Cantaurus, Vol. 29, 45-50, May 2021 © McPherson College Department of Natural Science

A literature review on the effects of the ketogenic diet on the gut microbiota and weight-loss

Allison Pamela Penalva Vanegas

ABSTRACT

As the epidemic of obesity continues to rise, the diet market also continues to rise leading to a lot of misinformation and bias. One of the most popular diets, the ketogenic diet, is a high fat low carbohydrate diet that was originally made to treat patients with epilepsy has raised in popularity for weight-loss. Results from many studies have showcased that weight loss is obtained under this diet, however, not many studies have been done in the long-term effects of the diet, and some of them also focus on the reintroduction of carbohydrates for the individual. In addition, the effects in the gut microbiota display that individuals that are under the diet have an increase on the Bacteroidetes ratio due them being on a caloric deficit which by assimilation also promotes weight loss. However, even if the results of the diet have showcased to be positive, with both weight loss and an increase of the Bacteroidetes ratio, these results wouldn't be any different in comparison to a low-calorie diet that doesn't have any restrictions. Which leads to the conclusion that it is more beneficial for a long-term weight loss plan to address the food preferences and appetite of the individual. As ketogenic diets might yield results but is better used for individuals that are making a dietary lifestyle change rather than for rapid weight loss.

Keywords: *ketogenic diet; gut microbiota; gut microbiome; Firmicutes: Bacteroidetes; and weight-loss*

INTRODUCTION

The CDC states that obesity is an epidemic, which trend has increased since the past century, 30% in 2000 to over 40% in 2018 (CDC, 2020). This increasing trend influences the market, specifically the weight loss diet market. However, some diets have extreme claims with little to extremely bias research. And this bias is fed by some members of the medical profession going to the public and giving advices and dietary suggestions to the public without having the specialty in metabolism or endocrinology (Ertin and Özaltay, 2011). In 2018 around 36% of Americans showcase that they are following a specific diet, showcasing that the amount has almost doubled from 14% that was in 2017 (Meyers, 2019). However said survey, has also stated that eight in ten respondents agree with the following, "there is a lot of conflicting information about what foods I should eat or avoid," which 59% said that it made them doubt their choices (Meyers, 2019). This statement suggests that there is a lot of information and misinformation on dieting flooding the internet. This overload of information, without backing research can lead to confusion for the public. Furthermore, as of today, many diets can be found with a simple online search and one of the most prevalent results is the ketogenic diet.

A ketogenic diet is a low carbohydrate and high in fats diet, as the objective is to make the body undergo ketosis. To provide energy to the body, cells break down glucose molecules in a process called cellular respiration. Glucose is also stored in the body in the form of glycogen by a pathway that insulin activates. However, after three to four days of fasting or low consumption of carbohydrates, the glucose reserves, the glucose reserves become insufficient for the central nervous system, forcing the body to find new sources of energy (Paoli et al., 2013). One source of energy is fats that are in the body, which are broken down and converted into ketone bodies (KBs), such as acetoacetate, b-hydroxybutyric acid, and acetone. This process is also known as ketogenesis and occurs in the mitochondrial matrix in the liver (Paoli et al., 2013). This process has effects on the body, as it is changing the source of energy that it uses to keep homeostasis; however, one can question what other effects it might have.

The gut microbiome can be affected by diets, as the change can alter the microbial composition within just 24 hours of initiation. Besides, within 48 hours, the composition can go back to the baseline after diet discontinuation. People with obesity have been characterized to have an altered intestinal Bacteroides:Firmicutes ratio, with Firmicutes being abundant (Singh, 2017). In obese people, it is common to see a low count of Bacteroides in the gut, which has an inverse relation with weight. As the lower the weight, the more Bacteroides in the gut can be found (Fava et al., 2013).

Furthermore, a high-fat diet has showcased to reduce the bacterial number in the gut microbiome. Besides, high-carbohydrate diets influence human fecal saccharolytic bacteria, including Bacteroides and bifidobacterial (Fava et al., 2013). Another influence of a high fat diet on the gut microbiome is shown to not an impact on the firmicutes phylum but has showcased that it lowers the count on Bifidobacterium spp. Generally high fat diets increase the amount of

leptin protein (Chaplin et al., 2015) and causes gut microbe dysbiosis, neuroinflammation and cognitive decline. However, as the microbe population did change in the gut, there was no effect in the spatial working memory (Deshpande et al., 2019). Nevertheless, research rats on high fat and high fructose diets express behaviors of depression and anxiety (Gancheva et al., 2017).

Ketogenic diets have been around since the 1920s, as it was developed to treat patients with epilepsy, in addition to other low carbohydrate diets; such as the Atkins diets, the Zone diet, and the South Beach Diet (Lubin and Campbell., 2018) (Brouns, 2017). The usage of the ketogenic diet as an epilepsy treatment is more common in patients that are drug-resistant, with some pediatric patients experiencing more than 50% reduction on seizure (Lubin and Campbell., 2018). However as for weight loss treatment, Ketogenic diets have contrasting theories regarding the mechanisms on how they work. One of them is that ketogenic diets do not present a metabolic advantage and that weight loss is due to the low caloric intake as satiety increases. And another is that there is a metabolic advantage (Paoli et al., 2013). Leading to the question what the mechanism behind weight loss and ketogenic diet is.

In addition, as it was mentioned before the gut microbiome plays a role on how the bacteria ratio can influence the likelihood of obesity. As animal models have shown that mice fed a high-fat diet had signs of a clear disruption in their microbiota composition, and these changes can have an effect in fat storage (Guirro et al., 2019). However, according to the results in Deshpande et al., there should be an increase of Firmicutes to Bacteroidetes ratio, as a ketogenic diet is a high-fat diet, and this would make any organism more prompt to develop obesity. Leading to the next question, what is happening in the gut microbiota when the body is under ketosis, and in addition if the fats consumed for the diets are in a way different.

METHODS

All studies used for the following paper were published in the last decade, 2010-2020 to be kept up to date with the information given. Only peer-reviewed papers were chosen and had to be in English. Most papers were searched using the EBSCO database, and as some of them were not available as full text, they were requested through Inner Library Loan. Another database used was Google Scholars. Papers vary from other literature reviews in topics that involves the topic of interest, to research papers. In addition, papers had to not have any conflict of interest, as it is preferable to have data that is unbiased.

For the topic of Ketogenic diets papers that involved the words ‘Ketogenic diet’, ‘weight-loss’, ‘long-term effects’ were chosen using the Boolean operators AND, OR, NOT. Also, papers that involved the effects of ketogenic diet on gut microbiota or high fat diets on the gut microbiota were chosen. The criteria for papers involving the gut microbiota the focused was mainly on Bacteroidetes:Firmicutes ratio and other health effects involving this ratio. Papers that were chosen did not have to be specifically on overweight/obese people, it also involves healthy people to learn about other effects that might happen. Lastly, if a high-fat diet/ketogenic diet was involved it had to have a carbohydrate intake between 5%-10%.

KETOGENIC DIET

Ketogenic diets have been around since the 1920s originally to treat people that have epilepsy, and up to this date, this diet is still used to treat people that suffer different epilepsy syndromes such as myoclonicastatic epilepsy, Dravet syndrome, infantile spasms, and the most common one Lennox-Gastaut syndrome (Lubin and Campbell., 2018) (Lemmon et al., 2012). During the years the usage of ketogenic diet has expanded to other areas, and with the current obesity pandemic, this diet has also been studied in the weight loss area and weight related issues that ketogenic diet might be able to treat. However, studies in the diet vary on the daily limit of carbohydrate intake, varying from 4% to 40% of daily caloric intake (Lacovides and Meiring, 2018). However, when it comes to low levels of consumption in a ketogenic diet (5-10%) it allows to enhance the effects of ketone production in the body (Paoli et al., 2019). Hence allowing to understand the variation.

In addition, there is a lot of contradictions when it comes to data from research involving ketogenic diets. As some studies suggest that the ketogenic diet as involves high consumptions of total and saturated fats, adversely affects blood lipid levels and increases the risk of cardiovascular disease. However, this is a diet used to treat patients that are obese/overweight with high risks of cardiovascular disease. This leads to many studies showcasing that individuals that undergo the diet showcase favorable effects on cardiovascular health, showcasing significant increases in high-density lipids (HDL), but no significant difference in low-density lipids (Lacovides and Meiring, 2018). However this inconsistencies to the results can lead to the question whether it is the diet involved in the effects or the imminent weight loss that occurs on the individuals, as they are in a caloric deficit, which would allow them to lose the weight and have the positive effects.

However even when ketogenic diets have some positive effects and it is used as a treatment for multiple diseases, it also has some adverse effects. Short-term effects that are up to 2 years of the diet have been studied thoroughly, and are the following nausea, vomiting, headache, fatigue, dizziness,

insomnia, difficulty in exercise tolerance and constipation. These symptoms usually resolve in a few days to few weeks. However long-term effects are not well known as there is limited research on the topic, however some that are listed are hepatic steatosis, hypoproteinemia, kidney stones and vitamin and mineral deficiencies (Masood, Annamaraju and Uppaluri 2020). In addition, we could say that there is a lack of long-term effects research as the diet has a trend that the long-term compliance is low.

Weight-loss

As it has been expressed before, ketogenic diets have become a trend for weight-loss and the contradicting results. However it is important to note that any type of diet on which there is a reduced energy intake will result in weight loss (Brouns, 2018), due to the individual being on a caloric deficit. However the effects of ketogenic diets in the body leads for the diet to be recommendable if the individual consults it with a medical professional as conditions like disorders of fatty acid transport and oxidation (Gupta et al., 2017).

During short term experiments weight-loss of patients were around 7.5% of their original weight, and most participants on the studies were female (Castaldo et al., 2016)(Paoli et al., 2011). However the diets used in the research consisted of a period on which it was only ketogenic diet followed by a period of recovery. The recovery stage was allowing at a slow rate the addition of more complex carbohydrates to the diet.

An issue usually presented with diets that have fast results is the effects on the resting metabolic rate, a decrease on it can be determinant to regaining weight. Hence it has been suspected that ketogenic diets due to the fast results that it provides can have an effect on resting metabolic rate and leading to individuals gaining all the weight back or more. However, on a research done by Gomez-Arbelaez et al., there was no statical significance between the baseline and the final results, meaning that there was no metabolic adaptation. The reasons to why this was observed in the research is due to the lack of lean mass loss when following the diet.

GUT MICROBIOTA

The gut microbiota used to be considered to make up 1-3% of total body mass, however current revisions this ratio is considered to be closer to 1:1 for the total number bacteria and human cells (Proctor et al., 2017). The composition of the gut microbiota varies from person to person, as it involves both genetical and environmental factors. However, several studies have showcased that the composition of the core gut microbiota is established at birth and it is heavily influenced by the maternal genetics. The core microbiota begins to form within a few hours of birth and concludes after three to four years of age. Some of the environmental factors that influenced the composition are breast feeding, and geographical location. (Proctor et al., 2017) (Paoli et al., 2019). The gut microbiota has an influence on maintaining homeostasis; according to Kolaida et al., metagenomic studies also showcase that the gut microbiota in obese individuals is more efficient than the gut microbiome of lean individuals at recovering the energy resistant dietary components. Which means that the gut microbiota has an influence in how different interactions take place in the body.

The gut microbiota depends on the interactions between the diet, gut, and the resident microbiota, which when in homeostasis can be beneficial for the individual's health (James et al., 2019). As the two major phyla that compose 99% of the diversity of the gut microbiota are Firmicutes and Bacteroidetes (Proctor et al., 2017). The second mentioned is responsible of overlooking the stability of the microbiome between the ages of two and five years old, when the core composition is being formed. Bacteroidetes is the largest phylum composed of gram-negative bacteria. While the firmicutes phylum is composed mostly of gram-positive bacteria (Paoli et al., 2019). The ratio between both phyla corresponds to the overall health of the organism, under homeostatic conditions the ratio of firmicutes to Bacteroidetes is 10.9/1 (Proctor et al., 2017). And an imbalance to the ratio can correspond to many health issues.

Diet influence

The Firmicutes/Bacteroidetes ratio are the most common organisms that are causal factors in the development of obesity. As in obese individuals it is noticed that there is an increase of the Firmicutes and decrease on Bacteroidetes, in comparison to the lean individuals, regardless of their diet and activity level. However as weight loss is achieved by the obese individual, the increased firmicutes/Bacteroidetes ratio begins to decrease (Kolaida et al., 2017).

As it has been mentioned before, diet has an influence on the formation of microbial metabolites. The diet intake can shift the ratio between Bacteroidetes and firmicutes. Diets that are commonly composed of high fats can lead to an increase of firmicutes which shift has been linked to obesity. In contrast on high-carbohydrate diets there is an increase on the Bacteroidetes ratio (Proctor et al., 2017). Changes on the gut composition can lead to irritable bowel syndrome, which individuals usually have low intakes of milk, yogurt, and fruit (James et al., 2019). In addition, dietary fatty acids may have a potent antimicrobial activity, which leads to the hypothesis that high fat diets may have an implication in the reduction of the gut microbiota richness, intestinal permeability, systemic inflammation and

disruption of the immune system (Cândido et al., 2018). Which also, recent studies have displayed that the diets that were high in saturated fatty acids leads to negative results on the gut microbiota. In addition some studies have concluded that highly monounsaturated diets also can lead to negative effects in the gut microbiome whereas diets rich in polyunsaturated fatty acids does not present any change in the richness and diversity of the bacteria. However also, randomized controlled studies have revealed that diets containing a high content of fat increased the Bacteroides while reducinf the number of butyrate producers (Paoli et al., 2019).

This leads to the complexity that diets have in the gut microbiota and how they can affect the diversity of it. In addition, to understand why the ketogenic diet has the popularity as a solution for weight loss, and why it can work without promoting an increase of the Firmicutes ratio.

DISCUSSION

Ketogenic diets have proved to have had an effect on weight-loss and as an alternative for people that suffer from type-2 diabetes. And results from multiple experiments have showcase the benefits that it brings to parameters in obese patients in addition to weight loss. However there is still an issue as the diet is restrictive and the lack of long-term effects, one cannot conclude those ones. However ketogenic diets or low-carb high-fat diets have an issue of low compliance, that ranges from 20% to 59% and in addition the lack of long-term compliance of the diet (Paoli et al., 2011).

In addition, most research conclude that they cannot attribute that a ketogenic diet has better mechanism on weight-loss in comparison to any low-calorie diet. However for people that have metabolic issues this type of diet wouldn't be something that they can follow without the consultation with a medical practitioner. Which leads to question, the effects of the ketogenic diet.

As it is known, high fat diets can increase the Firmicutes/Bacteroidetes ratio however it is also important to know why individuals gain weight and why this ratio is increased. According to Kolaida et al., a possible explanation to this, is that Firmicutes are more effective as an energy source than Bacteroidetes, which promotes a more efficient absorption of calories and leads to weight gain. This explanation showcases the role that the gut microbiota has on homeostasis and attempting to balance the dietary changes that the individual is having. However, there is still a need to understand why a ketogenic diet has an effect of weight loss, even when the diet itself is high in fats, which could lead to assume that there would be a higher concentration of firmicutes and allowing the individual to gain weight. In a review article by Fan et al., there is a figure on which it summarizes the results from different articles and in two that there is a focus on the Bacteroidetes concentration, showcased that there was an increase on this type of bacteria when the subject was under a ketogenic diet. And the reason why this is happening is because when the subject is under ketogenic diet they are also in a caloric deficit. And when someone is getting less calories than the ones that they are burning, they will lose weight. Hence why there is an increase of Bacteroidetes in the gut microbiota.

If the individual wishes to lose weight using the ketogenic diet, they will achieve the desired results as long as they are on a caloric deficit. However, the results could be obtained by just following a normal low-calorie diet that doesn't restrict any food group. Although in some research obese people will choose a low-carbohydrate ketogenic diet over a low-calorie diet, even if the results from both are not so different and it is more beneficial to assess the individual's food preference and appetite for weight loss (Wylie-Rosett et al., 2013). Longer proving that for the long-term benefits for weight loss that is the main reason why people choose the ketogenic diet, it is better to undergo a low-calorie diet that matches the individual's preferences.

In addition as it was mentioned before there is a lack of studies that focuses on the long-term effects of the ketogenic diet, which should be an area for further research; however there are complications to this as many people drop out of the diet and won't continue. The only way to find results from this would be to analyze people that use the diet as a lifestyle change, which is the case for individuals that suffer from epilepsy. But there is still a gap in research when it comes to the effects of the diet on individuals that don't suffer from epilepsy, especially obese people that undergo the diet and might continue it. In conclusion, if an individual wants to proceed with a ketogenic diet, it is better for it to be consulted with a physician or a nutritionist so it can meet their needs. And if they wish for it to be just a short-term diet for rapid weight loss, they should work on a plan that will allow them to be re-introduced to carbohydrates without gaining the weight that they once lost.

ACKNOWLEDGEMENTS

I would like to thank my advisor Dr. Karrie Rathbone and my co-advisor, Dr. Manjula Koralegedara for their support and assistance. I also would want to thank the Mcpherson natural science department for their constant support. And lastly would like to thank Mcpherson Miller library for the tools and resources to find the material to complete this project.

LITERATURE CITED

Adult Obesity Facts. 2020. https://www.cdc.gov/obesity/data/adult.html

Brouns, F. 2018. Overweight and diabetes prevention: is a low-carbohydrate-high-fat diet recommendable? European Journal of Nutrition, 57(4):1301–1312.

Cândido, FG, FX Valente, LM Grześkowiak, APB Moreira, DMUP Rocha and RG Alfenas. 2018. Impact of dietary fat on gut microbiota and low-grade systemic inflammation: mechanisms and clinical implications on obesity. Journal of Food Sciences and Nutrition. 62(2):125-143.

Castaldo, G, L Monaco, L Castaldo, G Galdo and E Cereda. 2016. An observational study of sequential protein-sparing, very low-calorie ketogenic diet (oloproteic diet) and hypocaloric Mediterranean-like diet for the treatment of obesity. International Journal of Food Sciences and Nutrition. 6(6):696-706.

Chaplin, A, P Parra, F Serra, and A Palou. 2015. Conjugated Linoleic Acid Supplementation under a High-Fat Diet Modulates Stomach Protein Expression and Intestinal Microbiota in Adult Mice. PLoS ONE, 10(4):1-13.

Deshpande, NG, J Saxena, TG Pesaresi, CD Carrell, GB Ashby, MK Liao, and LR Freeman. 2019. High fat diet alters gut microbiota but not spatial working memory in early middle-aged Sprague Dawley rats. Plos One, 14(5). doi: 10.1371/journal.pone.0217553

Ertın, H, and B Özaltay. 2011. Some ethical reflections on weight-loss diets. Turkish Journal of Medical Sciences, 41(6):951–957.

Fan, Y, H Wang, X Liu, J Zhang, and G Liu. 2019. Crosstalk between the Ketogenic Diet and Epilepsy: From the Perspective of Gut Microbiota. Mediators of Inflammation, 1–9. https://doi-org.mcpherson.idm.oclc.org/10.1155/2019/8373060

Fava, F, R Gitau, BA Griffin, GR Gibson, KM Tuohy, and JA Lovegrove. 2013. The type and quantity of dietary fat and carbohydrate alter faecal microbiome and short-chain fatty acid excretion in a metabolic syndrome “at-risk” population. International Journal of Obesity, 37(2):216–223

Gancheva, S, B Galunska, and SM Zhelyazkova. 2017. Diets rich in saturated fat and fructose induce anxiety and depression-like behaviours in the rat: is there a role for lipid peroxidation? International Journal of Experimental Pathology, 98(5):296–306. https://doi.org/10.1111/iep.12254

Gomez-Arbelaez, D, AB Crujeiras, AI Castro, MA Martinez-Olmos, A Canton, L Ordoñez-Mayan, I Sajoux, C Galban, D Bellido and FF Casanueva. 2018. Resting metabolic rate of obese patients under very low-calorie ketogenic diet. Nutrition & Metabolism. 15(18) doi:10.1186/s12986-018-0249-z

Guirro, M, A Costa, A Gual-Grau, P Herrero, H Torrell, N Canela, and L Arola. 2019. Effects from diet-induced gut microbiota dysbiosis and obesity can be ameliorated by fecal microbiota transplantation: A multiomics approach. PloS One, 14(9), e0218143. https://doi-org.mcpherson.idm.oclc.org/10.1371/journal.pone.0218143

Gupta, L, D Khandelwal, S Kalra, P Gupta, D Dutta and S Aggarwal. 2017. Ketogenic diet in endocrine disorders: current perspectives. Journal of Postgraduate Medicine. 63:242-51.

Koliada, A, et al. 2017. Association between body mass index and Firmicutes/Bacteroidetes ratio in an adult Ukranian population. BMC Microbiology. 17:120 DOI 10.1186/s12866-017-1027-1

James, SC, K Fraser, W Young, WC McNabb, and NC Roy. 2019, Gut microbial metabolites and biochemical pathways involved in irritable bowel syndrome: effects of diet and nutrition on the microbiome. The Journal of Nutrition 150(5):1012-1021. https://doi.org/10.1093/jn/nxz302

Lacovides, S, and RM Meiring. 2018. The effect of a ketogenic diet versus a high-carbohydrate, low fat diet on sleep cognition, thyroid function, and cardiovascular health independent of weight loss: study protocol for a randomized controlled trial. Trials 19(62). https://doi.org/10.1186/s13063-018-2462-5

Lemmon, ME, NN Terao, NG Yu-Tze, W Reisig, JE Rubenstein and EH Kossoff. 2012. Efficacy of the ketogenic diet in Lennox-Gastaut syndrome: a retrospective review of one institution’s experience and summary of the literature. Developmental medicine and child neurology 54(5):394-395.

Lubin, FD, and SL Campbell. 2018. A Gut Feeling About Seizures. Epilepsy Currents, 18(6):389–390. https://doi-org.mcpherson.idm.oclc.org/10.5698/1535-7597.18.6.389

Masood, W, P Annamaraju, and KR Uppaluri. 2020. Ketogenic Diet. https://www.ncbi.nlm.nih.gov/books/NBK499830/

Meyers, M. 2019. 2018 Food and Health Survey. https://foodinsight.org/2018-food-and-health-survey/.

Paoli, A, L Mancin, A Bianco, E Thomas, JF Mota and F Piccini. 2019. Ketogenic Diet and Microbiota: Friends or Enemies? Genes 10(7):534. https://doi.org/10.3390/genes10070534

Paoli, A, L Cenci and A Grimaldi. 2011. Effect of ketogenic Mediterranean diet with phytoextracts and low carbohydrates/high-protein meals on weight, cardiovascular risk factors, body composition and diet compliance in Italian council employees. Nutirtion Journal 10(112)

doi:10.1186/1475-2891-10-112
Paoli, A, A Rubini, JS Volek, and KA Grimaldi. 2013. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. European Journal of Clinical Nutrition, 67(8):789–796. https://doi.org/10.1038/ejcn.2013.116
Proctor, C, P Thiennimitr, N Chattipakorn, SC Chattipakorn. 2017. Diet, gut microbiota and cognition. Meta Brain Dis, 32:1-17.
Singh, RK, HW Chang, D Yan, KM Lee, D Ucmak, K Wong, and W Liao. 2017. Influence of diet on the gut microbiome and implications for human health. Journal of translational medicine, 15(1):73. doi:10.1186/s12967-017-1175-y
Wylie-Rosett, J, K Aebersold, B Conlon, CR Isasi and NW Ostrovsky. 2013. Health Effects of Low-Carbohydrate Diets: Where Should New Research Go? Current Diabetes Reports 13:271-278