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A RANDOMISED CONTROLLED TRIAL OF INNOVATIVE SPECIALISED MEAT PRODUCT FOR PATIENTS WITH CARDIOVASCULAR AND METABOLIC DISORDERS

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ABSTRACT

Cardiovascular diseases remain one of the leading causes of death globally. A lot of dietary patterns for CVD prevention have been proposed, but special attention is paid to functional foods. Bioactive proteins and peptides from animal sources are also considered tools for the prevention of CVDs. Here, 40 overweight or obese adult men and women aged between 61 and 66 years, with a body-mass index between 28 and 61 kg.m^{-2}, were enrolled into a randomised controlled trial of new meat products for specialised nutrition. Participants in the control group (n = 20) consumed a standard hyponatric low-calorie diet for 28-30 days (10 days inpatient and 18-20 days outpatient), and in the experimental group – a low-calorie diet and 100g developed meat product (ratio of the porcine aorta to hearts 1:3) per day. Total cholesterol, triglyceride, cholesterol low-density lipoprotein, and cholesterol high-density lipoprotein levels were measured in the serum; from this, the atherogenic index was calculated. The positive effect of developed meat products on the serum lipid profile of patients during the trial was mild but noticeable. A significant reduction in cholesterol levels was noticed in the experimental group, by 18.2% and 14.0% after 7 – 10 and 28 – 30 days, respectively, while the cholesterol level in the control group returned to its original level after 28 – 30 days of dieting. The difference between the control and experimental groups was not significant, while data in the percentiles were. Therefore, it is more preferable to use a developed product as a component in diet therapy for hyperlipidaemic humans for over 28 – 30 days. Pronounced effects of the product could be linked to the unique proteome and peptidome of heart and aorta tissues based on organ-specific gene expression and the presence of tissue-specific substances.

Keywords: CVD; metabolic disorder; functional food; hyperlipidemia; cholesterol

INTRODUCTION

According to World Health Organisation data, cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year. An unhealthy diet is one of the main risk factors for CVD, as well as high blood cholesterol and high blood sugar or glucose levels. Therefore, CVDs are often accompanied by metabolic syndrome and diabetes **(Han and Lean, 2016; Saklayen, 2018)**.

A lot of dietary patterns for the prevention of CVDs have been proposed, such as low-fat diets enriched with monounsaturated (MUFA) and polyunsaturated (PUFA) fats, low-carbohydrate diets enriched with fibres, the Dietary Approach to Stop Hypertension (DASH) diet providing more calcium, potassium, magnesium, and dietary fibre and less fat, saturated fatty acids (SFA), cholesterol, and sodium, and the Mediterranean diet characterised by a relatively high fat intake (40–50% of total daily calories), of which SFA comprises ≤8% and MUFA 15–25% of calories **(Eilat-Adar et al., 2013; Anand et al., 2015; Mozaffarian, 2016)**.

Composition modification (fatty acids modification, sodium chloride control), fermentation (formation of bioactive compounds) and the introduction of functional additives (plant components (oils, extracts, fibres), soy protein, natural and synthetic antioxidants, lactic acid bacteria, and fish oil are successfully used in functional food processing **(Mine and Shahidi, 2006; Cencic and Chingwaru, 2010; Alissa and Ferns, 2012; Hui, 2012; Griffiths et al., 2016; Lordan et al., 2018)**.

Peptides of animal origin released from milk and meat proteins during proteolysis, fermentation or food processing possess hypotensive, antioxidant, antimicrobial, antitumor, antithrombotic, lipid-lowering, and opioid *etc.* actions, and can be considered functional additives to food **(Arihara, 2006; Ahhmed and Muguruma, 2010; Ryan et al., 2011; Udenigwe and Howard, 2013; Lafarga and Hayes, 2014; Bhat, Kumar and Bhat, 2015; Liu et al.,**

2016; Sánchez and Vázquez, 2017). However, tissue-specific proteins and peptides contained natively in slaughter by-products have still not been well-studied.

In previous studies, we confirmed the lipid-lowering effect of functional meat products derived from the porcine heart and aorta on hyperlipidaemic rats **(Chernukha et al., 2018; Kotenkova and Chernukha, 2019)**. This paper reports the analytical results of a randomised controlled trial of meat products for specialised nutrition in patients with cardiovascular and metabolic disorders.

Scientific hypothesis

A wide range of tissue-specific proteins and peptides were identified in raw porcine heart and aorta, some of which were decomposed during meat product processing. The hypothesis that tissue-specific proteins could decompose into active peptides with similar biological action was proven in hyperlipidaemic rats that consumed the innovative product.

Nevertheless, the effectiveness of the product on rodents and humans can vary significantly; therefore, the hypolipidaemic action was studied during a randomised controlled trial on patients with cardiovascular and metabolic disorders.

MATERIAL AND METHODOLOGY

Meat products (MsP) for specialised nutrition were produced on ZAO "Yoshkar-Olinskiy Myasokombinat". Porcine hearts were chopped with a particle size of 2 – 3 mm and salted for 12 h. Porcine aortas were chopped with a particle size of 2 – 3 mm and homogenised in a cutter at 3000rpm for 2 – 3 min. Minced hearts with the juice were quantitatively transferred in the cutter and homogenised at 3000rpm for 6 – 8 min (ratio of the aorta to hearts 1:3). The obtained mince was packed in cans of lamister and sterilised at 115 °C and a pressure of 0.23 MPa for 40 min. Meat products contained 17.53 ±0.95% protein, 3.82 ±0.13% fat, 0.305 ±0.015% sodium chloride, and 2.35 ±0.25% starch.

Study design

The open, prospective, and randomised study was conducted based on the Department of Cardiovascular Pathology of the Federal Research Centre of Nutrition and Biotechnology from June 01, 2019, to October 15, 2019.

The study protocol was approved by the Ethics Committee of the Federal Research Centre of Nutrition and Biotechnology (Protocol No. 7 of 03.12.2018). In accordance with the GCP program, all participants signed written informed consent.

Randomization and study groups

Forty overweight or obese adult men and women aged between 61 and 66 years, with a body-mass index between 28 and 61 $kg.m^{-2}$, were enrolled.

Patients were randomised into two groups by flipping a coin. The participants were not blinded to their group assignment. Participants in the control group (n = 20) consumed a standard hyponatric low-calorie diet (LCD) for 28 – 30 days (10 days inpatient and 18 – 20 days outpatient), and in the experimental group received LCD and 100g MP per day.

Dietary intake

LCD is a diet with a significant restriction of fat and easily digestible carbohydrates, normal protein, and complex carbohydrates, with an increased amount of dietary fibre and a reduction of table salt (3 – 5 g/day). Dishes are boiled, stewed, baked, pureed, and not pureed, as well as steamed. The food temperature ranged from 15 °C to 60 – 65ºC, while the free liquid is 0.8 – 1.5 L. Nutrition is fractional, with addition 4-6 times a day.

Comparative characteristics of the chemical composition of LCD and modified diet with the inclusion of MP are presented in Table 1.

Biochemical analysis

Blood samples for biochemical studies were taken on 0, 7 – 10 and 28 – 30 days. Biochemical investigations were carried out on an automatic analyser BioChem FC-360 (HTI, USA) according to the instructions supplied with the measurement kits (HTI, USA). Total cholesterol (TCL), triglyceride (TG), cholesterol low-density lipoprotein (CL LDL), and cholesterol high-density lipoprotein (CL HDL) levels were measured in serum. Atherogenic index (AI) = (TCL - CL HDL)/CL HDL.

Statistical analysis

STATISTICA 10.0 software was used in this study for the statistical analyses. The results were calculated as "middle value ± standard deviation" (*M* ±*SD*) and "percentile" ($P_{25\backslash75}$). Significant differences were tested by nonparametric statistical Mann-Whitney U tests for independent variables and Freidman ANOVA for dependent variables. Differences with *p*-values less than 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

The null hypothesis about the influence of control and experimental diets on serum lipid profile inside the group were checked according to Freidman's ANOVA for all patients and patients with a BMI below 40 $kg.m^{-2}$ ($n_{control}$ = 11, $n_{experimental}$ = 10) and above 40 $kg.m^{-2}$ ($n_{control}$ = 9, $n_{experimental}$ = 10). The results are presented in Table 1. It was shown that LCD consumption (control) for 7 – 10 days led to total cholesterol reduction by 11.2%, mainly due to its reduction in the serum of patients with a

Table 1 Comparative characteristics of the chemical composition of LCD and modified diet with the inclusion of MP.

Diet	Chemical composition			
	Energy value, kcal/day	Proteins, g/day	Fat, g/day	Carbohydrates, g/day
LCD	1350.0 – 1550.0	70.0 – 80.0	60.0 – 70.0	130.0 – 150.0
LCD+MP	1437.0 – 1682.0	86.5 – 98.0	63.0 – 76.0	131.0 – 151.5

Table 1 Serum lipid profile of patients during trial.

Groups	0 days	7 – 10 days	28 – 30 days	*p*-value (Freidman ANOVA)
Total Cholesterol, mmol.L^{-1}				
Control group				
Total patients	3.829 ±0.777	3.400 ±0.695	4.025 ±1.225	0.1423
Patients with BMI >40 kg.m^{-2}	3.600 ±0.817	3.513 ±0.773	3.860 ±1.386	0.7165
Patients with BMI <40 kg.m^{-2}	4.016 ±0.726	3.307 ±0.647	4.160 ±1.127	0.1496
Experimental group				
Total patients	4.637 ±1.411	3.791 ±1.109	3.989 ±0.955	**0.0008**
Patients with BMI >40 kg.m^{-2}	4.474 ±1.564	3.202 ±0.606	3.901 ±0.839	**0.0018**
Patients with BMI <40 kg.m^{-2}	4.800 ±1.303	4.381 ±1.208	4.078 ±1.097	0.0672
Cholesterol LDL, mmol.L^{-1}				
Control group				
Total patients	1.981 ±0.535	1.708 ±0.469	2.241 ±1.008	**0.0174**
Patients with BMI >40 kg.m^{-2}	2.041 ±0.479	1.769 ±0.459	2.296 ±1.193	0.3679
Patients with BMI <40 kg.m^{-2}	1.931 ±0.596	1.658 ±0.493	2.196 ±0.888	**0.0379**
Experimental group				
Total patients	2.691 ±1.151	2.089 ±0.884	2.230 ±0.697	**0.0024**
Patients with BMI >40 kg.m^{-2}	2.517 ±1.264	1.601 ±0.466	2.093 ±0.617	**0.0018**
Patients with BMI <40 kg.m^{-2}	2.864 ±1.064	2.576 ±0.951	2.367 ±0.777	0.1496
Cholesterol HDL, mmol.L^{-1}				
Control group				
Total patients	1.145 ±0.286	1.131 ±0.269	1.191 ±0.245	**0.0150**
Patients with BMI >40 kg.m^{-2}	0.965 ±0.297	1.066 ±0.342	1.028 ±0.231	0.1211
Patients with BMI <40 kg.m^{-2}	1.291 ±0.179	1.185 ±0.192	1.323 ±0.169	**0.0116**
Experimental group				
Total patients	1.118 ±0.258	1.016 ±0.258	1.155 ±0.262	**0.0106**
Patients with BMI >40 kg.m^{-2}	1.147 ±0.283	1.015 ±0.201	1.193 ±0.278	**0.0055**
Patients with BMI <40 kg.m^{-2}	1.090 ±0.242	1.016 ±0.178	1.117 ±0.254	0.4966
Triglycerides, mmol.L^{-1}				
Control group				
Total patients	1.039 ±0.433	1.000 ±0.452	1.098 ±0.493	0.2466
Patients with BMI >40 kg.m^{-2}	1.193 ±0.541	1.157 ±0.404	1.147 ±0.492	0.8948
Patients with BMI <40 kg.m^{-2}	0.913 ±0.290	0.872 ±0.465	1.058 ±0.514	0.1482
Experimental group				
Total patients	1.919 ±0.987	1.689 ±0.777	1.585 ±0.866	0.3499
Patients with BMI >40 kg.m^{-2}	1.760 ±0.781	1.600 ±0.833	1.341 ±0.482	0.9048
Patients with BMI <40 kg.m^{-2}	2.078 ±1.179	1.778 ±0.751	1.829 ±0.104	0.2725
Serum atherogenic index				
Control group				
Total patients	2.494 ±0.798	2.085 ±0.628	2.465 ±1.048	0.0863
Patients with BMI >40 kg.m^{-2}	2.924 ±0.837	2.398 ±0.603	2.830 ±1.225	0.1211
Patients with BMI <40 kg.m^{-2}	2.141 ±0.587	1.828 ±0.545	2.167 ±0.817	0.1777
Experimental group				
Total patients	3.192 ±0.968	2.756 ±0.936	2.540 ±0.864	0.0863
Patients with BMI >40 kg.m^{-2}	2.959 ±1.107	2.190 ±0.503	2.352 ±0.707	0.2725
Patients with BMI <40 kg.m^{-2}	3.425 ±0.795	3.320 ±0.941	2.728 ±0.999	0.2019

Note: p <0.05 mean that diet consumption influence on lipid parameter in serum.

BMI below 40 kg.m^{-2} by 17.7%.

The cholesterol level returned to its original level after 28–30 days of dieting. Revealed changes were not significantly reliable. LCD with MP consumption (experimental) led to a statistically significant total cholesterol reduction by 18.2% and 14.0% after 7 – 10 and 28 – 30 days, respectively, mainly due to its reduction in the serum of patients with a BMI above 40 kg.m^{-2} by 28.4% and 12.8%, respectively. Despite the lack of statistical significance, it was noted that the total cholesterol level reduction was higher in patients with a BMI below 40 kg.m^{-2} and equal to 15.0% compared with day 0.

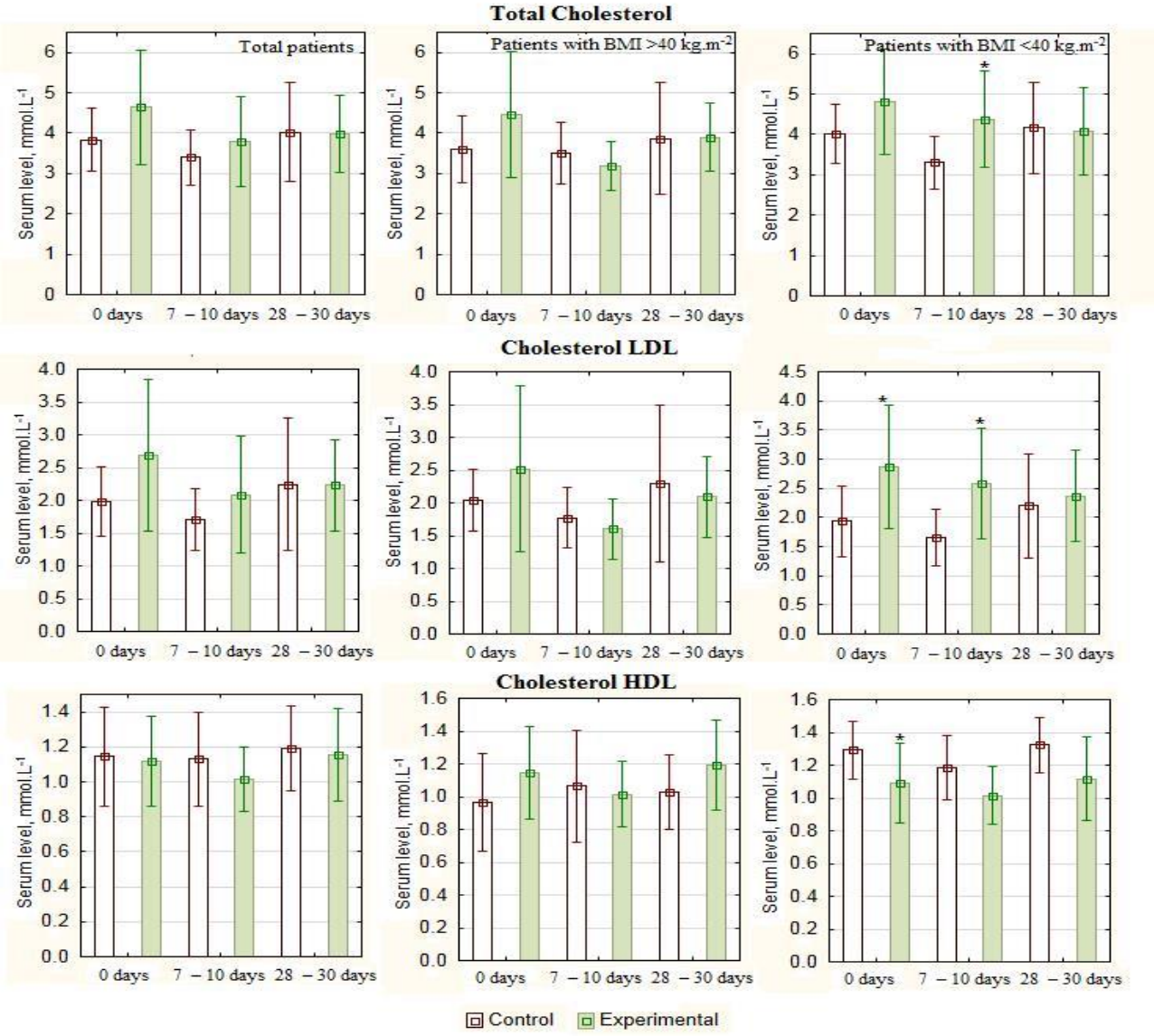

Figure 1 Cholesterol distribution in the serum of patients during the trial. Note: * - significant difference between the control and experimental groups (p <0.05)

In the control group, a statistically significant cholesterol LDL reduction by 13.8% was noticed after 7 – 10 days, mainly due to its reduction in the serum of patients with a BMI below 40 kg.m^{-2} by 14.1%. LDL cholesterol level decline was also marked in the serum of experimental patients and was equal to 22.4% after 7 – 10 days, mainly due to its reduction in the serum of patients with a higher BMI of 40 kg.m^{-2} by 36.4%. The cholesterol LDL level returned to its original level in both groups after 28 – 30 days of dieting. The same tendency was noticed concerning the cholesterol HDL level.

There were no significantly reliable changes to triglyceride levels and serum atherogenic index in both groups. However, after 7–10 days after the diets, a decrease in triglyceride levels in the control group amounted to only 3.9% and returned to its original level after 28 – 30 days, while the reduction in experimental patients was equal to 12.0% and continued to reduce until 28 – 30 days to 17.4%. The same tendency was noticed concerning serum atherogenic index (AI). Also, 7 – 10 days after the diets, the decrease in AI in the control group amounted to 16.4% and returned to its original level after 28 – 30 days, while the reduction was equal to 13.7% in experimental patients and continued to reduce until 28 – 30 days to 20.4%.

Cholesterol levels on days 0, 7 – 10 and 28 – 30 days were compared between the control and experimental groups according to the Mann-Whitney U test. There were no significantly reliable changes in cholesterol levels in the two groups for all patients and patients with a BMI higher 40 kg.m^{-2}. Cholesterol LDL on day 0 in the serum of experimental patients with a BMI lower than 40 kg.m^{-2} was higher than in the control group by 48.3% (p <0.05), while cholesterol HDL was lower by 15.7%; therefore, there was no difference between total cholesterol levels.

After 7 – 10 days, the cholesterol LDL in the serum of experimental patients with a BMI below 40 kg.m^{-2} was still higher than in the control group by 55.4% (p <0.05), but returned to the original level in both groups after 28 – 30 days of dieting.

With such heterogeneity of groups, it is advisable to consider changes in the lipid profile in dynamics and compare changes in parameters between groups. Dynamics were evaluated between 0 day and 7 – 8 days and 0 day and 28 – 30 days and are presented in Table 2 in percentiles ($P_{25\backslash75}$); statistical differences were calculated according to Mann-Whitney U tests.

There were no significantly reliable changes in Δ total cholesterol after 7 – 10 days of diet consumption, but after 28 – 30 days in the serum of experimental patients it was significantly lower than in the control, mainly due to LDL cholesterol reduction especially in patients with a BMI below 40 $kg.m^{-2}$. The same tendency was noticed concerning Δ triglycerides. There was still no significantly reliable changes in the Δ serum atherogenic index, despite its remarkable reduction in the experimental group by 13.7% and 20.4% at 7 – 10 and 28 – 30 days, respectively (Table 1). Nevertheless, a positive effect of MP on the activity (**Chernukha et al., 2016; Chernukha et al., 2018; Kotenkova and Chernukha, 2019**).

On the other hand, numerous authors also considered animal proteins as abundant sources of functional peptides, including those which demonstrated a lipid-lowering effect **(Bauchart et al., 2006; Ahhmed and Muguruma, 2010; Toldrá et al., 2012; Udenigwe and Howard, 2013; Lafarga and Hayes, 2014; Cicero, Fogacci and Colletti, 2017)**. **Nakade et al. (2009)** revealed that cattle heart protein hydrolysate could suppress cholesterol absorption in Caco-2 cells.

It is known that aorta tissue is enriched with collagen and elastin, while collagen-derived peptides have been better studied and are characterised by their lipid-lowering effect **(Koyama and Kusubata, 2013; Hongdong and Bo, 2017; Tometsuka et al., 2017; Tomosugi et al., 2017; Yazaki et al., 2017; Arrutia et al., 2017; Wahart et al., 2019)**. In this regard, aorta tissue is a good source of

Table 2 Dynamics of serum lipid profile changes in patients during the trial.

Days	Control group			Experimental group		
	Total	BMI >40 $kg.m^{-2}$	BMI <40 $kg.m^{-2}$	Total	BMI >40 $kg.m^{-2}$	BMI <40 $kg.m^{-2}$
Δ total Cholesterol, $P_{25/75}$						
7 – 10	-0.024/1.314	-0.380/1.211	-0.008/1.502	0.349/0.784	0.372/2.139	0.325/0.652
28 – 30	-0.597/0.368	-0.556/0.117	-0.608/0.953	-0.218/1.631*	-0.406/1.564	-0.045/1.698
Δ Cholesterol LDL, $P_{25/75}$						
7 – 10	-0.094/0.756	-0.163/0.753	-0.025/1.010	0.244/0.687	0.279/1.682	0.110/0.627
28 – 30	-0.465/0.034	-0.325/0.050	-0.642/0.017	-0.142/1.144*	-0.399/1.274	-0.114/0.977*
Δ Cholesterol HDL, $P_{25/75}$						
7 – 10	-0.036/0.177	-0.038/0.153	0.045/0.186	-0.014/0.206	0.002/0.223	-0.028/0.141
28 – 30	-0.186/0.077	-0.173/-0.019	-0.198/0.082	-0.148/0.047	-0.155/0.074	-0.137/0.020
Δ Triglycerides, $P_{25/75}$						
7 – 10	-0.083/0.218	-0.226/0.246	-0.071/0.216	-0.273/0.421	-0.215/0.395	-0.303/0.446
28 – 30	-0.174/0.125	-0.081/0.081	-0.296/0.168	-0.148/0.794*	-0.183/0.862	-0.051/0.606*
Δ Serum atherogenic index, $P_{25/75}$						
7 – 10	-0.155/0.730	-0.207/0.944	-0.103/0.713	-0.023/0.822	-0.017/1.493	-0.158/0.605
28 – 30	-0.537/0.703	0.101/0.475	-0.693/0.822	-0.021/1.489	-0.040/1.642	-0.002/1.444

Note: * -significant differences between the control and experimental groups (p <0.05)

serum lipid profile of patients during the trial is noticeable.

In a previous study it was shown that meat products characterised by milder hypolipidaemic action compared with native raw material or isolated active fractions; a slight effect was observed after 28 days of consumption by hyperlipidemic rats, while a significant effect was only seen after 42 days of consumption **(Kotenkova and Chernukha, 2019)**.

The pronounced effect of meat product could be linked to the unique proteome and peptidome of the heart and aorta tissues based on organ-specific gene expression and the presence of tissue-specific substances **(Fagerberg et al., 2014; Breschi et al., 2016; Guschanski, Warnefors and Kaessmann, 2017; Sonawane et al., 2017; Barbeira et al., 2018)**. Previously, we also observed that sterilisation led to the decomposition of most parts of the target tissue-specific proteins and peptides into active peptides with apparently similar biological actions or retained residual glyproline peptides with hypolipidaemic action **(Lyapina et al., 2015; Shabalina Lyapina et al., 2015; Myasoedov et al., 2016)**. Presumably, active peptides could be generated both during meat product processing and digestion processes.

CONCLUSION

The positive effect of developed meat products on the serum lipid profile of patients during the trial was mild but noticeable. Presumably, it is more preferable to use this as a component in a diet therapy for hyperlipidaemic humans for 28 – 30 days. Earlier, the same effect was revealed on hyperlipidaemic rodents, which confirms the lipid decreasing ability effect of innovative products and can be recommended as part of a diet to fight CVD. The pronounced effect of the product could be linked to the unique proteome and peptidome of the heart and aorta tissues based on organ-specific gene expression and the presence of tissue-specific substances.

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