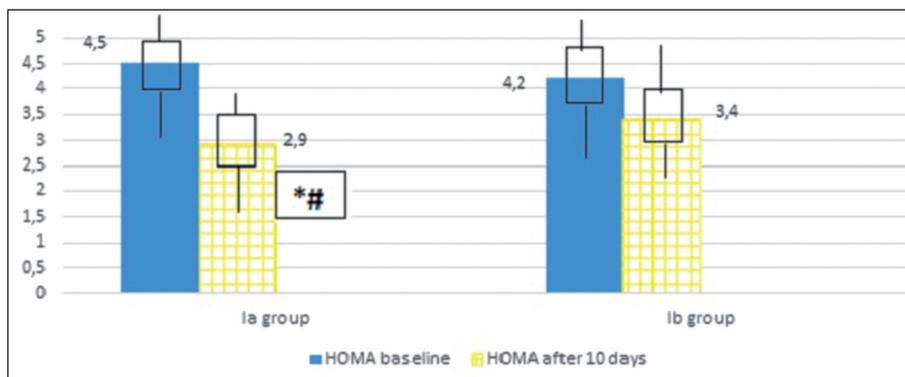

FIGURE 2: Dynamics of insulin resistance in patients of the main group depending on the hormone sensitivity. Notes; * Significance of differences at the beginning and at the end of the observation, p <0.05 (according to the Wilcoxon test). # Significance of differences compared with group 2, p <0.05 (according to Mann-Whitney test).

nitine was included in the composition of complex therapy, the mean insulin index and HOMA index decreased by 15.4% (p=0.001) and 19.2% (p=0.003), respectively, in the standard treatment group these indicator dynamics were not significantly different. The supplementation of L-Carnitine in the complex therapy contributed to a more pronounced decrease in IR in patients with ischemic heart disease in combination with the hormone-sensitive form of prostate adenocarcinoma (Figure 2).

It was established that the supplementation of L-Carnitine in standard therapy contributed to a significant decrease in serum creatinine level and an increase in the level of GFR in Group I patients (Figure 3).
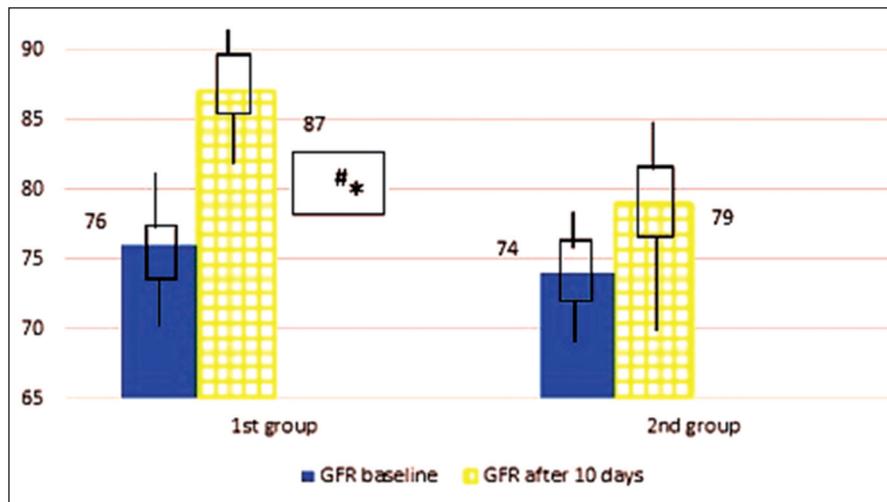
FIGURE 3: Dynamics of GFR in patients of the main group. Notes; * Significance of differences at the beginning and end of observation, p <0.05 (according to the Wilcoxon test). # Significance of differences compared with group 2, p <0.05 (according to Mann-Whitney test).
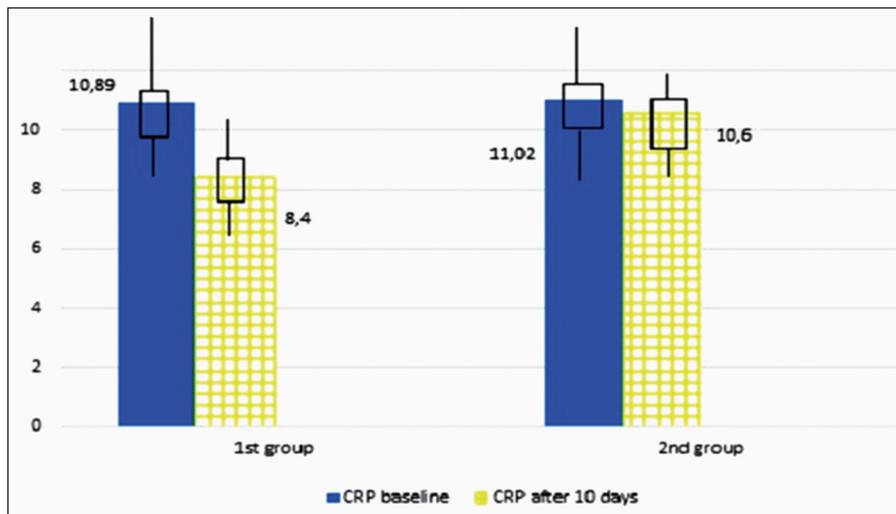

FIGURE 4: Dynamics of CRP in patients of the main group depending of L-Carnitine supplementation.

At the beginning of the study, the level of CRP in patients with CAD on the background of prostate adenocarcinoma ranged from 4.1 to 12.5 mmol/ml, the median was 10.3 [5.2; 11.1] OD/ml, in the control group-7.4 [3.1; 8.6] mmol/ml, respectively (p=0.0002), there were no significant differences depending on hormone sensitivity. Increased CRP level was established in 26 (61.9%) patients of main group and 9 (45%) of controls (p<0.05). Correlations between the indicator of CRP in patients of the main group of GFR, BMI-R=-0.52 (p<0.05), R=0.61 (p<0.05), respectively, were determined. In the group of patients to whom

L-Carnitine was included in the complex therapy, a tendency to a decrease in the average CRP was found (p = 0.056), in the standard treatment group, these indicators did not differ significantly in dynamics (Figure 4).

There were no significant side effects with the inclusion of L-Carnitine to the standard therapy in the dynamics of observation, and was no need to change the daily dose or discontinue treatment. The supplementation of L-Carnitine in the complex treatment contributed to a significant improvement in exercise tolerance according to the test results with a six-minute walk. At the end of

the observation, the levels of ALT, AST, bilirubin did not change significantly compared with the initial state.

DISCUSSION

Cardio-oncology, which includes all aspects of the relationship between cardiovascular and malignant disease, is an area of increasing interest in clinical practice. However, there are less frequent and less well-known interactions, such as induction and aggravation of atherosclerosis by chemotherapy and radiation.

As known, the pathogenesis of atherosclerosis in oncological patients is complex and depends on multiple cardiovascular factors. Search for therapeutic options of cardiovascular risk correction to improve prognosis in patients with CAD and prostate adenocarcinoma remains topical. American College of Cardiology Foundation/American Heart Association (ACCF/AHA) recommendations note that a number of toxic agents may lead to left ventricle dysfunction and CHF. Particularly, the deficiency in L-Carnitine may be associated with a syndrome of progressive skeletal myopathy and cardiomyopathy.[17,18] Thus, L-Carnitine may be useful in patients with toxic injuries, particularly in oncology profile patients.

The recent meta-analysis performed by Ying Xu and al. demonstrated that the L-Carnitine was useful in treating patients with IR with more effectively for prolonging the medication time.[19] Thus, the result of 5 studies showed L-Carnitine was effective in the treatment of IR (WMD-0.724, CI-0.959-0.488, p<0.0001), evaluation at 3, 6, 9, 12 months, the p-values were 0.875, 0.165, 0.031, 0, 007, respectively.[19] Our research showed that the use of L-Carnitine (Metakartin, World Medicine, MefarIlac San. A.S.) at a dose of 2 g (10 ml) intravenously for 10 days causes an additional positive clinical effect with a significant decrease in IR on 19.2% (p=0.003) in the complex therapy of patients with CAD with prostate adenocarcinoma. However, RCTs with long-term L-Carnitine treatment of IR are needed to confirm the viewpoint for this population of patients.

The overall findings of another meta-analysis has found the clinically relevant benefit of L-Carnitine supplementation in lowering the circulating levels of CRP.[17] In this meta-analysis the obtained combined weighted mean reduction in CRP concentrations was-0.39 mg/L [95% CI (-0.62- -0.16)]. The present study results demonstrated a tendency in CRP level decrease with maximum effect in the group of patients with hormone-sensitive prostate adenocarcinoma. In this way it could be perspectival to evaluate CRP dynamics with prolongation of L-Carnitine therapy in patients with CAD and prostate adenocarcinoma.

Data are available indicating that reduced circulating and tissue carnitine levels, possibly lead to impaired mitochondrial function, have been postulated to be involved in the pathogenesis of insulin resistance, kidney dysfunction. Thus, this assumptions could explain obtained results. The established data determine the feasibility of further research to clarify the mechanisms of L-Carnitine infusion to carbohydrate metabolism, systemic inflammation, and kidney function in patients with a cardio-oncology profile.

LIMITATIONS

However, the results of this study should be interpreted with caution because of several limitations. Therefore, only patients with stable angina and post-infarction cardiosclerosis on prostate adenocarcinoma were chosen for this study, and consequently the results can only be applied to this population. It should be noted that there is no oral L-Carnitine for continuation treatment after administering it intravenously. It could be perspectival to evaluate the hard end point with prolongation of this therapy.

CONCLUSION

In the majority of patients with coronary artery disease in combination with prostate adenocarcinoma, relevance was established to insulin resistance, laboratory indicators of systemic inflammation associated with obesity age and renal function. The supplementation of L-Carnitine in the complex therapy of patients with coronary artery disease in combination with prostate adenocarci-

noma and renal dysfunction contributes to a significant decrease in insulin resistance, improves the functional state of the kidneys and is well tolerated.

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