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第 48 卷 第 3 期
2021 年 3 月

湖南大学学报（自然科学版）
Journal of Hunan University（Natural Sciences）

Vol. 48. No. 3.
Mar. 2021

Open Access Article

A Long-Term Ketogenic Diet Decreases Serum Insulin-Like Growth Factor-1 Levels in Mice

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Abstract: Cancer and obesity prevalence are still increasing worldwide. Insulin-Like Growth Factor-1 (IGF-1) is a factor in cancer proliferation, and its increase is associated with chronic inflammation in obesity. The ketogenic diet is a trend and recently developed as a therapy for cancer and obesity. This study aimed at examining the effect of long-term ketogenic diet exposure on decreasing serum IGF-1 levels in mice. This study was a true experimental study with a post-test-only control group design. Twelve male mice (20-30 g) aged 2-3 months, randomly divided into K1 (n=6, standard diet) and K2 (n=6, ketogenic diet), were given diet for eight weeks *ad libitum*. Serum IGF-1 levels were measured post-interventionally using Enzyme-Linked Immunosorbent Assay (ELISA). Bodyweight baseline and post-intervention were also measured. Data were analyzed for normality test using Shapiro-Wilk Test, mean difference was analyzed using Independent T-test for normal distribution, and Mann-Whitney Test for abnormal distribution. Data analysis was performed using Statistic Package for Social Science Version 16. Difference (Δ) of body weight on K1 (11.500±7.036) g and K2 (-2.000±5.060) g with p=0,008. Serum IGF-1 levels on K1 (138,693±23,858) ng/mL and K2 (104,705±25,458) ng/mL with p=0,038. This study showed that a long-term ketogenic diet for eight weeks decreases serum IGF-1 levels and body weight.

Keywords: IGF-1, ketogenic diet, long-term, mice.

长期的生酮饮食可以降低小鼠的血清胰岛素样生长因子-1 水平

摘要：在世界範圍內，癌症和肥胖症的患病率仍在上升。胰島素樣生長因子-1（IGF-1）是癌症擴散的一個因素，其增加與肥胖症中的慢性炎症有關。生酮飲食被認為是一種趨勢，並且最近被發展為一種用於癌症和肥胖症的療法。這項研究旨在檢查長期生酮飲食對降低小鼠血清 IGF-1 水平的影響。這項研究是一項真正的實驗性研究，僅具有測試後對照組。十二個月的雄性小鼠（20-30 g），年齡 2-3 個月，隨機分為 K1（n = 6，標準飲食）和 K2（n = 6，生酮飲食），隨意飲食八週。干預後使用酶聯免疫吸附測定法（酶联免疫吸附）測定血清 IGF-1 的水平。還測量了體重基線和乾預後。使用夏皮罗·威尔克檢驗分析數據的正態性檢驗，使用獨立 T 檢驗分析正態分佈的均值差異，使用異常分佈檢驗使用曼·惠特尼檢驗的均值差異。使用《社會科學統計軟件包》第 16 版進行數據分析。K1（11.500±7.036）g 和 K2（-2.000±5.060）g 的體重差異（·），p = 0,008。 K1（138,693±23,858）纳克/毫升和 K2（104,705±25,458）纳克/毫升的血清 IGF-1 水平，p = 0,038。這項研究結果表明，長期生酮飲食八周可降低血清 IGF-1 水平和體重。

关键词：IGF-1，生酮饮食，长期，小鼠.

Received: 3 January 2021 / Revised: 6 February 2021 / Accepted: 10 February 2021 / Published: 31 March 2021

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1. Introduction

Cancer still ranks the second mortality cause in the world, with 9.6 million deaths in 2018 [1]. Incidence of cancer increased by the year in Indonesia, from 1.4/1000 in 2013 to 1.8/1000 in 2018 [2]. One of the risk factors for cancer that has been reported is obesity [1]. Obesity is abnormal; the excessive fat accumulation with multifactorial causes is characterized by being overweight [3], [4]. Around 650 million adults (≥ 18 years) worldwide were obese, and more than 124 million cases of obesity also occur in children and adolescents (5-19 years) [4]. An increase was also found in the prevalence of obesity in Indonesia, from 14.8% in 2013 became 21.8% in 2018 [2]. Several diets were developed for cancer and obesity management, and the ketogenic diet is one of them. The ketogenic diet is a low-carbohydrate diet with a high intake of fat and moderate protein. There will be a decrease in glucose and insulin under low carbohydrate intake, increasing lipolysis and fatty acid oxidation to trigger the ketosis condition [5]. Due to its mechanism, the ketogenic diet continues to be a trend in the community, and its use has increased in recent years as a management option for weight loss in obesity [6]. Modulation of glucose, insulin, and Insulin-Like Growth Factor-1 (IGF-1) in the ketogenic diet is also starting to be studied as target management in cancer [7]. However, the effects of its long-term administration are still unknown certainly.

IGF-1 is cell growth and proliferation stimulant that is essential for normal growth and development. IGF-1 is largely synthesized in the liver from the Growth Hormone [8]. The increase in IGF-1 is known to be a stimulation factor in the proliferation of cancer cells through increase activation of Mitogen-Activated Protein Kinase (MAPK) and Phosphatydilinositol-3 Kinase (PI3K) [9]. A recent study also showed that chronic inflammation in obesity correlates with IGF-1 levels enhancement that stimulates cancer progression [10]. Therefore, IGF-1 level decrease was expected to administer the ketogenic diet according to several studies [11], [12]. On the other hand, IGF-1 is an important factor in bone growth [13], so that modulation of IGF-1 levels in a ketogenic diet should be a special concern. In a previous study, a ketogenic diet with the composition of 60% fat, 30% protein, and 10% fiber showed the most optimal effect on weight loss and decrease of visceral fat mass [14]. However, the effect of this ketogenic diet composition with long-term administration is still unclear whether this diet will increase or decrease IGF-1 levels. According to the background above, this study focuses on determining the long-term ketogenic diet's effect on serum IGF-1 levels in mice.

2. Methods/Materials

2.1. 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).

2.2. Experimental Design

This study was a true experimental study with a post-test-only control group design. Twelve male mice (*Mus musculus*) aged 2-3 months with a bodyweight of 20-30 grams were used as subjects of the study. All subjects were acclimatized for seven days with a given standard diet *ad libitum* and divided randomly into two groups. The control group (K1) was given a standard diet (n=6), and the intervention group (K2) was given a ketogenic diet comprising 60% fat, 30% protein, and 10% fiber (n=6) for eight weeks *ad libitum*.

2.3. Animal Handling

This study was conducted at the Laboratory Animals of Biochemistry, Faculty of Medicine, Universitas Airlangga, for nine weeks. The room temperature used for animal handling was 37±0.5°C. The cages were 30x45x20 cm, made of plastic covered with wire mesh, equipped with a drinking bottle. Each cage contained a single group of six mice. Lighting was set on a dark-light cycle with the regulation of 12 hours of light and 12 hours of darkness. Standard diet and ketogenic diet 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.

2.4. Bodyweight Measurement

The bodyweight measurement baseline was done on the first day (before the diet was given), and for the post-intervention, body weight was carried out 24 hours after the last diet was given. The body weights were measured using Harnic HL-3650 Heles Digital Scale (scale 0-5 kg).

2.5. Blood Samples

Blood samples were collected 24 hours after the last meal through the cardiac puncture method. Blood samples collected were centrifuged at 4000 rpm for 5 minutes to obtain serum samples.

2.6. Measurement of Serum IGF-1 Levels

Serum IGF-1 levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalog No. E-EL-M3006; Elabscience Biotechnology, Wuhan, China) with a detection range 15.63-1000 ng/mL and sensitivity up to 9.38 ng/mL.

2.7. Statistical Analysis

Data were analyzed for distribution normality by the Shapiro-Wilk Test. Mean difference of body weight and serum IGF-1 levels were analyzed using Independent T-Test for normal distribution and Mann-Whitney Test for abnormal distribution. Data analysis performed using Statistic Package for Social Science Software, Version 16 (SPSS Inc., Chicago, IL, the USA). All data were presented as Mean±SD.

3. Results

Results of body weight pre and post-intervention could be seen in Table 1. The difference (Δ) of body weight results showed a weight loss on the K2 (-2.000±5.060) g and an increase on the K1 (11.500±7.036) g. There was a significant difference between Δ body weight in K1 and K2 groups with p=0.008 (Figure 1). Our study results showed that serum IGF-1 levels on K2 (104.705±25.458) ng/mL were lower than the K1 (138.693±23.858) ng/mL. There was a significant difference between serum IGF-1 levels be4tween K1 and K2 groups with p=0.038 (Figure 2).

Table 1 Bodyweights of subjects

Variable	K1 (n=6)	K2 (n=6)	Independent T-Test (*p*-Value)
Body Weight Pre-intervention (g)	24.000±2.280	25.670±2.338	0.240
Body Weight Post-intervention (g)	35.500±6.025	23.670±6.802	0.010*

Note: Data are presented as Mean ± SD. K1: Standard Diet Group; K2: Ketogenic Diet Group. *There was a significant difference ($p<0.05$).

4. Discussion

Based on our study results, a long-term ketogenic diet for eight weeks significantly decreases serum IGF-1 levels in mice. This result in line with another study that showed that the ketogenic diet for seven days could reduce plasma IGF-1 levels in mice [11]. In normal human population, the ketogenic diet for 42 days causes a decrease in IGF-1 levels [12]. Whereas in a population of women with endometrial cancer or ovarian cancer, a ketogenic diet for 12 weeks can reduce IGF-1 levels, although not significantly [9]. A study of the ketogenic diet in children with epilepsy also showed a decreasing IGF-1 level and keeping the levels balance for one year [15].

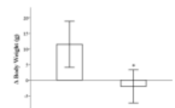

Fig. 1 Bodyweight difference (Δ) after eight weeks diet intervention
* There was a significant difference ($p<0.05$) in Mann-Whitney Test.

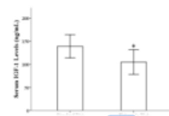

Fig. 2 Serum IGF-1 levels after eight weeks diet intervention
* There was a significant difference ($p<0.05$) in Independent T-Test.

Condition of high-fat and low-carbohydrate intake in the ketogenic diet will cause the shifting of the main energy source from glucose to ketone bodies [7], [16]. In addition to producing a decrease in IGF-1 levels, several studies have shown that the ketogenic diet causes a decrease in glucose levels followed by a decrease in insulin levels [9], [11], [12]. Low carbohydrate intake within a few days will stimulate gluconeogenesis. If the body still cannot compensate for low glucose conditions, there will be a decrease in insulin and an increase in glucagon to elevate ketogenesis [5]. Low insulin levels and high glucagon levels induce lipolysis in the adipocyte tissue through the sensitive lipase hormones [17]. Fatty acids produced from lipolysis will be converted into acetyl-CoA and ketone bodies through β-oxidation [18]. Increasing fat metabolism on the ketogenic diet will also lead to a ketosis state [11], [19]. The accumulation of ketone bodies in the blood that occurs in the ketogenic diet results in a nutritional ketosis state [17]. In several studies, it is known that ketosis can reduce ghrelin secretion [19], [20].

Besides a role in blood glucose regulation, insulin is important for IGF-1 synthesis regulation by elevating the Growth Hormone (GH) receptors in the liver [21].

Ghrelin is a hormone that plays a role in stimulating GH secretion through Growth Hormone Releasing Hormone (GHRH) induction. It directly stimulates GH secretion in the pituitary gland to be later converted into IGF-1 in the liver [5]. In line with several previous studies, the ketogenic diet can reduce IGF-1 levels and decrease glucose, insulin, and ghrelin. IGF-1 decrease under a ketogenic diet is inversely correlated with increased β-hydroxybutyrate levels and ketosis occurrence [19]. This hormone regulation explains the most likely mechanism of ketogenic diet contribution to decreasing serum IGF-1 levels.

Our study results also showed that the long-term ketogenic diet for eight weeks significantly decreases body weight in mice. There was a significant change in body weight between the groups receiving the standard diet and the ketogenic diet. In the previous study, a ketogenic diet with a composition of 60% fat, 30% protein, and 10% fiber for four weeks had the most optimal effect on weight loss in mice [13]. Another study in mice also shows that ketogenic diet administration for one week significantly reduced body weight and maintained a stable weight for up to 8 weeks [22]. Some studies for regular human populations evidenced that the ketogenic diet can lead to weight loss and fat proportion reduction [6], [12], [14].

The mechanism of weight loss in a ketogenic diet is related to decreased insulin levels and nutritional ketosis occurrence [23]. An increase in ketosis and ketone bodies (especially in β-hydroxybutyrates) accompanied by ghrelin values decrease can suppress appetite [20]. As shown in another study, Weeks 3 and 12 of the ketogenic diet in epileptic patients significantly increased serum Cholecystokinin-8 (CCK-8) [24]. CCK is a hormone that stimulates satiety after food consumption [25]. Ketogenesis enhancement and appetite-related hormone regulation clarify the most likely mechanisms of ketogenic diet impact on weight loss.

Nutritional ketosis in the ketogenic diet is known to have several benefits, such as reducing oxidative stress, hepatic glucose release, and insulin resistance. Through these mechanisms, the ketogenic diet can be an option for dietary interventions in patients with type 2 diabetes mellitus [16], [26]. An increase in ketone bodies also affects appetite suppression [20]. As shown in this study, the ketogenic diet can induce weight loss [6], [12], [14]. These mechanisms support the existing evidence that apart from being a treatment option for diabetes, the ketogenic diet can also be an option to treat obesity [16].

The ketogenic diet's ability to reduce serum IGF-1 levels could be a target mechanism of using it as a cancer adjuvant therapy. Increased IGF-1 levels are associated with an increased risk of several cancers such as breast, lung, colorectal, and prostate cancer [27]. IGF-1 can induce cancer cell proliferation by activating Ras/MAPK and PI3K/Akt pathways. Increased activation of this pathway will stimulate cancer cell growth initiation and progression [9], [27]. Under conditions of a ketogenic diet in cancer patients, increased ketosis and β-hydroxybutyrate levels accompanied by lower IGF-1 levels are thought to create a metabolic environment that is not suitable for the proliferation of cancer cells [9].

On the other hand, the ketogenic diet use needs special concern regarding its potential in reducing serum IGF-1 levels, especially when used in adolescence. IGF-1 normally increases in children and puberty, reaches the highest level in adolescence [28], then decreases in levels linear with age and aging [29]. IGF-1 will be secreted physiologically into peripheral tissues such as muscle, bone, and adipocytes to regulate adolescents' growth and maintenance of anabolic processes in adults [30]. GH and IGF-1 also play a role in bone growth, including osteoblast differentiation, collagen deposition, and bone mineralization [13]. As shown in children with dwarfism, apart from having GH deficiency, they are also known to have lower serum IGF-1 levels [37]. Another study proved that a decrease in serum IGF-1 levels after exposure to the ketogenic diet resulted in muscle mass decrease and muscle atrophy induction in mice [11]. In epileptic children administering a ketogenic diet, IGF-1 levels decreased parallel to growth disruption in the form of body mass index and growth speed decreases [15].

5. Conclusion

In conclusion, a long-term ketogenic diet significantly decreases serum IGF-1 levels and induces weight loss. The long-term ketogenic diet mechanism affecting serum Growth Factor and IGF-1 values decrease most likely results from downregulation of glucose, insulin, and ghrelin levels. Advanced studies are required to examine the effects of a long-term ketogenic diet on growth hormone, growth hormone-releasing hormone, glucose, ketone, ghrelin, and cholecystokinin. Through the ability of a long-term ketogenic diet in decreasing serum IGF-1 levels and body weight, it can be a perspective for the use of ketogenic diet in several diseases such as cancer, obesity, and type 2 diabetes mellitus. However, further studies and examinations on the effects of the long-term ketogenic diet are needed to explain its possible impacts on growth.

Acknowledgment

The authors would like to thank the Directorate of Research and Community Service, the Deputy for Strengthening Research and Development, the Ministry of Research and Technology/National Research, and the Innovation Agency for funding this study. The authors would also like to thank all the parties of

Laboratory Animals of Biochemistry, Faculty of Medicine, Universitas Airlangga that have contributed to the experimental study.

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