



## Metabolism and Weight Loss: Genomic Perspective and Ketogenic Diet in Obesity

Faheem Mustafa<sup>1,2</sup>, Atif Amin Baig<sup>2</sup>, Nordin Bin Simbak<sup>2</sup>, Malaysian Obesity Bank (MOB) Team

<sup>1</sup>University of Management and Technology, Pakistan

<sup>2</sup>Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), Medical Campus, Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu

### Abstract

Dietary modifications and healthy lifestyle have become important tools in managing rapidly increasing obesity prevalence globally. These dietary and lifestyle modifications for weight loss are time-consuming and for that reason, dietary modifications with speedy effects are becoming popular. Ketogenic diet is one of these examples and it is being practiced by many individuals due to its tremendous weight-reducing effect by downregulating lipogenic gene expression. The objective of this review paper is to investigate the effects of ketogenic diet on weight loss and metabolic gene expression. To study these effects; specific keywords such as ketogenic diet, genes expression, high fat diet; and weight loss were used in the PubMed portal and Cochrane library to curate studies. It was found that ketogenic diet reduces body weight by altering metabolic genes expression; decreases gene expression of lipogenic enzymes inclusive of fatty acid synthase (FASN), acetyl-CoA synthetase2 (ACS2), glycerol-3-phosphate acyltransferase and malic enzyme. In addition, ketogenic diet had been found to increase the expression of enzymes responsible for lipolysis ([acyl-CoA oxidase 1 (ACOX1), acetyl-coenzyme acyltransferase 1 (ACAA1), and HMG-CoA lyase (HMGCL)]). Other hypotheses on the effectiveness of ketogenic diet in weight loss included increase in energy expenditure through gluconeogenesis, appetite suppressant effect and increase in fat oxidation. There is a need to study and associate specific genes and epigenetics with a specific type of ketogenic diet for personalized implementation in the future.

**Keywords:** Ketogenic diet in obesity; Genetics; Ketogenic diet; Weight loss

### Introduction

With the rising epidemic of obesity around the globe, dietary modifications for health promotion and weight management are gaining importance more than ever. Weight management through mindful healthy eating, physical activity, and overall lifestyle and behavior pattern change are highly effective in weight management for patients with obesity. Lifestyle changes require a high degree of commitment and it is time-consuming. However, in this fast pacing world

where immediate gratification is considered most efficient, it is not odd that dietary patterns with immediate effects on weight are gaining popularity. Ketogenic diet (low carbohydrate, moderate protein and high fat diet), a popular and effective method of weight loss (Moraleda, Martinez-Argudo et al. 2019), is being adopted by numerous overweight and obese people around the world these days. However, certain complications associated with this diet have been reported, especially if it is not followed under the supervision of a health professional (Dashti, Mathew et al. 2004, Masood, Annamaraju et al. 2020).

The main objective of this study is to review in published literature, the effects of ketogenic diet

**Received:** 8 May 2020; **accepted revised manuscript:** 6 November 2020 **Published online:** 30 November 2020  
**\*Corresponding author:** Assoc. Prof. Dr. Atif Amin Baig, Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), Medical Campus, Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu  
**Tel:** +09-6275646 **Email:** atifamin@unisza.edu.my

on obesity and gene expression. Relevant data were collected from the PubMed database and Cochrane Library by using the keywords; ketogenic diet, gene expression, high fat diet, and weight loss. Those articles related to the effects of a ketogenic diet on weight loss and gene expression were included in this review.

Despite the recent hype among consumers and overwhelming amounts of data related are available online for beginners, ketogenic diet has been used as a therapeutic plan for patients with epilepsy, especially in children. Ketogenic diet involves the production of ketone bodies through a very low carbohydrate and a high-fat diet with fat comprising more than 70% of total calories. Low carbohydrate diets have been regarded as more promising in reducing obesity rates and related metabolic risks than low-fat diets (Ludwig 2020). Gary et al reported that a low carbohydrate diet results in greater weight loss (about 4 percent) than other conventional diets in the first 6 months (Foster, Wyatt et al. 2003).

Long term exposure to ketogenic diet (high fat, low carbohydrate, and moderate protein) expresses numerous metabolic genes. Expression of genes encoding lipogenic enzymes (FASN, acetyl-CoA synthetase2 (ACS2), glycerol-3-phosphate acyltransferase, and malic enzyme) decrease significantly in mice given a high-fat diet (Morgan et al., 2008). Genes encoding enzymes involved in the biosynthesis of cholesterol such as; squalene epoxidase (SQLE), farnesyl-diphosphate farnesyltransferase 1 (FDFT1), NAD(P)-dependent steroid dehydrogenase-like, and sterol-C4-methyl oxidase-like also showed a decrease in expression

in mice on a high-fat diet (ketogenic diet) (Kim, Sohn et al. 2004).

In contrast, numerous genes expression [acyl-CoA oxidase 1 (ACOX1), acetyl-coenzyme acyltransferase 1 (ACAA1), and HMG-CoA lyase (HMGCL)] involved in  $\beta$ -oxidation, are increased in mice on a high-fat diet. Expression of hydroxysteroid dehydrogenase (enhance estradiol oxidation and fatty acid  $\beta$ -oxidation) is also elevated in mice exposed to a ketogenic diet (De Launoit and Adamski 1999). A high-fat diet up-regulates the mRNA levels of gene CD36 that carry long-chain fatty acids (LCFAs) to muscle and adipose tissue (Coburn, Knapp et al. 2000, Inoue, Ohtake et al. 2005). Expression of genes in cytochrome P450 families (Cyp3a11, Cyp4a10)[9], aldehyde dehydrogenase family 1 member B1, aldehyde dehydrogenase family 3 subfamily A2, AMP deaminase 3, and genes involved in the metabolism of carbohydrates (sorbitol dehydrogenase 1, FBP2, and aldolase 1 A isoform) were also increased (Kim, Sohn et al. 2004).

Importantly, on the contrary, a few studies do not support the above-explained concept of a ketogenic diet reducing the expression of genes responsible for lipogenesis and upregulates genetic expression involved in lipolysis. Gregoire and colleagues (2002) showed an increase in gene expression of enzymes FASN and glycerol-3-phosphate acyltransferase involved in lipogenesis (Gregoire, Zhang et al. 2002). However, further studies are warranted to investigate the effect of a ketogenic diet on gene expression at wider and personalized scales. The genes with their effective expressions are summarized in Table 1.

Table 1. Genes Expression on Exposure to Ketogenic Diet in the Liver, Adopted from (Kim, Sohn et al. 2004)

Genbank ID	Gene Name	Type of Expression
AI854239	acetyl-CoA synthetase 2, ADP forming	Decrease
BG071187	dihydrolipoamide S-acetyltransferase	Decrease
BG064680	malic enzyme, supernatant	Decrease
AA209041	glycerol-3-phosphate acyltransferase, mitochondrial	Decrease
AW552727	fatty acid synthase	Decrease
AI841574	HMG-CoA synthase 1	Decrease
AI850456	NAD(P) dependent steroid dehydrogenase-like	Decrease
BG069211	farnesyl diphosphate farnesyl transferase 1	Decrease

AI836437	squalene epoxidase	Decrease
BG083949	sterol-C4-methyl oxidase-like	Decrease
BG079889	isopentenyl – diphosphate delta isomerase	Decrease
AA261287	acyl –CoA oxidase 1, palmitoyl	Increase
BG087037	acetyl –CoA acyltransferase 1	Increase
BG078698	HMG –CoA lyase	Increase
BG080183	hydroxysteroid (17-beta) dehydrogenase 4	Increase
AA028760	hydroxysteroid dehydrogenase-1, delta < 5>-3-beta	Increase
AA260409	cis-retinol/3alpha hydroxysterol short-chain dehydrogenase-like	Increase
BG069668	sorbitol dehydrogenase 1	Increase
AI893900	fructose bisphosphatase 2	Increase
AA518639	aldolase 1, A isoform	Increase
AA268120	cytochrome P450, family 3, subfamily a, polypeptide 11	Increase
AA109684	cytochrome P450, family 4, subfamily a, polypeptide 10	Increase
AA122925	carbonic anhydrase 2	Increase
BG087349	aldehyde dehydrogenase 1 family, member B1	Increase
BG086218	aldehyde dehydrogenase family 3, subfamily A2	Increase
BG076616	glutamate dehydrogenase	Increase
BG080773	AMP deaminase 3	Increase

Ketogenic diets can lead to short-term symptoms of keto flu including nausea, vomiting, headache, fatigue, dizziness, insomnia, difficulty in exercise tolerance, and constipation. These symptoms may be alleviated through proper fluid and electrolyte balance. Long term adverse effects including hepatic steatosis, hyponatremia, kidney stones and micronutrient deficiencies. Ketogenic diet is contraindicated in patients with pancreatitis, liver failure, and disorders of fat metabolism. It should be used with caution in diabetic patients especially those taking oral hypoglycemic drugs or insulin. Beyond fatigue or transitional short-lived symptoms, a well-formulated keto diet does not appear to have safety concerns for the general population (Dashti, Mathew et al. 2004, Masood, Annamaraju et al. 2020).

In ketogenic diet, the body uses free fatty acids as the main energy source originating from fat in the diet or stored fat in adipose tissues (Phinney, Bistrian et al. 1983, Van den Berg, Bogaard et al. 1994, Bisschop, Arias et al. 2000). In a very low

carbohydrate and very high-fat diet, the insulin to glucagon ratio decreases and results in lipolysis (the breakdown of stored triglycerides) in adipocytes (Pilkis and Granner 1992, Bollen, Keppens et al. 1998, Westman, Mavropoulos et al. 2003). Free fatty acids are transported to the liver, broken down to Acetyl-CoA through  $\beta$ -oxidation, and synthesize ketone bodies (ketogenesis). Ketone bodies denote: acetoacetate,  $\beta$  – hydroxybutyrate, and acetone. Acetoacetate and  $\beta$ -hydroxybutyrate provide energy to extrahepatic tissues through the tricarboxylic acid (TCA) cycle in mitochondria (Westman, Mavropoulos et al. 2003). Acetone does not provide energy and it is excreted through the lungs and gives a fruity smell. Ketone bodies synthesis in ketogenic diet fulfill maximum body energy requirements and prevent the breakdown of protein as an energy source and its glucose sparing effect enhances glucose availability for the brain (Neely and Morgan 1974, Westman, Mavropoulos et al. 2003).

To maintain continuous energy supply to glucose-dependent tissues, (erythrocytes, cornea, retina, lens) gluconeogenic pathway is activated by ketogenic diet due to decreased glucose production (Hoffer, Bistran et al. 1984). Amino acids source for gluconeogenesis is from dietary protein (Figure 1). A minimum of 1-1.5g/kg/d protein is required for positive nitrogen balance and to prevent muscle mass deterioration (Volek, Sharman et al. 2002). Fifty-grams of glucose is required to prevent lipolysis and ketogenesis (Krebs 1964). The conversion rate of protein to glucose is 50%, and a minimum of 100g protein is

required to produce 50g glucose through gluconeogenesis. Glycerol from the diet can be converted to glucose also via gluconeogenesis. The conversion rate of triglycerides to glycerol is 5% and 1000g fat (if only fat is consumed) is required to produce 50g glucose to prevent lipolysis and ketogenesis (Neely and Morgan 1974). Under the influence of ketogenic diet, insulin to glucagon ratio decreases and glucose from carbohydrates and protein is low. As a result, lipolysis and ketogenesis might occur (Neely and Morgan 1974).

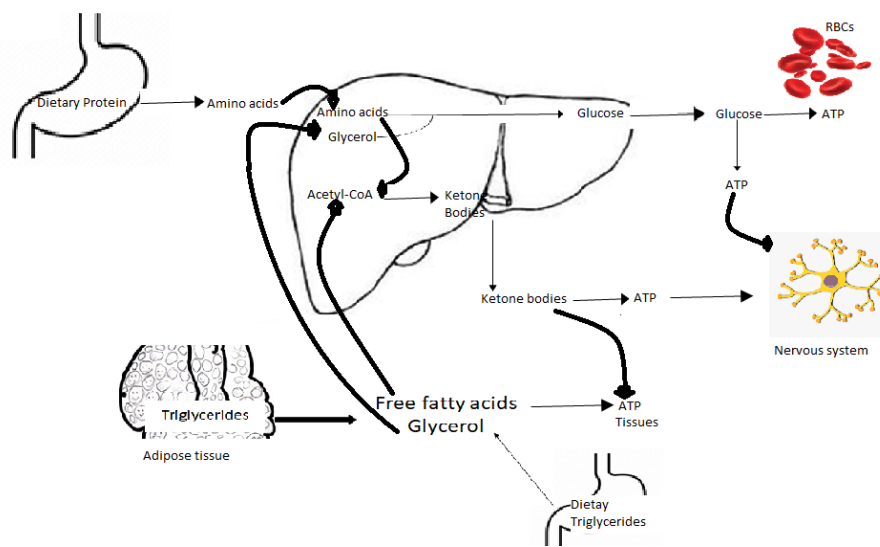


Figure 1. Metabolic overview in the Ketogenic Diet

There are numerous hypotheses regarding the mechanism of ketogenic diet in weight loss. One of them is; in a ketogenic diet, about 60-65g glucose is required per day and 84% of this amount is provided by protein through the gluconeogenesis pathway and 16% is produced from glycerol. Approximately 400-600kcal/day is used during gluconeogenesis and this energy utilization during gluconeogenesis lead to weight loss (Westerterp-Plantenga, Nieuwenhuizen et al. 2009). Some studies showed that ketogenic diet reduces body weight due to its appetite suppressant property as a result from increased satiety effect of protein (Veldhorst, Smeets et al. 2008, Sumithran, Prendergast et al. 2013) and a few showed that it was due to the effects on hormones (elevate the level of cholecystokinin hormone) controlling appetite (Johnstone, Horgan et al. 2008). Ketone bodies ( $\beta$ Hb) also directly suppress appetite (Paoli, Grimaldi et al. 2012). An

increase in fat oxidation is underlined by a decrease in resting respiratory quotient due to ketogenic diet, also leads to weight loss (Veldhorst, Westerterp-Plantenga et al. 2009). A few studies showed ketogenic diet also reduces weight by increasing the expression of enzymes responsible for lipolysis and decreasing expression of enzymes involved in lipogenesis (Bortz, Paul et al. 1972)

Ketogenic diet recommendations should not be for everyone. A complete assessment must be done to decide on the personalized diet regime in each obese individual. For example, dietary management for obesity in polycystic ovarian syndrome (PCOS) and hypothyroidism will be different from others. But ketogenic diet showed remarkable effectiveness in diseases such as neurological disorders, cancer, heart diseases, and type-II diabetes (Axe 2019). There are 9 types of

ketogenic diet (Axe 2019), and every type is not effective in all individuals. However, further research is needed to clearly understand its mechanism of action.

## References:

- Axe, J. (2019). The Ultimate Guide to "Keto". Retrieved February 25, 2019.
- Bisschop, P., et al. (2000). The effects of carbohydrate variation in isocaloric diets on glycogenolysis and gluconeogenesis in healthy men. *The Journal of Clinical Endocrinology & Metabolism* 85(5): 1963-1967.
- Bollen, M., et al. (1998). Specific features of glycogen metabolism in the liver. *Biochemical Journal* 336(1): 19-31.
- Bortz, W. M., et al. (1972). Glycerol turnover and oxidation in man. *The Journal of clinical investigation* 51(6): 1537-1546.
- Coburn, C. T., et al. (2000). Defective uptake and utilization of long chain fatty acids in muscle and adipose tissues of CD36 knockout mice. *Journal of Biological Chemistry* 275(42): 32523-32529.
- Dashti, H. M., et al. (2004). Long-term effects of a ketogenic diet in obese patients. *Experimental & Clinical Cardiology* 9(3): 200.
- De Launoit, Y. and J. Adamski (1999). Unique multifunctional HSD17B4 gene product: 17 $\beta$ -hydroxysteroid dehydrogenase 4 and D-3-hydroxyacyl-coenzyme A dehydrogenase/hydratase involved in Zellweger syndrome. *J Mol Endocrinol* 22(3): 227-240.
- Foster, G. D., et al. (2003). A randomized trial of a low-carbohydrate diet for obesity. *New England Journal of Medicine* 348(21): 2082-2090.
- Gregoire, F. M., et al. (2002). Diet-induced obesity and hepatic gene expression alterations in C57BL/6J and ICAM-1-deficient mice. *American Journal of Physiology-Endocrinology and Metabolism* 282(3): E703-E713.
- Hoffer, L. J., et al. (1984). Metabolic effects of very low calorie weight reduction diets. *The Journal of clinical investigation* 73(3): 750-758.
- Inoue, M., et al. (2005). Increased expression of PPAR $\gamma$  in high fat diet-induced liver steatosis in mice. *Biochemical and biophysical research communications* 336(1): 215-222.
- Johnstone, A. M., et al. (2008). Effects of a high-protein ketogenic diet on hunger, appetite, and weight loss in obese men feeding ad libitum. *The American journal of clinical nutrition* 87(1): 44-55.
- Kim, S., et al. (2004). Hepatic gene expression profiles in a long-term high-fat diet-induced obesity mouse model. *Gene* 340(1): 99-109.
- Krebs, H. (1964). The metabolic fate of amino acids. *Mammalian protein metabolism, Elsevier*: 125-176.
- Ludwig, D. S. (2020). The ketogenic diet: evidence for optimism but high-quality research needed. *The Journal of Nutrition* 150(6): 1354-1359.
- Masood, W., et al. (2020). Ketogenic Diet. StatPearls [Internet], StatPearls Publishing.
- Moraleda, E., et al. (2019). Ketogenic diet and physical activity intervention to weight loss analyzing different FTO and AdipoQ polymorphisms. *Annals Of Nutrition And Metabolism, Karger Allschwilerstrasse 10, Ch-4009 Basel, Switzerland*.
- Morgan, K., Uyuni, A., Nandgiri, G., Mao, L., Castaneda, L., Kathirvel, E., French, S. W., & Morgan, T. R. (2008). Altered expression of transcription factors and genes regulating lipogenesis in liver and adipose tissue of mice with high fat diet-induced obesity and nonalcoholic fatty liver disease. *European Journal of Gastroenterology and Hepatology*.  
<https://doi.org/10.1097/MEG.0b013e3282f9b203>
- Neely, J. R. and H. E. Morgan (1974). "Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle." *Annual review of physiology* 36(1): 413-459.
- Paoli, A., et al. (2012). Medium term effects of a ketogenic diet and a Mediterranean diet on resting energy expenditure and respiratory ratio. *BMC Proceedings, Springer*.

Phinney, S. D., et al. (1983). The human metabolic response to chronic ketosis without caloric restriction: preservation of submaximal exercise capability with reduced carbohydrate oxidation. *Metabolism* 32(8): 769-776.

Pilkis, S. J. and D. Granner (1992). Molecular physiology of the regulation of hepatic gluconeogenesis and glycolysis. *Annual review of physiology* 54(1): 885-909.

Sumithran, P., et al. (2013). Ketosis and appetite-mediating nutrients and hormones after weight loss. *European journal of clinical nutrition* 67(7): 759-764.

Van den Berg, B., et al. (1994). High fat, low carbohydrate, enteral feeding in patients weaning from the ventilator. *Intensive care medicine* 20(7): 470-475.

Veldhorst, M., et al. (2008). Protein-induced satiety: effects and mechanisms of different proteins. *Physiology & behavior* 94(2): 300-307.

Veldhorst, M. A., et al. (2009). Gluconeogenesis and energy expenditure after a high-protein, carbohydrate-free diet. *The American journal of clinical nutrition* 90(3): 519-526.

Volek, J. S., et al. (2002). Body composition and hormonal responses to a carbohydrate-restricted diet. *Metabolism-Clinical and Experimental* 51(7): 864-870.

Westerterp-Plantenga, M., et al. (2009). Dietary protein, weight loss, and weight maintenance. *Annual review of nutrition* 29: 21-41.

Westman, E. C., et al. (2003). A review of low-carbohydrate ketogenic diets. *Current atherosclerosis reports* 5(6): 476-483.