Revista Brasileira de Nutrição Esportiva
ISSN 1981-9927 ***versão eletrônica***

Periódico do Instituto Brasileiro de Pesquisa e Ensino em Fisiologia do Exercício

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SYSTEMATIC REVIEW ABOUT THE EFFECT OF WHEY PROTEINS ON THE RENAL FUNCTION OF RATS AND MICE IN RELATION TO CREATININ, UREIA, PROTEINURIA, AND RENAL GLOMERULES AND TUBULES

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ABSTRACT

Introduction: Diets with whey proteins raise the glomerular filtration rate in an acute or chronic manner as well as increase the concentration of creatinine, urea and serum uric acid in the urine. Aim: The aim of the study was to perform a systematic review on the effect of whey protein consumption on the renal function of rats and mice in relation to the biomarker's creatinine, urea, proteinuria and tissue histological changes in the glomeruli and renal tubules. Materials and methods: Systematic review in Lilacs, Scielo.org, Dialnet, Pubmed, Web of Science databases, with constant search terms in the VHL/WHO health descriptors. Results: Twenty-eight papers were selected. Discussion: from the analyzed studies, it is observed that there are still few that directly address the relationship between the variables whey proteins and renal function/damage; the majority of studies have addressed renal function biomarkers and / or histological analyzes of the kidney, and do not present significant changes in the use of whey protein supplementation, both acute and chronic. Conclusion: The studies show that the use/supplementation with whey proteins does not significantly alter the biomarkers creatinine, urea, proteinuria and tissue histological alterations of the glomeruli and renal tubules, thus, renal function.

Key words: Whey Proteins. Creatinine. Urea. Proteinuria. Renal damage.

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RESUMO

Revisão sistemática sobre o efeito de whey proteins na função renal de ratos e camundongos em relação a creatinina, ureia, proteinuria e nos glomérulos e túbulos renais

Introdução: Dietas com whey proteins elevam a taxa de filtração glomerular de forma aguda e/ou crônica, bem como no aumento da concentração de creatinina, ureia e ácido úrico sérico na urina. Objetivo: o objetivo do estudo foi realizar uma revisão sistemática sobre o efeito do consumo de whey proteins na função renal de ratos e camundongos em relação aos biomarcadores creatinina, ureia, proteinúria e alterações histológicas teciduais nos glomérulos e túbulos renais. Materiais e métodos: Revisão sistemática nas Bases de Dados Lilacs, Scielo.org, Dialnet, Pubmed, Web of Science, com termos de busca constantes nos descritores em saúde da BVS/OMS. Resultados: vinte oito artigos foram selecionados. Discussão: a partir dos estudos analisados, observa-se que ainda são escassos os que abordam diretamente a relação entre as variáveis whey proteins e função/dano renal; a maioria dos estudos abordaram biomarcadores de função renal e/ou análises histológicas do rim, e não apresentam alterações significativas na utilização da suplementação de whey proteins, tanto em caráter agudo, quanto crônico. Conclusão: Os estudos apontam que a utilização/suplementação com whey proteins não altera de forma significativa os biomarcadores creatinina, ureia, proteinúria e nas alterações histológicas teciduais dos glomérulos e túbulos renais, dessa forma na função renal.

Palavras-chave: Whey Proteins, creatinina, ureia, proteinúria, dano renal.

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ISSN 1981-9927 ***versão eletrônica***

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INTRODUCTION

Whey Proteins and Renal Function

Serum Milk protein as known as Whey proteins can be extracted from the aqueous portion of the milk during the cheesemaking process, accounting for about 20% of the protein content of the cheese and it already has nutritional aspects widely studied over the last decades (Krissansen, 2007; Haraguchi, Pedrosa and Paula, 2009).

Whey proteins is consisted basically by four protein portions: β-lactoglobulin (45-57%), α-lactalbumin (15-25%), bovine serum albumin (10%) and immunoglobulins (10%) (Haraguchi, Abreu and Paula, 2006).

It is also known that nowadays whey proteins is regarded as a fast absorbing protein and which can be correlated with the stimulation of muscle protein synthesis (Aparício et al., 2011a, Macedo, 2018; Marques, 2018).

Fischborn (2012) classifies whey proteins as an effective anabolic supplement because its amino acid profile is very similar to that of skeletal muscle proteins, thus providing almost all amino acids in a similar proportion to that.

Another factor that contributes to its anabolic status is the action of whey proteins on the release of hormones responsible for the process of muscular anabolism, such as insulin, which favors the uptake of amino acids into the cell (Haraguchi, Abreu, Paula, 2006).

Studies Layman (2003a), Layman et al. (2003b), Layman and Baum (2004) and a meta-analysis by Santesso et al., (2012) show that diets with higher ratio protein/carbs are more efficient for the control of blood glucose and of post-prandial insulin, thus favoring the reduction of body fat and the preservation of muscle mass during the slimming process .

Face to many benefits, the consumption of whey proteins with purity of 80% or even higher than 90% has become increasingly common among the population (Cribb, 2005).

However, studies have shown that diets with increased protein content raise the glomerular filtration rate (GFR) acutely (Vibert et al., 1987; Cahn et al., 1988; Simon et al., 1998) and also after chronic consumption (Skov et al, 1999; Frank et al, 2009; Juraschek et al, 2013), as well as increase the concentration of urea and uric acid serum and urine in individuals with normal renal function (Frank et al., 2009).

Due to that, the effects with high doses of whey proteins need to be checked for any changes that may occur and may impair renal function (Martin et al., 2005; Jia et al., 2010, Santesso et al., 2012), due to increased glomerular filtration rate and renal acid load (Aparicio et al., 2011b; Palatini, 2012; Goroya, Wesson, 2012).

Creatinine

In the context of the laboratory evaluations to verify the renal function, as more used procedure is the measurement of glomerular filtration rate (GFR), which can be performed by standard-gold considered methods which involve injection of drugs and their excretion , but in routine clinical and animal testing, GFR is generally estimated by methods that rely on urine/serum creatinine and 24-hour urine (Medeiros et al., 2009).

Obtained as a residual product of the creatine and phosphocreatine reaction, creatinine is an amino acid derivative of 113 Daltons, derived from muscle metabolism and meat intake (Stevens, Levey, 2005). The production and release of creatinine by the muscle are practically constant and its generation is directly linked to the amount of muscle mass (Rule et al., 2004).

Creatinine may have its values altered because it is not simply a product of the biochemistry of muscle tissue, but influenced by function and the same, as well as physical exercise, diet and health status (Ross et al., 1998).

Thus, to watch the progression of renal disease, the assessment of endogenous creatinine clearance (DEC) or creatinine clearance , measured in 24-hour urine, although overestimating GFR and depending on mass muscle is an alternative for more reliable evaluation compared the plasma creatinine concentrations and because of this remains one of the most commonly used markers for assessment of renal function (Rosner and Bolton, 2006).

Urea

Another important biomarker of renal function is urea. Being the urea, the main nitrogen metabolite derived from the degradation of proteins by the organism, 90%

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is excreted by the kidneys and corresponding to approximately 75% of the excreted non-protein nitrogen.

On the other hand, just as creatinine is, the urea has good clinical utility, due to the serum urea/serum creatinine ratio may indicate several pathological states. This ratio in high amounts with creatinine normal values may indicate processes that lead to decreased renal blood flow, protein intake increased or gastrointestinal bleeding, already creatinine above the normal range signals denoting post-renal obstructive processes, such as tumors or stenosis of the urinary tract.

Serum urea/ serum creatinine ratio below normal may indicate pathologies such as acute tubular necrosis, low protein intake, reduction of urea synthesis due to hepatic insufficiency or food deprivation (Rule et al., 2004).

Proteinuria

A widely used parameter in the evaluation of kidney function and injury, proteinuria is a generic term that related to the quantification of urinary excretion of albumin and any other type of protein, which can be evaluated by the 24 hour microalbuminuria technique, 24-hour proteinúria (24hr), by the albumin/ creatinine ratio in an isolated urine sample or by the protein / creatinine ratio (rP/C) (Cholongitas et al., 2010; Levey et al., 2002).

More than 200 different types of proteins may be present in the urine, and those with molecular weights less than 60 kDa are freely filtered by the glomeruli and then reabsorbed in the proximal tubules. Histological lesions in these structures can create conditions that increase the amount of proteins in the glomerular filtrate or decrease tubular reabsorption, leading to proteinuria (Vidigal, 2009).

In general, when there glomerular proteinuria, the electrophoretic pattern of urinary proteins are quite similar to that found in plasma, characterized by the loss of albumin and proteins of similar size (such as antithrombin pre-albumina, a1-acid glycoprotein, transferrin and a1-antitrypsin) and protein (a2-macroglobulin and lipoprotein b) when the lesion is aggravated.

In turn, tubular proteinuria is characterized by the loss of low molecular weight proteins, such as hemoglobin, and Bence-Jones' protein, as these pass freely through the glomeruli but are not reabsorbed in the proximal tubules, unlike post-renal proteinuria, where there is production of proteins through the lower urinary tract due to tumors or inflammation (Johnson, 2008).

Thus, the purpose of this study was to perform a systematic review on the effect of the consumption of whey proteins on the renal function of rats and mice in relation to the biomarkers as creatinine, urea, proteinuria and tissue histological alterations in the glomeruli and renal tubules.

MATERIALS AND METHODS

Conceptualization

For this study we used the revision concepts proposed by Thomas, Nelson and Silverman (2012), and the search followed procedures proposed by Navarro and Navarro, (2012).

Procedures

This review was based on the publications listed below and we present their respective electronic addresses: Lilacs (http://lilacs.bvsalud.org); Scielo.org (http://scielo.org); Dialnet (https://dialnet.unirioja.es/); PubMed (http://www.ncbi.nlm.nih.gov/ pubmed); Web of Science (http://appswebofknowledge.ez14.periodicos.capes.gov.br/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch&SID=5ECdOJq7NG1DWiIA62D&preferencesSaved=).

In order to start the study, we verified the adequacy of the following terms: whey proteins; renal; kidney; creatinine; urea; proteinuria; histology; morphology; damage; inj ury, in the Health Sciences Descriptors (DeCS) of the Virtual Health Library (BVS).

We then quantified the extent of these terms in each database, reaching an expressive result totaling 17,165,147 possible studies for this narrative review, as shown in chart 1.

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ISSN 1981-9927 ***versão eletrônica***

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Chart 1 - Quantitative results of the search of terms.

Search of term	Lilacs	Scielo. org	Dialnet	Pubmed	Web of Science
Whey Proteins	116	210	351	16.733	1.7071
Renal	16.799	9.261	8.544	634.496	612.450
Kidney	11.891	5.549	2.390	800.441	461.969
Creatinine	1.778	1.711	1.261	120.542	91.274
Urea	1.458	2.652	1.667	165.918	117.143
Proteinuria	2.029	582	426	57.648	33.289
Histology	12.190	2.105	847	4.747.215	110.640
Morphology	15.888	10.745	5.341	4.724.450	785.407
Damage	6.451	9102	9.392	487.025	926.233
Injury	19.299	6.976	4.789	1.264.275	819.128
Partial total	87.899	48.893	35.008	13.018.743	3.974.604
Total	17.165.147				

After the quantitative confirmation of the search, the procedures were refined with the combination of two terms, namely: Whey Proteins + Renal; Whey Proteins + Kidney; WheyProteins + Creatinine; Whey Proteins + Urea; Whey Pr oteins + Proteinuria resulting in a total of 1,327 articles, see chart 2.

Chart 2 - Quantitative results of the search of terms combined.

Search of terms combined (2 terms)	Lilacs	Scielo.org	Dialnet	Pubmed	Web of Science
Whey Proteins + Renal	4	4	4	131	50
Whey Proteins + Kidney	4	3	5	242	73
Whey Proteins + Creatinine	5	4	3	34	29
Whey Proteins + Urea	5	11	5	414	282
Whey Proteins + Proteinuria	1	1	0	13	0
Total	1.327				

In followed by three terms : Whey Proteins + Renal + Creatinine; Whey Proteins + Renal + Urea; Whey Proteins + Renal + Proteinuria; Whey Proteins + Renal + Histology; Whey Proteins + Renal + Morphology; Whey Proteins + Renal + Damage; Whey Proteins + Renal + Injury; Whey Proteins + Kidney + Creatinine; Whey Proteins + Kidney + Urea; Whey Proteins + Kidney + Proteinuria; Whey Proteins + Kidney + Histology; Whey Proteins + Kidney + Morphology; Whey Proteins + Kidney + Damage; Whey Proteins + Kidney + Injury ;Whey Proteins + Renal + Creatinine; Whey Proteins + Renal + Urea; Whey Proteins + Renal + Proteinuria; Whey Proteins + Renal + Histology; Whey Proteins + Morphology; Whey Proteins + Renal + Damage; Whey Proteins + Renal + Injury; resulting in a total of 360 articles , as chart 3.

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Chart 3 - Quantitative result of the search of three terms combined.

Search of terms combined (3 terms)	Lilacs	Scielo.org	Dialnet	Pubmed	Web of Science
Whey Proteins + Renal + Creatinine	4	3	0	10	7
Whey Proteins + Renal + Urea	2	2	1	12	8
Whey Proteins + Renal + Proteinuria	1	1	0	4	0
Whey Proteins + Renal + Histology	0	0	0	32	0
Whey Proteins + Renal + Morphology	0	0	2	32	1
Whey Proteins + Renal + Damage	1	0	1	7	5
Whey Proteins + Renal + Injury	1	1	1	9	1
Whey Proteins + Kidney + Creatinine	4	2	1	8	5
Whey Proteins + Kidney + Urea	2	2	1	13	5
Whey Proteins + Kidney + Proteinuria	1	1	0	6	0
Whey Proteins + Kidney + Histology	0	0	0	60	1
Whey Proteins + Kidney + Morphology	0	0	2	60	2
Whey Proteins + Kidney + Damage	1	0	1	9	4
Whey Proteins + Kidney + Injury	1	1	1	13	4
Total	360				

From the sum of the results of Table 2 and Table 3, there are a total of 1687 studies, to which the inclusion and exclusion criteria were applied for subsequent observations of the variables to be considered in the scientific publications according to the purpose of this review.

Inclusion criteria

The inclusion criteria established for this review are: access through electronic, open access, full text available, written in Portuguese and/ or English and/ or Spanish and with mice and or mice as experimentais samples.

Exclusion Criteria

Were excluded from this review, theses texts, essays, editorials, newspaper texts and repeated items in different bases, systematic reviews, cell culture studies, human studies, animal studies (except rats and mice), studies which not evaluated the use of whey proteins, and the effect on creatinine in urea, proteinuria in tissue histologic changes in glomeruli and renal tubules.

Thus, out of a total of 1,687 articles reviewed, excluded 1,659 articles, and thus 28 articles remained, according to the flowchart of the study design.

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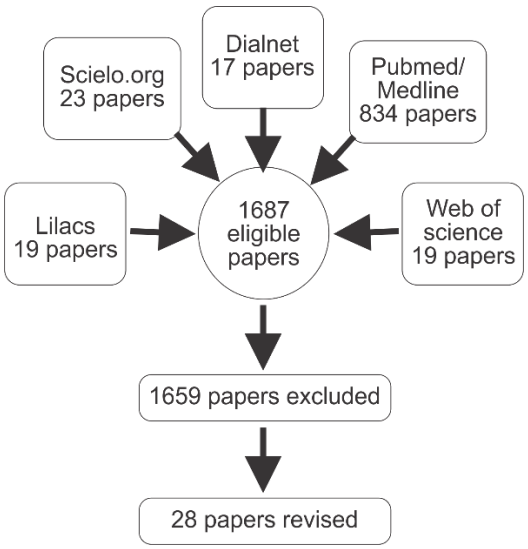

Figure 1: Flowchart - Study design.

All the terms and criteria of the procedures for searching for articles, reading and analyzing the variables in the articles, assigning the index to the Galna's scale for the articles and the wording of the presented text are agreed among the researchers of this review study.

We present the description of the 28 articles qualified for this review, obeying the following descriptive procedures: author(s) and date, study objective, sample size and its characteristics, such as, lineage, age and body mass, the experimentais procedures adopted, then the results and conclusion of the study.

RESULTS AND DISCUSSION

ACUTE SUPPLEMENTATION EFFECTS OF WHEY PROTEINS

- Acute effects of cow's milk supplementation

Nagai et al., (2011) performed an immunohistochemical evaluation from milk aspiration. For this purpose, 40 wistar rats with 10 weeks of life divided into 2 groups (the authors did not report the mean of the body mass in grams of the sample). In one group, 20 rats received 0.5 ml of cow's milk intratracheally, and in the remaining 20 rats, 1.0 ml of cow's milk was given intratracheally. In both groups, 2 rats were euthanized immediately after, 1, 3, 6, 12 hours the administration of cow's milk and also 1, 2, 4, 7 and 14 days after and the organs (lung, liver, kidney and spleen) were removed for further immunohistochemical analysis.

For immunohistochemical analysis, sections 2-3 mm thick were prepared and immunostained with lactalbumin-anti-human antibody and tissue specimens containing at least one minimal substance showing a positive antibody reaction were considered positive.

As a result of the research, milk aspirated into the alveoli was identified immunohistochemically up to 2 days after inoculation, neutrophil infiltration was not observed in any rat and no milk remained in the alveoli 4 days after instillation or later. In both groups, a positive reaction against lactalbumin-anti-human antibody was observed on the inner side of the renal tubules, 1 to 3 hours after instillation, and the amount of ingested milk had little effect on the pathological findings.

Macrophages containing vesicles that showed a positive reaction against the antibody appeared in the red splenic part 3 hours after inoculation and persisted up to 14 days after inoculation, regardless of the volume of milk, however, when the amount of inoculated milk was lower (0.5 ml), reactivity tended to become smaller in the histological sections of the spleen obtained 7 and 14 days after inoculation .

No positive immunohistochemical reaction against lactalbumin-anti-human antibody was observed in the liver in both groups.

From these results, the study can state that although the results in rats can't be

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applied directly in human cases, the detection of milk aspirated in organs other than the lungs is a clear evidence of intravital aspiration of milk and the immunohistochemical examination of the spleen using antibodies against milk components may be useful for the pathological diagnosis of anterior or recurrent aspiration of milk.

This study allows new horizons for experimental research that correlates either the intratracheal aspiration of milk or its components (such as whey proteins) and their possible deleterious effects on the organism, as well as later on the standardization of laboratory procedures aimed at identifying the occurrence of such phenomenon, since in humans in general occurs in individuals not yet able to communicate.

- Acute effects of supplementation of whey proteins and captopril

Costa et al., (2005) evaluated the effects of intraperitoneal administration of hydrolyzed whey proteins on systolic blood pressure (SBP) and handling of renal sodium in spontaneously hypertensive rats (SHR) weighing in grams between 270 and 300 (the author did not report age of mice).

To evaluate the dose effect of hydrolyzed whey proteins on SBP compared to control (NaCl 0.15 M) and administration of captopril, the rats received non-cumulative intraperitoneal injections in a 1 mL volume containing different doses of hydrolyzed whey proteins (0.25, 0.5, 0.75 and 1.0 g / kg).

Systolic blood pressure was measured 2 hours later in conscious and contained rats (n = 8 for each dose or experimental group). For renal function studies, the rats were weighed and lodged individually in metabolic cages, with admission of 60 mmol LiCl / 100 g body weight per gavage 14 hours prior to renal testing.

After overnight fasting, each unanesthetized rat received water by gavage (5% of body weight), followed by a second gavage of the same volume 1 hour later. Twenty minutes after the second gavage, according to each group, 0.15 M NaCl (controle), 1.0 g whey proteins / kg body weight or 10 mg captopril / kg body weight (the two last dissolved in 1 mL of 0.15 M NaCl) were administered intraperitoneally, after which the urine was collected over a period of 2 hours. At the end of the experiment, blood samples were collected by cardiac puncture and urine and plasma samples were collected for analysis and study data demonstrated that intraperitoneal administration of hydrolyzed whey proteins in a volume of 1 ml dose decreased systolic blood pressure in SHR rats 2 hours after administration at doses of 0.5 g / kg (p=0.001) and 1.0 g / kg (p=0.0018).

Creatinine clearance decreased significantly (p=0.0084) in the treated group with hydrolyzed whey protein compared to the treated group with sodium chloride and treated group with captopril.

Similarly, fractional potassium excretion in rats treated with hydrolyzed whey proteins was significantly lower (p=0.0063) than in control and treated group with captopril.

Intraperitoneal administration of 1.0 g of whey proteins hydrolyzed per kilogram also reduced fractionated sodium excretion compared to rats treated with 0.15 M sodium chloride and captopril, respectively (p=0.033).

Thus, this study demonstrates a decrease in systolic blood pressure in SHR rats following the administration of hydrolyzed whey proteins associated with an increase in sodium reabsorption in the tubules, despite an in vitro inhibitory activity of the angiotensin-I converting enzyme.

Finally, the nature of the study is important because it opens the way for the possibility of using non-medicated substances (in this case whey proteins) in the treatment of chronic non-communicable diseases, such as hypertension, focusing on the use of whey proteins outside its anabolic and hypertrophic locus that are already further studied , thereby allowing an exploration of other possible effects of its use.

CHRONIC EFFECTS OF WHEY PROTEINS SUPPLEMENTATION

- Chronic effects of whey protein supplementation

Haraguchi et al., (2009) to evaluate the influence of serum proteins on liver enzymes, lipid profile and bone formation of rats hypercholesterolemic. For this, we used 32 adult Fisher rats with average weight in grams of 209 (the author did not report the age of the rats), were divided into 4 groups:

1 - Group C with standard diet (n = 8);

2 - Group H with hypercholesterolemic diet (n = 8);

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3 - OS group with standard diet and serum proteins (n = 8);
4 - PSH group with hypercholesterolemic diet and serum proteins (n = 8).

Each group received their respective diet and water ad libitum for 8 weeks. They were dosed by colorimetric and enzymatic methods using commercial kits: total proteins, albumin, urea, creatinine, aspartate aminotransferase (ASP) activity, total cholesterol alanine aminotransferase (ALT), high density lipoproteins (HDL cholesterol) and triglycerides.

The enzymatic activity of paraoxonase (PON) was measured based on the rate of hydrolysis speed of phenylacetate and the concentrations of sulfhydryl were determined using the Ellman's reagent.

The femur was weighed with posterior gauging of the length and diameter using a pachymeter.

The rats that received a hypercholesterolemic diet (H and PSH) consumed less food but presented greater weight gain.

However, hypercholesterolaemic diets promoted an increase in total cholesterol concentrations and atherogenic fractions, as well as a reduction in HDL cholesterol concentration.

These also caused an increase in liver weight (ALT) levels (AST), alkaline phosphatase, total protein concentration and a decrease in albumin concentration, but the kidney weight was similar between groups as well as the concentration of urea, contrary to the creatinine concentration that was increased by the hypercholesterolemic diet (the author does not report the value of p, only of significance value).

The PS and PSH diets generated significantly larger femur, heavier females with a larger diameter than the diets C and H (the author does not report the p value, only the significance level).

In this sense, it was observed that serum proteins did not present a hypocholesterolemic effect and that they prevented the occurrence of changes in the indicative parameters of hepatic and renal functions.

Finally, the data also suggest that diets containing whey proteins positively affected bone formation, when compared to diets containing casein, hypercholesterolemic or not.

Aparicio et al., (2011a) used 32 Wistar rats with initial weight in grams of 150 ± 8 (the author did not report the age of the rats) to study the effects of resistance training and metabolic acidosis in renal and liver hypertrophy.

For this, rats were divided into four experimental groups (n = 8 / group) that received for 90 days normoproteic (10% protein) or hyperprotein (45% protein) enriched with whey proteins, with and without resistance training. The groups of experimental exercises performed a strength training protocol on a treadmill with loads in a bag tied to the tail.

The training was performed on alternate days, at a constant speed of 40 cm/s throughout the experimental period (12 weeks). After 90 days of experimental design, rats were euthanized for analysis.

The concentrations of urea, liver and kidney weight, urinary parameters of metabolic acidosis and liver profile were analyzed. After the analysis, the adipose tissue deposits were observed after the consumption of the hyperproteic diet and the plasma concentrations of cholesterol and triglycerides were reduced (-25.7% and -41.6%, respectively).

Likewise, the consumption of a hyperproteic diet caused a significant increase in hepatic and renal weight ($p<0.001$) and metabolic acidosis (urinary hypercalcemia and hypocitraturia, acidification of urinary pH and high plasma urea concentrations) (the author does not report the value of p, only that of significance). resistance training, however, showed a particularly significant protective effect in reducing liver weight, kidneys, plasma urea concentrations, and plasma and hepatic triglycerides ($p<0.001$).

Regarding the results found, 12 weeks of resistance training reduced metabolic acidosis and hepatic and renal hypertrophy caused by consumption of a diet with high protein in rats, while improving the plasma and hepatic lipid profile.

In another study by Aparicio et al., (2011b) the effects of ingestion of whey proteins and resistance training on renal, bone and metabolic parameters in rats were verified. For this, we used 96 young male rats wistar with an initial weight 150 ± 8 grams were divided into 4 groups with 24 rats in each group:
1 - Normal protein sedentary group (10% protein);
2 - Resistance training group with normal proteins;

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3 - Sedentary group with high protein (45% proteins);
4 - Resistance training group with high protein.

Each group was divided into three subgroups (n = 8 each) to which they were euthanized at 1, 2 and 3 months after the beginning of the experiment.

Bone and renal ashes were prepared by calcination at 5008 ° C until a constant weight and the calcium content was determined by atomic absorption spectrophotometry using a spectrophotometer.

Since urinary pH was analyzed using a bench pH meter, urinary citrate was measured using a commercial kit and plasma urea, total cholesterol, TAG and HDL-cholesterol were measured using an autoanalyzer.

The experimental group was trained following a protocol of resistance in treadmill with weights in a bag tied with a cord in the tail, exercising on alternate days (3-4 sessions/week), with a constant speed of 40 cm/s throughout the experimental period (4, 8 or 12 weeks).

As a result of the research, food intake was higher in the normal protein groups when compared to the high protein groups ($p<0.01$), and no significant differences were observed between the sedentary and exercise groups.

The final body weight was lower in the training and normal protein groups when compared to the sedentary groups with high protein, especially after 2 to 3 months of intervention ($p<0.01$).

However, plasma cholesterol concentrations were the lowest values for the high protein groups compared to the normal proteins groups ($p<0.001$), as well as for the groups trained in relation to the sedentary groups ($p<0.01$ in the first 2 months and (the author does not report the value of the p, only the meaning) after the third month.

There was also a significant interaction between diet and training in plasma triglyceride concentrations (the author does not report the p value, only that of significance), with a greater reduction in plasma triglycerides derived from training in the high protein groups when compared with the groups with normal protein.

HDL concentrations were considerably lower in the high-protein groups ($p <0.001$) when compared to the normal protein groups, whereas the differences between the exercise and the sedentary groups and the buffering action of the resistance training on dietary proteins were especially evident as plasma TAG concentrations ($p<0.003$ in the 90-day euthanized group).

In relation to the percentage of white fat (related to carcass weight), it was lower in the high protein groups when compared to the normal protein groups, especially after the third day (the author did not report the p value, only the significance value) and in the groups compared to sedentary groups, with greater effect in the second and third month.

Finally, the consumption of diets with high protein increased the kidney weight ($p<0.001$), urinary volume ($p<0.001$) and acidity, as well as the excretion of Ca urine, with a combined reduction in urinary citrate excretion (the author did not report the value of p, only of significance) and no apparent deleterious effect on bone mineral content was found.

From this study it can be inferred that resistance training had a protective action against changes in renal health status and some metabolic parameters and that consumption of high protein diets caused changes in renal health status and some metabolic parameters but did not seem to affect the bone parameters.

In Study by Chen et al., (2014) verified that whey proteins improve exercise performance in mice trained (the authors did not report the linage). For this they used 40 male mice at 4 weeks of age that were divided into four groups with 10 mice per group:
Group 1 - sedentary control that received vehicle by oral (SC);
Group 2 - supplementation of whey protein (SC WP + - 4.1 g / kg);
Group 3 - trained group that received vehicle by oral (ET);
Group 4 - trained group with supplementation of whey protein (ET + WP - 4.1 g / kg).

The ET and WP mice were submitted to resistance training of swimming for six weeks, 5 times a week and were influenced by the body variables in the biochemical parameters at the end of the experiment by the grip strength and by the time of exhaustive swimming.

As a result of the research , the Grupo ET significantly decreased the final body weight ($p=0.0283$), muscle ($p=0.0038$), and albumin concentration ($p<0.0001$), total protein ($p<0.0001$), blood urea nitrogen ($p=0.0015$), creatinine ($p=0.0468$), total cholesterol ($p=0.0045$) and triacylglycerol ($p<0.0001$).

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In contrast, the ET group significantly increased the relative grip strength (p= 0.0005) and absolute (p<0.0001); relative weight of brown adipose tissue (p<0.0001) and heart (p=0.0040); and the concentration of aspartate amino transferase (p<0.0001), alanine amino transferase (p=0.0077), alkaline phosphatase (p<0.0001), lactate dehydrogenase (p<0.0001), creatine kinase (p<0.001) and total bilirubin (p<0.0001).

In addition, whey proteins supplementation significantly enhanced the rate of resistance (p=0.0229) and significantly increased the grip strength (p <0.0001) and as albumin concentrations (p=0.0035) and total protein (p=0.0002). Thus, the study reported that whey protein supplementation improved body composition, effects on biochemical assessments in mice and can be an effective ergogenic aid in aerobic exercise training.

In study by Franzen et al., (2016) it was studied the effect of whey proteins on blood glucose, triglycerides and body weight control in Wistar rats. For this, 24 rats with 80 days of age and weight in 200 to 250 were divided into 3 experimental groups, all groups receiving their diets for 8 weeks:

1 - CTL group - Control with standard diet (n=8) composed of 55% carbohydrates, 22% protein, 4.5% lipids and other constituents;

2 - WPD Group - Diet with low dose of whey proteins concentrate (n=8), with the standard diet enriched with 10% of the same.

3 - CAF Group - Cafeteria diet (n=8) consisting of about 60% carbohydrates, 20% lipids, 15% proteins, and 5% of other constituents, having 8 weeks as the experimental period.

The values of urea, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), glucose, triglycerides, total cholesterol and fractions as well as body weight, epididymal fat and Lee's Index were measured.

The results presented by the study showed that the CAF group had a more expressive weight gain over the initial weight (p<0.001) than the WPD and CTL groups and that the CAF diet had significant weight gain compared to CTL (p< 0.01) and WPD (p<0.001).

Regarding the Lee's Index, there was no increase in the WPD group. On the other hand, the plasma glucose values in the CAF group had higher plasma glucose values than the baseline and the WPD group showed a reduction and when the experiment was concluded between the groups , the WPD group presented a reduction in plasma glucose values when compared to the CTL group and the CAF group presented an increase in these values in relation to the WPD group (the author does not report the value of p, only that of significance).

In the case of triglyceride values, when comparing the final treatment results between groups, the WPD group had the triglyceride values reduced in relation to the CTL group (the author does not report the triglyceride value, only the significance value).

In addition, the CAF group presented greater epididymal adiposity than the CTL group (p<0.01) and WPD (p<0.001).

Regarding the values of urea, creatinine, AST and ALT, the differences between baseline and end-of-treatment values were not found in any experimental group or between groups.

From such results, may be inferred que Low doses of whey proteins concentrate are effective on the reduction of blood glucose, triglycerides, control body weight, pointing and opening space for the possibility to be used as nutritional alternative for Obese Patients, overweight or normal and the prevention or control of metabolic disorders and obesity.

Hegazy et al., (2016) studied the renoprotective effect of lactoferrin against acute kidney injury induced by chromium in rats through the inhibition of IL-18 (interleukin-18) and IGF-1 (insulin-like growth factor-1). For this, 36 male Wistar rats with body mass in grams of 200 to 250 (age not informed by the authors) were used. They were divided into 6 groups (n = 6 each), being:

Group 1 - treated with saline solution;

Group 2 - treated with lactoferrin (200mg / kg / day);

Group 3 - treated with lactoferrin (300mg / kg / day);

Group 4 - treated with saline solution and with nephrotoxicity induced by single injection of DPC (potassium dichromate);

Group 5 - treated with lactoferrin (200mg / kg / day) and with nephrotoxicity induced by single injection of DPC;

Group 6 - treated with lactoferrin (300mg / kg / day) and with nephrotoxicity induced by single injection of DPC.

All groups were treated for 14 days and those with induced nephrotoxicity were performed at the end of this period. A procedure, 24 hours after the injection of PDC, blood samples were collected from rats of all

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groups via retro-orbital vein under light ether anesthesia and the serum was used to estimate serum concentrations of urea, creatinine, and protein using specific diagnostic kits.

After That, the rats were euthanized by cervical dislocation and the two kidneys Were removed, weighed and homogenized and subsequently stored at -20 °C. Kidney markers of IL-18, IL-4, nuclear factor kappa B (NFκB), IGF 1 and the phosphorolytic form of the O1 protein (FoxO1) were also evaluated using specific diagnostic kits and the number of mRNA copies of interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) were evaluated by quantitative RT-PCR in RNA extracts in renal tissue homogenates of all groups.

For histological analysis, 5μm thick sections were stained with hematoxylin and eosin, where 10 random microscopic fields (x40) per section were examined for evaluation of histopathological lesions. The tubular damage was classified as follows:

Grade 1 - very mild damage with swelling of renal tubular epithelium;

Grade 2 - mild damage with granular degeneration of the renal tubular epithelium;

Grade 3 - moderate damage with granular and / or vacuolar degeneration of the renal tubular epithelium with the presence of a few intracytoplasmic hyaline drops;

Grade 4 - severe damage with tubular necrosis with presence of intraluminal renal cylinders and interstitial inflammation.

Demonstration of antigen-immunoreactive cell proliferation (PCNA) was performed by counting in three random microscopic fields per group.

The results presented by the studies demonstrated that the administration of lactoferrin had no effect on the normal biomarkers of renal function in rats, however, there was a significant increase (the author does not report the p value, only that of significance) in serum concentrations of urea, creatinine and total protein were observed in rats treated with PDC compared to those in group 1. On the oxidative stress, normal concentrations of these biomarkers were observed in control groups treated with lactoferrin.

In continuity, no significant difference was detected between the mean concentrations of mRNA copies for IFN-γ in the groups studied in this experiment. In histopathology, renal sections of normal and lactoferrin-treated rats showed normal histological structures with glomeruli and normal renal tubules; in the groups treated with PDC, there were variable and severe histopathological changes, such as degenerative, inflammatory and hyperplastic conditions.

Finally, in the immunohistological results, PCNA-positive renal tubular cells and proliferating mononuclear cells in the renal interstitial tissue and periglomerular area in the PDC-treated group were more abundantly observed in comparison to the groups pretreated with lactoferrin, but without difference between them.

From these results, the study states that oxidative stress and inflammation play important roles in PDC-induced acute kidney injury and that IL-18 involvement which could be one of the most important mediators of renal tissue damage and induced tubular injury by the same.

In addition, the study showed the involvement of IGF-1, which is known to play an important role in pathogenic renal tissue hypertrophy, where, however, pretreatment of lactoferrin rats produced protective effects against PDC-induced acute nephrotoxicity, evidenced by biochemical results, histopathological and immunohistochemical tests.

In a study conducted by Mahmoud, Badr, Shinnawy (2016) it was studied the effects of whey proteins on improving lymphocyte function and protection against diabetes in the offspring of diabetic mice.

For this, 30 female BALB/c mice with body mass in gram of 25 to 30, (no age informed by the authors) were used, which were fasted for 20 hours before the induction of diabetes by streptozotocin (STZ). Female mice became diabetic using intraperitoneal injections for five consecutive days of streptozotocin (60 mg/kg body weight), starting two weeks prior to mating. In 10 non-diabetic female mice, 0.01 M citrate buffer, pH 4.5, was injected.

All female mice, including diabetic and non-diabetic, were mated to healthy male mice. The female mice were then distributed into 3 experimental groups (10 mice per group):

Group 1 - non-diabetic control administered with distilled water (250 μL/mouse /day for one month orally by gavage);

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Group 2 - diabetic mice receiving distilled water (250 µL / mouse / day for one month orally by gavage);
Group 3 - diabetic mice receiving undenatured whey proteins (100 mg / kg body weight dissolved in 250 µl / mouse / day for one month orally by gavage).

To assess hyperglycemia during the gestation period, blood glucose concentrations were measured in blood samples taken weekly after overnight fasting by cutting off the tail tip of each mouse, which were collected from the day of the injection of streptozotocin to two weeks after birth.

At the end of the experiment, after overnight fasting, the three-month-old pups in each group were anesthetized with pentobarbital (60 mg / kg body weight) and the abdominal cavity of each mouse was opened and all blood was collected by abdominal aorta and the serum was stored for further analysis of the cytokine profile.

After that, the serum triglycerides (TG), aspartate amino transferase (AST), alanine amino transferase (ALT) and creatinine were determined, as well as the measurement of the insulin concentration and then the B and T cell immune response, interleukins (IL IL-7, IL-7, and TNF-α) and reactive oxygen species (ROS) in adult male offspring (n = 15 in each group) using flow cytometry, Western blotting and ELISAs.

The results of the study demonstrated that the offspring of diabetic mothers exhibited several postpartum complications, such as expressive overexpression of activator-3 transcription factor (ATF-3), significant elevation of plasma concentrations of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) and reactive oxygen species (ROS), marked reductions in plasma concentrations of IL-2 and IL-7, significant inhibition of CCL21 and CXCL12-mediated chemotaxis of B and T lymphocytes, and decreased proliferative capacity of B lymphocytes stimulated by antigens (the author does not report the value of p, only that of significance).

However, administration of whey proteins in diabetic rats substantially restored ATF-3 expression and ROS concentrations, proinflammatory cytokines, IL-2 and IL-7 in offspring (the author does not report the value of p, only the of significance).

In addition, the chemotaxis of B and T lymphocytes to CCL21 and CXCL12 and the proliferative abilities of these lymphocytes were restored in the male offspring of diabetic mice from mothers given whey proteins (the author does not report the p value, only that of significance).

After this, it can be inferred that there are evidences of a protective role for whey proteins present in camel milk in reducing the tendency of offspring of diabetic mothers to develop diabetes and related complications.

Finally, the results also demonstrated a significant and time-dependent reductive effect of serum proteins on the proinflammatory cytokines IL-1α, IL-1β, IL-10 (the author does not report the value of the p, only that of significance).

In addition, a significant elevation of IL-8 in a time-dependent manner was recorded in groups supplemented with whey proteins (the author does not report the value of p, only that of significance).

From this point, the study may build the hypothesis that non-denatured whey proteins may play a relevant role in the progress and process of wound healing in diabetic models, providing the critical insight into future nutritional intervention strategies aimed at improving anti-inflammatory and antioxidant properties.

In the research of Avila et al., (2018) The effects of the high protein diet containing whey proteins were verified in rats submitted to resistance training in water. For this, 32 male Wistar rats aged 60 days and body mass in 90 ± 2 grams were used, which were separated into four groups (n=8 / group):
1 - SN Group - sedentary rats with normoprotein diet (14% protein);
2 - TN Group - sedentary rats with hyperproteic diet (35% protein, enriched with whey proteins isolate);
3 - Group SH - rats trained with normoprotein diet (14% protein);
4 - Group TN - rats trained with hyperprotein diet (35% protein, enriched with whey proteins isolate.

The rats were submitted to 8 weeks of resistance training in water jumps. The determination of the overload and adjustment were performed daily, through body weight multiplied by the percentage of overload of the previous week plus 5%.

After euthanasia, blood collection and extraction of adipose tissue, muscle and organs for histological procedures and analysis of the muscle protein expression of GLUT-4 and p-p70 s6 k were performed.

As a result of the research, omental ($p<0.02$) and subcutaneous ($p<0.03$) adipose

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tissues were higher in NS compared to SH; epididymal adipose tissue ($p<0.01$) was higher in NS compared to other groups and perirenal and retroperitoneal adipose tissues were lower in SH and TH compared to NS.

In relation to organs and muscles, the gastrocnemius was smaller ($p=0.04$) in SN compared to other groups; soleus larger ($p<0.001$) in HS compared to the other groups and heart weight ($p<0.01$) was higher in HT compared to TN and SN, but not SH; kidney ($p<0.001$) and liver ($p<0.001$) larger in TH and SH compared to SN and TN.

Inthe biochemical indicators, triglyceride concentrations (mg / dL) were reduced in TH groups ($p<0.03$) compared to SH, TN and SN, and there were no changes in adiponectin and leptin concentrations and protein expression of GLUT-4 and p70s6k.

Finally, the study infers that high protein diet containing whey proteins isolate kept the normal muscle histomorphology and liver and, associated resistance, reduced serum concentrations of triglycerides and improved body composition, increased weight heart, kidneys, liver and gastrocnemius and soleus muscles.

On the other hand, the research conducted by Kerasioti et al., (2018) to study the effects of dietary supplementation of sheep / goat whey protein on rat redox status used 12 Wistar rats at 26 weeks of age and with mean weight in grams of 470.

To perform the experiment, the rats were divided into 2 groups that received their diets for a period of 28 days, as follows: 1 - control group (n=6), fed a standard commercial diet; 2 - experimental group (n=6); fed standard commercial diet plus sheep / goat serum protein (1g / kg body weight / day).

At the end of the experiment blood samples were collected by cardiac puncture and the rats were euthanized by decapitation under deep anesthesia. Subsequently, tissues of the liver, spleen, pancreas, brain, heart, quadriceps muscle, lung, small intestine and kidney were resected, frozen in liquid nitrogen and stored at -80 ° C until analysis.

Finally, reduced glutathione, catalase activity, total antioxidant capacity, thiobarbituric reactive substances, carbonyl proteins and H_2O_2 decomposition rate were measured in blood and tissues.

According to the results, rats fed sheep / goat serum protein exhibited an improved antioxidant status and decreased the free-radical-induced toxic effects on lipids and proteins (the author does not report the value of p, only that of significance).

Specifically, in blood, concentrations of glutathione synthetase and catalase were significantly increased while the thiobarbituric reactive substances and carbonyl protein concentrations were significantly lower compared to the control group (the author does not report the p value, only the significance level).

In relation to the effects on the tissues, it was observed that the concentrations of glutathione synthetase were significantly increased in small intestine ($p=0.032$), quadriceps muscle ($p=0.044$), pancreas ($p=0.013$) and lung tissue ($p=0.004$) compared to the control group.

The rate of hydrogen peroxide decomposition was significantly decreased in the liver ($p=0.012$), brain ($p=0.042$) and quadriceps muscle ($p=0.048$) but was significantly increased ($p=0.009$) in splenic tissue compared to the control group.

Concentrations of thiobarbituric-reactive substances were significantly decreased in the liver ($p=0.006$), brain ($p=0.000$), quadriceps muscle ($p=0.005$), pancreas ($p=0.031$), lung ($p=0.031$) and spleen ($p=0.017$) compared to the control group.

Finally, protein carbonyl concentrations were significantly decreased in brain tissue ($p = 0.002$), small intestine ($p=0.032$), kidney ($p=0.009$), pancreas ($p=0.045$) and spleen ($p=0.018$) compared to the control group.

Thus, the present results show the beneficial effects of the sheep / goat serum protein on the redox state in an in vivo model as it enhanced the mechanisms of antioxidant defense in blood and tissues and protected against the damaging effects of oxidative stress.

Finally, the investigation of its moleculares mechanism of action for whey proteins to be incorporated as a bioactive ingredient in food products would be of relevance.

In summary, although serum milk protein already has nutritional aspects widely investigated over the last decades , having a research approach more focused on its anabolic, hypertrophic and performance effects in the exercise, in recent years researches such as those exposed, have been performed to elucidate the interaction and effects on hepatic, lipid, hormonal, bone, metabolic, immunological and renal parameters in order to understand the

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complexities of the possible beneficial and/or deleterious effects of whey proteins.

- Chronic effects of supplementation of whey proteins and other proteins / peptides / amino acids

Royle, Mcintosh and Clifton (2008) studied the influence of whey protein isolate (WPI) and glycomacropeptide (GMP) on weight gain and body composition. For this, 50 Wistar rats 12 weeks old (body weight not reported by the authors) were evaluated and fed *ad libitum* for 7 weeks with five semi-purified diets of the American Institute of Nutrition differing in protein type: (1) casein; (2) meat; (3) control with whey protein isolate (WPI) without glycomacropeptide; (4) WPI with glycomacropeptide at 100 g / kg and (5) WPI with glycomacropeptide at 200 g / kg.

At the end of the experiment, body composition was evaluated and plasma samples were tested for triglycerides, insulin and glucose. As a result, data analysis showed no effect of any type of protein or GMP concentration on final body weights, nor was there any significant difference between groups in food intake.

There was a significant difference between WPI-fed rats when compared to casein-fed rats ($p<0.01$) and there also was a significant reduction in body weight gain (the author does not report the value of p, only that of significance) with rats fed with GMP compared to rats fed with beef and casein.

Regarding body composition, there was a significant decrease in the mass of testicular and abdominal fat when WPI rats with GMP (200 g / kg) when compared to casein-fed rats (the author does not report the value of p, only that of significance), as well as decreased perirenal fat deposition in rats fed both GMP concentrations compared to casein-fed rats (the author does not report the p value, only significance).

Concerning biochemical data, insulin concentrations in rats fed both doses of GMP were significantly lower ($p<0.01$) than in control WPI-fed rats and plasma triglyceride concentrations of WPI-fed rats + GMP at 200 g / kg were significantly lower than the rats fed casein and meat protein (the author does not report the p value, only significance).

Finally, from the study it can be inferred that the whey protein isolate has the predominant influence representing (70%) the overall effect on the body weight gain, as well as the glycomacropeptide has a significant additional influence (the author does not informs the value of p, only that of significance) when combined with WPI in the accumulation of fat, but the mechanisms for this effect were not identified.

Haraguchi et al., (2010) to verify the biological and biochemical quality of whey proteins, it was used 32 Fisher rats with 40 grams and 3 weeks of age were divided into 4 groups of 8 rats each.

The aim of the study was to compare the biological quality of a commercial whey protein with casein and its effect on biochemical parameters of rats.

The experimental design over 4 weeks the casein group (Group C) received a standard diet (AOAC), whey proteins group (group W) received modified AOAC diet with whey proteins rather casein, and casein group / whey proteins (CW group) received a modified AOAC diet with 70% casein and 30% whey proteins.

In addition, a protein-free group (PF group) was used to determine the losses of endogenous nitrogen. The net protein ratio, protein efficiency coefficient and true digestibility were determined, and blood was collected for biochemical analysis.

Total cholesterol, triglycerides and glucose were measured by enzymatic methods and high-density lipoprotein (HDL) cholesterol was measured in the supernatant after the selective precipitation of low-density lipoprotein and very low density lipoprotein.

Total protein and albumin were measured by colorimetric measurement, aspartate aminotransferase and alanine aminotransferase were measured by kinetic assay and creatinine by the alkaline picrate reaction, all using commercial kits. Finally, the paraoxonase activity (PON) was measured by the rate of hydrolysis of the phenylacetate.

As a result of the research, food intake and protein intake did not differ between groups C, W and CW and weight gain for W and CW groups were higher than for group C (the author does not report the value of p, only that of significance).

In the results of the biological tests, the W group showed higher values for net protein ratio, protein efficiency ratio and digestibility, but this was not observed for the CW group and no significant difference between CW and C groups was found.

Only the W diet has significantly different values for total protein, albumin,

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glucose and HDL cholesterol concentrations and paraoxonase activity (the author does not report the p value, only that of significance).

Finally, total cholesterol in the W and CW groups were different from each other ($p<0.05$), although similar to group C and triglycerides and non-HDL cholesterol concentrations did not present statistical difference between all groups.

Thus, from the study it can be inferred That whey proteins in comparison with casein had higher values of the biological parameters and biochemical evaluation revealed an improvement in glycemic homeostasis, lipid profile and paraoxonase activity in rats.

Adechian et al., (2011) with the aim of comparing the capacity of casein with milk soluble proteins (MSP) as a limitation for the loss of lean mass induced by energy restriction.

Obesity was induced in 30 wistar rats (body weight in grams and 315.3 ± 1.8 Age was not informed) with a power of 5 weeks with a diet rich in fat and high sucrose content. The energy restriction effect was then studied with protein-rich diets (32%) containing casein, MSP or a mixture of 50/50 of both proteins for 3 weeks (n=10 per group).

Food intake, body weight, nitrogen balance, creatinine and excretion of 3-methy-lhistidine were measured during energy restriction and then tissue weights, plasma metabolic parameters (amino acids, glucose, insulin, cholesterol, triglycerides) and *in vivo* muscle protein synthesis and long finger extensor (EDL) were measured in the post-absorbing period at the end of the experimental period.

As a result of the study , food intake was not different between groups during the period of high intake of sucrose, prior to energy restriction and storage weights of peri-renal and peri-genital adipose tissue, liver, posterior limb muscles (individually or the sum of all of them) and kidney were different between the groups at the end of the energy restriction period.

Plasma concentrations of amino acids measured in the post-absorption state at the end of the restriction period were not different between the groups, except for leucine and phenylalanine (the author does not report the p-value, only the significance level).

However, nitrogen balance was significantly reduced during the first week of energy restriction compared to the high fat meal period, but remained positive in all groups (the author does not report the value of the p, only that of significance).

Although significant differences in protein metabolism were observed between the groups (protein intake, plasma amino acid concentrations, fecal nitrogen excretion, muscle protein synthesis rates (the author does not report the value of p, only that of significance), week by week, there were no significant differences in nitrogen balance, regardless of the protein used.

Thus, in rats with energy restriction with overweight, it was shown that, in the long run, the body's muscle mass evolution during the energy restriction was the same regardless of the protein used.

Thus, to minimize the loss of lean body mass during energy restriction, it is important to provide sufficient amount of protein, although the nature of the protein intake is of no relevance.

In a study by Adechian et al., (2012) the effects of consumption of leucine-rich protein in overweight and energy restricting mice on muscle protein were verified. For this purpose, 27 male Wistar rats were given a hypercaloric diet for 5 weeks and then with energy restriction and fed a high protein diet containing casein, soluble milk proteins (MSP) or a mixture of casein-MSP (n=9 per group) for 3 weeks and body composition was measured by dual energy x-ray absorptiometry before and after energy restriction.

After 3 weeks, hind limb muscles, kidneys, intestine, liver and spleen, plasma metabolic parameters and protein synthesis rates of the liver and long finger extensor were measured in the postprandial state.

As a result of the study, dietary intake was similar in all groups and the induced energy restriction significant decrease in body weight and fat mass ($p<0.001$) and halted the slow growth of lean body mass without differences between groups.

Among all tissues, a significant effect was detected only for the intestine ($p=0.0012$), with a higher weight in the casein group, as well as the plasma concentrations of glucose, insulin, cholesterol and triglycerides were different between the groups and only plasma urea content was significantly lower in the casein group than in the MSP group ($p=0.0143$).

Among the postprandial plasma amino acid values, only tyrosine (higher in casein than in the MSP group, $p=0.0082$), leucine

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(lower in the casein and blend groups than in the MSP group, p=0.0005), proline (higher in the casein group and higher in the blend group than in the MSP group, p=0.0001), and the sum of glutamine and glutamic acid (higher in casein than in the MSP group, p=0.0490) were significantly different between groups, the rates of hepatic protein and postprandial muscle synthesis were not different between the groups.

Finally, the study affirms that despite the high leucine content of MSP and the brevity of the post-absorbing period, there was no difference in the evolution of body protein mass between the groups.

Thus, when protein intake is high, the nature and moment of protein intake does not influence changes in lean body mass during energy restriction.

Lollo et al., (2012) in order to investigate the effect of dose-response to chronic supplementation of whey protein (WP) and casein enriched with leucine in via s anabolic MTOR and p70S6K in the diaphragm of Exercised and sedentary Wistar rats.

For that purpose, 96 male Wistar rats 21 days of age and body mass 133.82 ± 5.6 grams were divided into eight groups and fed for 30 day with a diet containing casein or whey proteins, with crescent concentrations (0, 3, 4.5 and 6 % of the diet) of leucine and a parallel set of eight groups was exercised for comparison.

For analysis, serum uric acid, creatinine, glucose, AST, ALT, CK, LDH and cholesterol, were determined by standard methods, and MTOR and p70S6K, using Western Blot analysis.

In this sense, long-term supplementation had no effect on the muscle mass of the diaphragm in relation to the dietary protein source.

However, while supplementation resulted in slightly lower body mass gains (the author does not report the p value, only that of significance), the mass of the diaphragms was virtually unchanged, but showing a small increase when the addition concentration was of 4.5 % leucine.

Long-term supplementation with leucine of normal rats produced an overall increase in both phosphorylated and non-phosphorylated MTOR and p70S6K proteins in the diaphragm, and the 6% concentration of leucine supplementation was more effective in promoting a significant increase in MTOR concentration in both forms the author does not report the value of p, only that of significance).

The consequences of supplementation on the activities of AST, ALT, CK and LDH enzymes plus serum concentrations of glucose, uric acid, creatinine and cholesterol were determined in order to evaluate long-term supplemental leucine changes but were not observed significant changes in liver (ALT and AST) and renal (creatinine and uric acid) health parameters analyzed in relation to chronic supplementation.

In addition, muscle damage markers, CK and LDH, were increased by any of the leucine supplementation concentrations tested, and the complete serum amino acid profiles did not detect changes except for alanine and branched chain amino acids.

Regarding leucine, increases (the author does not report the p-value, only significance) were observed at all supplementation concentrations, except that the sedentary maintained leucine concentrations 20% higher than the trained rats.

From These results, the study can be inferred que the combination of milk protein (whey proteins and casein), leucine and exercise was able to activate the MTOR pathway in the diaphragm to obtaining maximum activation when the leucine addition concentration was of 4.5% or 6%, as well as different sources of protein, whey proteins or casein, may be viable alternative to maximize activation of the MTOR pathway and provide amino acids for protein synthesis in the diaphragm.

In a study Ebaid, Badr, Metwalli (2012) who investigated on immunostimulatory properties of the denatured whey proteins derived from three species of camels in mice. For this it was used 75 male mice (the authors of the study has not rams lineage) with body mass of 25 to 30 grams and they were divided into five groups (n = 15/group):

Group 1 - control group;

Groups 2, 3 and 4 - supplemented orally with the non-denatured whey protein from Majaheim (second group, WPA), Maghateer (third group, WPB) and Soffer (fourth group, WPC) at a dose of 100 mg/kg body weight daily for 6 days;

Group 5 - The fifth group was supplemented orally with bovine serum albumin (BSA) at the same dose (100 mg/kg body weight daily for 6 days).

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The mice were anesthetized with pentobarbital (60 mg / kg body weight) and samples (blood, liver and skin) were obtained 2, 4 and 6 days after supplementation of serum proteins. The determination of glutathione, measurement of reactive oxygen species, hydroperoxide concentrations, blood glucose, lipid profile, determination of alanine aminotransferase, aspartate aminotransferase, creatinine and plasma cytokine profile, and polyacrylamide gel electrophoresis (SDS-PAGE) for the determination of interleukins - 1α, IL-β, IL-10, IL-2, IL-6 and IL-8) was made.

As a result of the study, analysis by SDS-PAGE of these three serum proteins revealed a similar electrophoretic pattern indicating relative structure of the protein and carbohydrate components and in the serum proteins of the three camel species, lactoferrin, serum albumin and α-lactalbumin are distributed in molecular weights of approximately 80, 66 and 14 kDa, respectively. The similarity of the electrophoretic distribution clearly indicated the bioactivity similar to that expected.

In addition, a significant inhibition of oxidative stress parameters was observed in similar behaviors for the three serum proteins (the author does not report the value of p, only that of significance).

A significant decrease of reactive oxygen species in isolated leukocytes and liver and skin homogenates was observed in the three groups of whey proteins compared to control and BSA groups (the author does not report the value of p, only that of significance).

The concentration of hydroperoxide was measured in whole blood samples and statistical analysis revealed that 3 groups supplemented with whey proteins (WPA, WPB WPC) showed a significant reduction of hydroperoxide in the control group and glutathione were significantly increased in mice supplemented with whey proteins in a time-dependent manner compared to the mice from BSA and control group (the author does not report the value of p, only significance).

Chevalier et al., (2013) verified how the energy restriction influences the protein metabolism and for that they used 56 male Wistar rats, with weight between 300-320 grams, divided into 7 groups of 8 rats each.

For 5 weeks, all rats were fed an obesity-inducing diet. After this period, they were then submitted to a 45% energy restriction using the obesity induction diet (OI-R group) or a high protein balanced diet for 3 weeks, while a control group was fed the diet of obesity induction ad libitum (OI group).

Rats with caloric restriction and high protein (HP) were divided into 5 groups, differing only in terms of their protein source: total milk proteins (MP-HP-R group), casein (C-HP-R group), (W-HP-R group), a mixture of 50% casein and whey (CW-HR-R group) and soybean (S-HP-R group).

At the end, the rats were euthanized in the postprandial state and their body composition was determined.

Protein synthesis rates were determined in the liver, gastrocnemius muscle, and kidney using a subcutaneous dose of ^{13}C valine.

The concentrations of mRNA were measured for key enzymes involved in the three proteolysis pathways.

As a result of the research, the study demonstrated the body weight of OI-R rats was 10% lower than that of OI rats ($p<0.0001$) and did not differ from the other five high protein (HP) restricted groups.

It was found that the energy restriction and not the composition of the diet that influenced weight loss and adiposity, while the lean tissue mass (with the exception of the kidney ($p=0.01$) was not influenced by diet composition.

The concentrations of neoglycogenic amino acids tended to decrease under energy restriction ($p<0.06$), but this was reversed in diets with high protein (HP).

In other hand, uremia was 64% higher in rats with high protein (HP) than in the obese (OI) diet ($p<0.0001$), but was not influenced by energy restriction, while the rates of postprandial proteins in different organs were similar in all groups.

In contrast, the mRNA concentrations which encode proteolytic enzymes in increased energy restriction in muscle and kidney, but it was neutralized by s high protein diets.

At the end of the study, it was inferred that in obese adult rats, energy restriction rather than diet composition affected fat reserves and had little alteration in protein metabolism, despite marked effects on proteolysis in muscle and kidney.

In another study by Aparicio et al., (2014) the effects of whey proteins intake, whey proteins (WP) and soy protein (PS) on renal parameters, urinary and morphological in rats were examined. For this, 120 male Wistar rats weighing 165 ± 8 grams were used and divided into 2 groups: WP group, being a diet enriched with whey

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proteins (having 10.4% dietary protein and 73.8% whey) and SP group, being a diet enriched with soy protein (having 9.8% protein in the diet and 77.5% of the same from whey).

The groups were fed their respective diets over 12 weeks. At the 11th week of the experiment, a urine sample from each rat was collected for biochemical analysis.

Urine volumes were recorded and the samples were transferred to graduated centrifuge tubes for pH, calcium and citrate analysis.

At the end of the experimental period, rats were anesthetized with ketamine-xylazine and euthanized by cannulation of the abdominal aorta. Blood was collected and centrifuged at 3,000 rpm for 15 minutes to separate the plasma which was subsequently frozen in liquid nitrogen and stored at - 80 °C.

The carcass weights were recorded and the left kidneys were extracted, weighed and immediately stored in formalin for further histological analysis.

As a result of the research, urinary pH was more acidic in the WP diet group compared to the SP diet group ($p<0.001$) and the urinary calcium content was higher in the WP diet compared to the SP diet group ($p<0.001$) whereas urinary citrate concentration was lower ($p<0.001$), however, no differences were observed between the groups for any of the analyzed renal morphological parameters or other renal plasma markers, such as concentrations of albumin or urea.

In relation to kidney morphology and weight, no differences were observed between the groups in any of the renal morphological parameters analyzed (all, $p>0.05$) and the wet mass of the kidney, expressed as absolute value, was lower in the WP group in compared to the SP group ($p=0.015$), but there was no difference when the renal wet mass was expressed in relation to the final body weight or carcass weight.

After the experiments were carried out, the study showed that although the WP group presented a worse acid-base profile, no significant morphological renal changes were observed, as well as the use of SP instead of WP seems to promote more alkaline plasma and urinary profile, with consequent renal advantages.

A study by Oh, Igawa, Naka (2015) the effects of ingestion of skimmed milk powder and treadmill exercise exercise on renal, bone and metabolic parameters in obese rats were found. A total of 47 Sprague-Dawley rats (SD) at 14 weeks of age (body weight not reported by the authors) were used to verify the effects of ingestion of skimmed milk powder and treadmill exercise on renal, bone parameters and metabolic.

The rats were divided into 4 groups:
group 1 - without exercise and diet control (n=12);
group 2 - with exercise and diet control (n=12);
group 3 - without exercise and with 17% of diet with skimmed milk powder (n=11);
group 4 - with exercise and with 17% of diet with skimmed milk powder (n=12).
For exercise group training, rats aged 27 weeks ran on a treadmill five times a week for 12 weeks.

At the end of the study, bone, renal and metabolic parameters were analyzed and as results the groups without exercise / normal diet and with normal exercise / diet the creatinine concentration presented significantly higher values ($p<0.05$) in relation to the exercise / diet with skimmed milk.

The exercise group also had normal body weight significantly lower at the end of the experiment ($p<0.05$) than in the exercise group / diet with skimmed milk.

The bone surface/bone volume, bone volume/tissue volume, trabecular thickness, trabecular number and trabecular bone pattern factor were significantly lower (the author does not report the value of p, only that of significance) in the exercise/normal diet group, without exercise/diet with skimmed milk and with exercise/diet with skimmed milk when compared to the group without exercise/normal diet.

Regarding tissues, there was no significant difference in liver and soleus muscle weight. In contrast, the weight of the long extensor digitorum at the time of dissection differed from dietary intake, since the group without exercise/ normal diet had significantly lower values (the author does not report the p value, only that of significance) than the others. Faced with such results, the study findings suggest that rats fed a skimmed milk diet would have higher structural and bone strength parameters than rats fed a normal diet.

In the other hand, Tranberg et al., (2015) who carried out two experiments in their study. In one experiment, with 72 male C57BL/6NTac mice with age of 3 weeks (the study does not provide the initial weight of the mice) were allocated in groups of 6 for 2 weeks

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adaptation, all mice were fed a standard rodent diet.

At the age of 5 weeks, the mice were matched by body weight and divided into four experimental groups:
1 - high fraction casein; 2- casein / high fraction serum milk; 3 - high fraction serum milk; 4 - high fraction casein - to be fed a hyperlipid diet with casein, a hyperlipid diet with a casein isolate and whey proteins, a hyperlipid diet isolated from whey proteins and a control diet with low fat and casein.

The groups were fed their respective test diets for 1, 3 or 5 weeks followed and with subsequent euthanasia.

Body weights and food intake were recorded twice weekly, and body composition was analyzed weekly by magnetic resonance imaging (MRI) in mice not anesthetized.

Prior to the challenge of the meal, the mice were fasted overnight (10 hours) in individual cages. After baseline (0 hour) blood and urine collection, the mice had free access to a known amount of their usual test diet for 1 hour, which was then removed and weighed.
Blood and urine were collected at food withdrawal (1 hour) and again 2 hours later (3 hours) and urine was collected in uncoated microtubes by spontaneous urination during handling.

In the experiment two, with 32 mice with 4 weeks of age (the s authors of the study do not provide m initial average weight of the mice) were allocated in adaptation cages for 3 days and transferred to a calorimetry system for measurement of energy expenditure basal by an indirect calorimetry system.

The rate of oxygen uptake, respiratory exchange rate, total activity, and food and water intake were measured simultaneously for each mouse.

At 5 weeks of age, the same diets described for the study were implemented in the calorimetry system and the effect of the modified diet on energy expenditure was measured for 1 week (n = 8). Body weight was recorded twice a week.

At the end, the mice were submitted to magnetic resonance imaging and anesthetized. Blood was collected by puncture of the periorbital plexus in EDTA coated tubes and centrifuged for plasma which was stored at -80 °C along with the tissues collected for analysis.

As a result of weight and body composition, in experiment one, body weight gain was significantly reduced ($p<0.01$) by whey proteins during the first week of dietary intervention compared to the other high fraction groups.

The fat mass was significantly reduced by serum compared to the high fraction casein of the first week of the intervention and throughout the study (the author does not report the value of p, only that of significance).
As for food consumption, the weekly and total accumulated consumption was not statistically different between the groups and after the first week, there were no differences in food intake, weight gain or food efficiency between groups.
On the body length, the group fed with high fraction milk serum was significantly reduced compared to high fraction casein ($p<0.01$).

IGF-1 was significantly reduced with age ($p<0.001$), however, there was no significant effect of the protein source at any time point.

In continuation, urea production and urea cycle activity were not affected by the protein source. There was also no influence of the protein source on respiratory exchange rate or maximal volume of oxygen (VO_2).

Finally, the study allows us to infer that whey proteins decreased growth-related parameters exclusively during the first week of dietary intervention. The initial effect of whey proteins could not be explained by food intake, energy expenditure, urea production or urea cycle activity.

Santos et al., (2016) carried out a study to determine the effects of dietary supplementation with whey proteins and leucine in normal rats. For this, they used 28 rattus novergicus/wistar with age of 90 days and mean total body mass in grams of 237 ± 24, divided into five groups with n sample of 5 to 7 rats per group, two of these groups being supplemented with leucine (LEU1 and LEU2 at doses 0.675 and 1.35g/kg/day), two groups supplemented with whey proteins (WP1 and WP2 at 0.45 and 1.8 g / kg / day) and 1 group with water during the period of 4 weeks.

At the end of this period, blood samples were collected and processed for biochemical measurements of creatinine, urea, triglycerides, total cholesterol, and fasting glycemia. There was significant weight gain in WP2 ($p<0.001$) and LEU2 ($p<0.001$) and also significant, less food intake in WP1 ($p<0.001$), WP2 ($p<0.001$) and LEU1 ($p<0.001$) to the control group.

There was no increase in the concentration of plasma urea and creatinine, nor even indicative of renal dysfunction. In

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addition, a significant reduction of triglycerides, total cholesterol ($p<0.001$), and fasting glycemia ($p<0.005$) were observed in the LEU1 group when compared to the control group.

Because of this, when taking into consideration renal function biomarkers, dietary supplementation with whey proteins and leucine did not result in renal damage and the LEU group had a significantly better lipid profile (LDL) ($p<0.001$).

In a study by Singh et al., (2016) that verified energy balance, preventing morbidity and renal damage from diets rich in whey proteins and casein, they have used 49 rats SHR (spontaneously hypertensive rats) for performing two experiments.

In experiment 1 with 33 SHR male mice at 4 weeks of age were allocated in individual metabolic cages for one week. After this period, they were weighed (110 ~ 115g) and divided into 4 groups of diets:

1 - Control group (CON, 7% whey + 7% casein - n=9);
2 - Whey group (WHY, 40% whey - n=8);
3 - Casein group (CAS, 40% casein - n=8);
4 - Standard ration group (CHW, n=8).

All groups received diets over 12 weeks. The ration consumption of each group was recorded and the energy expenditure was monitored.

Body weight was recorded twice weekly and body composition was measured weekly in the rat not anesthetized by a quantitative magnetic resonance imaging method.

Blood pressure measurements were recorded at the 4th and 6th week, using a sphygmomanometer.

At the end of the experiment, each rat received a score of 0 to 4 based on neurological deficit, tests of tolerance to intraperitoneal glucose (IPGTT) and insulin (IPITT) were performed, besides renal histology.

In experiment 2 with 16 SHR male mice at 8 weeks of age, they were allocated in individual cages with standard diet for 4 days, they had their weights measured and were randomized to two dietary groups ad libitum (n=8 / group): diets WHY and CAS. During the four training periods that lasted 8 days, on alternate days, the rats of group 1 received a diet CON and WHY, also on alternate days and the rats of group 2 received CON or CAS diet in the same way.

After the training periods, a feed preference test was performed in which each group received the CON diet and one of the experimental diets (WHY or CAS) simultaneously for two consecutive days.

During the feed preference tests, food intake was recorded at 1, 2, 4, 6 and 24 hours.

The results of experiment 1 demonstrated that both WHY and CAS diet produced short-term hypophagia, as well as significantly increased energy expenditure ($p<0.01$) and significantly decreased respiratory quotient ($p<0.01$), weight ($p<0.01$) and lean mass (the author does not report the value of p, only that of significance), with effects of the WHY diet being longer.

Both WHY and CAS diet prevented stroke-associated morbidity ($p<0.01$) and significantly decreased renal inflammation rates (tumor necrosis factor-α, interleukin-6 - the author does not report the p value, only the of significance) and renal damage, in contrast, only the WHY diet significantly decreased fat mass (the author does not report the value of p, only that of significance) and blood pressure (the author does not report the p value, significance).

In experiment 2, after four initial conditioning tests, the preference for the CON, WHY or CAS diet was determined. During the four conditioning trials, on days with WHY and CAS diets, there was a decrease in food intake compared to COM diet days (the author does not report the p value, only that of significance).

During the preference test, there was a significant reduction (the author does not report the value of p, only that of significance) in the WHY dietary preference for NOC on day 1 (14%) and day 2 (4.5%).

Likewise, the preference for the CAS diet tended to decrease on both day 1 (14%) and day 2 (4.5%). Together, these data show that diets enriched with WHY and CAS were less preferred than the CON diet.

As can be seen that whey or casein-enriched diets improved energy balance (7%), increased survival ($p<0.01$) and prevented renal damage in spontaneously hypertensive.

In a study by Khairallah et al., (2017) basal muscle performance was evaluated in 50 adult Sprague-Dawley rats (no specific age reported by the authors) and with body mass in grams of 473 ± 3 , after which they were distributed in one of the five semi-purified diets (n = 10/group), differing only in the protein source and having 19% protein.

These were: group 1 - milk protein (MPI); group 2 whey protein isolate or whey

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proteins (WPI); group 3 - soy protein isolate (SPI); group 4 - soy protein concentrate (SPC); group 5 - enzyme-treated soy protein (SPE).

The rats were fed for 8 weeks and at the end the muscle performance test was repeated, as well as tissues collected for histological analysis and blood for analysis of biomarkers (cholesterol, creatinine, triglycerides and myostatin), as well as ration and weight monitored.

As a result of the research, there was no significant difference in dietary intake or body weights over time between diet groups, nor were there differences in body and terminal muscle weights or in serum lipids, creatinine or myostatin.

On muscle performance, compared to rats fed with MPI, rats fed with WPI and SPC exhibited a higher maximal rate of contraction using in vivo measurement of muscle performance and when maximal strength was normalized to body weight, rats fed with SPC showed higher strength compared to MPI, whereas when normalized to gastrocnemius weight, rats fed WPI with showed greater strength compared to MPI (the author does not report the value of p, only that of significance).

At the end of the study, it can be stated that the consumption of soy protein in the high fat diet resulted in muscle function comparable to whey protein and improved in comparison to milk protein and that the benefits observed with the protein of soy or whey were independent of changes in muscle mass or in the transverse area of the fiber.

Although studies have compared whey proteins or their fractions with other proteins or peptides in the most diverse metabolic parameters, few have specifically treated kidney function or isolated parameters. In addition, we had six studies that analyzed creatinine values (Haraguchi et al., 2010), Adechian et al., (2011), Lollo et al., (2012), Oh, Igawa and Naka, (2015), Santos et al., Khairallah et al., (2017)), three studies that addressed urea (Aparicio et al., 2014), Tranberg et al., (2015), Santos et al., (2016) and only one is the total protein / proteinuria (Haraguchi et al., 2010), where the biomarkers did not present values that were out of order, but these studies are relevant because they explore the effects of whey proteins within other parameters to other approaches.

ACUTE AND CHRONIC EFFECTS OF WHEY PROTEINS SUPPLEMENTATION

- Acute and chronic effects of whey protein supplementation

In the study by Toedebusch et al., (2012) the serum insulin and leucine responses were compared after hydrolyzed whey protein supplementation versus a whey protein isolated in rats during the postprandial stage, complete toxicological analysis was performed in rats given different doses of hydrolyzed whey protein supplementation over a period of 30 days.

For this, 60 male Wistar rats weighing 250 grams and two objectives were used. objective 1, with 40 rats, serum concentrations of insulin and leucine were quantified up to 120 minutes after a human equivalent dose of one whey proteins or hydrolyzed whey proteins supplement and in a second cohort for objective 2 with 20 rats, serum/blood and liver/kidney histopathological markers were examined after 30 days of low feed (1 human equivalent dose or 1.1 g / dose), mean (3 doses) and high (6 doses) of the hydrolyzed whey proteins supplement.

As a result of the study, in objective 1, the highest concentrations of leucine existed at 15 minutes after intake of hydrolyzed whey protein versus whey protein isolate ($p=0.04$), followed by higher concentrations of insulin at 60 minutes ($p=0.002$).

In objective 2, liver and kidney histopathology toxicology markers were not different 30 days after feeding with supplementation based on low, medium and high dose hydrolyzed whey protein or water.

There were also no differences between the conditions of body fat or lean mass or circulating clinical chemical markers after 30 days of feeding intervention.

Kimoto et al., (2013) carried out a research to study the protective effect of lactoferrin on nephrotoxicity induced by cisplatin in rats. For this, three research experiments were carried out. In the first experiment, 24 wistar rats at 7 weeks of age (no mean weight reported by the authors) were randomly divided into 4 groups of 6 rats each:
Group 1 - rats were given orally with saline (3 ml / kg) daily from day 0 to day 5 and had intraperitoneal injection of saline solution (14 ml / kg) on day 1;
Group 2 - mice were administered orally with beta-lactoferrin (300 mg / kg) daily from day 0

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to day 5 and had intraperitoneal injection of saline solution (14 ml / kg) on day 1;
Group 3 - rats were given orally with saline (3 ml / kg) daily from day 0 to day 5 and had intraperitoneal injection of cisplatin (7 mg / kg) on day 1;
Group 4 - rats were given orally with beta-lactoferrin (300 mg / kg) daily from day 0 to day 5 and had intraperitoneal injection of cisplatin (7 mg / kg) on day 1. On day 5, the rats were anesthetized with sodium pentobarbital and blood samples were collected from the caudal cave for biochemical analysis. After being euthanized, both kidneys were removed and each kidney was cut longitudinally, one piece on each side of the kidney fixed in 10% neutral buffered formalin and the renal tissues were processed for histological examination.

In the second experiment, the effect of beta-lactoferrin on the accumulation of cisplatin in the kidneys was studied. For this, 40 wistar rats were randomly divided into 4 groups of 10 rats each (control, lactoferrin alone, cisplatin alone and cisplatin + lactoferrin) at 7 weeks of age (no mean weight reported by the authors).

The collection of blood and kidneys was performed on day 2, as the onset of oxidative damage in the kidney occurs around 48 hours after the injection of cisplatin. One kidney was removed from each rat and weighed and then stored at -20 °C until analysis of cumulative deplatin content. Kidney tissue was decomposed to imitate the pyrolysis by the addition of nitric acid and hydrogen peroxide and platinum was measured using an inductively coupled plasma optical emission spectrometry system.

In the third experiment of the research, the diuretic effect of beta-lactoferrin in rats was verified. For this, 7 rats 7-week-old (no mean weight reported by the authors) were used in the experiment. An abdominal midline incision was made in each rat, and the bladder and both ureters were exposed. Polyethylene tubes were placed in both ureters. Beta-lactoferrin was administered to rats via the external jugular vein in three doses (3, 10 and 30 mg / kg) at 40, 100 and 160 min after urine sampling. During the procedures, urine samples were collected in plastic tubes every 10 min, and the urine volume was measured.

After the tests, the study found the following results:

Experiment 1: Administration of beta-lactoferrin alone did not alter plasma urea or creatinine. Cisplatin caused a significant increase in urea and creatinine. These cisplatin-induced renal abnormalities were significantly improved ($p<0.01$) by pretreatment with oral beta-lactoferrin (the cisplatin + beta-lactoferrin group). Histopathological examination of the kidney revealed that cisplatin strongly impaired the proximal tubule, but the lesions in the cisplatin + beta-lactoferrin group were smaller and lighter than those in the cisplatin group alone. Beta-lactoferrin administration reduced cisplatin-induced epithelial damage.

Experiment 2: Platinum content in the kidney was significantly decreased ($p<0.05$) by treatment with beta-lactoferrin. Administration of beta-lactoferrin (300 mg / kg) alone did not affect BUN or creatinine, whereas cisplatin caused a slight increase in both (cisplatin group alone - $p<0.01$). These cisplatin-induced changes were significantly ($p<0.01$) improved by pretreatment with oral beta-lactoferrin (cisplatin + beta-lactoferrin group).

Experiment 3: Intravenous administration of beta-lactoferrin caused a significant ($p<0.01$) increase in urine volume in a dose-dependent manner and compared to mean urine volume during the first 30 minutes, values after 10 and 30 mg / kg of beta-lactoferrin resulted in increments of 157 and 250%, respectively.

Thus, the study indicates that pretreatment with beta-lactoferrin produces a protective effect against cisplatin-induced nephrotoxicity, and it is suggested that it increases diuresis and reduces the accumulation of renal cisplatin.

From these studies, we noticed the research with acute and chronic nature of the whey proteins or their components , and on the one hand we had the research of Toedebusch et al., (2012) investigating the positive effects of supplementation of whey proteins, in an acute way , about anabolic markers such as insulin and the leucine , and chronic , on serum histopathological markers, kidney and liver, on the other hand, saw Kimoto et al., (2013) with the objective of studying lactoferrin being used to analyze the protective effect on renal function.

However, whether through the study of deleterious or protective effects, such studies indicate a neutral or positive relationship between the use of whey proteins and renal function, whether acute or chronic.

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- Acute and chronic effects of whey protein and captopril supplementation

The effect of whey proteins on the inhibitory activity of angiotensin I am converting enzyme (ACE) and the antihypertensive effect of whey protein hydrolyzate (WPH) after administration was studied in a study conducted byWang et al., (2012) oral (short term) or continuous for 20 days were investigated.

For this, 50 10-week-old male spontaneously hypertensive rats (SHR) and mean body mass in grams of 228 ± 5 were divided into five groups each consisting of 10 rats:

- one negative control group administered orally with only 0.9% saline;
- a positive control group administered orally with captopril (50 mg / kg / day);
- three groups of rats administered orally with different dosages of whey proteins 80, 240 or 1200 mg/kg/day.

Body weight was measured every 5 days and systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were measured by the tail cuff method.

As results presented by the study, the body weight of SHR rats supplemented with whey proteins and treated with captopril was significantly higher than that of the negative control group (the author does not report the value of the p, only that of significance), while there was no significant difference between the groups treated with whey proteins and captopril.

The interaction between treatment and time did not show significant effect for the WPH or captopril group supplemented groups, but there was statistical significance at the time for each specific group ($p<0.01$).

The heart rate of the groups treated with whey proteins (240 mg/kg/day and 1200 mg/kg/day) and the captopril group was lower than that of the negative control group (the author did not report the p value, only the of significance), while there was no significant difference between the 80 mg whey proteins/kg group and the negative control group.

The heart rate of the 1200 mg/kg/day group of whey proteins was significantly lower than the captopril group (the author did not report the p value, only that of significance) and compared to the negative control group, there was a decrease significant reduction in systolic blood pressure, diastolic blood pressure and mean blood pressure after oral administration of whey proteins and captopril.

In contrast, mean arterial pressure and diastolic blood pressure did not differ significantly between 240 mg/kg/day, 1,200 mg/kg/day of whey proteins and the captopril group.

There was a significant difference in the systolic blood pressure between the different treatment groups and the systolic blood pressure in the captopril group was the lowest (the author does not report the p value, only the significance level).

The maximum effect of systolic blood pressure reduction was observed when the daily dose of hydrolyzed whey proteins was 240 mg / kg / day of whey proteins. Compared with the negative control group, the groups treated whey proteins and captopril resulted in a significant decrease in blood pressure (the author does not report the value of p, the only significant).

However, the body weight of the groups of SHR mice supplemented with whey proteins and treated with captopril was significantly higher than the negative control group (the author does not report the p value, only that of significance), while there was no significant difference between the groups treated with whey proteins and captopril.

The interaction between treatment and time did not show significant effect for the whey proteins or captopril group supplemented groups, but there was statistical significance in time for each specific group ($p<0.01$).

The heart rate of the groups treated with whey proteins (240 and 1200 mg/kg/day of whey proteins) and the captopril group was lower than that of the negative control group (the author does not report the value of p, only that of significance).

The heart rate in the 1200 mg/kg/day group of whey proteins was significantly lower than the captopril group (the author does not report the value of p, only that of significance).

The Systolic Blood Pressure and the Diastolic Blood Pressure of rats SHR after oral intake of whey proteins and captopril were significantly lower than the negative control group and Diastolic Blood Pressure significantly lower in the captopril group than the whey protein groups are suggesting that captopril had an antihypertensive activity more effective than whey proteins (the author does not report the value of p, only the significance).

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Administration of whey proteins also significantly reduced ECA activity in the lung compared to the negative control and the positive control group, whereas no significant difference was observed between the three groups of different dosages of whey proteins administrations.

Finally, ECA activity was reduced by treatment with captopril compared to the negative control group, in the 240 and 1200 mg/kg/day groups of whey proteins was significantly lower than the negative control group and the group treated with captopril was the lowest (the author does not report the value of p, only that of significance).

After these experiments, the results suggest whey proteins through an ECA inhibitory activity may suppress the development of hypertension in SHR.

Although the research does not deal directly with the correlation whey proteins x renal function, it is already well known and explored in the literature that one of the main risk factors for it is hypertension. The study explores well in both acute and chronic nature, as in accordance micro (measures not the ECA) and macro physiologic (gauging SBP, DBP), taking into account the protective effect of whey proteins for renal function, as well as opening space for possible use outside its anabolic and hypertrophic locus , after confirming this extrapolation of results in humans.

- Acute and chronic effects of whey protein and methylated soya supplementation

A study by Sitohy et al., (2013) on the potential toxicity of methylated soy protein and methylated beta-lactoglobulin in male Wistar rats. For this, the study was divided into two phases.

In the first phase, 70 wistar rats with total body mass in grams of 160 ± 10 (without age informed by the authors) were divided into 7 groups with 10 rats each. All treatments were administered by gavage dissolved in 2 mL of distilled water:

Group 1 - received 2 mL of distilled water free of any external treatment; Groups 2, 3 and 4 - received a single dose of methylated soy protein at 2500, 5000 and 10,000 mg/kg body weight, respectively;

Groups 5, 6 and 7 - received a single dose of methylated beta-lactoglobulin at 2500, 5000 and 10,000 mg/kg body weight, respectively.

All rats were kept on observation for 24 hours to record any toxicity or mortality symptoms and maintained for another 14 days to observe behavioral and body weight changes. A similar experiment was conducted exactly, except that the test proteins were the native proteins - soy protein and beta-lactoglobulin.

In the second phase of the study, with 50 rats Wistar with total body mass 160 ± 10 g (Ageless reported by the authors) divided into 5 groups of 10 rats each:

Group A - received the same amounts of distilled water by gavage without any external treatment and served as control;

Group B and C - received methylated soy protein at doses of 500 and 2500 mg / kg body weight / day, respectively;

Group D and E - received methylated beta-lactoglobulin at doses of 500 and 2500 mg / kg body weight / day, respectively;

Each group was submitted to gavage 5x a week for 28 days. The body weight difference, histopathological examination of the kidneys, liver, heart, brain, and spleen were also analyzed and serum analysis was performed for biomarkers of liver function, such as alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), acetylcholinesterase (AChE), cholesterol, triglycerides, electrolytes, total proteins, albumin and globulin; renal (urea and creatinine) and hematological functions, including leukocytes (white blood cells), red blood cells (RBCs), platelet counts (PLT), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (HCM).

As a result of the study, changes in body weight, organ weight, hematological parameters, histopathological images of selected organs, serum albumin, globulin and albumin / globulin ratio, cholesterol, triglycerides and electrolytes were all within normal amounts in rats fed with these two methylated proteins and not significantly different from the controls. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine and urea concentrations were significantly reduced ($p < 0.01$) by administration of these two modified proteins, indicating absence of any adverse effects on liver or kidney function.

After the results, the study decided to support the overall security of proteins methylated to compare them with

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ISSN 1981-9927 ***versão eletrônica***

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fractions of whey proteins, but at the same time puts a limitation the fact of providing hematology in full, clinical chemistry and histopathology and use only male rats.

CONCLUSION

From the s shown studies, it is concluded that few directly address the two main variables proposed are the revision systematic, the whey proteins and kidney function, being most would addressing the whey proteins as main variable and the kidney function of secondary form.

However, when we noticed at the biomarkers of function (creatinine, urea and proteinuria) in isolation, we found that in relation to creatinine, no study showed a significant alteration in relation to the use of whey proteins.

In addition, the biomarker urea did not show any significant changes, except for the study by Aparicio et al., (2011a), although there was a significant increase in the same, we observed the protective effect of physical exercise on this. Already and m relation to proteinuria, it is observed that this is still a relatively unexplored biomarker, not appearing in any of the studies in this review.

Finally, it can be concluded that the isolated results of the biomarkers points to the non-impairment of renal function in relation to the use / supplementation of whey proteins.

In summary, studies that performed renal histological analyzes such as Hegazy et al., (2016); Avila et al., (2018) and Toedebusch et al., (2012) also showed no alterations in kidney morphology in relation to the use of whey proteins.

FINANCING

The first author was awarded a masters scholarship by FAPEMA, Process BM-02312/17.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Received for publication in 06/12/2019
Accepted in 08/19/2019