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Nutritional ketosis is well-tolerated, even in type 1 diabetes: the ZeroFive100 Project; a proof-of-concept study

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Purpose of review

The objective of this study was to test the feasibility of exercising over a 5-day period while fasting, in those with and without type 1 diabetes mellitus (T1DM).

Eight individuals, ages 29–62 years, two with T1DM, walked/ran around 20 miles per day for five consecutive days while only consuming water. All eight individuals completed the project with no physical injuries or problems with diabetes control. The blood glucose levels ranged from less than 3 mmol/l to 7 mmol/l in those without T1D, and less than 3 mmol/l to 9 mmol/l in those with T1D. The continuous glucose traces in those with T1D showed little variability in glucose levels. The participants without T1D had no symptoms from blood glucose under 3 mmol/l. Ketone levels ranged from 0.3 to 7.5 and the ketones for those with T1D were no different to ketones in those without T1D. The respiratory quotient was overwhelmingly in the fat-burning range. There was very little subjective hunger, nor did it negatively affect mood. In keto-adapted individuals, with or without T1DM, prolonged exercise for 5 days while in nutritional ketosis was feasible, and well tolerated.

Recent findings

Eight adults, ages 28–62 years, trained for and completed a 5-day zero calorie fast covering 100 miles over 5 days. Training involved each individual preparing for the event according to their own programme. Typically, it involved both cardiovascular and strength training with the addition of practice water only fasts over 24–72 h or more based upon the individual's assessment of what was needed to complete the event. There was no formal protocol provided for this. The recommendation was that the participants would be keto adapted and trained to a level sufficient to complete the 5-day event. Keto adaptation was measured by ketone blood testing of betahydroxybutyrate. Two people had type 1 diabetes. All but one person was keto-adapted ahead of the event. All eight individuals completed the project with no physical injuries or problems with diabetes control. Prolonged fasting did neither lead to hunger nor did it negatively affect mood, which, if anything, was enhanced in most individuals. All keto-adapted people were shown to be burning fat stores throughout the 5 days, and everyone was measured to be in a state of nutritional ketosis. In type 1 diabetes, and ketones were in the same range as those without diabetes, insulin volumes were considerably reduced, and glucose control was close to physiological: nutritional ketosis is not a risk factor for diabetic ketoacidosis; consumption of sugar for energy is not required for distances of up to 100 miles in keto-adapted people; people who inject insulin do not necessarily need to consume carbohydrates unless rescuing a hypoglycaemic attack.

Summary

The findings from this project should provide reassurance to those clinicians who want to provide the option of a ketogenic lifestyle to their patients with type 1 diabetes. They also confirm that the fat stores are available for aerobic respiration without apparent negative consequences on physical or mental function.

Video abstract

http://links.lww.com/COE/A24.

Keywords

fasting, fat burning metabolism, ketogenic, ketogenic diets in type 1 diabetes, nutritional ketosis, type 1 diabetes, zerofive100

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KEY POINTS

- People do not need to consume carbohydrates for energy for distances of up to 100 miles.
- People who inject insulin for type 1 diabetes management do not need to consume carbohydrates just because they are injecting insulin unless they need to rescue a hypoglycaemic episode.
- Nutritional ketosis is not a risk factor for diabetic ketoacidosis.

INTRODUCTION

It is common to find advice on sport for people with type 1 diabetes that is solely focussed on carbohydrate consumption and insulin management [1–3]. The current dietary guidelines for the UK produced by Scientific Advisory Committee on Nutrition recommend that the macronutrient components for a healthy human diet are 50% energy from carbohydrates, 15% of energy from protein and 35% of energy from fat, with 10% or less of the fat being in the form of saturated fat. A recommendation was made to reduce refined sugars only [4]. DiabetesUK recommends avoidance of ketosis levels in sport that would be normal in someone who is in nutritional ketosis a result of a ketogenic lifestyle [1]. Over the past 5 years, there has been increasing interest in managing metabolic diseases with reduced carbohydrate diets. There has now been sufficient research to show that low carbohydrate diets can aid remission of type 2 diabetes, reverse prediabetes and nonalcoholic fatty liver disease [5–9]. At very low carbohydrate levels, it can improve control in type 1 diabetes [10,11]. A major and influential charity, DiabetesUK, states that there is insufficient research to incorporate low carb as a recommendation in type 1 diabetes [12]; however, other organisations take a different view based on other evidence [8]. Current dietary recommendations are for around 250 g of carbohydrates per day [13]. Low carbohydrate for research purposes is 100–150 g of carbohydrate a day and very low carbohydrate diet is below 50 g of carbohydrates per day.

Low carbohydrate and high carbohydrate diets have fundamentally different effects on metabolism and also many biomarkers of health and disease. It is not always the case that one can transfer evidence from one type of metabolism to another [14▪].

But this has led to assumptions around the safety of low carbohydrate diets that are not necessarily valid.

One such assumption, often requoted anecdotally by patients recalling diabetes clinic advice in personal contact and through online forums is that nutritional ketosis is a risk factor for diabetic ketoacidosis. In fact, in a poll of 300 dietitians at the 2020 Nutricia conference, one-third still believed this to be true (this was a private vote during the presentation [15]). Anecdotally, this remains a significant barrier that prevents clinicians from adopting low carbohydrate diets for their patients, and clearly, they have clinical safety in mind. But the metabolic mechanisms of nutritional ketosis and diabetic ketoacidosis are different. Ketones will be scarce in a high carbohydrate diet but abundant in nutritional ketosis at a level well below diabetic ketoacidosis.

People who practice keto lifestyles are often cautioned that ketones are a sign of starvation and a risk for diabetic ketoacidosis in those with T1D (see DiabetesUK advice on sport in type 1 diabetes) [1].

A finding from an online survey of people with T1D on a keto diet shows that half were actively advised against this lifestyle, presumably on the grounds of clinical safety [16].

One almost universal assumption about energy transfer is that one needs to consume sugar or carbohydrates to fuel the body during exercise [3,17]. This cannot be refuted with a simple answer as it is true that anaerobic exercise absolutely requires glucose. Specific neural tissues have a reliance on glucose. As they are devoid of mitochondria, erythrocytes rely on glucose metabolism through enzymes located in the cell membrane.

In these situations, glucose can be synthesized through gluconeogenesis from liver glycogen, glucogenic amino acids and the glycerol component of triglycerides.

In all other situations, glucose can be replaced by the metabolism of fat.

Glucose will always be metabolized ahead of fat if carbohydrates are consumed. This is because glucose is a relatively toxic substance and needs to be rapidly metabolized into ATP or stored as glycogen and fat. There is the equivalent of only one teaspoon of glucose in the whole blood volume required to maintain normoglycaemia. So, glucose homeostasis is maintained within tight margins.

The stores of glucose as glycogen are small compared with the fat stores. A well trained athlete will have around 2400 calories or more of glycogen stores [17]. This compares with over 100 000 calories of energy stored as fat in an average weight individual [18].

Research shows that fatty acid oxidation during aerobic exercise enables a high level of muscle function. An increasing number of athletes rely on fat-burning metabolism and are successful in many types of endurance competitions [19,20▪].

Anecdotally one hears clinicians equating fat burning with starvation. Fat is indeed burned during periods of fasting. But to define healthy metabolic fat burning as starvation is not accurate. Actual starvation begins when glycogen cannot be replaced by glycerol or visceral proteins. Muscle protein will then be used to cover the shortfall [21▪▪,22].

The vast fat stores are often quoted in presentations on low carbohydrate lifestyles. It seemed essential to prove that this was true in practice. The reason for this project in part was to examine the fat store potential.

The final assumption that causes concern amongst clinicians caring for people with T1D is that if one takes insulin, one needs carbohydrates to counter insulin's effects. It is an argument used to discourage time-delayed eating in T1D. In T1D, there will be occasions when insulin causes hypoglycaemia, which has to be managed with glucose as a matter of urgency. But in all other scenarios, if the dose of insulin is optimized, carbohydrates are unnecessary.

This project was designed to demonstrate that carbohydrates can largely be dispensed by people who use a ketogenic diet to control their diabetes. To date, we think this project is unique. Intermittent fasting, religious fasting and time-delayed eating are not new concepts. One review study looked at variations of fasting in both obese and nonobese individuals. The trials were neither seemingly performed using any form of ketogenic diet nor were the fasting periods were as long as the one used in this time-delayed eating experiment. Therefore, the conclusions from this article cannot necessarily be applied to the findings presented here [23].

METHODS

Eight individuals volunteered to take part in the project. They were a selected sample of friends and colleagues who had a good knowledge of the theory and practice of ketogenic diets and lifestyle. The ages ranged from 28 to 62 years. Two of the group had T1D managed by pen injection.

Each individual was asked to develop their own training plan, include periods of fasting, and ensure that they were adapted to a fat-burning metabolism. There was no training protocol but a discussion group based around What's App, with several specialists in metabolism and sport contributing to the discussion.

Each participant was provided with glucose-measuring equipment, both a finger prick device and continuous glucose meter (CGM) [24,25]. They also had blood ketone-measuring instruments to measure ketones twice a day [24]. Metabolism was measured using an Ecal breath analyser to measure respiratory gases [26]. Morning salivary cortisol was measured before the test to improve the accuracy of the result.

Weight was measured before and after the 5-day event in the clothes used for running without footwear.

Simple mood and hunger scores were recorded daily. Participants each had mobile phones, and apps for accurate location, in case safety issues arose. Transport was available for emergencies, and medical assistance was available. Essential first aid equipment was provided.

The event took place between Henley on Thames and Bristol in the UK along flat trails, mostly following the gravelled towpath of the Kennet and Avon Canal. Each individual adopted their own strategy and some chose to meet in groups, some to travel alone. The endpoint of each day was a hotel where a small amount of distanced socializing was possible limited by the coronavirus disease-2019 (COVID-19) restrictions in place at the time. Each member of the group carried a mobile phone and sufficient supplies of water. They had two location-tracking devices available. A basic medical pack was provided on the transport back-up vehicle, where water was made available. Medical support was available, consisting of both participants and medically qualified support crew. In that way, support was provided at multiple points on each daily route. The 100 mile distance was roughly divided into 5 equal segments of 20 miles, but accommodation en-route was also prioritized wherever possible. This gave participants flexibility around route planning and minimized, potentially, long waits for others to catch-up.

RESULTS

The metrics of the participants were as follows: age range 28–62 years, average 46 years. Ethnicity seven white, one preferred to be described as 'other'. Female participants two, male participant six. BMI of participants ranged from 20.9 to 32.7 kg/m^2, average 24.75 kg/m^2. Weight range 64–106 kg, average 80.7 kg.

All eight participants completed the project without incident. Respiratory quotient analysis was done by the scientific team from the company that supplied the equipment. Their report concluded that in seven out of the eight cases, fat-burning predominated (Fig. 1). The person whose data was less clear was an Olympic athlete who had spent a lifetime on a carbohydrate-loading diet and entered the project late. It is likely that in this case, fat adaptation was not complete. All eight participants' ketone levels were in nutritional ketosis

62 yrs - 182cm							
Day	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	74	2097	0.61	15.91%	5.98	1.17	3.40%
Day two		2520	0.72	15.70%	4.8	1.67	4.06%
Day three		2019	0.7	16.33%	6.75	1.12	3.52%
Day four		1662	0.59	14.93%	4.54	1.04	3.96%
Day Five	70.5	2259	0.78	16.34%	7.21	1.17	3.82%

35yrs - 183cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	80	3402	0.68	15.02%	6.65	1.46	4.34%
Day two		1922	0.55	14.29%	7.28	0.66	4.10%
Day three		2527	0.53	14.73%	8.13	0.83	3.73%
Day four		2209	0.66	15.56%	8.57	0.82	3.87%
Day Five	77.1	1988	0.65	15.53%	9.28	0.67	3.88%

44yrs - 176cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	64	2380	0.68	16.88%	12.9	0.76	3.68%
Day two		2673	0.55	16.72%	14.31	0.74	3.62%
Day three		2511	0.53	17.11%	16.56	0.66	3.07%
Day four		2160	0.66	16.63%	11.87	0.72	3.46%
Day Five	61.3	2032	0.65	16.80%	14.36	0.65	3.33%

47yrs - 190cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	80	2681	0.78	16.15%	9.95	0.93	3.99%
Day two		2711	0.74	16.54%	12.21	0.84	3.52%
Day three		2337	0.7	16.38	10.65	0.81	3.45%
Day four		1884	0.69	16.50%	9.94	0.72	3.33%
Day Five	75.5	2522	0.74	16.58%	10.77	0.74	3.46%

53yrs - 168cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	65.3	2059	0.73	15.39%	5.67	1.08	4.30%
Day two		1685	0.54	15.82%	6.76	0.81	3.10%
Day three		1576	0.63	15.67%	6.93	0.73	3.65%
Day four		1869	0.74	16.33%	7.12	0.96	3.67%
Day Five	62.3	2042	0.94	17.24%	8.66	1.07	3.57%

48yrs - 192cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	92.5	2999	1.02	17.07%	2.3	5.67	3.99%
Day two		2438	0.64	14.81%	3.04	2.99	4.32%
Day three		1793	0.52	14.23%	7.52	1.68	3.89%
Day four		3548	0.71	16.10%	2.34	5.3	3.72%
Day Five	86.2	2672	0.91	16.66%	2.44	4.3	4.03%

54yrs - 173cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	84.3	3031	1.06	17.27%	14.49	0.94	3.91%
Day two		2829	0.83	16.74%	12.5	0.89	3.68%
Day three		2833	0.88	17.16%	15.08	0.83	3.47%
Day four		2768	0.85	17.14%	8.55	1.45	3.42%
Day Five	80.02	2940	0.73	16.08%	6.56	1.56	3.84%

29yrs - 180cm							
	Weight	RMR	RQ	FEO2	RR	Vol Ex	CO2
Day one	106	2978	0.73	15.64%	15.03	0.62	4.18%
Day two		2334	0.73	15.96%	10.92	0.72	3.93%
Day three		2624	0.78	16.57%	9.98	1	3.65%
Day four		2765	0.85	17.22	11.88	1.06	3.31%
Day Five	101.6	2566	0.71	16.36	7.76	1.22	3.52%

FIGURE 1. Respiratory quotient (blue bars) and serum cortisol (orange line) for each participant. respiratory quotient 0.7 is fat burning, 1.0 glucose burning metabolism.

range throughout, and levels in those with T1D could not be distinguished from those without that condition (Fig. 2).

This was expected, considering that fat was the fuel used, and ketone bodies are the inevitable consequence of burning fat.

Glucose reports were of particular interest. In both people who had T1D, the 5 days' glucose levels were very close to physiological. Each person with T1D reported a reduction in insulin volumes required. One person chose to stop basal insulin in favour of frequent bolus doses, the other reduced basal and used bolus insulin for fine control. In both cases, insulin volumes reduced considerably. In the author's case, daily insulin dropped to 6 units/day compared with 20 units/day on a typical keto diet (Figs. 3 and 4).

One unexpected finding was that the two people who wore a CGM but did not have diabetes regularly recorded asymptomatic low glucose levels for significant amounts of time. In one case, this was 30% of the time. It did not affect their mental or physical performance (Figs. 5 and 6).

Psychometric testing was performed on mood and perception of hunger (Figs. 7 and 8). Training sessions suggested that psychological adaptation to time-delayed eating was something that could improve with training. However, it was a surprise to find that mood was elevated, and hunger suppressed for the event's duration in all participants.

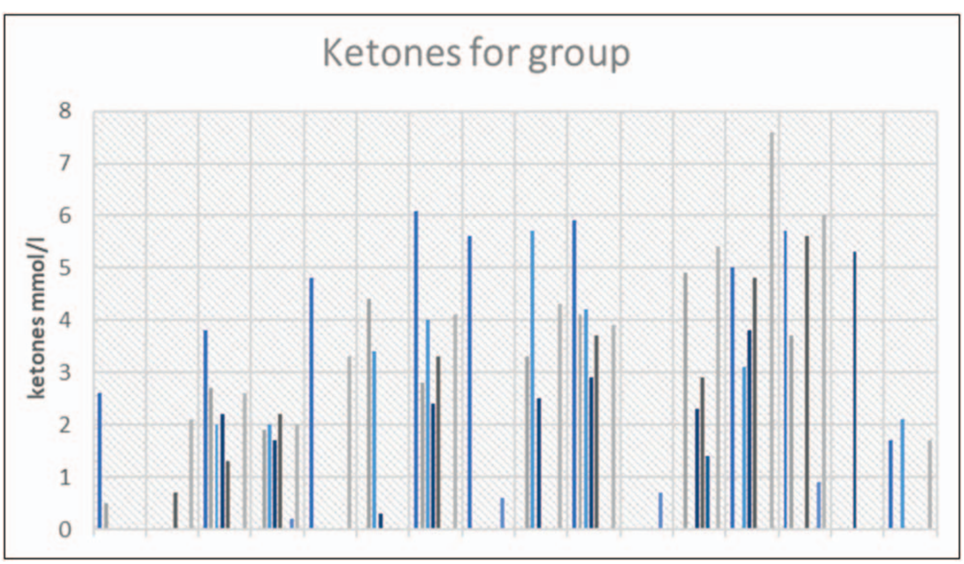

FIGURE 2. Ketone levels from day 1 to day 5; all participants. It is impossible to separate out those with type 1 diabetes.

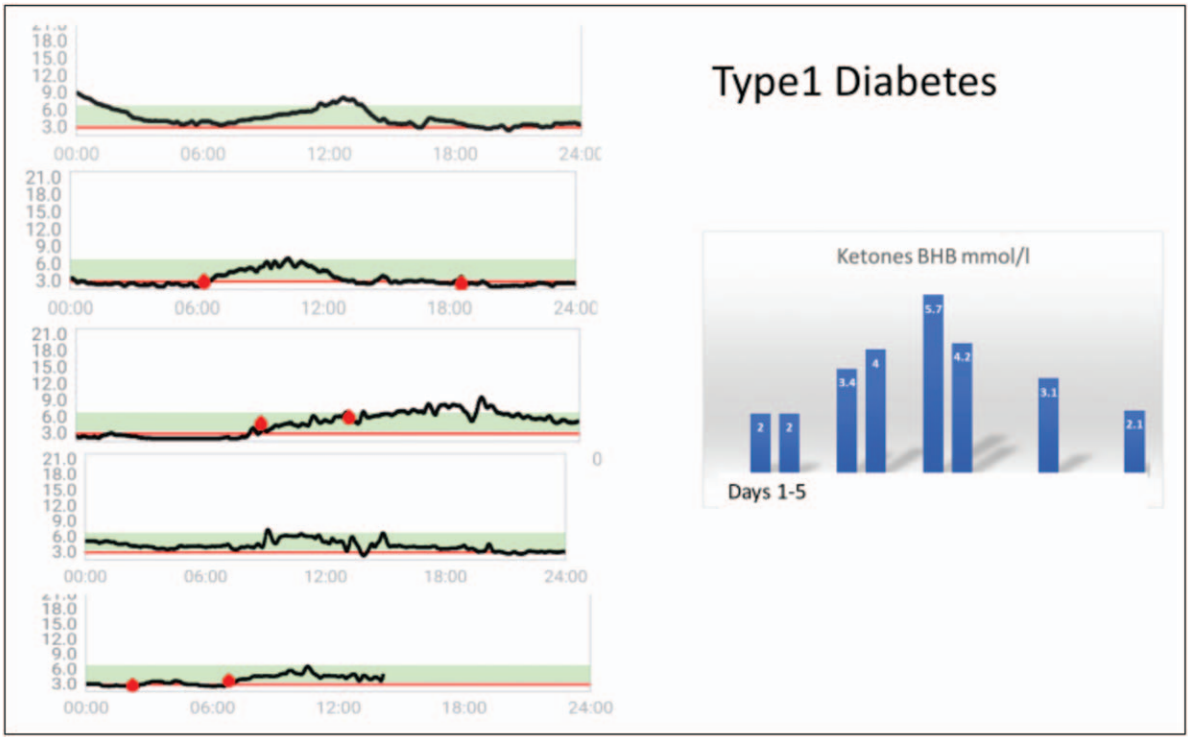

FIGURE 3. CGM trace of participant 1 with type 1 diabetes. CGM trace and ketone levels in both participants with type 1 diabetes showing near normal glucose traces throughout the whole duration of the project and levels of ketones in the nutritional ketosis range. CGM, continuous glucose meter.

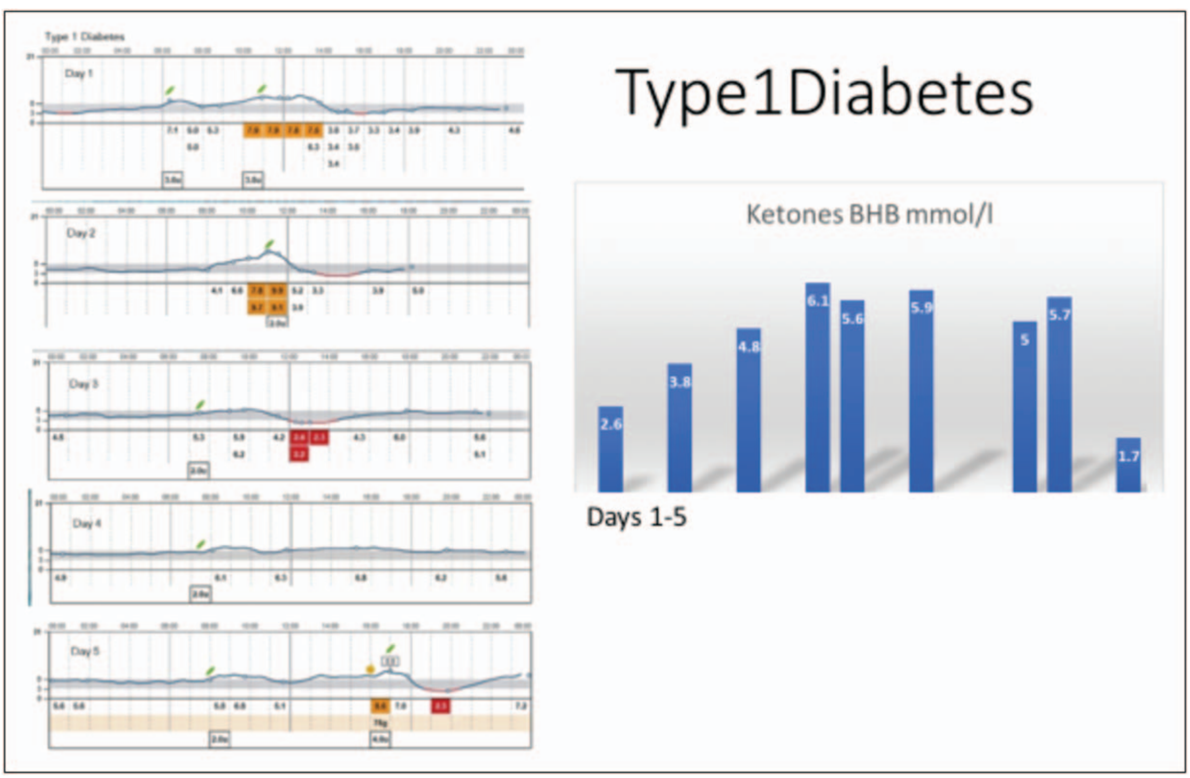

FIGURE 4. CGM trace of participant 2 with type 1 diabetes. CGM trace and ketone levels in both participants with type 1 diabetes showing near-normal glucose traces throughout the whole duration of the project and levels of ketones in the nutritional ketosis range. CGM, continuous glucose meter.

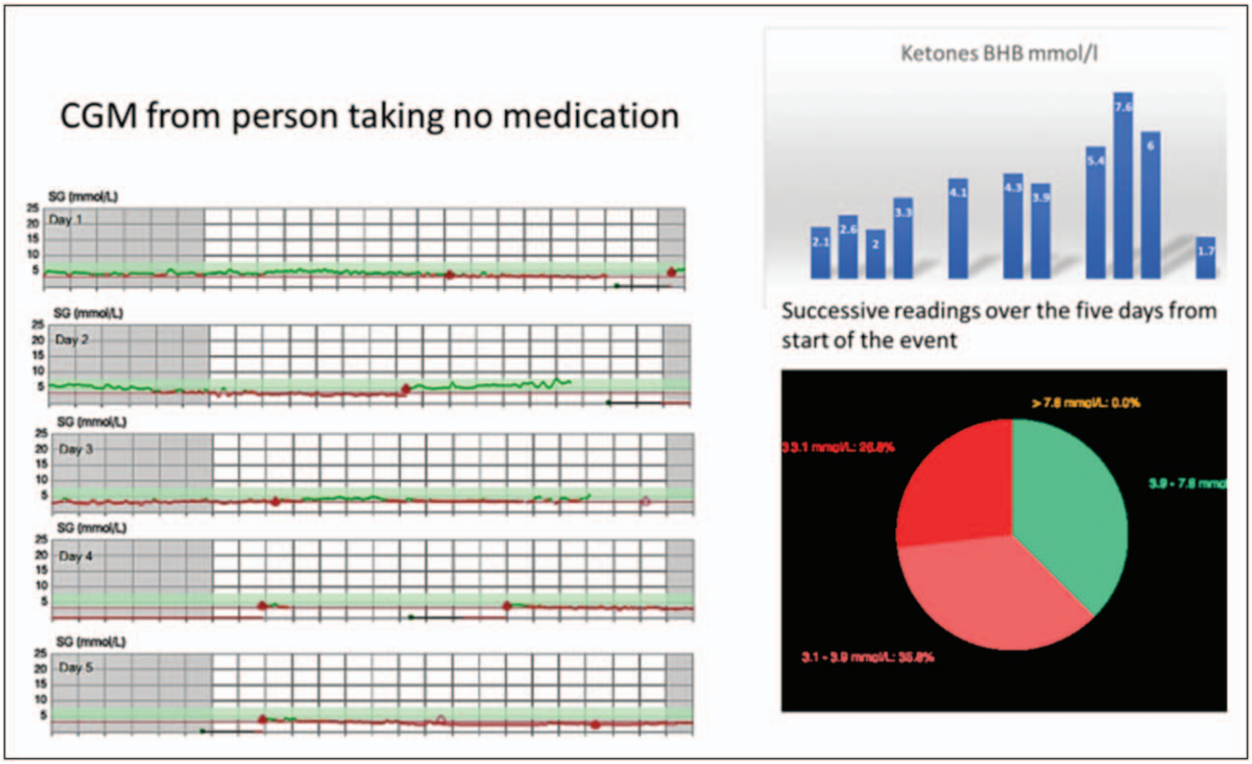

FIGURE 5. CGM trace of participant 3 with no medical condition. The pie chart's upper left segments show that the two people who did not have diabetes and were wearing had blood glucose levels in the usually considered hypo range for a significant percentage of the time. CGM, continuous glucose meter.

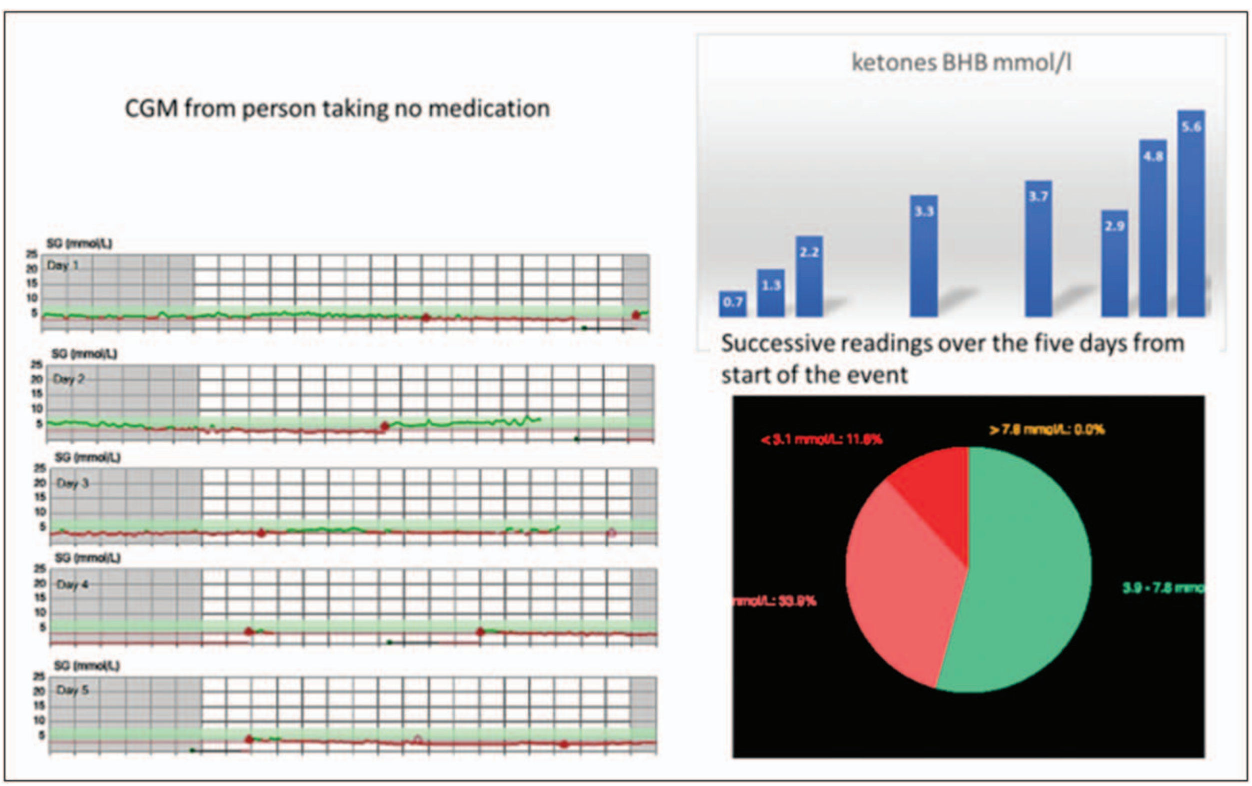

FIGURE 6. CGM trace of participant 4 with no medical condition. The pie chart's upper left segments show that the two people who did not have diabetes and were wearing had blood glucose levels in the usually considered hypo range for a significant percentage of the time. CGM, continuous glucose meter.

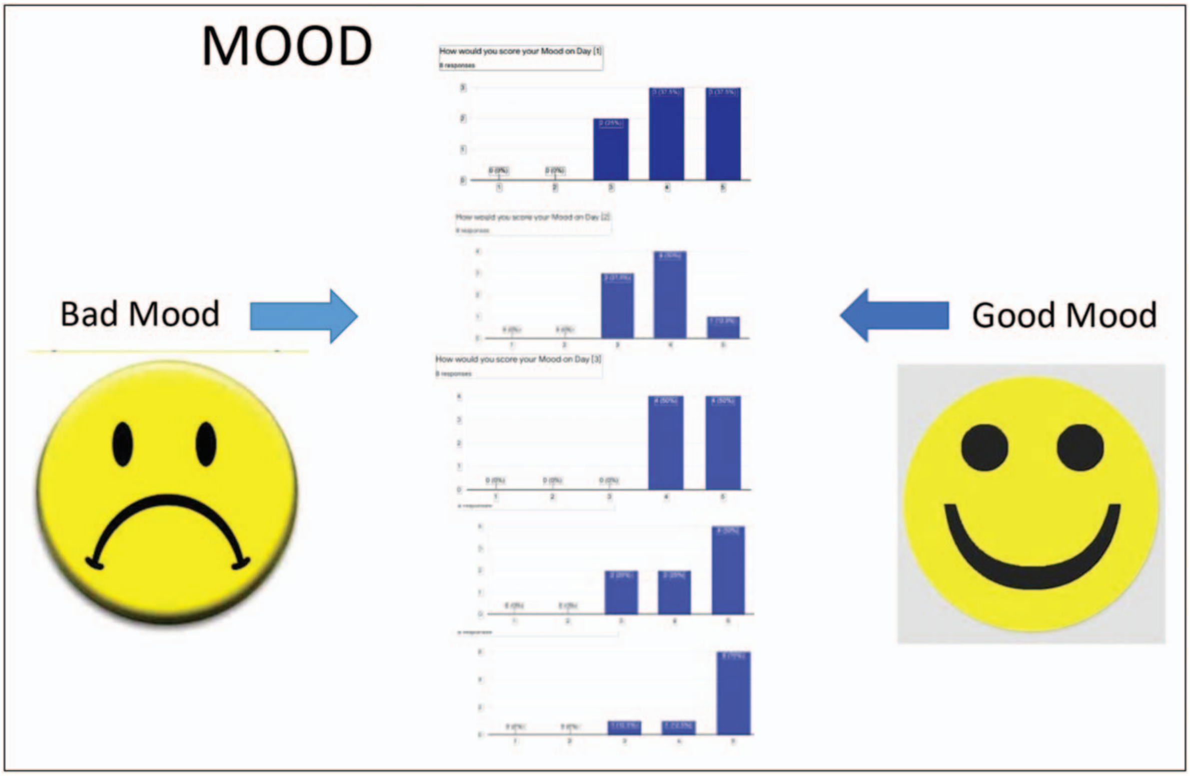

FIGURE 7. Mood score for each participant over 5 days. Mood assessment for each day (*x*-axis).

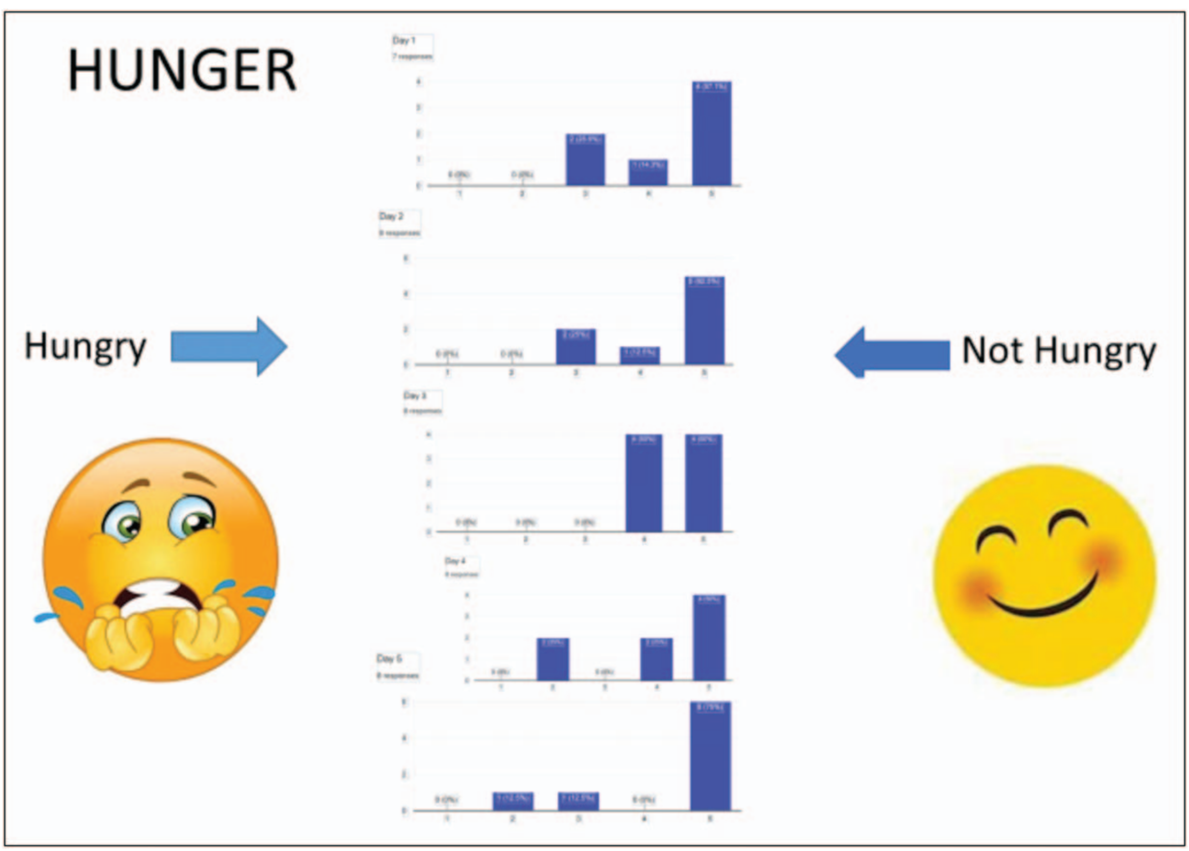

FIGURE 8. Hunger Score for each participant over 5 days. Hunger assessment for each day (*x*-axis).

Weight loss was in line with predictions for most people based on calorie expenditure. However, there were exceptions. One person's weight loss was far less than predicted by the calorific burn of fat. The most weight loss happened to be in the person least well adapted for fat burning. One explanation for this weight loss is that the blood insulin levels dropped. Insulin regulates sodium balance, so the increased excretion of salt would cause simultaneous water loss, and hence weight. Alternatively, or in addition, it might be that water was lost as the larger glycogen stores in this top class athlete depleted. This would need to be elaborated on in any future experiments of this nature. It is an observation only in this project.

DISCUSSION

The project was designed in part around T1D management concerns. It also set out to explore the internal fat store metabolism with time-delayed eating.

For T1D, the two participants in the group who had this condition had no problems either in the planning and training phase or the actual event.

The data collected was entirely in line with predictions based around ketogenic dietary management of this condition.

A growing number of people with T1D explore the benefits of improved glucose control and reduced insulin volumes. Many are finding improvements in often-ignored areas, such as musculoskeletal pain and mental health. Clinicians must adequately support these early adopters. This project has, to some extent, provide evidence to reassure clinicians who have concerns about keto diets' clinical safety.

Firstly, nutritional ketosis does not lead to diabetic ketoacidosis. There is no evidence for this idea, and indeed, it cannot be backed up even with biochemical or cell biological models of metabolism.

It is unclear why this mistaken belief is so persistent in healthcare. This project has not provided new information but it has shown beyond doubt that a keto diet leading to nutritional ketosis is well tolerated concerning DKA risk. Time-delayed eating often forms part of a ketogenic lifestyle, and a 5-day fast should once and for all demonstrate that it is well tolerated for people with T1D to skip the occasional meal.

The project has shown that the body can metabolize fat and generate enough glucose for its daily needs throughout 5 days and 100 miles without ingesting carbohydrates. As mentioned previously, this is becoming standard practice amongst endurance athletes who rely on the superior energy density and size of fat stores for their performance. Metabolic breath testing is too crude to assess protein metabolism, which was not commented on during the data analysis. However, there is evidence from other studies that during fat-burning metabolism, muscle protein breakdown is protected [21▪▪,22].

This would make sense from a primal perspective when hunting prowess relied on muscle bulk. The participants and medical advisors to the project think that fat-burning metabolism does not represent starvation. It is a healthy state of being. It can be argued that carbohydrates ingested in the quantities recommended is the unhealthy state, leading to fat deposition and, eventually, metabolic illness. In temperate climates, carbohydrate supply is not all year round but seasonal, ahead of winter. One theory is that humans fatten up during this abundance of carbohydrates to use the fat stored from excess carbohydrates to help them get through the winter when energy supplies are scarce. Part of the problem might be eating carbohydrates all year round for the winter that never comes [27].

Finally, it is true that if insulin volumes are well managed, then carbohydrate is not a necessary part of the diet, hypoglycaemia being the exception. The reverse is not valid. If one consumes significant quantities of carbohydrate, then one needs insulin.

Management of T1D with a keto diet is quite well tolerated and reduces insulin volumes.

Perhaps the most interesting finding of the project was the persistent and asymptomatic low glucose levels in people who wore a CGM but did not have diabetes (Figs. 5 and 6). The author has brought this to the attention of people who do not have diabetes but have personally experimented with CGM. It appears to be a common finding.

Further research is needed, but low blood glucose might be physiologically normal in someone with T1D on a ketogenic lifestyle. Research has suggested that low glucose is pathological [28]. This was not the case in our study. It has legal implications, especially around driving. The recommendations for driver safety are based around high levels of carbohydrate, the most common type of dietary management for T1D [29]. The rules are not sensitive enough to allow for keto diets where so called 'looming hypoglycaemia' [30] is considered normal and asymptomatic in a ketogenic lifestyle. Additional work should be encouraged to explore asymptomatic hypoglycaemia.

CONCLUSION

This proof-of-concept project set out to explore nutritional ketosis under conditions that lie outside the normal parameters of daily life but with a margin of safety against long-term or short-term harm. Metabolic measurements from a small number of individuals with and without T1D appear from this study to show that nutritional ketosis gives predictable biological measurements based on the understanding of metabolic processes. In addition, the measurements from keto-adapted people with T1D found that the glucose, metabolic testing and ketone levels were close to those of people without diabetes. There were also favourable findings in psychometric testing, which will have implications for use of ketogenic diets in situations where nutritional ketosis might be used therapeutically.

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Clinical advisors: Dr Shaun Scott, Consultant Anaesthetist, Dr Campbell Murdoch, GP, Dr Dan Maggs, GP, Eric Smith, metabolic researcher.

Website, www.zerofive100.com.

There were no applications made with respect to the ethical requirements of clinical trials. However, the project collaborators explored this area and were satisfied that there were no ethical issues of concern regarding the experimentation methods used in the trial.

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Medtrum provided the CGM devices; Prime Motion, massage and stretching; Keto-Mojo, ketone and glucose monitors plus test strips; Primal Living, transport, cameras, accommodation, safety back up; Meterbolic Project, test equipment. The author made up the balance. No conditions were placed on the help offered.

Conflicts of interest

There are no conflicts of interest.

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

■ of special interest
■■ of outstanding interest

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This review suggests that glycogen availability is possibly a problem in some types of sport and recommends that athletes undergo assessment for their specific sport. In this zerofive100 project with prolonged moderate-level activity, there were no issues with fatigue in any participant. No direct measures of glycogen were done in the zerofive100.

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