Biological Forum – An International Journal **15(1): 75-81(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Scope of Low Carbohydrate Diets as Therapeutics

Monika Yadav and Vibha Mandhan*
Department of Botany, BMU, Rohtak (Haryana), India.

(Corresponding author: Vibha Mandhan)*
(Received: 19 November 2022; Revised: 18 December2022; Accepted: 26 December, 2022; Published: 06 January, 2023)
(Published by Research Trend)

ABSTRACT: The low-carbohydrate diets were recently used to treat various illnesses. The low-carbohydrate diets have emerged as a substitute for medicines. Weight reduction and its maintenance are the key targets to dietary modulations. Meal replacements can be beneficial in improving the efficacy of dietary modulations. The nutrient-enriched diet needs to be used for the long term to show promising health outcomes. Additionally, dietary interventions have been used in various illnesses such as cardiovascular diseases, diabetes, kidney health, neurological disorders, as well as acne. Thus, it becomes mandatory to remove conventional medications from dietary habits and add nutrient-enriched foods to avoid the harmful side effects of conventional therapies. Dietary modification becomes the need of the hour for healthy well-being. Additionally, the keto diets suffer various challenges such as causing various human illnesses, disregulated eatings, and social isolation. This review highlights the role of ketogenic diets as therapeutics for various human disorders.

Keywords: Low-carbohydrate diet, Human disorders, Weight loss, Dietary modulations, Ketogenic diet.

INTRODUCTION

Over the years, various studies have demonstrated the use of a low-carbohydrate ketogenic diet for relieving various illnesses. The ketogenic diets were found efficient in mitigating epilepsy (Ułamek-Kozioł *et al.*, 2019). The addition of the Atkins diet and various other dietary modifications has popularized the need for dietary modulations for a healthy life (Churuangsuk *et al.*, 2020). Diet has shown promising effects on various clinical disorders (Merrill *et al*., 2020) (Table 1).

Table 1: Targeted functioning of ketogenic diet in various disorders.

Disease	Targeted mechanism	Reference
Cardiovascular disorder	Reduction in blood insulin and increase in LDL production	(Paoli *et al*., 2011)
Weight loss	Reduction in appetite, lipid synthesis, increased lipid metabolism	(Kreider *et al.*, 2011)
Diabetes	Reduction in blood insulin and increased mitochondrial homeostasis	(Leow *et al.*, 2018)
Polycystic ovary syndrome	Reduced blood insulin and reduced activity of insulin-like growth factor	(Mavropoulos *et al.*, 2005)
Acne	Reduced activity of insulin-like growth factor	(Paoli *et al*., 2012)
Neurological disease	Reduction in blood insulin and increased mitochondrial homeostasis	(Stafstrom and Rho 2012)

As dietary modifications are more economic than conventional pharma-based medications, more research needs to be done to prepare a standardized dietary regime for a healthy body (Merrill *et al.*, 2020). The low-carbohydrate ketogenic diet includes more proteins and low carbohydrates (approximately 50g per day) (Veech, 2004). The significance of ketogenic diets can be traced back to the early 1920s (Owen *et al*., 1967) when it was first used to treat epilepsy (Kessler *et al.*, 2011). Additional research efforts were done to explore the effects of ketogenic diets on metabolism. Low carbohydrate diets reduce insulin levels which further reduce fat deposition and lipid synthesis. Insulin activates the formation of energy molecules from carbohydrates through enzyme activation (Owen *et al.*, 1967). As the central nervous system depends on glucose for energy, alternative approaches such as acetyl coenzyme A production needs to be targeted for CNS health (Owen *et al.*, 1967). During fasting as well as low-carbohydrate dietary intake, the energy molecules such as acetoacetate, acetone, and hydroxybutyric acid are produced in the liver mitochondria (Fukao *et al.*, 2004). The normal levels of free acetoacetate are metabolized by muscles but the overproduction of acetoacetic acid leads to its conversion to ketone bodies that cause ketonuria and

ketonemia. The formation of acetone and its removal from the lungs causes bad breath. Additionally, even though blood glucose levels are reduced, it stays within acceptable levels due to the presence of glucose from two sources: glucogenic amino acids and glycerol liberated during triglyceride breakdown (A. Paoli *et al.*, 2011). Several recent studies have explored the role of ketogenic diet in maintaining healthy body (Churuangsuk *et al*., 2020). In-line with the current efforts, this review focuses on the therapeutic roles of the low-carbohydrate diets in various human disorders. Additionally, the challenges and drawbacks of the ketogenic diets have also been highlighted in detail.

THERAPEUTIC ROLE OF THE KETOGENIC DIET

Cardiovascular system. There is concrete evidence that a low-carbohydrate ketogenic diet has a positive impact on cardiovascular risk factors. Previous worries have been raised about their superior effectiveness in comparison to "balanced" diets and long-term safety, as well as widely negative opinions related to possible negative effects on triglyceride and cholesterol levels. Nonetheless, the bulk of modern research has come to support the idea that cutting carbohydrates to a level that activates physiological ketosis can indeed lead to positive outcomes on blood lipid profiles (Volek *et al.*, 2009). Specifically, the low-carbohydrate ketogenic diet outcome seems to be particularly pronounced on triglyceride levels (Paoli *et al*., 2011), but it has also been observed to bring about lower total cholesterol and higher levels of high-density lipoprotein (Paoli *et al*., 2011).Furthermore, researchers have observed that a low-carbohydrate ketogenic diet amplifies the mass and size of low-density lipoprotein-cholesterol particles (Volek et al., 2005), which is suspected to reduce the chance of cardiovascular disorder since smaller low-density lipoprotein molecules tend to be more atherogenic. Additionally, there are direct consequences of diet on the general production of endogenous cholesterol. 3-hydroxy3-methylglutaryl-CoA reductase, an essential enzyme in cholesterol biosynthesis and a goal of statins, is activated by insulin, so a rise in blood glucose and thus of insulin levels will cause an increase in endogenous cholesterol manufacture.

Weight loss

Meal replacement. The best method assumed for weight loss is the replacement of current meals as it is considered a safe way without any side effects (Davis *et al.*, 2010). The diets are decided based on sufficient nutrient uptake (Ditschuneit and Flechtner-Mors, 2001). The high-fat diets can be replaced by low-calorie, nutrient-dense meals such as low-fat foods. The liquids containing low-energy components can be used as weight loss regiments. In a study, two groups were made- one with intense physical activity and the other with planned dietary modifications. Both groups were found to have similar effects (LeCheminant *et al.*, 2005). Low-fat meal usage has shown a good impact on weight management during obesity (Davis *et al.*, 2010). In a study, 100 patients were divided into two groups- one with a low-energy diet and the other with the same calorie diet (replaced with two meals) (Ditschuneit and Flechtner-Mors 2001). Although weight reduction was observed in both groups but the second group was observed with more weight loss and weight maintenance (Ditschuneit and Flechtner-Mors 2001). As meal replacement does not affect dietary satisfaction, dietary habits, appetite, as well as diet quality, it is an ideal way for weight loss and management. It was observed that dietary modifications along with intense physical exercise help in maintaining weight (Kreider *et al*., 2011). The dietary modifications may suffer certain economic issues as certain people cannot afford nutrient-enriched meals (Ditschuneit and Flechtner-Mors 2001). Additionally, diet repetitions may bring out dietary sickness (LeCheminant *et al*., 2005).

Addition of nutrient-enriched meals. Weight can also be managed with the addition of nutrients to the daily dietary regime. The use of a low-fat, low-carbohydrate, and high-protein diet may help in body weight maintenance. Low-protein and high-glycemic index diets were found more effective in weight loss than the high-protein and low-glycemic-index diets (Layman *et al.,* 2009). The high-protein and low glycemic index diet induced a continued weight loss. Even though less glycemic index diet accompanies fewer calories, it was not found effective in weight maintenance (Philippou *et al.,* 2009). Weight regain can be avoided with the use of a high protein diet during high content of CRP and leptin (Redman *et al.,* 2009). Low-energy and medium-fat diet was found more effective in weight management than a low-fat diet (Azadbakht *et al.*, 2007). The appetite could not be controlled due to the low-energy diet as the satiety signals were found to be induced. The low-carbohydrate diet and the diet with high protein and carbohydrates were given to two different groups of people. The group on a low-carbohydrate diet was found to regain weight while the group with a high protein and carbohydrate diet was found to have continuous weight reduction and lower appetite. Craving was found to play a significant role in weight loss (Jakubowicz *et al.,* 2012).

Dietary patterns. The people who sleep early at night, do more physical activity and consume less sugar maintain a weight loss regime and are less prone to weight regain. The efficacy of weight loss, weight monitoring, and including healthy foods in the diet are significant for weight management (Phelan *et al.*, 2010). Lower calorie intake accompanies a lean body (Vanderwood *et al.,* 2011). A healthy diet must include low-fat grains, high fiber, fruits, and vegetables (Raynor *et al.,* 2011). Weight regain differentiates with differential hunger and cognitive habits (Legenbauer et al., 2010). Eating habits, continuous eating, and emotional distress need to be controlled for regular weight maintenance (Karhunen *et al.,* 2012). Calcium may help in reducing weight regain (Ochner and Lowe 2007). Additionally, the inclusion of fewer food varieties can help in avoiding weight regain (Raynor *et al*., 2005).

Other dietary changes. Dietary approaches have been used to avoid hypertension that simultaneously

maintains body weight (Azadbakht *et al*., 2011). The diet must include low-fat products, fruits, and vegetables. This diet helps in weight loss as well as weight management due to low-fat dairy products (Champagne *et al.,* 2011). Similarly, milk protein was found effective in long-term weight loss maintenance (Hochstenbach-Waelen *et al.,* 2010). The re-feeding period is crucial during weight maintenance (Gripeteg *et al*., 2010).

Diabetes

Type-1 Diabetes. Ketogenic diets increase glycemic conditions in diabetic patients and may cause hyperlipidemia, reduced bone mass, malnutrition, and amenorrhea. Additionally, they may affect mood behaviors (McClean *et al.,* 2019). The ketogenic diet may be beneficial as well as harmful during diabetes. The ketogenic diet regulates blood glucose (Leow *et al.*, 2018) and causes hypoglycemia. It can also generate dyslipidemia, a potential risk in heart patients (Leow *et al.*, 2018). Reduced ketosis was observed during type-1 diabetes (Kanikarla-Marie and Jain, 2016). Diabetic patients suffer from ketonuria due to metabolic deformities. These patients are at a potential risk of reduced functioning of the brain, liver, and kidney. Additionally, ketone production causes a high risk of inflammation, oxidative stress, and NAFLD (Kanikarla-Marie and Jain 2016).

Type-2 Diabetes. The low-carbohydrate diet decreases appetite, blood glucose, and thus improves weight loss (Westman *et al.,* 2008). Improved insulin sensitivity due to low fat has been observed due to the ketogenic diet (Goday *et al.,* 2016). In a study where a diet containing nearly half of the carbohydrates was given to a group of people and after 4 weeks the diet was shifted to the ketogenic diet, increased lipoproteins, cholesterol, and reduced insulin were observed. Thus, a carbohydrate-enriched diet reduced insulin sensitivity (Rosenbaum *et al.,* 2019). Further exploration revealed that a plant-based diet was more effective in improving insulin content than the animal-based ketogenic diet and glucose tolerance was affected during the ketogenic diet as compared to the plant-based diet. A study showed that insulin sensitivity was retained for 6 months and reversed after 1 year (Foster *et al*., 2003). The ketogenic diet reduced glucose formation in healthy people (Bisschop *et al*., 2001). Similar retrograded effects were observed for hemoglobin A1c during ketogenic diets (Goldenberg *et al.,* 2021). Thus, dietary modulations can effectively treat diabetes and reduce the potential risk of conventional medications (Vilar-Gomez *et al*., 2019). Thus, weight loss can be maintained in diabetic patients fed on the ketogenic diet (Kosinski and Jornayvaz 2017). Conclusively, there are both short as well as long-term implications of ketogenic diets on diabetic patients (Brouns, 2018).

Polycystic ovary syndrome. Polycystic ovary syndrome (PCOS) is the most prevailing disorder in females causing other disorders such as ovary dysfunctions, insulin resistance, as well as obesity (DeUgarte *et al.,* 2005). It is usually accompanied by obesity (Fauser *et al*., 2012). PCOS is usually a result of hyperinsulinemia where high blood insulin increases ovarian hormone release (Tosi *et al.,* 2012). Increased insulin content impairs the inhibition of progesterone (Blank *et al*., 2009). Insulin also increases the adrenal synthesis of steroids and ACTH release (Moghetti *et al.,* 1996). Although medications and lifestyle changes such as exercise may improve the increased insulin content and help in reducing body weight further relieving the PCOS symptoms, the exact mechanism of the ketogenic diet in PCOS is still not understood (Mavropoulos et al., 2005).

Kidney Health. The low-carbohydrate diet has been found effective in kidney health (Joshi *et al*., 2019). But the ketogenic diet leads to the development of kidney stones (McNally *et al.,* 2009). As the ketogenic diet relies on animal-based products, it increases the chances of kidney stones (Tracy *et al*., 2014). The acidity during stone formation further reduces pH and citrate and increases calcium concentration in the kidney. Additionally, the ketogenic diet also increases the albumin levels in urine (Lin et al., 2010). Other animal proteins were also found to show similar effects (Mirmiran *et al*., 2020). Low-protein diet was found effective in reducing the risk of renal failure (Yan *et al.,* 2018). The consumption of high proteins causes hyperfiltration leading to long-term renal damage (Kalantar-Zadeh and Fouque 2017). The high acidity due to the ketogenic diet further increases acidosis and kidney stones (Banerjee *et al.,* 2015). Thus, ketogenic diets need to be standardized in patients with kidney failure.

Acne. Acne development is directly related to nutrition consumption through diet. The high glycemic and milk protein-enriched foods increase acne development due to the activation of certain proliferative pathways responsible for acne (Paoli *et al.,* 2012). Individuals on traditional diets are comparatively less prone to acne development due to low glycemic loads (Cordain, 2005) than people on western diets (Smith and Mann 2007). High glycemic food increase acne due to increased insulin, androgen, and insulin-like growth factor production. Low glycemic foods improve skin quality and reduce weight as well as blood glucose (Smith *et al.,* 2007). Increased insulin levels improve androgen levels and induce enzyme levels for steroid synthesis (Kristiansen *et al*., 1997). Insulin further improves the activity of insulin-like growth factors(Powell *et al.*, 1991). Thus, insulin affects various factors that lead to acne development. Insulin increases the keratinocyte development within pilosebaceous ducts, causes disarrangement of follicular epithelium, increases sebum production due to androgen induction, and increases skin inflammation due to the overgrowth of *Propionibacterium acnes*(Cordain, 2005). Conclusively, low-carbohydrate diets may reduce acne development as well as its progression (Paoli *et al.,* 2012).

Alzheimer's disease. Alzheimer's disease is accompanied by seizures (Palop and Mucke 2009) with an increase in brain excitability (Noebels, 2011), and an alteration in mitochondria homeostasis (Kapogiannis and Mattson 2011). The low-carbohydrate diet is highly efficient in the clinical treatment of Alzheimer's disease

(Henderson *et al.*, 2009). The ketogenic diet relieved mitochondrial dysfunctioning and protected the neural cells against beta-amyloids (Kashiwaya *et al*., 2000). Less amyloid deposition and less oxidative stress were observed in Alzheimer's disease patients fed on the ketogenic diet (Van der Auwera *et al*., 2005). More intensive research efforts need to be done to explore the beneficial aspects of the ketogenic diet in disease betrayal.

Parkinson's disease. The maintenance of mitochondrial homeostasis by the ketogenic diet helps in the treatment of Parkinson's disease (Vanitallie *et al.*, 2005). The low-carbohydrate diet was found effective in the healing of the mitochondrial respiratory chain during the neural disorder (Kashiwaya *et al*., 2000). A deep understanding of the mechanism by which diet influences this change thus becomes mandatory.

Brain trauma. Brain trauma is the initial stage of epilepsy. As the low-carbohydrate diet relieves seizures, it helps in healing the clinical implications of brain injury through the reduction of the severity of brain injury (Stafstrom and Rho 2012). The low-carbohydrate diet reduced cortical injury and this treatment was found dependent on the age and differential metabolism of brain ketone bodies (Prins *et al*., 2005). The low-carbohydrate diet even decreased cognitive-motor functions after brain trauma (Appelberg *et al.*, 2009). Further explorations of the targeted mechanism need to be done for a better understanding of the role of the ketogenic diet in healing brain trauma (Schwartzkroin *et al*., 2010).

THE HARMFUL IMPACTS OF KETOGENIC DIETS

The toxic effects of ketogenic diets include increased fatigue, constipation, nausea, hypoglycemia, as well as acidosis (Roehl and Sewak, 2017). Additionally, hypertriglyceridemia, hypercholesterolemia, hypomagnesemia, hyperuricemia, hyponatremia, dehydration, hepatitis, and pancreatitis can also occur (Włodarek, 2019). The ketogenic diet may also bring other symptoms such as brain fog, reduced energy, and irregulations in the heartbeat (Bostock *et al.*, 2020). Ketogenic diets facilitate bone remodeling in athletes (Heikura *et al.*, 2020). Even long-term usage of the low-carbohydrate diet leads to anemia, neurological pathologies, and decreased bone mass (Hoyt and Billson 1979). Most people cannot tolerate the long-term usage of ketogenic diets (Brouns, 2018). Even the ketogenic diet was found to increase fatality rates (Noto *et al.*, 2013). The low-carbohydrate and high-protein diets additionally increase the risk of kidney failure due to an increased release of nitrogen (Westerterp-Plantenga *et al.*, 2009). Conflicts still occur among the studies conferring the harmful and neutral roles of ketogenic diets on kidney failures(Wakefield *et al*., 2011; Martin *et al.*, 2005). It was found that kidneys are highly adapted to the long-term usage of ketogenic diets (Welle and Nair 1990). The blood flow was found affected during a ketogenic diet. Additionally, metabolic disorders such as obesity, diabetes, and individuals on kidney transplants are more prone to the negative impacts of high-protein diets (Praga, 2005). The reduced kidney functions were also documented in diabetic patients (Westerterp-Plantenga, 2007). Low-protein diet was observed to decrease the risk of albuminuria in diabetic patients (Pijls *et al.*, 1999), but this protein deprivation in the diet soon needs to be recovered for normal body functions. The high-protein and low-carbohydrate diet was even found effective in reducing nephron damage during diabetes (Westerterp-Plantenga, 2007; Poplawski *et al*., 2011). Although ketogenic diets usually cause acidosis, their beneficial aspects cannot be neglected.

CONCLUSION

The low-carbohydrate diets are considered key tools to reduce weight. They are far more beneficial than low-fat diets but various concerns arise regarding the safety of ketogenic diets. The ketogenic diets are significant in providing therapeutic efficacy during various human disorders such as cardiovascular disease, obesity, acne, diabetes, PCOS, and neural pathologies. They are a key factor in the reduction of body weight and their long-term exposure can even reduce the risk of weight regain. The low-carbohydrate diet reduces blood glucose and helps in reducing the risk of diabetes.

FUTURE SCOPE

Further explorations need to be done to assess the efficacy and safety of ketogenic diets. These diets are highly efficient in relieving brain disorders such as epilepsy. But the ketogenic diets may suffer certain risks such as the rise of low-density lipoproteins as well as reduced/stunted brain development of the fetus during pregnancy. Thus, these diets may make the child prone to certain diseases such as neurological disease, cardio-vascular diseases, cancer, and diabetes. The reduced intake of plant-based products may increase the toxic effects of ketogenic diets. Even these risks can sometimes overcome the beneficial aspects of low-carbohydrate diets.

Conflict of Interest. None.

REFERENCES

Appelberg, K. S., Hovda, D. A. and Prins, M. L. (2009). The effects of a ketogenic diet on behavioral outcome after controlled cortical impact injury in the juvenile and adult rat. *Journal of Neurotrauma, 26*, 497–506.

Azadbakht, L., Fard, N. R. P., Karimi, M., Baghaei, M. H., Surkan, P. J., Rahimi, M., Esmaillzadeh, A. and Willett, W.C. (2011). Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. *Diabetes Care, 34*, 55–57.

Azadbakht, L., Mirmiran, P., Esmaillzadeh, A. and Azizi, F. (2007). Better dietary adherence and weight maintenance achieved by a long-term moderate-fat diet. *British Journal of Nutrition, 97*, 399–404.

Banerjee, T., Crews, D. C., Wesson, D. E., Tilea, A. M., Saran, R., Ríos-Burrows, N., Williams, D. E. and Powe, N. R. (2015). High Dietary Acid Load Predicts ESRD among Adults with CKD. *Journal of the American Society of Nephrology, 26*, 1693–1700.

Bisschop, P. H., de Metz, J., Ackermans, M.T., Endert, E., Pijl, H., Kuipers, F., Meijer, A. J., Sauerwein, H. P. and Romijn, J.A. (2001). Dietary fat content alters insulin-

mediated glucose metabolism in healthy men. *The American Journal of Clinical Nutrition*, *73*, 554–559.

Blank, S. K., McCartney, C. R., Chhabra, S., Helm, K. D., Eagleson, C. A., Chang, R. J. and Marshall, J. C. (2009). Modulation of gonadotropin-releasing hormone pulse generator sensitivity to progesterone inhibition in hyperandrogenic adolescent girls--implications for regulation of pubertal maturation. *The Journal of Clinical Endocrinology and Metabolism*, *94*, 2360–2366.

Bostock, E. C. S., Kirkby, K. C., Taylor, B. V. and Hawrelak, J. A. (2020). Response: Commentary: Consumer Reports of "Keto Flu" Associated With the Ketogenic Diet. *Frontiers in Nutrition*, *7*, 575713.

Brouns, F. (2018). Overweight and diabetes prevention: is a low-carbohydrate–high-fat diet recommendable? *European Journal of Nutrition*, *57*, 1301–1312.

Champagne, C.M., Broyles, S. T., Moran, L. D., Cash, K. C., Levy, E. J., Lin, P. H., Batch, B. C., Lien, L. F., Funk, K. L., Dalcin, A., Loria, C. and Myers, V.H. (2011). Dietary intakes associated with successful weight loss and maintenance during the Weight Loss Maintenance trial. *Journal of the American Dietetic Association*, *111*, 1826–1835.

Churuangsuk, C., Lean, M. E. J. and Combet, E. (2020). Low and reduced carbohydrate diets: challenges and opportunities for type 2 diabetes management and prevention. *Proceedings of the Nutrition Society*, 2020, 1-16.

Cordain, L. (2005). Implications for the role of diet in acne. *Seminars in Cutaneous Medicine and Surgery*, *24*, 84–91.

Davis, L.M., Coleman, C., Kiel, J., Rampolla, J., Hutchisen, T., Ford, L., Andersen, W. S. and Hanlon-Mitola, A. (2010). Efficacy of a meal replacement diet plan compared to a food-based diet plan after a period of weight loss and weight maintenance: a randomized controlled trial. *Nutrition Journal*, *9*, 11.

DeUgarte, C. M., Bartolucci, A. A. and Azziz, R. (2005). Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. *Fertility and Sterility*, *83*, 1454–1460.

Ditschuneit, H. H. and Flechtner-Mors, M. (2001). Value of structured meals for weight management: risk factors and long-term weight maintenance. *Obesity Research & Clinical Practice*, 9 Suppl 4, 284S-289S.

Fauser, B. C. J. M., Tarlatzis, B. C., Rebar, R. W., Legro, R. S., Balen, A. H., Lobo, R., Carmina, E., Chang, J., Yildiz, B. O., Laven, J. S. E., Boivin, J., Petraglia, F., Wijeyeratne, C. N., Norman, R. J., Dunaif, A., Franks, S., Wild, R. A., Dumesic, D. and Barnhart, K. (2012). Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertility and Sterility*, *97*, 28-38.e25.

Foster, G. D., Wyatt, H. R., Hill, J. O., McGuckin, B.G., Brill, C., Mohammed, B. S., Szapary, P. O., Rader, D. J., Edman, J. S. and Klein, S. (2003). A Randomized Trial of a Low-Carbohydrate Diet for Obesity. *The New England Journal of Medicine*, *348*, 2082–2090.

Fukao, T., Lopaschuk, G. D. and Mitchell, G. A. (2004). Pathways and control of ketone body metabolism: on the fringe of lipid biochemistry. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *70*, 243–251.

Goday, A., Bellido, D., Sajoux, I., Crujeiras, A. B., Burguera, B., García-Luna, P. P., Oleaga, A., Moreno, B. and Casanueva, F. F. (2016). Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus. *Nutrition & Diabetes*, *6*, e230–e230.

Goldenberg, J. Z., Day, A., Brinkworth, G. D., Sato, J., Yamada, S., Jönsson, T., Beardsley, J., Johnson, J. A., Thabane, L. and Johnston, B. C. (2021). Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. *The BMJ*, m4743.

Gripeteg, L., Torgerson, J., Karlsson, J. and Lindroos, A. K. (2010). Prolonged refeeding improves weight maintenance after weight loss with very-low-energy diets. *British Journal of Nutrition*, *103*, 141–148.

Heikura, I. A., Burke, L. M., Hawley, J. A., Ross, M. L., Garvican-Lewis, L., Sharma, A.P., McKay, A. K. A., Leckey, J. J., Welvaert, M., McCall, L. and Ackerman, K. E. (2020). A Short-Term Ketogenic Diet Impairs Markers of Bone Health in Response to Exercise. *Frontiers in Endocrinology*, *10*, 880.

Henderson, S. T., Vogel, J.L., Barr, L. J., Garvin, F., Jones, J. J. and Costantini, L.C. (2009). Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutrition & Metabolism*, *6*, 31.

Hochstenbach-Waelen, A., Westerterp, K. R., Soenen, S. and Westerterp-Plantenga, M. S. (2010). No long-term weight maintenance effects of gelatin in a supra-sustained protein diet. *Physiology & Behavior*, *101*, 237–244.

Hoyt, C. S. and Billson, F. A. (1979). Optic neuropathy in ketogenic diet. *British Journal of Ophthalmology*, *63*, 191–194.

Jakubowicz, D., Froy, O., Wainstein, J. and Boaz, M. (2012). Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults. *Steroids*, *77*, 323–331.

Joshi, S., Ostfeld, R. J. and McMacken, M. (2019). The Ketogenic Diet for Obesity and Diabetes—Enthusiasm Outpaces Evidence. *JAMA Internal Medicine*, *179*, 1163.

Kalantar-Zadeh, K. and Fouque, D. (2017). Nutritional Management of Chronic Kidney Disease. *The New England Journal of Medicine*, *377*, 1765–1776.

Kanikarla-Marie, P. and Jain, S. K. (2016). Hyperketonemia and ketosis increase the risk of complications in type 1 diabetes. *Free Radical Biology and Medicine*, *95*, 268–277.

Kapogiannis, D. and Mattson, M. P. (2011). Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *Lancet Neurology*, *10*, 187–198.

Karhunen, L., Lyly, M., Lapveteläinen, A., Kolehmainen, M., Laaksonen, D. E., Lähteenmäki, L. and Poutanen, K. (2012). Psychobehavioural factors are more strongly associated with successful weight management than predetermined satiety effect or other characteristics of diet. *Journal of Obesity*, 2012, 274068.

Kashiwaya, Y., Takeshima, T., Mori, N., Nakashima, K., Clarke, K. and Veech, R. L. (2000). D-beta-hydroxybutyrate protects neurons in models of Alzheimer's and Parkinson's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *97*, 5440–5444.

Kessler, S. K., Neal, E. G., Camfield, C. S. and Kossoff, E. H. (2011). Dietary therapies for epilepsy: future research. *Epilepsy & Behavior*, *22*, 17–22.

Kosinski, C. and Jornayvaz, F. (2017). Effects of Ketogenic Diets on Cardiovascular Risk Factors: Evidence from Animal and Human Studies. *Nutrients*, *9*, 517.

Kreider, R. B., Serra, M., Beavers, K. M., Moreillon, J., Kresta, J.Y., Byrd, M., Oliver, J. M., Gutierrez, J., Hudson, G., Deike, E., Shelmadine, B., Leeke, P., Rasmussen, C., Greenwood, M., Cooke, M. B., Kerksick, C., Campbell, J. K., Beiseigel, J. and Jonnalagadda, S. S. (2011). A structured diet and exercise program promotes favorable changes in weight loss, body composition, and weight maintenance. *Journal of the American Dietetic Association*, *111*, 828–843.

Kristiansen, S. B., Endoh, A., Casson, P. R., Buster, J. E. and Hornsby, P. J. (1997). Induction of steroidogenic enzyme genes by insulin and IGF-I in cultured adult human adrenocortical cells. *Steroids*, *62*, 258–265.

Layman, D. K., Evans, E. M., Erickson, D., Seyler, J., Weber, J., Bagshaw, D., Griel, A., Psota, T. and Kris-Etherton, P. (2009). A moderate-protein diet produces sustained weight loss and long-term changes in body composition and blood lipids in obese adults. *Journal of Nutrition*, *139*, 514–521.

LeCheminant, J. D., Jacobsen, D. J., Hall, M. A. and Donnelly, J. E. (2005). A comparison of meal replacements and medication in weight maintenance after weight loss. *Journal of the American Nutrition Association*, *24*, 347–353.

Legenbauer, T. M., de Zwaan, M., Mühlhans, B., Petrak, F. and Herpertz, S. (2010). Do mental disorders and eating patterns affect long-term weight loss maintenance? *General Hospital Psychiatry*, *32*, 132–140.

Leow, Z. Z. X., Guelfi, K. J., Davis, E. A., Jones, T. W. and Fournier, P. A. (2018). The glycaemic benefits of a very-low-carbohydrate ketogenic diet in adults with Type 1 diabetes mellitus may be opposed by increased hypoglycaemia risk and dyslipidaemia. *Diabetic Medicine*, *35*, 1258–1263.

Lin, J., Hu, F. B. and Curhan, G. C. (2010). Associations of Diet with Albuminuria and Kidney Function Decline. *Clinical Journal of the American Society of Nephrology*, *5*, 836–843.

Martin, W. F., Armstrong, L. E. and Rodriguez, N. R. (2005). Dietary protein intake and renal function. *Nutrition & Metabolism*, *2*, 25.

Mavropoulos, J. C., Yancy, W. S., Hepburn, J. and Westman, E. C. (2005). The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: a pilot study. *Nutrition & Metabolism*, *2*, 35.

McClean, A. M., Montorio, L., McLaughlin, D., McGovern, S. and Flanagan, N. (2019). Can a ketogenic diet be safely used to improve glycaemic control in a child with type 1 diabetes? *Archives of Disease in Childhood*, *104*, 501.1-504.

McNally, M. A., Pyzik, P. L., Rubenstein, J. E., Hamdy, R. F. and Kossoff, E. H. (2009). Empiric Use of Potassium Citrate Reduces Kidney-Stone Incidence With the Ketogenic Diet. *Pediatrics*, *124*, e300–e304.

Merrill, J. D., Soliman, D., Kumar, N., Lim, S., Shariff, A. I. and Yancy, W. S. (2020). Low-Carbohydrate and Very-Low-Carbohydrate Diets in Patients With Diabetes. *Diabetes Spectrum*, *33*, 133–142.

Mirmiran, P., Yuzbashian, E., Aghayan, M., Mahdavi, M., Asghari, G. and Azizi, F. (2020). A Prospective Study of Dietary Meat Intake and Risk of Incident Chronic Kidney Disease. *Journal of Renal Nutrition*, *30*, 111–118.

Moghetti, P., Castello, R., Negri, C., Tosi, F., Spiazzi, G. G., Brun, E., Balducci, R., Toscano, V. and Muggeo, M. (1996). Insulin infusion amplifies 17 alpha-hydroxycorticosteroid intermediates response to adrenocorticotropin in hyperandrogenic women: apparent relative impairment of 17,20-lyase activity. *The Journal of Clinical Endocrinology and Metabolism*, *81*, 881–886.

Noebels, J. (2011). A perfect storm: Converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation. *Epilepsia*, 52 Suppl *1*, 39–46.

Noto, H., Goto, A., Tsujimoto, T. and Noda, M. (2013). Low-Carbohydrate Diets and All-Cause Mortality: A Systematic Review and Meta-Analysis of Observational Studies. *PLOS One*, *8*, e55030.

Ochner, C. N. and Lowe, M. R. (2007). Self-reported changes in dietary calcium and energy intake predict weight regain following a weight loss diet in obese women. *Journal of Nutrition*, *137*, 2324–2328.

Owen, O. E., Morgan, A. P., Kemp, H. G., Sullivan, J. M., Herrera, M. G. and Cahill, G. F. (1967). Brain metabolism during fasting. *Journal of Clinical Investigation*, *46*, 1589–1595.

Palop, J. J. and Mucke, L. (2009). Epilepsy and cognitive impairments in Alzheimer disease. *Archives of neurology*, *66*, 435–440.

Paoli, A., Canato, M., Toniolo, L., Bargossi, A. M., Neri, M., Mediati, M., Alesso, D., Sanna, G., Grimaldi, K. A., Fazzari, A.L. and Bianco, A. (2011). [The ketogenic diet: an underappreciated therapeutic option?]. *Clinical Therapeutics*, *162*, e145-153.

Paoli, Antonio, Cenci, L. and Grimaldi, K. A. (2011). Effect of ketogenic Mediterranean diet with phytoextracts and low carbohydrates/high-protein meals on weight, cardiovascular risk factors, body composition and diet compliance in Italian council employees. *Nutrition Journal*, *10*, 112.

Paoli, A., Grimaldi, K., Toniolo, L., Canato, M., Bianco, A. and Fratter, A. (2012). Nutrition and acne: therapeutic potential of ketogenic diets. *Skin Pharmacology and Physiology*, *25*, 111–117.

Phelan, S., Wing, R. R., Loria, C. M., Kim, Y. and Lewis, C. E. (2010). Prevalence and predictors of weight-loss maintenance in a biracial cohort: results from the coronary artery risk development in young adults study. *American Journal of Preventive Medicine*, *39*, 546–554.

Philippou, E., Neary, N. M., Chaudhri, O., Brynes, A. E., Dornhorst, A., Leeds, A. R., Hickson, M. and Frost, G. S. (2009). The effect of dietary glycemic index on weight maintenance in overweight subjects: a pilot study. *Obesity (Silver Spring)*, *17*, 396–401.

Pijls, L. T., de Vries, H., Donker, A. J. and van Eijk, J. T. (1999). The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Nephrology Dialysis Transplantation*, *14*, 1445–1453.

Poplawski, M. M., Mastaitis, J. W., Isoda, F., Grosjean, F., Zheng, F. and Mobbs, C. V. (2011). Reversal of diabetic nephropathy by a ketogenic diet. *PLOS One*, *6*, e18604.

Powell, D. R., Suwanichkul, A., Cubbage, M. L., DePaolis, L. A., Snuggs, M. B. and Lee, P. D. (1991). Insulin inhibits transcription of the human gene for insulin-like growth factor-binding protein-1. *Journal of Biological Chemistry*, *266*, 18868–18876.

Praga, M. (2005). Synergy of low nephron number and obesity: a new focus on hyperfiltration nephropathy. *Nephrology Dialysis Transplantation*, *20*, 2594–2597.

Prins, M. L., Fujima, L. S. and Hovda, D. A. (2005). Age-dependent reduction of cortical contusion volume by ketones after traumatic brain injury. *Journal of Neuroscience Research*, 82, 413–420.

Raynor, H. A., Jeffery, R. W., Phelan, S., Hill, J. O. and Wing, R. R. (2005). Amount of food group variety consumed in the diet and long-term weight loss maintenance. *Obesity Research & Clinical Practice*, *13*, 883–890.

Raynor, H. A., Van Walleghen, E. L., Bachman, J. L., Looney, S. M., Phelan, S. and Wing, R. R. (2011). Dietary energy density and successful weight loss maintenance. *Eating Behaviors*, *12*, 119–125.

Redman, L. M., Heilbronn, L. K., Martin, C. K., de Jonge, L., Williamson, D. A., Delany, J. P., Ravussin, E. and Pennington CALERIE Team (2009). Metabolic and behavioral compensations in response to caloric restriction: implications for the maintenance of weight loss. *PLOS One*, *4*, e4377.

Roehl, K. and Sewak, S. L. (2017). Practice Paper of the Academy of Nutrition and Dietetics: Classic and Modified Ketogenic Diets for Treatment of Epilepsy. *Journal of the Academy of Nutrition and Dietetics*, *117*, 1279–1292.

Rosenbaum, M., Hall, K. D., Guo, J., Ravussin, E., Mayer, L. S., Reitman, M. L., Smith, S. R., Walsh, B. T. and Leibel, R. L. (2019). Glucose and Lipid Homeostasis and Inflammation in Humans Following an Isocaloric Ketogenic Diet. *Obesity*, *27*, 971–981.

Schwartzkroin, P. A., Wenzel, H. J., Lyeth, B. G., Poon, C. C., Delance, A., Van, K. C., Campos, L. and Nguyen, D. V.

(2010). Does ketogenic diet alter seizure sensitivity and cell loss following fluid percussion injury? *Epilepsy Research*, *92*, 74–84.

Smith, R. and Mann, N. (2007). Acne in adolescence: A role for nutrition? *Nutrition & Dietetics*, *64*, S147–S149.

Smith, R. N., Mann, N. J., Braue, A., Mäkeläinen, H. and Varigos, G. A. (2007). The effect of a high-protein, low glycemic-load diet versus a conventional, high glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *Journal of the American Academy of Dermatology*, *57*, 247–256.

Stafstrom, C. E. and Rho, J. M. (2012). The ketogenic diet as a treatment paradigm for diverse neurological disorders. *Frontiers in Pharmacology*, *3*, 59.

Tosi, F., Negri, C., Perrone, F., Dorizzi, R., Castello, R., Bonora, E. and Moghetti, P. (2012). Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *97*, 1712–1719.

Tracy, C. R., Best, S., Bagrodia, A., Poindexter, J. R., Adams-Huet, B., Sakhaee, K., Maalouf, N., Pak, C. Y. C. and Pearle, M. S. (2014). Animal Protein and the Risk of Kidney Stones: A Comparative Metabolic Study of Animal Protein Sources. *The Journal of Urology*, *192*, 137–141.

Ułamek-Kozioł, M., Czuczwar, S. J., Januszewski, S. and Pluta, R. (2019). Ketogenic Diet and Epilepsy. *Nutrients*, 2019, *11*(10), 2510.

Van der Auwera, I., Wera, S., Van Leuven, F. and Henderson, S. T. (2005). A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutrition & Metabolism*, *2*, 28.

Vanderwood, K. K., Hall, T.O., Harwell, T. S., Arave, D., Butcher, M. K. and Helgerson, S. D. (2011). Factors associated with the maintenance or achievement of the weight loss goal at follow-up among participants completing an adapted diabetes prevention program. *Diabetes Research and Clinical Practice*, *91*, 141–147.

Vanitallie, T. B., Nonas, C., Di Rocco, A., Boyar, K., Hyams, K. and Heymsfield, S. B. (2005). Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. *Neurology*, *64*, 728–730.

Veech, R. L. (2004). The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *70*, 309–319.

Vilar-Gomez, E., Athinarayanan, S. J., Adams, R. N., Hallberg, S. J., Bhanpuri, N. H., McKenzie, A. L., Campbell, W. W., McCarter, J. P., Phinney, S. D., Volek, J. S. and Chalasani, N. (2019). Post hoc analyses of surrogate markers of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis in patients with type 2 diabetes in a digitally supported continuous care intervention: an open-label, non-randomised controlled study. *BMJ Open*, *9*, e023597.

Volek, J. S., Phinney, S. D., Forsythe, C. E., Quann, E. E., Wood, R. J., Puglisi, M. J., Kraemer, W. J., Bibus, D. M., Fernandez, M. L. and Feinman, R. D. (2009). Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. *Lipids*, *44*, 297–309.

Volek, J. S., Sharman, M. J. and Forsythe, C. E. (2005). Modification of lipoproteins by very low-carbohydrate diets. *Journal of Nutrition*, *135*, 1339–1342.

Wakefield, A. P., House, J. D., Ogborn, M. R., Weiler, H. A. and Aukema, H. M. (2011). A diet with 35% of energy from protein leads to kidney damage in female Sprague-Dawley rats. *British Journal of Nutrition*, *106*, 656–663.

Welle, S. and Nair, K. S. (1990). Relationship of resting metabolic rate to body composition and protein turnover. *American Journal of Physiology*, *258*, E990-998.

Westerterp-Plantenga, M. S. (2007). How are normal, high- or low-protein diets defined? *British Journal of Nutrition*, *97*, 217–218.

Westerterp-Plantenga, M. S., Nieuwenhuizen, A., Tomé, D., Soenen, S. and Westerterp, K. R. (2009). Dietary protein, weight loss, and weight maintenance. *Annual Review of Nutrition*, *29*, 21–41.

Westman, E. C., Yancy, W. S., Mavropoulos, J. C., Marquart, M. and McDuffie, J. R. (2008). The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutrition & Metabolism*, *5*, 36.

Włodarek, D. (2019). Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). *Nutrients*, *11*, 169.

Yan, B., Su, X., Xu, B., Qiao, X. and Wang, L. (2018). Effect of diet protein restriction on progression of chronic kidney disease: A systematic review and meta-analysis. *PLOS One*, *13*, e0206134.

How to cite this article: Monika Yadav and Vibha Mandhan (2023). Scope of Low Carbohydrate Diets as Therapeutics. *Biological Forum – An International Journal*, *15*(1): 75-81.