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UNDERSTANDING THE BIOCHEMICAL BASIS OF KETOGENIC DIET CONTRAINDICATIONS

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ABSTRACT

Ketogenic diet KD is a human diet which is composed of high lipid, very low carbohydrate and adequate protein with the ability to establish nutritional ketosis and stabilize insulin level. This diet regime has for long been used for therapeutic and weight management purposes. But recently, it has gain more popularity in weight management most especially amongst women. Being non pharmacological, most of the users perceive it as completely safe and therefore no need for professional prescription. This review is focused on highlighting some individual specific contraindications and the basis of the contraindications of KD. This nutrition is contraindicated in individuals with fatty acid transport and oxidation due to inability of the fatty acids to be metabolized. It is contraindicated in individuals with pyruvate carboxylase deficiency because hypoglycemia and triacylglyceremia are induced. It is contraindicated in individuals with porphyria due to its ability to induce hypoglycemia which aggravates the symptoms of porphyria. Because of the pivotal role liver and pancreas play in central metabolism, any individual with disorder of these organs cannot adapt to the shift in metabolism induced by KD. Individuals with uncontrolled type 1 diabetes face the problem of ketoacidosis which is aggravated by KD. It is therefore a recommendation that attention of professionals be sought before embarking on the use of KD for all reasons.

KEYWORDS: Biochemical basis; ketogenic diet; non pharmacological; contraindications.

1.1 INTRODUCTION

The energy requirements of the human systems are derived from the major macro molecules namely carbohydrate serving as immediate energy store, lipid as long-term energy stock and

protein as minor energy source utilized as last resort.[1][2] The diversity of these sources of energy brings about metabolic flexibility which provides survival mechanism to different nutritional and physio-psychological conditions of either fed, fasting, starvation or stressed conditions like diseased, anxiety, trauma or anger. However, under normal physiological condition, carbohydrate is the ultimate and suitable energy source for all the organ-systems[3] with the exception of heart which prefers fatty acids before glucose.[4] The shift to other sources of energy is normally a move for adaptation which is necessitated by nutritional or physio-psychological status of the body.

The monomeric form of carbohydrate which is glucose is the end product of carbohydrate digestion. All cells in the body have the metabolic capacity of metabolizing glucose obtained from either diet, glycogen store (storage form of carbohydrate) or endogenous synthesis. However, during conditions like fasting, starvation, stress or ketogenic nutrition, glucose availability is limited as the glycogen store depletes within two to three days.[1] This forces the system to use the alternative energy sources to ensure survival. The first alternative the body falls back on is fatty acids that come from either fat stores (adipose tissue) due to lipolysis[5] or from diet (most especially during ketogenic nutrition). All the body cells have the capacity of utilizing fatty acids for energy with the exception of red blood cells which depend solely on glucose due lack of mitochondria needed for lipid metabolism, central nervous system (brain cells) whose blood brain barrier cannot allow the passage of fatty acids, and liver which lack the enzyme thiophorase.[4] Nevertheless, fatty acids still contribute significantly to the brain's energy requirements as exogenous glucose deprivation continues beside glucose that comes from glycogenolysis and gluconeogenesis[6] through the conversion of the excess fatty acids oxidation products to smaller molecules known as ketone bodies which are permeable to the blood brain barrier. The ketone bodies concentration rise as glucose scarcity continues thereby replacing glucose as energy source in most of the body cells.[7] This metabolic flexibility forms the basis of using ketogenic diet as therapeutic as well as weight management and control nutrition.

The term "ketogenic diet" was first used by Russel Wilder in 1923 to describe a high-fat, low-carbohydrate diet that produced ketonemia which he used then for the management of epilepsy as an alternative to fasting.[8] defined ketogenic diet (KD) to be a high-fat, low-carbohydrate diet, with adequate protein content, which forces the body to utilize fat, rather than carbohydrate, as a preferred energy substrate. According to[9] there are four different

types of ketogenic diet based on their constitution and mode of administration. Standard ketogenic diet *(SKD)* contains very low-carbohydrate with moderate-protein and high-fat diet. It typically contains 70 per cent fat, 20 per cent protein and only 10 per cent carbohydrates. Cyclical ketogenic diet *(CKD)* involves periods of higher-carbohydrates in between the ketogenic diet cycles, for example, five ketogenic days followed by two high-carbohydrate days as a cycle. Targeted ketogenic diet *(TKD)* permits adding additional carbohydrates around the periods of the intensive physical workout. High-protein ketogenic diet *(HPKD)* includes more protein and the ratio is around 60 per cent fat, 35 per cent protein and five per cent carbohydrates but as can be seen, it is still a very high fat diet. Notwithstanding that, all ketogenic diets contain very low carbohydrate. Ketogenic diet is used in therapeutic interventions as well as weight management and control.[10]

1.1.1 Biochemistry of Therapeutic and Weight Management Application of Ketogenic Diet

As reported in literature, ketogenic diet has gained ground in therapeutic and weight management. It is non- pharmacological in nature, but has an explicit mechanism of action[8],[11] stated that ketogenic diet has proved its ability in weight management. According to[12], many works over the last few decades have provided evidence for the therapeutic potential of ketogenic diets in many pathological conditions, including diabetes, acne, neurologic diseases (epilepsy, Alzheimer's, CVA), cancer, and the amelioration of respiratory and cardiovascular disease risk factors. The therapeutic as well as weight management activity of ketogenic diet can be attributed to the appetite suppressing effect, satiety effect, insulin stabilization, lipolytic effect, anti- angiogenic effect, along with proapoptotic mechanisms, free radical amelioration and/or hypolipidemic activity which cannot be explicitly dealt with as it is beyond the purview of this article. Nevertheless, the administration and consumption of ketogenic diet requires attention of professionals like nutritionists, physicians, psychiatrists etc as this diet poses life threatening dangers to individuals with disorders of fatty acid oxidation and transport, porphyria, a disorder of heme biosynthesis, where deficient porpohobilinogen deaminase exists and patients having deficiency of the enzyme pyruvate carboxylase.[13] Ketogenic diet is also contraindicated in individuals with hepatic and pancreatic disorders as well as those at risk of ketoacidosis.[8] This review focuses on elucidating the biochemical basis of individual specific contraindications. In this review, the hormonal interplay in ketogenic diet metabolism was firstly discussed. This was then followed by the mechanism of its contraindication in certain

conditions including lipid metabolism disorder, pyruvate carboxylase deficiency, porphyria, defective liver and pancrease and uncontrolled type 1 diabetes.

1.1.2 Hormonal Interplay in Ketogenic Diet

Insulin and glucagon are hormones produced by the pancreatic β and α cells respectively. These hormones exhibit a see-saw relationship and play key roles in the metabolism of the major macromolecules to ensure proper energy homeostasis. Under normal physiological condition, carbohydrate whose monomeriac form is glucose serves as the immediate and ultimate source of energy to all the body cells most especially after taking balanced diet. Glucose obtained from the digestion of carbohydrate is transported to all body parts via the circulatory system to provide energy. The energy supply of glucose is achieved through the catabolism of glucose from glycolysis through the tricarboxylic acid cycle and oxidative phosphorylation. However, conditions like fasting, starvation, disease conditions or low carbohydrate diet (ketogenic nutrition) does not ensure adequate glucose availability for the body thus forcing the body to fall on alternatives such as lipids through lipolysis and ketone bodies through ketogenesis (lipid derivatives utilized by some organs that cannot utilize fatty acid during glucose scarcity) to ensure survival. Very low or absence of carbohydrate as in ketogenic diet leads to drop in insulin and rise in glucagon concentrations[14] which leads to activation of lipogenic and ketogenic pathways due to change in the molar ratio of glucagon to insulin[15], [8]said that ketogenetic diet induces a state of physiological ketosis due to the carbohydrate starvation. Fats that enter the liver after absorption are converted to fatty acids and then ketone bodies due to excessive beta oxidation (acetoacetate, beta-hydroxybutyrate, and acetone)[16] by the hepatic mitochondria to compensate the inability of the tricarboxylic acid cycle to meet up the energy requirement of extrahepatic tissues like the central nervous system.[17] Ketone bodies produced are permeable to the blood brain barrier and are transported via the blood stream to the brain and most tissues to provide energy[3] through ketolysis. Thus, nutritional ketosis is an essential survival mechanism that ensures metabolic flexibility during prolonged fasting or lack of carbohydrate ingestion which signifies a shift from an insulin-mediated glucose dependent state to an increased ability to use dietary fat and adipose stores for fuel.[18][11]

1.2 Biochemical Basis Of Ketogenic Diet Contraindications

Recent literatures revealed that ketogenic diet has important therapeutic as well as weight management applications. Nevertheless, this nutrition is contraindicated in individuals with specific disorders.

1.2.1 M*echanism in Defective Fatty Acid Transport*

Regardless of the source (exogenous, *de novo* synthesis or intracellular hydrolysis), intracellular fatty acids undergo thio- esterification to acyl- CoA, a process catalyzed by acyl-CoA synthases (ACSs) and results in the formation of acyl- CoA products an activated form of intracellular fatty acids.[19] [20] stated that mitochondria and perixisomes are the key players in fatty acid oxidation.

Under physiological condition, oxidation of long- and medium- chain fatty acids which our diet as well as adipose store are constituted of most[21] is primarily handled by the mitochondrial β- oxidation system, with only minimal contribution from the peroxisomal system.[22] Preferential substrates of peroxisomal β- oxidation are very long chain fatty acids which cannot enter mitochondria example, pristanic acid (2,6,10,14-tetramethylpentadecanoic acid), di- and trihydroxycholestanoic acid, the tetracosaenoic acid (C24:6n-3), and long-chain dicarboxylic acids.[23] The mitochondrial membrane is however impermeable to acyl- CoAs and fatty acids must be conjugated to carnitine; a hydrophilic quaternary amine (β-hydroxy-γ-trimethylammonium butyrate) to enter mitochondria. This three step process involves covalently linking carnitine to the long-chain fatty acyl- CoA via a transferase (CPT1), movement across the inner mitochondrial membrane by a sodium-dependent carnitine transporter, and then removal of the long-chain fatty acyl- CoA from carnitine by a second transferase (CPT2).[20] [24]

Carnitine homeostasis reflects the balance among absorption from the diet, endogenous biosynthesis and efficient renal reabsorption.[25] Carnitine daily requirement (75%) is obtained from the diet; mainly meat and dairy products[26] while the balance of 25% is obtained from endogenous synthesis from lysine and methionine.[27] Carnitine is efficiently reabsorbed by active transport through the high affinity carnitine transporter called organic cation transporter novel 2 (OCTN2), localized in the renal brush border membrane.[28] Defect in the OCTN2 carnitine transporter causes primary carnitine deficiency and results in urinary carnitine wasting, low serum carnitine levels (0–8 μM, normal 25–50 μM), and decreased intracellular carnitine accumulation.[26] These metabolic disorders are associated with

accumulation of acylcarnitines that can inhibit renal carnitine reabsorption and are lost in urine resulting in secondary carnitine deficiency.[29]

Defects in the biosynthesis of carnitine have been reported as clearly elucidated by.[20] According to them, other causes of carnitine deficiency include a number of organic acidemias and defective carnitine cycle (carnitine palmitolytransferases 1 and 2) which was discussed in details by.[24] Thus, deficiency in carnitine means that fatty acid oxidation becomes inefficient or defective as the movement of the fatty acids to the oxidation site (in this, case mitochondria) is virtually impossible. For that reason, consumption of lipid or condition that can lead to rise in fatty acid concentration can be deleterious to the individual.[20] Stated that all defects that can result into carnitine deficiency can lead to early in life hypoketotic hypoglycemia, or later in life cardiomyopathy and sudden death from cardiac arrhythmia. As such, consumption of high lipid diet like ketogenic diet requires the attention of experts.

1.2.2 Mechanism in Defective Fatty Acid Oxidation

Ketone bodies are produced from the excess product of fatty acid oxidation (acetyl- CoA) due to low carbohydrate diet, intense exercise, fasting, starvation or complete lack of insulin during untreated type 1 diabetes.[11] This means that ketogenesis is dependent on fatty acid oxidation, thus any defect in fatty acid oxidation will impair ketogenesis. Defects of fatty acid oxidation such as very long chain acyl- CoA dehydrogenase (VLCAD), medium chain acyl-CoA dehydrogenase (MCAD), long-chain 3-hydroxyacyl- CoA dehydrogenase (LCHAD), carnitine palmitoyl transferase 2 (CPT-2), and carnitine-acylcarnitine translocase (CACT) deficiencies have been reported and explained in many literatures.[20][24] Inherited defects of fatty acids oxidation are transmitted as autosomal recessive traits in humans.[26]

Consumption of ketogenic diet by individuals with fatty acid oxidation defect results to fat accumulation in tissues including liver, heart and skeletal muscles whose consequences are always unfavorable which can include impaired organ/tissue function such as cardiomyopathy/myopathy or hepatic steatosis. Free fatty acids and long-chain acylcarnitines can alter the electrical activity of cardiac cells resulting in arrhythmia.[30][31] Also, this defect results to hypoglycemia since acetyl CoA from fatty acid oxidation is not available for activation of pyruvate carboxylase for gluconeogenesis and feeding tricarboxylic acid cycle to provide the ATP and reducing equivalents for gluconeogenesis to occur.[32]

This occurs during conditions that lead to rise in blood lipid level and high fat diet (ketogenic diet). On the other hand, defective fatty oxidation hampers ketone body synthesis due to unavailability of acetyl CoA a substrate for ketone body synthesis and ketone bodies serve as alternative fuel source during fasting, starvation and low carbohydrate intake (ketogenic diet). The cumulative consequence of fatty oxidation defect leads to impairment of brain function with loss of consciousness due to lack of usable energy precursors for the brain to function., In the light of this, consumption of high lipid diet (ketogenic diet) should be based on professional recommendation.

1.2.3 Mechanism in Defective Pyruvate Carboxylase

Pyruvate carboxylase (PC) is a biotin-containing enzyme that catalyses the HCO_3^- and MgATP dependent carboxylation of pyruvate to form oxaloacetate thereby replenishing oxaloacetate to Krebs cycle for various pivotal biochemical pathways like gluconeogenesis.[33] PC is therefore considered as an enzyme that is crucial for intermediary metabolism, controlling fuel partitioning toward gluconeogenesis, lipogenesis and insulin secretion.[34]

Accrding to[35] PC deficiency is a rare autosomal recessive inborn error of metabolism with an incidence of 1:250,000. Three forms of this disorder type A, B and C have been reported and their molecular basis extensively discussed by.[34] Pyruvate carboxylase is involved in glycerogenesis which provides glycerol necessary for esterification of free fatty acids in *de novo* lipid synthesis. This pathway is important for reducing elevated levels of free fatty acids in the plasma due to lipolysis or consumption of a high fat diet.[36]

Pyruvate carboxylase provides oxaloacetate for conversion to phosphoenol pyruvate by phosphoenol pyruvate carboxykinase, and then to glycerol.[34] During starvation or very low carbohydrate intake, tissues completely or partly dependent on glucose for their energy must find a means of obtaining glucose and this has been achieved through gluconeogenesis.

However, pyruvate carboxylase catalyses the first committed step in gluconeogenesis, providing oxaloacetate for subsequent conversion to phosphoenol pyruvate by phosphoenol pyruvate carboxykinase. Thus, deficiency of this enzyme can lead to the impairment of the major pathways of the intermediary metabolism.[34] The deficiency of this enzyme can lead to lactoacidosis due the accumulation of pyruvate which is subsequently converted to lactate by

lactate dehydrogenase.[34] Gluconeogenic substrates cannot be converted to oxaloacetate, and hence there is a limiting amount of oxaloacetate, a starting material for gluconeogenesis.

This explains the basis of why some patients face severe hypoglycemia caused by diminished neonatal gluconeogenesis. Deprivation of oxaloacetate leads to the failure of the liver to oxidize acetyl CoA derived from fatty acids, and this leads to ketoacidosis. The lack of oxaloacetate also impairs TCA cycle activity, affecting various TCA cycle intermediates to be used for various biosynthetic pathways e.g. the argininosuccinic acid in urea cycle, thus leading to the accumulation of urea cycle intermediates.

These defects explain why some patients exhibit metabolic ketoacidosis and elevated levels of citrulline and hyperammonemia, thus it is a basis of individual specific contraindication. As such, detrimental consequencies that arise due to pyruvate carboxylase deficiency in different metabolic conditions including ketogenic diet consumption calls for the need of professional guidance.

1.2.4 Mechanism in Porphyria

[37]Defined porphyria as hereditary disorders caused by the de-regulation of the heme pathway due to a deficiency in some of its enzymes, which lead to lower heme formation. Enzyme de-regulation is due to autosomal dominant inheritance of mutated genes coding the key enzymes (5-aminolevulinic acid synthase and hydroxymethylbilane synthase also known as 5-aminolevulinic acid dehydratase) of heme biosynthesis[38] which leads to the accumulation of heme precursors such as 5-aminolevulinic acid, porphobilinogen and porphyrins[39] resulting in the condition termed porphyria.

Heme biosynthesis takes place mainly in hepatocytes and developing erythroid cells of bone marrow in humans and other higher animals.[39] It is on this basis that porphyria is classified into hepatic and erythropoietic porphyrias based on the organ system in which heme precursors (5-aminolevulinic acid (ALA), porphobilinogen and porphyrins) are chiefly overproduced.[39]

The hepatic porphyrias are further classified as acute or inducible porphyrias and chronic hepatic porphyrias. This is based on the acuity of clinical manifestations and does not signify the duration of the disease. The acute hepatic porphyrias include; acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and porphyria due to

severe deficiency of 5-aminolevulinic acid dehydratase porphyria (ALADP). The chronic hepatic porphyrias are porphyria cutanea tarda (PCT) and hepatoerythropoietic porphyria (HEP).[40] In most populations, AIP is the most common and 5-aminolevulinic acid dehydratase porphyria the least common acute porphyria.

The most common presenting symptoms are recurrent episodes of pain, nausea, vomiting, constipation, dark red urine, severe abdominal pain especially occurring in women aged 18–45 years, or evidence of acute or chronic photosensitivity.[39][41]

According to[38] lifestyle factors, including a low intake of carbohydrates, dieting, alcohol consumption, cigarette smoking and stress are some of the possible triggers of attacks in acute intermittent porphyria (AIP). It is for these reasons that the American Porphyria Foundation (APF) advices patients with AIP to avoid prolonged fasting, and to have a carbohydrate intake of 55–60% of the total energy intake (E%).[38] [42] stated that glucose significantly improves the biochemical and clinical conditions of porhpyria patients.

The first line of treatment is to remove any known triggering factor including low carbohydrate diet (ketogenic diet) and fasting. In hospitals, intravenous infusion of glucose and/or of synthetic heme can be administered.[43] The inhibiting effect of glucose on the heme synthesis is probably related to peroxisome proliferator activated cofactor 1α (PGC-1α).[44] For this reason, very low carbohydrate nature of ketogenic diet renders ketogenic diet detrimental to individuals suffering from porphyria, thus necessitating the consent of professionals.

1.2.5 Mechanism in Defective Liver and Pancreas

Liver is the major site of systemic metabolic regulation.[15] Pathways of metabolism of lipids and carbohydrates are controlled by complex interactions in the hepatocytes.[45] Catabolic and anabolic processes that favor metabolic flexibility and adaptations including adjustments to change in diets are carried out and regulated by the liver and other endocrine exocrine hormones.

Pancreas is one of the exocrine organs that produce metabolically important hormones (insulin and glucagon) which plays a pivotal role in energy metabolism.[46] Any form of dysfunction by these organs, acute or chronic attenuates their metabolic capacities. Thus, consumption of ketogenic diet by individuals with defective organs can lead to metabolic

catastrophe including hypoketotic- hypoglycemia, coma or even death as the regulatory machineries are not in place to carry out the homeostatic functions. As such, professional recommendation is paramount in the application of ketogenic diet for whatever reason.

1.2.6 Mechanism in Uncontrolled Type 1 Diabetes

During high fat intake (as observed in ketogenic diet intake) or low carbohydrate intake, there is usually a rise in the uptake of non esterified fatty acids by the liver. This fed state does not favor the rise in the insulin level but rather a rise in glucagon[11] which promotes ketogenesis through the activation of carnitine palmitoyl transferase-1 by inducing excessive uptake of fatty acids into the hepatic mitochondria.[47] This leads to a surge in the level of the ketone bodies (acetoacetate and β-hydroxybutyrate) in the blood.

Similarly low or lack of insulin in cases of untreated diabetes type 1 leads to rise in glucagon hence rise in ketogenesis[11] manifested as hyperketonemia. This means that intake of ketogenic diet in uncontrolled Type 1 diabetes leads to hypoglycemic-hyperkenonemia, a condition that aggravates the clinical conditions of the patients. The aggravated clinical condition is due to the insulin suppression effect of ketogenic diet as well as its role in compounding the hyperketonemic condition leading to ketoacidosis. Rise above normal in the concentration of ketone bodies in the circulation tend to illicit various pathological complications by activating injurious pathways leading to cellular damage as manifested in complications of the brain, kidney, liver, and microvasculature. Reports in literature demonstrate a plausible link between elevated levels of circulating ketones and oxidative stress, linking hyperketonemia to innumerable morbid conditions.[46] For these reasons, consumption of ketogenic diet by individuals suffering from type 1 diabetes should be under strict medical supervision.

1.3 CONCLUSION

Ketogenic diet (KD) is a high-fat, low-carbohydrate diet, with adequate protein content, which forces the body to utilize fat, rather than carbohydrate, as a preferred energy substrate. Recent literatures revealed that this diet has important therapeutic application as well as weight management. Nevertheless, the consumption of keto diet has been found to be detrimental in individuals with lipid metabolism disorders, pyruvate carboxylase deficiency, porphyria, defective liver and pancreas as well as individuals with uncontrolled type 1 diabetes. Thus, the use of ketogenic diet for either therapeutic or weight management reasons

should be under supervision of a qualified and experienced team of nutrition and endocrine professionals to avoid unintended negative ramifications contraindicated individuals.

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