REVIEW

OPEN

Effect of low carbohydrate diets on insulin resistance and the metabolic syndrome

Peter J. Foley

Purpose of review
This review outlines recent research in the application of low carbohydrate diets (LCD) for insulin resistance (IR) and metabolic syndrome (MetS).

Recent findings
Studies included in this review explore how a LCD can be used in the management of patients with IR and MetS. LCDs have been shown to result in Type 2 Diabetes Mellitus (T2DM) remission, improve lipid profiles and dramatically reduce intrahepatic fat.

Summary
The field of nutritional science is notoriously complex. The LCD has a simple narrative, which can easily and safely be applied in clinical practice. Current guidelines recognise and encourage the use of LCD as a valid option for patients with T2DM and obesity. Structured, evidence-based education should be available for all clinicians to increase confidence and ensure consistency and quality control. Further real-world evidence into the application and scalability of a LCD are required. The use of digital health solutions and improved health technology should see significant advances in this field, with dietary habit being driven by patient-derived health data in response to food, and not population-based food guidelines. The narrative around MetS and IR needs to change from progression to remission, with a LCD being a valid option for this.

Keywords
diabetes remission, insulin resistance, low-carbohydrate diet, metabolic syndrome

INTRODUCTION

Humans are not designed for modern living. Long before the COVID-19 pandemic, healthcare professionals have been battling a silently spreading endemic of insulin resistance (IR) and metabolic syndrome (MetS). This is in part due to the overconsumption of calorie dense, nutrient poor foods, coupled with sedentary habits, resulting in a tidal wave of lifestyle-related illnesses linked with IR. According to the WHO Global Report on Diabetes [1], an estimated 422 million adults worldwide were living with diabetes in 2014 compared to 108 million in 1980, with this number estimated to be 463 million at present with a projected incidence of 700million by 2045 [2]. In the UK, 10% of the NHS annual budget is spent on diabetes, and when indirect costs are considered, this rises from £10billion to £40billion by 2035 [3]. Previous views on MetS were that this was a progressive condition with limited proven treatment options, as evidenced by its prevalence of more than 1 in 3 adults in the USA [4]. In this paper, I aim to explore the relationship between IR and MetS and the role in which a low carbohydrate diet (LCD) can have in this cohort.

WHAT IS METABOLIC SYNDROME?

The central features of the MetS are; IR, visceral adiposity, atherogenic dyslipidemia and endothelial dysfunction. Various definitions for MetS exist, with the two most commonly used being either the updated National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) [5] or the international diabetes federation criteria [6]. The NCEP ATP III defines MetS if 3 or more of the following are present; sex-specific raised waist circumference, hypertension, fasting triglyceride level >150 mg/dl, sex-specific fasting high-density lipoprotein, sex specific total cholesterol and fasting glucose >100 mg/dl[5]. In contrast,

Hanham Health, Bristol, UK

Correspondence to Peter J. Foley, Hanham Health, 33 Whittucks Rd, Hanham, Bristol BS15 3PJ, UK. E-mail: peter.foley2@nhs.net

Curr Opin Endocrinol Diabetes Obes 2021, 28:463–468

DOI:10.1097/MED.0000000000000659

KEY POINTS

- Insulin resistance and metabolic syndrome are intimately related, which can lead to many preventable lifestyle-related diseases.
- A low carbohydrate diet is a safe dietary approach in this cohort.
- Clinicians should have access to structured education in how to use therapeutic carbohydrate restriction.
- Type 2 diabetes remission is now a realistic target for patients and clinicians.
- Advances in digital health and health technology can result in bespoke, patient-derived, real-time data to support sustained behaviour change at scale.

INTERNATIONAL DIABETES FEDERATION criteria include the same criteria but requires obesity as an absolute requirement, with 2 or 3 supporting biomarkers to be present for MetS to be diagnosed [6].

WHAT IS A LOW CARBOHYDRATE DIET?

It is generally accepted that a LCD reduces carbohydrate [CHO] consumption to <130 g/day [7], however, no universally accepted definition exists. This therapeutic restriction reduces or omits sources of starch and other sugars in the form of refined carbohydrates, grains and certain fruits and vegetables. A LCD tends to be *ad libitum* with a focus on high-fibre sources of carbohydrate such as leafy greens, cruciferous vegetables and low GI fruits, vegetables, nuts and seeds. Patients are encouraged to eat their preferred sources of protein and also include healthy sources of fat. The diet can be nutrient rich, with an abundance of phytochemicals and phytonutrients along with essential fatty acids and amino acids, resulting in tighter blood sugar control and insulin sensitivity, leading to significant improvements in type 2 diabetes and obesity [8▪]. A LCD is now recognised by the American Diabetes Association and is promoted as an approach to achieve Type 2 Diabetes Mellitus (T2DM) remission [9▪]. A consensus has yet to be reached on an agreed global definition for T2DM remission. There is agreement, however, that fasting plasma glucose or HbA1c needs to be below the WHO diagnostic threshold on two separate occasions separated by 6 months, and the complete cessation of glucose-lowering therapies [52].

What is insulin?

Insulin is integral for human survival, with direct impact on substrate use in multiple peripheral tissues [10]. These include glucose uptake – and subsequent glycogen synthesis – in the liver and skeletal muscle and the promotion of lipid storage in adipocytes by triglyceride synthesis and lipolysis inhibition [11].

What is insulin resistance?

IR results from the failure of target cells to respond to circulating levels of insulin, leading to hyperglycaemia. In order to ensure homeostasis, more insulin is then secreted which results in a combined state of hyperglycaemia *and* hyperinsulinaemia in both fasted and postprandial states [10]. IR is strongly linked with physical inactivity, obesity and low-grade inflammation, beta cell failure, T2DM, cardiovascular disease, altered liver function, polycystic ovarian syndrome, and certain cancers [12]. What is particularly alarming is that these processes can be seen decades before diagnosis, resulting in a long lag from potentially reversible processes to established end-organ disease. Despite links between obesity and IR, the underlying pathogenesis remains unclear. The twin-cycle hypothesis postulates that chronic calorie excess leads to ectopic fat accumulation, most notably in the liver and pancreas with IR ensuing [13].

Peripheral Insulin resistance

Liver IR results in both unsuppressed endogenous glucose production and reduced glucose uptake [14] *and* the un-suppression of de novo lipogenesis and very low density lipoprotein (VLDL) production, driving elevated VLDL secretion [15]. *Skeletal muscle IR* impairs glucose uptake via the GLUT4 transporter, which leads to elevated postprandial glucose levels and reduced glucose tolerance. The role of *adipocyte IR* is more indirect. Patients with IR can have high levels of plasma free fatty acids, which are taken up by peripheral tissues (liver, pancreas and skeletal muscle), contributing to ectopic fat accumulation and exacerbating the impact of IR [16]. There is no doubt that the greater the volume of ectopic visceral fat in the body, the greater the risk of developing IR. Although patients can be obese and remain 'healthy' – these patients are the exception and not the norm [17].

Obesity is also associated with inflammatory factors characterised by high levels of chemokines, adipokines, pro-inflammatory cytokines, and adipose tissue macrophages. These in turn have a contributory effect to both impaired immunity and immune memory for subsequent immune system adaptivity [18]. This relationship has been acutely apparent during the COVID-19 pandemic, with poor metabolic health increasing morbidity [19] and mortality [20].

NUTRITION

A systematic review [21] found that patients with IR eat about the same proportions of macronutrients as the general population [22]. Although it is true that a calorie is a calorie, the *source* of calories can have a wide-ranging impact on subsequent metabolic responses, especially insulin and blood glucose levels. 200 kcal from broccoli or salmon will have a different metabolic impact than 200 kcal from refined carbohydrates or indeed ultraprocessed foods. It is known that metabolic responses to food can influence cardiometabolic disease risk, however, there are as yet no high-scale high-resolution studies [23▪▪].

One study exploring the role of a LCD in patients with MetS found that a rapid reversal could be achieved in just 4 weeks with lasting improvements in postprandial insulin sensitivity, with these findings independent of weight loss, which was locked out of the equation in this study [24].

Although not definitive, there can be a credible role of carbohydrate overconsumption [24] in the pathogenesis of MetS and the obesity epidemic [25]. There are no 'essential' carbohydrates for human survival, with the amount of carbohydrate required for optimal health unknown. Although glucose itself is crucial for human survival, we have inbuilt physiological processes enabling glucose production in the liver if dietary sources are low, to fulfil the body's metabolic processes.

Although the 'diet wars' continue between carbohydrates and fat being prime causes of the obesity epidemic, it is protein, which is perhaps the most important macronutrient to focus on in my personal opinion. One study revealed significant low levels of protein intake in an older patient population, with <50% achieving the lower end of recommended daily intake and protein intake negatively correlating BMI [26▪].

Certainly the ease in availability of calorie dense ultraprocessed food – high in sugar, fat *and* salt – does appear to have significant impact on caloric intake, with one study suggesting that a diet with ultra-processed food increases food intake by 500kcl per *day* [27]. Although this study shows how ultra-processed foods can lead to overeating, it also further supports the argument of certain foods having an impact on appetite far superior to their unprocessed counterparts, which requires future research.

PRACTICAL ADVICE FOR LOW CARBOHYDRATE DIET

The concept of a LCD is simple. Reduce dietary intake of glucose to improve hyperinsulinaemia. Dietary sources of glucose are often obvious to patients, but many are unaware of 'hidden sugar' in foods - often forming the foundation of a 'healthy' diet - which do not taste sweet, yet can dramatically influence blood glucose levels, such as starchy carbohydrates. Basic education about dietary sources of glucose, and identifying where the sugar is in *their* diet can lead to dramatic improvements in blood glucose control, weight and other metabolic health parameters for patients.

Patients enjoy the freedom of eating to satiety ad libitum, which can result in patients feeling as though they have more autonomy without the constraints of calorie counting. When a LC diet is used appropriately, patients can be in a negative energy balance, whereas *also* feeling satiated and *satisfied* with their diet. This is in part due to appropriate protein intake and the stabilisation of blood sugar.

Real-world evidence in support of a LCD reports 93% remission of prediabetes and 46% drug-free remission of T2DM over a 6 years period in an NHS primary care setting. This was achieved through standard 10 min appointments with regular follow-up, the option of attending group classes and a series of patient information sheets and illustrative infographics to explain the role in which starchy carbs can have on blood sugar [28▪▪].

Clinicians should be familiar with patient risk profiles when considering a LCD, not least with medication de-prescribing, however, practical advice is available [29]. Ongoing clinical monitoring is essential to ensure that health markers are showing improvement, and that no unwanted effects of the approach occur such as an increase in LDL or worsening end-stage renal function. It must be stressed that these are the exception and not the rule, but warrant consideration when offering this approach to our patients. Patients can also be reminded of the abundance of dietary fibre when using a LCD especially from sources like non-starchy-veg.

LIVER

> 'Before the diagnosis of Type 2 Diabetes, there is a long silent scream from the liver' [30].

Non Alcoholic Fatty Liver Disease (NAFLD) is defined as >5% IHF in the absence of alcohol abuse and affects about 25% of the world population [31], which can progress to steatohepatitis, liver-cirrhosis and hepatocellular carcinoma [32]. IR is though to be central in the accumulation of intrahepatic fat (IHF) and is associated with raised liver enzymes (ALT), T2DM, cardiovascular risk and extrahepatic malignancies [33]. More recently, NAFLD has been associated with decreased gut microbiome diversity and gut microbial imbalance [23▪▪].

The current evidence based strategy for NAFLD supports weight loss through lifestyle interventions [34]. It would appear obvious that any diet improving IR will have a positive impact on improving NAFLD. We know from the DIRECT trial that low-carb low-calorie meal replacements showed magnetic resonance imaging evidence of significant IHF reduction among the intervention cohort [35], with a further study showing reduced IHF after just 6 weeks of a LCD [36].

Among other studies with varied carbohydrate intake, some reported a significant reduction of aminotransferases [37], with a recent meta-analysis from 10 clinical trials showing that a LCD in this patient cohort led to a significant reduction in IHF [38] with further paper suggesting that a plant-based Mediterranean style diet - supplemented with green tea, walnuts and polyphenols - reduced NAFLD by 50% [39].

CARDIOVASCULAR HEALTH AND INSULIN RESISTANCE

The adverse effect of obesity and abnormal lipid profiles at a young age (20s) has strongly been linked with future IR [40]. Clinical studies demonstrate that 50% of hypertensive subjects have comorbid hyperinsulinaemia or glucose intolerance with 80% of patients with T2DM having hypertension [41]. The 'dyslipidemia lipid triad' induced by IR, coupled with the direct impact of chronic hyperglycaemia on cardiovascular cellular functions, including hypertension, endothelial dysfunction, oxidative stress and alterations in cardiac metabolism, result in a significant impact on cardiovascular health. A resulting underlying increased inflammatory state can contribute to or is associated with atherosclerosis and the development of coronary artery disease [41].

There is growing interest in reviewing the widely held view that saturated fat should continue to be restricted to <10% of calorie intake. Different saturated fatty acids (SFA) have different metabolic impacts, with recent studies suggesting that several SFAs (whole fat dairy, dark chocolate, unprocessed meat) are not associated with increased CVD or T2DM risk [42]. It is prudent to consider the cardiovascular risk profile of a patient when considering the merit of a LCD. Although a LCD can improve lipid profiles [43], there is a potential for a subcohort of patients to become 'hyperresponders' to a LCD, which may increase cardiovascular risk, however, this appears to be the exception, thus monitoring of such cardiac risk is essential in all patients.

DIGITAL HEALTH AND TECHNOLOGY

The downstream economical impact of MetS and IR on healthcare systems is significant [3].

The potential for digital solutions, offering scalable interventions for IR and MetS and enhancing healthcare ecosystems is promising. Promising data have suggested up to 60% remission of T2DM at 1 year, using nutritional ketosis through remote digital monitoring [44]. Furthermore, the digital delivery of a structured nutrition-focused, low-carb intervention can also result in significant health improvements, with one intervention reporting 25% remission rates [45], using established evidence-based behaviour-change techniques, shown to be effective in digital platforms and improving self-efficacy of chronic disease management [46].

Continuous glucose monitoring technology gives further insight into the intricate relationship between diet and metabolic health. In my view, this technology can change the landscape for all patients with IR. Patients can learn how certain foods can impact *their own* health data, leading to bespoke personal data-driven behaviour change using real-world, real-time feedback. Such digital solutions and technological tools need to be explored further, as a means to offer proven, scalable, low-cost interventions.

A NEW DIABETES PARADIGM

IR is strongly linked with T2DM [12]. The current diabetes management narrative describes T2DM as a progressive disease [47] and promotes a low-fat diet, where carbohydrate intolerant patients consume high levels of refined carbohydrate. Inevitable hyperglycaemia and hyperinsulinaemia ensues, compounding the problem further. This standard of care has a remission success rate of 0.25% [48].

We have seen a seismic shift in thinking over the last 15 years, with an acceptance of the possibility of T2DM remission having transatlantic recognition [49]. This is in part thanks to landmark studies, which showed 1-year remission rates of 46% when participants took low calorie [700kcal] low-carb meal replacements, with a gradual re-introduction of food [33]. We know that diabetes remission is achievable, using LCD, bariatric surgery or very low-calorie diets [50], with a recent meta-analysis showing no adverse consequences of a LCD after 6 months [8▪]. Long-term maintenance of remission remains unproven for both LC and VLCD, with the best evidence base for sustained remission being bariatric surgery, with 10-year remission rates of 83% [51].

CONCLUSION

As with all change, if you don't measure it, you cannot change it. The narrative surrounding MetS and IR needs to change from progression to remission. We need to act on patient's *early* metabolic derangements and address 'false wellness' before end organ damage ensues. Although not the only option available for patients, a LCD can be used safely and effectively, with improvements seen in just 1 month. Further research is required in this field, particularly in exploring the scalability of LCD in real-world studies. With the ongoing developments in digital health and medical technology, I hope that we will be soon living in a world using patient-derived data, empowering sustained behaviour change *at scale*. This should see a move away from population-based food guidelines to more bespoke nutrition based on an individual's metabolic responses to food. The future looks promising for this cohort, with a LCD and the potential for digital-health and technology offering hope as we turn the tide on this epidemic.

Acknowledgements

P.F. is the solo author of this review. He thanks Tara Kelly and Dr Kesar Sadhra for their comments on an early draft.

Financial support and sponsorship

P.F. did not receive any financial support or sponsorship for the writing of this review.

Conflicts of interest

P.F. is the Clinical Safety Officer and a Medical Advisor for Diabetes Digital Media, for which he receives financial compensation. He declares no other conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Roglic G. WHO Global report on diabetes. A summary. Int J Non-Commun Dis 2016; 1:3–8.
2. International Diabetes Federation. IDF Atlas 9th edition. [Accessed 10th February 2021] <https://www.diabetesatlas.org/en/resources/>.
3. Morris E, Aveyard P, Dyson P, *et al.* Dietary approaches to the management of type 2 diabetes (DIAMOND): protocol for a randomised feasibility trial. BMJ Open 2018; 9:e026460.
4. Hyde PN, Sapper TN, Crabtree CD, *et al.* Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss. JCI Insight 2019; 4:e128308.
5. Grundy SM, Cleeman JI, Daniels SR, *et al.* American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112:2735–2752.
6. IDF Epidemiology Task Force Consensus Group. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome – a new worldwide definition. Lancet 2005; 366:1059–1062.
7. 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; 31:1–13.
8. ■ Goldenberg JZ, Day A, Brinkworth GD, *et al.* 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. BMJ 2021; 372:m4743.

This systematic review and meta-analysis evaluated 23 trials, with 1357 participants. Studies lasting at least 12 weeks were included, with low carbohydrate diets being either <130 g/Day or <26% of a 2000 kcal/day diet. Compared with control trials, low carbohydrate diets achieved higher rates of remission. On the basis of moderate to low certainty evidence, patients adhering to a LCD for 6 months may experience remission of diabetes without adverse consequences. Limitations include continued debate around what constitutes remission of diabetes.

9. ■ American Diabetes Association. Prevention or delay of type 2 diabetes: Standards of Medical Care in Diabetes 2021. Diabetes Care 2021; 44(Suppl. 1):S34–S39.

The American Diabetes Association (ADA) 'Standards of Medical Care in Diabetes' includes the ADAs current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. This publication recognises that there is no ideal percentage of calories from carbohydrates and advises that macronutrient distribution should be based on an individuals current eating patterns, preferences and metabolic goals. It also recognises the role of low-carbohydrate eating for patients with T2DM and prediabetes.

10. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Investig 2016; 126:12–22.
11. Duncan RE, Ahmadian M, Jaworski K, *et al.* Regulation of lipolysis in adipocytes. Annu Rev Nutr 2007; 27:79–101.
12. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005; 365:1415–1428.
13. Taylor R. Type 2 diabetes and remission: practical management guided by pathophysiology. J Intern Med 2020; 289:754–770.
14. Reaven GM, Chen YD, Donner, *et al.* How insulin resistant are patients with noninsulin-dependent diabetes mellitus? J Clin Endocrinol Metab 1985; 61:32–36.
15. Winocour PH, Mallik TH, Ishola M, *et al.* A randomized cross-over study of the effects of proinsulin on lipid metabolism in type 2 diabetes. Diabet Med 1991; 8:22–27.
16. Unger RH. Mini review: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. Endocrinology 2003; 144:5159–5165.
17. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. J Clin Investig 2019; 129:3978–3989.
18. Weisberg SP, McCann D, Desai M, *et al.* Obesity is associated with macrophage accumulation in adipose tissue. J Clin Investig 2003; 112:1796–1808.
19. Muniyappa R, Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. Am J Physiol Metab 2020; 318:E736–E741.
20. Cummings MJ, Baldwin MR, Abrams D, *et al.* Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020; 395:1763–1770.
21. Ferguson S, Swan M, Smaldone A. Does diabetes self-management education in conjunc- tion with primary care improve glycemic control in Hispanic patients? A systematic review and meta-analysis. Diabetes Education 2015; 41:472–484.
22. Wheeler ML, Dunbar SA, Jaacks LM, *et al.* Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature. Diabetes Care 2012; 35:434–445.
23. ■■ Berry SE, Valdes AM, Drew DA, *et al.* Human postprandial responses to food and potential for precision nutrition. Nat Med 2020; 26:964–973.

This study involved the recruitment of 1,002 twins and unrelated healthy adults and assessed postprandial metabolic responses in both a clinical and domestic setting. Large inter-individual variability was observed in postprandial responses of blood triglyceride, glucose and insulin following identical meals. Person-specific factors, such as gut microbiome, had a greater influence than did meal macronutrients for postprandial lipemia, but not for postprandial glycaemia. Genetic variants had a modest impact on predictions, with 9.5% for glucose, 0.8% for triglyceride and 0.2% for C-peptide. A machine-learning model was developed which predicted both triglyceride and glycaemic responses to food intake, which can be informative for developing personalised diet strategies.

24. Cohen E, Cragg M, deFonseka J, *et al.* Statistical review of US macronutrient consumption data, 1965–2011: Americans have been following dietary guidelines, coincident with the rise in obesity. Nutrition 2015; 31:727–732.
25. Hales CM, Fryar CD, Carroll MD, *et al.* Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. JAMA 2018; 319:1723–1725.

26. Morris S, Cater JD, Green MA, *et al.* Inadequacy of protein intake in older UK ■ adults. Geriatrics 2020; 5:6. https://doi.org/10.3390/geriatrics5010006.
This study re-assessed two existing datasets with rich diet information for older adults in the Yorkshire region of England. Data was extracted from food diaries of 256 adults aged between 65 and 89 years old. Quantity and timing of intake were coded using Nutrics software and compared to recommendations. Fewer than 50% of the participants met current UK recommendations (0.75 g/Kg/Day) and fweer than 15% met the SEPEN 1.2 g/kg/day age-specific recommendation.

27. Hall KD, Ayuketah A, Brychta R, *et al.* Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. Cell Metab 2019; 30:67–77.e3.

28. Unwin D, Khalid AA, Unwin J, *et al.* Insights from a general practice service ■■ evaluation supporting a lower carbohydrate diet in patients with type 2 diabetes mellitus and prediabetes: a secondary analysis of routine clinic data including HbA1c, weight and prescribing over 6 years. BMJ Nutr Prev Health 2020; 3:285–294.
This secondary analysis of routine clinic data was taken from a single primary care surgery in the UK. Advice on a lower carbohydrate diet was routinely offered to patients with newly diagnoses and preexisting T2Dm of prediabetes between 2013 and 2019. By 2019, 27% of the practice population with T2DM and patients with prediabetes (128 and 71 respectively) chose to follow a lower carbohydrate diet for a mean duration of 23 months. Drug-free remission occurred in 46% of participants with T2Dm and 93% of patients with prediabetes. This was also associated with significant reductions in practice spending on diabetes medication with a relative reduction of £50,885 per year.

29. Murdoch C, Unwin D, Cavan D, *et al.* Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. Br J Gen Pract 2019; 69:360–361. doi: 10.3399/bjgp19X704525. PMID: 31249097; PMCID: PMC6592353.

30. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. Diabet Med 2013; 30:267–275. doi:10. 1111/dme.12039.

31. Hazlehurst JM, Woods C, Marjot T, *et al.* Nonalcoholic fatty liver disease and diabetes. Metabolism 2016; 65:1096–1108.

32. Ekstedt M, Hagström H, Nasr P, *et al.* Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015; 61:1547–1554.

33. Younossi ZM, Koenig AB, Abdelatif D, *et al.* Global epidemiology of non-alcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64:73–84.

34. Chalasani N, Younossi Z, Lavine JE, *et al.* The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018; 67:328–357.

35. Lean ME, Leslie WS, Barnes AC, *et al.* Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018; 391:541–551.

36. Skytte MJ, Samkani A, Petersen AD, *et al.* A carbohydrate-reduced high-protein diet improves HbA_{1c} and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. Diabetologia 2019; 62:2066–2078.

37. Tendler D, Lin S, Yancy WS, *et al.* The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. Dig Dis Sci 2007; 52:589–593.

38. Haghighatdoost F, Salehi-Abargouei A, Surkan PJ, *et al.* The effects of low carbohydrate diets on liver function tests in nonalcoholic fatty liver disease: a systematic review and meta-analysis of clinical trials. J Res Med Sci 2016; 21:53. doi: 10.4103/1735-1995.187269.

39. Yaskolka Meir A, Rinott E, Tsaban G, *et al.* Effect of green-Mediterranean diet on intrahepatic fat: the DIRECT PLUS randomised controlled trial. Gut 2021; 0: gutjnl-2020-323106. doi: 10.1136/gutjnl-2020-323106.

40. Ferreira AP, Oliveira CE, Franca NM. Metabolic syndrome and risk factors for cardiovascular disease in obese children: the relationship with insulin resistance (HOMA-IR). J Pediatr 2007; 83:21–26.

41. Zhou MS, Schulman IH, Zeng Q. Link between the renin-angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med 2012; 17:330–341.

42. Astrup A, Magkos F, Bier DM, *et al.* Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC State-of-the-Art Review. J Am Coll Cardiol 2020; 76:844–857.

43. Volek JS, Fernandez ML, Feinman RD, Phinney SD. Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome. Prog Lipid Res 2008; 47:307–318.

44. Athinarayanan SJ, Adams RN, Hallberg SJ, *et al.* Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year nonrandomized clinical trial. Front Endocrinol 2019; 10:1–22.

45. Saslow LR, Summers C, Aikens JE, Unwin DJ. Outcomes of a digitally delivered low-carbohydrate type 2 diabetes self-management program: 1-year results of a single-arm longitudinal study. JMIR Diabetes 2018; 3: e12.

46. Summers C, Curtis K. Novel digital architecture of a 'low carb program' for initiating and maintaining long-term sustainable health-promoting behaviour change in patients with type 2 diabetes. JMIR Diabetes 2020; 5:e15030.

47. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009; 32 Suppl 2(Suppl 2):S151–S156. doi: 10.2337/dc09-S301. PMID: 19875543; PMCID: PMC2811457.

48. Karter AJ, Nundy S, Parker MM, *et al.* Incidence of remission in adults with type 2 diabetes: the diabetes and aging study. Diabetes Care 2014; 37:3188–3195.

49. Management of Hyperglycemia in Type 2 Diabetes. Davies MJ, D'Alessio DA, Fradkin J, *et al.* A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018; 41:2669–2701.

50. Hallberg SJ, Gershuni VM, Hazbun TL, Athinarayanan SJ. Reversing type 2 diabetes: a narrative review of the evidence. Nutrients 2019; 11:766. doi: 10.3390/nu11040766.

51. Pories WJ, Swanson MS, MacDonald KG, *et al.* Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995; 222:339–352.

52. Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primacy Care Diabetes Society (PCDS) The British Journal of Diabetes 2019; 19:73–76.