CARBOHYDRATE FREE DIET AND ITS METABOLIC CONSEQUENSES

[1]Kushwaha Pratibha, [2]Paul Virginia

[1] Research Scholar, Department of Food Nutrition and Public Health, SHUATS, Prayagraj

[2]Professor, Department of Food Nutrition and Public Health, SHUATS, Prayagraj

Email-pratibha2019k@gmail.com

ABSTRACT

Low-carbohydrate diets (LChD) have become very popular among the general population. These diets have been used to lose body weight and to ameliorate various abnormalities like diabetes, nonalcoholic fatty liver disease, polycystic ovary syndrome, narcolepsy, epilepsy, and others. Reports suggest that body weight reduction and glycemic control could be attained while following LChD. However, these advantages are more notably found in short periods of time consuming an LChD. Indeed, the safety and efficacy of the latter diets in the long term have not been sufficiently explored. In contrast to what has been proposed, other mentioned pathologies are not improved or are even worsened by carbohydrate restriction. Therefore, the aim of this review is to define the concept of LChD and to explain their clinical effects in the short and long term, their influence on metabolism, and the opinion of nutrition or health authorities. Finally, evincing the research gaps of LChD that are here exposed will later allow us to reach a consensus with regard to their utilization.

Keywords:-low carbohydrate diet, metabolism of carbohydrates, carbohydrate restriction, obesity.

INTRODUCTION

Low carbohydrate diet have increased in popularity in recent years due to their proposed influence on satiety and weight loss. Low carbohydrate contain less than 200 g of carbohydrates per day, or less than 30% of the total energy requirement. When the carbohydrate intake is reduced, the fat and protein content in the diet increases, resulting in a low-carbohydrate hyperproteic diet or nonketogenic low-carbohydrate high-fat diet. An example of an Low carbohydrate diet is the Zone diet, consisting of a distribution of 30% protein, 40% carbohydrates, and 30% fat.

Very low carbohydrate hyperproteic diet can have a macronutrient distribution of 25–35% of fat from the total energy intake and 55–65% from proteins. On the other hand, very low carbohydrate diet generally have a content of ≤20–50 g/day of carbohydrates and a high fat and/or high protein content.

Effects of Low carbohydrate diet on health

Obesity and Diabetes

Low carbohydrate diet have been widely used for weight control or treatment of obesity. Randomized controlled trials have shown that low carbohydrates diet are just as effective at controlling body weight as low-fat diets ; nevertheless, blood glucose and glycemic control are clearly reduced by Low carbohydrate diet in comparison with low fat diet. These beneficial effects are markedly dependent on the duration of the studies.

In nutritional studies with obese diabetic subjects, the use of very low carbohydrate diet was shown to reduce body weight, body mass index, blood glucose, triglycerides, and LDL cholesterol.

Fat and protein sources may influence whether low carbohydrate diet are associated with type 2 diabetes since animal protein and fat was related to an increased risk of diabetes, but vegetable protein and fat was inversely associated with diabetes risk. Very low carbohydrate diet, such as the Atkins diet, are usually high in protein and fat (particularly, saturated fat) to attain successful weight loss. These observations led to the use of low carbohydrate diet for medical nutrition therapy not only for obesity but also to treat diabetes. Clinical studies that have lowered the percentage of dietary carbohydrates and/or the glycemic index of the carbohydrates have consistently shown improvements in glycemic control among individuals with type 2 diabetes.

A reduced-glycemic index diet without weight loss can also lead to improvement in diabetic control, when compared with higher-glycemic diets of similar carbohydrate content

Epilepsy

Very low carbohydrate diet or ketogenic diets are commonly used in the treatment of refractory pediatric epilepsy because ketosis induced by diet has been demonstrated to have an anticonvulsant effect .In fact, a prospective study that followed 22 children with the same type of refractory epilepsy for 25 months reported a ketotic state, hypoglycemia, refusal to drink fluids, constipation, renal calculi, nausea, and vomiting .There is evidence as well of relevant relapse of schizophrenia symptoms with low carbohydrate diet, but this conclusion implies the elimination of gluten in addition to the low carbohydrate consumption.

Non-alcoholic Fatty Liver Disease

Low carbohydrate diet could also represent a dietary treatment for non-alcoholic fatty liver disease. **Wanless and Lentz *et al.*,** mentioned that 70% of obese patients had liver steatosis, and the degree of steatosis was proportional to the degree of obesity..

Mechanisms Regulating the Effects of low carbohydrate diet

It is plausible that the effects of the very low carbohydrate or low carbohydrate diet are mainly or partially regulated by ketone production and by modifications in gluconeogenesis velocity. ketosis could have a beneficial or a negative influence on various pathologies. Obese humans and rats have decreased blood ketone bodies because of their impaired capability for β-oxidation and ketogenesis . Ketosis during weight loss in obese subjects maintains the same cholecystokinin concentrations before weight loss, suggesting that ketones promote satiety via cholecystokinin .On the other hand, diabetes is an abnormality typically accompanied by increased ketogenesis, sometimes independent of glucose or insulin infusion. Stimulation of adult cardiomyocytes with 3HB induces insulin resistance via the PI3K/Akt pathway. In addition, AcAc-mediated ketoacidosis impairs insulin binding and decreases insulin receptor protein, as well as mRNA and phosphorylation of insulin receptor substrate in adrenal chromaffin cells. Proteolytic and lipolytic responses to very low carbohydrate or starvation are enhanced in order to generate glucose from amino acids or glycerol .Therefore, gluconeogenesis increases in healthy men following a carbohydrate-restricted diet to sustain glycemia .Diabetes also stimulates gluconeogenesis and endogen glucose production despite the presence of hyperinsulinemia and hyperglycemia .Thus, carbohydrate restriction in diabetic patients should be cautioned since the mentioned diet and condition contribute to an exacerbated glucose production. Gluconeogenesis is also up regulated during the development of NAFLD, which could mean enhanced deleterious effects of reduced carbohydrate consumption as exposed before.

Metabolic consequences of a Very low carbohydrate diet.

(1) Serum insulin is decreased by carbohydrate restriction, which leads to lipolysis in adipose tissue and proteolysis in skeletal muscle.

(2) Fatty acids from lipolysis are oxidized in the liver, where production of acetyl-CoA induces ketogenesis (synthesis of AcAc and 3HB). Glycerol from lipolysis is used to generate glucose by gluconeogenesis. Amino acids released from muscle are used to produce glucose or ketone bodies according to their glucogenic or ketogenic nature.

(3) NEFAs from lipolysis and urea from amino acid utilization are drained into circulation. Also, synthesized glucose and ketone bodies are delivered into circulation and subsequently used by the central nervous system, kidney, heart, and other organs. In addition, pyruvate and lactate, produced by the heart and kidney, are gluconeogenic substrates for the liver.

(4) Organ function can be altered by these metabolic changes since ketosis alters neuron excitability. The kidney is forced to excrete nitrogen, water, and calcium, which affects bone density. Cardiovascular risk, insulin resistance, and liver steatosis could be developed due to the elevated NEFA serum concentration. Another factor that could be involved in the shown effects of LChD is oxidative stress because accelerated lipolysis and increased citric acid cycle flux mediated by carbohydrate restriction promotes reactive oxygen species (ROS) production. Free fatty acid release and decreased triglyceride storage leads to adipocyte

lipotoxicity and increased oxidative stress. In endothelial cells, palmitate promotes ROS production and endothelial dysfunction. Not only fatty acids promote ROS formation given that high glucose stimulation induces the same effects in various cell types. High glucose mediates ROS formation in adipocytes, human aortic endothelial cells, and pancreatic β cells In postprandial conditions, a meal that causes a higher degree of hyperglycemia increases oxidative stress markers and the susceptibility to oxidize LDL .Therefore, both low and high glucose consumption could contribute to oxidative stress via distinct mechanisms.

Low-carbohydrate metabolism

The study of LCD metabolism has been used to illustrate metabolic pathways in medical school curricula and has also highlighted some of the gaps in our current understanding of biochemistry and metabolism. Whereas a spontaneous reduction in caloric intake is a major effect of LCDs, there are many reports indicating a so-called "metabolic advantage"—that is, a greater amount of weight lost per calorie consumed. This is a controversial idea, and there are perceptions that variable weight loss with isocaloric diets would somehow violate the laws of thermodynamics and that there must be some experimental error. It is widely held that only caloric intake is important (as expressed by the statement, "A calorie is a calorie."). Variable energy efficiency, however, is known in many contexts: hormonal imbalance, studies of weight regain, and, most strikingly, in knockout experiments in animals. The fat-specific insulin receptor knock-out mouse weighs only ≈60% as much as the wild-type mouse, even though the 2 types of mice eat the same amount of food. Most of the time, of course, a calorie *is* a calorie, and we do not maintain that, in carbohydrate restriction, metabolic advantage always occurs, but only *1*) that it can occur that it is not excluded by a correct thermodynamic analysis that, because of the importance of obesity, it is sensible to try to identify the conditions under which it can occur and to maximize the effect. The thermodynamic analysis leads to the conclusion that variable efficiency is the expected outcome from physical principles, and therefore, when a calorie is a calorie, it is not explained by thermodynamics but rather by the unique characteristics of living systems. In other words, it is energy balance that needs to be explained. The mechanisms that explain metabolic advantage emphasize the inefficiencies introduced by substrate cycling and the requirements for increased gluconeogenesis. In addition, that thermogenesis varies for different macronutrients is widely accepted, but it is somehow expected to be ignored in weight-loss experiments, even though the levels are in the range of 20% for protein compared with 5% for carbohydrate. Moreover, discussion generally centers on equilibrium thermodynamics, but living systems are maintained far from equilibrium, and nonequilibrium thermodynamics, which emphasizes kinetic fluxes as well as thermodynamic forces, is more relevant. Most simply, the argument that "a calorie is a calorie" rests on the fact that free energy and other thermodynamic variables are state variables—that is, that they are independent of mechanism or path. In fact, the change in a weight-loss experiment is extremely far from the total change embodied in free energy values, and the change that is measured (technically, the partial derivative of the energy with respect to reaction) is not path-independent and is notably influenced by the activity of enzymes.

Studies suggested that xylulose-5-phospate (Xu-5-P) is a signal for the coordinated control of glucose metabolism and lipogenesis (42). Xu-5-P is generated from glucose metabolism in the hexose monophosphate pathway, which activates phosphofructokinase and promotes the transcription carbohydrate-responsive element–binding protein (ChREBP), thereby increasing the enzymes of lipogenesis, the hexose monophosphate shunt, and glycolysis, all of which are required for lipogenesis. The control of both glycolysis and lipogenesis by one transcription factor shows the close relation between these pathways. It is also likely that the regulation of hepatic glucose output is substantially altered after adaptation to an LCKD (keto-adaptation). For example, one study compared a very-low-energy (624 kcal), low-carbohydrate (20% of daily energy intake) diet to a baseline isoenergetic (30 kcal/kg), high-carbohydrate (55%) diet in obese subjects with type 2 diabetes. After 3 wk of adaptation, the very-low-energy, LCD diet resulted in significantly less hepatic glucose output, and, across all subjects and diets, basal hepatic glucose output was negatively correlated with plasma ketones ($r = -0.71$, $P < 0.05$).

Insulin resistance is reduced with an LCKD, possibly by a reduction in the availability of dietary glucose, which causes hyper insulinemia. A consideration of the physiology of very-low-carbohydrate dieting leads to a different perspective on insulin resistance. That is, rather than treating insulin resistance by increasing glucose disposal through an increase in non-storage cellular influx (eg, by increasing either the insulin dose or its effect), it could be treated by reducing glucose availability to insulin-resistant tissue (e.g., by reducing carbohydrate intake or absorption and basal hepatic glucose output), which would reduce the non-storage cellular influx. Reductions in dietary carbohydrate should be used as a strategy to treat insulin resistance.

Effects low carbohydrate diet on appetite and satiety factors

Several studies confirm that there is a spontaneous reduction in caloric intake when carbohydrate intake only is restricted to 5–10% of caloric intake. In the most controlled study to date, an LCD led to hunger levels similar to those of a low-fat diet, even though the daily caloric intake with the LCD was 1000 kcal lower. Another study used the Eating Inventory, a validated questionnaire assessing hunger and cognitive restraint, and found that hunger was reduced by 50% when measured after 1 week of an LCD. Another study examining a 20-g carbohydrate diet found that fasting serum leptin was reduced by 50% and fasting serum neuropeptide Y was reduced by 15%. It may also be that the mere lowering of serum insulin concentrations, as is seen with LCDs, may lead to a reduction in appetite. In support of this idea, several studies have found that insulin increases food intake, that foods with high insulin responses are less satiating, and that suppression of insulin with octreotide leads to weight loss.

In summary, new metabolic studies of very-low-carbohydrate conditions have found that serum glucose homeostasis is maintained and serum ketone concentrations are increased. Muscle glycogen is reduced but still present. With the exception of one study, these

metabolic studies are limited by the short study duration (typically, 7–14 d), which probably does not allow sufficient time for full adaptation to low-carbohydrate conditions.

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