

Artículo de Revisión / Review Article

Ketogenic diets in weight loss: a systematic review under physiological and biochemical aspects of nutrition

Dietas cetogénicas en la pérdida de peso: una revisión sistemática bajo aspectos fisiológicos y bioquímicos de la nutrición

ABSTRACT

Countless strategies have been proposed to change dietary patterns to promote weight loss. Many of these strategies are controversial, with questions of effectiveness and possible negative consequences to health, even if weight loss effects are achieved. Ketogenic diets, with or without calorie restrictions, are framed in this context. In the present systematic review, evidence on ketogenic diets for weight loss was investigated. Studies on ketogenic diet with or without calorie restriction related to weight loss published between 2012 and 2017 were selected from MEDLINE, Scielo and Web of Science databases. Results show there is a lack of knowledge on specific physiological mechanisms involved in the ketogenic diet. Much of the evidence published, despite showing specific effects on weight loss, BMI and fat percentage reduction, did not precisely assess its effects on specific physiological and biochemical parameters, mainly on the hepatic, cardiac and renal tissues. We conclude that strategies to control overweight and obesity do not necessarily need to impose restrictions on certain nutrients, especially carbohydrates, or increase the intake of food groups whose excessive consumption has been associated with different pathologies.

Keywords: Body composition; Ketogenic diet; Metabolic parameters; Systematic review.

RESUMEN

Innumerables estrategias se han propuesto para cambiar el patrón de la dieta y así promover la pérdida de peso. Muchas de estas estrategias aún son controversiales con respecto a la efectividad y las consecuencias negativas para la salud. Las dietas cetogénicas, con o sin restricciones calóricas, se enmarcan en este contexto. En la presente revisión sistemática, se investigaron las evidencias sobre las dietas cetogénicas para la pérdida de peso. Para esto, se seleccionaron los estudios de dieta cetogénica con o sin restricción calórica relacionada con la pérdida de peso publicados entre 2012 y 2017 a través de las bases de datos MEDLINE, Scielo y Web of Science. Los resultados muestran falta de conocimiento

sobre mecanismos fisiológicos específicos implicados en la dieta cetogénica. Gran parte de la evidencia publicada, a pesar de mostrar efectos específicos sobre la pérdida de peso, IMC y reducción del porcentaje de grasa, no evaluó con precisión sus efectos sobre parámetros fisiológicos y bioquímicos, principalmente en los tejidos hepático, cardíaco y renal. Concluimos que las estrategias para controlar el sobrepeso y la obesidad no necesariamente tienen que imponer restricciones sobre nutrientes, especialmente los carbohidratos, o aumentar la ingesta de grupos de alimentos cuyo consumo excesivo se ha asociado con diferentes patologías.

Palabras clave: Composición corporal; Dieta cetogénica; Parámetros metabólicos; Revisión sistemática.

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INTRODUCTION

Obesity has become a global epidemic in recent years, and what was once considered a problem only for developed countries, is advancing in underdeveloped and developing economies, especially in the urban environment¹. This scenario is explained by changes in lifestyle of the population, marked by diets rich in fats and simple carbohydrates that, along with sedentary lifestyle, are among the main factors that led to an increase in the obesity prevalence².

However, it is known that this condition is recognized as the main risk factor for noncommunicable diseases (NCDs), such as type 2 diabetes mellitus, dyslipidemias, cardiovascular diseases (CVD) and some types of cancer³. This is because obesity is related to a low-intensity, but chronic inflammatory condition that affects the body systemically⁴.

Indeed, the development of obesity is closely related to changes in modern man's dietary patterns. It is worth pointing out that the increase in calorie intake may be due to the increased amount of food intake and changes in diet composition (qualitative value). This can be characterized by the incorporation of foods with higher caloric density⁵.

Thereby, countless strategies have been proposed to change dietary patterns and food habits of individuals and to promote weight loss and maintenance at appropriate levels. However, many of these strategies may be still controversial, with a lack of information on effectiveness and possible negative consequences to health, despite the fact that weight loss may occur. Ketogenic diets, with or without calorie restrictions, are framed in this context.

In the ketogenic diet, almost 90% of daily calories are derived from proteins and lipids. A composition often reported in the literature is that, from the total energy value, 50-55% of calories should be derived from proteins, 35-40% from lipids and up to 10% from carbohydrates. Therefore, this type of diet induces ketosis as a metabolic response to low carbohydrate intake, causing an increase in the concentration of circulating ketones (β -hydroxybutyrate, acetoacetate and acetone) produced by liver from β -oxidation of free fatty acids⁶.

Several studies have reported the efficacy of these strategies for weight loss or improvement of risk factors for chronic diseases⁷. However, in these studies, some physiological and biochemical aspects, besides the experimental limitations themselves, are not properly considered in relation to the

multiple biological aspects involved in human metabolism, preventing the ability to conclusively determine diet effectiveness.

These considerations are particularly important for health professionals who need to overcome tendentious or even limited scientific evidence in their practices, which may bring risk and discomfort to patients.

Therefore, the present review aims to systematically describe ketogenic diets when indicated for weight loss, specifically the biochemical and physiological approaches using evidence published in the last five years in the scientific literature.

The review also discusses the restrictive aspects of the diet, its negative consequences on health, biological and nutritional aspects, economic, social and cultural factors, food quality and the health of individuals.

METHODS

Studies on the ketogenic diet with or without calorie restriction related to weight loss were selected through MEDLINE - PubMed, Scielo and Web of Science databases using the following keywords: "ketogenic diet" and "weight loss".

The inclusion criteria for the selection of articles were: clinical trials; with obese individuals with or without some specific pathology; published between 2012 and 2017 and reporting original research data. Research that assessed the efficacy of diet on specific pathologies (e.g., refractory epilepsy) were excluded.

The selection of articles was performed in two stages. First, abstracts were reviewed. Duplicates were excluded. In the second stage, studies were carefully analyzed in relation to the inclusion criteria of the study, thus excluding those that did not fit the study objective.

RESULTS

A total of 166 records initially found were analyzed in relation to duplicity and context, and later for the adequacy to the inclusion criteria and objectives. A total of 17 articles on ketogenic diet were considered suitable for the proposed discussion.

Table 1 summarizes these studies, considering the methodological aspects and assessed parameters.

Table 1. Biochemical, physiological and experimental aspects of the studies published in the last five years that investigated the effects of the ketogenic diet (KD) on weight loss and body fat in humans.

Main outcomes of KD	Biochemical measures	Metabolic effects	n	Intervention	Duration	Active phase (KD)	Calorie value (KD)	Control	Ref
- ↓% body fat.	No	No	32	KD + Mediterranean diet	100 days	20 days	848 Kcal/day	Mediterranean diet - 1400 Kcal/day	7
- ↓ body weight and BMI; - positive changes blood pressure, fasting glucose, HbA1c, triacylglycerol, LDL-c and HDL-c.	Yes	Yes	245	KD + Mediterranean diet	1 year	proportional to individual weight loss	-	-	8

Continuación tabla 1.

Main outcomes of KD	Biochemical measures	Metabolic effects	n	Intervention	Duration	Active phase (KD)	Calorie value (KD)	Control	Ref
- ↓ BMI, % body fat, HOMA-IR; - ↑ uric acid, creatinine, AST.	Yes	Yes	20	KD + essential amino acid supplementation	3 weeks	3 weeks	< 800 Kcal/day	-	9
- ↓ anthropometric parameters; - ↓ glycemia, insulin, HOMA-IR, triacylglycerol, LCL-c, C-reactive protein, resistin, TNF-α and leptin.	Yes	No	29	KD + DHA	6 months supplementation	6 months	600 - 800 Kcal/day	-	10
- ↓ body weight, waist circumference; - HbA1c, glycemia; - adverse effects: asthenia, headache, nausea, vomiting and constipation.	Yes	Yes	89	KD + balanced diet	4 months	30 - 45 days	600 - 800 Kcal/day	Hypocaloric diet with restriction of 500 - 1000 Kcal/day	11
- ↓ body weight, % body fat; - ↓ lean body mass (in maximum ketogenesis period).	No	No	20	KD + balanced diet	4 months	proportional to individual weight loss	600 - 800 Kcal/day	-	12
- ↑ energy expenditure; - ↓ % body fat.	No	No	17	KD or high-carb diet	8 weeks	4 weeks Kcal/day	2394	High-carb diet	13
- ↓ body weight, waist circumference, BMI; - ↓ triacylglycerol, LDL-c, glycemia and urea; - ↑ HDL-c, HbA1c.	Yes	No	363	KD or diet with calorie restriction	24 weeks	24 weeks	-	Low-calorie diet - 2200 Kcal	14
- ↓ body weight (lower than control), abdominal circumference, waist circumference, total body fat, BMI; - ↔ lean body mass.	No	No	18	KD or diet with calorie restriction	3 weeks	3 weeks	450 - 700 Kcal/day	Low-calorie diet - 450 - 700 Kcal/day	15
- ↓ body weight, % body fat; - modulation SOD1 mRNA; - ↓ CRP and glycemia.	Yes	No	54	KD + essential amino acid supplementation	9 weeks	6 weeks	450 - 700 Kcal/day	-	16
- ↓ body weight, % body fat; - ↔ biochemical parameters; - ↑ ALT, creatinine, uric acid.	Yes	Yes	53	KD + Mediterranean diet or diet with calorie restriction	1 year	30 - 45 days	600 - 800 Kcal/day	Low-calorie diet - 1400 - 1800 Kcal/day	17
- ↓ body weight, % body fat, waist circumference.	No	No	55	KD + Mediterranean diet or diet with calorie restriction	2 years	30 - 45 days	600 - 800 Kcal/day	Low-calorie diet - 1400 - 1800 Kcal/day	18
- ↑ hunger.	Yes	No	31	KD + balanced diet	12 weeks	8 weeks	550 - 660 Kcal/day	-	19
- ↓ body weight, % body fat, BMI; - ↓ total cholesterol, LDL-c, triacylglycerol and glycemia; - ↔ ALT, AST, creatinine and BUN.	Yes	Yes	89	KD + Mediterranean diet	1 year	40 days (two phases of 20 days each)	900 - 1000 Kcal/day	Mediterranean diet - 1800 Kcal/day	20
- ↓ body weight, % body fat; - ↓ total cholesterol, LDL-c, triacylglycerol and glycemia, insulin; - ↔ IL-10 and IL-1Ra creatinine, urea and uric acid.	Yes	No	34	KD + w-3 supplementation	4 weeks	4 weeks	1200 Kcal	-	21

Continuación tabla 1

Main outcomes of KD	Biochemical measures	Metabolic effects	n	Intervention	Duration	Active phase (KD)	Calorie value (KD)	Control	Ref
- ↓ body weight, glycemia.	Yes Kcal	No	25	KD or diet control	32 weeks	32 weeks	1768 Kcal	Standard balanced diet-1749	22
- ↓ body weight, % body fat; - ↓ glycemia, insulin; - ↔ triacylglycerol, HDL-c; - ↑ total cholesterol, LDL-c.	Yes	No	42	KD	6 weeks	6 weeks	2300 Kcal	-	23

DISCUSSION

Ketogenic diets have been prescribed since the 1920s as treatment for epilepsy, completely replacing the use of medications in some cases. From the 1960s onwards, however, they became popular for the promotion of weight loss and considered an alternative for obesity treatment. Currently, some studies also indicate the potential of the ketogenic diet in the treatment of other pathologies, such as diabetes, polycystic ovary syndrome, acne, neurological diseases and cancer, and in the control of risk factors for cardiovascular and respiratory diseases⁶.

At the physiological level, the ketogenic diet leads the body to seek alternative sources of energy due to insufficient amounts of glucose reserves resulting from low carbohydrate intake. Considering that glucose is responsible for the production of oxaloacetates involved in the oxidation of lipids in the Krebs cycle and the single energy source for the central nervous system (due to the blood-brain barrier, the use of fatty acids as an energy source is not possible), the organism thus seeks energy derived from the overproduction of acetyl-CoA, with consequent production of so-called ketone bodies (acetate, β -hydroxybutyrate and acetone). This process is called ketogenesis and occurs primarily in the mitochondrial matrix of liver cells. Under normal physiological conditions, the production of ketone bodies is insignificant, being transported to the bloodstream and easily metabolized by tissues (mainly skeletal and cardiac muscle) or eliminated by respiration (in the case of acetone, due to its greater volatility). However, these compounds are accumulated at levels higher than normal under overproduction conditions, and are therefore used as an energy source by tissues. This mechanism involves first the conversion from β -hydroxybutyrate to acetate, which is subsequently converted to acetoacetyl-CoA and finally to two acetyl-CoA molecules, used in the Krebs cycle⁷.

Concerning its prescription in the treatment of obesity and in weight loss, some hypotheses explain weight loss and body fat induced by these diets. Feinman and Fine²⁵ state that weight loss may be related to the use of protein as an energy source, which is a process with greater

energy expenditure in relation to the normal physiological process. Some studies also mention that weight loss can be attributed to reduced appetite due to the increased satiety provided by proteins⁶, to the action of ketone bodies on the direct suppression of appetite⁶, or reduced lipogenesis and increased lipolysis⁸.

In fact, several studies considered in this review corroborate some of these hypotheses, showing weight loss, reduction of body fat and BMI. However, it is not possible to conclude that these changes are due only to the ketogenic diet in the performed experimental design. This issue was mentioned as a limitation in one of the studies, which stated that the observed effects may not be associated with the ketogenic diet, but to the caloric reduction and dietary re-education intrinsic to the phase in which the participants followed the Mediterranean diet⁹.

Based on this reasoning, from the 17 studies, eight assessed the ketogenic diet at medium and long-terms (from three months to two years) by associating it with other periods of Mediterranean diet or another type of diet balanced in nutrients^{8,9,12,13,18,19,20,21}. In these studies, there was significant weight loss, reduced body fat and BMI. However, the effective active phase of ketogenic diet lasted only between 30 and 45 days. Another nine studies assessed the exclusive effect of the ketogenic diet, but five did not use any type of control for comparisons^{10,11,17,22,24}. From the four remaining studies that used a control group, three used unbalanced controls in relation to the caloric values of different treatments, i.e., the groups that received the control diet ingested a higher quantity of calories in relation to the group that received the ketogenic diet^{14,15,23}. For instance, in the study by Hussaim et al.¹⁴ it was stated that the control group received a low-calorie diet, but this diet corresponded to 2200 Kcal/day, which does not seem correct within what is considered a low calorie diet. Only in the study by Merra et al.¹⁶ the control group followed a diet with the same caloric value of the ketogenic diet (450 - 700 Kcal/day). In this study, however, weight loss and body fat was equally proportional to the group that followed the ketogenic diet.

Another clear limitation is the heterogeneity of participants at the beginning of the research, which was cited as a limitation by Alessandro et al.⁸ and Cicero et al.⁹. In the study by Merra et al.¹⁶ although not described as a limitation, in the data presented by the authors, the difference in the initial parameters among groups is clear, which prevents accurate comparisons among diets. Body weight, BMI, total body fat and total lean body mass initially assessed were, respectively, 33%, 15%, 12% and 35% higher in the group that followed the ketogenic diet in relation to the control group.

However, it is known that the loss of body fat and weight is dependent on initial values and other parameters, as demonstrated by Handjjeva-Darlenska et al.²⁶ In this study, authors verified that volunteers with higher initial body composition indices had greater weight losses during a low-calorie diet intervention during eight weeks in relation to those with the lowest initial indices.

Among experimental limitations, we noted that most studies reported significant changes in anthropometric measurements in the first days or weeks of treatment. In these cases, it should be highlighted that the diet, for a short period or not, besides being ketogenic, was calorie-restricted. From the 17 studies, 11 used diets with < 800 Kcal/day. Only four studies used normal caloric diets and two studies did not report the energetic value of prescribed diets^{14,23}. However, the effects of calorie restriction on weight loss and adipose tissue are well established in the scientific literature^{27,28,29}, although the negative effects of these strategies on health are also not yet fully understood.

In the studies evaluated in the present review, another important parameter not considered in many of them was the adverse effects reported by the participants throughout the ketosis period. Based on the 17 studies considered, only eight described whether or not there were reports of any clinically relevant adverse events, which was positive in three^{12,18}. Among the most reported effects were asthenia, headache, nausea, vomiting and constipation.

Indeed, the adverse effects of the ketogenic diet is one of its limitations, even when indicated for treatment of refractory epilepsy. A systematic review published by Cai et al.³⁰ investigated safety and tolerance to ketogenic diet in children with refractory epilepsy by monitoring adverse effects reported by patients. Among the 45 considered studies, from which seven were randomized controlled trials, more than 40 categories of adverse effects were reported: with gastrointestinal disturbances (40.60%), hyperlipidemia (12.80%), hyperuricemia (4.40%), lethargy (4.10%), infectious diseases (3.80%) and hypoproteinemia (3.80%). The review emphasized that approximately half of the patients considered in the studies abandoned the refractory epilepsy treatment with diet due to its low efficacy. The authors also emphasized the need for constant medical monitoring in order to avoid adverse effects of the diet on children's health.

In adults (n= 15), a prospective multicenter study has

provided preliminary evidence that the ketogenic diet may be effective in the treatment of refractory epilepsy. However, some adverse effects have been reported, including metabolic acidosis, hyperlipidemia, constipation, hypoglycemia, hyponatremia, and weight loss³¹.

Regarding the metabolic parameters that indicate possible risks of ketogenic diet mainly on liver, renal and cardiac tissues, from the 17 considered studies, only four reported the assessment of these parameters. The main markers assessed were AST and ALT, uric acid and creatinine. In two studies, no significant differences were observed in the treatment with ketogenic diet. The results of Moreno et al.¹⁸ showed that ALT, creatinine and uric acid levels were significantly increased during the treatment period.

Colica et al.¹⁰ in turn, concluded that the ketogenic diet might contribute to fat loss without negative metabolic and hematological consequences, especially on hepatic, cardiac and renal tissues. However, the results presented by the same authors showed a significant increase in uric acid levels (35% in ketogenic diet and 63% in ketogenic diet and amino acid supplementation), creatinine (5.9%) and AST (25.5 %) in ketogenic diet. The authors also cite that the study was limited in terms of the small number of involved participants, besides the short period of diet administration. If even the short time was sufficient to provide significant changes in the levels of uric acid, creatinine and AST, it is noted that there are divergences among conclusions and the reported results, since there is well established evidence of negative metabolic consequences, especially in hepatic, renal and cardiovascular tissue, including increased levels of uric acid³², creatinine³³ and AST³⁴.

Other studies also report adverse effects on osteoporosis³⁵ and hyperlipidemia³⁶, insulin resistance³⁷, glucose intolerance³⁸ and hepatic steatosis³⁹.

The study by Garbow et al.³⁹ showed that in C57BL/6J mice, the ketogenic diet led to the development of glucose intolerance, endoplasmic reticulum stress, steatosis, cell damage and accumulation of macrophages in relation to traditionally Western diets (high content of simple carbohydrates and saturated fat).

It should be emphasized that in the studies considered in this review that assessed specific metabolic parameters and proposed the safety of this diet, mainly in the medium and long-terms (from six months to one year), the active phase in which the volunteers followed a ketogenic diet was between 30 and 40 days. In the remainder of the period, the volunteers followed a standard or Mediterranean diet, which are intrinsically unbalanced diets for nutrients and their food groups and do not impose extreme restrictions, especially for foods rich in complex carbohydrates, recognized as beneficial to health as already reported in several studies.

Systematic reviews and recent meta-analyses provide robust evidence of this fact^{40,41,42,43}. Particularly, the study by McRae⁴⁰ has important implications. In the study, the author collected several meta-analyses on the beneficial intake of grains and whole grains, published between 1980

and 2016 and concluded that there is strong evidence that the consumption of cereals and whole grains is beneficial for the prevention of numerous pathologies including obesity, type 2 diabetes, cardiovascular diseases, and some cancers. The beneficial potential of these findings suggests that the consumption from two to three servings of food per day (approximately 45 g) can be established as a global public health goal for health promotion.

Many of these benefits are associated to the fact that these foods, despite being rich in carbohydrates, have low glycemic index, besides the presence of fibers and other bioactive compounds. It is worth mentioning that, in the scientific literature, there is consistent evidence of the benefits that diets with low glycemic index, rich in fiber and bioactive compounds bring on numerous physiological conditions, including obesity, diabetes, cardiovascular diseases and cancer^{43,44,45,46}.

In contrast, there is consistent evidence demonstrating the negative influence of a high intake of meat and fats, especially saturated fat, on these same conditions^{47,48,49}.

Considering that ketogenic diets are restricted to foods of plant origin, rich in complex carbohydrates, and abundant in protein and lipids, including the use of formulas and supplements, these diets can be considered nutritionally unbalanced and unsafe, which is corroborated by the most current evidence on nutritional and dietary recommendations. This is based both on the very restrictive nature of the diet and on the lack of scientific evidence that, based on the physiological and metabolic point of view, attests to its safety, as found in the present review.

Another important point to consider is the need for nutritional monitoring. The nutritionist, in the exercise of his or her professional role, should use his or her knowledge to emphasize the importance of the role of healthy eating on the individuals' quality of life and especially to enable the training of subjects in their food choices in order to observe nutritional benefits in the long-term⁵⁰.

Thus, in order to be effective, weight-loss strategies should consider not only the biological food aspects, but also the cultural, social and economic context that equally affect the formation of an individuals' eating habits.

CONCLUSIONS

Based on the above, the data collected in this review shows that there is a great lack of knowledge on the specific physiological mechanisms involved in the ketogenic diet. Much of the evidence published in the scientific literature dealing with this subject, despite showing specific effects on weight loss, BMI reduction and fat percentage, and lowering blood sugar, also demonstrates an unbalanced diet with potential side effects on specific physiological and biochemical parameters, specifically to the hepatic and renal tissues. These side effects have not been investigated properly in the studies.

Furthermore, strategies to control overweight and obesity do not necessarily impose restrictions on certain nutrients,

especially carbohydrates, and, paradoxically, increase the intake of food groups whose excessive consumption has been associated with different pathologies.

REFERENCES

1. World Health Organization. *Obesity and overweight. Fact sheet.* World Health Organization, 2016.
2. Dragano NR, Marques Ay, Cintra DE, Solon C, Morari J, Leite-Legatti AV, Velloso LA, Maróstica-Júnior MR. Freeze-dried jaboricaba peel powder improves insulin sensitivity in high-fat-fed mice. *Br J Nutr* 2013; 110(3): 447-455.
3. Kopelman PG. Obesity as a medical problem. *Nature* 2000; 404: 635-643.
4. Dixit VD. Adipose-immune interactions during obesity and caloric restriction: reciprocal mechanisms regulating immunity and health span. *J Leukoc Biol* 2008; 84(4): 882-892. Cintra DE, Ropelle ER, Pauli JR. *Obesity and Diabetes. Physiology and cellular signaling.* Sarvier, São Paulo, 2011.
5. Gibson AA, Sainsbury A. Strategies to improve adherence to dietary weight loss interventions in research and real-world settings. *Behav Sci* 2017; 7(3): 44.
6. Paoli A. Ketogenic diet for obesity: Friend or foe? *Int J Environ Res Public Health* 2014; 11(2): 2092-2107.
7. Alessandro R, Bosco G, Lodi A, Cenci L, Parmagnani A, Grimaldi K, Zhongjin Y, Paoli A. Effects of twenty days of the ketogenic diet on metabolic and respiratory parameters in healthy subjects. *Lung* 2015; 193(6): 939-945.
8. Cicero AFG, Benelli M, Brancaleoni M, Dainelli G, Merlini D, Negri R. Middle and long-term impact of a very low-carbohydrate ketogenic diet on cardiometabolic factors: a multi-center, cross-sectional, clinical study. *High Blood Press Cardiovasc Prev* 2015; 22(4): 389-394.
9. Colica C, Merra G, Gasbarrini A, De Lorenzo A, Cioccoloni G, Gualtieri P, Perrone MA, Bernardini S, Bernardo V, Di Renzo L, Marchetti M. Efficacy and safety of very-low-calorie ketogenic diet: a double blind randomized crossover study. *Eur Rev Med Pharmacol Sci* 2017; 21(9): 2274-2289.
10. de Luis D, Domingo JC, Izaola O, Casanueva FF, Bellido D, Sajoux I. Effect of DHA supplementation in a very low-calorie ketogenic diet in the treatment of obesity: a randomized clinical trial. *Endocrine* 2016; 54(1): 111-122.
11. Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP, Oleaga A, Moreno B, Casanueva FF. Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. *Nutr Diabetes* 2016; 6(9): e230.
12. Gomez-Arbelaez D, Bellido D, Castro AI, et al. Body composition changes after very-low-calorie ketogenic diet in obesity evaluated by 3 standardized methods. *J Clin Endocrinol Metab* 2017; 102(2): 488-498.
13. Hall KD, Chen KY, Guo J, Lam YY, Leibel RL, Mayer LE, Reitman ML, Rosenbaum M, Smith SR, Walsh BT, Ravussin E. Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am J Clin Nutr* 2016; 104(C):1-10.
14. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* 2012; 28(10): 1016-1021
15. Merra G, Miranda R, Barrucco S, Gualtieri P, Mazza M, Moriconi E, Marchetti M, Chang TF, De Lorenzo A, Di Renzo L. Very-low-calorie ketogenic diet with amino acid supplement

- versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study. *Eur Rev Med Pharmacol Sci* 2016; 20(12): 2613-2621.
16. Merra G, Gratteri S, De Lorenzo A, Barrucco S, Perrone MA, Avolio E, Bernardini S, Marchetti M, Di Renzo L. Effects of very-low-calorie diet on body composition, metabolic state, and genes expression: A randomized double-blind placebo-controlled trial. *Eur Rev Med Pharmacol Sci* 2017; 21(2): 329-345.
 17. Moreno B, Bellido D, Sajoux I, Goday A, Saavedra D, Crujeiras AB, Casanueva FF. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. *Endocrine* 2014; 47(3): 793-805.
 18. Moreno B, Crujeiras AB, Bellido D, Sajoux I, Casanueva FF. Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. *Endocrine* 2016; 54(3): 681-690.
 19. Nymo S, Coutinho SR, Jørgensen J, Rehfeld JF, Truby H, Kulseng B, Martins CI. Timeline of changes in appetite during weight loss with a ketogenic diet. *Int J Obes* 2017; 41(8): 1224-1231.
 20. Paoli A, Bianco A, Grimaldi KA, Lodi A, Bosco G. Long term successful weight loss with a combination biphasic ketogenic Mediterranean diet and Mediterranean diet maintenance protocol. *Nutrients* 2013; 5(12): 5205-5217.
 21. Paoli A, Moro T, Bosco G, Bianco A, Grimaldi KA, Camporesi E, Mangar D. Effects of n-3 polyunsaturated fatty acids (ω -3) supplementation on some cardiovascular risk factors with a ketogenic Mediterranean diet. *Mar Drugs* 2015; 13(2): 996-1009.
 22. Saslow LR, Mason AE, Kim S, Goldman V, Ploutz-Snyder R, Bayandorian H, Daubenmier J, Hecht FM, Moskowitz JT. An online intervention comparing a very low-carbohydrate ketogenic diet and lifestyle recommendations versus a plate method diet in overweight individuals with type 2 diabetes: A randomized controlled trial. *J Med Internet Res* 2017; 19(2): 1-16.
 23. Urbain P, Strom L, Morawski L, Wehrle A, Deibert E, Bertz H. Impact of a 6-week non-energy-restricted ketogenic diet on physical fitness, body composition and biochemical parameters in healthy adults. *Nutr Metab* 2017; 14(1): 17.
 24. Feinman RD, Fine EJ. Nonequilibrium thermodynamics and energy efficiency in weight loss diets. *Theor Biol Med Model* 2007, 4. doi:10.1186/1742-4682-4-27.
 25. Handjieva-Darlenska T, Handjiev S, Larsen TM, van Baak MA, Jebb S, Papadaki A, Pfeiffer AFH, Martinez JA, Kunesova M, Holst C, Saris WHM, Astrup A. Initial weight loss on an 800-kcal diet as a predictor of weight loss success after 8 weeks: the Diogenes study. *Eur J Clin Nutr* 2010; 64(9): 994-999.
 26. Bogdanov AR, Derbeneva SA, Bogdanova AA, Feofanova TB, Panfilova NV, Nesierova VE. Low calorie diet influence optimization on body composition at obese patients with secondary diastolic heart failure. *Vopr Pitan* 2015; 84(4): 37-46.
 27. Norén E, Forssell H. Very low calorie diet without aspartame in obese subjects: improved metabolic control after 4 weeks treatment. *Nutr J* 2014; 13: 77.
 28. Salehi-Abargouei A, Izadi V, Azadbakht L. The effect of low calorie diet on adiponectin concentration: a systematic review and meta-analysis. *Horm Metab Res* 2015; 47(8): 549-555.
 29. Cai QY, Zhou ZJ, Luo R, Gan J, Li SP, Mu DZ, Wan CM. Safety and tolerability of the ketogenic diet used for the treatment of refractory childhood epilepsy: a systematic review of published prospective studies. *World J Pediatr* 2017. doi:10.1007/s12519-017-0053-2.
 30. Cervenka MC, Hocker S, Koenig M, Bar B, Henry-Barron B, Kossoff EH, Hartman AL, Probasco JC, Benavides DR, Venkatesan A, Hagen EC, Ditttrich D, Stern T, Radzik B, Depew M, Caserta FM, Nyquist P, Kaplan PW, Geocadin RG. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. *Neurology* 2017; 88(10): 938-943.
 31. Mortada I. Hyperuricemia, type 2 diabetes mellitus, and hypertension: an emerging association. *Curr Hypertens Rep* 2017; 19(9): 69.
 32. Schiffil H, Lang SM. Update on biomarkers of acute kidney injury: moving closer to clinical impact? *Mol Diagn Ther* 2012; 16(4): 199-207.
 33. Kunutsor SK, Apekey TA, Khan H. Liver enzymes and risk of cardiovascular disease in the general population: a meta-analysis of prospective cohort studies. *Atherosclerosis* 2014; 236(1): 7-17.
 34. Bergqvist AG. Long-term monitoring of the ketogenic diet: Do's and Don'ts. *Epilepsy Res* 2012; 100(3): 261-266.
 35. Kossoff EH, Wang HS. Dietary therapies for epilepsy. *Biomed J* 2013; 36(1): 2-8.
 36. Bisschop PH, de Metz J, Ackermans MT, Endert E, Pijl H, Kuipers F, Meijer AJ, Sauerwein HP, Romijn JA. Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *Am J Clin Nutr* 2001; 73(3): 554-559.
 37. Bielhuby M, Sisley S, Sandoval D, Herbach N, Zengin A, Fischereder M, Menhofer D, Stoehr BJ, Stemmer K, Wanke R, Tschöp MH, Seeley RJ, Bidlingmaier M. Impaired glucose tolerance in rats fed low-carbohydrate, high-fat diets. *Am J Physiol Endocrinol Metab* 2013; 305(9): E1059-1070.
 38. Garbow JR, Doherty JM, Schugar RC, Travers S, Weber ML, Wentz AE, Ezenwajaku N, Cotter DG, Brunt EM, Crawford PA. Hepatic steatosis, inflammation, and ER stress in mice maintained long term on a very low-carbohydrate ketogenic diet. *Am J Physiol Gastrointest Liver Physiol* 2011; 300(6): G956-967.
 39. McRae MP. Health benefits of dietary whole grains: an umbrella review of meta-analyses. *J Chiropr Med* 2017; 16(1): 10-18.
 40. Li B, Zhang C, Tan M, Zhao L, Jin L, Tang X, Jiang G, Zhong K. Consumption of whole grains in relation to mortality from all causes, cardiovascular disease, and diabetes: Dose-response meta-analysis of prospective cohort studies. *Medicine* 2016; 95(33): e4229.
 41. Zong G, Gao A, Hu FB, Sun Q. Whole grain intake and mortality from all causes, cardiovascular disease, and cancer: a meta-analysis of prospective cohort studies. *Circulation* 2016; 133(24): 2370-2380.
 42. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, Tonstad S, Vatten LJ, Riboli E, Norat T. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2016; 353: i2716. doi: 10.1136/bmj.i2716.
 43. Clar C, Al-Khudairy L, Loveman E, Kelly SA, Hartley L, Flowers N, Germanò R, Frost G, Rees K. Low glycaemic index diets for the prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017; 7: CD004467.
 44. Gomes JMC, Fabrini SP, Alfenas RCG. Low glycemic index diet reduces body fat and attenuates inflammatory and metabolic responses in patients with type 2 diabetes. *Arch Endocrinol Metab* 2017; 61(2): 137-144.
 45. Juanola-Falgarona M, Salas-Salvadó J, Ibarrola-Jurado N, Rabassa-Soler A, Díaz-López A, Guasch-Ferré M, Hernández-

- Alonso P, Balanza R, Bulló M. Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation, and other metabolic risk factors: a randomized controlled trial. *Am J Clin Nutr* 2014; 100(1): 27-35.
46. Grosso G, Micek A, Godos J, Micek A, Godos J, Pajak A, Sciacca S, Galvano F, Boffetta P. Health risk factors associated with meat, fruit and vegetable consumption in cohort studies: A comprehensive meta-analysis. *PLoS One* 2017; 12(8): e0183787.
47. Hooper L, Abdelhamid A, Moore HJ, Brown T, Summerbell CD, Skeaff CM. Effect of reducing total fat intake on body weight: systematic review and meta-analysis of randomised controlled trials and cohort studies. *BMJ* 2012; 345: e7666.
48. Hooper L, Abdelhamid A, Bunn D, Brown T, Summerbell CD, Skeaff CM. Effects of total fat intake on body weight. *Cochrane Database Syst Rev* 2015; (8): CD011834.
49. Pereira T de S, Pereira RC, Angelis-Pereira MC de. Influence of pedagogical interventions on knowledge about food and nutrition in adolescents from a public school. *Cien Saude Colet* 2017; 22(2): 427-435.