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Prolonged remission followed by low insulin requirements in a patient with type 1 diabetes on a very low-carbohydrate diet

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Summary

The use of a low-carbohydrate diet (LCD) reduces insulin requirements in insulinopenic states such as type 1 diabetes mellitus (T1DM). However, the use of potentially ketogenic diets in this clinical setting is contentious and the mechanisms underlying their impact on glycaemic control are poorly understood. We report a case of a patient with a late-onset classic presentation of T1DM who adopted a very low-carbohydrate diet and completely avoided insulin therapy for 18 months, followed by tight glycaemic control on minimal insulin doses. The observations suggest that adherence to an LCD in T1DM, implemented soon after diagnosis, can facilitate an improved and less variable glycaemic profile in conjunction with temporary remission in some individuals. Importantly, these changes occurred in a manner that did not lead to a significant increase in blood ketone (beta-hydroxybutyrate) concentrations. This case highlights the need for further research in the form of randomised controlled trials to assess the long-term safety and sustainability of carbohydrate-reduced diets in T1DM.

Learning points

- This case highlights the potential of low-carbohydrate diets (LCDs) in type 1 diabetes mellitus (T1DM) to mediate improved diabetes control and possible remission soon after diagnosis.
- Could carbohydrate-reduced diets implemented early in the course of T1DM delay the decline in endogenous insulin production?
- Adherence to an LCD in T1DM can facilitate an improved and less variable glycaemic profile.
- This case suggests that LCDs in T1DM may not be associated with a concerning supraphysiological ketonaemia.

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Background

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder characterised by rapid destruction of insulin-producing pancreatic beta-cells. Approximately 400 000 people have been diagnosed with T1DM in the UK, accounting for around 10% of people living with diabetes (1). Historically, carbohydrate reduction was one of the few effective treatments for T1DM in the pre-insulin era (2, 3). Currently, with the availability of insulin replacement therapy, the strategy has been to match insulin doses to carbohydrate (CHO) intake. This has transformed the life expectancy of patients with T1DM but achieving stable glycaemic control by accurately adjusting the timing and dosage of the insulin administered remains an ongoing challenge. This has been partially mitigated by advancements in continuous glucose monitoring (CGM), insulin pumps, closed loop systems, and education including carbohydrate counting techniques such as DAFNE (i.e. Dose Adjustment for Normal Eating).

A recent trend observed by T1DM healthcare professionals, and an area of growing research interest, is the self-selected patient adherence to an LCD or very low-carbohydrate diet (4, 5, 6). Despite this, there is limited literature specifically investigating carbohydrate reduction initiated in T1DM soon after diagnosis with the aim of altering the expected clinical trajectory of the disease process. The impetus for this case report was provided by anecdotal observations in people with T1DM showing that LCDs were associated with much tighter glycaemic control, and a possible prolongation of the honeymoon period, followed by minimal insulin requirements.

Case presentation

A 37-year-old man with no relevant past medical history, presented to the outpatient diabetes clinic with a 3-week history of polydipsia and blurred vision. Capillary blood glucose was 16 mmol/L and HbA1c was 103 mmol/mol (11.6%) at presentation. Plasma ketone concentrations were 0.4 mmol/L with some signs of dehydration and hypovolemia (Hb: 161 g/L and S-albumin: 48 g/L). He weighed 81.1 kg (BMI: 26.7 kg/m^2) and engaged in regular moderate intensity physical activity. He occasionally drank alcohol and was a non-smoker. Autoimmune diabetes was confirmed by the presence of glutamic acid decarboxylase antibodies (148 U/mL). He was initiated on insulin Levemir with NovoRapid as required. His symptoms improved and after 2 months his HbA1c had dropped to 55 mmol/L (7.2%). However, the patient's perceived glycaemic variability and concern over hypoglycaemic events prompted his own research into carbohydrate-reduced diets for the purpose of improving his glycaemic control.

Investigation

Following his initial diagnosis in March 2017, the patient underwent standard-of-care laboratory investigations at the outpatient clinic. Regular annual routine bloods including full blood count, urea and electrolytes and thyroid function were within the reference range from the point of diagnosis until the present date. The only metabolic abnormality, not diagnostically in keeping with T1DM, was a moderate hypercholesterolaemia at 2 months after diagnosis (total cholesterol 6.9 mmol/L of which LDL-C was 4.8 mmol/L). Routine HbA1c measurements were collected at multiple time points annually (Table 1). In addition, the patient tracked the CHO content of his meals from the point of LCD initiation (September 2017) to ensure his intake was within his targeted range. To better evaluate the metabolic profile of this patient we also asked him to complete a food diary, note daily insulin usage, and take regular measurements of diurnal blood/interstitial fluid glucose and blood beta-hydroxybutyrate concentrations at set daily metabolic intervals for a consecutive 3-day period (June 2021).

Treatment

Within 6 months of diagnosis, a self-directed LCD was commenced (85–100 g/24 h). To start with, he typically consumed ~40 g CHO for breakfast and lunch and 10–20 g CHO for dinner. The patient increased his dietary intake of both fat and protein to remain isocaloric on this dietary regime and his weight remained stable. About 6 months later he continued to reduce his CHO intake to ~15 g/day, which was later confirmed by a 3-day food diary including photographs and analysed by a specialist research dietician (June 2021). An example of the types of food consumed on a typical day can be seen in Table 2.

Outcome and follow-up

The follow-up period from the point of diagnosis is now 6.5 years. With the adherence to a moderate LCD initially (started 6 months after diagnosis of T1DM), followed by an extreme LCD, his HbA1c showed a remarkable temporal improvement: 6.6% (+5 months) and 6.2% (+11 months). The glycaemic control further improved with the more extreme CHO reduction (estimated to be 15 g/day). At this point the patient had completely stopped insulin administration (+16 months after LCD initiation) and initially achieved remission of diabetes. Whilst off exogenous insulin and continuing this dietary regime, his HbA1c was 39–42 mmol/mol (+16 to +27 months) but then rose to 50 mmol/mol (+37 months). He has now resumed a minimal insulin dose, taking ~2 NovoRapid units per day with maintained tight glycaemic control (Table 1). CGM data were not available

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Table 1 A table showing the patient's insulin regime, carbohydrate intake, capillary blood glucose, HbA1c, and C-peptide from the point of diagnosis until the present date.

Timeline			CHO intake		HbA1c	C-peptide
Date*	Description	**Insulin regime**	(g/day)	**CBG**† (mmol/L)	(mmol/mol (%))	(pmol/L)
03/17	Diagnosis	Nil	85–100	7.2–8.9	103 (11.6)	499
05/17		Levemir 4 units BD; NovoRapid PRN	15–85	4.8 – 9.7	55 (7.2)	N/A
02/18	+5 months on LCD	Levemir 4 units BD; NovoRapid PRN	15–85	6.1–7.9	49 (6.6)	N/A
08/18	+11 months on LCD	NovoRapid 2–3 units	15–85	N/A	44 (6.2)	N/A
01/19	+16 months on LCD	Nil	15–85	4.8–5.9	39 (5.7)	N/A
12/19	+27 months on LCD	Nil	15–85	5.0–6.9	42 (6.0)	N/A
10/20	+37 months on LCD	Nil	15–85	3.9–6.5	50 (6.8)	N/A
03/21	+42 months on LCD	Levemir 2 units	15–85	N/A	50 (6.7)	240
06/21	+45 months on LCD	Levemir 2 units; NovoRapid PRN	15–85	N/A	43 (6.1)	N/A
10/21	+49 months on LCD	Levemir 2 units; NovoRapid PRN	15–85	N/A	43 (6.1)	294
08/22	+59 months on LCD	NovoRapid 2 units	15–85	N/A	48 (6.6)	N/A

†Daily range; *Presented as mm/yy.
CHO, carbohydrate; CBG, capillary blood glucose; N/A, data not available.

following his diagnosis and dietary changes. Notably, plasma C-peptide concentrations have been largely maintained during this follow-up period (Table 1). It is unclear whether adherence to an LCD contributed to his preserved endogenous pancreatic function or whether his maintained C-peptide may be the reason why carbohydrate reduction was so effective in achieving tight glycaemic control.

Data from the 3-day metabolic evaluation conducted by the patient demonstrated minimal diurnal variability in glycaemic control with most values in the normoglycaemic range (Fig. 1). The patient also reported a strong perception of being more in control of his diabetes whilst adhering to an LCD, without the need to worry about hypoglycaemia. There were no hypoglycaemic episodes reported whilst adhering to the LCD (Gold score 1). No other noteworthy side effects were expressed by the patient and there was no change in body weight.

Another key question that the 3-day metabolic evaluation aimed to address was whether the physiological nutritional ketosis seen with LCDs in T1DM translates into an increased risk of pathological ketoacidosis (7). The patient had blood beta-hydroxybutyrate concentrations ranging from 0.3 to 1.2 mmol/L during the metabolic evaluation (in total 18 measurements over 3 days). Furthermore, these ketone concentrations appeared to be relatively stable

Table 2 A typical day of eating for the patient with times, description of food intake, and weight of food.

Time	Description of food	**Weight** (g)
09:00	Tea (caffeinated) and milk (full fat)	–/–
10:30	Tea (decaffeinated) and milk (full fat)	–/–
12:45	Steak (rump)	275
	Scrambled eggs (×4) and butter	200
	Mayonnaise	1 tbsp
	Red Leicester cheese	75
13:10	Tea (decaffeinated) and milk (full fat)	–/–
16:09	Tea (decaffeinated) and milk (full fat)	–/–
18:10	Minced beef and taco seasoning (homemade)	400
	Cheese taco shells	100
	Sour cream	3 tbsp
20:20	Tea (decaffeinated) and milk (full fat)	–/–

tbsp, tablespoon.

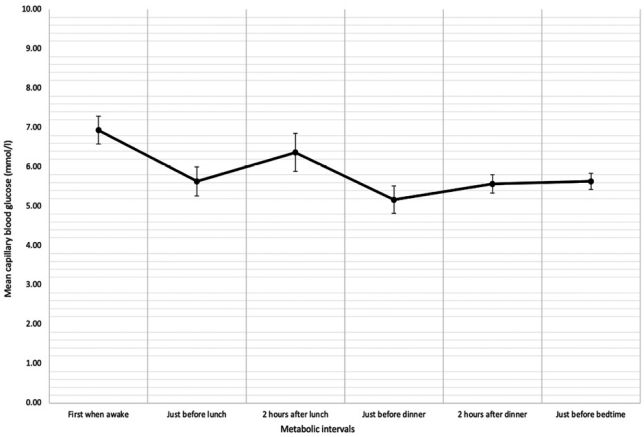

Figure 1

A graph showing diurnal mean capillary blood glucose concentration at key metabolic intervals over a 3-day metabolic evaluation.

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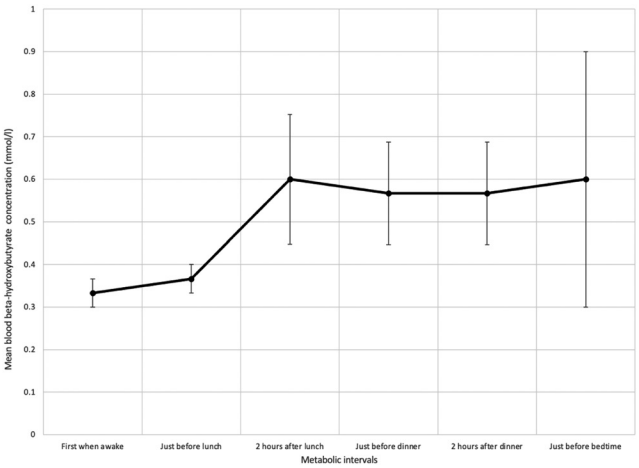

Figure 2

A graph showing diurnal mean beta-hydroxybutyrate concentrations at key metabolic intervals over a 3-day metabolic evaluation.

throughout the day with no concerning spikes that would indicate metabolic maladaptation (Fig. 2).

One concerning aspect of this patient's metabolic adaptation to an LCD was a gradual increase of serum cholesterol with eventual extreme hypercholesterolaemia. Whilst a moderate hypercholesterolaemia (total cholesterol: 6.9 mmol/L) was noted before the self-selected LCD (LDL-C: 4.8 mmol/L, HDL-C: 1.6 mmol/L, triglyceride level: 1.2 mmol/L), his total cholesterol peaked at 10.8mmol/L (LDL-C: 7.7 mmol/L, HDL-C: 1.7 mmol/L, triglyceride level: 2.96 mmol/L) after 16 months on an LCD. Over the 6.5-year follow-up period on an LCD his LDL-C, HDL-C, and triglyceride levels have ranged between 4.7 and 7.7 mmol/L, 1.2 and 1.8 mmol/L and 1.24 and 4.23 mmol/L respectively. These results are concerning, not least because a first degree relative (father) had suffered a myocardial infarction in his 50s. A genetic test for familial hypercholesterolaemia was conducted, but this did not identify a monogenic cause of his hypercholesterolaemia. However, a weak signal for polygenic hypercholesterolaemia was detected using the 12-point LDL-C genetic risk score: he was in the seventh decile of the population distribution. Together, this strongly suggests that his escalating hypercholesterolaemia was attributed to his extreme diet rich in animal-derived fats (saturated fats). The patient was advised to start a statin but was unwilling to do so.

The patient continues to follow an LCD consisting of low CHO/high fat with high protein intake and is very content with quality of life and glycaemic control.

Discussion

This study demonstrates that adherence to a CHO-reduced diet in T1DM could offer an additional therapeutic approach. The patient we have analysed was able to achieve tighter glycaemic control with a reduced insulin requirement, culminating in temporary remission. These changes appear to occur in a manner that did not lead to a concerning, supraphysiological ketonaemia. Whilst the conclusions drawn from this case are limited by its observational nature and scale, other studies of CHO reduction in T1DM are in agreement with our findings (8, 9).

The key question from this clinical case is whether adherence to an LCD has extended this patient's honeymoon period and, if so, how this has been achieved. Indeed, male gender, older age at onset and less severe symptoms at presentation have all been associated with an increased likelihood of clinical remission in patients with T1DM (10). However, the prolonged remission achieved upon dietary intervention in this patient could suggest a role for LCDs in extending the honeymoon period. The LCD reduced the overall insulin requirements and certainly normalised glycaemia. One possibility is that CHO reduction rectifies 'glucotoxicity' leading to beta cell rest and recovery (11). This diet-immune interaction may be implicated in the downregulation of autoimmunity and induction of subsequent immune tolerance. This effect may have been exacerbated by implementing dietary carbohydrate reduction soon after diagnosis, a time when endogenous beta cell function is at its most preserved in the course of the disease. Furthermore, LCDs have also been associated with increased production of the incretin hormones including GLP-1 (12), which increase insulin sensitivity and inhibit glucagon secretion. Thus, LCDs in T1DM may facilitate increased production and sensitivity to gut hormones which could have mitigated the diabetes progression seen in this patient. The lack of glucose spikes (as a result of the more stable glycaemic profile) may have reduced both the number and intensity of signals for endogenous insulin secretory events. Of course, the counter argument to this is that exogenous insulin administration (i.e. conventional therapy) should also reduce demands for endogenous insulin production, but may not reduce glycaemic variability to the same degree.

The earlier diagnosis of T1DM in adults may provide a window of opportunity to intervene and achieve temporary normoglycaemia. Our case highlights how LCDs in T1DM not only provide a safe approach to achieve glycaemic targets but also that dietary intervention initiated soon after diagnosis may maximise this therapeutic benefit.

Interestingly, our patient reported that adherence to an LCD has given him a perception of greater freedom over his dietary choices and eliminated the requirement for CHO counting. Even though this intervention involved the near-complete removal of a macronutrient group, he reported a feeling of positive liberation over his choice of food groups containing protein and/or fat. The increased quality of life reported by the patient is in itself an impetus for further research into LCDs in T1DM.

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With regards to the safety and sustainability of this dietary approach, one concern that remains is whether LCDs in T1DM can harmfully affect lipid profiles (13). Whilst this patient had a concerning lipid profile even prior to adopting the LCD, it is very likely that this dietary intervention exacerbated his hypercholesterolaemia. The lipid profile seen in our patient raises two important questions. First, whether his hypercholesterolemia and raised LDL-C secondary to dietary carbohydrate reduction would be the typical response of most individuals with T1DM and secondly whether this response translates to adverse cardiovascular risk. Of course the sample size ($n=1$) and duration of follow-up (6.5 years) limits our ability to conclusively answer these questions. Nonetheless, it is important to recognise that LDL-C has limited utility as an independent predictor of cardiovascular events relative to interpreting a full lipid panel (including total cholesterol, LDL-C, HDL-C and triglyceride levels) which can provide a more comprehensive picture of the metabolic adaptation taking place in the context of an LCD in T1DM. One important point to raise from the literature is the lipid energy model in the context of the lean mass hyper-responders (LMHRs) (14) hypothesis. In some lean metabolically healthy subjects, elevated lipoprotein lipase mediated turnover of VLDL has been shown to produce elevated LDL-C, elevated HDL-C, and low TGs. Management of raised LDL-C in individuals adhering to LCDs remains a contentious field, however a growing body of evidence suggests that a default to a statin prescription purely due to a high LDL value, which is independent of a genetic/familial predisposition, may not be appropriate. Indeed, a more comprehensive understanding of LCDs and lipidology has revealed that statin therapy in individuals on an LCD with elevated LDL-C and non-atherogenic lipid profiles (low triglyceride–HDL-C ratios) may not be warranted for primary and secondary prevention of cardiovascular disease (15). Further research in the form of randomised controlled trials, specifically investigating the long-term effects of CHO-reduction on T1DM lipid profiles is certainly warranted, with an emphasis on cardiovascular outcomes.

Finally, the macronutrient and micronutrient content of our patient's diet and quality of food intake is an important point of discussion as there is significant scope for it to be optimised. The saturated fat content of his diet is particularly high and certainly has room for reduction whilst still meeting the requirements of carbohydrate reduction. This would likely mitigate, at least to some degree, his raised LDL-C (16). Furthermore, the diet of our patient is largely devoid vegetables and fibre, both of which are widely recognised to reduce cancer risk and mortality in epidemiological studies (17, 18).

To conclude, this case highlights how the prolongation of normoglycaemia following the diagnosis of T1DM may be increased by adherence to a CHO-reduced diet. This form of medical nutrition therapy may be a means of achieving temporary remission in T1DM and stabilised glycaemia.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
HO and FK researched data, contributed to discussion and wrote, reviewed, and edited the manuscript. PD provided diet and nutrient evaluations. GT, PD, and PG contributed to discussion and reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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