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IMPACT OF METABOLIC THERAPY WITH TRIMETAZIDINE, PROPER NUTRITION AND PHYSICAL ACTIVITY ON QUALITY OF LIFE AND ON INCIDENCE OF REHOSPITALIZATIONS OF PATIENTS WITH ISCHEMIC HEART DISEASE

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Summary

Aim: To investigate whether additional treatment of ischemic heart disease with trimetazidine, proper nutrition and physical activity could decrease the number of rehospitalizations and overall quality of life of patients with ischemic heart disease. **Methods:** The study included 200 patients with ischemic heart disease. The sample is divided into 2 randomly selected groups: the experimental and control group. The diagnostic procedures included: trade-mill test according to Bruce protocol, heart ultrasound for assessment of ejection fraction, test for the assessment of quality of life and subjective problems (Short Form SF 36). Patients were tested on time of discharge from hospital, after 6 and 12 months, including reevaluation of the overall condition of the previous period. **Results:** Patients have been tested for the endurance of effort with the measurement Metabolic Equivalent of TASK (METs) which is the equivalent of physical labor. Patients treated with trimetazidine since the time of hospital discharge have achieved an average of 3.68, after 6 months 5.68, and after 12 months 7.79 METs. Control and experimental groups showed a significant difference in the number of hospitalizations for the periods of 6 months and 12 months after treatment. Fewer hospitalizations were in the group treated with trimetazidine than in those with only conventional therapy after 6 and 12 months. There is a significant difference in values Respondents' attitudes about how much they shortened their time at work or other activities as a result of physical health before starting therapy (Ppt <0.001), as well as for a period of 12 months after starting therapy shows a significant difference (P12 <0.001). The results we have for HDL and LDL after the clinical study show that patients who were on conventional therapy and trimetazidine and who used a proper diet as well as those who had physical activity, that their HDL and LDL values were better than at the beginning studies. **Conclusion:** Patients treated with conventional therapy including trimetazidine have better tolerance to effort and fewer hospitalizations in the comparison with those treated without trimetazidine, so trimetazidine has a beneficial effect on reducing the number of hospitalizations and productiveness at work and improving the quality of life. They had a better lipid status compared to patients who only used conventional therapy. BMI index was better in patients who used trimetazidine along with conventional therapy and had better psychological health.

Keywords: ischemic heart disease, quality of life with heart ischemia, metabolic therapy, rehospitalization

Introduction

Ischemic heart disease is a clinical syndrome that occurs after structural heart diseases that directly lead to heart function disorders, due to which the heart can not provide enough blood to reconcile the body's need for oxygen. These patients have symptoms of heart failure (suffocation, fatigue, edema), as well as objective signs of cardiac dysfunction while the patient is at rest, with a positive response to treatment (McMurray et al., 2012; Mohan SB et al., 2012). Physiologically cardiomyocytes are replaced with connective tissue in elderly people. This process is known as cardiac remodeling (Vlodaver Z and et al., 2012).

Significant changes have taken place in recent years in the treatment and rehabilitation of heart patients, especially those diagnosed with coronary heart disease. Physical training is accepted as an important way of prevention and rehabilitation of cardiovascular patients. There are two main reasons for this. First, physical inactivity is one of the risk factors for the development of atherosclerosis and coronary heart disease. Although it does not belong to the group of so-called of the main risk factors - arterial hypertension, dyslipidemia and smoking, its importance is not small. During physical activity, the cardiovascular system goes through numerous changes, such as an increase in the cardiac output, which is closely related to the degree of expansion of the blood vessels of the skeletal muscles, which means also to the metabolic changes that occur in the skeletal muscles during physical activity. In addition to this basic relationship in relation to metabolic events, there is also a reflex activation of sympathetic nerves in relation to the heart, as well as in relation to the resistance and capacity of blood vessels of the systemic circulation. As a result, there is a reflex

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regulation of peripheral vascular resistance, so that the increased cardiac output from the left ventricle is directed to the active muscles, and systemic arterial pressure is maintained within reasonable limits, despite a large increase in cardiac output.

A proper (healthy, sensible) diet implies a healthy intake of all necessary nutrients nutrients (carbohydrates, fats, proteins, vitamins, minerals and water), in moderation quantitative, diverse, suitable for age, physical and mental constitution, work and intellectual efforts, the climate and working environment in which we live Science confirms that improper nutrition, the dangers that come from food, and in a big way measures lifestyle, risk factors of chronic non-communicable diseases that are the causes of 65% of mortality in the world and which have become a worrying public health problem (Colić-Barić 2007).

Heart failure (HF) is a dominant and growing problem of public health and society as a whole, accounting for about 1.2 million hospitalizations per year, despite all available therapeutic agents, new generations of drugs, and diagnostic devices (Abraham WT et al., 2011).

In developed countries heart failure occurs in late phases of life, but in underdeveloped countries heart failure occurs earlier. It is known that if one person does not suffer from any other disease, they will die from heart failure (Task Force Members, Montalescot et al., 2013). If there are no other diseases, atherosclerosis develops in blood vessels and in the heart at the same time. The dynamic of this process is affected by many factors, including metabolic, genetic, dietary, physical activity, hormonal, and many others (Roffi M. et al., 2016). It is estimated that in the countries of the European Union, about 2% of adults suffer from heart failure, while that number grows after the age of 65 to 6-10%. Epidemiological studies conducted over the years suggest that the incidence of HF of a certain age and sex has increased three to four times in the last few decades. In contrast, the incidence of age- and sex-specific HF increased from the 1970s to the early 1990s, due to improved survival of patients with HF (McMurray JJ. et al., 2012, Abouezzeddine OF, Redfield MM, 2011).

Converting enzyme inhibitors (ACE inhibitors) are among the most important drugs today, whose primary goal is to stop the progression of the cardiovascular continuum. In addition to ACE inhibitors, conventional therapy includes calcium channel blockers, diuretics, and beta-blockers (Wijins et al., 2010; Stergiopoulos et al., 2014; Teerlink JR, Sliva L, Opie LH., 2013; Munzel T et al., 2011).

Trimetazidine as a metabolic drug in combination with standard therapy in ischemic heart disease acts by selectively inhibiting KAT-(catalytically active). enzymes and reducing oxidation of fatty acids, stimulating glycolysis with the formation of a higher amount of ATP (Adenosine triphosphate) (Belardinelli R, Solenghi M, Volpe L, Purcaro A., 2011). It proves acidosis in the cell by increasing the calcium concentration, increasing the metabolic rate of phospholipids (Fragasso G, et al., 2011). In the same time it protects the cell membrane from oxidative stress caused by beta-oxidation of fatty acids, increases myocardial contractility, prevents myocardial apoptosis (through MAPKYAKT pathway), reduces cardimyocytes sensitivity to oxygen radicals and reduces the occurrence of interstitial myocardial fibrosis (through ROS / CTGF pathway) (Belardinelli R et al., 2007).

Heart failure could be asymptomatic for a few months or a few years. The first symptoms of heart failure will develop during an effort, in the beginning just during great effort, but later with just limited effort (Ng K et al., 2016).

Patients and methods

Patients and study design

The study was performed in the Department of Cardiology in University Clinical Center (UCC) in Tuzla during the year 2017. The study includes 200 patients with ischemic heart disease, by randomization divided into two groups. The first one, experimental, was treated with conventional therapy and metabolic drug trimetazidine in dose of 35 mg daily. Patients were on a special diet that included smaller meals several times a day, reduced carbohydrate intake, fatty and spiced food, but included larger amounts of fruits and vegetables, cooked dishes and not fried dishes. Olive was preferred for cooking. Patients had physical activity for half an hour every day.

The second group was treated only with conventional therapy, without trimetazidine, and on special diet same as the experimental groupe of patients and physical activity for half an hour every day. At the end of the study, after one year, in experimental group 95 patients were completely followed up (47 females and 48 males), and in control group 84 (44 females and 40 males).

All patients signed informative consent.

Methods

Patients were examined for conventional risks of ischemic heart disease, including blood cell count, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL)

cholesterol, triglycerides, urea, creatinine, and fasting blood glucose.

Patient's tolerance to effort was examined by trade-mill stress testing according to Bruce protocol (Guazzi et al., 2013). For all patients echocardiography were performed with measurement of ejection fraction (EF) (Lang RM er al., 2015; Komajda M et al., 2014).

The ergometry test and measurement of ejection fraction on echocardiography, as well as analysis of quality of life considered with standardized questionnaires, were performed on time of discharge from hospital, after six months and after 12 months (Alagiakrishnan et al., 2013).

Standardized and authoritative questionnaires were used for a realistic assessment of the all aspects quality of life, including personal satisfaction with emotional life, life energy, emotional state, mood or depression, especially parameters of the physical effort. Laboratory diagnostic conditions, the Bruce protocol of ergometry, and on the tolerance to the effort that affects the possibility of daily activities, such as staging along the stairs, was analyzed in all patients. Gradation applied as: easily climbing to the third floor along the stairs represents a good tolerance to effort, fatigue already at the beginning of the second floor, as moderate restriction, and fatigue already in the climb to the first floor as a significant limitation of the possibility of climbing the stairs.

Quality of life was assessed with standardized questionnaire, short version (Short Form SF 36) (Ware JE, Sherbourne CD., 1992; Gužić et al., 1998).

Patients were assessed after discharge from hospital, after six months and after twelve months.

Statistical analysis

Laboratory dana were assessedusing Kolmogorow-Smirnov test with nonparametric Mann-Whitney test. The results of quality of life questionnaire were calculated using nonparametric Fisher exact test, if frequency was less than 5, otherwise by χ^2 test. $p<0.05$ was used as statistically significant.

Results

All 200 patients were followed up during twelve months. In both groups, there were 100 respondents at the beginning of the study, and by the end of the expert group, 93 respondents (45 women and 48 men) were followed, and in the control group, 80 respondents (38 women and 42 men) were followed. The experimental group received trimetazidine while the control group did not and both groups had the same diet and exercise plan. Both groups have approximately the same anthropological and social characteristics.

On the day of discharge from the hospital, there was no difference between the patients in the effort tolerance by measure of the achieved METs, 3.6774 METs in experimental and 3.6838 control group ($p=0.880$). After six months of treatment trade-mill showed statistically significant difference e. g., patients of experimental group had better tolerance to effort ($p<0.001$). Greater tolerance for effort was recorded after 12 months, 7.77 METs and 3.87 METs, respectively (Figure 1).

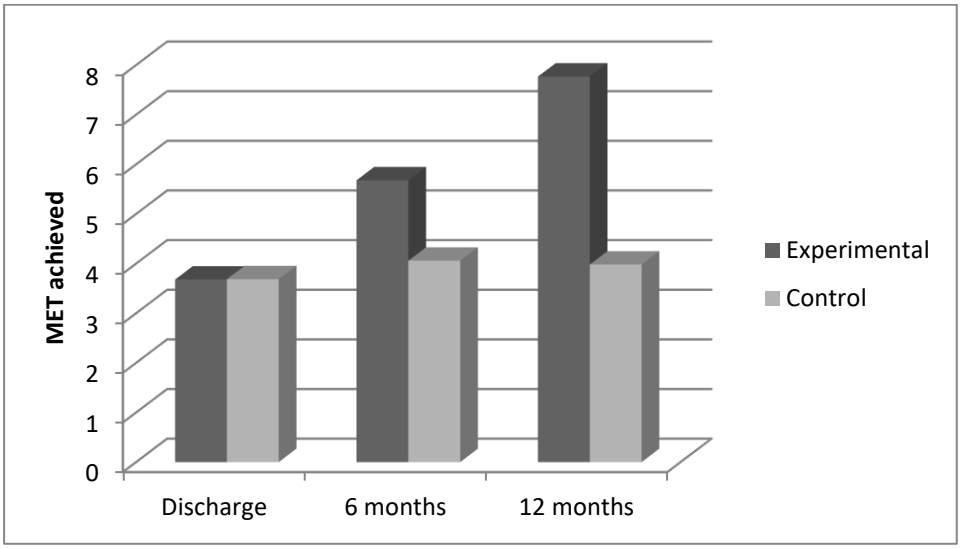

Figure 1. Achievment of Metabolic Equivalent of TASK (METs) in ergometry, trade-mill exercise testing according to Bruce protocol, in three periods of assessement

The number of hospitalizations between the control and experimental groups showed a significant difference for the period of 6 months after treatment (P6 <0.001), as well as a significant difference for 12 months after treatment (P12 <0.001) and a significant difference in values before the start of therapy (Ppt <0.001) (Figure 2). The treated group had a significantly lower number of hospitalizations after 6 and 12 months of metabolic therapy used compared to the control group.

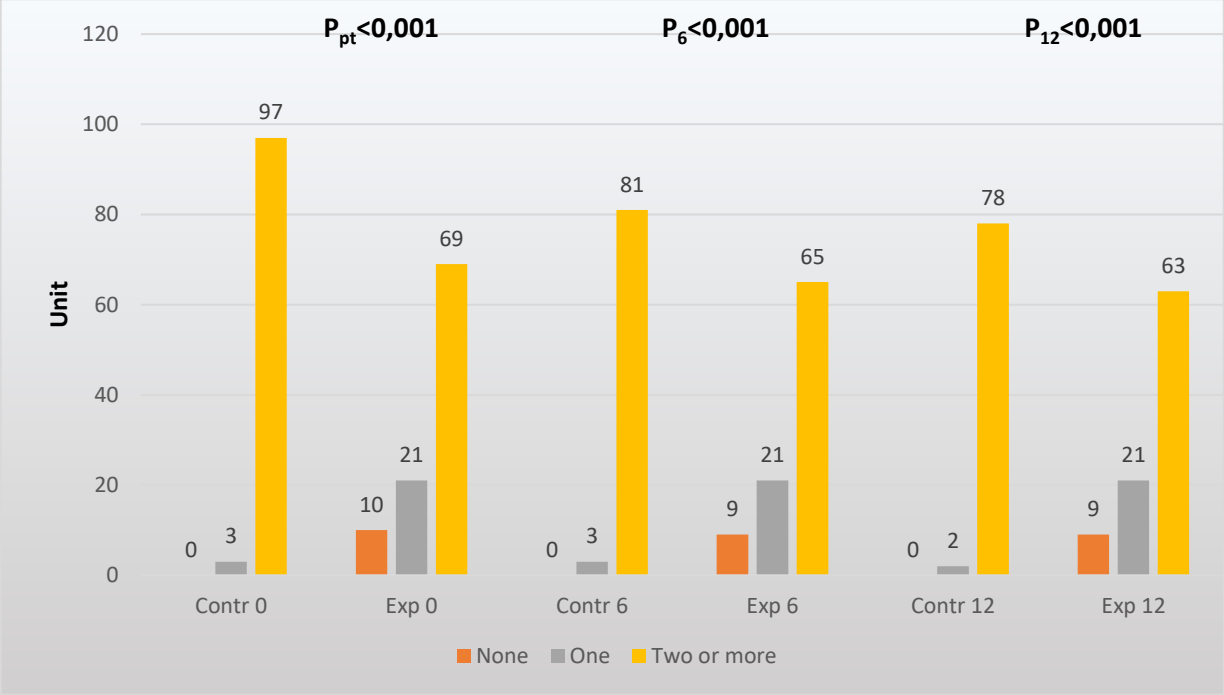

Figure 2. Number of hospitalizations

Results of value comparison Respondents' attitudes about how much they shortened their time at work or other activities as a result of physical health between the control and experimental groups did not show a significant difference for 6 months after treatment (P6 = 0.741), while there is a significant difference in values for before starting therapy (Ppt <0.001), as well as for a period of 12 months after starting therapy shows a significant difference (P12 <0.001) (Table 1).

Table 1. Respondents' attitude about how much they shortened their time at work or other activities as a result of physical health

	Before therapy		**6 months after therapy**		**12 months after therapy**	
	Control group	**Experimental group**	**Control group**	**Experimental group**	**Control group**	**Experimental group**
	Frequency (n=100)	**Frequency (n=100)**	**Frequency (n=84)**	**Frequency (n=95)**	**Frequency (n=80)**	**Frequency (n=93)**
Without change	3	0	0	0	0	10
A small part of time	0	0	3	7	17	34
Part of time	24	0	21	18	17	28
Most of the time	0	5	27	36	30	18
All the time	73	95	33	34	16	3
Total:	**100**	**100**	**84**	**95**	**80**	**93**
P	**P_{pt}<0.001**		**P_6=0.741**		**P_{12}<0.001**	

The results we have for HDL and LDL after the clinical study show that patients who were on conventional therapy and trimetazidine and who used a proper diet as well as those who had physical activity, that their HDL and LDL values were better than at the beginning studies.

Table 2. Body mass index (BMI)

	Before therapy		**6 months after therapy**		**12 months after therapy**	
	Frequency (n=100)	**Percentage (%)**	**Frequency (n=95)**	**Percentage (%)**	**Frequency (n=93)**	**Percentage (%)**
Less than 19,0	**0**	**0**	**0**	**0**	**0**	**0**
19,1 – 24,9	**42**	**42**	**38**	**40**	**39**	**42**
25,0 i više	**58**	**58**	**57**	**60**	**54**	**58**
In total:	**100**	**100**	**95**	**100**	**93**	**100**

Source: Own research

Table 2 shows the body mass index of the subjects. More than half of the respondents who were examined before therapy, i.e. 58% of them had a high BMI, and 42% had a normal BMI, while none of the subjects from the experimental group had a low BMI. Furthermore, 6 months after therapy, i.e. 60% had an increased body mass index, while 40% of them had a normal BMI. None of the subjects had a low BMI. The body mass index before therapy and 12 months after therapy was identical, and there were 58% of those with a high BMI, i.e. above 25.0, and 42% of those with a normal BMI, i.e. between 19.1 – 24.9. none of the subjects had a low BMI 12 months after therapy.

Table 3. Physical activity of the patients

	Before therapy		**6 months after therapy**		**12 months after therapy**	
	Frequency (n=100)	**Percentage (%)**	**Frequency (n=95)**	**Percentage (%)**	**Frequency (n=93)**	**Percentage (%)**
Yes	83	83	78	82	83	89
No	17	17	17	18	10	11
In total:	**100**	**100**	**95**	**100**	**93**	**100**

Source: Own research

Table 3 shows whether the respondents engaged in physical activity before the therapy and 6 months after the therapy. The results showed that 83% of the respondents examined before the therapy were engaged in physical activity, and 17% were not. Furthermore, 82% of the respondents examined 6 months after therapy engaged in physical activity, while 18% did not. Finally, 89% of subjects who were examined 12 months after therapy were engaged in physical activity, while 11% were not.

Table 4. Adherence to a proper diet

	Before therapy		**6 months after therapy**		**12 months after therapy**	
	Frequency (n=100)	**Percentage (%)**	**Frequency (n=95)**	**Percentage (%)**	**Frequency (n=93)**	**Percentage (%)**
Yes	93	93	88	93	87	94
No	7	7	7	7	6	6
In total:	**100**	**100**	**95**	**100**	**93**	**100**

Source: Own research

Table 4 shows whether the respondents followed the recommendations on proper nutrition. Namely, 93% of respondents followed the recommendations on proper nutrition before therapy and 6 months after therapy, while 7% did not. Also, 12 months after therapy, 94% of respondents followed the recommendations on proper nutrition, and 7% did not.

Table 5. HDL level

	Befor therapy		**6 months after therapy**		**12 months after therapy**	
	Frequency (n=100)	**Percentage (%)**	**Frequency (n=95)**	**Percentage (%)**	**Frequency (n=93)**	**Percentage (%)**
Low	34	34	11	12	11	12
Normal	62	62	80	84	82	88
High	4	4	4	4	0	0
In total:	**100**	**100**	**95**	**100**	**93**	**100**

Source: Own research

Table 5 shows the level of HDL that the experimental group of subjects had before therapy, and 6 and 12 months after therapy. The results showed that 62% of the subjects had normal HDL before therapy, 34% low, and 4% high. Six months after therapy, 84% of subjects had normal HDL, 12% low, and 4% high. Furthermore, 12 months after therapy, 88% of subjects had normal HDL, 12% had low, and none of the subjects had high HDL.

Table 6. LDL level

	Befor therapy		6 months after therapy		12 months after therapy	
	Frequency (n=100)	**Percentage (%)**	**Frequency (n=95)**	**Percentage (%)**	**Frequency (n=93)**	**Percentage (%)**
Low	0	0	0	0	0	0
Normal	56	56	61	64	59	63
High	44	44	34	36	34	37
In total:	**100**	**100**	**95**	**100**	**93**	**100**

Source: Own research

Table 6 shows the LDL level of the experimental group of subjects treated with conventional therapy with trimetazidine, before therapy, and 6 and 12 months after therapy. The results showed that 56% of subjects had normal LDL before therapy, 44% had low, and none had high LDL. Six months after therapy, 64% of subjects had normal LDL, 36% had low, and none had high LDL. Furthermore, 12 months after therapy, 63% of subjects had normal LDL, and 37% had low, while none of the subjects had high LDL.

Discussion

Heart failure (HF) is classified as an epidemic and represents both clinical and public health problems associated with high mortality rates, morbidity and health expenditures, frequent hospitalizations, especially among those ≥ 65 years of age. HF is a major public health issue, with a prevalence of over 5.8 million in the U.S. and over 23 million worldwide. In clinical practice, the effectiveness of treatment for a patient with advanced heart failure is often assessed using parameters such as clinical status, hemodynamics, neurohormonal status, and echo / MRI indices. From the patient's perspective, parameters related to the quality of life, such as functional capacity, exercise, psychological status, and frequency of rehospitalization, are much more significant parameters (Nieminen et al., 2015; Bui Al et al., 2011).

One study examined the need for hospitalization in patients with diabetes mellitus and ischemic heart disease. The need for hospitalization was significantly lower in the trimetazidine-treated group (Zhang L et al., 2012). Particular attention has been shown to comorbidities of coronary heart disease, especially with diabetes mellitus. The positive effect of trimetazidine in diabetics has been shown (Belardinelli R et al., 2007).

Similar to numerous studies, ours has shown significant effectiveness in better endurance, reducing the number of nitroglycerin linguals used equivalent to the number of anginal attacks during the week. Several questionnaires examined the effectiveness of many aspects of quality of life (feelings of self-reliance, improvement of strength for everyday life, hidden or larvae depression). Quality of life was better in patients who used trimetazidine, compared to those who did not, in virtually all relevant respects.

To conclude, the result of this study has shown that the addition of trimetazidine to conventional therapy improves ischemic cardiomyocyte's metabolism with the improvement of patient's ability for effort, results in fewer hospitalizations in the comparison with those treated without trimetazidine, and productiveness at work so as well as the quality of life is raised.

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