BACKGROUND INFORMATION

Importance of the study

Type 2 Diabetes (T2D) is a chronic condition characterised by high blood glucose levels brought about due to the inability of the body to produce and/or use insulin. Obesity and poor lifestyle choices are the dominant risk factors for developing T2D and its related complications. The current management of T2D relies heavily on the health care sector to prescribe and manage medication, under the premise that T2D is chronic and progressive.

New research on T2D has shown that low carbohydrate diets and lifestyle modifications can lead to improvements in blood glucose levels, as well as weight loss, reduction in the use of medications, and over time effectively put T2D into "remission". T2D remission is defined as having a HbA1c < 6.5% measured at least 3 months after cessation of glucose-lowering pharmacotherapy.

Over the last two decades, technological advances have led to the development of health-related applications (apps) including a high proportion dedicated to the management of diabetes. Given the rate of adoption of smartphone usage these apps provide enormous potential to support the management of T2D.

A recent survey of users of the Defeat Diabetes app found that 52% achieved T2D remission, 84% improved their glycaemic levels and 30% who had prediabetes or T2D were able to reduce or discontinue medication. Defeat Diabetes - 2022 Member Survey.

At present there are only a limited number of research studies providing evidence on the effectiveness of using an app for the management of T2D. This research project seeks to address this knowledge gap, and discover if there is evidence to support a low carbohydrate diet and lifestyle intervention delivered via the Defeat Diabetes app.

Aim and Potential Significance

Our aim is to examine the effect of using the intervention of the Defeat Diabetes smartphone app on the clinical features of type 2 diabetes (fasting blood glucose and HbA1c), in a community-based participant cohort over a 12 month period. The potential significance of this research project is that it may provide an adjunct modality to support the current management of T2D by the broader healthcare community.

CPD ACCREDITED ACTIVITY

Members of the Royal Australian College of General Practitioners (RACGP) who participate by referring and managing **at least one patient throughout the full study period (12 months)** may be eligible for RACGP GP-led educational activities Self Directed CPD Activity - GP Research on completion of the study. GP Group Research has the capacity to span across all three of the new Medical Board of Australia CPD requirements (Measuring Outcomes, Reviewing Performance and Educational Activities). CPD requirements and allocation are subject to the new RACGP guidelines for the **2023-2025 Triennium**. A process evaluation survey addressing the requirements of the RACGP will be provided at the completion of the study. The GP group research activity submission to the RACGP is being co-ordinated by **GP Principal Investigator Dr Liz Fraser, MBBS, MEd, FRACGP.**

Members of the Australian College of Rural and Remote Medicine (ACRRM), who participate may be eligible for CPD. This study is an accredited as an Educational Activity and an Outcome Measurement Activity. Please see the ACRRM website for further details on CPD requirements and enrolment Search (acrrm.org.au).

Our study has received Latrobe University Human Research Ethics Committee approval (No. HEC22117) and is registered with the Australian and New Zealand Clinical Trials Registry as "Effectiveness of digitally delivered continuous care intervention on the self-management of type 2 diabetes. A 12-month single-arm, pre-post intervention study" (Trial Id: ACTRN12622000710729).

Who can I contact for questions or want more information?

If you would like to speak to us, please use the contact details below:

Name/Organisation	Position	Telephone	Email
Despina Kolivas, La Trobe University	PhD Candidate	0456 843 778	d.kolivas@latrobe.edu.au
Prof George Moschonis, La Trobe University	Principal Investigator	03 9479 3482	g.moschonis@latrobe.edu.au

RESEARCH PROPOSAL

Study Intervention

The intervention requires participants to follow the recommendations outlined in the Defeat Diabetes app to make dietary and lifestyle changes over a 12-month period.

The Defeat Diabetes app is a subscription based commercial application for download on smartphone (Android and Apple OS) and provides a guided educational program on how a low carbohydrate diet can manage type 2 diabetes. Additional support is also provided by the interactive private Defeat Diabetes Community Facebook group.

GP referral, eligibility, and management of participants

By expressing interest in this study you will be given complimentary lifetime access to the Defeat Diabetes app.

The success of this study is heavily reliant on **your support** to refer and provide medical management of participants. We will provide you with patient handouts that you can distribute to people who you deem eligible, to assist with the recruitment process.

Note: Patients presenting with prediabetes are ineligible for participation.

Although prediabetes is a significant medical concern, we only wish to recruit patients with a clinical diagnosis of type 2 diabetes.

We hope to recruit **100 participants** with type 2 diabetes, meeting the eligibility criteria below:

Inclusion criteria

- Adults (men and women) meeting the clinical diagnostic criteria for type 2 diabetes
- Willingness to participate (i.e. adopt a low carbohydrate diet and make necessary lifestyle changes as detailed in the app) and be available throughout the study period of 12 months
- Be willing to attend general practitioner appointments at 3, 6 and 12 months
- Not currently using the Defeat Diabetes app, nor using a low carbohydrate diet to manage their type 2 diabetes
- **Have a smartphone and can use digital technology (download and install digital applications)**

Exclusion criteria

- Unable to understand written and spoken English
- Liver disease (other than metabolic associated fatty liver disease) or secondary causes of MAFLD and cirrhosis
- Renal failure and patients undertaking dialysis
- Have a diagnosis of type 1 diabetes
- Are pregnant
- Are using insulin to manage their type 2 diabetes
- Excluded from participating for existing medical conditions at the discretion of their GP

Consent and Data collection

On the participant's baseline GP visit (at initial referral to the study), they will need to have laboratory bloodwork tests, blood pressure, waist circumference and weight and height measurements, and if prescribed anti-hyperglycaemic medications, have these reviewed and/or adjusted.

Note: If your patients are prescribed anti-hyperglycaemic medications, it is important that these are reviewed upon commencement of a low carbohydrate diet, and throughout the study in line with the Defeat Diabetes medication management recommendations (please refer to MEDICAL INFORMATION attached).

Patients who are interested in participating can express their interest via the weblink on the patient handout and sign the online consent forms. We will send participants a set of online survey questionnaires, to collect demographic data (initially) and questionnaires to assess their physical activity levels, sleep, quality of life, diabetes distress and self-efficacy, and adverse events reporting. In addition, participants will need to record (for 3 days) their dietary intake. This data will also need to be collected at 3, 6 and 12 months.

In terms of the time commitment required by the participant, the surveys will take no more than 15 minutes to complete. The 3-day food record will be via a handwritten template, which can then be photographed and uploaded into an online survey instrument. The food record should take around half an hour to complete.

Note: It would be helpful if you can very briefly explain these requirements.

After consent to participate (and baseline measurements are received), participants will be given complimentary lifetime access to the Defeat Diabetes app, where they can access educational resources and a private Defeat Diabetes Facebook community group.

Note: It is very important that baseline measures are received before participants can access the app, or commence a low carbohydrate diet as we would like to understand their current dietary habits as measured by a 3-day food record at baseline.

Please see data collection template below for a detailed description of what is required at each time point. Most of the data collection requirements are in line with the RACGP Medical examinations to assess the person with type 2 diabetes, from the Management of type 2 diabetes: A handbook for general practice. Inflammatory marker CRP or hs-CRP, and Liver Enzymes ALT and GGT are optional and at your discretion. However, should you be collecting these we would appreciate it if you can provide this data to us. At 12 months we would also like to understand if the patient has experienced T2D remission, defined by having HbA1c < 6.5% measured at least 3 months after cessation of glucose-lowering pharmacotherapy.

Data Collection	**Baseline**	**3 months**	**6 months**	**12 months**
Fasting blood glucose, HbA1c	**X**	**X**	**X**	**X**
Lipid panel (TC, HDL-c, LDL-c, Trig)	**X**		**X**	**X**
Renal function (eGFR)	**X**		**X**	**X**
Liver function tests (ALT, GGT)[1]	**X**		**X**	**X**
Inflammatory marker CRP / hs-CRP[1]	**X**		**X**	**X**
Blood Pressure	**X**	**X**	**X**	**X**
Body weight, height (baseline only), waist circumference	**X**	**X**	**X**	**X**
Prescription medication use, dose, and change 1) Anti-hyperglycaemic agents 2) Anti-hypertensives 3) Cholesterol lowering	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**
Diabetes remission criteria				**X**

NOTE: [1] Inflammatory marker CRP/ hs-CRP and Liver function tests (ALT, GGT) are optional.

Participant follow up

When one of your patients consents to participate, we will send you a unique weblink via email to request their baseline data (see example email – Request for Baseline Data).

> Dear Dr Liz Fraser
>
> Please open the **weblink below** for you to upload the baseline data required for:
>
> **Patient Name: Sam Smith.**
>
> **Study Id: 6**
>
> Should you have any questions please contact Despina on 0456 843 778 or email defeatdiabetes@latrobe.edu.au.
>
> You may open the survey in your web browser by clicking the link below:
> Defeat Diabetes Research Study - Baseline Data Entry Form
>
> If the link above does not work, try copying the link below into your web browser:
> https://redcap.latrobe.edu.au/redcap/surveys/?s=VqifqcHMfpYsyhuj
>
> This link is unique to you and should not be forwarded to others.

When you open the unique weblink, the following Baseline data entry form will appear in your browser (see example Baseline Data Entry Form).

We have provided two options to complete this data submission: Option 1: File Upload of patient information **OR** Option 2: Complete data entry form manually.

A **template for future data collection requirements** is also included that you can either print out or cut and paste electronically to include in the patient file, as a reminder that the patient is participating in this study.

The research team will coordinate data collection at all time points in line with patient appointments.

Medical appointment reminders to patients and data collection submissions for 3, 6 and 12 month visits will be managed by the research team via text/phone/email, however scheduling in follow-up appointments at the time of initial consultation would be appreciated.

Note: We understand that while we wish to collect data at the specified timepoints this may not always be possible and have made an allowance for ± 4 weeks either side of these.

At every follow up time point **and after each patient appointment**, will email you a unique weblink to complete the data collection for each of your patients, as per the process outlined above.

Defeat Diabetes Research Study - Baseline Data Entry Form

Please provide the following data and press submit below once complete.

- Blood Tests
  - Fasting blood glucose, HbA1c
  - Lipid panel (TC, HDL-c, LDL-c, Trig)
  - Renal function (eGFR)
  - Liver function tests (ALT, GGT) - Optional and at your discretion
  - Inflammatory marker CRP/hs-CRP - Optional and at your discretion
- Blood Pressure
- Body weight, height, waist circumference
- Prescription medication (Anti-hyperglycaemic agents, Anti-hypertensives, Cholesterol lowering) use and dose - if prescribed

Two options have been provided to complete this data submission, please choose the method that is easiest for you:

Option 1 : File Upload of patient information **OR** Option 2 : Please complete data entry form

Also please find a signed letter of consent to release the participant's health information to us.

If you have any questions please call Despina on 0456 843 778.

Participant ID : 6

Participant Name: Sam Smith

A record of the signed participant consent to release medical and health information to the research team.	ParticipantConsentForGPTo..._1308.pdf (0.03 MB) Upload new version or Remove file
Data Collection Options	
Option 1: Please upload a copy of the requested data in a file generated by your practice management software here.	Upload file
Option 2 : Please complete the following data entry	
Diabetes related	
Fasting Blood Glucose mmol/L	
Hemoglobin A1c %	
Lipids	
Total Cholesterol mmol/L	
LDL mmol/L	
HDL mmol/L	
Triglycerides mmol/L	
Renal Function	
eGFR	

Defeat Diabetes

LA TROBE UNIVERSITY

Liver Function - Optional and at your discretion	
ALT U/L	
GGT U/L	
Inflammatory Marker - Optional and at your discretion	
CRP	
hs-CRP	
Blood Pressure	
Systolic mmHg	
Diastolic mmHg	
Anthropometry	
Weight kg	
Waist Circumference cm	
Height m	
Medications (if prescribed)	
Current prescribed medications (including dose) : 1) Anti-hyperglycaemic agents 2) Anti-hypertensives 3) Cholesterol lowering	Expand
If you have any questions or would like any to share any information with us please let us know.	Expand

Please find attached a copy of the data collection requirements for the Defeat Diabetes Research Study.
You may wish to print this out or electronically cut and paste to include in your patient file for future reference.

Attachment: Defeat Diabetes Research Study - Data Collection Requirements .docx (0.05 MB)

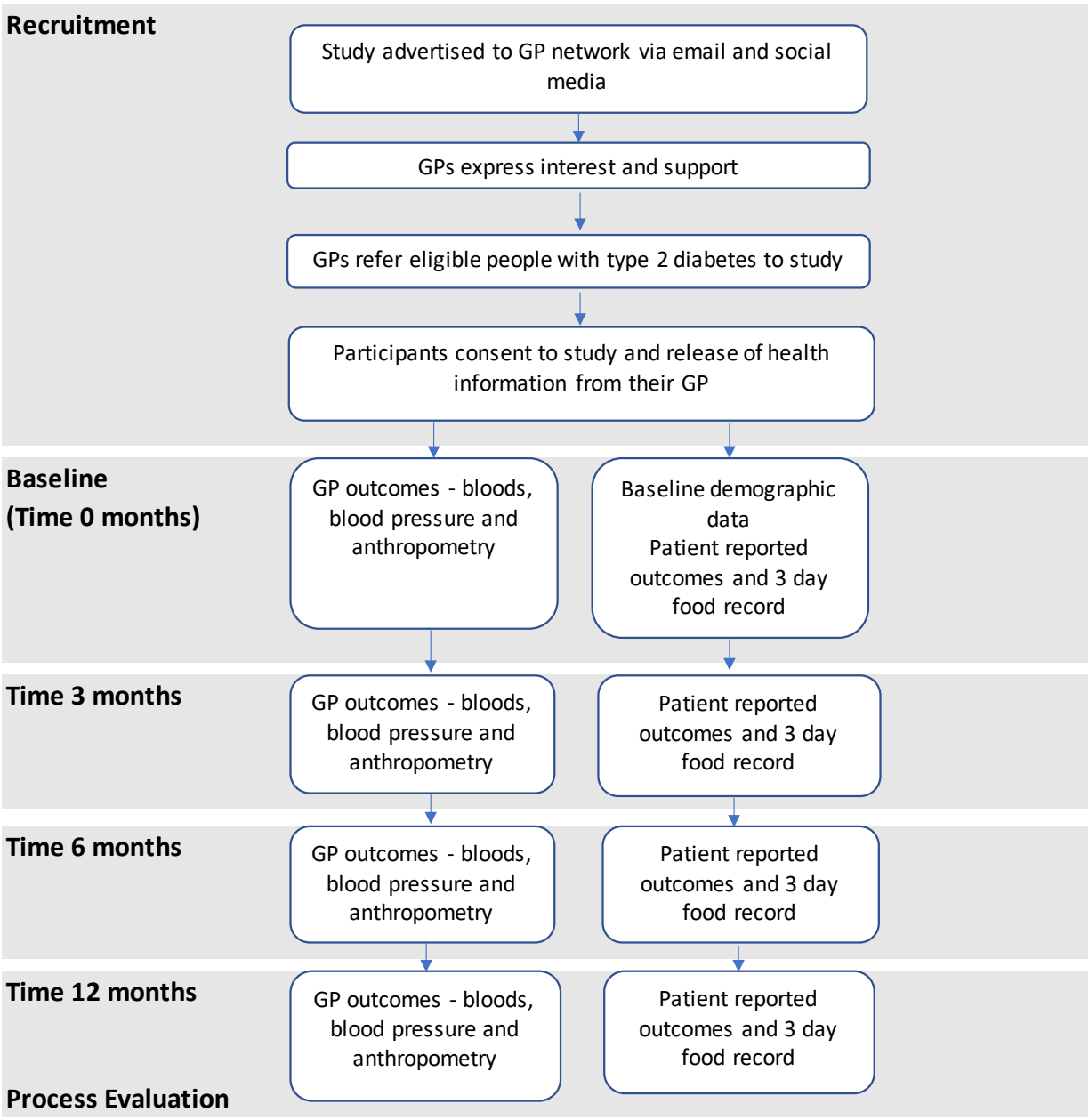
Date Submitted

* must provide value

Today D-M-Y

Submit

Study process chart



MEDICAL INFORMATION

IMPORTANT SAFETY INFORMATION:

Patients who are using insulin are EXCLUDED from this study, due to the high risk of hypoglycaemic episodes.

LOW CARBOHYDRATE DIETS HAVE AN IMMEDIATE POTENT HYPOGLYCAEMIC EFFECT

Therefore: Patients who are currently prescribed Sulphonylureas (Glimipiride, Gliclazide) **MUST HAVE THESE MEDICATIONS REDUCED OR CEASED** to avoid the risk of hypoglycaemic episodes.

ALSO: LOW CARBOHYDRATE DIETS MAY LEAD TO NUTRITIONAL KETOSIS.

This has never caused ketoacidosis, but there is possibly a slight increased risk in people taking SGLT2 inhibitors. Therefore: Patients who are currently prescribed SGLT2 inhibitors (Dapagliflozin, Empagliflozin) **MUST CEASE THESE MEDICATIONS** before the commencement of a low carbohydrate diet due to the risk of euglycemic ketoacidosis.

For information on suggested medication management and other health related issues that may present on commencement of a low carbohydrate diet please refer to the **Defeat Diabetes Doctor Letter** attached (please note: this letter is provided as part of the normal Defeat Diabetes app subscription and contains information about deprescribing insulin that is not relevant to this study).

Also, please see the following article attached "Reality Check: De-prescribing medication for T2D" containing detailed information specifically on medication management and de-prescribing medications.

The degree to which a patient's blood glucose levels can normalise when adopting a diet lower in carbohydrates will vary depending on the degree of carbohydrate reduction. Should a patient embrace the Defeat Diabetes guidelines and reduce carbohydrate intake to a very low level (intake of less than 30g a day) they will require early and continual monitoring and adjustment of anti-hyperglycaemic medications, if prescribed**. We would advise you to counsel your patients to monitor their blood glucose levels daily and to contact you immediately should they decrease rapidly.**

Note: If your patient is also being managed by an endocrinologist, we would appreciate it if you can advise them of their participation in this research study. Our suggested advice in this situation would be as follows:

"This patient is participating in a 12-month dietary intervention trial for their diabetes where they will be encouraged to avoid processed food and focus on eating real food especially protein-based food. It would be appreciated if during this trial that no new anti-diabetic medications are added unless in an emergency."

Concerns about blood lipid dysregulation

Many medical professionals are concerned that a low carbohydrate diet and the inclusion, by default, of a greater proportion of dietary fat, may lead to dysregulated blood lipids. A recent review on the application of low carbohydrate diets, and their impact on blood lipids however, has found this concern to be unwarranted. Please see the following attached article "Effect of low-carbohydrate diets on cardiometabolic risk, insulin resistance, and metabolic syndrome", for further information.

ADDITIONAL EDUCATIONAL RESOURCES

Interactive online Q &A sessions

To support GPs who may be new to the low carbohydrate dietary management of type 2 diabetes, Dr Liz Fraser and Dr Ron Schweitzer will host online interactive education sessions throughout the study period. Dr Liz Fraser is a GP in Canberra and GP Principal Investigator. Dr Ron Schweitzer is a GP in Melbourne, Victoria, with an interest in low-carb dietary approaches.

A GP guide to reversing diabetes with low-carb diets.

Emails will be sent out with a weblink to join in to discuss any specific issues to patient management or share any concerns.

Should you wish to learn more about the application of low carbohydrate diets more generally, here are a list of recommended resources.

Online video resources:

Dr David Unwin - Defeat Diabetes - National Diabetes Week 2022 Webinar

Dr David Unwin, GP, is an award-winning general practitioner known for pioneering the low-carb approach in the UK. Through the years, Dr. Unwin has been highly recognised for his work within his field and has had great success with de-prescribing medications and type 2 diabetes remission.

Dr. Penny Figtree - 'The Life of a Low Carb GP'

Dr Penny Figtree graduated from the University of Sydney in 1993 with first class honours. With over 20 years in general practice, she has now decided to focus on weight loss and diabetes.

Dr. Figtree has now been practising low carb medicine for 2 years. She describes this as the most rewarding part of her career, stopping medications and helping patients feel well.

Dr Paul Mason - 'Treating Metabolic Syndrome'

Dr Paul Mason obtained his medical degree with honours from the University of Sydney, and holds degrees in Physiotherapy and Occupational Health. He is a Specialist Sports Medicine and Exercise Physician.

Dr Mason developed an interest in low carbohydrate diets in 2011. Since then, he has spent hundreds of hours reading and analysing the scientific literature.

Dr. Peter Brukner - 'Defeat Diabetes: How an online program might eradicate type 2 diabetes'

Peter Brukner OAM, MBBS, FACSP, FACSM, FASMF, FFSEM is a medical doctor and specialist sports and exercise medicine physician. Peter has had two passions during this medical career.

The first was sports medicine. Peter is a world renowned sports medicine clinician and researcher. He was the founding partner at the Olympic Park Sports Medicine Centre in Melbourne, has served two terms as president of the Australasian College of Sports Physicians, is the co-author of the 'bible' of sports medicine Brukner & Khan's Clinical Sports Medicine, and has been team doctor to amateur and professional sporting teams such as Melbourne and Collingwood (AFL), National swimming, hockey, athletics, soccer and cricket teams as well as Liverpool Football Club in the English Premier league. Peter is Professor of Sports Medicine at La Trobe University in Melbourne.

Peter's second passion, which has developed over the last few years, is nutrition. He believes that most of what we have been told about what to eat over the last 40 years has been wrong, and as a result we have epidemics of obesity and chronic diseases such as type 2 diabetes. Peter is the Founder and Chair of the "Sugar By Half" campaign and has authored the popular book A Fat Lot of Good.

Webpage: Low Carb Down Under

A place to learn the Low Carb High Fat approach with science-based YouTube videos, books, articles, publications, recipes and discussions. Low Carb Down Under Events are held regularly around Australia and New Zealand.

Facebook: Low Carb/Keto Doctors Down Under | Facebook

Low Carb/Keto Doctors Down Under Low Carb/Keto Doctors Down Under is a supportive and interactive resource where medical professionals can interact and share their experience.

Defeat Diabetes

Dear Doctor,

Your patient has enrolled in the *Defeat Diabetes* Program which takes a low carbohydrate eating approach to improve glycaemic control in patients with type 2 diabetes (T2D).

As you may be aware, there has been increased interest in low carb and ketogenic ('keto') approaches to T2D, and it is recognised by leading bodies such as the *CSIRO* and the *American Diabetes Association*.

The *Defeat Diabetes* Program has been formulated by Australian doctors and dietitians and is based on the latest scientific literature.

This is not a crash diet, does not use shakes or supplements, and is <u>not</u> extremely low in calories.

It is a real food approach which minimises the intake of sugars and starches (bread, potato, pasta, rice). A similar program in the UK with over 400,000 participants has had a success rate of over 50% and is endorsed by the NHS. Details of our program are available at www.defeatdieabetes.com.au.

Medication Information

Medications for type 2 diabetes often need adjustment when carbohydrate intake is reduced to reduce the risk of hypoglycaemic episodes (insulin, sulfonylureas), or more rarely, ketoacidosis (SGLT2 inhibitors). Specific considerations are shown below, along with some further background information.

1. Anti-hyperglycaemic agents

a) ***Insulin***

Very low carbohydrate eating (VLC) containing less than 30 grams of daily dietary carbohydrates is recommended for patients on insulin therapy. This is to minimise post-prandial glycaemic variability and the associated risk of hyper- or hypoglycaemic episodes during the transition period.

Consider changing long-acting insulins to insulin glargine (or similar).

- Very low carb eating (VLC) < 30g/day:
  - Cease fast-acting insulin, reduce basal insulin doses by 50-80% from day one
  - Monitor blood sugar before and after meals and titrate as needed

- Low carb eating (<100g/day):
  - Cease fast-acting insulin, reduce basal insulin doses by 30-50% from day one
  - Monitor blood sugar before and after meals and titrate as needed

b) ***Metformin***

No need for dose reduction.

Please Note: The information pertaining to insulin is not relevant for this research study

c) ***Sulfonylureas***
Reduce by 50% if pre commencement HbA1c <7.5% (discontinue if on minimum dose)

d) ***SGLT2 inhibitors***
Cease due to increased risk of euglycaemic ketoacidosis.

e) ***Incretins***
No need for dose reduction if used in isolation.

f) ***Glitazones (thiazolidinediones)***
Discontinue if pre-commencement HbA1c < 7%

2. Anti-hypertensives

a) ***ACE I / ARBS / Calcium-channel blockers / Beta blockers / Thiazides / thiazide-like diuretics***

If BP <120mmHg systolic, or 20mmHg less than prior to commencement of low carbohydrate eating, withhold next dose of anti-hypertensive and consider dose reduction. Consideration should be given to ceasing diuretics should be ceased first, followed by beta-blockers.

b) ***Warfarin***
Dose changes may be necessary. Increased frequency of INR monitoring is recommended.

c) ***Valproate***
Monitor levels for changes due to narrow therapeutic range.

Background

Low-carbohydrate approaches to eating are gaining increasing acceptance as a first-line treatment for diabetes, including as a recognised diet by the *American Diabetes Association*. In Australia, a private medical Facebook group dedicated to low carb and ketogenic eating currently has more than 1,800 members. Indeed, many medical professionals now consider the balance of evidence is overwhelmingly in favour of low carbohydrate eating and its use in diabetic patients should be a foregone conclusion. Despite these changing tides, information regarding the use of low carbohydrate eating in a medical sense remains extremely limited at all levels of medical education. Consequently, many doctors may feel they lack the required knowledge to oversee the transition of diabetic patients to low carbohydrate eating. The goal of this document is to provide an overview of common areas requiring medical oversight.

The most important thing for medical practitioners to be aware of with respect to the commencement of reduced carbohydrate approach is the potential need for **medication changes** including de-prescribing. This most commonly includes *diabetic and anti-hypertensive medications*. Many

patients may also be able to down titrate other medications, including those for gastro-oesophageal reflux, analgesics and antidepressants. Some patients may also wish to engage in discussion regarding the benefits of ongoing cholesterol-lowering therapy.

The most dramatic impact on physiology of commencing a low carbohydrate approaches is the *rapid reduction in glucose levels* due to the removal of large amounts of dietary glucose in the form of sugar or starch.

Insulin and sulfonylurea medications present a high risk of *hypoglycaemic* episodes if not reduced prior to commencement of a low carbohydrate approach. For patients on these medications, very low carbohydrate eating (VLC) containing less than 30 grams of daily dietary carbohydrates is recommended. This is to minimise postprandial glycaemic variability and the associated risk of hyper- or hypoglycaemic episodes during the transition period.

Understand that the most important goal in the transition period is not to achieve normoglycemia, but to safely wean patients off insulin or other hypoglycaemic medications. It is, therefore, preferable to aim for mild hyperglycaemia (8-10 mmol/L) rather than risk hypoglycaemia.

Sliding scale insulin is unlikely to be needed on very low carbohydrate eating as patients will not be consuming a significant amount of carbohydrate-containing foods. If a sliding scale is to be continued, then doses should be appropriately reduced to reflect the reduced carbohydrate content of meals. Short-acting insulin may be needed to correct blood glucose excursions over 11 mmol/L to bring them towards 8mmol/L.

It is recommended that all fast-acting insulin be ceased at the time of initiation of a very low carbohydrate eating, and basal insulin levels be reduced by 50% to 80%. Blood glucose levels should be measured at least four times per day, with the use of a continuous glucose monitor preferred. Sulfonylurea drugs may be halved in dose or ceased completely depending on glycaemic control assessed via HbA1c.

There is a risk of euglycaemic diabetic ketoacidosis in patients taking SGLT2 inhibitors. These should always be ceased on commencement of a low carbohydrate eating.

Reduction in blood pressure is both predictable and common on reduced carbohydrate eating. This results from a reduction in glucose-stimulated insulin release which inhibits the sodium retaining function of four renal transporters activated by insulin. Two recommendations arise from this:

1. Firstly, patients should be advised to ensure an adequate sodium intake of 4 g or more per day (equivalent to approximately 2 teaspoons). Given low carbohydrate approaches generally eschew processed foods, the regular sodium intake of many patients may drop dramatically. If attention is not given to adequate sodium intake, symptoms such as postural hypotension and headache are common. Since 2017, the *Australian Dietary Guidelines* have not recommended an upper limit of sodium intake for individuals. Over time, blood pressure should be monitored to allow for appropriate down titration of antihypertensive therapy. We suggest the removal of diuretic medication first, followed by beta-blockers.

2. There is a perception that a low carbohydrate approach to eating is necessarily **low in fibre**. While a discussion regarding the merits of dietary fibre is beyond the scope of this letter,

many patients may actually consume higher levels of dietary fibre on low carbohydrate eating by way of fibrous vegetables such as cauliflower and broccoli, nuts and seeds, and fruits such as berries. Ironically, this high fibre intake can actually lead to abdominal discomfort by way of fermentation by gas-producing microbes, and moderation of high fibre foods may actually improve symptoms. Another common cause of gastrointestinal distress on low carb eating arises through excess consumption of artificial sweeteners as contained in commercial low carbohydrate bars. These artificial sweeteners, commonly sugar alcohols all polyols, can exert an osmotic effect which leads to diarrhoeal symptoms.

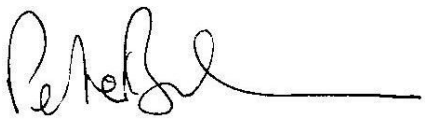
High fat low carbohydrate foods are generally very well tolerated in those who have had a **previous cholecystectomy**. If there are any concerns, a history seeking any signs of malabsorbed fat such as on oil slick in the toilet bowl should be taken. A trial of bile salts could also be considered, however, this has never been necessary in the authors' experience.

A history of **gout** or elevated uric acid is not a contraindication to low carbohydrate eating. While a transient elevation of uric acid may be seen due to competition between uric acid and ketone bodies for renal excretion in the early phase of the diet, this does not appear to increase the risk of gout attacks over baseline.

As with any dietary change, **INR** may be subject to change. Because LCK eating often involves changes in consumption of vitamin K-containing vegetables, monitoring of International Normalized Ratio (INR) should be more frequent in patients taking warfarin.

If you have any queries, please do not hesitate to contact one of us through the website (www.defeatdieabetes.com.au).

Best wishes,



Peter Brukner OAM, MBBS, FACSP
Professor of Sports Medicine
Founder, *Defeat Diabetes*

Paul Mason MBBS, FACSEP
Sport & Exercise Medicine Physician
Chief Medical Officer, *Defeat Diabetes*

References

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Kelly T, Unwin D, Finucane F. Low-carbohydrate diets in the management of obesity and Type 2 Diabetes: A review from clinicians using the approach in practice. *Int J Environ Res Public Health* 2020;17(7):2557.

Cucuzzella M, Hite A, Patterson K, et al. A clinician's guide to inpatient low carbohydrate diets for remission of type 2 diabetes: toward a standard of care protocol. *Diabetes Management* 2019;9(1),7-19.

DE-PRESCRIBING MEDICATION FOR T2D

In the opinion of our Reality Check authors:
IT'S SIMPLER THAN YOU THINK

People in remission from T2D need to reduce their medications. **Drs Liz Fraser**, **Ron Schweitzer** and **Penny Figtree**, GPs with a special interest in de-prescribing for people with diabetes who do well on low carbohydrate diets, share their evidence-based opinions and experience.

As the concepts of reversal and remission of T2D gain traction, clinicians need to grapple with another concept: de-prescribing. Trained to prescribe and intensify therapy, de-prescribing implies a new and unfamiliar set of skills for many primary care practitioners.[1]

Reversal and remission of T2D can be achieved in several ways. Bariatric surgery and Very Low Energy Diets (VLEDs, e.g., meal replacements) are widely promoted.[2] Less well publicised are the low carbohydrate (LC) dietary approaches.[3]

The authors of this article have an active interest in how LC diets can result in better outcomes with less medication for people with T2D. Here they focus on the principles of de-prescribing in the context of diabetes reversal and remission, particularly when initiating low carbohydrate dietary change, but the principles also apply to de-prescribing for people in remission from T2D post-surgery or VLED.

Why change the treatment approach to T2D?

Living with and managing T2D imposes a significant burden on people living with disease and the health care system.[4] Dietary change that helps blood glucose management and lowers need for medication can reduce the workload of treatment for people living with chronic disease.[5]

Low carbohydrate eating patterns are increasingly popular in the community, and many GPs will know people who want to, or who are already practicing low carb eating. Thus, GPs need to know how to respond appropriately to individuals making dietary changes, and have confidence to manage medication change, as part of a comprehensive approach to T2D.

Individual assessment, careful monitoring and a strong therapeutic alliance – all characteristics of primary care – are central to successful implementation of dietary and medication changes. It is vital to offer people choice in the framework of person-centred care with shared decision making.[6] The person's capacity for change may be a consideration.[5] In some circumstances, it may be simpler to stick with established medication regimes. However, an individual's willingness and ability to change lifestyle should not be underestimated.

For GPs, knowledge and understanding of diabetes medications is essential, and will inform which medications are reduced and/or ceased and the timing of any changes (Table 1).

Medications that increase the risk of hypoglycaemia must be adjusted from Day One of the low carbohydrate diet. Sulphonylureas and insulin must be withdrawn rapidly (usually ceased within days to weeks). SGLT2 inhibitors must be ceased due to the risk of euglycaemic ketoacidosis. Other diabetes medications may be continued until blood glucose is stabilised.[7] Close monitoring and excellent communication is key.[1]

Diabetes reversal and remission are important topics for conversation (Box 1).

Special considerations: Insulin

Insulin may present a particular challenge for doctors and people with diabetes alike. The use of insulin does not represent the natural progression of T2D for everyone.

Nonetheless, GPs may feel daunted by the prospect of reducing or ceasing a medication that was initiated by a specialist or in hospital, or that a person has been using for many years. People using insulin for T2D have often had diabetes for longer, are older, have more comorbidities, are more likely to be obese, and have more cardiovascular risk factors.[8] However, reducing and even ceasing insulin is still possible.

In our experience, the person's age and the duration of insulin treatment are not barriers to reducing insulin in motivated people. This will delight many people, while others may need reminding of insulin's disadvantages (Box 2).

Table 1: **Medication adjustments for therapeutic carbohydrate restriction.** (Main sources: Cucuzzella *et al*[1] and Murdoch *et al*[7])

Medication class	Examples	Comment on mechanism of action	Hypoglycaemia risk	Recommendation	Comments
A. Medications that are dangerous with low carb and must be adjusted					
Sulphonylureas	Glimipiride, Gliclazide	Increase pancreas insulin secretion	Yes	Reduce or cease. Gradual withdrawal if slower carbohydrate reduction	Sulphonylureas are associated with weight gain. Ineffective in the absence of functioning beta cells
Insulin	Basal insulin Bolus insulin Mixed insulins	Multiple adverse effects including: Hypoglycaemia Fat storage Inflammation Salt and water retention	Yes	Change to long acting. Withdrawal – see main text	Supraphysiological doses of insulin in those with insulin resistance may increase hunger and contribute to weight gain. Adverse effects include hypoglycaemia and lipodystrophy
SGLT2 inhibitors	Dapagliflozin Empagliflozin	Increase renal glucose loss	No, but risk of euglycemia ketoacidosis	Stop. Consider other drugs if needed to maintain glycaemic control	Mimics the effect of low carbohydrate dietary strategy[10]
B. Medications that may be useful in combination with low carb					
Biguanides	Metformin	Reduces insulin resistance; decrease hepatic neogenesis	No	May be continued if needed	Consider pleiotropic actions Adverse effects include poor gut tolerance and B12 depletion
GLP-1 agonists	Exenatide Liraglutide Semaglutide Dulaglutide	Increase insulin to glucagon ratio Delay gastric emptying, enhance satiety	No	May continue, consider pros and cons	Assist weight loss Significant GI adverse effects
C. Other diabetic medications to consider					
DPP-4 inhibitors	'Gliptins'	Inhibit breakdown of GLP-1, hence lower glucagon and slow gastric emptying	No	May be continued if needed	Less effect on weight compared to GLP-1 agonists, but less adverse effects as well
Thiazolidinediones	Pioglitazone	Improve peripheral insulin resistance, lower insulin requirement[16]	No	Consider stopping	Concerns over long term risks means these are little used; but consider in specific situations[16]
Alpha-glucosidase inhibitors	Acarbose	Inhibit gut absorption of carbohydrate	No	Cease, as they become redundant with LC diet	Gut adverse effects are due to carbohydrate malabsorption

Box 1: **Diabetes reversal & remission definition**

Reversal	Improved metabolic control as indicated by lower blood glucose, lowered A1c, weight loss, and/or less medication. The authors regard reversal as an important shift in the direction of what has been usually understood as a chronic and progressive disease.
Remission	HbA1C maintained below 6.5% in the longer term, without medication.[13]

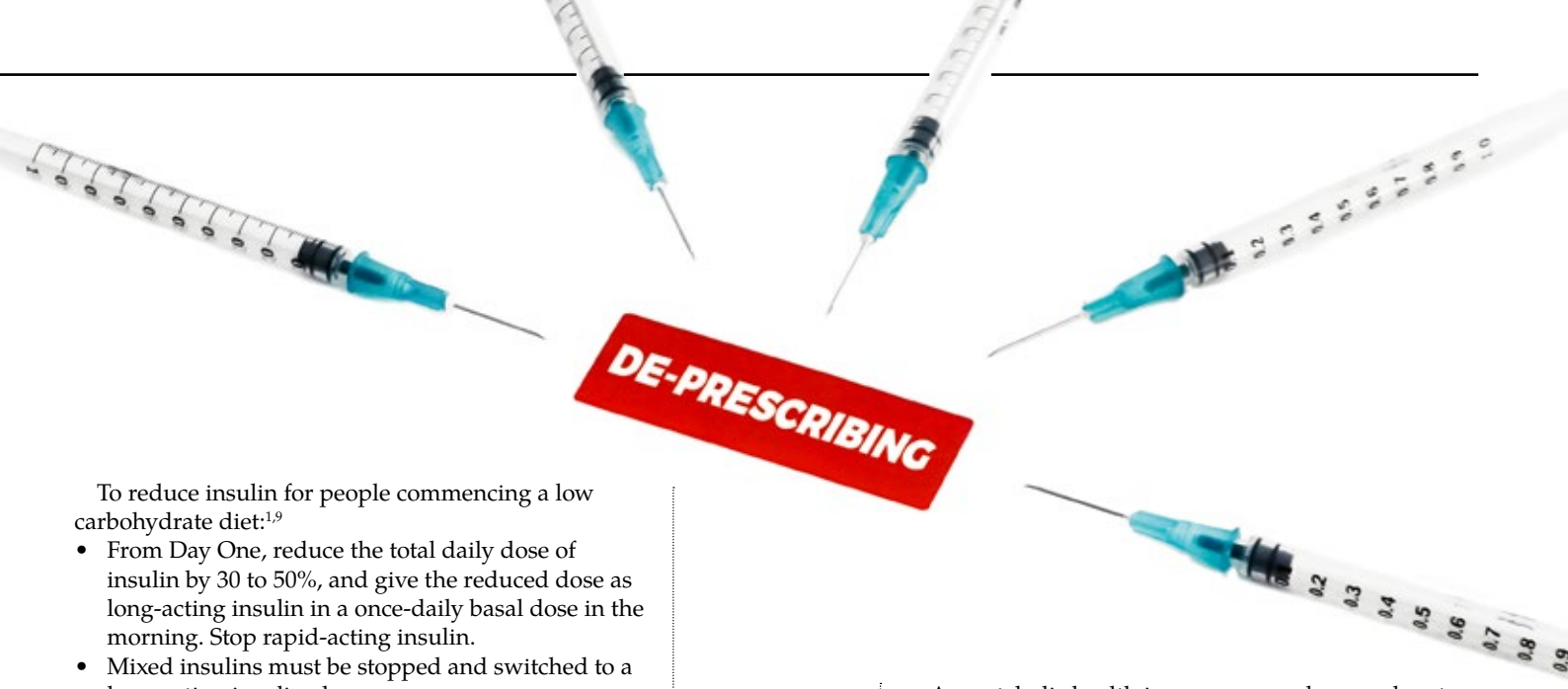
Box 2: **Adverse effects of insulin**

Insulin is a complex hormone. Amongst its many effects, it

- Promotes hunger
- Promotes storage of glucose as fat, and inhibits the release of fatty acids from fat cells
- Is pro-inflammatory
- Promotes excess synthesis of cholesterol[10]
- Augments the expression of renal SGLT2, thus promoting glucose and sodium retention, thus exacerbating hyperglycaemia and sodium and fluid retention.[10]

Iatrogenic over-insulinisation such as prescription of insulin to people with insulin resistance (i.e., some with T2D) is associated with worsening components of metabolic syndrome: obesity, hypertension, atherosclerosis, hypertension, inflammation and dyslipidaemia.[14] Insulin has a poor short- and long-term safety profile.[14]

In the authors' experience, it does not make sense to treat a condition characterised by hyperinsulinaemia and insulin resistance with more insulin, except to achieve short term glycaemic management.[8,15]



To reduce insulin for people commencing a low carbohydrate diet:[1,9]

- From Day One, reduce the total daily dose of insulin by 30 to 50%, and give the reduced dose as long-acting insulin in a once-daily basal dose in the morning. Stop rapid-acting insulin.
- Mixed insulins must be stopped and switched to a long-acting insulin alone.
- The person measures blood glucose before and two hours after each meal and liaises with the prescriber, for example by text, to determine the next day's insulin dose.
- If BGLs are < 10 mmol/L, then the following day's dose can be further reduced.
- BGLs > 10 mmol/L are acceptable in the short term and indicates that the insulin dose reduction should be postponed. The real danger in the initial phase is hypoglycaemia and the person should be warned to watch for symptoms and signs of hypos.

When reducing insulin, some people may require additional assistance with blood glucose management. The addition of a GLP-1 agonist may help with reduction of insulin as well as assist with weight loss.

We have observed that some people are able to significantly reduce insulin to a small dose such as 10u daily, but then need to stay on this low dose for some months for glycaemic management before they are able to cease insulin. It is likely that during this period pancreatic beta-cell function may recover enough to allow some of these people to cease insulin.

Other medications may require adjustment

When a person commences a low carb diet, other medications, especially antihypertensives, may need to be reduced. This is well known in the aftermath of bariatric surgery or the commencement of VLEDs and is attributed to rapid metabolic adjustments.[1] The same principle applies to LC practice.

Hyperinsulinaemia promotes the retention of glucose, sodium and water.[10] Conversely, lowering insulin through carbohydrate restriction results in diuresis. Lightheadedness and falling BP is a known initial 'side effect' of ketogenic diets and the usual advice is to add salt to the diet to prevent this. Doctors can also encourage people to monitor their BP at home and provide instructions to decrease and cease diuretic and other antihypertensives medication to avoid hypotension.[1]

As metabolic health improves, people may also stop PPIs used for GORD, NSAIDS and analgesics used for arthritic conditions, and migraine medication.[1]

Conclusion

Chronic disease carries a substantial treatment burden for people living with the disease. Studies show that people who adopt LC diets can dramatically reduce their medication requirements,[11] including insulin.[12]

Low carbohydrate eating patterns can deliver drug-like outcomes without the financial costs or adverse effects of taking medication, thus reducing the person's health care workload and improving their wellbeing.[10]

For some people, dietary change will be preferable to medication. Prescribers need to know how to work with those motivated to make these changes.

The authors declare no conflict of interest.
References: www.diabetesaustralia.com.au/diabetes-management-journal.

Dr Ronald Schweitzer MBBS, FRACGP is a GP in Melbourne, and senior lecturer, Monash University, Melbourne.

Dr Liz Fraser, MBBS, MEd, FRACGP is a GP in Canberra.

Dr Penny Figtree MBBS (Hons 1), FRACGP is a GP in Port Macquarie and Conjoint Lecturer UNSW Rural Medical School.

PRACTICE TAKEAWAYS:

1. Low carb diets (LCD) are gaining popularity as well as acceptance by professional bodies such as Diabetes Australia and the American Diabetes Association. GPs need to know how to manage medications for patients on these diets.
2. LCD can powerfully lower glucose levels, and rapid reduction of hypoglycaemic medications including insulin and sulphonylureas will be needed.
3. Use of SGLT2 inhibitors increase the risk of euglycaemic ketoacidosis when combined with LCD.
4. LCD often decrease people's blood pressure. Careful monitoring of blood pressure and decreasing anti-hypertensive medications is crucial.
5. Some individuals following LCD should be warned that the need to buy new clothes can make this an expensive lifestyle change.

Image: Jeremy Bezanger / Unsplash

Effect of low-carbohydrate diets on cardiometabolic risk, insulin resistance, and metabolic syndrome

Blair J. O'Neill

Purpose of review
An obesity epidemic has resulted in increasing prevalence of insulin resistance, hyperinsulinemia, metabolic syndrome (MetS), and cardiovascular disease (CVD). The Diet-Heart Hypothesis posited that dietary fat is the culprit. Yet dietary fat reduction has contributed to the problem, not resolved it. The role of hyperinsulinemia, the genesis of its atherogenic dyslipidemia and systemic inflammation in CVD and its reversal is reviewed.

Recent findings
Overnutrition leads to weight gain and carbohydrate intolerance creating a vicious cycle of insulin resistance/hyperinsulinemia inhibiting fat utilization and encouraging fat storage leading to an atherogenic dyslipidemia characterized by hypertriglyceridemia, low HDL, and small dense LDL. The carbohydrate-insulin model better accounts for the pathogenesis of obesity, MetS, and ultimately type 2 diabetes (T2DM) and CVD. Ketogenic Diets reduce visceral obesity, increase insulin sensitivity, reverse the atherogenic dyslipidemia and the inflammatory biomarkers of overnutrition. Recent trials show very high adherence to ketogenic diet for up to 2 years in individuals with T2DM, reversing their metabolic, inflammatory and dysglycemic biomarkers as well as the 10-year estimated atherosclerotic risk. Diabetes reversal occurred in over 50% and complete remission in nearly 8%.

Summary
Therapeutic carbohydrate-restricted can prevent or reverse the components of MetS and T2DM.

Keywords
carbohydrate restriction, metabolic syndrome, nutritional ketosis, obesity, weight loss

INTRODUCTION

There is an unparalleled epidemic of overweight and obesity [1]. Data from National Health and Nutrition Examination Survey (2013–2016) showed prevalence of obesity among adults was 38.3% (36.0% males and 40.4% females), including 7.7% with a BMI at least 40 kg/m^2 [2,3].

With increased prevalence of obesity has been increased occurrence of insulin resistance, metabolic syndrome (MetS), and type 2 diabetes (T2DM). As of 2020, approximately 34.1 million people Americans, 13% of the adult population, and 27% of those over 65, have T2DM. A further 88 million adults, or 34.5% of the population at least 18 years, had prediabetes [3,4].

When BMI increases from 23 to more than 35 kg/m^2, there is a 93-fold increase in T2DM [5,6]. Obesity also increases the risk of heart disease, hypertension, and other metabolic diseases. It is estimated that obesity is the second leading cause of preventable death after cigarette smoking in the USA [7].

T2DM occurs after a long process of insulin resistance initiated by visceral obesity, a systemic proinflammatory state, dyslipidemia, and finally overt dysglycemia. This can occur over decades [8,9]. However, this long 'incubation' period of prediabetes is also associated with accelerated atherosclerosis, hypertension, and cardiovascular disease (CVD).

MetS is the constellation of three of five characteristics, including low HDL, high-triglycerides, hypertension, fasting hyperglycemia, and increased waist circumference [10]. It is associated with poorer

Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Alberta, Canada

Correspondence to Blair J. O'Neill, MD, FACC, Division of Cardiology, Department of Medicine, Mazankowski Alberta Heart Institute, University of Alberta, 11220 83rd Avenue, Suite 3H2.0W1, Edmonton, AB, Canada T6G 2B7. Tel: +1 780 407 7954; fax: +1 780 407 6452; e-mail: Oneill2@ualberta.ca

Curr Opin Endocrinol Diabetes Obes 2020, 27:301–307
DOI:10.1097/MED.0000000000000569

KEY POINTS

- We are experiencing an unparalleled epidemic of overweight and obesity which is associated with increasing prevalence MetS and T2DM.
- Visceral obesity induces insulin resistance leading to chronic hyperinsulinemia which leads to indolent localized and systemic inflammation which promulgates worsened insulin resistance and anabolic metabolism.
- Hyperinsulinemia leads to atherogenic dyslipidemia which is further aggravated by carbohydrate intolerance.
- Therapeutic carbohydrate restriction (aka Ketogenic diets) lead to restoration of insulin sensitivity, return to normal basal, and postprandial insulin levels, and reversal of dyslipidemia, local and systemic inflammation, and glucose metabolism.
- Therapeutic carbohydrate restriction is sustainable with minimal support and particularly effective at reversing T2DM.
- It is time for randomized clinical trials of ketogenic diets to improve outcomes in high-risk populations with CVD (acute coronary syndromes, heart failure with preserved ejection fraction, atrial fibrillation).

outcomes [11,12], and is common especially with CVD. In the Euro Heart Study, 1/3 had known T2DM. However, less than 1/2 of these patients had normal glucose responses. 37% had impaired glucose tolerance and 18% had new diabetes [13]. Abnormal glucose metabolism is extremely common among patients presenting with CVD, highlighting the need for improved strategies for glucose screening and management [14].

Insulin-resistance/hyperinsulinemia is characterized by an atherogenic lipoprotein profile with fasting hypertriglyceridemia (high-triglycerides), and low HDL [15,16]. The atherogenic triad is completed with small dense LDL (sd-LDL-P) [17]. The usual clinical measure of atherosclerotic risk, LDL-cholesterol (LDL-C) can vary significantly between individuals in response to drug and lifestyle interventions. LDL-C levels do not always accurately reflect a patient's LDL-related risk [18]. This is especially true for patients with T2DM or MetS, who often have higher concentrations of LDL-P. LDL-P better predicts cardiovascular events than LDL-C, particularly in patients whose LDL-P and LDL-C levels are discordant [19–21].

DIET-HEART HYPOTHESIS VS. CARBOHYDRATE INSULIN MODEL

LDL-C has been recognized as the principle cause of CVD, but despite agents to effectively reduce LDL-C, patients have significant 'residual risk [22].' This has led to research to raise HDL cholesterol, lower triglycerides, reduce inflammation pharmacologically failing to recognize a common root cause of dyslipidemia and systemic inflammation. Insulin resistance/hyperinsulinemia and MetS are the thread often resulting in residual risk. There is growing recognition that the genesis of many modern diseases can be reversed through lifestyle changes alone, simply by restricting carbohydrates (CHO) in the diet.

The Diet-Heart Hypothesis, firmly established for the past half century, states that serum cholesterol is responsible for CVD and has strongly influenced primary and secondary prevention [23]. It is being challenged by the 'Carbohydrate-Insulin' Model [24▪▪]. This model proposes that a high-CHO diet produces postprandial hyperinsulinemia, promoting deposition excess energy in the form of fatty acids (FAs) and/or triglycerides into adipocytes instead of oxidation in muscle, predisposing to weight gain through increased hunger, slowing metabolic rate, or both. The effect has been amplified with the vilification of fat, resulting in decreased consumption, in favor of CHO, results clearly associated with the growing obesity since the 1980s [24▪▪,25,26▪▪].

Hyperinsulinemia predicts the presence of the components of MetS, including central adiposity, high circulating concentrations of high-triglycerides, low levels of HDL-C, high blood pressure, glucose intolerance, and now includes fatty liver and chronic inflammation, all predisposing to T2DM and CVD [27–29].

LOW-CARBOHYDRATE DIETS

A problem in determining the efficacy of low-carbohydrate or carbohydrate-restricted diets is their definition. Very low carbohydrate diet (VLCD) 'ketogenic' diet requires less than 20 g, and certainly less than 50 g/day. Low-carbohydrate diets are defined as being 50–100 g/day, which is above the threshold necessary to induce ketosis, but well below the population average of 150–200 g [30]. Nutritional ketosis occurs with prolonged fasting or by intentional severe restriction of dietary CHO intake. Reduced basal and postprandial insulin liberates lipid release from adipocyte storage and accelerates production of ketones in the liver. The overall metabolic effect stabilizes blood sugar, minimizes insulin release mitigating the downstream anabolic effects of longstanding hyperinsulinemia [31▪].

A 'well formulated' ketogenic diet is composed of 5–10% CHO (<20–50 g/day), adequate protein (1–1.5 g/kg/day), and fat until satiated so that ad lib

eating of properly chosen foods occurs. A spontaneous decrease in daily calorie consumption occurs. Nutritional ketosis attains blood ketone levels of 0.5–3 mg/dl [32].

It has been proposed that MetS is a CHO intolerance syndrome [33]. Ketogenic diets have a profound impact on hepatic gene expression, increasing activation of genes of lipid oxidation and decreasing expression of genes of lipogenesis [34]. Given the importance of dietary CHO as an insulin signaling agent, its dietary reduction improves markers of metabolic dysfunction more effectively than low-fat diets. Since low-fat high-carbohydrate intake exacerbates MetS, the corollary implies that carbohydrate-restricted is therapeutic [35].

VLCDs preferably metabolize metabolically active visceral fat. In a short-term cross-over design study, devised to be hypoenergetic (–500 calories), 28 overweight but healthy volunteers, underwent randomized sequential low-carbohydrate (<10% calories) and low-fat (58% CHO) dietary interventions [36]. The study showed a distinct advantage of a low-carbohydrate over a low-fat diet for weight loss, total fat loss, and truncal fat loss (despite an unintended greater energy intake of the low-carbohydrate group).

The preponderance of evidence does suggest that low-carbohydrate is superior to low-fat. In a meta-analysis comparing low-carbohydrate (<120 g) and low-fat interventions for overweight and obese adults, 17 randomized clinical trials (RCTs) (1797 participants) were reviewed [37]. For the low-carbohydrate group, the mean daily intake of macronutrients was 60 g CHO, 90 g fat and 106 g protein. The low-fat group consumed 205 g CHO, 37 g fat and 70 g protein. Both diets were associated with significant weight loss (−7.8 vs. −5.9 kg) and reduction in predicted risk of CVD events, but low-carbohydrate had a statistically significantly greater improvement in both [37].

IMPACT ON LIPID PROFILE

Carbohydrate-restricted uniquely promotes weight and fat loss [36,37] and reverses features of the insulin-resistant phenotype including atherogenic dyslipidemia and T2DM diabetes [31▪,33–36].

In insulin resistance, CHO consumption leads to an exaggerated hyperinsulinemic response leading to the atherogenic triad of high-triglycerides and smaller HDL and LDL particles. Carbohydrate-restricted attenuates cardiovascular risk factors, particularly through the impact on hepatic triglyceride synthesis. Basal and postprandial insulin levels following carbohydrate consumption leads to inhibition of lipolysis, enhanced delivery of FAs for hepatic esterification and overproduction and secretion of high-triglycerides-rich VLDL. Exchange of high-triglycerides in VLDL for cholesteryl ester in LDL results in high-triglycerides-rich LDL particles, a preferred substrate for hepatic lipase. This favors production of sd-LDL species. Similarly, high-triglycerides-rich HDL is hydrolyzed by lipoprotein lipase, resulting in smaller HDL particles which are more rapidly removed from the circulation [16,38–40]. The likely mechanism of therapeutic carbohydrate-restricted is prevention of these insulin-mediated lipid modifications.

Hypertriglyceridemia has been reported to be an independent risk factor for CVD [41], as has low HDL-C [42], but at the time, these authors did not recognize the common dyslipidemic thread-that they represented a sine qua non of insulin resistance.

Dietary carbohydrate-restricted, even in the absence of greater weight loss, consistently results in greater improvements in atherogenic dyslipidemia [33,43▪]. In addition to reduced plasma glucose (–12%) and insulin (–50%) concentrations, insulin sensitivity (–55%), weight loss (–10%), decreased adiposity (–14%), compared with low-fat, carbohydrate-restricted showed more favorable responses in fasting high-triglycerides (–51 vs. –19%), HDL-C (+13 vs. −1%), and the high-triglycerides/HDL-C ratio (–54 vs. –20%) [36]. The Total Cholesterol/HDL-C ratio had a greater reduction during carbohydrate-restricted than during low-fat diet (–14 vs. –4%). The Apo B/Apo A-1 ratio, considered the best indicator of risk for CVD [45,46] was improved following carbohydrate-restricted, but slightly worse subjects on low-fat (−16 vs. +8%).

The third component of the dyslipidemia of insulin resistance/MetS is the increased presence of sd-LDL. LDL-C becomes more atherogenic packaged as sd-LDL. These sd-LDL particles are cleared more slowly from the circulation and are more readily scavenged and oxidized in the subintimal space [18–21].

Krauss identified a genetically influenced pattern B in people whose plasma contains sd-LDL particles. This subpopulation, composing at least 30% of the US population, responded to Low Fat Diet by lowering LDL, but pattern B persisted. The remaining subpopulation with larger buoyant (lb-LDL) particles (pattern A) responded to reduction in fat intake by a shift towards the more atherogenic pattern B [46]. Thus, for most of the populations studied, replacing dietary fat with CHO leads to a worsening of the LDL size distribution [47,48].

Conversely, reducing CHO and replacing it with fat increases LDL-P size and shifts to the healthier pattern A. The atherogenic dyslipidemia of insulin

resistance/MetS is strongly influenced by dietary CHO as shown in many prior studies [36,43▪, 47,48]. This research suggests that decreasing CHO while increasing fat intake results in a stepwise increase in more physiological lb-LDL-P, and a corresponding decrease in the concentration of atherogenic sd-LDL particles.

INFLAMMATION

Visceral adipose tissue (VAT) has been closely linked to an increasing incidence of insulin resistance, T2DM, and a higher risk of CVD [49▪]. VAT is associated with a high production of proinflammatory adipocytokines, oxidative stress, and renin–angiotensin–aldosterone system activation [50]. The stressed visceral fat mass induces a number of inflammatory signaling pathways which regulate protein phosphorylation and post transcriptional events resulting in increased production of proinflammatory molecules [51,52]. These include TNF-α, IL-6, leptin, and resistin, as well as chemokines such as monocyte chemoattractant protein 1 (MCP-1), and other proatherogenic mediators, such as plasminogen activator inhibitor-1 (PAI-1). Endothelial adhesion molecules (e.g., ICAM-1 and Vascular Cell Adhesion Molecule-1) recruit more monocytes and other inflammatory cells into the expanding VAT. FAs likely contribute to local and systemic inflammation via several mechanisms. In macrophages, FA signaling leads to activation of nuclear factor-kappa beta (NF-kB) and expression of cyclooxygenase-2 [53,54]. NF-kB is a ubiquitous transcription factor regulating over 100 genes, associated with inflammatory responses and atherosclerosis. It is a crucial link between FA, MetS and atherogenesis [55].

Inflammatory and prothrombotic mediators such as the interleukins, C-reactive protein, and PAI-1 play critical roles in accelerated atherosclerosis and cardiovascular events in MetS and T2DM. Improvement in several of these have been demonstrated in trials of LCD [56,57]. Compared with low-fat, VLCD showed greater reduction in TNFα, IL-6, IL-8, MCP-1, E selectin, intercellular adhesion molecule, and PAI-1 [58].

Reducing dietary total and saturated fat has only a small effect on circulating inflammatory markers whereas carbohydrate-restricted leads to considerably greater reduction in a number of proinflammatory cytokines, chemokines, and adhesion molecules [59]. Dietary CHO is a far greater nutritional factor in inflammation than fat. High-CHO and high glycemic diets induce an increase in reactive oxygen species, activation of proinflammatory pathways and are associated with increased biomarkers of inflammation [60–62].

Supporting a therapeutic antinflammatory role, the collective metabolic and hormonal responses to carbohydrate-restricted have been linked with diminished oxidative stress, thus attenuating proatherosclerotic inflammatory responses that occur after eating overladen CHO meals. These responses reduce the associated hormone resistance to insulin, and leptin, essentially the root causes of MetS. The dysfunctional metabolic abnormalities induced by VAT increase throughout the range of carbohydrate-restricted [36,44,63,64].

The NLRP3 inflammasome is a multimeric protein complex that initiates an inflammatory form of apoptosis, triggering the release of proinflammatory cytokines IL-1β and IL-18. It has been implicated in the pathogenesis of several chronic inflammatory disorders, such as gout, rheumatoid arthritis, T2DM, and atherosclerosis [65]. Of importance to Insulin resistance/MetS and T2DM, the NLRP3 inflammasome appears to mediate an inflammatory response to nutrient excess and mitochondrial dysfunction. Significantly, the major metabolite of nutritional ketosis, beta-hydroxybutyrate (BHB), is not simply a metabolite, but is major signalling molecule [66,67]. BHB downregulates NLRP3 inflammasome performing a direct anti-inflammatory function. Ketogenic diets upregulate antioxidant pathways limiting Reactive Oxygen Species generation, thereby mitigating NLRP3-mediated inflammation [68,69▪]. Since systemic and local inflammation are integral to MetS and T2DM, there is intuitive merit to a state of nutritional ketosis to reverse and maintain metabolic health in these carbohydrate intolerant disorders.

DIETARY CARBOHYDRATE RESTRICTION IMPROVES GLYCEMIC AND INSULIN CONTROL

Clinicians routinely use Hemoglobin A1c (HbA1c) as a biomarker of diabetic control. However, it is only a surrogate measure and although pharmacotherapy can improve HbA1c, agents like sulfonylureas and insulin cause weight gain and worsen long-term diabetic outcomes [70▪]. Carbohydrate-restricted actually treats the root cause of T2DM, carbohydrate intolerance.

In obese insulin resistant individuals, low-carbohydrate diets were more effective than higher carbohydrate (low-fat) diets at improving fasting glucose and insulin levels and insulin sensitivity as measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [71–73].

In one of the earliest studies of use of VLCD in patients diagnosed with T2DM, 28 patients with a mean BMI of 42.2 were treated for 16 weeks [74]. HbA1c decreased by 16% from 7.5 to 6.3% from baseline to week 16. Diabetes medications were

discontinued in seven participants, reduced in 10 participants, and unchanged in four participants.

A recent meta-analysis of nine RCTs with 734 participants diagnosed with T2DM found that low-carbohydrate interventions had a positive effect on HbA1c, high-triglycerides, and HDL-C concentrations. In this metanalysis, LCD had no impact on total or LDL-C concentrations [75].

An important clinical trial into the potential real-world impact of VLCD was recently reported [76▪▪]. This trial involved 262 patients receiving a VLCD, using individualized support with telemedicine, health coaching, and guidance in nutritional ketosis using an individualized VLCD diet, while 87 controls receiving a diet based on standard American Diabetes Association guidelines in a University Hospital Diabetes Clinic.

The VLCD group was treated with a diet with blood measurements confirming nutritional ketosis, with BHB levels between 0.4 and 0.6 mmol/l. These patients lost 10–15% of body weight. Inflammatory responses decreased significantly, while they did not change or continued to increase in the University Hospital Diabetes Clinic group. Virtually every important biomarker changed in a positive direction including triglycerides, HDL, sd-LDL particle count (−21.8%) and, most importantly, the 10-year risk of atherosclerotic CVD (ASCVD) decreased (−11.9%) despite an increased LDL (+9.9%) cholesterol level [77▪▪]. Conversely, in the University Hospital Diabetes Clinic group, virtually every biomarker continued to deteriorate over the 1-year follow-up including the 10-year ASCVD. LDL-C, however, decreased. Not surprisingly, in the VLCD intervention group, the average HbA1c decreased from 7.6 to 6.3%. Medication utilization was reduced, with half the patients completely discontinuing insulin, and all discontinuing sulfonylureas. In the University Hospital Diabetes Clinic group insulin dosages and sulfonylurea use continued to increase.

Little data exists on long-term sustainability for improved metabolic and glycemic changes with ketogenic diets. However, Hallberg *et al.* [78▪▪] continued to follow this cohort of patients for 2 years. Retention was a primary endpoint and was essentially the same in both arms –74% in the VLCD arm and 78% in the University Hospital Diabetes Clinic group. After 2 years, VLCD subjects continued to demonstrate improved HbA1c, fasting glucose and insulin, and HOMA-IR. The HbA1c reduction of 0.9% was comparable with that observed in pharmaceutical trials. This was achieved while discontinuing 67% of diabetes-specific prescriptions, including most insulins and all sulfonylureas. At

Excess of dietary carbohydrate leads to:	Carbohydrate restriction leads to:
Hyperinsulinemia Progressive Insulin Resistance	Reduced Insulin levels and restoration of insulin sensitivity
Systemic and local Inflammation Further Insulin Resistance	Reduced markers of inflammation
Atherogenic Dyslipidemia Elevated triglycerides, small HDL, sdLDLp	Improved lipid profile and subfractions
Increased visceral adipose tissue (Overweight/obesity)	Reduced Visceral Adipose Tissue and effective sustained weight loss
Hypertension	Improved Blood Pressure
MetSyn, T2DM, Atherosclerosis, Atrial fibrillation, HFpEF	Improved HbA1c and Diabetes reversal
Metabolic Dysfunction	**Restored Metabolic Health**

FIGURE 1. Impact of carbohydrate excess vs. carbohydrate restriction on metabolic health and dysfunction.

2 years, the Intervention group continued to demonstrate a mean 10% weight loss, along with significant decreases in SBP and DBP and triglycerides in the VLDL intervention but not University Hospital Diabetes Clinic group. Prediabetes also was reversed significantly more often with the ketogenic diet. At 2 years, 27.2% of Continuous Care Intervention participants vs. 6.5% of University Hospital Diabetes Clinic patients showed resolution of MetS.

CONCLUSION

There is now compelling evidence that low-carbohydrate diets can sustainably reverse the metabolic abnormalities and quell the pathologic inflammation resulting from CHO excess in individuals and in our population as a whole. Figure 1 summarizes the effect of carbohydrate excess compared to carbohydrate restriction on the balance of metabolic health. The only missing part of the puzzle, beyond surrogate measures and biomarkers, is conclusive outcome data showing reduction in CVD events and mortality.

Acknowledgements

My patients who have committed to changing their lives by pursuing low carbohydrate lifestyles and inspired me through their journeys.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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