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> Title of your paper: Long-Term Ketogenic Diet Alters Kidney Function Through Increasing Serum Creatinine Levels in Mice
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> Keywords: ketogenic diet, kidney, long-term, mice, serum creatinine
> Abstract: In recent years, ketogenic diet has become a choice not only for overweight or obese people to lose

weight, but also for healthy people to maintain health. However, the adverse events of long-term ketogenic diet in kidney are not very clear. The aim of this study was to determine the long-term effect of ketogenic diet on serum creatinine as a biomarker of renal function. 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 diet for 8 weeks ad libitum. Body weight were 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. ï€„Body weight on K1 (17.000Â±7.089) g, K2 (5.222Â±4.549) g with p=0.002. Serum creatinine levels on K1 (19.958Â±4.458) Âµg/mL, K2 (27.835Â±7.918) Âµg/mL with p=0.019. In conclusion, long-term ketogenic diet increase serum creatinine levels and induced slower body weight gain.

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

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Abstract : In recent years, ketogenic diet has become a choice not only for overweight or obese people to lose weight, but also for healthy people to maintain health. However, the adverse events of long-term ketogenic diet in kidney are not very clear. The aim of this study was to determine the long-term effect of ketogenic diet on serum creatinine as a biomarker of renal function. 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 diet for 8 weeks *ad libitum*. Body weight were 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, long-term ketogenic diet increase serum creatinine levels and induced slower body weight gain.

Keywords : *ketogenic diet, kidney, long-term, 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

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摘要：近年来，生酮饮食不仅成为超重或肥胖者减肥的选择，而且成为健康人保持健康的选择。但是，长期的生酮饮食对肾脏的不良影响还不是很清楚。这项研究的目的是确定生酮饮食对血清肌酐作为肾脏功能的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 8 周。在干预前后测量体重，在干预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 Mann-Whitney 分析。Δ 体重在 K1（17.000±7.089）g，K2（5.222±4.549）g 上，p = 0.002。 K1（19.958±4.458）μg / mL，K2（27.835±7.918）μg / mL 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，长期，小鼠，血清肌酐

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1. Introduction

Obesity is a complex disease and become a global epidemic with prevalence rate still increasing. In 2016 obesity affects 650 million people in the world, there was 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 has correlation with some diseases such as diabetes [3], cancer [4], hypertension [5], and cardiovascular disease [6]. Obesity is known as a multifactorial disease which has multifactorial causes such as genetic, lifestyle, and environment [7]. Obesity is determined by Body Mass Index (BMI) more than 30 kg/m^2 [1]. Weight loss is the main goal in many therapies of obesity. Factors correlate with weight loss are diet, physical activity, environmental, behavioral, physiological factor, and regulation from hormone and peptide [6]. Ketogenic diet (KD) is one of non-pharmacological treatments for obesity. Ketogenic diet was first used as a treatment of epilepsy [8] and neurodegenerative diseases [9]. Since 1800, trend of ketogenic diet for weight loss to treat diseases such as obesity was keep increasing [10]. Ketogenic diet is a low-carbohydrate diet (<50 g/day), high ratio of fat, and moderate to relatively increase protein [11]. In some studies, high fat diet is not safe for kidney and can induce kidney dysfunction [12,13]. Nevertheless, the effect of long-term ketogenic diet on serum creatinine as biomarker of kidney function was not explained clearly.

Intake of 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 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, production of 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]. Ketogenic diet with the composition of 60% fat, 30% protein, and 10% fiber was proven as the composition which has optimal effect for weight loss and decreasing visceral fat mass [16]. However, long-term ketogenic diet can induce accumulation of lipid 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 of can detect abnormalities in the glomerulus and kidney tubules, easy to obtain, cheap, and has been known since a long time as the gold standard for examining kidney function [21]. Increasing serum creatinine levels is a sign of impaired kidney function [22]. Previous study showed different result. Ketogenic diet in rats with composition of 86.19% fat for 60 days did not significantly increase serum creatinine levels [23], nevertheless in another study showed significant increase of serum creatinine levels in mice with composition of 43% fat for 32 weeks [24]. According to several studies mentioned above, the expected benefits of the ketogenic diet are still contradicting with the side effects and the effect of long-term ketogenic diet in serum creatinine levels is not known clearly, so it is necessary to conduct research to determine the long-term effects of the ketogenic diet on the kidneys using serum creatinine. The aim of this study was to determine the long-term effect of the ketogenic diet 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. Subjects of the study were 18 male mice (*Mus musculus*), aged 2-3 months, 20-30 gram. The eighteen mice were acclimated using 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) given standard diet (n=9) and the treatment group (K2) 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 or 9 mice. Standard and ketogenic diet 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 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

Body weight were measured on pre-treatment (before the diet was given) and post-treatment (24-hours after the last diet). Body weight were 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 which has normal distribution were analyzed with *Independent t-test, while the data which has not* normal distribution were analyzed by Mann-Whitney test. 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 no significant difference on K1 and K2 pre-treatment body weight ($p>0.05$). Body weight on K1 and K2 post-treatment showed significantly different ($p<0.05$). Ketogenic diet group has a lower weight at the end of this study. Statistical analysis result of delta (Δ) body weight is displayed in Figure 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 Body weight on ketogenic diet is lower than standard diet. The analytical result of post-intervention serum creatinine levels is showed in Figure 2. After 8 weeks on diet, serum creatinine levels were significantly increased on ketogenic diet compared to the standard diet (19.958±4.458 vs. 27.835±7.918 µg/mL, (p-value=0.019)).

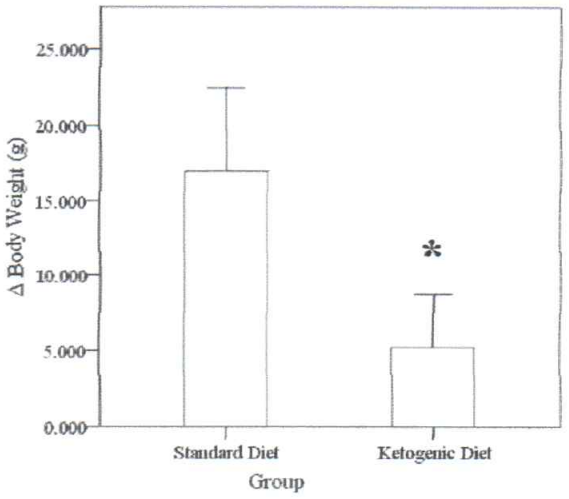

Fig. 1 Delta (Δ) body weight (g). *There was significant difference ($p<0.05$) in Mann-Whitney test

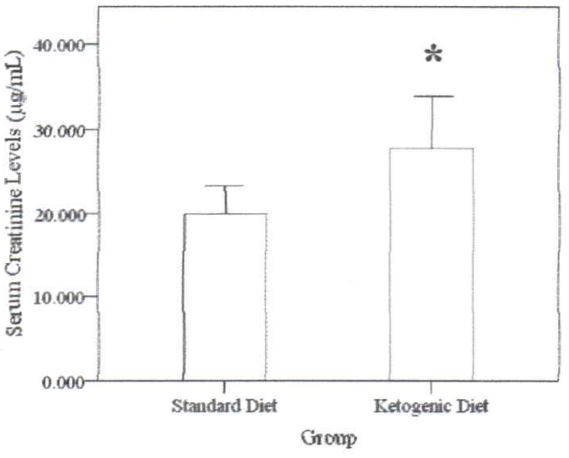

Fig.2 Serum creatinine levels. *There was significant difference ($p<0.05$) in Independent T-Test

4. Discussion

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

This diet causes a condition that mimic 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 in pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-α [17]. Inflammation that occurs 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 kidney function because kidneys have a microvascular system to maintain balance of the osmotic gradient in fluid absorption and urine concentration. Increased production of reactive oxygen/nitrogen species, bioactive compounds in lipids, and intermolecular adhesion that occurs in the inflammatory process will lead to progression of Chronic Kidney Disease (CKD) [24].

Fat accumulation can stimulate a vasoactive hormone (angiotensin II) which caused glomerular retraction due to contraction of glomerular mesangial cells [18]. Furthermore, this regulatory disorder can causes damage to podocyte cells, proximal tubules, and tubulointerstitial tissue [14]. This causes proteinuria, loss of podocyte cells, insulin resistance, oxidative stress, fibrosis, apoptosis, hypertrophy which can lead to chronic kidney disease (CKD) [28]. Kidney function as an excretory organ can be impaired and cause decreasing of GFR value. Decrease of GFR can be identified through one of the biomarkers, namely serum creatinine. An increase in serum creatinine levels indicates a decrease in 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, and the most visible thing is the presence of tubular vacuolation and tubular dilation [25]. In physiological conditions, the kidneys have 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 extent of glomerulosclerosis. Crescent glomerulosclerosis in more than 25% of the glomerulus causes progressive progression of disease and requires early pharmacological therapy. Global glomerulosclerosis is an indicator of a rapidly progressing irreversible structural disorder, failure of therapy, and a worse decline in renal function [31]. Elevation of serum creatinine levels and decrease of eGFR were seen in patients with focal segmental glomerulosclerosis (FSGS), which indicate 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].

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

The mechanism of the slowdown weight gain in the ketogenic diet is not completely clear. One of the mechanisms that occurs is changes in resting energy expenditure [14]. A decrease in the composition of carbohydrates, accompanied by fixed amount of protein and total calories can induce changes in energy expenditure. In the carbohydrate-insulin hypothesis, it is explained that a decrease in the ratio of carbohydrates to fat accompanied by 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, fat consumed has 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 compared to diabetic mice without treated by ketogenic diet with or without aerobic exercise. Mice

that received a ketogenic diet with or without aerobic exercise experienced a decrease intake of food and drink, resulting in weight loss [36]. Elevated ketone levels, ketosis, can trigger central and peripheral stimuli that can induce anorexigenic effects [37]. Ketone bodies have ability to reduce appetite, especially in β-hydroxy butyrate 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].

Significant increase of serum creatinine levels in long-term ketogenic diet is important cautions. Based on this study, 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 use of 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 suffer kidney disease should avoid using this diet to prevent the development of chronic kidney disease [28]. Weight loss in ketogenic diet is a benefit to treat overweight or obesity. It also can be the option to treat DMT2 because 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 long-term ketogenic diet in 8 weeks increases serum creatinine levels and slows down weight gain. Slowed weight gain resulting from ketogenic diet can be used as non-pharmacological treatment for obesity and diabetes patients. Nevertheless, long-term effect of ketogenic diet should be an important caution, especially the adverse event in kidney such as kidney stone. Patients suffer kidney disease should avoid using this diet to prevent the development of chronic kidney disease. 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 ketogenic diet which has optimal benefits with 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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