Very low-carbohydrate diets in the management of diabetes revisited

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ABSTRACT

Humans can derive energy from carbohydrate, fat, or protein. The metabolism of carbohydrate requires by far the highest secretion of insulin. The central pathology of diabetes is the inability to maintain euglycaemia because of a deficiency in either the action or secretion of insulin. That is, because of either insulin resistance often accompanied by hyperinsulinaemia, or insulin deficiency caused by pancreatic beta cell failure. In individuals dependent on insulin and other hypoglycaemic medication, the difficulty of matching higher intakes of carbohydrates with the higher doses of medication required to maintain euglycaemia increases the risk of adverse events, including potentially fatal hypoglycaemic episodes. Thus, mechanistically it has always made sense to restrict carbohydrate (defined as sugar and starch, but not soluble and insoluble fibre) in the diets of people with diabetes. Randomised clinical trials have confirmed that this action based on first principles is effective. The continued recommendation of higher-carbohydrate, fat-restricted diets has been criticised by some scientists, practitioners and patients. Such protocols when compared with very low-carbohydrate diets provide inferior glycaemic control, and their introduction and subsequent increase in carbohydrate allowances has never been based on strong evidence. The trend towards higher-carbohydrate diets for people with diabetes may have played a part in the modern characterisation of type 2 diabetes as a chronic condition with a progressive requirement for multiple medications. Here we will introduce some of the evidence for very low-carbohydrate diets in diabetes management and discuss some of the common objections to their use.

Data from the 2008/2009 New Zealand Nutrition Survey placed the prevalence of diabetes among adults at 7%. The incidence of pre-diabetes, defined as HbA1c, 41 to 49 mmol/mol (5.8% to <6.7%), was 25.5%, predicting a further increase in the incidence of diabetes in coming decades.[1] The systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes by Ajala et al (2013) found that the low-carbohydrate diet "appeared to provide superior weight loss, glycemic control, and lipid profile compared with low-fat diets and, in one of 2 studies, was superior to the low-GI diet for all 3 variables".[2] Yet there is still resistance to the acceptance of low-carbohydrate diets in New Zealand. The Ministry of Health's document *Eating and Activity Guidelines for New Zealand Adults* (2015) advises a low-fat diet supplying most energy from starch, and counsels the use of lean meat and low-fat dairy products to meet saturated fat recommendations.[3] Although weight control is important for diabetes prevention, the 'Topical Questions and Answers' supplement to the guidelines is briefly dismissive of low-carbohydrate diets for weight control, and does not refer to any other benefits such as improved glycaemic control. A similarly low-fat diet plan can be found on the Diabetes New Zealand website, which states that,

> *Most people need 3–4 serves of carbohydrate food at each of the three main meals [ie, 135–180g/day]. Very active people may need larger serves of carbohydrate foods or between meals snacks to maintain blood glucose levels.*[4]

However, it is our view that the current evidence is sufficiently in favour of the modern, nutritionally adequate, very low-carbohydrate diet as belonging in the front rank of dietary treatments for type 2

diabetes. We also present some evidence supportive of benefit from carbohydrate restriction in type 1 diabetes.

We accept that there are useful methods of managing diabetes aligned with carbohydrate restriction, including glycaemic index (GI), Mediterranean diet, ancestral diets designed on evolutionary principles, and drugs such as metformin and acarbose. However, our focus will be on carbohydrate restriction itself and the relative effect of carbohydrate and fat as sources of energy. The basic principle of carbohydrate restriction in the management of diabetes underlies many of these other approaches, and sufficient clinical evidence supports its use. We highlight evidence relating to very low-carbohydrate diets, to best illustrate the mechanisms and effects of carbohydrate restriction.

What is a very low-carbohydrate diet?

Studies differ in the exact degree of carbohydrate restriction tested for effect on glycaemic control. Feinman et al (2015), in their critical review of carbohydrate restriction for diabetes, proposed that "very low-carbohydrate" be defined as 20–50g/day of carbohydrate.[5] This is an attainable figure rooted in the pre-insulin history of diabetes and the physiology of carbohydrate metabolism.[6,7] Setting the goal carbohydrate intake as low as practicably possible is consistent with the meta-analysis of randomised controlled trials of low-carbohydrate diets for diabetes by Kirk et al (2008), which found that levels of fasting serum glucose, HbA1c, and triglycerides were inversely proportional to the percentage of carbohydrate consumed in each diet phase.[8] Diets that exceed the putative normal carbohydrate requirement of 130g/day should not be considered 'low-carbohydrate', as the desired physiological changes (lowered insulin demand or secretion, decreased appetite, inhibition of lipid synthesis, and increased fatty acid oxidation) depend on adaptations to carbohydrate deprivation.[7]

An absolute or percentage of energy carbohydrate limit can sometimes be omitted altogether in clinical practice, with a focus on avoiding specific foods instead. For example, in the very low-carbohydrate pilot trial of Unwin et al (2015), patients with type 2 diabetes (n=68) were advised to avoid sugar, bread, pasta, rice, and other carbohydrate-dense foods.[9]

Is dietary carbohydrate necessary?

Some authorities consider dietary carbohydrate essential to provide fuel, especially for the brain, and are concerned about an increased possibility of hypoglycaemia or ketoacidosis when carbohydrate is restricted. Although very low-carbohydrate diets still supply some carbohydrate from non-starchy vegetables and low-sugar fruits, as well as optimal amounts of fibre, there is little evidence that dietary carbohydrate is essential in the human diet.[10] The claim sometimes made that carbohydrates are necessary in the diet of people with type 2 diabetes is also not supported by the physiology of the disease. Type 2 diabetes is characterised by a higher than usual hepatic production of glucose from amino acids and glycerol.[11] In normal metabolism this production of glucose is reduced whenever carbohydrate is consumed, but in type 2 diabetes it is not, and this, as well as delays in peripheral glucose clearance due to insulin resistance, results in post-prandial and fasting serum glucose elevation.[12] A person with type 2 diabetes who is not using glucose-lowering medication is thus an unlikely candidate for symptomatic hypoglycaemia on a low-carbohydrate diet. If glucose-lowering drugs are being used, then doses will need to be adjusted appropriately (an all-important caveat).[5] Glucose requirements are also reduced by the switch to utilising fat and ketone bodies for fuel when carbohydrate is unavailable for prolonged periods.[7] Ketone bodies are sufficiently supportive of brain function and neuronal health that it is well-recognised that a ketogenic diet is a viable treatment option for certain forms of epilepsy and other neurological disorders.[13]

Type 1 diabetes results from the autoimmune destruction of beta cells, which no longer supply insulin to lower serum glucose and inhibit lipolysis. A diagnosis

of type 1 diabetes is often a medical emergency and will require the life-long use of exogenous insulin, whereas people with type 2 diabetes are potentially able to reverse dependence on medication through diet and lifestyle changes. Insulin is the hormone that facilitates the removal of glucose from the bloodstream, and the use of insulin introduces a risk of hypoglycaemia if insulin dose is not matched exactly to food intake. People with insulin-dependent diabetes, including those on very low-carbohydrate diets, are advised to use glucose tablets or 'emergency foods' to treat hypoglycaemic episodes.[14]

Although rare cases of ketoacidosis have been reported in people without diabetes using very low-carbohydrate diets for weight loss, we have only found one report of ketoacidosis in a person with diabetes using a low-carbohydrate diet. A 32-year-old woman with Prader-Willi syndrome and type 2 diabetes had tolerated the diet for 11 years, but developed ketoacidosis when prescribed the SGLT2 inhibitor ipragliflozin.[15] A very low-carbohydrate, high-fat diet was used to prevent diabetic ketoacidosis in the pre-insulin era.[6] This limited evidence suggests a low risk of ketoacidosis from using very low-carbohydrate diets for diabetes management.

Is there evidence for the safety of higher-carbohydrate diets for diabetes?

Are high-carbohydrate diets safe for people with diabetes? Low-carbohydrate diets have been used to treat type 2 diabetes since 1797, and until the discovery of insulin in 1921 carbohydrate restriction or severe energy restriction, or both, were the most reliable methods used to treat diabetes, defined by glycosuria. If carbohydrate or protein in excess of glucose tolerance was fed to these patients, they developed glycosuria and were at risk of diabetic ketoacidosis. The starvation diet developed by Frederick Allen from 1914 has caught the attention of medical historians, but it is less well known that from 1918 Newburgh and Marsh developed an adequate energy, very low-carbohydrate, high-fat diet similar in composition to today's diets.[6] The efficacy of this diet was shown in clinical practice and its safety in terms of blood sugar, blood lipids, and ketoacidosis was tested experimentally throughout the 1920s and 1930s. The first high-carbohydrate diet for diabetes that did not carry a high risk of diabetic ketoacidosis dates from 1926 and required the initiation of insulin treatment.[16] Low-carbohydrate, high-fat diets therefore have a long history of usefulness in the treatment of diabetes and only went out of fashion when the diet-heart hypothesis (proposing a link between saturated fat and heart disease) emerged. The safety net provided by glucose-lowering drugs, earlier diagnosis of type 2 diabetes, and increasing access to self-monitoring equipment provided a context that allowed higher-carbohydrate diets to flourish. To our knowledge, no trials that compared very low-carbohydrate and low-fat, low-saturated fat (<30% fat, <10% saturated fat) diets were carried out before low-fat diet advice for the management of diabetes was introduced.

One problem with high-carbohydrate diets in type 2 diabetes is that progressive increases in medications are often required to prevent hyperglycaemia, yet often glycaemic control remains poor because of the risk of hypoglycaemia. In the UK Prospective Diabetes Study, a well-designed, long-term cohort study (n=4,075), only 8% of those randomised to a high-carbohydrate, high-fibre, low-fat diet (similar to New Zealand recommendations) achieved fasting plasma glucose levels of less than 7.8 mmol/L (140 mg/dL) after 9 years, and only 9% achieved HbA1c levels below 7% (53 mmol/mol). These are very mediocre levels of glycaemic control given the increased risk of cardiovascular disease and microvascular complications associated with higher HbA1c. Due to the risk of hypoglycaemia when glucose-lowering medications are used to cover high-carbohydrate meals, lower targets were not considered realistic in this study even when multiple medications were used.[17]

Conversely, trials of restricted carbohydrate regimes show evidence of improved glycaemic control, including limited evidence from small uncontrolled trials suggestive of a decreased risk of hypoglycaemia during the intensive management

of glycaemia with insulin in people with type 1 diabetes. In one small case-series of intensive glycaemic control with drugs and diet, subjects diagnosed with type 1 diabetes (n=10) and type 2 diabetes (n=20) were placed on the same very low-carbohydrate diet (30g/day carbohydrate).[14] HbA1c in those with type 1 diabetes was reduced in all cases, the mean reduction being from 6.8% to 5.5% (50.8 to 36.6 mmol/mol). In participants with type 2 diabetes, the mean HbA1c reduction was from 8.4% to 5.8% (68.3 to 39.9 mmol/mol). No cases of severe hypoglycaemia were reported over the study period of 21.4 months (standard deviation (SD): 22.3). In a small clinical audit (n=48) of a low-carbohydrate diet (defined as 75/g day carbohydrate) for type 1 diabetes, mean HbA1c in those adherent to the diet for the full 4-year period (48%) was reduced from 7.7% to 6.4% (60.7 to 46.4 mmol/mol).[18] The mean rate of symptomatic hypoglycaemia was reduced from 2.9 (SD: 2.0) to 0.5 (SD: 0.5) episodes per week.

What is the evidence for the safety of the high fat content of the very low-carbohydrate diet?

A frequently heard criticism of very low-carbohydrate diets for diabetes is that "eating more protein and fat may increase your risk of heart disease in the long term". It is well-known that a diagnosis of diabetes greatly increases the risk of cardiovascular disease. It is less well-known that there is also a reciprocal relationship; a cardiovascular event predicts a future diabetes diagnosis.[19] We would submit that few things can be worse for the coronary arteries than the metabolic and hormonal changes that result in a diagnosis of type 2 diabetes. Reversing the progression of diabetes and the related metabolic syndrome should be the first priority.

Support for the safety of high-fat diets in people with diabetes comes from trials which show improved markers of cardiovascular risk in the low-carbohydrate, compared to the usual care group. A recent, well-designed, randomised controlled trial (n=115) by Tay et al (2015) compared a very low-carbohydrate diet with the conventional low-fat diet for type 2 diabetes over 52 weeks.[20] In this trial, in which saturated fat was restricted, lipids, including low-density lipoprotein cholesterol (LDL-C) improved on the very low-carbohydrate diet. In a 2008 very low-carbohydrate weight-loss randomised controlled trial in obese subjects without type 2 diabetes (n=88) by the same group, saturated fat was not restricted (saturated fat was 20% of energy) in the very low-carbohydrate arm.

High-density lipoprotein cholesterol (HDL-C) and triglycerides improved, while LDL-C decreased overall but increased by 10% in 24% of the participants.[21] However, apolipoprotein beta (ApoB) did not increase in this subgroup. It is notable that LDL-C is a calculated proxy for ApoB, small, dense LDL-C particles (sdLDL), and other atherogenic factors within the LDL-C fraction.[22] Evidence for the effect on cardiovascular health of low-carbohydrate diets to date seems to show overall improvement in glycaemic and lipid metabolic risk factor surrogate endpoints compared to other diets in low-carbohydrate diet trials, in only some of which saturated fat was restricted.[2] We have argued previously that analyses of long-term cardiovascular disease risk diet trials which restricted saturated fat (but did not include low-carbohydrate arms) have not shown any major detrimental or beneficial effect of saturated fat restriction on overall mortality.[23]

Some studies show better metabolic health in people who consume higher intakes of full-fat dairy foods. In the most recent meta-analysis of epidemiological prospective cohort studies of saturated fat and trans-fat consumption, highest versus lowest consumption of the naturally-occurring trans-fats found in dairy was associated with a significant reduction (relative risk 0.58, 95%, CI: 0.46–0.74) in the incidence of type 2 diabetes.[24] In a recent prospective cohort study [n=26,930] from Malmö, Sweden, which used a 7-day food diary and a 1 hour interview, as well as a food frequency questionnaire to assess dietary intake, both dairy fat consumption (including butter and cream) and intake of the short- and medium-chain saturated fats (C4:0–C14:0) found in dairy were associated with a significantly reduced incidence of

type 2 diabetes over 14 years of follow-up.[25] Lean red meat consumption was associated with type 2 diabetes, but fatty red meat consumption was not. This evidence seems to contradict the low fat, saturated fat-restricted diabetes prevention recommendations of New Zealand authorities, who continue to advise the consumption of low-fat dairy foods.[3,4]

Does the very low-carbohydrate diet have any unique advantages over other dietary approaches?

The conventional approach to diet, weight loss and glycaemic control in type 2 diabetes can fairly be summarised as "all diets improve glycaemic control if they cause weight loss, all diets that reduce energy intake cause weight loss if adhered to, therefore there is little reason to prefer one type of diet over another". However, some trial evidence contradicts these assertions. In a 2014 subgroup analysis of subjects with type 2 diabetes (n=46) within a 48-week, well-designed, randomised controlled weight-loss trial, serum glucose improved significantly more on a very low-carbohydrate diet compared to a low-fat diet plus orlistat, even when weight loss was equal.[26] Furthermore, in a series of well-designed carbohydrate restriction experiments, improvements in glycaemic control and hormonal and lipid parameters were demonstrated under conditions where patients were maintained at a constant weight.[5,27]

One suggested explanation for these results is that triglycerides stored in different parts of the body have different effects on insulin sensitivity. In the aetiology of type 2 diabetes, hyperinsulinaemia and hyperglycaemia result from the accumulation of triglycerides in the liver and subsequently in the pancreas, impairing endocrine and paracrine insulin signalling.[28] The development of non-alcoholic fatty liver disease (NAFLD) leads to a higher output of hepatic glucose and triglycerides and is associated with an increased risk of type 2 diabetes and cardiovascular disease.[29] The reduced insulin and blood sugar response to a very low-carbohydrate diet rapidly leads to the mobilisation and oxidation of accumulated hepatic lipids.[30] In the pilot trial of Unwin et al (2015) of a very low-carbohydrate diet for type 2 diabetes, serum gamma-glutamyl transferase (GGT), a surrogate marker of NAFLD, decreased from 76.9 iu/L (95% CI: 58.3, 95.6) to 49.8 iu/L (95% CI: 33.0, 50.3) in the patients for whom data was available (n=64/68).[9] It is notable that this change was not correlated with weight loss. If metabolic improvement is less dependent on weight loss on a very low-carbohydrate diet compared to other diets, this is a potentially important advantage for patients who do not lose weight easily, or for normal-weight individuals diagnosed with type 2 diabetes.

It should be noted that low-carbohydrate diets as advised in practice necessitate higher quality, micronutrient-dense food, such as non-starchy vegetables, nuts and seeds, and low-sugar fruits. The importance of micronutrient status in the management of diabetes and metabolic syndrome, and the benefit from a higher intake of nutrient-dense foods, are well-documented.[31]

Motivated people with diabetes can be advised to restrict their carbohydrate intake. Adherence to this advice has the potential to improve their quality of life, decrease their dependence on drugs, and reduce their risk of mortality based on their metabolic profile. In people with insulin-dependent diabetes, the risk of hypoglycaemic episodes is also likely to improve. As we have outlined, this alternative approach, which challenges high-starch, low-fat guidelines, is supported by many lines of evidence. We suggest that clinical dietary advice for the treatment of diabetes, as well as population prevention guidelines, be urgently revised.

Competing interests:
Nil

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REFERENCES:

1. Coppell KJ, Mann JI, Williams SM, Jo E, et al. Prevalence of diagnosed and undiagnosed diabetes and prediabetes in New Zealand: findings from the 2008/09 Adult Nutrition Survey. N Z Med J. 2013;126(1370):23-42.
2. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr. 2013;97(3):505-16.
3. Ministry of Health. Eating and Activity Guidelines for New Zealand Adults. Wellington: Ministry of Health; 2015. http://www.health.govt.nz/publication/eating-and-activity-guidelines-new- zealand-adults
4. Diabetes New Zealand. FAQ. [accessed 2015 15 November] Available from: http://www.diabetes.org.nz/food_and_nutrition/questions_and_answers#faq-8
5. Feinman RD, Pogozelski WK, Astrup A, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. Nutrition. 2015;31(1):1-13.
6. Newburgh LH, Marsh PL. Further observations on the use of a high fat diet in the treatment of diabetes mellitus. Arch Intern Med. 1923;31(4):455-490.
7. Westman EC, Feinman RD, Mavropoulos JC, et al. Low-carbohydrate nutrition and metabolism. Am J Clin Nutr. 2007;86(2):276-84.
8. Kirk JK, Graves DE, Craven TE, et al. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc. 2008;108:91- 100.
9. Unwin DJ, Cuthbertson DJ, Feinman R, Sprung VS. A pilot study to explore the role of a low-carbohydrate intervention to improve GGT levels and HbA1c. Diabesity in Practice. 2015;4:102–8.
10. Westman EC. Is dietary carbohydrate essential for human nutrition? Am J Clin Nutr. 2002;75(5):951-953.
11. Magnusso, I, Rothman DL, Katz LD, et al. Increased rate of gluconeogenesis in type II diabetes mellitus. A 13C nuclear magnetic resonance study. J Clin Invest. 1992;90(4):1323–1327.
12. Rizza RA. Pathogenesis of Fasting and Postprandial Hyperglycemia in Type 2 Diabetes: Implications for Therapy. Diabetes. 2010;59(11):2697–2707.
13. Barañano KW, Hartman AL. The ketogenic diet: uses in epilepsy and other neurologic illnesses. Curr Treat Options Neurol. 2008;10(6):410-419.
14. O'Neill DF, Westman EC, Bernstein RK. The effects of a low-carbohydrate regimen on glycemic control and serum lipids in diabetes mellitus. Metab Syndr Relat Disord. 2003;1(4):291-8.
15. Hayami T, Kato Y, Kamiya H. et al. Case of ketoacidosis by a sodium- glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Investig. 2015;6(5):587-90.
16. Sansum WD, Blatherwick NR, Bowden R. The use of high-carbohydrate diets in the treatment of diabetes mellitus. JAMA. 1926;86(3):178-181.
17. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. Progressive requirement for multiple therapies (UKPDS 49).

JAMA. 1999;281(21):2005-2012.

18. Nielsen JV, Gando C, Joensson E, Paulsson C. Low carbohydrate diet in type 1 diabetes, long-term improvement and adherence: a clinical audit. Diabetol Metab Syndr. 2012;4:23.
19. Hu FB, Stampfer MJ, Haffner SM, et al. Elevated risk of cardiovascular disease prior to clinical diagnosis of type 2 diabetes. Diabetes Care. 2002 July;25(7):1129-1134.
20. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. Am J Clin Nutr. 2015;102(4):780-90.
21. Tay J, Brinkworth GD, Noakes M, et al. Metabolic effects of weight loss on a very-low-carbohydrate diet compared with an isocaloric high-carbohydrate diet in abdominally obese subjects. J Am Coll Cardiol. 2008;51(1):59-67.
22. Siri-Tarino PW, Chiu S, Bergeron N, Krauss RM. Polyunsaturated fats versus carbohydrates for cardiovascular disease prevention and treatment. Annu Rev Nutr. 2015;35:517–43.
23. Thornley S, Henderson G, Schofield G. Chewing the saturated fat: should we or shouldn't we? N Z Med J. 2014;127(1394):94-6.
24. de Souza RJ, Mente A, Maroleanu A, Cozma, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ. 2015;351:h3978.
25. Ericson U, Hellstrand S, Brunkwall L, et al. Food sources of fat may clarify the inconsistent role of dietary fat intake for incidence of type 2 diabetes. Am J Clin Nutr. 2015 May;101(5):1065-80.
26. Mayer SB, Jeffreys AS, Olsen MK, et al. Two diets with different hemoglobin A1c and antiglycemic medication effects despite similar weight loss in type 2 diabetes. Diabetes Obes Metab. 2014;16(1):90-93.
27. Gannon MC, Nuttall FQ. Control of blood glucose in type 2 diabetes without weight loss by modification of diet composition. Nutr Metab. 2006;3:16.
28. Taylor R. Type 2 Diabetes. Etiology and reversibility. Diabetes Care. 2013;36(4):1047-1055.
29. Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2(11):901-10.
30. Hollingsworth KG, Abubacker MZ, Joubert I, Allison MED, Lomas DJ. Low-carbohydrate diet induced reduction of hepatic lipid content observed with a rapid non-invasive MRI technique. Br J Radiol. 2006;79:712–715.
31. Kaur B, Henry J. Micronutrient status in type 2 diabetes: a review. In: Henry J, editor. Advances in food and nutrition research. 71. Cambridge, Massachusetts: Academic Press; 2014. p. 55-100.