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Cardiometabolic and antioxidative effects of lyophilized goat whey supplementation

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Abstract

Milk and dairy products exhibit a beneficial nutritional and health effects and represent 20% to 30% of global food consumption. Whey proteins have great anabolic and cardioprotective role. Increased concentration of cholesterol contained in high density lipoproteins (HDL), paraoxonase 1 (PON1) higher activity, and diminished relative proportion of small dense low density lipoproteins (sdLDL) reduce cardiovascular diseases (CVD) risk. Current longitudinal study enrolled 10 healthy volunteers. All participants consumed lyophilized goat whey (LGW) (Koza Nostra®) for two months (3 g per day). Concentrations of basic biochemical parameters were measured by routine methods. Concentration of oxidative stress status parameters were measured spectrophotometrically. Serum PON1 activity was measured kinetically using paraoxon as a substrate. Lipoproteins subfractions were separated by gradient-gel electrophoresis. A significant decrease in urea concentrations ($p<0.05$) and trend toward higher albumin concentrations were observed after LGW supplementation. A significant increase in values of prooxidative-antioxidative balance ($p<0.05$) and PON1 activity ($p<0.05$), as well as a trend toward lower malondialdehyde concentrations were observed after supplementation. Trends toward higher relative proportion of HDL 3c subclasses and an increase in LDL lipoprotein particle diameter were observed. The findings of the present study have shown that increased protein synthesis, PON1 enzyme activity and shift toward increased HDL 3c relative proportions could indicate that LGW has a positive effect on synthetic liver function and CVD risk reduction. Our findings suggest that LGW may protect against free radicals by stimulating the antioxidant defense mechanisms and promoting a mild prooxidative effect.

Key words: *lyophilized goat whey, prooxidative-antioxidative balance, paraoxonase 1, HDL, cardiovascular disease.*

INTRODUCTION

The positive nutritional and health benefits of milk and milk products have been known since ancient times [1,2]. Nowadays, dairy products are considered an excellent source of various essential and non-essential amino acids and represent 20% to 30% of global food consumption [3]. In some Middle Eastern and Sub-Saharan cultures, fermented dairy products such as sour milk, yogurt, cheese, and whey represent one of the most important groceries in the food pyramid, due to their better digestive characteristics [1,2]. However, according to data obtained from the US National Agriculture Statistics Service, only 0.08% of total milk manufacturing is produced by goat and sheep milk. Goat milk has not been widely used due to the consumers' sensitivity to the goat's milk aroma, which is mainly derived from the caproic (C-6) and caprylic (C-8) free fatty acids released from milk fat [4]. The current consumption of goat's milk has increased mainly because it is a good alternative for children and adults who are allergic to cow's milk [3]. The functional characteristics of milk and dairy products are closely related to milk-protein composition. Milk proteins have several biologically active properties, including antioxidant, antibacterial, immunomodulatory and even antihypertensive [3]. Goat and cow's milk have similar protein composition; however, goat's milk has higher digestibility, iron bioavailability and buffering capacity with higher therapeutic value of its proteins, bioactive peptides and oligosaccharides [3]. In malabsorption and malnutrition states, goat's milk and whey are highly recommended, as a manda-

tory dietary supplement, especially in young children and adolescents [5]. Goat whey represents a heterogeneous protein mixture with wide-ranging nutritional, biological and functional food properties [6]. Although considered to be a by-product and an environmental pollutant, whey is increasingly used in food manufacturing and diet due to its nutritional properties [7]. It is well known that whey proteins (WP) have great biological value [8]. A study by Haraguchi et al., comparing biological value parameters between WP and casein, showed that WP had better protein nutritional quality markers (net protein ratio, protein efficiency ratio, and true digestibility) [9]. The most common WP are α-lactalbumin (20-25%) and ß-lactoglobulin (50-55%). α-lactalbumin is an important source of essential amino acids, primarily tryptophan, and is the only WP that binds calcium. β-lactoglobulin is an excellent source of branched-chain amino acids (BCAAs) (valine, leucine, and isoleucine) [8].

The antioxidant activity of WP has been confirmed by inhibition of lipid peroxidation and this is due to the chelation of transition metals by lactoferrin and scavenging by sulfur-containing amino acids [10]. Compared to cow's milk, goat's milk has 4 times higher vitamin A concentration, 14 times higher vitamin C concentration, and almost 10 times lower copper and iron content [10]. Consequently, goat milk and dairy products with this composition can be beneficial for antioxidative defense by several mechanisms and thus have a significant cardioprotective role. Well-known atheroprotective characteristics of high density lipoprotein particles (HDL) are reflected in the reverse cholesterol transport, but also the antioxidant capacity of the HDL particle provided by the paraoxonase 1 enzyme (PON1) [11]. Although there is unambiguous evidence of an inverse relationship between the concentration of cholesterol contained in HDL (HDL-c) and CVD risk, this effect is related to HDL particle functionality [12]. A nascent, discoidal HDL particle is synthesized in the liver and intestine, and cholesterol is taken up from peripheral tissues. This allows nascent particle maturation, from HDL 3 subclasses to a larger, more mature HDL 2 which has a more cholesterol-enriched core [13]. PON1 belongs to antioxidant enzymes and it is an integral part of HDL particles [11]. A key physiological role of PON1 enzymes is the protection of low density lipoprotein (LDL) and cell membrane proteins from oxidative modification and consequent atherosclerotic lesion development [11]. Gugliucci suggested that PON1 was distributed across all HDL subclasses, but with the highest affinity for small HDL 3 particles [14]. Decreased PON1 activity is associated with the development of atherosclerosis, diabetes, renal disease, Parkinson's disease, and cancer [11].

The aim of this study was to investigate the potential effects of lyophilized goat whey (LGW) (Koza Nostra®) on basic biochemical and oxidative stress parameters. The functionality of the HDL lipoprotein particle by measuring PON1 activity and changes in the distribution of HDL subclasses after consuming LGW were also examined.

MATERIAL AND METHODS

Study design and patients

This study was designed as longitudinal and enrolled 10 healthy, male volunteers without signs and symptoms of cardiovascular, renal and liver disease. They were carefully examined and questioned about their health status and family history. The subjects were not on chronic therapy and did not consume dietary supplements. All participants consumed 3 g per day of LGW for two months. According to the manufacturer's specification, the energy value was 368 kcal per 100 g while fat content was 5.5 g, carbohydrates 64.5 g and protein 14.5 g per 100 g of product. The study was conducted by the principles laid down in the Declaration of Helsinki. All participants signed informed consent before enrolment.

Laboratory analyses

Serum and EDTA plasma were collected after 12-h fasting period and obtained by centrifugation at 1500 × g for 10 min at 4 °C. Concentrations of total protein, albumin, creatinine, urea, uric acid, glucose, total cholesterol (TC), HDL-c, and triglycerides (TG) were measured by routine methods on an Ilab 300+ analyzer (Instrumentation Laboratory, Bedford, MA, SAD) using BioSystems reagents (BioSystems, Barcelona, Spain). The concentration of cholesterol contained in LDL (LDL-c) was calculated with the Friedewald equation. Advanced oxidation protein products (AOPP) were determined using a reaction with glacial acetic acid and potassium iodide [15]. Malondialdehyde (MDA) concentration was determined spectrophotometrically measuring the absorbance of MDA-thiobarbituric acid (MDA-TBA) complex at 535 nm [15]. Serum PON1 activity was measured kinetically using paraoxon as a substrate [15]. Total oxidative status (TOS) was measured by a spectrophotometric method using o-dianisidine, total antioxidative status (TAS) was measured by a spectrophotometric method using ABTS as a chromogen, and prooxidative-antioxidative balance (PAB) was measured using a method with 3, 3`, 5, 5`-tetramethylbenzidine [15]. Plasma superoxide dismutase (SOD) activity was measured by a method based on the enzyme's ability to inhibit autoxidation of epinephrine in an alkaline medium [15]. Levels of SH-groups (SHG) were measured using DTNB (dinitrodithiobenzoic acid) as a reagent [15]. Plasma HDL and LDL particles were separated using a gradient gel electrophoresis method previously published elsewhere [16]. The relative content of five HDL subclasses was established by assess-

ing the areas under the peaks obtained from the densitometric scan. Also, densitometric scan at or below 8.8 nm in HDL region represented the relative proportion of small-sized HDL particles and densitometric scans at or below 25.5 nm in the HDL region represented the relative proportion of small dense LDL (sdLDL) particles. The estimated diameter of the major peak in the LDL and HDL regions of each scan was referred to as the dominant particle diameter [16].

Statistical analysis

All data were analyzed using IBM® SPSS® Statistics version 22 software. Shapiro-Wilk test was used for data distributions assessment. All variables were asymmetrically distributed and were shown as median (interquartile range). Continuous variables were compared by the Wilcoxon signed-rank test. A p-value of less than 0.05 was considered statistically significant.

Table 1. Concentrations of basic biochemical parameters before and after LGW supplementation.

	Before supplementation (N=10)	After supplementation (N=10)	p[1]
ALT, U/L	34.5 (21.5 – 43.5)	25.0 (15.5 – 40.0)	0.498
AST, U/L	29.0 (25.2 – 45.2)	27.0 (18.2 – 31.0)	0.141
CK, U/L	182.8 (116.9 – 455.5)	186.0 (123.2 – 285.5)	0.889
Total proteins, g/L	76.7 (73.1 – 79.5)	77.2 (72.2 – 87.6)	0.575
Albumin, g/L	51.4 (50.9 – 53.3)	52.8 (51.6 – 55.6)	0.080
Creatinine, ìmol/L	106.6 (87.2 – 125.8)	99.5 (84.3 – 116.4)	0.123
Urea, mmol/L	6.96 (5.46 – 8.18)	5.21 (4.40 – 5.88)	**0.05**
Uric acid, µmol/L	419.8 (388.7 – 440.2)	390.7 (356.1 – 467.7)	0.208
Glucose, mmol/L	5.40 (4.58 – 6.35)	5.80 (5.17 – 6.30)	0.362
Total cholesterol, mmol/L	5.95 (5.60 – 6.32)	6.25 (5.85 – 6.37)	0.205
HDL-cholesterol, mmol/L	1.46 (1.33 – 1.54)	1.33 (1.20 – 1.42)	0.236
LDL-cholesterol, mmol/L	3.91 (3.63 – 4.42)	4.23 (4.11 – 4.79)	0.237
Triglycerides, mmol/L	0.98 (0.70 – 1.22)	0.70 (0.57 – 0.83)	0.362

Data are shown as median (interquartile range)

ALT – alanine aminotransferase; AST – aspartate aminotransferase; CK – creatine kinase; HDL-cholesterol – high density lipoproteins cholesterol; LDL-cholesterol – low density lipoproteins cholesterol

[1]Continuous variables were compared using Wilcoxon signed-rank test.

RESULTS

The study included adult, male middle-aged participants, with an average age of 54.5 (40.7-56.0) years. **Table 1** represents concentrations of biochemical parameters and enzymes activity before and after 2-months-long LGW consummation. The activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatine kinase (CK) enzymes did not change during treatment. Also, creatinine and uric acid levels remained unchanged. Although there were no changes in total protein and albumin concentrations, there was a trend toward higher albumin concentrations after LGW consummation. Urea concentration decreased significantly after treatment. Glucose concentrations and lipid status parameters did not change after 2-months-long LGW consummation. There was a trend towards higher glucose, TC and LDL-c concentrations, as well as lower TG concentrations after treatment.

Table 2 shows changes in concentrations of oxidative stress status parameters after 2-months-long LGW consummation. Among the oxidative stress status parameters, there were no changes in the AOPP, TAS, TOS, SHG concentrations and TAS/TOS ratio, but our results show a trend toward lower MDA concentration and SOD activity after consuming LGW. A significant increase in PON1 enzyme activity and PAB values were observed after supplementation (**Table 2**).

Table 2. Concentrations of oxidative stress and anti-oxidant defense markers before and after LGW supplementation.

	Before supplementation (N=10)	After supplementation (N=10)	p[1]
AOPP, µmol/L	31.9 (26.5 – 39.8)	28.8 (26.5 – 33.8)	0.674
PON1, U/L	338 (189 – 781)	364 (262 – 1067)	**<0.05**
MDA, µmol/L	2.44 (1.96 – 5.39)	1.76 (1.68 – 2.29)	0.161
TAS, µmol/L	1066 (921 – 1158)	1086 (968 – 1199)	0.612
TOS, µmol/L	7.20 (3.70 – 12.60)	10.30 (5.00 – 17.63)	0.799
TAS/TOS	170 (82.5 – 296)	92 (67 – 240)	0.600
SOD, U/L	123 (108 – 140)	101 (78 – 114)	0.058
PAB, U/L	75.4 (61.5 – 103.5)	103.3 (93.1 – 113.9)	**<0.05**
SHG, mmol/L	0.466 (0.423 – 0.556)	0.316 (0.296 – 0.398)	0.161

Data are shown as median (interquartile range)

AOPP – advanced oxidation protein products; PON1 – paraoxonase 1; MDA – malondialdehyde; TAS – Total antioxidative status; TOS – Total oxidative status; SOD – Superoxide dismutase; PAB – Prooxidative-antioxidative balance; SHG – SH-groups

[1]Continuous variables were compared using Wilcoxon signed-rank test.

Dominant HDL particle diameter and relative proportion of HDL subclasses before and after LGW supplementation are shown in **Table 3**. There was no change in the diameter of the dominant HDL particle after supplementation. Further on, the results of our study have shown that after 2-months-long supplementation there were no significant changes in the majority of HDL subclasses distribution. During the study period, our results have shown a trend towards an increase in the relative proportion of HDL 3c subclasses after supplementation. A relative proportion of sdLDL was not significantly different after the LGW supplementation. However, a trend toward higher LDL diameter was observed (**Table 3**).

DISCUSSION

The present study was conducted to investigate the changes in biochemical and oxidative stress parameters, as well as the distribution of HDL lipoprotein subclasses after 2-months-long LGW administration. In the present study, we analyzed for the first time the changes in HDL functionality after LGW consumption.

We observed that ALT, AST, and CK enzyme activities, as well as creatinine and uric acid concentrations, did not change significantly during LGW administration (**Table 1**). This may indicate that structural and functional changes in liver, muscle, and kidney did not occur during LGW consumption. In a study with experimental animals, Haraguchi et al. study showed that supplementation with whey protein did not affect hepatic and renal functions [9]. On the other hand, the results of a study conducted by Abdel-Wahhab WP concentrate had a beneficial effect on liver enzymes activity in rats with hepatotoxicity induced by tienilic acid [6]. In the same study ALT and AST enzyme activities, as well as total and direct bilirubin concentrations were significantly lower in the subgroup administered with WP concentrate [6]. The conclusion was that WP could ameliorate hepatocyte structural damages as seen from the abovementioned parameters [6]. Goat's milk, as well as goat's whey, have the highest content of several amino acids (threonine, serine, alanine, isoleucine, tyrosine, phenylalanine, histidine, and lysine) compared to cow, buffalo and sheep milk [10]. It has been shown that, after the administration of WP, the concentration of albumin significantly increased in experimental animals [9]. WP contains about 26% of branched chain amino acids (BCCAs) [17]. It has been demonstrated that in cirrhotic patients the administration of these amino acids leads to albumin concentrations increase, energy metabolism regulation, and alleviation of disease symptoms, as well as the improvement of the clinical picture and overall quality of life [8,18]. BCAAs are also known to participate in protein and glucose homeostasis, and lipid metabolism [17]. Additionally, it has been reported that BCAAs administration reduces muscle damage induced by exercise and promotes protein synthesis in skeletal muscles [19]. During intensive exercise, it is recommended that bodybuilders consume WP due to its proven positive effects on muscle mass gain [20]. The results of our study showed no change in TP concentration, but we have observed a trend toward higher albumin concentrations after 2-months-long LGW consumption. However, urea concentrations decreased significantly after supplementation. It is known that urea concentrations are decreased when protein anabolism is promoted [21]. Further on, the results of the study that monitored the effects of sheep/goat WP administration in rats showed a significant reduction in free amino acid levels in plasma [17]. In that study, levels of 22 plasma amino acids were examined, 15 of them were significantly reduced (29-52%) in the administrated group [17]. Our results may indicate decreased protein breakdown and decreased amino acid catabolism over 2-months-long LGW consumption. As WP is rich in glycogenic amino acids, a study in experimental animals showed a significant increase in glucose concentration after WP administration [9]. Our results showed no changes in glucose concentration, but a trend toward higher concentrations after LGW consumption was observed. When it comes to changes in the concentrations of the lipid status parameters after consuming WP, the results of the previous studies are conflicting [9,22]. The results of some studies indicate favorable

Table 3. Dominant LDL particle diameter and sdLDL relative proportion, HDL particle diameter and relative proportion of HDL subclasses before and after LGW supplementation.

	Before supplementation (N=10)	After supplementation (N=10)	p[1]
LDL diameter, nm	23.8 (23.5 – 25.0)	24.0 (23.7 – 25.2)	0.345
sdLDL, %	62.3 (56.0 – 67.0)	58.7 (56.7 – 65.5)	0.463
HDL diameter, nm	9.33 (8.88 – 9.73)	9.25 (8.71 – 9.79)	0.249
HDL 2b, %	37.4 (34.0 – 43.1)	35.2 (33.8 – 46.2)	0.917
HDL 2a, %	23.2 (22.2 – 24.9)	21.1 (18.8 – 25.7)	0.173
HDL 3a, %	15.3 (13.6 – 17.0)	16.3 (12.4 – 17.2)	0.917
HDL 3b, %	9.4 (8.5 – 11.1)	10.0 (7.5 – 11.6)	0.753
HDL 3c, %	13.3 (10.3 – 15.0)	15.8 (11.6 – 17.5)	0.075
HDL 2, %	61.4 (56.8 – 67.8)	60.4 (53.7 – 64.7)	0.116
HDL 3, %	38.6 (32.2 – 43.2)	39.6 (35.3 – 46.3)	0.116

Data are shown as median (interquartile range)

LDL – low density lipoproteins; HDL – high density lipoproteins; sdLDL – small dense LDL

[1]Continuous variables were compared using Wilcoxon signed-rank test.

changes in cholesterol concentrations through the rise of HDL-c, while some studies suggest that WP supplementation has a reducing effect on the LDL-c concentration [9,22]. However, no changes in the lipid status parameters were observed in our study.

The antioxidant effect of goat whey in preventing lipid and protein oxidation, as well as its effect on enhancing the synthesis and activity of PON1 enzymes, has received special attention [6,10,17]. In our study, we examined changes in MDA and AOPP concentrations as well as PON1 enzyme activity after 2-months-long LGW consumption. A trend toward lower MDA and AOPP concentrations was observed (**Table 2**). MDA is produced as the end product of polyunsaturated fatty acids peroxidation [15,23]. Its reactivity, and thus its toxicity, is reflected in reactions with apoB-100 and oxidative modifications of LDL particles. The findings of previous studies discussed the role of MDA in atherogenesis [23], and Viigima et al. propose MDA modification of LDL particles as an independent marker of atherosclerosis [24]. AOPP values reflect concentrations of highly oxidized proteins, especially albumin. The increased values of AOPP have been detected in the plasma of chronic uremic patients [25]. Kerasiot and associates showed that in rat serum and tissues, TBARS (thiobarbituric acid reactive substances, a chemical measure of MDA and other less present aldehydes evolved as lipid peroxides degradation products) concentrations and protein carbonyl levels were significantly decreased after sheep/goat WP dietary supplementation compared to the control group [17]. The most important finding of our current study is a significant increase in PON1 enzyme activity after LGW consumption (**Table 2**). The results of the study conducted by Abdel-Wahhab et al. indicate the effect of goat WP on the antioxidant status of rats with thianilic acid-induced hepatotoxicity [6]. After supplementation with goat WP, PON1 enzyme values increased significantly while MDA concentrations decreased significantly [6]. The results of our study may indicate a beneficial LGW antioxidant effect, which is primarily realized by increased activity of PON1. Additionally, the observed parallel increase of SHG level, PON1 activity, and PAB can be regarded as a measure of the prooxidative-antioxidative state. This could be at first sight unexpected, but in fact, has a strong scientific background. In a study conducted by Halliwell et al., the best antioxidants have been shown to have a mild pro-oxidative effect, triggering a potent antioxidant response [26].

As our results indicate elevated liver protein synthesis, as well as increased PON1 enzyme activity, we additionally wanted to examine the HDL particle functionality by analyzing the distribution of individual subclasses before and after LGW consumption. To the best of our knowledge, this is the first study to examine the distribution of HDL particles after consuming LGW. The results of the Framingham Heart Study demonstrating the association of lowered HDL-c concentrations with an increased risk of CVD have been consistent and widely confirmed [12]. In our study, there was no change in the concentration of HDL-c (**Table 1**). A study by Voight et al. confirmed that biomarkers of HDL particle function are crucial determinants of its atheroprotective properties, rather than the HDL-c concentration [27]. Although the results of our study did not show statistically significant changes in the distribution of HDL subclasses before and after LGW consumption, a trend towards a higher proportion of HDL3c subfraction after supplementation was observed (**Table 3**). Albers et al. indicated that HDL 3c particles are primarily responsible for the reverse relationship between HDL-c and cardiovascular risk [28]. On the other hand, sdLDL represents the most atherogenic lipoprotein particle [16]. Additionally, the results of our study have shown a trend toward decreased relative proportion of sdLDL particles and increased LDL particle dominant diameter, which may indicate lipid profile improvement. Based on our results, we can hypothesize that these changes might have favorable effects on human health.

In conclusion, the findings of the present study have shown that increased protein synthesis, increased PON1 enzyme activity and shift toward nascent HDL forms, could lend support to the hypothesis that LGW has a positive effect on synthetic liver function and CVD risk reduction. This result may also be partially confirmed by lower MDA values after supplementation. Our findings suggest that LGW protects against free radicals by stimulating the body's antioxidant defense mechanisms and promoting a mild prooxidative effect.

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Kardiometabolički i antioksidativni efekti suplementacije liofiliziranom kozjom surutkom

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Kratak sadržaj

Dobro su poznati pozitivni nutritivni i zdravstveni efekti mleka i mlečnih proizvoda. Danas ovi proizvodi čine 20% do 30% globalne potrošnje hrane. Proteini surutke imaju značajnu anaboličku biološku funkciju i kardioprotektivnu ulogu. Povećana koncentracija holesterola sadržanog u lipoproteinskim česticama visoke gustine (HDL), povećana aktivnost enzima paraoksonaze 1 (PON1) i smanjen relativni udeo malih gustih lipoproteinskih čestica niske gustine (sdLDL) smanjuju rizik od kardiovaskularnih bolesti (KVB). Ova longitudinalna studija je uključila 10 zdravih dobrovoljaca. Svi učesnici su tokom dva meseca konzumirali liofilizovanu kozju surutku (LKS) (Koza Nostra®) (3 g dnevno). Koncentracije osnovnih biohemijskih parametara merene su rutinskim metodama. Koncentracije parametara oksidativno-stresnog statusa merene su spektrofotometrijskim metodama. Aktivnost enzima PON1 u serumu određena je kinetičkom metodom uz korišćenje paraoksona kao supstrata. Subfrakcije lipoproteina razdvojene su gradijent-gel elektroforezom. Koncentracija uree se značajno smanjila ($p<0,05$), a primećen je trend ka višim koncentracijama albumina nakon LKS suplementacije. Primećen je značajan porast vrednosti prooksidativno-antioksidativnog balansa ($p<0,05$) i aktivnosti enzima PON1 ($p<0,05$), kao i trend ka nižim koncentracijama malondialdehida nakon suplementacije. Uočen je trend ka većem relativnom udelu HDL 3c subklasa i porastu dijametra LDL lipoproteinskih čestica. Rezultati ove studije pokazali su da povećanje sinteze proteina, aktivnosti enzima PON1 i udela HDL 3c subklasa mogu ukazati da LKS ima pozitivan uticaj na sintetsku funkciju jetre i smanjenje rizika za razvoj KVB. Naši rezultati ukazuju da LKS štiti od oksidativnog stresa stimulišući antioksidativne odbrambene mehanizme organizma i podstičući blagi prooksidativni efekat.

Ključne reči: *liofilizirana kozja surutka, prooksidativno-antioksidativni balans, paraoksonaza 1, HDL, kardiovaskularne bolesti.*