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Low-carbohydrate diet - application in the treatment of type 2 diabetes - review

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Abstract

Introduction: A very low carbohydrate diet called the ketogenic diet has been shown to be effective in the management of drug-resistant epilepsy. In the recent years it has been studied as a potential remedy for conditions such as insulin resistance, type 2 diabetes, obesity, cardiovascular diseases as well as various psychological disorders including drug-resistant depression and schizophrenia. This approach seems to be promising in managing abovementioned issues given a sufficient amount of commitment. There is an abundance of papers looking into the said diet yet not many of them seem to have been well deigned and carried out.

Methods and materials: A review of chosen literature from PubMed database, GoogleScholar database between the years 2000-2024 was carried out using the following keywords:
"low-carbohydrate", low-carb", "low carbohydrate diet", "low-carb diet", "type 2 diabetes", "insulin", "insulin resistance", "obesity".

Aim of study: Review of the current knowledge on the influence of the therapeutic carbohydrate restriction on health, especially type 2 diabetes.

Results: The introduction of the low-carbohydrate diet may have a beneficial influence on metabolism-related diseases. There is quite strong evidence proving it help with the management of type 2 diabetes and limit the amount of medication necessary to manage the disease as well as lower one's body fat and blood pressure. It is however not an intervention without its limitations.

Conclusions: Low carbohydrate diets seem to be safe and effective in the treatment of Type 2 diabetes. Further large-scale, randomized, well-designed studies with clearly set guidelines as to what constitutes a low-carbohydrate intervention using high-quality protein and fat sources are necessary to determine the efficacy and safety of the carbohydrate restriction in the long term.

Keywords: "low-carbohydrate", low-carb", "low carbohydrate diet", "low-carb diet", "type 2 diabetes", "insulin", "insulin resistance", "obesity".

Introduction

The use of carbohydrate restriction is not a novel approach. In fact, it has been used as a remedy for drug-resistant epilepsy. It has also been looked into as a potential cure for a wide array of diseases, among them being Type 2 diabetes, obesity and hypertension, yet many studies published as of today seem to have quite many flaws. Oftentimes they do not meet the criteria of what constitutes a low-carbohydrate diet, fail to distinguish the difference of fat and protein sources used in the trials, use questionnaires which are not an appropriate tool to record one's exact diet and are carried out for a short period of time, not giving this intervention a sufficient amount of time to produce its benefits. As a result of that, this diet has been criticized and described as not safe and effective. The goal of this review is to go through
the evidence and objectively look at available data on the subject.

The low carbohydrate intervention

There is no universal definition as to what constitutes a low-carbohydrate diet but generally a low carbohydrate dietary approach (LCD) and a very low-carbohydrate dietary approach (VLCD) consist in administration of less than 130g and 50g of carbohydrates per day respectively. Another measure is the percentage of energy provided by the abovementioned macronutrients amounting to 26% in the LCD and 10% in the VLCD. This issue is important for a number of reasons the main one being that as of today many of the studies looking into this matter do not restrict the carbohydrates to a low enough level which leads to the drawing of misleading conclusions and putting a perhaps unnecessary stigma onto these kinds of approaches.

Possible beneficial mechanisms of the low carbohydrate diet

The low-carbohydrate diet seems to have a number of different mechanisms which could result beneficial in the treatment of Type 2 diabetes (T2D). Potential routes through which LCDs affect people suffering from said disease include the improvement of blood glucose control, weight management and blood pressure, the reduction of hunger, insulin resistance, hepatic and pancreatic fat storage as well as glucotoxicity and triglyceride levels.

In most cases type 2 diabetes evolves from insulin resistance.[1,2] This is to say that the majority of people with T2D have a reduced capacity to transfer glucose from their blood into their tissues. This condition also entails impaired gluconeogenesis [3] as well as higher release of glucose from the liver despite the molecule entering the bloodstream via food intake.[4] Because glucose has the most profound impact on glycemic control [5] reducing its consumption can lead to the alleviation of these problems. It can also cause a marked and prompt betterment of blood glucose levels which seems to appear even before the weight reduction in observed.[6] According to the statement made by the American Diabetes Association "Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycaemia".[7] What is more, provided that the patient adheres to the LCD they need to reduce the doses of glucose lowering medications very soon after applying this dietary strategy. In addition, some data suggest that said intervention may even put T2D into remission.[8]

LCDs are also effective in reducing body fat.[9] It can be explained by the fact that when adopting this approach processed and ultra-processed foods are generally eliminated from one's diet since they usually contain high amounts of refined carbohydrates. In consequence, avoiding the intake of these energy-packed devoid of nutrients foods results in energy intake reduction and consequently in weight loss.[10] Since insulin's mechanism of action is to inhibit lypolisys and increase lipogenesis [11] it leads to the increase in body's fat storage, a state often observed in patients during therapy with this peptide.[12] Recent data suggest that elevated levels of said hormone precede obesity [13] and therefore the reduction of insulin levels should be considered a priority. Furthermore, LCDs may increase energy expenditure in the long term [14] which also leads to the improvement in body weight management. Another important factor to consider is the reduction of appetite in individuals following this intervention.[15] This might be due to increased availability of energy in the late postprandial period [16,17] as well as reduced ghrelin, the so-called "hunger hormone", levels.[18] Additionally, it could be a result of the improvement of the quality of meals consumed including intake of high-quality protein which is the main component responsible for the feeling of satiety.[19,20] Nutritional ketosis, a state occurring in patients following a VLCD, might decrease the levels of hunger even further.[21,22,23,24,25]

Blood pressure is also a parameter which could be improved through a LCD. The abovementioned weight loss helps in achieving this effect, although is not the only explanation for it. It also occurs due to the changes in the sodium levels [26] whose excess

leads to the increase in blood pressure. A drop in insulin levels results in less sodium being retained in the body. This in combination with smaller amounts of the ion consumed with healthier foods leads to increased excretion of sodium to such an extent that some individuals even require adding additional amounts of salt to their meals. [27,28] Similarly to blood-glucose lowering drugs, antihypertensive medication needs to be altered soon into adopting the LCD which further proves that this intervention is effective in reducing said parameter.

As previously mentioned, the majority of patients suffering from T2D have insulin resistance [1,2] which typically precedes the onset of diabetes. Fat loss, especially from liver and other central organs, can lower the levels of insulin resistance which leads to the reduction in gluconeogenesis [4] and improves blood glucose levels. There might occur a physiological insulin resistance at the beginning of the dietary change to LCDs as an adaptive reaction in order to avoid hypoglycemia and provide sufficient amounts of glucose the the glucose-dependent cells, examples of which are the brain or kidneys. Further studies are necessary to determine the mechanism and significance of this finding.

Research has shown that reduction in the storage of fat in the liver is rapid while on the LCD. It occurs through weight loss but evidence suggests there are more factors involved in this process.[29,30,31] Excessive carbohydrate intake leads to lipogenesis, this is especially dangerous when taking into account fructose which is metabolized by the liver before it can be processed by other cells of the body.[32] Therefore, the LCD, by decreasing the amount of glucose and fructose being delivered to the tissues, addresses the issue of increased fat storage at its very root. The decreased amount of hepatic fat promotes a reduction in its levels in the pancreas. This is due to the fact that less triglyceride rich lipoproteins are excreted by the liver acting directly on the pancreas.[33] The reduction in hepatic fat also means smaller amount of triglycerides being released into the bloodstream 1. causing the levels of said lipids to drop. A decrease in these markers leads to the improvement of cardiovascular disease risk.[34]

When the blood glucose levels are elevated for an long period of time it leads to glucotoxicity which negatively impacts insulin production and secretion [35,36] leading to the damage of the beta-cells. On that account, reduction of glucose intake brings benefits to these pancreatic cells.

Systematic Reviews and Meta-Analyses

There is an abundance of systematic reviews and meta-analyses looking at the efficacy of LCDs in patients with Type 2 diabetes. The majority of said papers concludes that carbohydrate restriction provides greater weight loss and diabetes control in the short-term, however over longer periods of time (usually over 6 months) the differences between LCDs and control arms (most often low fat diets) seem to be insignificant.

Experts in the field propose that this may be due to diminishing adherence to the diet over time. It is however difficult to determine the exact cause of these results and therefore is considered a limitation of the available research.

Regardless of the reasons why the advantages are not being maintained over time, the research clearly suggests that LCDs can be at least as beneficial as other dietary interventions in the management of T2D. What is more, there are notable differences between the dietary approaches, favoring low-carbohydrate diets. Among the parameters improved most markedly by LCDs were body weight [37,38,42,46], glycated hemoglobin (HbA1c) [37,38,39,40,41,42], triglycerides [37,38,40,42,43,44] and high-density lipoprotein (HDL) cholesterol. [37,38,40,42,44,45,46] It is worth to mention that the changes in total cholesterol and low-density lipoprotein (LDL), parameters most often thought to be raised through the restriction of carbohydrates, were similar in both the experimental and the control groups.

Another issue necessary to take into consideration are the changes in the medication requirements occurring during the introduction of various dietary approaches. The available research suggests that the reductions in diabetes medication are greater with low-carbohydrate diets, [37,42] allowing the patients to take smaller doses or even cease taking their medication with the introduction of the LCD.[47]

Other sources

While randomized-control trials and systematic reviews are considered to provide the most valuable evidence, it is often useful to look at alternative sources as they may have their own advantages such as ecological validity.

An example of an alternative source of information could be the work of Virta Health. Their research provides data supporting the safety and efficacy of LCDs in patients with Type 2

diabetes allowing them to better manage or even put their disease into remission.[48,49] The goal of the study was to achieve and sustain nutritional ketosis through the restriction of carbohydrates in their diet to less than 30g per day (a VLCD). The results at the 2-year follow-up were as follows: 55% of the subjects had a decrease in HbA1c that qualified them as non-diabetic, 67% of the diabetic medications used at the beginning of the trial were no longer necessary, there was a reduction in mean insulin by 81% and more than 60% of subject using insulin could cease doing so. There were also marked improvements in cardiovascular disease risk 82, triglycerides (-22%) and CRP (-37%) levels as well as the resolution of metabolic syndrome in 29% of participants. A decrease of small LDL particles and no deterioration of carotid intima media thickness [50] were observed at the 2-year analyses. This study only included individuals who voluntarily adopted this intervention and therefore the results should be analyzed cautiously. However, it provides an example of how an informed decision and high levels of motivation can influence an individual to adhere to the VLCD over longer periods of time, achieving clinically significant improvements by doing so.

Primary care in the UK also demonstrates the safety and effectiveness of the LCDs in subjects with Type 2 diabetes.[51,52] A remission of said disease, defined as lowering the levels of HbA1c below 48mmol/mol (6,5%), not requiring the use of diabetic medication, was achieved in 46% of patients following the carbohydrate restriction in one practice lii135. This intervention also brought financial benefits, mostly due to the reduction of the demand for diabetes drugs.[53]

The application of LCD in a community-based setting in the US offers further prove of its usefulness and efficacy in lowering HbA1c levels as well as body weight in individuals suffering from T2D.[54] A reduction in said parameters was respectively 1,29% and 12,8kg greater than in the usual care control group. The patients were also able to lower or set aside the insulin they had been taking prior to the intervention. Each participant kept a detailed food log and it was determined that overall adherence, defined as consumption of less than 20g of carbohydrates per day, was high. In addition, no serious side effects were reported.

Controversies

Long term safety and efficacy

One of the primary arguments against the application of LCDs is the lack of evidence of its long-term efficacy and safety. Yet none of the currently promoted dietary approaches can be qualified as such on the basis of high quality evidence. It is likely that this is due to the difficulties and limitations of all research having to do with nutrition. Two examples of longer-term studies looking at the effects of low-fat diets are the LookAHEAD trial and the Women's Health Initiative. The first determined that there was no reduction in cardiovascular disease risk while following said diet and was stopped when the median follow-up was 9,6 years [55] while the latter showed a poorer glycemic control in the low fat arm after 6 years.[56] A question of why this approach is considered to be superior to others and why it is not held to the same level of evidence as LCDs can be raised.

Furthermore, wrongful conclusions concerning the side effects of LCDs are often drawn from studies where the intake of carbohydrates was not properly controlled or not low enough, in some trials amounting to 48% of energy provided by these macronutrients, [57] level far too great to be considered a low-carbohydrate diet. This study and those alike are not representative of what constitutes a LCD and therefore cannot be used as a valid representation of this dietary approach and its potential benefits or side effects.

Another matter worth looking into is the so-called user bias. Some individuals tend to ignore not just the dietary advice but also other health-related guidelines and exhibit behaviors such as smoking or being inactive which have negative effects on their health (unhealthy user bias). On the other hand, some people are health conscious above the average and therefore introduce beneficial changes beyond adopting a healthy diet (healthy user bias).

Cardiovascular risk is often mentioned as a potential concern when adopting a LCD. However, there is no long-term evidence proving that LCDs increase said parameter when compared to other diets. Studies measuring the changes in cardiovascular markers show their similar shifts in both the LCD arms and control groups (most often based on low fat diets), often in favor of the prior. In their 2019 statement concerning nutrition in adults with T2D the American Diabetes Association (ADA) concluded that taking into account the existing evidence the overall cardiovascular risk in individuals adopting a low-carbohydrate diet did not increase, even in trials with diets higher in saturated fats 10. In addition, the total cholesterol and LDL cholesterol levels did not differ meaningfully between the LCDs and control groups while other cardiovascular markers were improved by the low-carbohydrate approach.[58,59] Importantly, there is evidence that the number of LDL or apolipoprotein-b particles are a

better predictor of cardiovascular risk than LDL cholesterol itself.[60] When adopting the LCD the amount of smaller particles reduces while the size of the LDL particle tends to increase with the total number of LDL particles at a lower or unchanged level.[48,50] This could be an indicator of the potential of the abovementioned dietary intervention to lower or at least not to change the cardiovascular disease risk.

Adherence

Of concern to many is the adherence to the low-carbohydrate dietary approach over the long-term, typically thought of as following the diet for more than a year. The data suggest that permanent changes to one's diet result in the most beneficial outcomes and therefore introducing and following a certain change to one's dietary habits is an important issue. It highlights the significance of presenting the patients with a variety of options from which they can chose those appropriate and suitable for themselves. Nonetheless, the research does not indicate that LCDs are more complicated to follow in comparison to other dietary interventions.

With the right amount of motivation and proper diet selection patients follow LCDs over long periods of time. In the Virta Health study the percentage of individuals adhering to a very low-carbohydrate diet (which is thought to be even more difficult to maintain than a low-carbohydrate diet) at 1 year and at 2 years were 83% 130 and 75% 38 respectively. Worth mentioning is the fact that during the trials patients are sometimes provided with the exact food they should consume or with support from the researchers making it easier to stick to this intervention. However, in everyday life people might face various obstacles which make it more difficult for them to follow through with the carbohydrate restriction. Among them are the low availability of high-quality low-carbohydrate foods in grocery stores or restaurants and lack of acceptance or understanding from their relatives who are in favor of the popular low-fat dietary approach. Despite that, some individuals report that given the right amount of motivation and appropriate support it is possible to maintain a LCD.[61] Some data suggest that people suffering from either Type 1 or Type 2 diabetes following the adaptation of a LCD or a VLCD notice such positive changes and so many health benefits that they are willing to keep this lifestyle indefinitely despite being advised to the contrary by the current guidelines.[62]

Nowadays LCDs are becoming more and more popular and there are new "low-carb" or "keto" products being introduced to the market which could help people adhere to such diets.

Yet the food industry alongside with dietary guidelines and general knowledge on nutrition leave much to be desired and many important changes need introduction in order to address the root cause of many popular diseases, including Type 2 diabetes and obesity. Thus it is of great importance that individuals willing to adopt a LCD are provided with support and education so as to make an informed decision concerning their lifestyle and diet. There are a number of channels providing practical advice such as education platforms, mobile phone applications and various websites. Supporting the healthcare professionals in order to help them learn about LCDs and how to adopt them in clinical practice also seems to be crucial.

Conclusions

The available data suggest that LCDs are safe and efficacious in the treatment of Type 2 diabetes. Other dietary interventions do not seem to be more effective than the low-carbohydrate diet as far as blood glucose levels and cardiovascular risk are concerned. Additionally, LCDs seem to bring greater benefits in the form of reduction of the requirement for diabetic medication as well as potential remission of said disease. Available evidence suggests that LCDs are no more difficult to adhere to than other dietary interventions. Thus adopting a low-carbohydrate diet could be advised to patients suffering from Type 2 diabetes in order to manage their disease. It is important that they make an informed decision and receive the right amount of support from their healthcare providers. Further research on the subject is necessary, though it is crucial that the studies are well designed, take into consideration only diets that restrict carbohydrates sufficiently, document the exact consumption of the macronutrients, look into the quality and sources of food consumed as well as provide the subjects with support, all that in order to be able to draw clear and correct conclusions.

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