The effect of long term ketogenic diet on serum adiponectin and insulin-like growth factor 1 levels in mice

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Abstract

Objectives: Noncommunicable disease (NCD) including obesity, cancer, and diabetes has become particular concern worldwide due to its morbidity and mortality which keep increasing annually. Adiponectin and insulin-like growth factor-1 (IGF-1) are known to be substances that are involved in the development of NCD. Several diet regimens have been developed to treat NCD, one of which is the ketogenic diet (KD). This study aimed to analyze the long-term KD effect on serum adiponectin and IGF-1 levels in mice.

Methods: This study was a real experimental with post-test only controls group design. The subjects were 14 male mice (2–3 months, 20–30 g) were randomly divided into two groups, K1 (n=7, standard diet) and K2 (n=7, KD with a composition of 60% fat, 30% protein, and 10% fiber). All subjects were given diet intervention for 8 weeks *ad libitum*. Serum adiponectin and IGF levels were measured in post-intervention using Enzyme-Linked Immunosorbent Assay. Distribution of normality was analyzed by the Shapiro–Wilk Test, mean difference using Independent T-Test, and linear correlation using Pearson's Correlation Test. Data analysis was performed using Statistic Package for Social Science Version 16.

Results: Serum adiponectin levels in K1 (0.080 ± 0.012) pg/mL and K2 (0.099 ± 0.005) pg/mL, with p=0.003. Serum IGF-1 levels in K1 (133.535 ± 25.702) ng/mL and K2 (109.987 ± 27.118) ng/mL, with p=0.121. Coefficient correlation between serum adiponectin and serum IGF-1 levels [r]=−0.401, with p=0.155.

Conclusions: Long-term KD increases serum adiponectin levels and has no effect on serum IGF-1 levels. There was no significant correlation between serum adiponectin and serum IGF-1 levels.

Keywords: adiponectin; IGF-1; ketogenic diet; long-term; mice; obesity.

Introduction

Noncommunicable disease (NCD) including cancer and diabetes has become the major health concern particularly for developing countries and contributed to 71% of all deaths in each year globally [1]. On the other hand, there are many risk factors contributing to NCDs including metabolic changes caused by obesity [2]. Based on GLOBOCAN data, estimated that there were 19.3 million new cancer cases associated with almost 10 million deaths in 2020 [3]. Meanwhile, the global diabetes prevalence is estimated to increase from 9.3% to 10.2% between 2019 and 2030, which is equivalent to 578 million people living with diabetes [4]. Furthermore, obesity prevalence which also plays a role in these diseases has increased from 3.2% to 10.8% in adult men and from 6.4% to 14.9% in adult women between 1975 and 2014 [5]. Many nonpharmacological approaches have been developed as therapeutic treatments for these diseases, one of which is the ketogenic diet (KD) [6]. KD is characterized by a reduction in dietary carbohydrate intake of less than 20 g/day or less than 5% of total daily calories, followed by high dietary fat intake and moderate intake of protein. Decrease in blood glucose levels due to low carbohydrate intake switches the body metabolism toward fat oxidation to produce ketone bodies as an alternative energy source, which eventually results in increased ketone body levels known as nutritional ketosis [7].

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Obesity can increase the risk of cancer and diabetes through modulation of adiponectin and insulin-like growth factor-1 (IGF-1) [8]. Adiponectin is the most abundant anti-inflammatory peptide secreted by adipose tissue whose acts as an active regulator of glucose intake, increase insulin sensitivity, and its level physiologically increases during weight loss [9]. Meanwhile, IGF-1 is a polypeptide hormone that is structurally similar to human pro-insulin which plays a role in normal cell growth [10]. High glucose and carbohydrate intake in obesity lead to an increase in insulin secretion that promotes IGF-1 elevation [6]. Chronic inflammation that also occurs in obesity leads to insulin resistance that is known to increase IGF-1 levels, which later contribute to cancer cells development by stimulating cell proliferation and inhibiting apoptosis [10]. Insulin resistance in obesity also promotes suppression of adiponectin and this condition is associated with IGF-1 levels increasement [8]. Thus, adiponectin levels have been known to decrease under certain conditions including obesity, cancer, and diabetes [11].

Nowadays, increased adiponectin and decreased IGF-1 starting to be the targets of KD as a treatment of obesity and cancer. Short-term KD has been known to have beneficial effects against obesity by inducing weight loss associated with increased adiponectin levels [9]. Previous studies in mice using KD regimen consisting of 60% fat, 30% protein, and 10% fiber for 4 weeks also showed a decrease in body weight and visceral fat mass [12]. However, the long-term effect of this KD composition on IGF-1 and adiponectin levels is not clearly understood and still requires further research. Therefore, this study aimed to find out the long-term KD effect on serum adiponectin and IGF-1 levels in mice. A previous study regarding the correlation between adiponectin and IGF-1 showed that there was still an inconsistent association between adiponectin and IGF-1 [13]. Considering the involvement of adiponectin and IGF-1 in the development of several diseases, this study also evaluates the correlation between serum adiponectin and IGF-1 levels.

Materials and methods

Ethical approval

This experimental study was conducted under the approval of the Research Ethics Committee of Health Faculty, Faculty of Medicine, Universitas Airlangga (No. 235/EC/KEPK/FKUA/2020).

Experimental design

This study was a real experimental study with post-test-only control group design. The subjects of the study were 14 male mice (*Mus musculus*), aged 2–3 months, with bodyweight of 20–30 g. All subjects were acclimatized for 7 days with a given standard diet *ad libitum* and divided randomly into two groups. The control group (K1, n=7) was given a standard diet (2.99 kcal/g) and the intervention group (K2, n=7) was given a KD with a composition of 60% fat, 30% protein, and 10% fiber (4.74 kcal/g) for 8 weeks *ad libitum*.

Animal handling

This study was conducted at the Laboratory Animals of Biochemistry, Faculty of Medicine, Universitas Airlangga for 8 weeks. The room temperature used for animal handling was 37 ± 0.5 °C. The cage was 30 × 45 × 20 cm, made of plastic covered with wire mesh, equipped with a drinking bottle; each cage is filled with one group of seven mice. Lighting was set on a dark-light cycle with regulation of 12 h of light and 12 h of darkness. Standard diet and KD were given at 11.00 a.m.–12.00 p.m. The present study followed animal welfare principles in experimental science published in the European Convention for the Protection of Vertebrate Animal.

Measurement of body weight

Measurement of body weight was carried out on the first day (before the diet was given) and post-intervention (24 h after the last diet was given). Bodyweight was measured using Harnic HL-3650 Heles Digital Scale (scale 0–5 kg).

Measurement of blood glucose levels

Measurement of blood glucose levels was carried out on the first day (before the diet was given) and post-intervention (24 h after the last diet was given). Blood samples were obtained from the tail. Measurement performed using the Auto check Multi-Monitoring System (detection range 20–600 mg/dL).

Measurement of blood ketone levels

Measurement of blood ketone levels was carried out on the first day (before the diet was given) and post-intervention (24 h after the last diet was given). Blood samples were obtained from the tail. Measurement performed using the Abbott Freestyle Optimum Neo Blood Glucose and Ketones (detection range 0.0–8.0 mmol/L).

Blood and serum samples

Collection of blood samples were carried out 24 h after the last diet was given, through the bcardiac puncture method. Blood samples collected were centrifuged at 4,000 rpm for 5 min to obtain serum samples.

Measurement of serum adiponectin levels

Serum adiponectin levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalog No. E-EL-M0002;

Elabscience Biotechnology, Wuhan, China) with a detection range of 15.63–1,000 pg/mL and sensitivity up to 9.38 pg/mL.

Measurement of serum IGF-1 levels

Serum IGF-1 levels were measured using the ELISA kit (Catalog No. E-EL-M3006; Elabscience Biotechnology, Wuhan, China) with a detection range of 15.63–1,000 ng/mL and sensitivity up to 9.38 ng/mL.

Measurement of visceral fat mass

Following euthanasia, visceral fat was dissected and collected from the omental, retroperitoneal, perirenal, mesenteric, and pericardial parts. Then, the total visceral fat mass was measured using Pocket Digital Scale 200 g.

Statistical analysis

Data were analyzed for distribution normality by the Shapiro–Wilk Test. Mean differences in body weight, blood glucose levels, blood ketone levels, visceral fat mass, serum adiponectin levels, and serum IGF-1 levels were analyzed using Independent T-Test. Correlation between visceral fat mass and serum adiponectin levels, also between serum IGF-1 and serum adiponectin levels were analyzed using Pearson's correlation test. Data analysis was performed using Statistic Package for Social Science (SPPS) software version 16 (SPSS Inc., Chicago, IL, USA). All data were presented as Mean ± SD.

Results

The mean analysis results of body weight, blood glucose levels, and blood ketone levels in pre- and post-intervention can be seen in Table 1. There were no significant differences on all parameters in pre-intervention measurement between the control group (K1) and the KD group (K2) ($p \geq 0.05$). Post-intervention body weight in K2 was lower than K1 and the increase of body weight after 8 weeks of intervention was lower in K2 compared to K1. There were significant differences in post-intervention and delta (Δ) body weight between K1 and K2 ($p<0.005$). Post-intervention blood glucose levels in K2 were significantly lower than K1 ($p<0.005$). After 8 weeks of intervention, there was a decrease in blood glucose levels in K2 and an increase in K1. There was a significant difference between Δ blood glucose levels in K1 and K2 ($p<0.005$). Post-intervention blood ketone levels in K2 were significantly higher than the K1 ($p<0.005$). Results of Δ blood ketone levels after 8 weeks of diet intervention show an increase in K2 and a decrease in K1. There was a significant difference in Δ blood ketone levels between K1 and K2 ($p<0.005$). The results of the mean comparative analysis can be seen in Table 1.

After 8 weeks of diet intervention, the mean visceral fat mass in K2 (0.086 ± 0.426) g was lower compared to K1 (1.593 ± 0.826) g. There was a significant difference between visceral fat mass in K1 and K2, with p=0.014 (Figure 1). Serum adiponectin levels in K2 (0.099 ± 0.005) pg/mL was significantly higher than the K1 (0.080 ± 0.012) pg/mL, with p=0.003 (Figure 2). Serum IGF-1 levels in K2 (109.987 ± 27.118) ng/mL was lower compared to the K1 (133.535 ± 25.702) ng/mL. However, there was no significant difference in serum IGF-1 levels between K1 and K2, with p=0.121 (Figure 3).

The parametric analysis by Pearson's linear correlation test shows that serum adiponectin levels were significantly and negatively correlated with the visceral fat mass ($r=-0.709$, p=0.004) (Figure 4). Pearson's test also shows a negative correlation between serum adiponectin levels and serum IGF-1 levels. However, there was no statistically significant correlation was observed ($r=-0.401$, p=0.155) (Figure 5).

Discussion

Based on our study results, a long-term KD for 8 weeks significantly increased serum adiponectin levels in mice.

Table 1: Results of body weight, blood glucose levels, and blood ketone levels.

Variable	Time	K1 (n=7) (Mean ± SD)	K2 (n=7) (Mean ± SD)	p-Value
Body weight, g	Pre-intervention	26.290 ± 3.302	27.000 ± 1.826	0.626
	Post-intervention	42.570 ± 5.563	29.860 ± 6.067	0.002[a]
	Delta (Δ)	16.290 ± 5.155	2.860 ± 5.242	0.000[a]
Blood glucose levels, mg/dL	Pre-intervention	131.14 ± 22.952	139.67 ± 29.940	0.308
	Post-intervention	147.570 ± 20.280	89.570 ± 11.588	0.000[a]
	Delta (Δ)	16.430 ± 20.305	−55.710 ± 22.470	0.000[a]
Blood ketone levels, mmol/L	Pre-intervention	0.914 ± 0.241	0.700 ± 0.238	0.120
	Post-intervention	0.357 ± 0.098	0.786 ± 0.329	0.006[a]
	Delta (Δ)	−0.557 ± 0.207	0.086 ± 0.426	0.004[a]

[a]There was a significant difference ($p<0.05$) in Independent T-Test.

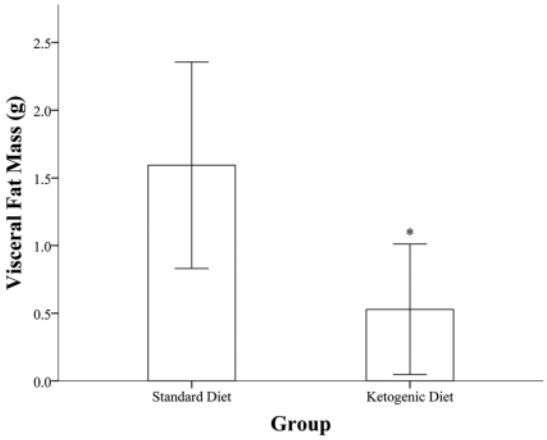

Figure 1: Visceral fat mass after 8 weeks of diet intervention. *There was a significant difference ($p<0.05$) in Independent T-Test.

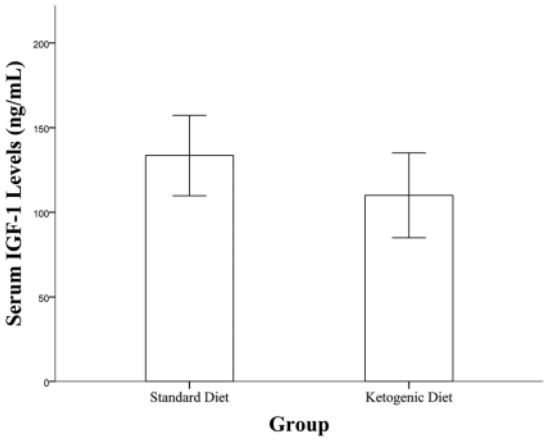

Figure 3: Serum IGF-1 levels after 8 weeks of diet intervention.

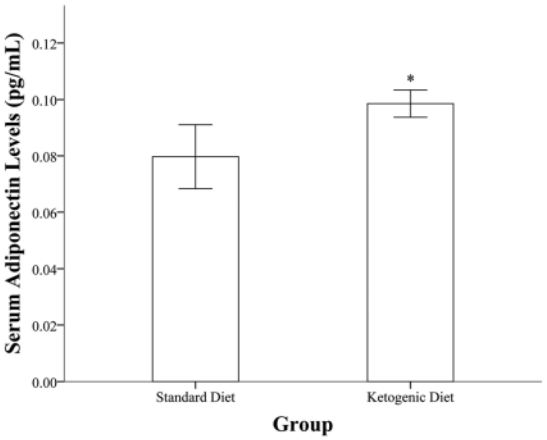

Figure 2: Serum adiponectin levels after 8 weeks of diet intervention. *There was a significant difference ($p<0.05$) in Independent T-Test.

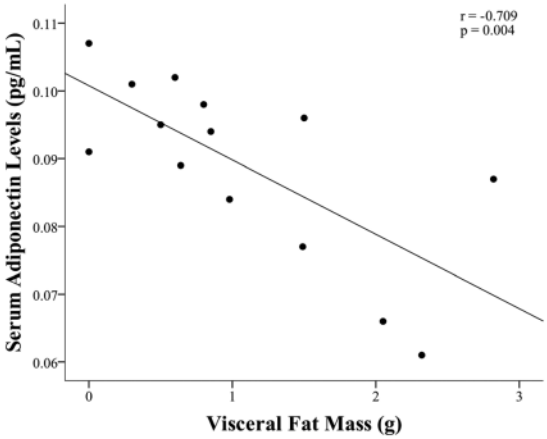

Figure 4: Serum adiponectin levels were negatively correlated with visceral fat mass.

This finding is consistent with several previous studies. A study conducted by Sena et al. [14] showed that a high-fat diet significantly increased adiponectin levels. As mentioned by Monda et al. [9], the study that investigated obese people who were given a very low-carbohydrate KD also showed that adiponectin levels increased significantly after 8 weeks of dietary intervention.

The KD is a high-fat diet with low-carbohydrate and adequate protein intake. In this condition, there will be a decrease in insulin secretion and an increase in glucagon levels. The body will increase lipolysis and ketogenesis to produce ketone bodies especially β-hydroxybutyrate (βHB) as the primary energy source to replace glucose [15]. Increase ketone bodies in circulation resulting from the nutritional ketosis state [7, 15]. Elevation of βHB levels is known to activate the GPR109A receptor which leads to adiponectin production [16]. Increased fatty acids also activate PPARα resulting in the suppression of pro-inflammatory cytokines such as IL-6 and TNF-α, which are inhibitors of adiponectin secretion in adipocytes [17]. TNF-α is also known as an inhibitor of FGF21 signaling, the regulator of adiponectin synthesis. Thus, a decrease in TNF-α will increase FGF21 signaling and adiponectin synthesis. The mechanism of KD that causes hepatic insulin resistance also can increase endogenous levels of FGF21, which elevates adiponectin secretion [18].

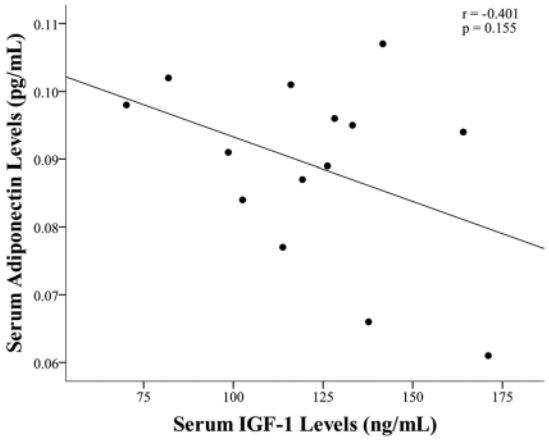

Figure 5: Serum adiponectin levels were not significantly correlated with serum IGF-1 levels.

Increase production of ketone bodies in KD can decrease the formation of free radicals via reducing coenzyme Q [17]. Condition of carbohydrate restriction can also induce secretion of stress response proteins which result in a decrease of reactive oxygen species (ROS) and the preservation of mitochondrial function [19]. Reduced mitochondrial membrane potential and lower ROS levels will improve mitochondrial activity and increase adiponectin synthesis [17]. This mechanism is in line with evidence that increased adiponectin levels are associated with reduced inflammatory processes in the body [9].

Our study results also showed that long-term KD for 8 weeks decreases serum IGF-1 levels although not significant. This result was in line with the previous study, KD in breast cancer patients during radiotherapy showed no significant decrease in IGF-1 levels [20]. Women with ovarian or endometrial cancer receiving KD in 12 weeks also experienced an insignificant reduction in IGF-1 level [21]. However, this result still remains inconsistent because several studies showed KD in a shorter duration has an effect in decreasing IGF-1 levels significantly. As shown in the study by Urbain et al. [22], a significant decrease of IGF-1 levels occurs after 6 weeks of nonenergy-restricted KD.

Theoretically, the ketosis state that occurs in KD not only can reduce insulin concentration but also IGF-1 levels in circulation [23]. In compromised nutrient availability such as caloric restriction also would reduce IGF-1 synthesis to limit growth and protein synthesis [24]. However, caloric without protein restriction in humans does not show a decrease in IGF-1 levels. In mice, protein restriction equal to <10% of diet composition accompanied by high carbohydrate or high fat could reduce IGF-1 concentration. Protein intake and total energy intake are dependent factors of nitrogen balance which can induce acute changes of nitrogen balances marked by alteration of IGF-1 concentration. KD followed by an isocaloric diet showed no significant changes in IGF-1 level [25]. The duration of treatment also considered has an effect on IGF-1 levels. In long-term administration, an adaptation in the calorie restriction can occur and cannot alter IGF-1 significantly. Different at shorter duration, the calorie restriction can decrease IGF-1 levels. In human subjects, fasting and restricting more than 50% of normal energy requirement in a day can decrease the IGF-1 level significantly [26].

The correlation between adiponectin and IGF-1 is currently becoming a concern because of their involvement in several diseases. This present study result showed that there was no significant correlation between IGF-1 and adiponectin levels. This finding is in line with several previous studies, where there was also no significant correlation between IGF-1 and adiponectin levels in healthy postmenopausal females and healthy elderly men [13, 27]. However, correlation studies between adiponectin and IGF-1 levels still show inconsistent results. In patients with heart failure, type 2 diabetes mellitus, cancer, and obesity, a significant inverse correlation between adiponectin and IGF-1 levels was observed [11, 28, 29]. These inconsistent results may occur due to the influence of pathological conditions on the regulation of circulating adiponectin and IGF-1 levels. In obese and diabetic patients, insulin resistance occurs which results in increased adiponectin and decreased IGF-1 levels. Meanwhile, in cancer and coronary heart disease patients, chronic inflammation state affect decreased adiponectin and increased IGF-1 levels [11, 30].

As the main mechanism and outcome of the KD, modulation of glucose, ketones, visceral fat mass, and body weight has become important parameters evaluated in post-dietary intervention. Based on our study results, subjects given KD for 8 weeks experienced slower weight gain, decreased blood glucose levels, increased blood ketone levels, and decreased visceral fat mass. These results are in line with the previous study; the KD-fed mice (67% fat, 0% carbohydrate) experienced slower weight gain and increased blood ketone levels compared to the control group [31]. Another previous study also reported that mice fed with KD for 10 weeks showed an increase in βHB and decreased blood glucose levels, nevertheless associated with weight loss [32, 33].

Low-carbohydrate intake in KD leads to decreased glucose levels and the body will increase gluconeogenesis. If it is still not enough to compensate for the lack of energy sources, the body increases ketone bodies synthesis, which later induces a ketosis state [7]. Ketosis in KD is known to

decrease ghrelin levels that suppress appetite [34, 35]. Ketosis in KD administration is also associated with increased leptin and cholecystokinin (CCK) levels [15, 36]. Leptin has critical functions in regulating nutritional status, body fat mass, glucose metabolism, and food intake [37]. As well as CCK, one of the hormones to stimulate full sensation after a meal [36] Increased leptin and CCK levels both can decrease food intake and body fat through its anorexigenic effect [36, 37]. Regulation of appetite hormones together with increased lipolysis that occurs in KD, can reduce visceral fat mass and stimulate slower body weight gain [12, 31].

In the past, adipose tissue was only considered as a passive organ mainly for storing excess energy. However, according to recent studies, adipose tissue has been considered as an active organ that produces several proteins, one of which is adiponectin. Increase adiponectin is also related to the breakdown of fat reserves in adipocytes during weight loss [9]. As shown in our study results, serum adiponectin levels have a strongly negative correlation with visceral fat mass. Maeda et al. [38] also stated that between adiponectin and body mass, incredibly visceral fat mass is negatively correlated, which means that the higher the adiponectin level, the lower the visceral fat mass.

According to our study result, the long-term KD has several perspectives for its use as a nonpharmacological management option for several diseases. Decreased visceral fat mass and slower weight gain after KD administration may underlie the use of this dietary regimen as a treatment option for obesity. Increased adiponectin in the ketogenic diet may also be a marker of reduced inflammatory processes in obesity and decrease visceral fat deposits [9]. Furthermore, adiponectin has a beneficial effect in inhibiting pro-inflammatory JNK kinases and suppressing endothelial cell apoptosis so that can promote endothelial repair and may have a beneficial effect for coronary heart disease patients [11, 14].

KD is mimicking fasting which can decrease circulating glucose and increase serum adiponectin. This result can be used as a target mechanism to treat diabetes. In addition, this decrease in glucose levels and occurrence of nutritional ketosis in KD are not suitable for cancer cells progression and lead to cancer cells starvation. It may be a perspective of KD use as adjuvant therapy for cancer, with measured diet composition and duration [6, 39]. Ketosis in KD targeting the Warburg effect does not have a negative effect for normal cells, nevertheless, it would decrease blood glucose level, cancer cachexia, muscle waste, and fatigue induced cancer cells starving [40]. However, further examinations are needed to evaluate other benefits and possible side effects of this long-term KD use. This study supports further research using different subjects and the duration of diet administration.

Conclusions

In conclusion, long-term KD increases serum adiponectin levels and has no effect on serum IGF-1 levels. There's no correlation between serum adiponectin and serum IGF-1 levels. Decreased visceral fat mass and increased ketone bodies as the result of lipolysis elevation in KD will suppress pro-inflammatory cytokines and activate the signaling of adiponectin synthesis. Thus, serum adiponectin also has a strongly negative correlation with visceral fat mass. The absence of changes in IGF-1 levels may be due to the adaptation mechanism to long-term diet administration and inadequate protein restriction in this diet composition. Through the ability of long-term KD to increased adiponectin serum associated with decreased visceral fat mass, this regimen can be used as a management option in obesity. However, this study did not evaluate the histological examination of visceral fat. The present study supports further research using this diet composition and duration to evaluate other effects of long-term KD by adding visceral fat histological examination.

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Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

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PAGE 1

PAGE 2

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PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8