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Long-Term Ketogenic Diet Alters Kidney Function through Increasing Serum Creatinine Levels in Mice

Alif Lutvyani[1], Artaria Tjempakasari[2], Purwo Sri Rejeki[3,*]

[1] Medicine Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[2] Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

[3] Department of Physiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Abstract: In recent years, the ketogenic diet has become a choice for overweight or obese people to lose weight and healthy people to maintain health. However, the adverse events of a long-term ketogenic diet in the kidney are not very clear. This study aimed to determine the ketogenic diet's long-term effect on serum creatinine as a renal function biomarker. Eighteen male mice (20-30 g) aged 2-3 months were divided into two groups: K1 (standard diet; n=9) and K2 (ketogenic diet; n=9) were given a diet for 8 weeks *ad libitum*. Body weight was measured in pre and post-intervention, serum creatinine levels were measured post-intervention. Serum creatinine levels were measured using a colorimetric assay. Data were analyzed for normality test, independent t-test, and Mann-Whitney using SPSS. ΔBody weight on K1 (17.000±7.089) g, K2 (5.222±4.549) g with p=0.002. Serum creatinine levels on K1 (19.958±4.458) μg/mL, K2 (27.835±7.918) μg/mL with p=0.019. In conclusion, a long-term ketogenic diet increases serum creatinine levels and induced slower body weight gain.

Keywords: ketogenic diet, kidney, mice, serum creatinine.

长期生酮饮食通过增加小鼠血清肌酐水平来改变肾脏功能

摘要：近年来，生酮饮食已成为超重或肥胖的人减肥和健康人保持健康的一种选择。但是，肾脏中长期生酮饮食的不良事件还不是很清楚。这项研究旨在确定生酮饮食对血清肌酐作为肾脏功能生物标志物的长期影响。将 2-3 个月大的 18 只雄性小鼠（20-30g）分成两组：随意给予 K1（标准饮食；n = 9）和 K2（生酮饮食；n = 9），饮食为 8 周。在干预之前和之后测量体重，在干预之后测量血清肌酐水平。使用比色测定法测量血清肌酐水平。使用 SPSS 对数据进行正态性检验，独立 t 检验和曼·惠特尼分析。ody 体重在 K1（17.000±7.089）g，K2（5.222±4.549）g 上，p = 0.002。 K1（19.958±4.458）微克/毫升，K2（27.835±7.918）微克/毫升的血清肌酐水平，p = 0.019。总之，长期生酮饮食会增加血清肌酐水平，并导致体重增加减慢。

关键词：生酮饮食，肾脏，小鼠，血清肌酐。

1. Introduction

Obesity is a complex disease and becomes a global epidemic, with the prevalence rate still increasing. In 2016 obesity affects 650 million people globally. There was a triple increase compared to 1975 [1]. The obesity prevalence in Indonesia increased significantly, 10.5% in 2007, 14.8% in 2013, and 21.8% in 2018 [2]. Meanwhile, obesity correlates with some diseases such as diabetes [3], cancer [4], hypertension [5], and cardiovascular disease [6]. Obesity is a multifactorial disease with multifactorial causes such as genetics, lifestyle, and environment [7]. Obesity is determined by a Body Mass Index (BMI) of more than 30 kg/m^2 [1]. Weight loss is the main goal in many therapies of

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About the authors: Alif Lutvyani, Medicine Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; Artaria Tjempakasari, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; Purwo Sri Rejeki, Department of Physiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Corresponding author Purwo Sri Rejeki, purwo-s-r@fk.unair.ac.id, purwo_faal@yahoo.com

obesity. Factors correlate with weight loss are diet, physical activity, environmental, behavioral, physiological factor, and regulation from hormone and peptide [6]. The ketogenic diet (KD) is one of the non-pharmacological treatments for obesity. The ketogenic diet was first used to treat epilepsy [8] and neurodegenerative diseases [9]. Since 1800, the ketogenic diet trend for weight loss to treat obesity has kept increasing [10]. The ketogenic diet is a low-carbohydrate diet (<50 g/day), high ratio of fat, and moderate to relatively increase protein [11]. A high-fat diet is not safe for kidneys in some studies and can induce kidney dysfunction [12, 13]. Nevertheless, the effect of a long-term ketogenic diet on serum creatinine as a biomarker of kidney function was not explained clearly.

Intake of a high-fat diet and low in carbohydrates can stimulate glucagon and reduce insulin activities. Therefore the ketogenesis process occurs, begins with lipolysis of fat, then the breakdown of glycogen in the liver. This process produces ketone bodies as an energy source. This ketogenesis process increases the levels of ketone bodies in the blood and urine. This condition is called ketosis [14]. Ketosis is believed to have anti-inflammatory effects by suppressing the NLRP3 inflammatory. Pro-inflammatory cytokines include IL-1β and IL-18 from macrophages, production of inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-18, and prostaglandin E2 [15]. A ketogenic diet with the composition of 60% fat, 30% protein, and 10% fiber was proven to have an optimal effect for weight loss and decreasing visceral fat mass [16]. However, a long-term ketogenic diet can induce lipid accumulation in the kidneys, triggering an inflammatory process characterized by increasing pro-inflammatory cytokines IL-1, IL-6, and TNF-α [17]. This inflammatory process can cause glomerular retraction [18]. Thus, kidney function for excretion of metabolic waste through urine and central homeostasis in the body will be disturbed [19]. Disturbances in kidney function can be measured using several biomarkers such as serum creatinine, serum urea, cystatin c, urine albumin, and others [20]. Serum creatinine is a commonly used biomarker because it can detect abnormalities in the glomerulus and kidney tubules. It is easy to obtain, cheap, and known for a long time as the gold standard for examining kidney function [21]. Increasing serum creatinine levels is a sign of impaired kidney function [22]. The previous study showed a different result. Ketogenic diet in rats with the composition of 86.19% fat for 60 days did not significantly increase serum creatinine levels [23]. Nevertheless, another study showed a significant increase in serum creatinine levels in mice with the composition of 43% fat for 32 weeks [24]. According to several studies mentioned above, the ketogenic diet's expected benefits still contradict the side effects. The effect of a long-term ketogenic diet on serum creatinine levels is not known clearly. Hence, it is necessary to research to determine the ketogenic diet's long-term effects on the kidneys using serum creatinine. This study aimed to determine the ketogenic diet's long-term effect for 8 weeks on serum creatinine levels.

2. Materials and Methods

2.1. Experimental Design

This study was a laboratory experiment with a pretest-posttest control group design. The study subjects were 18 male mice (*Mus musculus*), aged 2-3 months, 20-30 gram. The eighteen mice were acclimated using a standard diet and water *ad libitum* in the laboratory for 7 days before starting treatment. The mice were assigned randomly into 2 groups. The control group (K1) was given a standard diet (n=9), and the treatment group (K2) was given a ketogenic diet with a composition of 60% fat, 30% protein, and 10% fiber (n = 9) for 8 weeks and water *ad libitum*. The study was conducted at the Laboratory Animals of Biochemistry, Faculty of Medicine, Universitas Airlangga, for 9 weeks. Animals were maintained under the same condition, with room temperature 37°C±0.5°C, 12-h light/12-h dark cycle. The cage was 30x45x20 cm, made of plastic covered with wire mesh, equipped with a drinking bottle. Each cage is filled with 1 group of 9 mice. Standard and ketogenic diets were given at 11.00 a.m-12.00 p.m. All procedures in this experiment were performed in accordance with animal welfare principles in experimental science published in the European Convention for the Protection of Vertebrate Animal and approved by the Research Ethics Committee of Health Faculty, Faculty of Medicine, Universitas Airlangga (No. 236/EC/KEPK/FKUA/2020).

2.2. Body Weight Measurement

Bodyweight was measured on pre-treatment (before the diet was given) and post-treatment (24-hours after the last diet). Bodyweight was measured using Harnic HL-3650 Heles Digital Scale (scale 0-5 kg).

2.3. Blood Samples

Blood samples were collected through cardiac puncture 24-hours after the last diet, then centrifuged for 5 minutes with the rate of 4,000 rpm to collect the serum.

2.4. Serum Creatinine Levels Assessment

Serum creatinine levels were determined using a calorimetric assay (StressXpress Creatinine Serum Detection Kit, StressMarq Biosciences, Victoria BC, Canada) according to the instruction on the reagent kit. Kit sensitivity is 0.081 mg/dL and the assay range is 0.5 - 4 mg/dL.

2.5. Statistical Analysis

The obtained data were analyzed using Statistic Package for Social Science (SPPS) IBM 16 software. Data distribution was examined to determine the data distributed normally or not by the Shapiro Wilk test. The data with normal distribution were analyzed with an Independent t-test, while the Mann-Whitney test analyzed the data with no normal distribution. The result with $p<0.05$ shows a significant difference. All data were presented by mean±SD.

3. Result

Results of pre-treatment, post-treatment body weight are shown in Table 1.

Table 1 Characteristics of the subjects

Variable	K1 (n=9)	K2 (n=9)	Independent T-Test P-Value
Pre-treatment body weight (g)	25.333±2.398	27.111±2.088	0.113
Post-treatment body weight (g)	41.556±7.699	32.333±5.123	0.009

Note: Data are presented as mean±SD. K1: Standard Diet; K2: Ketogenic Diet.

This study results in no significant difference in K1 and K2 pre-treatment body weight ($p>0.05$). Bodyweight on K1 and K2 post-treatment showed significantly different ($p<0.05$). The ketogenic diet group has a lower weight at the end of this study. Statistical analysis result of delta (Δ) body weight is displayed in Fig. 1. The difference of body weight (Δ) also significantly different on K2 compared with K1 (17.000±7.089 vs. 5.222±4.549 g, (p-value=0.002)). Δ Bodyweight on the ketogenic diet is lower than the standard diet. The analytical result of post-intervention serum creatinine levels is shown in Fig. 2. After 8 weeks on a diet, serum creatinine levels were significantly increased on the ketogenic diet compared to the standard diet (19.958±4.458 vs. 27.835±7.918 µg/mL, (p-value=0.019)).

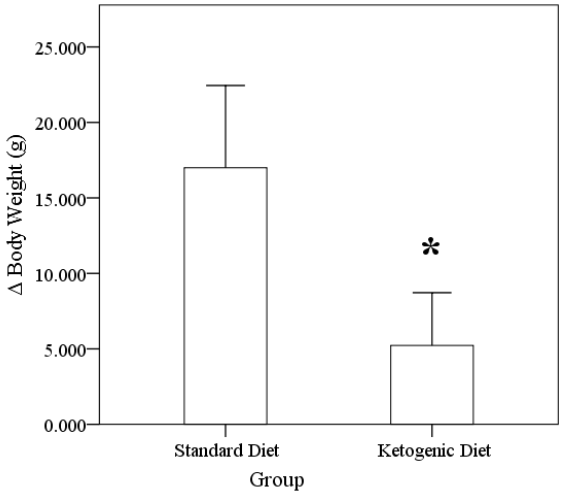

Fig. 1 Delta (Δ) body weight (g)
* There was a significant difference ($p<0.05$) in the Mann-Whitney test

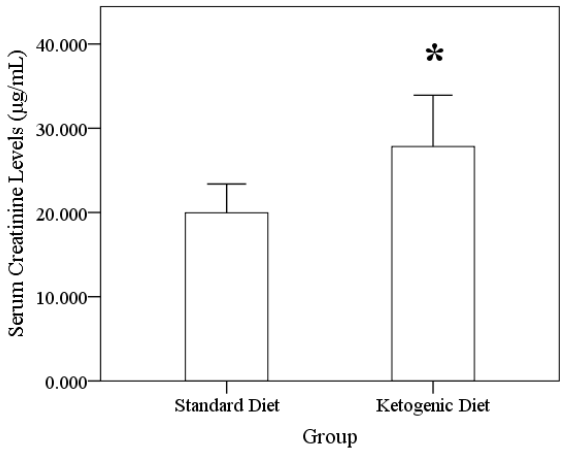

Fig. 2 Serum creatinine levels
* There was a significant difference ($p<0.05$) in independent T-test

4. Discussion

In this study, 8 weeks ketogenic diet in mice showed slowed weight gain and elevated serum creatinine levels compared with the standard diet. The mean serum creatinine levels post-intervention in the ketogenic diet showed a significant difference ($p=0.019$). Serum creatinine levels in the ketogenic diet were significantly increased compared with the standard diet. These results are consistent with the ketogenic diet in 30 days in rats with the composition of 65% fat [22] and the ketogenic diet in mice with the composition of 43% fat for 32 weeks [25].

This diet causes a condition that mimics fasting. The body will use stored fat as an energy source through the fat oxidation process, which produces ketone bodies. High levels of circulating ketone bodies result in a condition called ketosis [26]. Ketosis induced decrease insulin levels and increase glucagon levels, resulting in lipolysis, glycogenolysis, and gluconeogenesis [24]. This causes increase fat in the circulation, accumulation of fat in the visceral organs and bone marrow [17]. Accumulation of fat in the kidneys can occur in mesangial cells, podocytes, proximal tubules, and tubulointerstitial tissue, which will affect the structure and function of the nephrons [27].

Accumulation of fat in the kidneys can increase pro-inflammatory cytokines such as interleukin-1 (IL-1),

interleukin-6 (IL-6), and TNF-α [17]. Inflammation in the kidney and systemic will induce the secretion of hormones and vasoactive molecules such as prostaglandins, endothelin, kinins, medulipine, nitric oxide, and other molecules. Slight changes in the intermolecular balance can interfere with kidney function because kidneys have a microvascular system to balance the osmotic gradient in fluid absorption and urine concentration. Increased production of reactive oxygen/nitrogen species, bioactive compounds in lipids, and intermolecular adhesion in the inflammatory process will lead to the progression of Chronic Kidney Disease (CKD) [24].

Fat accumulation can stimulate a vasoactive hormone (angiotensin II), which caused glomerular retraction due to glomerular mesangial cells' contraction [18]. Furthermore, this regulatory disorder can cause damage to podocyte cells, proximal tubules, and tubulointerstitial tissue [14]. This causes proteinuria, loss of podocyte cells, insulin resistance, oxidative stress, fibrosis, apoptosis, and hypertrophy, leading to chronic kidney disease (CKD) [28]. Kidney function as an excretory organ can be impaired and cause decreasing in GFR value. A decrease in GFR can be identified through one of the biomarkers, namely serum creatinine. An increase in serum creatinine levels indicates decreased GFR, which can be caused by decreased kidney function [29].

PAS (periodic acid Schiff) staining carried out in the high-fat diet group at 32 weeks showed glomerulosclerosis score index was higher than the standard feed group, presence of tubulointerstitial fibrosis include interstitial dilation, accumulation of inflammatory cells, tubular atrophy, and tubular basement membrane, which shrink and/or thicken, cast on the tubule. The most visible thing is the presence of tubular vacuolation and tubular dilation [25]. In physiological conditions, the kidneys have the ability to heal on their own after minor structural abnormalities, but if there is continuous damage or severe damage can form fibrosis. This tubulointerstitial fibrosis can cause kidney function to decrease progressively [30]. There are two types of glomerulosclerosis, crescent and global glomerulosclerosis, high glomerulosclerosis score indicating the extent of glomerulosclerosis. Crescent glomerulosclerosis in more than 25% of the glomerulus causes progressive progression of the disease and requires early pharmacological therapy. Global glomerulosclerosis is an indicator of a rapidly progressing irreversible structural disorder, failure of therapy, and a worse renal function decline [31]. Elevation of serum creatinine levels and decrease of eGFR were seen in patients with focal segmental glomerulosclerosis (FSGS), which indicates a deterioration in the patient's prognosis. The prognosis of patients who develop end-stage kidney disease (ESKD) is confirmed if the elevated serum creatinine is accompanied by tubulointerstitial fibrosis [32].

Bodyweight before intervention shows no significant difference (p=0.113), it means the characteristic of all subjects in two groups was same before the intervention. In this experiment, body weight post-intervention was significantly different (p=0.009), and the ketogenic diet group showed lower body weight than the standard diet group. Delta (post – pre-intervention) body weight showed a significant difference (p=0.002), and lower weight gain was presented in the ketogenic diet. These results are consistent with the previous report concluding that a ketogenic diet with 90% lipid and 10% protein induced slower weight gain [33]. In another study, ketogenic and standard diet showed increased body weight after 4 weeks of the intervention [34]. The difference between the two groups is that the ketogenic diet increased body fat mass and decreased lean body mass. In contrast, the control group reported no change in the proportion between fat mass and lean body mass. This condition began in the second week. Moreover, significant weight loss is accompanied by reducing of visceral fat [16].

The mechanism of the slowdown weight gain in the ketogenic diet is not completely clear. One of the mechanisms that occur is changes in resting energy expenditure [14]. A decrease in carbohydrates' composition, accompanied by a fixed amount of protein and total calories, can induce energy expenditure changes. In the carbohydrate-insulin hypothesis, it is explained that a decrease in the ratio of carbohydrates to fat accompanied by a fixed amount of protein and total energy can reduce insulin levels in the circulation, therefore triggers lipolysis and oxidation of the stored fat cause an increase in energy demand. Otherwise, in the energy balance hypothesis, the fat consumed has the same calories as carbohydrates. The result showed no change in energy requirements [35].

Ketogenic diet with or without aerobic exercise for 6 weeks in mice with diabetes showed a lower body weight than diabetic mice without treated by ketogenic diet with or without aerobic exercise. Mice that received a ketogenic diet with or without aerobic exercise experienced decreased food and drink intake, resulting in weight loss [36]. Elevated ketone levels, ketosis, can trigger central and peripheral stimuli that can induce anorexigenic effects [37]. Ketone bodies have the ability to reduce appetite, especially in β-hydroxybutyrate, which is a signal of energy and satiety (central satiety signal) [38]. Significant weight loss can occur if orexigenic triggers were inhibited, such as inhibiting ghrelin and increasing leptin levels, so that appetite decreases [37].

A significant increase of serum creatinine levels in a long-term ketogenic diet is important cautions. Based on this study, a ketogenic diet for 56 days in mice showed increasing serum creatinine levels. If converted to human age, it will take about 6 years [39]. Therefore, the ketogenic diet for a duration of 6 years

in humans can harm the kidneys. Reduce renal function for creatinine excretion may induce renal injury or kidney disease such as kidney stone [40]. Patients who suffer from kidney disease should avoid using this diet to prevent chronic kidney disease development [28]. Weight loss in a ketogenic diet is a benefit to treat overweight or obesity. It also can be an option to treat DMT2 because it can resolve hyperglycemia, lowered fasting insulin levels, decreased insulin resistance, and minimum intake of oral glycemic or insulin medication [40].

5. Conclusion

This study showed that a long-term ketogenic diet in 8 weeks increases serum creatinine levels and slows down weight gain. Slowed weight gain resulting from a ketogenic diet can be used as a non-pharmacological treatment for obesity and diabetes patients. Nevertheless, the ketogenic diet's long-term effect should be an important caution, especially the kidney's adverse event, such as kidney stone. Patients who suffer from kidney disease should avoid using this diet to prevent chronic kidney disease development. Therefore, further studies and explanations are needed to analyze the kidney histopathology after ketogenic diet to certain the morphological damage and combining with other biomarkers such as cystatin c and urine albumin to creatinine ratio for better confirmation. Additional research is needed to determine the safe duration of the ketogenic diet, which has optimal benefits with a minimum side effect.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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