

# The Ketogenic Diet: Safety, Morbidity, and Mortality

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In normal daily diet consisting of 52-55% carbohydrate, 32-34% fat, and 14-18% protein, a couple hours following meal and absorption there is abundant fuel supply particularly from glucose oxidation in most tissues (Kathleen M Botham and Mayes, 2015; USDA, 2015). Conversely, in ketosis condition, most tissues replace its energy requirement from glucose to ketone bodies resulting from hepatic ketogenesis (Cervenka and Kossoff, 2013; McDonald and Cervenka, 2017). In extra hepatic tissues, adenosine triphosphate (ATP) is synthesized through revert back of acetoacetate to acetoacetyl-CoA catalyzed by succinyl-CoA-acetoacetate CoA transferase. By this reaction acetoacetyl-CoA is split into two acetyl-CoA catalyzed by thiolase and then inserted into Krebs's cycle to form ATP. Acetoacetate and  $\beta$  hydroxybutyrate are also able to traverse blood brain barrier and metabolized by cellular brain into ATP and used as energy also postulated as anticonvulsant (Freeman et al., 2007; J. L. Gamble et al., 1923). Moreover, when ketone bodies in circulation are increased, oxidation of ketone bodies also raised until saturation of the pathway is achieved at 12 mmol/L concentration (Kathleen M. Botham and Mayes, 2015). Concern to the energy synthesis, acetoacetate and 3- $\beta$  hydroxybutyrate are the prominent ketone bodies which are readily oxidized in extra-hepatic tissues. Whilst acetone have not metabolic function and in large extent is volatilized through the lung marked by breathe odor (Kathleen M. Botham and Mayes, 2015; Paoli, 2014). Ketosis is also able to suppress hunger feeling and appetite, therefore potential to be a good regulator of the body's calorie intake (Dashti et al., 2004). However, ketosis which is induced by ketogenic diet (KD), in the long term, its safety, morbidity, and mortality remain inconclusive.

The ketogenic diet (KD) is a type of diet characterized by high-fat, low-carbohydrate, and adequate protein (Freeman et al., 2007; Hemingway et al., 2001). The amount intake of fat in classical KD is up to 90%, carbohydrate 2%, and protein 8% (4:1) per day. In order to increase flexibility, palatability, and adherence of patients on KD, several variants were emerged in lower ratio such as modified Atkins diet consisting of fat 65%, protein 30%, and carbohydrate 5% (3:1) per day (Lafountain et al., 2019; McDonald

and Cervenka, 2017; Ye et al., 2015). Ketogenic diet is proposed mimic fasting and starvation state. In this condition, glucose and the body's glycogen reserve is very limited, therefore lipid metabolism through  $\beta$  oxidation is activated yielding acetyl-CoA and hence hepatic ketogenesis. Ketone bodies are synthesized from condensation of two acetyl-CoA located in mitochondria catalyzed by thiolase to form acetoacetyl-CoA (Kathleen M. Botham and Mayes, 2015). Moreover, acetoacetyl-CoA react with another acetyl-CoA to forms 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) catalyzed by HMG-CoA synthase. Furthermore, HMG-CoA is split off by HMG-CoA lyase yielding free acetoacetate (Kathleen M Botham and Mayes, 2015; Paoli, 2014). Subsequently, acetoacetate is converted to 3- $\beta$  hydroxybutyrate catalyzed by 3-hydroxybutyrate dehydrogenase or vice versa (Paoli, 2014). In addition, acetoacetate also undergo spontaneously decarboxylation resulting acetone. Consequently, concentration of ketone bodies in circulation increased, namely ketonemia, followed by elevation of ketone bodies in urine namely ketonuria. Both ketonemia and ketonuria is called ketosis (Kathleen M Botham and Mayes, 2015). This ketosis is called physiological ketosis, considering the concentration of ketone bodies in well fed not exceed 0.02 mmol/L and pH remain neutral in 7.4 (Kathleen M. Botham and Mayes, 2015; Paoli, 2014).

Ketogenic diet was firstly developed in 1920 and addressed to overcome the epilepsy seizure in children (Freeman et al., 2007). In year 1921, the efficacy of KD on epilepsy was based on the postulate made by Wilder RM from Mayo Clinic suggested that metabolic effect of starvation could be induced by a diet containing high in fat, low in carbohydrate, and in adequate protein (Freeman et al., 2007; Wilder R. M., 1921). The effectiveness of KD as an anticonvulsant therapy on epilepsy constantly appeared until 1938, in which the new anticonvulsant phenytoin (Dilantin) was coined; thereby the effectiveness of KD as anticonvulsant no more accepted (Wheless, 1995). However, in late 1980s, based on Kinsman's review on 58 patients indicated that although the sufferer from epilepsy use of many new anticonvulsant medications, including phenytoin, nevertheless KD remain demonstrated the same success rate with new anticonvulsant in refractory epilepsy

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(Kinsman et al., 1992). Some studies also showed that KD was capable of reducing seizure particularly to intractable seizure that refractory to multiple treatments (Freeman et al., 2007; Martin-McGill et al., 2018; Mcdonald and Cervenka, 2017). Lastly, a systematic review from Cochrane on KD, concluded that KD in children have short to medium term efficacy in seizure control, even the effects of which are comparable to modern antiepileptic drugs, however, many children intolerant to this diet (Levy et al., 2015).

Recently, KD also addresses to patients with adult onset epilepsy refractory to anticonvulsant or wish to limit anticonvulsant due to its adverse effect (Mcdonald and Cervenka, 2017). A study was reported by Hemingway C, et al., showed that following 3-6 years initiating KD 20 (13%) patients had seizure free 29 (14%), reducing seizure until 90-99%, and 29 of 150 patients free of medication (Hemingway et al., 2001). In addition, a meta analysis was published by Ye F, et al. demonstrated that classical KD have overall efficacy of 42%, constituting a promising complementary therapy in adult intractable epilepsy, however, the adherence rate was relatively low (Ye et al., 2015). Another review was reported by Payne NE suggested that classical KD was able to reduce seizure frequency more than 50% upon 49% of 206 patients, even 13% of these were seizure free (Payne et al., 2011).

Nowadays, KD is addressed to reduce body weight in obese people (Hemingway et al., 2001; Lafountain et al., 2019). It is plausible, since various evidences indicated that KD was able to reduce body fat rapidly. Other evidences also pointed out that KD was effective at least in the short to medium term to lose weight, hyperlipidemia, and some cardiovascular risk (Paoli, 2014). A study was reported by Dashti HM, et al., suggested that KD was able to decrease body weight, body mass index (BMI), LDL, triglyceride, glucose, and conversely increase HDL concentration significantly in eight week (Dashti et al., 2004). Ketogenic diet in this study contains 40-50 gram carbohydrate and completely micronutrient was also given. Trace elements supplementations were necessary, since some evidences indicated that children on KD maintenance more than two years experience deficient several micronutrients (Wheless, 2001). Related to LDL, this study was contradictory to the study was reported by Hernandez TL, et al. demonstrated that LDL and free fatty acid (FFA) concentration were elevated in KD (Hernandez et al., 2010). Moreover, KD had also been proven capable of reversing metabolic syndrome and type 2 diabetes mellitus. A study was reported by Volek JS, et al indicated that KD consisting of 59%

fat, 12% carbohydrate, and 28% protein in 40 samples with atherogenic dyslipidemia were more consistent in improvement of metabolic syndrome marker compared to that of low fat diet consisting of 56% carbohydrate, 24% fat, and 20% protein, albeit both of diets were capable of improving marker of metabolic syndrome (Volek et al., 2009, 2008). Another study was done by Hallberg SJ, et al. showed that nutritional ketosis approach on type 2 diabetes mellitus characterized by 0.5–3.0 mmol/L of  $\beta$  hydroxybutyrate capable of reducing HbA1c, medication, and body weigh within 70 days and can be maintained in one year afterward (Hallberg et al., 2018). The weakness of this study did not measure the mortality rate due to insufficient time duration.

Based on aforementioned data, KD or low carbohydrate diet in short term appear beneficial in refractory epilepsy, reduction of body weight, reversing metabolic syndrome, and type 2 diabetes. However, in the long term safety of KD and low carbohydrate diet remain unclear owing to some adverse effect during experience KD such as trace element and vitamin D deficiency, kidney stone, dyslipidemia, prolong QT interval, optic neuropathy, lethargy, even premature death (Mazidi et al., 2019; Wheless, 2001). A critically appraised on randomized control trial and meta-analysis was done by Manikam et al. demonstrated that short term and long term of KD poses adverse effect in increase of cardiovascular disease due to the reduction of flow-mediated dilatation of brachial artery (Manikam et al., 2018). It was plausible, since atherosclerosis can be induced by the increase in plasma free fatty acid caused by high fat diet (Kathleen M Botham and Mayes, 2015). This statement was supported by Hernandez's study showed that in high fat diet during 6 week had been proven capable of increasing LDL and FFA plasma (Hernandez et al., 2010). Elevation of LDL and FFA concentration particularly palmitic acid in plasma will induce endothelial dysfunction and atherosclerosis (Ghosh et al., 2017). Furthermore, A prospective study was published by Mazidi M, et al. suggested that low carbohydrate diet had the highest mortality rate of cardiovascular disease, cerebrovascular, and cancer. The relation between low carbohydrate diet and mortality rate was stronger in non-obese compared to that of obese subjects (Mazidi et al., 2019). Another prospective study and meta-analysis also demonstrated that during 25 years follow up on 15.428 adults aged 45–64 years; the increment of mortality rate was associated with both low and high percentage of carbohydrate diets, with the lowest mortality rate observed in 50% (Seidemann et al., 2018). Accordingly, to reduce body weight particularly

in subject with overweight and obese, reduction of 50% carbohydrate in daily diet is the rational choice.

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