



# **Type 2 Diabetes**

## **From diagnosis to remission: The Digital Age**

**The Low Carb Universe – LCU19 – Mallorca, Spain**

**Jan Vyjídák**  
**13<sup>th</sup> November 2019**



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## **Short introduction**

Over the past decade, I have worked as a management consultant on healthcare projects in the United Kingdom, Central and Eastern Europe and Asia, most recently in the Czech Republic and Slovakia.



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**What is remission?**

**There are various forms of diabetes, with slightly different diagnostic criteria, with different countries using different screening and diagnostic tests, notably in Gestational Diabetes.**

### CLASSIFICATION

Diabetes can be classified into the following general categories:

1. Type 1 diabetes (due to autoimmune  $\beta$ -cell destruction, usually leading to absolute insulin deficiency)
2. **Type 2 diabetes** due to a progressive loss of  $\beta$ -cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

**ADA (2019) lists four key diagnostic criteria for the diagnosis of diabetes, based on fasting plasma glucose, 120min Oral Glucose Tolerance Test, glycated haemoglobin or random plasma glucose.**

**FPG  $\geq 126$  mg/dL (7.0 mmol/L).**

**2-h PG  $\geq 200$  mg/dL (11.1 mmol/L) during OGTT.**

**A1C  $\geq 6.5\%$  (48 mmol/mol).**

**random plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L).**

**While Virta's criteria for diabetes reversal seem less "strict" than remission as defined by DiRECT trial, partial and complete remission set a higher bar (lower HbA1c plus longer duration without meds).**

Disease outcomes	Criteria and cut-offs used for assignment
<b>Diabetes reversal</b>	Sub-diabetic hyperglycemia and normoglycemia (HbA1c below 6.5%), without medications except metformin
<b>Diabetes partial remission(12)</b>	Sub-diabetic hyperglycemia of at least 1 year duration, HbA1c level between 5.7-6.5%, without any medications (two HbA1c measurements)
<b>Diabetes complete remission(12)</b>	Normoglycemia of at least 1 year duration, HbA1c below 5.7%, without any medications (two HbA1c measurements)



DiRECT trial defined remission of diabetes as HbA1c below 6.5% (48 mmol/mol) following at least 2 months without medication (less strict than Virta remissions).

## Outcomes

The co-primary outcomes were a reduction in weight of 15 kg or more, and remission of diabetes, defined as HbA<sub>1c</sub> less than 6.5% (<48 mmol/mol) after at least 2 months off all antidiabetic medications, from baseline to month 12.

A clinical trial investigating prediabetes remission also used fasting plasma glucose and 2h OGTT result to determine remission.

Subjects were considered to have remission of their pre-diabetes if at 6 months they had a fasting glucose of <100 mg/dL, and a 2-hour glucose level of <140 mg/dL during a single OGTT.

**Likewise, CDS suggests two methods – fasting plasma glucose below 5.6 mmol/l, and either A1c below 38 mmol/mol or 2h OGTT below 7.8 mmol/l.**

Kritéria pro posouzení účinku bariatrické chirurgie na remisi diabetu 2. typu (upravená evropská doporučení):

Hodnotí se podle glykémie v žilní plazmě nalačno a HbA1c (místo HbA1c je možné použít glykémie ve 120. minutě oGTT).

**Částečná remise** (odpovídá modifikované definici prediabetu/poruše glukózové homeostázy)  
Glykémie jsou pod diagnostickým prahem pro diabetes (tj. glykémie v žilní plazmě nalačno 5,6 – 6,9 mmol/l NEBO HbA1c 39 – 47 mmol/mol NEBO glykémie ve 120. minutě oGTT 7,8 -11,0 mmol/l) nejméně po dobu 1 roku, bez farmakoterapie s výjimkou metforminu.

#### **Kompletní remise**

Normální glykémie je třeba potvrdit dvěma ukazateli (glykémie v žilní plazmě nalačno je < 5,6 mmol/l a zároveň je HbA1c < 38 mmol/mol nebo je glykémie ve 120. minutě oGTT <7,8mmol/l) nejméně po dobu 1 roku, bez farmakoterapie s výjimkou metforminu.

#### **Prodloužená remise**

Kompletní remise trvající alespoň 5 let.

Po bariatrickém výkonu u nemocného s diabetem či prediabetem je vhodné bez ohledu na zlepšení či normalizaci glukózové homeostázy pokračovat v podávání metforminu.

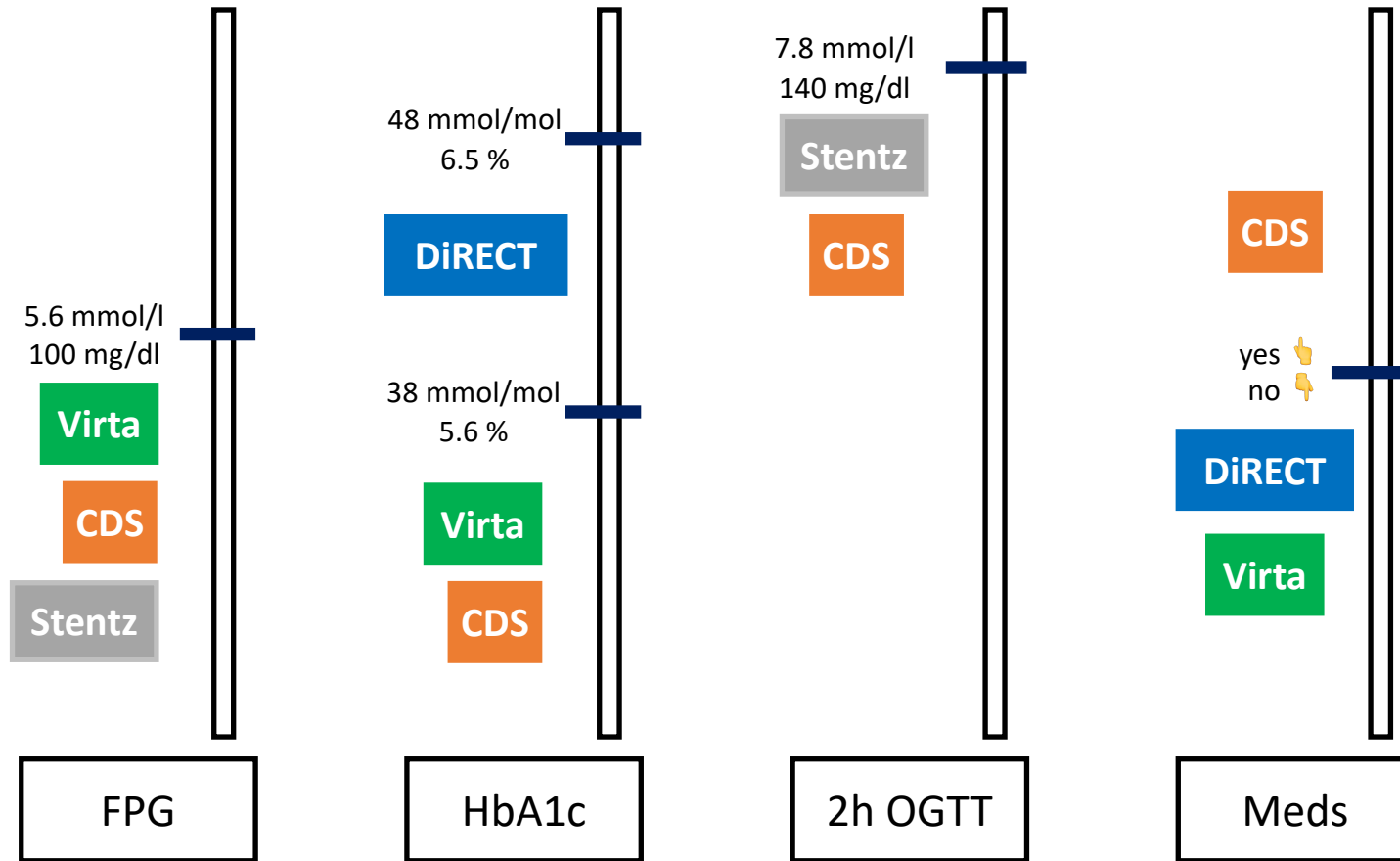
A comparative analysis of various definitions suggests that OGTT is not always required, and remission as defined by Virta Health being stricter than remission as defined by DiRECT trial.

	VIRTA	DiRECT	Stentz (2016)	ČDS (2017)
REVERSAL	subDM hypergly A1c < 6.5 % metformin	---	---	---
PARTIAL REMISSION	subDM hypergly 1y A1c 5.7 – 6.5 % (2x) no medication	---	---	FPG 100 – 125 mg/dl A1c 39 - 47 mg/dl 2h OGTT 140-200 mg/dl
COMPLETE REMISSION	normoglycaemia 1y A1c <5.7 % (2x) no medication	A1c <6.5 % after 2m without meds	FPG <100 mg/dl 2h OGTT <140 mg/dl	FPG < 100 mg/dl (2x) AND A1c < 5.6 % or 2h OGTT < 140 mg/dl
EXTENDED REMISSION	---	---	---	complete remission for 5y

A comparative analysis of various definitions suggests that OGTT not always required, and remission as defined by Virta Health being stricter than remission as defined by DiRECT trial.

	VIRTA	DiRECT	Stentz (2016)	ČDS (2017)
REVERSAL	subDM hypergly A1c < 48 mmol/mol metformin	---	---	---
PARTIAL REMISSION	subDM hypergly 1y A1c 39-48 mmol/mol 2x no medication	---	---	FPG 5.6 – 6.9 mmol/l A1c 39 - 47 mmol/mol 2h OGTT 7.8-11 mmol/l
COMPLETE REMISSION	normoglycaemia 1y A1c <38 mmol/mol (2x) no medication	A1c <48 mmol/mol after 2m without meds	FPG <5.6 mmol/l 2h OGTT <7.8 mmol/l	FPG < 5.6 mmol/l (2x) AND A1c < 38 mmol/mol or 2h OGTT < 7.8 mmol/l
EXTENDED REMISSION	---	---	---	complete remission for 5y

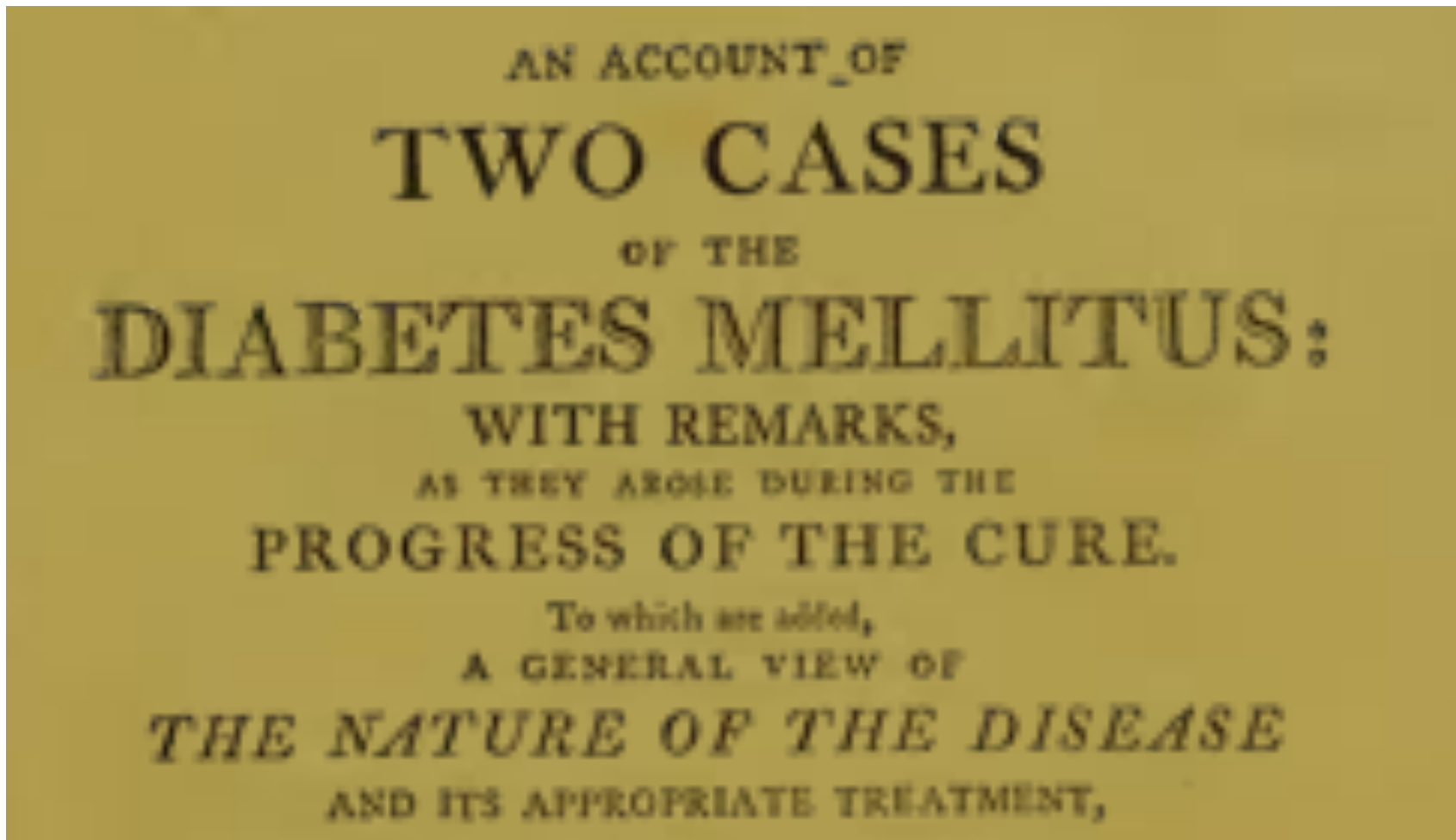
A visual guide to complete remission (Virta, CDS) and remission (DiRECT, Stentz).



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### Brief history

One of the earliest references to an animal (low carbohydrate) diet comes from John Rollo, the army surgeon, from 1797, in the context of diabetes cure.





Animal diet was noted several times in Rollo 1797.

16th April, 1797.

SINCE my last I think the GENERAL has gained some strength, and looks better. He has diligently persevered in the animal diet, and taken as much in a venifon state as he could obtain. This being the

Animal diet was noted several times in Rollo 1797.

THE TWO CASES treated at GLASGOW  
by DOCTOR CLEGHORN, shew also the good  
effects of entire animal food, and of the in-  
fluence of commotions in the bowels on the  
quantity of the urine.

THE CASE of the GENTLEMAN of 77  
likewise shews the efficacy of animal food ;  
but the MOST STRIKING CASE is that of  
CLARK, as related by DOCTOR GERARD.

The animal diet used by Rollo in the treatment of Captain Meredith included milk, bread, butter, blood-puddings, game, old meats, fat, pork etc.

and to diminish the appetite. Following initial bleedings, Rollo's treatment of Captain Meredith was as follows:

"*1st.* The diet to consist of animal food principally, and to be thus regulated:

*Breakfast.* One and a half pint of milk and half a pint of lime-water, mixed together; and bread and butter.

*Neon.* Plain blood-puddings, made of blood and suet only.

*Dinner.* Game, or old meats, which have been long kept; and as far as the stomach may bear, fat and rancid old meats, or pork. To eat in moderation.

*Supper.* The same as breakfast.

**Rollo suggested that diabetes developed due to morbid changes in stomach involving changes in the natural powers of digestion and assimilation, resulting in sugar/saccharine being developed from plants.**

A view held by some at that time was that diabetes was a primary affection of the kidneys. However, Rollo developed the idea that the disease was "a primary and peculiar affection" of the stomach in which, due to some morbid changes in "the natural powers of digestion and assimilation," sugar or saccharine material was formed in that organ, chiefly from vegetable matter. It was on this basis that he advocated the use of an animal diet together with certain medication designed to quiet the overactive stomach and to diminish the appetite. Following initial blood-

**The work of Rollo was picked up by Josef Thomayer in Prague, then part of the Austro-Hungarian Empire. In 1908, he described Rollo's diet as "a strict meat diet and a major therapy in most cases of diabetes."**

„Léčení. Rollo doporučil v r. 1797 při diabetu **přísnou masitou stravu.** Tohoto druhu dieta je dodnes hlavním terapeutickým výkonem naším při nemoci této. Při masité stravě ve veliké většině případů množství vyloučeného cukru se zmenší, v mnohých pak případech úplně z moči vymizí. Jísti tedy smí čisté masité polévky, všeho druhu maso, máslo, slaninu (poně-

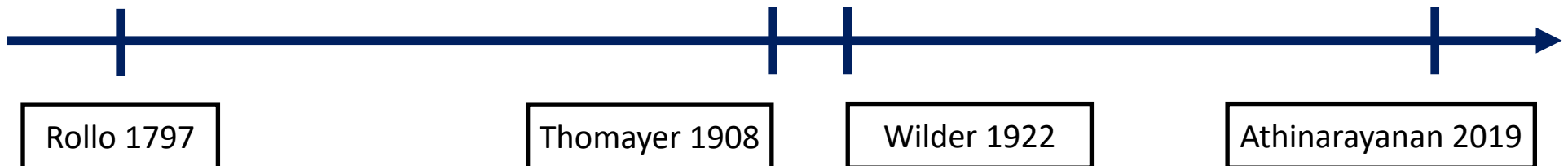
vadž diabetik nemá tratiť na váze a chřadnouti, jelikož by si život ohrozil, má zejména účast másla a tuků v potravě býti pokud možno značná), vejce, sýr, čistou smetanu, rosoly, ořechy, houby, mandle, smí píti: kávu neslazenou čistou či se smetanou, podobná thé, trpká vína (např. rakouská), minerální vody, dále smí jísti takové zeleniny, které neobsahují cukry (špenát, okurky, chřest), v malém množství mrkev, jahody a maliny. Při takovéto dietě se však nemocnému obyčejně po moučné potravě zasteskne.“ [3]

**At about the same, the founder of Czechoslovakian endocrinology, Josef Charvat, designed his slimming diet, which contained 60g CHO, 40g FAT and 70g PRO. He used it successfully in diabetes and obesity.**

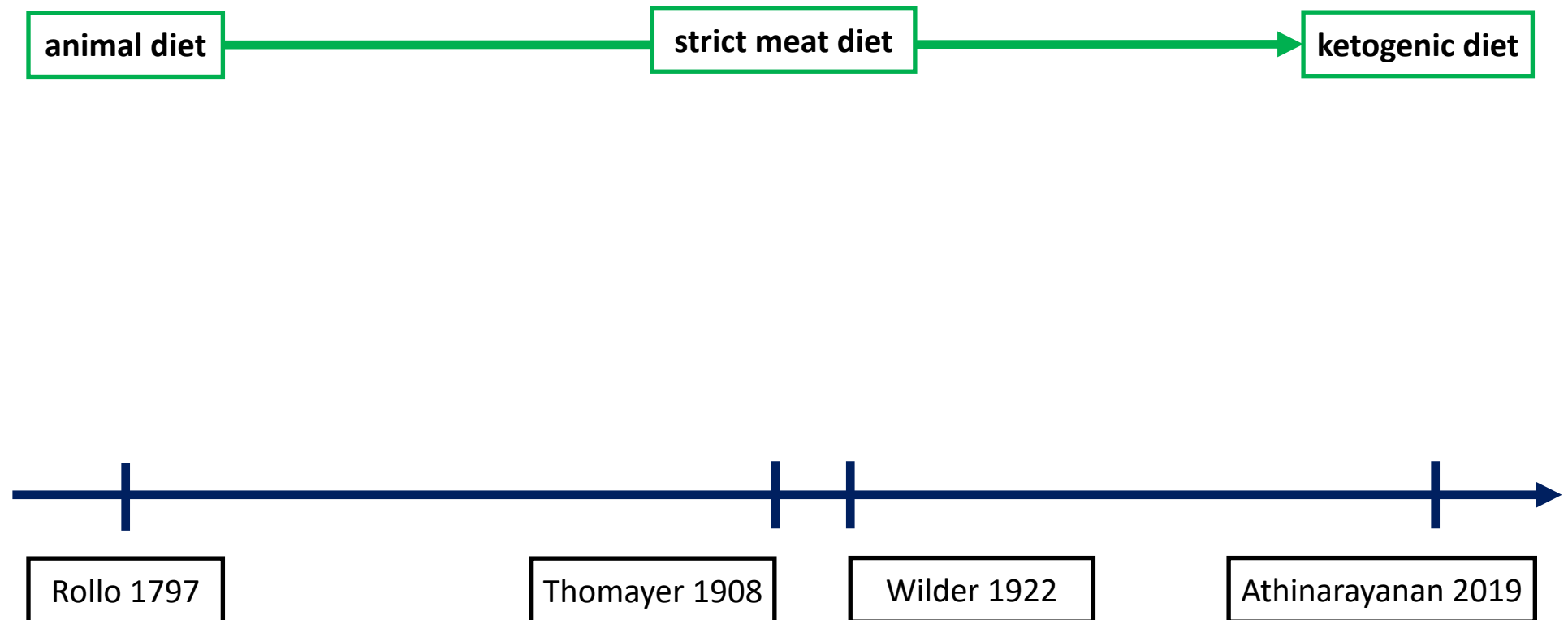
ní atrezií, označovaný dnes jako Bardetův-Biedlův syndrom (Biedl, 1922). Před téměř 80 lety navrhl profesor Josef Charvát redukční dietu. Charvátova dieta má energetický obsah 3700–4200 kJ a obsahuje 70 g bílkovin, 60 g sacharidů a 40 g tuků. Charvát ve své dietě doporučuje 100 g libového hovězího masa, 80 g libové šunky, 1 suchar, 2 vejce, 100 g brambor, 200 g ovoce, 300 g zeleniny, 10 g másla a 100 g mléka. Ve své době tato dieta bezpochyby představovala moderně koncipovanou dietoterapii obezity. Dnes bychom měli výhrady k vyššímu obsahu cholesterolu a nižšímu obsahu sacharidů v této dietě.

Nízkosacharidová strava není v léčbě diabetu novinkou. V předinzulinové éře byla jednou z prvních léčebných metod diabetu. Také u nás byla používána v léčbě obezity a diabetu zakladatelem české endokrinologie prof. J. Charvátem. S rozšířením farmakologických mož-

**Rollo's basic concept of an animal diet made it through two centuries all the way to an animal food based ketogenic diet, picked up some non-starchy vegetables and demonstrated great results for T2D remission.**

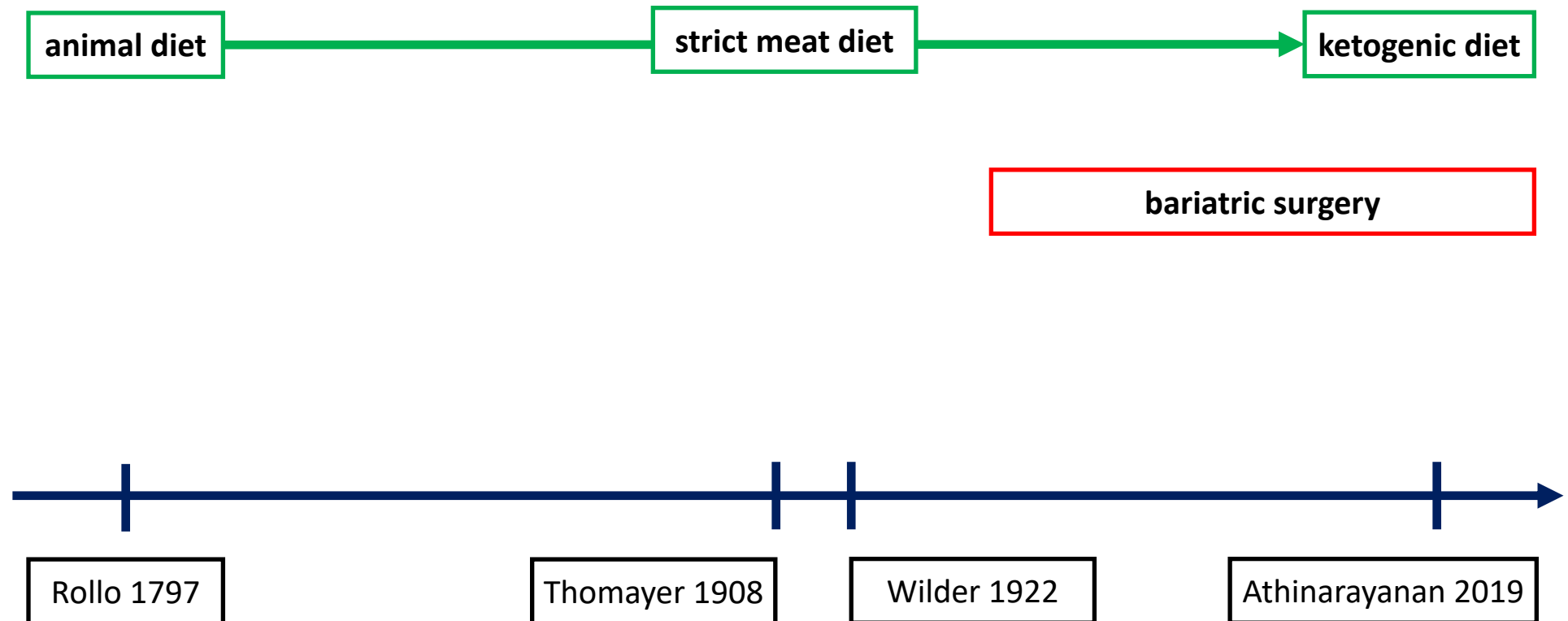


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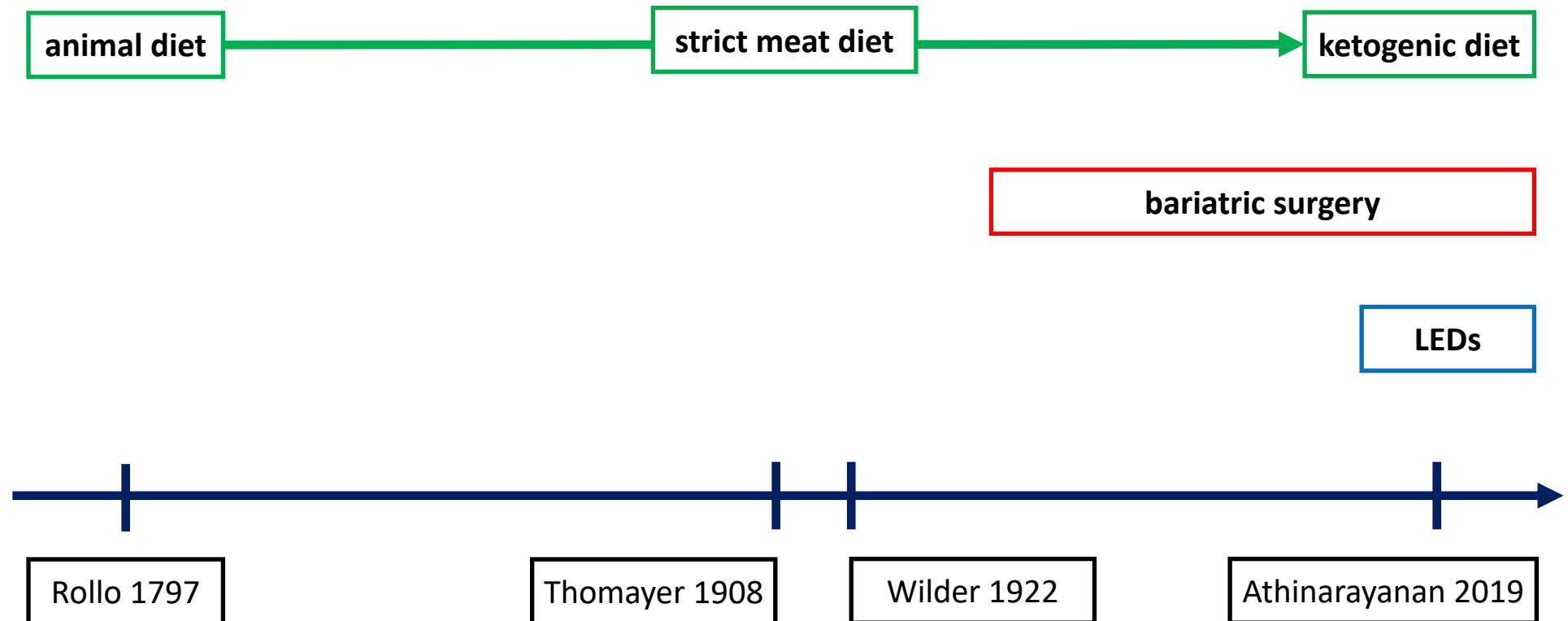




As of 1950s, surgeons began to notice that weight loss surgery had a positive effect on glycaemic control and T2D remission, believed to be the result of weight loss. First "bariatric remission" RCTs came in 2000s.



Beginning in 2011, a series of experiments with low energy formula diets eventually led to excellent weight loss and T2D remission results in the DiRECT trial – 36% remission rate at Year 2.



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## **Key measures en route to remission**

**While markers of glycaemic control will be key in terms of criteria for remission, there are other important markers which can help fine tune the progress towards remission.**

### GLYCAEMIC CONTROL

- fasting plasma glucose
- postprandial glucose
- HbA1c
- 2h OGTT
- glycaemic variability
- hypoglycaemic events
- beta-hydroxybutyrate

### LIPID PROFILE

- total cholesterol
- LDL-c
- LDL-p
- small LDL-p
- ApoB
- triglycerides
- HDL-c

### WEIGHT/BODY COMPOSITION

- weight
- waist circumference
- waist/hip ratio
- % muscle mass
- % body fat
- % ectopic fat (liver, pancreas)

### OTHER

- medication
- quality of life

**An example of some of the cardiovascular risk factors tracked by Virta Health.**

Weight-clinic (kg)**	Small LDL-P (nmol·L-1)**
Hemoglobin A1c (%)**	LDL-particle size (nm)**
Systolic blood pressure (mmHg)**	Total HDL-P (mmol·L-1)**
Diastolic blood pressure (mmHg)**	Large HDL-P (mmol·L-1)**
ApoB (mg·dL-1)	LP-IR score**
ApoA1 (mg·dL-1)**	hsC-reactive protein (mg·L-1)**
ApoB/ApoA1 ratio**	WBC (k·mm-3)**
Triglycerides (mg·dL-1)**	10-year ASCVD risk**
LDL-C (mg·dL-1)**	cIMT-average (mm)
HDL-C (mg·dL-1)**	Statin (%)
Triglycerides/HDL-C ratio**	Any antihypertensive medication (%)**
Large VLDL-P (nmol·L-1)**	ACE or ARB (%)
Total LDL-P (nmol·L-1)	Diuretics (%)**

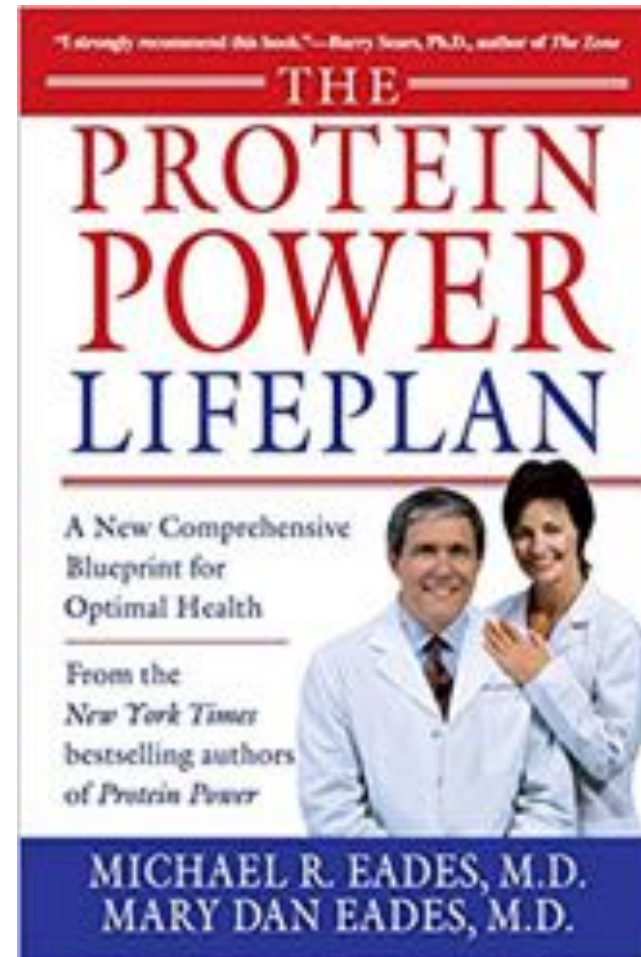
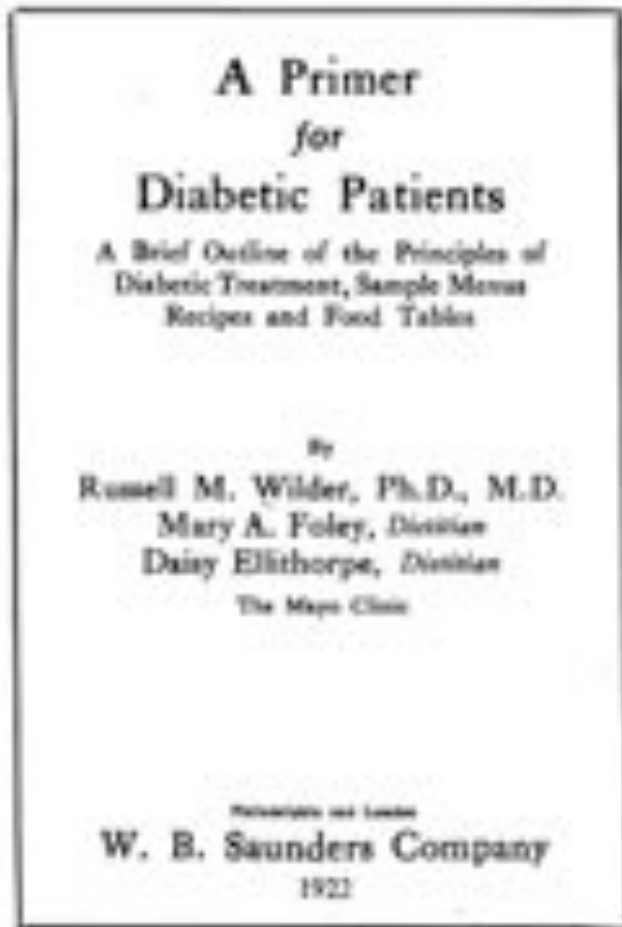
**5**

**Digital era**

**Back in the day, people could find books and scientific papers in libraries. Finding the right paper at the right time used to be a little more complicated than using Google from your bed.**



The problem was not that valuable information was not written or published – the challenge often was to be able to access it at the right time and make sense of the conflicting pieces of advice.

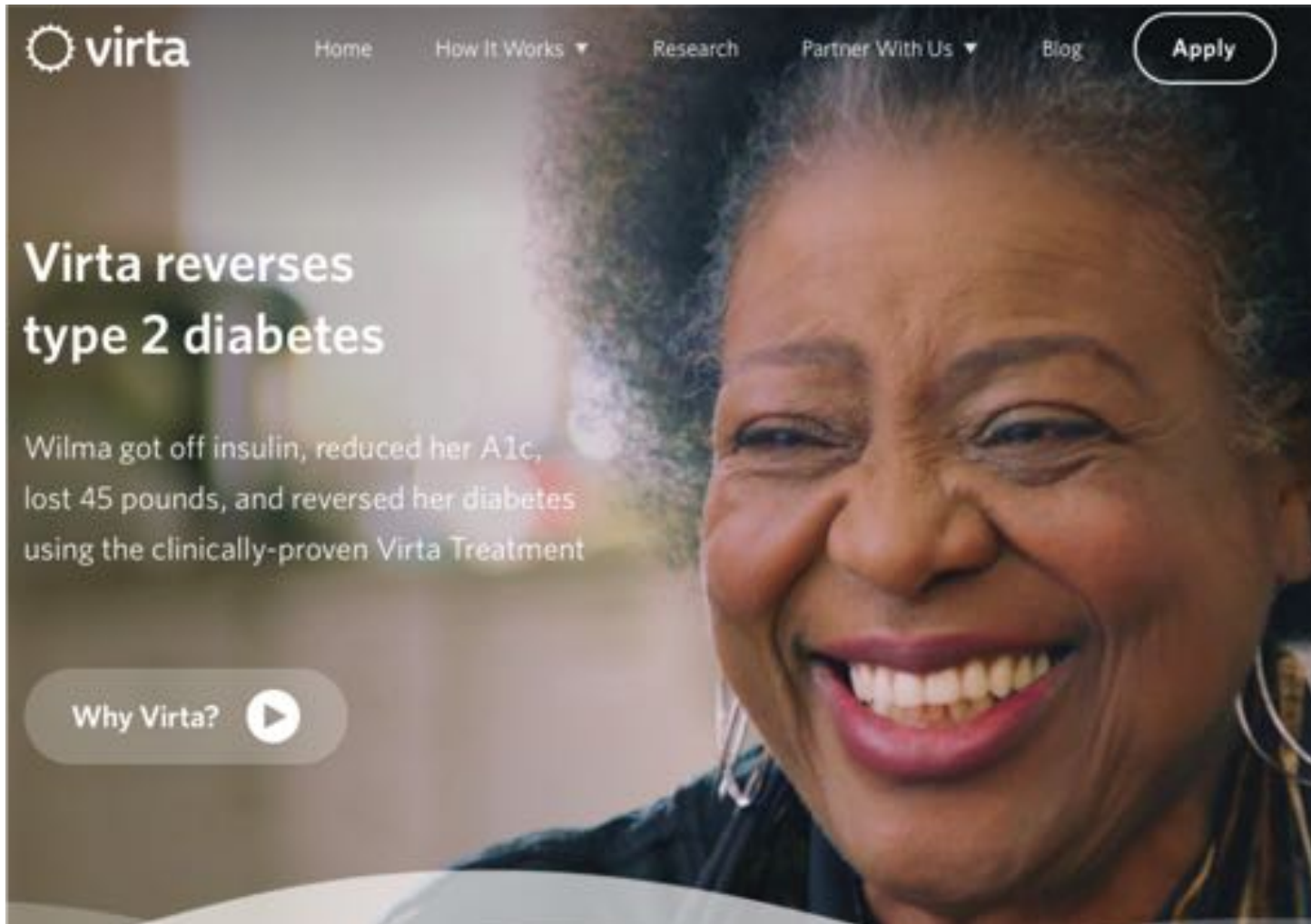




Measuring blood glucose was not always as cheap and simple as it is today. Reportedly, you had to marry a medical doctor to be able to measure your blood glucose.



Recently, Virta Health offered a remote continuous care intervention enabling patients to closely track important measures, access information and their clinical team every day.



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## App Store Preview

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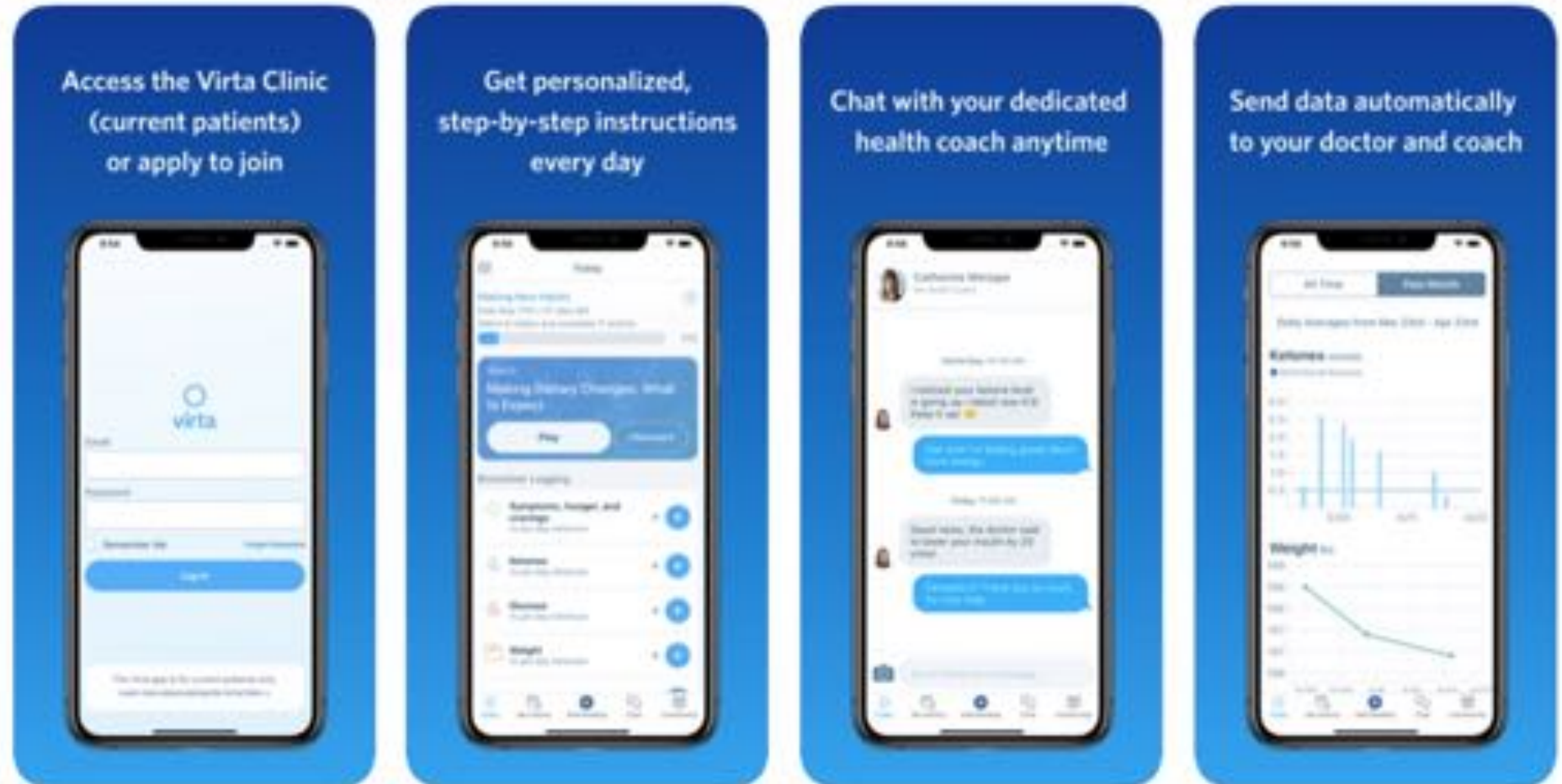
**Virta Health** 17+  
Diabetes Reversal Clinic  
Virta Health

★★★★★ 4.2, 33 Ratings

Free

Recently, Virta Health offered a remote continuous care intervention enabling patients to closely track important measures, access information and their clinical team every day.

### iPhone Screenshots





One of the largest diabetes forums/communities in the World, Diabetes.co.uk, hosts a Low Carb Program, a digital intervention designed to help users to improve health with a low carbohydrate diet.



The Dietdoctor website contains probably everything (and more) about low carbohydrate lifestyle. Some medical doctors even suggested closing their clinic and directing patients there.



# How to reverse your type 2 diabetes

By Adelle Hite, PhD, RD  medical review by Dr. Brett Scher, MD  - Updated November 4, 2019

Earlier this year, Keyto started offering a simple non-invasive method to test breath ketone levels, and track progress in an online community setting. Offers advice on ketogenic diet, incl. plant-based.



ORDER NOW

# Keto 101: The Ketogenic Diet Explained for Beginners

by Jackie C. | Dec 23, 2018

## What is the keto diet?

The keto diet, also known as the ketogenic diet, is a low-carb, high-fat and moderate-protein diet. The goal of the keto diet is to shift in to a nutritional state called ketosis – where your body changes from using carbohydrates to fat to fuel weight loss.

**The key benefits of technology all contribute to better results and greater sustainability of lifestyle changes.**

1. Rapid access to important information and guidance
2. Access to advice from experienced professionals
3. Ability to measure, track, respond, adapt
4. Social aspects – we are in this together
5. Access to troubleshooting advice

**RESULTS AND SUSTAINABILITY**



**6**

## **Medications**

Low carbohydrate diets and also weight loss require a careful consideration of medications to ensure that undesirable side effects can be avoided.

## Clinical Intelligence

Campbell Murdoch, David Unwin, David Cavan, Mark Cucuzzella and Mahendra Patel

# Adapting diabetes medication for low carbohydrate management of type 2 diabetes:

a practical guide

**While dose of some medications will need to be reduced, some medications are better stopped altogether in order to prevent hypoglycaemia, diabetic ketoacidosis or falls due to too low blood pressure.**

### Box 1. Summary guidance on adapting diabetes medication for low carbohydrate management of type 2 diabetes

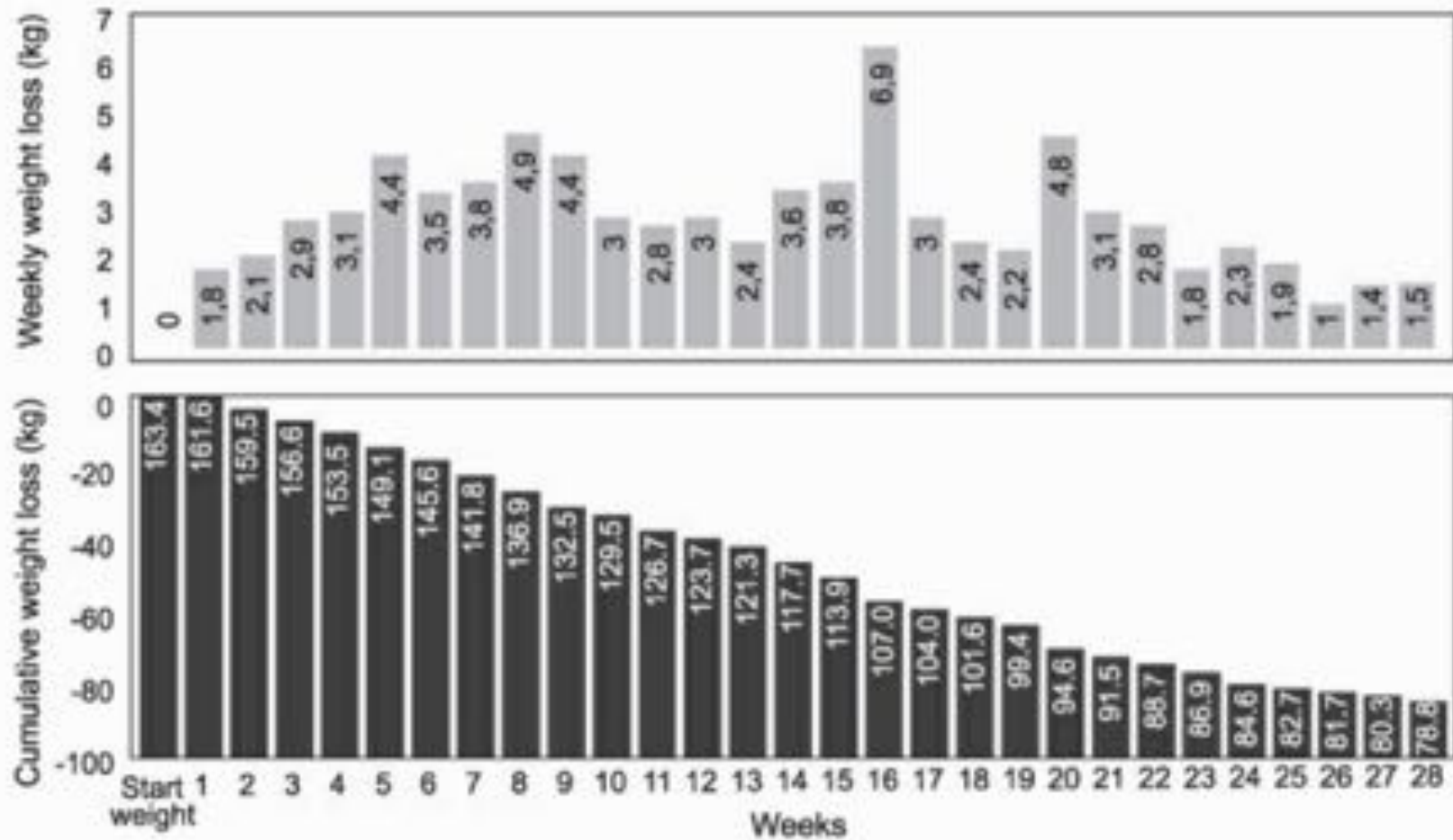
Drug group	Hypo risk?	Clinical suggestion
Sulphonylureas (for example, gliclazide) and meglitinides (for example, repaglinide)	Yes	Reduce/stop (if gradual carbohydrate reduction then wean by halving dose successively)
Insulins	Yes	Reduce/stop. Typically wean by 30–50% successively. Beware insulin insufficiency <sup>a</sup>
SGLT2 inhibitors (flozins)	No	Ketoacidosis risk if insulin insufficiency. Usually stop in community setting
Biguanides (metformin)	No	Optional, consider clinical pros/cons
GLP-1 agonists (-enatide/-glutide)	No	Optional, consider clinical pros/cons
Thiazolidinediones (glitazones)	No	Usually stop, concerns over long-term risks usually outweigh benefit
DPP-4 inhibitors (glipitins)	No	Usually stop, due to lack of benefit
Alpha-glucosidase inhibitors (acarbose)	No	Usually stop, due to no benefit if low starch/sucrose ingestion
Self-monitoring blood glucose	N/A	Ensure adequate testing supplies for patients on drugs that risk hypoglycaemia. Testing can also support behaviour change (for example, paired pre- and post-meal testing)

Note: [Murdoch \(2019\)](#), [Krejci \(2017\)](#)

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## Continuous improvement

The best results can usually be achieved by actively measuring progress and responding accordingly, for example by gradually adding the right type of exercise as appropriate.



**Newly diagnosed patients are more likely to search online, including on social media, to figure out the best options available to them. They are happy to ditch standard advice and go for remission instead.**



**“I am very grateful to my doctor – an excellent coach and a great person – and also to social media. Without Facebook, it might have taken me a few extra weeks or months to find out everything I needed to know about LCHF.”**

Skytte (2019) explored if HbA<sub>1c</sub> and liver fat can be lowered by a dietary change independent of weight loss.

## ARTICLE



## A carbohydrate-reduced high-protein diet improves HbA<sub>1c</sub> and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial

**Methods** The primary outcome of the study was change in HbA<sub>1c</sub>. Secondary outcomes reported in the present paper include glycaemic variables, ectopic fat content and 24 h blood pressure. Eligibility criteria were: men and women with type 2 diabetes, HbA<sub>1c</sub> 48–97 mmol/mol (6.5–11%), age >18 years, haemoglobin >6/>7 mmol/l (women/men) and eGFR >30 ml min<sup>-1</sup> (1.73 m)<sup>-2</sup>. Participants were randomised by drawing blinded ballots to 6 + 6 weeks of an iso-energetic CRHP vs CD diet in an open label, crossover design aiming at body weight stability. The CRHP/CD diets contained carbohydrate 30/50 energy per cent (E%), protein 30/17E% and fat 40/33E%, respectively. Participants underwent a meal test at the end of each diet period and glycaemic variables, lipid profiles, 24 h blood pressure and ectopic fat including liver and pancreatic fat content were assessed at baseline and at the end of each diet period. Data were collected at Copenhagen University Hospital, Bispebjerg and Copenhagen University Hospital, Herlev.

**In terms of macronutrient composition, the experimental diet was compared to a "standard healthy balanced diet".**

12 weeks (2 x 6 weeks in a crossover design)

30 subjects

A) Carbohydrate-reduced high protein diet (CRHP) - CFP 30:40:30

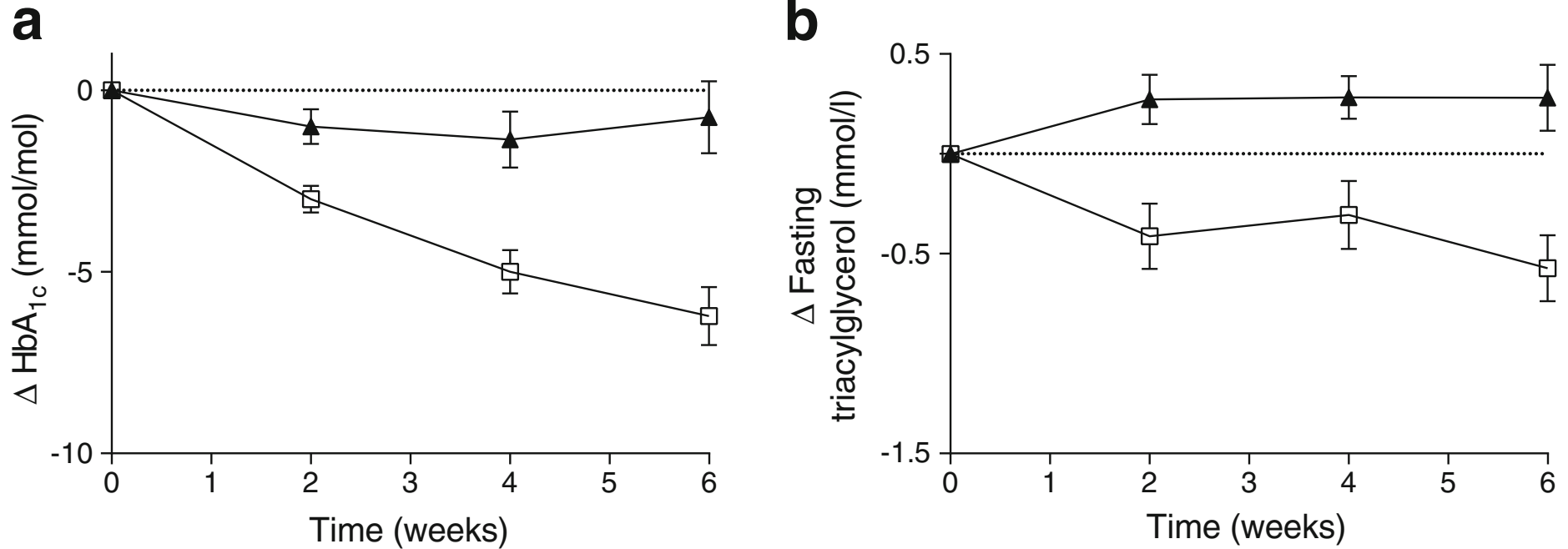
vs

B) Control diet (CD) - CFP 50:33:17

Primary outcome: glycated haemoglobin (HbA1c)

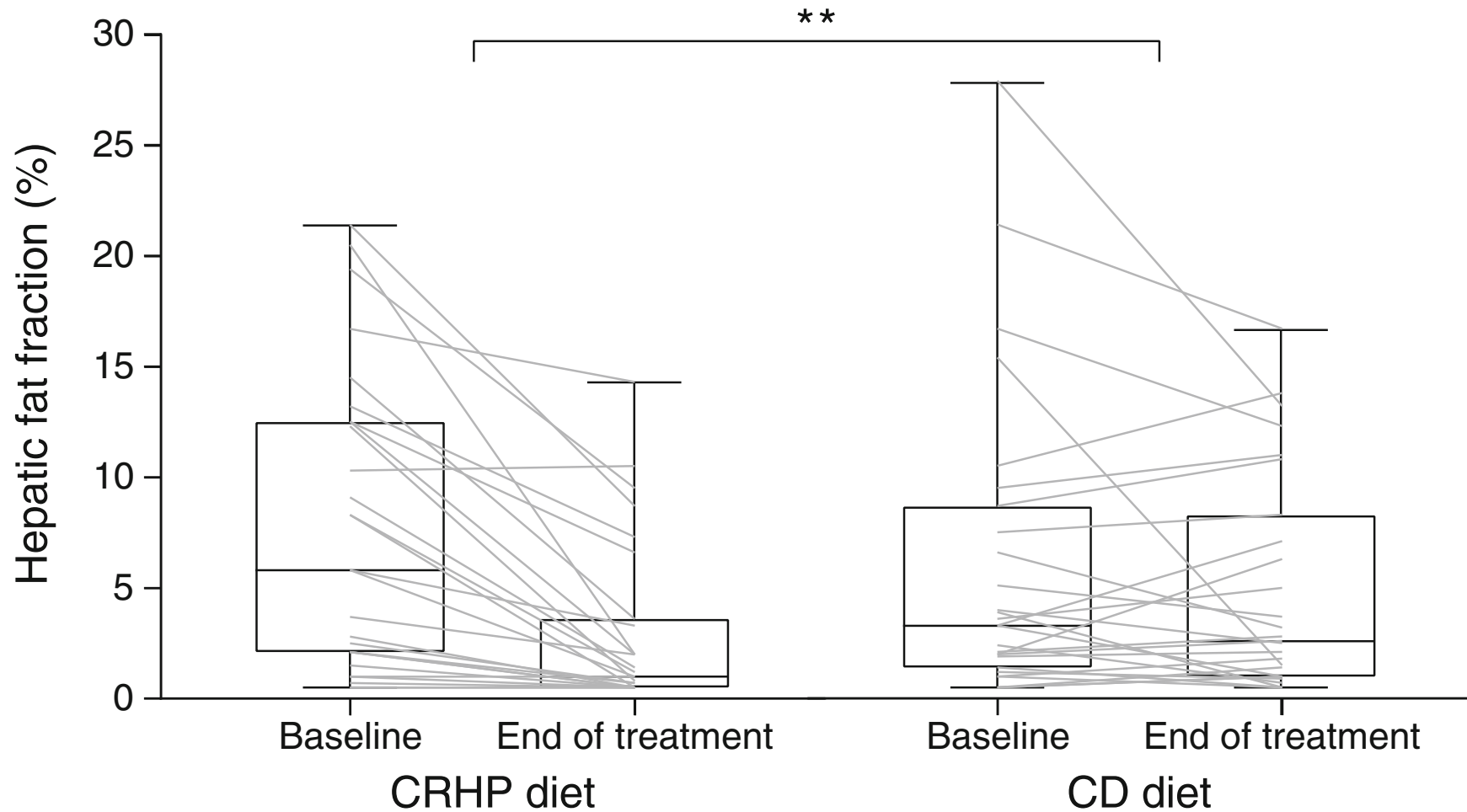


The experimental diet resulted in greater improvements of HbA<sub>1c</sub> and fasting triglycerides.



White squares, CRHP diet; black triangles, CD diet

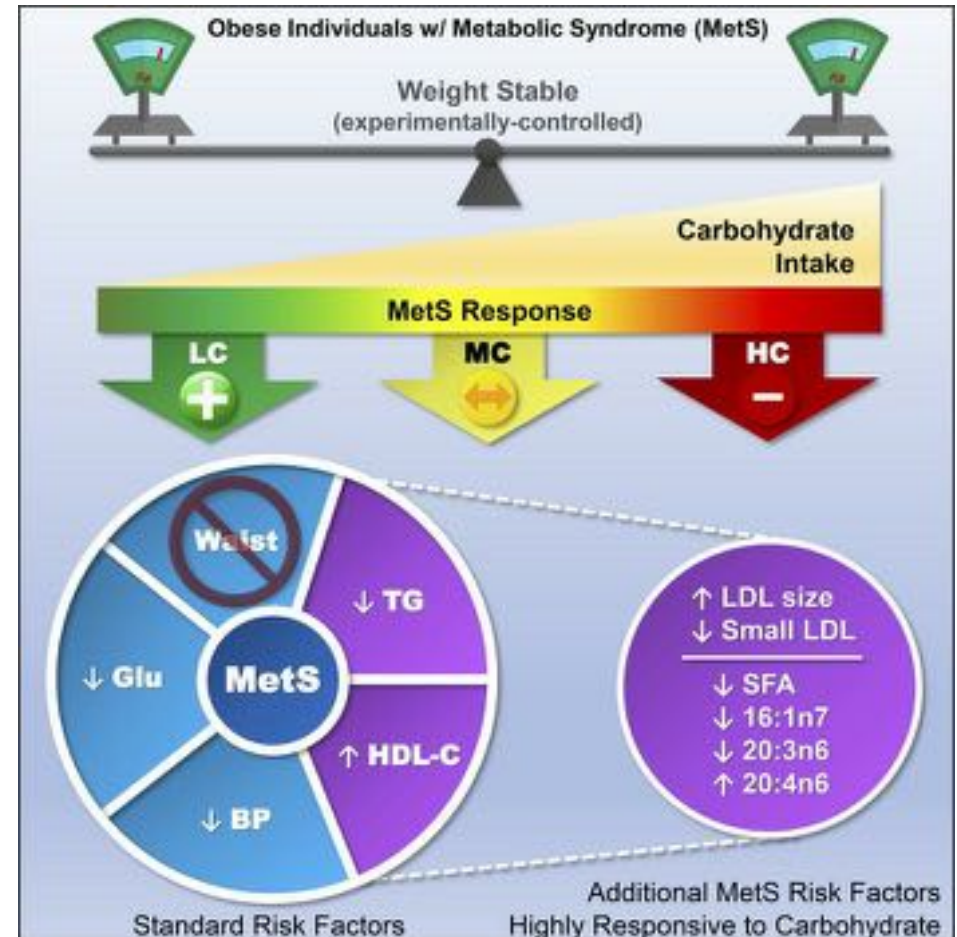
Notably, liver fat dropped significantly more on experimental diet.



Hyde (2019) showed that lower carbohydrate intake has a more beneficial effect on markers of metabolic syndrome in a weight stable scenario.

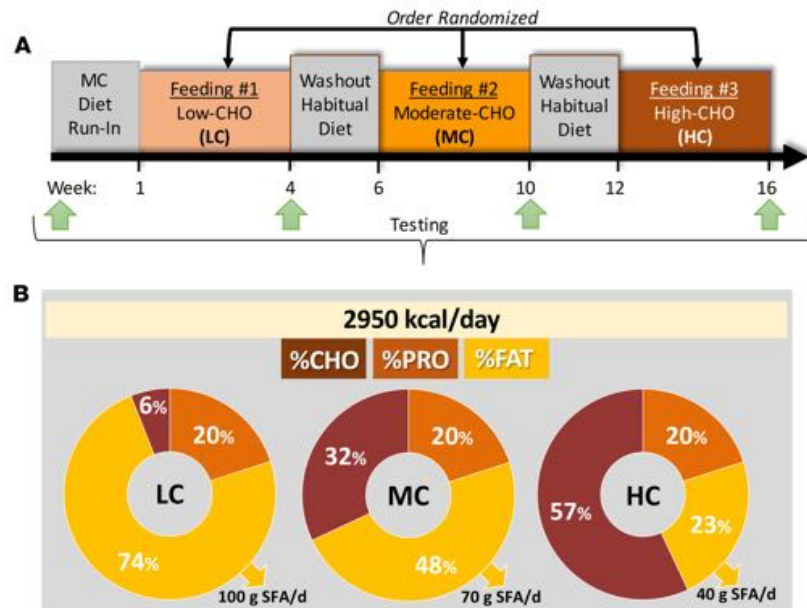
### Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss

Parker N. Hyde,<sup>1</sup> Teryn N. Sapper,<sup>1</sup> Christopher D. Crabtree,<sup>1</sup> Richard A. LaFountain,<sup>1</sup> Madison L. Bowling,<sup>1</sup> Alex Buga,<sup>1</sup> Brandon Fell,<sup>1</sup> Fionn T. McSwiney,<sup>2</sup> Ryan M. Dickerson,<sup>1</sup> Vincent J. Miller,<sup>1</sup> Debbie Scandling,<sup>3</sup> Orlando P. Simonetti,<sup>3</sup> Stephen D. Phinney,<sup>4</sup> William J. Kraemer,<sup>1</sup> Sarah A. King,<sup>5</sup> Ronald M. Krauss,<sup>5</sup> and Jeff S. Volek<sup>1</sup>

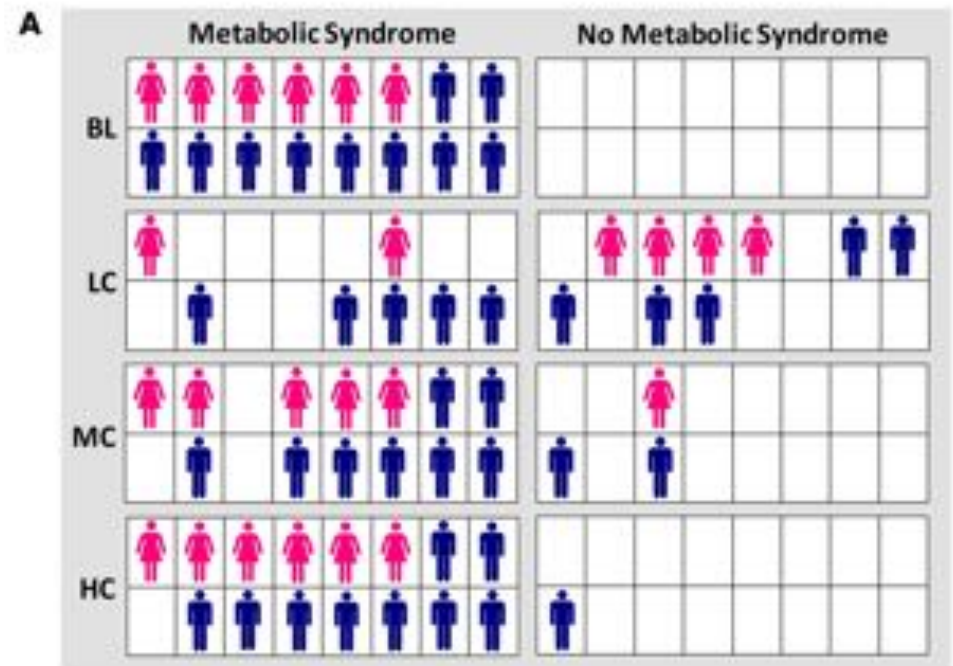


## IMPROVEMENTS WITHOUT WEIGHT LOSS

The study investigated three types of diet with different % of calories from CHO (6-32-57 %) and FAT (74-48-23 %) with PRO constant (20%). The lowest CHO intake resulted in MetS remission in 50 % of subjects.



**Figure 2. Overview of study design and experimental diets.** (A) Experimental approach. (B) Macronutrient distribution and daily saturated fat intake of controlled diets.



**Alpana Shukla works on temporal patterns of food within the same isocaloric meals and their effects on glycaemia. The assumption is that changing food order may be far easier for patients than changing diet.**

Open Access

Original research

**BMJ Open  
Diabetes  
Research  
& Care**

# **Carbohydrate-last meal pattern lowers postprandial glucose and insulin excursions in type 2 diabetes**

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Alpana P Shukla,<sup>1</sup> Jeselin Andono,<sup>1,2</sup> Samir H Touhamy,<sup>1,2</sup> Anthony Casper,<sup>1</sup>  
Radu G Iliescu,<sup>1</sup> Elizabeth Mauer,<sup>3</sup> Yuan Shan Zhu,<sup>4</sup> David S Ludwig,<sup>5</sup>  
Louis J Aronne<sup>1</sup>

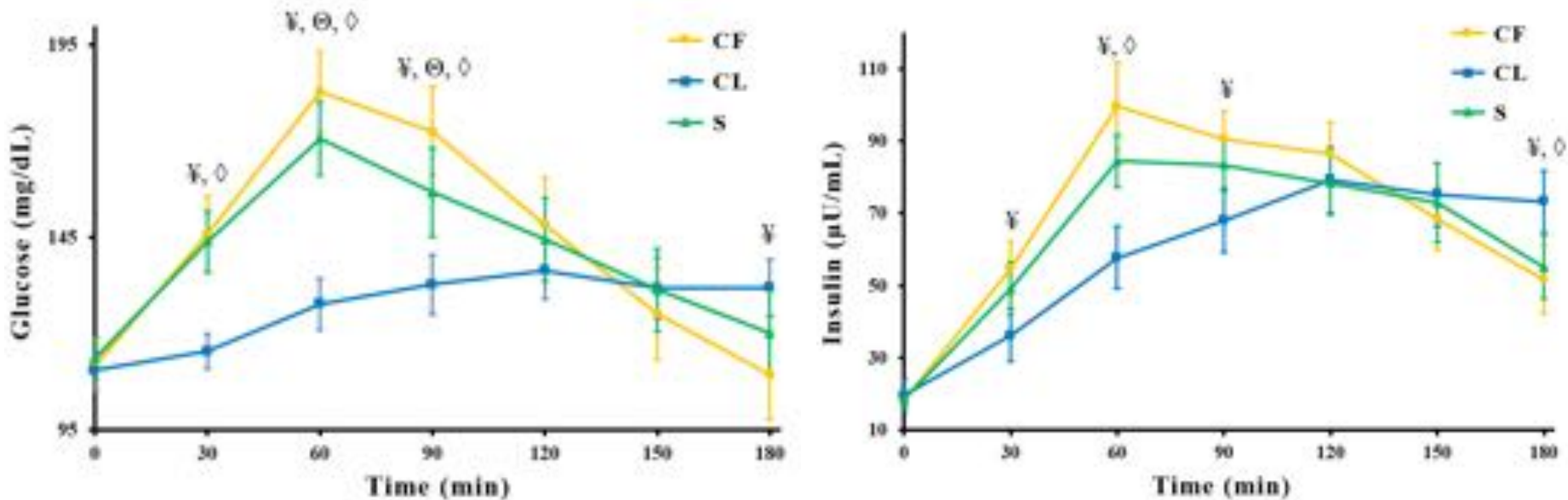
**16 subjects in a cross-over randomised trial consumed identical meals on three separate days one week apart after 12 hour fast.**

**Table 1** Meal composition

Orange juice (no pulp)	120 g		
Ciabatta bread	90 g		
Butter (unsalted)	5 g		
Chicken breast (skinless, flame grilled)	150 g		
Lettuce (Romaine)	45 g		
Tomatoes	50 g		
Cucumber (with skin)	75 g		
Salad dressing (Italian, fat free)	15 g		
Calories (kJ)	Protein (g)	Fat (g)	Carbohydrate (g)
2403.42	55.30	9.62	64.47

1. Carbohydrate first (CF) (ciabatta bread and orange juice) over 10 min, a 10 min rest interval, and then protein (skinless grilled chicken breast) and vegetables (lettuce, tomatoes and cucumber with Italian vinaigrette) over 10 min.
2. Protein and vegetables first over 10 min, a 10 min rest interval, and then carbohydrate over 10 min (carbohydrate last (CL)).
3. All meal components together as a sandwich with each half consumed with half the orange juice over 10 min and a 10 min interval in between (sandwich (S)).

Food order in an identical isocaloric meal affects postprandial glycaemia, insulinaemia and GLP-1, which improves glycaemic control in T2D.



**Table 2** Incremental areas under the curves (iAUCs) (0–180 min) during the three visits

	Time (min)†‡	Carbohydrates first (CF)	Carbohydrates last (CL)	Sandwich (S)
Glucose iAUC (mmol/L×min)*	0–180	372.0±50.2§	173.4±27.8§¶	310.08±46.0¶
Insulin iAUC (pmol/L×min)*	0–180	67850.6±6959.6§	51074.2±6231.7§	61541.0±7295.7
Glucagon-like peptide-1 iAUC (pmol/L×min)*	0–180	763.8±150.0§	1057.4±99.4§	956.1±136.3

Note: [Figure 1 a Table 2 in Shukla \(2017\)](#)

### Food order in an identical isocaloric meal affects postprandial glycaemia, insulinaemia and GLP-1, which improves glycaemic control in T2D.

#### CONCLUSIONS

In this study, we demonstrated that the temporal sequence of carbohydrate ingestion during a meal has significant impact on postprandial glucose regulation. These findings confirm and extend results from our previous pilot study<sup>11</sup>; the inclusion of a third nutrient order condition, a sandwich, had intermediate effects on glucose excursions compared with CL versus CF.

Previous studies investigating the effect of premeal ingestion of whey protein have demonstrated that the glucose-lowering effect is accompanied by an insulintropic response.<sup>6 7</sup> In contrast, our results demonstrate that consumption of protein and vegetables first, followed by carbohydrate, reduces both postmeal glucose and insulin excursions, suggesting that the CL meal pattern **requires less insulin** controlling for carbohydrate amount.

**Modifying the rate of nutrient absorption** is a therapeutic principle of particular relevance to diabetes. A plausible explanation for the attenuated glycemic response observed with the CL meal pattern is delayed gastric emptying and consequently slower rates of carbohydrate absorption, a mechanism that would not be entirely mediated by GLP-1. The finding of lower insulin iAUC in the context of increased GLP-1 excursions contrasts with the effect of protein preloads that augment both GLP-1 and insulin secretion<sup>6 7 12</sup> and suggests a role for vegetable fiber in moderating this response.



**Kahleova (2014) explored if meal frequency during a hypocaloric diet can affect glycaemic control in T2D. The prevailing view had been that patients with T2D should eat 5-6x a day to avoid glucose excursions.**

Diabetologia

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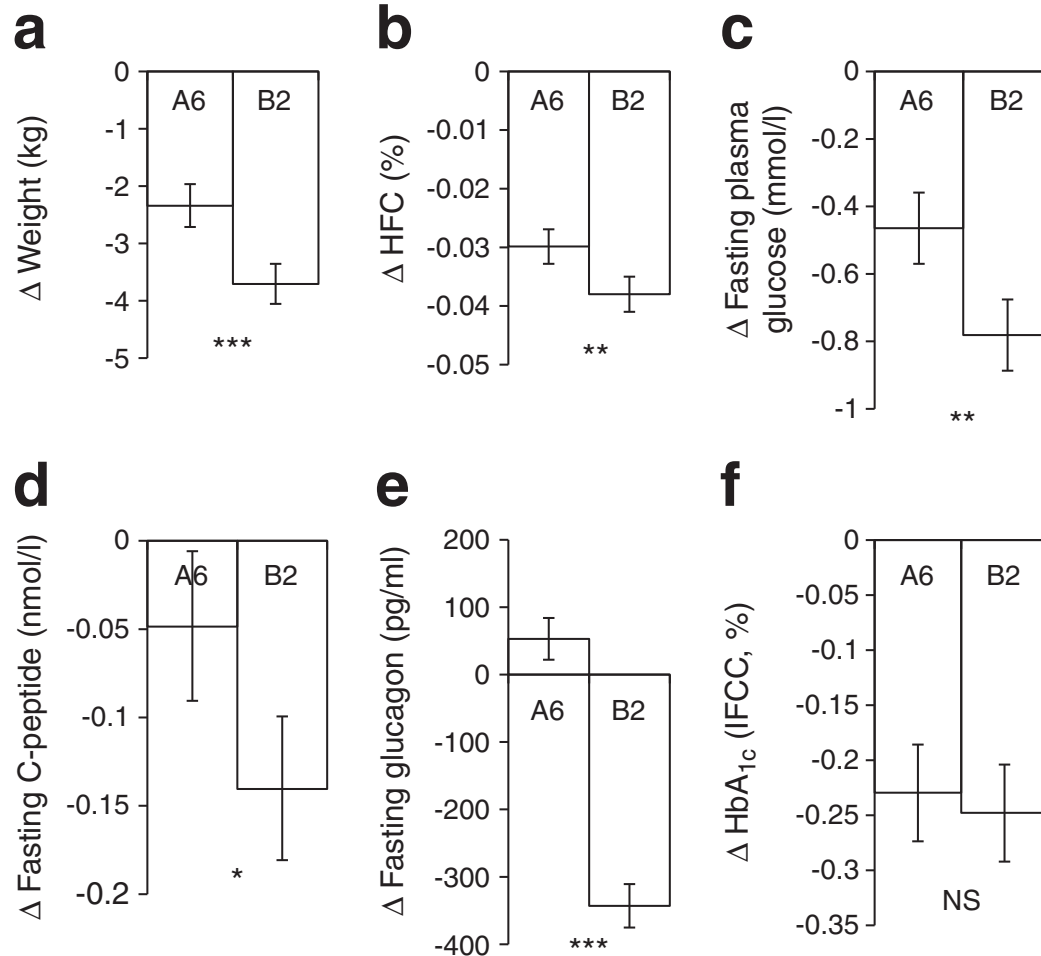
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ARTICLE

## **Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study**

**Hana Kahleova • Lenka Belinova • Hana Malinska • Olena Oliyarnyk •  
Jaroslava Trnovska • Vojtech Skop • Ludmila Kazdova • Monika Dezortova •  
Milan Hajek • Andrea Tura • Martin Hill • Terezie Pelikanova**

Two meals a day resulted in greater weight loss and lower fasting plasma glucose, becoming another piece of evidence that eating 5-6x per day is not necessary.



**More recent studies suggest that low carbohydrate intake, in contrast to common beliefs, does not prevent people from even strenuous and heavy exercise. Top elite athletes are in a different league.**

### **Effects of a 4-Week Very Low-Carbohydrate Diet on High-Intensity Interval Training Responses**

**Lukas Cipryan <sup>1</sup>✉, Daniel J. Plews <sup>2</sup>, Alessandro Ferretti <sup>3</sup>, Phil B. Maffetone <sup>4</sup> and Paul B. Laursen <sup>2</sup>**

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<sup>2</sup> Sport Performance Research Institute New Zealand (SPRINZ), Auckland University of Technology, Auckland, New Zealand; <sup>3</sup> Independent researcher, Stratford Upon Avon, United Kingdom; <sup>4</sup> Independent researcher, Arizona, USA

### **Effects of a 12-week very-low carbohydrate high-fat diet on maximal aerobic capacity, high-intensity intermittent exercise, and cardiac autonomic regulation: non-randomized parallel-group study**

Tomas Dostal<sup>1</sup>, Daniel J. Plews<sup>2</sup>, Peter Hofmann<sup>3</sup>, Paul B. Laursen<sup>2</sup>, Lukas Cipryan<sup>1\*</sup>

### **High Rates of Fat Oxidation Induced by a Low-Carbohydrate, High-Fat Diet, Do Not Impair 5-km Running Performance in Competitive Recreational Athletes**

**Philip J. Prins <sup>1</sup>✉, Timothy D. Noakes <sup>2</sup>, Gary L. Welton <sup>3</sup>, Sarah J. Haley <sup>1</sup>, Noah J. Esbenschade <sup>1</sup>, Adam D. Atwell <sup>1</sup>, Katie E. Scott <sup>1</sup>, Jacqueline Abraham <sup>1</sup>, Amy S. Raabe <sup>4</sup>, Jeffrey D. Buxton <sup>1</sup> and Dana L. Ault <sup>1</sup>**

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**Sleep deprivation can effectively prevent successful weight loss.**

## **Insufficient sleep undermines dietary efforts to reduce adiposity**

**Arlet V. Nedeltcheva, MD<sup>1</sup>, Jennifer M. Kilkus, MS<sup>2</sup>, Jacqueline Imperial, RN<sup>2</sup>, Dale A. Schoeller, PhD<sup>3</sup>, and Plamen D. Penev, MD, PhD<sup>1</sup>**

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**Conclusions—**The amount of human sleep contributes to the maintenance of fat-free body mass at times of decreased energy intake. Lack of sufficient sleep may compromise the efficacy of typical dietary interventions for weight loss and related metabolic risk reduction.

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**Low carbohydrate diet is subject to several legends and myths which lack biological explanation, or are based on misunderstanding of human physiology and nutrition.**

1. Dietary carbohydrate are necessary and basic source of energy for humans.
2. The brains requires glucose, and needs at least 120-130 grams of dietary carbohydrate per day.
3. Insufficient dietary carbohydrate results in ketogenesis, ketone bodies are harmful and their excess can result in ketoacidosis.
4. Low intake of carbohydrate in diabetics increases the risk of hypoglycemia.
5. Carbohydrate restriction results in insufficient intake of nutrients, fibre, vitamins and minerals.
6. Excessive intake of dietary fat results in fat gain.
7. Excessive intake of dietary fat has deleterious effects on lipid profile and increases cardiovascular risk.
8. Excessive intake of saturated fatty acids causes cardiovascular disease.
9. Insufficient stimulation of pancreas impairs its function and results in diabetes.
10. (INSERT ANY RANDOM UNSUBSTANTIATED OR REFUTED ARGUMENT)

8

## Summary

**The primary goal for non-diabetics should be to avoid Type 2 Diabetes in the first place. Once diagnosed, remission should be considered first, typically facilitated by improved diet and weight loss.**

1. Avoid Type 2 Diabetes if you can.
2. When diagnosed, remission should be the first and immediate goal.
3. There are various evidence-based routes to remission (Virta, DiRECT, bariatric surgery).
4. Healthcare professionals and patients should be aware of remission options.
5. If weight loss is not a possibility (eg. lean T2D patients), consider macronutrient changes.
6. Food order. Meal frequency.
7. Move around. Enjoy exercise.
8. Sleep. Sleep well, sleep long enough.
9. Enjoy life. Eliminate stress.







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**For some therapeutic areas – notably epilepsy, obesity and diabetes, there are several longer term RCTs for efficacy and safety, in other areas only non-randomised or pilot studies are available.**



*created 14 June 2017 (JV), edited 9 September 2019*

*(Czech version)*

**This page provides an overview of medical papers and other publications relevant to human physiology in the context of carbohydrate restriction, and to the role of carbohydrate-restricted diets in physical activity and in the treatment and/or prevention of chronic diseases. Although best efforts are taken to keep this overview updated regularly, it is not exhaustive and items are being added on an ongoing basis. For ease of reference, there are separate sections as follows:**

1. Systematic Reviews/Meta-analyses (22 publications, by date)
2. Randomised Controlled Trials (45 publications by date)
3. Other Trials (17 publications, by date)
4. Review papers (16 publications, by date)
5. Monographies and other books (16 items, by author)
6. Disease-oriented overview (31 items, by disease)
7. Extended list of resources (248 items, by author)

**Period covered: 1797 – 2019**

**Total items: 248**

Note: [Neslazeno \(2019\)](#)

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