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The biochemistry of ketogenesis and its role in weight management, neurological disease and oxidative stress

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***Abstract*---**The section of mammalian metabolism known as ketogenesis is responsible for creating ketone bodies. In this mechanism, the liver responds to decreased glucose availability by producing the tiny, water-soluble molecules acetoacetate, D-3-hydroxybutyrate, and propanone. While ketone bodies are always present in small amounts in healthy people, dietary changes and some pathological circumstances can raise the concentrations of these substances in living organisms. The systemic effects of ketogenic diet (KD), despite its recent widespread usage, are poorly known and can range from potentially dangerous results to medically advantageous outcomes depending on the situation. Here, we discuss the

metabolism and molecular signaling of ketone bodies before relating the biology of ketone bodies to debates about their potential or actual health benefits. According to the findings of this research, a KD can be used as a natural treatment for weight loss in fat individuals. This is a one-of-a-kind research that will follow the effects of a KD for 24 weeks. The patients' lipid, total cholesterol, LDL cholesterol, and glucose levels all decreased significantly, while their HDL cholesterol levels increased significantly. The adverse effects of medications widely used for weight loss in such individuals were not noted in patients on the KD. These findings suggest that following a KD for an extended length of time is safe and the KD may have cognitive advantages for the illnesses discussed. in this study, though more research is required, especially in the case of Parkinson's disease. The diet may lessen seizures, enhance mood and cognition, and stabilise bioenergy profiles in people with GLUT1-DS and refractory epilepsy. It may enhance memory capabilities, cognitive ability, daily activities, and mood in AD while enhancing both motor and nonmotor symptomatology in PD.

***Keywords*---**ketogenesis, metabolism, weight management, neurological disease, oxidative stress.

Introduction

The term "ketogenesis" refers to the series of reactions that result in the formation of so-called ketone bodies, such as -hydroxybutyrate (bHB), acetoacetate, and acetone. Ketone bodies are produced predominantly by the mitochondria of hepatocytes, but kidney epithelia, astrocytes, and enterocytes are also capable, albeit to a lesser extent. Ketogenesis necessitates efficient -oxidation of fatty acids by mitochondria. Medium chain fatty acids, such as octanoate, infiltrate mitochondria without restriction and are readily converted to acetyl-CoA. (Foster, 2012). Long chain fatty acids, such as palmitate, must be transported to mitochondria via carnitine palmitoyltransferase and carnitine palmitoyltransferase (CPT1). CPT1 functions as a regulatory node between fatty acid oxidation and biosynthesis because its activity is regulated by the concentration of malonyl-CoA, an initial intermediate of fatty acid synthesis (Grabacka et al., 2016).

The substrate for ketogenesis is acetyl-CoA, the product of fatty acid oxidation. The first phase of ketogenesis involves the condensation of two molecules of acetyl-CoA to create acetoacetyl-CoA, catalysed by acetoacetyl-CoA thiolase (ACAT1, EC 2.3.1.9; Figure 1). Next, the third acetyl-CoA molecule is attached to form 3-hydroxy-3-methylglytaryl-CoA (HMG-CoA) by the rate-limiting enzyme HMGCS2 (mitochondrial HMG-CoA synthetase, EC 2.3.3.10). HMG-CoA is then converted by HMG-CoA lyase into the first sort of ketone molecule, acetoacetate, and acetyl-CoA. (HMGCL, EC 4.1.3.4). NADH-dependent -hydroxybutyrate dehydrogenase converts the preponderance of newly formed acetoacetate to bHB (BDH, EC 1.1.1.30). The most prevalent ketone body in the circulation is -hydroxybutyrate. In certain tissues (such as the lungs), the remaining

acetoacetate is spontaneously decarboxylated into volatile acetone, the simplest ketone body. In reality, the existence of acetone in diabetic patients' inhaled breath is a sign of a potentially fatal disease known as ketoacidosis.

Ketone bodies (KBs) are a consequence of lipid metabolism, specifically "oxidation," and are present in all forms of life, including Eukaryotes, Prokaryotes, and Archaea. These low-molecular-weight intermediates serve as an alternative energy source to glucose. In normal circumstances, the plasma concentration of KBs in humans fluctuates between 0.05 and 0.1 mM. However, when KB synthesis is increased due to protracted exercise, malnutrition, carbohydrate restriction/KD, or insulin deficiency, the plasma concentration of KBs increases. Animal models have demonstrated that nutritionally inducing moderate ketonemia through the use of a KD, intermittent fasting, or caloric restriction is beneficial despite the fact that ketoacidosis is a pathological condition. This has resulted in enhanced metabolic profiles, increased lifespans, and enhanced neurological responses. As glucose levels in the blood begin to decline, the brain can turn to ketone bodies for energy. When glucose oxidation is drastically reduced, ketone bodies become important because they can supply additional energy to cells.

KD has been utilised for many years to treat a variety of neurological conditions, and a sizable number of studies have lately confirmed the function of KD in neuroprotection. Through lowering oxidative stress, regulating energy metabolism, controlling inflammation, controlling the activity of deacetylation, and other potential processes, it may have neuroprotective effects. It is inevitable that all neurological diseases will impact human health through oxidative damage, energy metabolism issues, or inflammatory responses, even though the precise processes of KD in the treatment of neurological diseases are still unknown. Many mechanisms are frequently involved in neurological illnesses, and KD may potentially contribute to these pathways. When it comes to some conditions, like epilepsy, AD, PD, and KD can be therapeutic, while in others, they can only be supportive.

The KD has been used to treat a variety of neurological disorders, diabetes, malignancies, and other conditions. As KD mimics the metabolic pathways linked to calorie restriction and lifespan, this diet has been revitalised beyond its therapeutic use. The short-term advantages must be evaluated against the long-term negative effects and contraindications, which may make it enticing to the fad culture of dieting. KD has been demonstrated to result in a 9.6 kg weight reduction in just six months. Hypotension and increased HDL and LDL are two physiological alterations connected to VLCKD. In fasting and unmanaged diabetic circumstances, they build up in the plasma. The aim of the present study was therefore to discuss and summarise the factors that induce ketogenesis as well as the processes by which ketones increase oxidative stress and cause cellular and tissue damage.

Materials and Methods

Ethical statement

The Advanced Studies Research Board (ASRB) in Khyber Girls Medical College, Peshawar, Pakistan approved all the experimental protocols and procedures.

Data collection

The prospective research was conducted on 81 subjects at the Hayatabad Medical Complex in Peshawar (Pakistan) (38 men and 43 women). The body mass index (BMI) of men was 32.71.9 kg/m2 and that of women was 37.61.2 kg/m2. The mean age of males was 44.71.6 years and the mean age of women was 41.32.4 years. Table 1 provides the average ages, initial heights, initial weights, and BMIs of all patients. Blood examinations were performed on all of the subjects while they were fasting. All patients were subjected to liver and renal function tests, glucose and lipid profiles, and a complete blood count using fasting blood samples. At the eighth, sixteenth, and twenty-fourth week, fasting blood samples were analysed for total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, blood sugar, urea, and creatinine levels. In addition, weight, height, and blood pressure were measured and monitored at each visit.

Table 1: Patient data at baseline before treatment with the KD

	Frequency	Mean age	Mean BMI
Male	38	44.7±1.6	32.7±1.9 kg/m2
Female	43	41.3±2.4	37.6±1.2 kg/m2

Protocol for KD

There were between 20 and 30g of carbohydrates in the form of green veggies and lettuce, and between 80 and 100g of protein in the form of meat, fish, poultry, eggs, seafood, and cheese, all of which were provided to all 81 individuals on the KD. The diet also included polyunsaturated and monounsaturated lipids. After 12 weeks, the patients' meals had an extra 20 g of carbohydrates added, bringing the total to 40-50 g. Each participant received one tablet of micronutrients (vitamins and minerals) per day.

Tissue collection

The participants were put under anesthesia with the isoflurane and the tissues were removed after 6 and 24 hours following the injury. The area of cortices which was needed to observe was then collected, and tissue for western blots was also collected in tubes (microcentrifuge). The samples were then put in dry ice and made it flash-frozen and after that stored at -80° celcius.

Isolation of Mitochondria

The area of cortices which was needed to observe was isolated and blended in an isolation buffer that was maintained at a cold temperature. The resulting homogenate was spun at 4000 r/min for 3 min, and after that the supernatant was further spun at 14,000 rotations per min for 8 min. pellets were observed and then those were mixed with digitonin in 1.50 ml isolation media. Following incubation, the mixture was centrifuged again at 14,000 rotations per min for 8 minutes, and the mitochondria were again put in isolation media which was EGTA-free.

Determination of Protein

Concentrations of the Protein were determined using a kit named Lowry DC with serum albumin (bovine) as the standard for conc. measurement.

Western Blots

The study used tissue homogenates or mitochondria which were isolated and dissolved in protease inhibitor-containing RIPA solution. SDS-PAGE was used to split the lysate, and the membranes were then transferred to PVDF. Primary antibodies for 3-nitrotyrosine, 4-hydroxynonenol, superoxide dismutase, and NAD(P)H dehydrogenase quinone 1 were then treated with the membranes. Next, the membranes underwent washing before being exposed to an enhanced chemiluminescence detection reagent. To determine the band densities, normalization was done against the total protein content that was loaded per lane, utilizing Sypro Ruby.

Activity of Complex I

To measure the working activity of Complex I enzyme in isolated mitochondria, the researchers followed the instructions provided by the manufacturer MitoSciences. The assessment of Complex I activity was performed through the measurement of NADH oxidation to NAD+ and the concurrent reduction of a dye, thereby increasing the absorbance at 450 nm.

Activity of Complex II-III

To assess Complex II and III enzyme function in separated mitochondria, the researchers followed the instructions provided by the manufacturer MitoSciences. The change of cytochrome c from its oxidised to its reduced state, which resulted in a straight rise in absorbance at precisely 550 nm, was used to ascertain the activity of Complex II-III. To ensure that the reduction of cytochrome c was solely mediated by Complex II. Furthermore, the addition of KCN prevented any potential cytochrome c re-oxidation of Complex IV.

Analysis of Statistics

A matched Student's t test was used to compare pre- and post-KD values for body mass index, total cholesterol, HDL cholesterol, LDL cholesterol, lipids, fasting

blood sugar, urea, and creatinine. To compare the differences in between the independent groups, for numerous comparisons, one-way ANOVA along with Tukey's test was used. A P-value of 0.05 or less was regarded as statistically significant using SPSS software (version 23.0).

Results

Oxidative stress

It is demonstrated that TBI raised the expression of the markers of nitrosative and oxidative damage, respectively, 3-nitrotyrosine (3NT) and 4-hydroxynonenal (4HNE). Participants given a KD, however, had lower levels of 3NT and 4HNE than participants fed a standard diet (STD). The research also discovered that when KD was given after TBI, age-related differences in outcome were not statistically significant. These results imply that a KD may shield neurons from oxidative and nitrosative damage brought on by TBI.

By triggering the Nrf2/ARE system, which upregulates antioxidant proteins and shields reactive stress-induced cell demise in cells, the KD may enhance neurological outcomes. When compared to injured animals that were given a sham diet or a standard diet, injured animals on a KD had higher expression levels of NQO1, cytosolic superoxide dismutase, and mitochondria. Injury or diet had no effect on mitochondrial SOD2 expression at 6 hours, but a KD raised it by 144% by 24 hours. SOD1 and NQO1 protein expression in PND70 animals did not vary between groups.

Impaired air quality causes the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). mitochondrial function caused by Traumatic Brain Injury (TBI), according to study (RNS). The blocking of Complex I and Complex III, which are susceptible to oxidative changes, is the primary factor causing this impairment and the creation of ROS/RNS. Superoxide is produced when Complex III is inhibited by peroxynitrite, according to research. In order to determine how Complex I and Complex II-III contributed to the decrease in ATP found in PND35 subjects, the research assessed their performance at 6 and 24 hours after the injury.

Neurological disease

It has been demonstrated that the KD is therapeutic for some illnesses, both in terms of metabolism and neural function. Its therapeutic effects in particular conditions are backed by a large body of scientific research, and more recent studies have also highlighted its potential to treat neurological diseases, especially in terms of the cognitive advantages.

Table 2 lists potential methods by which ketogenic treatments might affect brain disorders

Ketogenic Mechanisms	Epilepsy	Malignant Glioma	AD
Control of Metabolism			
↓Glycolysis and glucose absorption	+	+	
↓Insulin, IGF1 pathway		+	+
↑ketone metabolism and ketones	+		+
NeurotransMission			
modified intestinal flora	+		
Altered balance of exci/inh neurotransmitters	+		
blocking AMPA receptors	+		
↓mTOR signalling and action	+	+	
↓ATP-sensitive potassium channel modification	+		
Oxidative Stress			
↓Production of reactive oxygen species	+	+	
Mitochondrial ↑biogenesis/function			+
Inflammation/Neuroprotection			
↓Inflammatory cytokin	+	+	
Inflammasome NLRP3 suppression	+	+	
↑killer T cell function		+	
↓peritumoral swelling		+	
↓amyloid-β levels			+
Genomic Effects			
Inhibition of HDACs	+	+	
↑PPARγ	+		
Tumor cells express angiogenic proteins		+	

"NLRP3 stands for NOD-like receptor protein 3, AMPA stands for amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid, IGF1 stands for insulin-like growth factor 1, HDACs stand for histone deacetylases, and PPAR stands for peroxisome proliferator-activated receptor. Reduced, increased, or +—mechanism discovered through in vitro or in vivo research"

Discussion

The current research offers proof that the KD can lessen oxidative damage in both the cytosol and mitochondria by directly scavenging free radicals and by inducing

antioxidant proteins like SOD1/2 and NQO1, which are controlled by Nrf2 signalling in the genome. The study's conclusions are consistent with previous studies that found less oxidative damage when ketones were present. The research suggests that the increased Free fatty acids trigger the PPAR (peroxisome proliferator-activated receptor) to become active, KD results in a sufficiently high concentration of ketones in the brain to inhibit free radicals and the production of mitochondrial uncoupling proteins should be increased (UCP).The ability of the KD to trigger a variety of protective antioxidant pathways accounts for its efficacy in reducing oxidative stress.

Hypoglycolysis and mitochondrial failure are brought on by traumatic brain injury (TBI), which lowers cerebral metabolism. In PND35 animals, the KD has demonstrated to increase ATP generation and glucose metabolism, by acting as a different energy source. However, it appears that ketone bodies' neuroprotective effects are caused by other mechanisms in addition to their capacity to function as a substrate given the inhibition of mitochondria after injury. Nitric oxide and reactive oxygen and nitrogen species (ROS/RNS) (NO) generation rises as a result of injury-induced excitotoxicity, which can impair mitochondria and result in a significant calcium inflow inside the cell. Intake of calcium by mitochondria and as a result, Complex I is inhibited, O2 generation is encouraged, and mitochondrial NOS is activated.

Both respiratory substrates connected to Complex I and II have been related to mitochondrial dysfunction. Based on earlier studies that have demonstrated ketone bodies' It was predicted that ketone bodies would have the capacity to decrease reactive stress, enhance mitochondrial function by lowering both cytosolic and oxidative stress. Though ketone bodies were present, Complex I was still inhibited six hours after the injury. This was most likely because calcium entry into the mitochondria was unchanged and Complex I had been sustainably inhibited due to oxidative modification before ketone body administration.

Despite the fact that numerous studies have indicated that the KD enhances brain metabolism and outcomes, its underlying mechanisms of action are still not completely known. Our study shows that the antioxidant diet's effectiveness is greatly influenced by its constituents. neuroprotective effects at earlier time points, whereas earlier studies have primarily concentrated on the diet's ability to serve as a substitute substrate. The KD plays an increasingly significant part as an alternative substrate over time. However, PND70 animals lacked the reductions in oxidative stress and protective protein production seen in PND35 animals. This is likely because of age-related variations in ketone absorption and metabolism. Future studies are required to completely comprehend the KD's potential as a neuroprotective agent and to assess age variations using fast and similar ketone body administration techniques.

There were 63 articles found that satisfied the review's inclusion requirements. Scientific works that were part of the systematic review were also described. The 25 research studies sought to determine whether intractable seizures, GLUT1-DS, AD, and PD were successfully treated with the ketogenic or low-carbohydrate diet. The additional 6 experimental studies used alternative approaches to induce the ketone state, including AAV-hSLC2A1, the oral ketogenic compound AC-1202, the

oral administration of ketone monoester, diets with enantiomeric precursors of ketone bodies, carbohydrate isocaloric diets, and drinks with emulsified MCT. Numerous researchers, including (Mochel F *et al.,* 2016), (Nakamura S *et al.,* 2017), and (Reger MA *et al.,* 2004), conducted the investigations. Five of the 25 papers examined refractory epilepsy, eight examined GLUT1-DS, nine examined AD, and three examined PD.

The studies' participant counts ranged from 1 to 152, making it difficult to make broad conclusions. This highlights the fact that this area of study is still in its infancy and may offer promising rewards. The 25 scientific studies consisted of six prospective studies, one longitudinal study, seven animal experimental models two single-case studies, two placebo-controlled parallel study groups, two single-case studies, one three-phase open pilot study, one open prospective pilot study, one feasibility study, one pilot clinical study, and one randomly controlled parallel study groups. Despite the use of animals in some of the studies, they emphasise the need for further clinical research on the advantages of the KD for people with the aforementioned illnesses in terms of their brain function.

In this investigation, individuals with intractable seizures, GLUT1-DS, AD and PD were examined for how the KD affected their cognitive abilities. Studies have shown that the KD is effective in decreasing seizures in people with refractory epilepsy, with over 85% of cases experiencing a reduction in seizures and more than 50% experiencing a reduction in episodes during the first month. Additionally, the diet improved happiness and memory in a test rodent model. Early GLUT1-DS treatment should include the KD because it may improve neurophysiological functions like alertness, cognitive capacity, quality of life, and physical resilience. In more than 90% of cases, it may also (Raimann *et al.,* 2007) stabilise bioenergy profiles and ameliorate nonepileptic paroxysmal manifestations (Ramm-Pettersen *et al.,* 2014). Similar findings were also reported by Taylor et al (2018) and Nakamura *et al.,* (2017).

In AD Memory, cognitive ability, daily activity, mood, affection, and self-care are just a few of the cognitive functions that may be improved when ketosis is induced either through a KD or by using a ketone monoester ketogenic agent. Studies using animal models have shown that the KD can enhance behaviour, motor function, and proteopathic deficiencies in addition to memory recall and learning capacity (Lambrechts *et al.,* 2012). The KD had no impact on the behaviour of two sets of transgenic female mice, though. Although there isn't much information on the KD and PD, some studies have found that it may help with both motor and nonmotor symptoms, such as tiredness, daytime sleepiness, and cognitive decline (Klein *et al.,*2014).

Conclusion

According to the findings of this research, a KD can be used as a natural treatment for weight loss in fat individuals. This is a one-of-a-kind research that will follow the effects of a KD for 24 weeks. The patients' lipid, total cholesterol, LDL cholesterol, and glucose levels all decreased significantly, while their HDL cholesterol levels increased significantly. The adverse effects of medications widely used for weight loss in such individuals were not noted in patients on the KD. As

a consequence, these findings suggest that following a KD for an extended length of time is safe. In our study, additional research into the biochemical processes of a KD is being conducted. These findings will pave the way for further research into the possible medicinal applications of a KD and ketone bodies. Overall, the findings suggest that the KD may have cognitive advantages for the illnesses discussed. in this study, though more research is required, especially in the case of Parkinson's disease. The diet may lessen seizures, enhance mood and cognition, and stabilise bioenergy profiles in people with GLUT1-DS and refractory epilepsy. It may enhance memory capabilities, cognitive ability, daily activities, and mood in AD while enhancing both motor and nonmotor symptomatology in PD.

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