Journal of Monno Medical College
December, 2023; 9 (2):34-36

Editorial

Impact of Ketogenic Diet in Metabolic & Brain Health

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The ketogenic diet, commonly known as the keto diet, has gained considerable popularity in recent years as a weight loss and health improvement strategy. While proponents praise its potential benefits, the diet has not been without its fair share of controversy and debate within the scientific and medical communities. Idea of keto diet originated from "Fasting" as a treatment of disease. In 1911, fasting was used as "cure" for epilepsy. In early 20th century, fasting included in mainstream treatment of epilepsy as reported by Dr. McMarray in NYMJ. Ketogenic diet is recommended still to treat epilepsy in children of all ages including infants. In 1921-Rollin Woodyatt noted that ketone bodies (acetone, β-hydroxybutyrate and acetoacetate) were produced by the liver as a result of prolonged fasting and starvation. He also noted that, diet low in carbohydrate & high in fat also produces the ketone bodies. In 1921, Russel Wilder from the Mayo Clinic called this type of diet as "Ketogenic Diet (KD)". In 1970, ketogenic diet started as weight reducing strategy.[1] In Bangladesh, weight-loss "keto-craze" started in 2019 since promotional video by some physician and online activists. A good number of obese, diabetic and hypertensive started to follow ketogenic diet with aim to reduce weight in a magical way. A ketogenic diet is a specialized diet that involves consumption of highly restricted carbohydrates, moderate protein and a high proportion of fat. KD restricts carbohydrate intake to < 25-50 grams/day in an attempt to enhance tissues to use fat or ketones as fuel and shifting the body into a state of ketosis. KD typically recommend that only 5% of calories come from carbohydrates along with 75% from fat and 20% from protein.[2] Nutritionists designed various types of ketogenic diet out of which only 4 major types of ketodiet have gained attention till now. These are Standard Ketogenic Diet, Cyclical Ketogenic Diet, Targeted Ketogenic Diet & High protein Ketogenic Diet.Low carbohydrate intake, prolonged starvation / fasting causes lowering of primary source of energy i.e. glucose. As a result, body breaks down fatty acid from fat and produce ketones bodies (ketogenesis). This ketosis state is called nutritional ketosis where in the serum ketone concentration is within 0.5 to 3.0 mmol/L and there is compensatory mechanism to maintain the blood p^H in the physiological range (7.35-7.45). In the absence of compensations serum ketone may exceed 10.00 mmol/L which can manifest as ketoacidosis.[3]

Ketone bodies can be used as an alternative energy source by many cells in the body such as kidneys, cardiac & skeletal muscles and the neural tissues via blood brain barrier. RBCs have no mitochondria and hepatocytes lack the enzyme beta-ketoacyl Co-A transferase in its mitochondrial matrix and so are unable to use ketones. The utilization of ketones leads to a reduction in production of ROS (Reactive Oxygen Species) and thus reduces oxidative stress. The epigenetic modulation is targeted via specific inhibition of the class I histone deacylases by β-hydroxybutyrate thus causing down regulation in transcripts of genes FOXO3A and MT2, responsible for oxidative stress resistance.[4] Low carb, moderate protein & high fat intake in KD follow the same phenomena of KB synthesis. Low carb intake in KD will cause nutritional ketosis by decrease insulin & increase glucagon which stimulate lipolysis, fatty acid oxidation that ultimately leads to ketogenesis. KD helps in weight loss by increasing concentration of "satiety" hormones, such as glucagon-like peptide-1 and leptin & decreasing the hormone "ghrelin" that stimulate appetite. Both causes satiating effect and decrease hunger. Mechanism of KD in reducing seizure in epilepsy is still not clear. Several hypothesis are proposed like i. Ketone bodies stabilize neuronal activity and thus decreases seizure. ii. KD decrease excitatory neurotransmitters glutamate and increase inhibitory neurotransmitters GABA thus reduce the frequency and severity of seizures.[5] The efficacy of keto diet was also

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How to cite this article: Akhtaruzzaman M. Impact of Ketogenic Diet in Metabolic & Brain Health [Editoiral]. J Monno Med Coll. 2023 December;9(2):34-36.

proved in some other studies in neurological diseases such as Alzheimer's disease (AZ) & Parkinson's disease (PD). These patients were treated with medium -chain triglyceride drinks and scored significantly higher in the AD & PD patients compared to placebo treated patients.[6,7] Ketone bodies are metabolized anaerobically decreasing the energy available and leading to a higher seizure threshold.[8] The Modified Atkinson's Diet (MAD), a modified version of KD that has more flexibility and palatability, renders better suited in children compared to KD in treating children with drug resistant epilepsy.[9] MAD is also found to be effacious in treating drug resistant epilepsy in adolescents and adults however the rate of seizure reduction is lower than that of the children population.[8] Kawamura et al. in several in vivo and in vitro studies in animal models and patients with epilepsy had shown that feeding KD for 2-3 weeks lead to reduce neuronal excitability in the seizure prone area region of the CA3 region. Furthermore, the binding of adenosine to the adenosine A1 receptor (A1R) leads to an inhibitory effect that decreases neuronal excitability. Therefore, increased adenosine levels in taking KD is one possible mechanism for seizure prevention specially in drug-resistant epilepsy.[8] Individual taking KD there is excessive production of ketone bodies which leads to mitochondrial stress and increased levels of reactive oxygen species and increase ratio of NAD+/ NADH and AMP/ATP that ultimately results in protective adaptive (hormetic) response. In the heart, the adaptive response improves resistance to damage after ischemic attack.[10]

Proponents argue that the keto diet, which involves a significant reduction in consumption of carbohydrates and an increase in consumption of healthy fats, can lead to rapid weight loss, improved mental clarity, and better control of blood glucose levels. However, critics express concerns about potential long-term health risks associated with the diet, including nutritional deficiencies, increased cholesterol levels, and the strain on vital organs. One of the key aspects of the keto diet is the induction of a state called ketosis, where the body shifts from using glucose as its primary energy source to burning fat. While some studies suggest positive outcomes, the long-term effects of sustained ketosis remain unclear, raising questions about its safety and sustainability. Moreover, concerns about the potential lack of essential nutrients cannot be ignored. The restrictive nature of the keto diet may make it challenging to obtain an adequate amount of certain vitamins and minerals, potentially leading to nutritional imbalances over time. On the flip side, supporters argue that the keto diet's positive impact on weight loss and metabolic health outweigh these concerns. They point to success stories and studies showing improvements in conditions such as epilepsy and type 2 diabetes. As we navigate this nutritional landscape, it is crucial to approach the keto diet with caution. Individuals should consult healthcare professionals before embarking on such a dietary regimen, especially those with pre-existing health conditions. The one-size-fits-all approach may not be suitable for everyone, and personalized guidance is essential to ensure that nutritional needs are met. In conclusion, the keto diet sparks a compelling debate within the scientific and medical communities. While it shows promise in certain areas, unanswered questions and potential risks underscore the need for further research and a nuanced understanding of its long-term effects. As the popularity of the keto diet continues to grow, it is imperative that individuals approach it with informed decision-making and a focus on overall health and well-being.

Received: 26 September, 2023; **Manuscript ID:** 11450923Ed; **Accepted:** 31 October, 2023; **DOI:** 10.3329/jmomc.v9i2.76486

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