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Use of a very low carbohydrate diet for prediabetes and type 2 diabetes: An audit

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Background: Type 2 diabetes (T2D) is viewed as a progressive chronic condition, yet recent research has raised hopes for reversal of this trajectory through innovative approaches.

Aim: This audit assessed the impact of a very low carbohydrate ketogenic diet (VLCKD) on glucose control, weight and medication usage in T2D and prediabetes patients. The Glandt Center for Diabetes Care, in Tel Aviv, Israel, from 2015 to 2022.

Setting: The Glandt Center for Diabetes Care, in Tel Aviv, Israel, from 2015 to 2022.

Methods: A cohort of 344 T2D or prediabetes patients following a VLCKD diet for 6 months at a specialised diabetes centre was analysed. Patient records were reviewed for glucose control, weight, blood pressure, lipid profile, liver function and medication usage, with paired t-tests used for analysis.

Results: Patients (mean age: 62 years; T2D duration: 12.3 years) showed significant improvements. Among patients with diabetes (N = 244), median HbA1c dropped from 59 mmol/mol (7.6%) to 45 mmol/mol (6.3%), with 96.3% showing improvement. Prediabetes patients (N = 100) experienced a drop from 42 mmol/mol (6%) to 38.7 mmol/mol (5.7%), with 84% improving. Weight loss occurred in both groups (median changes: −6.5 kg and −5.7 kg). Blood pressure, triglycerides and liver enzymes also improved. Initially, 78 patients were on insulin, reduced to 16 patients at 6 months, with average dose of those remaining on insulin reduced by 72%.

Conclusion: Very low carbohydrate ketogenic diet is effective in enhancing glucose control, weight loss and cardiovascular risk factors in T2D. Most patients achieved insulin independence, with others significantly reducing insulin dosage. The study underscores the potential of integrating a VLCKD with medication management in comprehensive T2D treatment.

Contribution: The audit shows the application of a KD in patients with long-standing diabetes.

Keywords: obesity; metabolic syndrome; type 2 diabetes; ketogenic diet; low carb diet.

Introduction

According to the current standard of care, type 2 diabetes (T2D) is a chronic progressive disease, a depressing prospect for the people involved. However, over the last few years, there has been a surge in more optimistic publications that show drug-free remission of T2D.[1,2,3,4] In our diabetes centre, based on our own clinical experience and lessons learned from the many randomised controlled trials published over the last 20 years,[5,6,7,8,9,10,11,12,13,14,15,16,17] we have implemented a comprehensive very low carbohydrate programme to treat our patients with T2D.

Our setting is a specialised clinic based on treatment by a consultant endocrinologist. In this audit of service provision, we looked at a selected cohort of patients with prediabetes or T2D who followed the diet for 6 months. We were interested to quantify what was possible in terms of improvement in glucose control, weight and use of medications and reflect on lessons learned over the 7 years of offering this approach.

Methods

Study Population

This cohort consists of 344 patients with T2D (N = 244) or prediabetes (N = 100) who followed a very low carbohydrate diet for 6 months while treated at the Glandt Center for Diabetes Care, in Tel Aviv, Israel, from 2015 to 2022. Specifically, it is a very low carbohydrate ketogenic diet

Note: Additional supporting information may be found in the online version of this article as Online Appendix 1.

(VLCKD) defined as carbohydrate content between 20 g/day and 50 g/day or < 10% of the 2000 kcal/day diet, whether or not ketosis occurs.[18]

We arrived at this cohort in the following way (Figure 1): 3235 patients have been seen by the staff of the Glandt Center for Diabetes Care since 2015. Of these, 600 patients were not recorded in our current medical record system and hence were excluded. In our electronic medical record (EMR), 2635 people had some visit notes recorded. Of these patients, we excluded 171 patients who had type 1 diabetes, MODY or latent autoimmune diabetes in adults (LADA) as their diagnosis. We looked at patients who had a note in the chart at the 6-month mark after the initial visit, which excluded 1777 patients, leaving a cohort of 687 patients.

Because we decided to focus on T2D and prediabetes, of these 687, we excluded 184 patients who had come to the clinic to treat metabolic disease other than hyperglycaemia, meaning that they had a HbA1c below 39 mmol/mol (5.7%) at the baseline visit (using the ADA definition of prediabetes,[19] with 503 patients remaining in the cohort). We also excluded a woman with T2D who became pregnant in the 6-month observation period and three patients with creatinine greater than 3.5 mg/dL because fluid retention leads to overestimation of weight, and anaemia of kidney disease leads to underestimation of HbA1c. Patients who had undergone renal transplants but who had creatinine under 3 were included, leaving a total of 499 in the cohort. Although patients had a visit at time 0 and time 6, they did not always have a corresponding HbA1c at both times. In order to have a consistent cuffoff, 59 patients who did not have Hb A1c at the time baseline and 6 months (± 1 month) were excluded, leaving a cohort of 441 patients. Of these 441 patients, 44 of them were never explained or offered the diet and were treated only with medications (the majority of these were in the years 2015 and 2016). The remaining 397 patients were offered a VLCKD defined by 20 g – 50 g of net carbohydrates per day. Of these 397 patients, 344 (87%) made the lifestyle change and adopted the diet, as stated in the follow-up clinic notes and/or the presence of ketone levels of more than 0.3 mmol/L in their clinic notes.

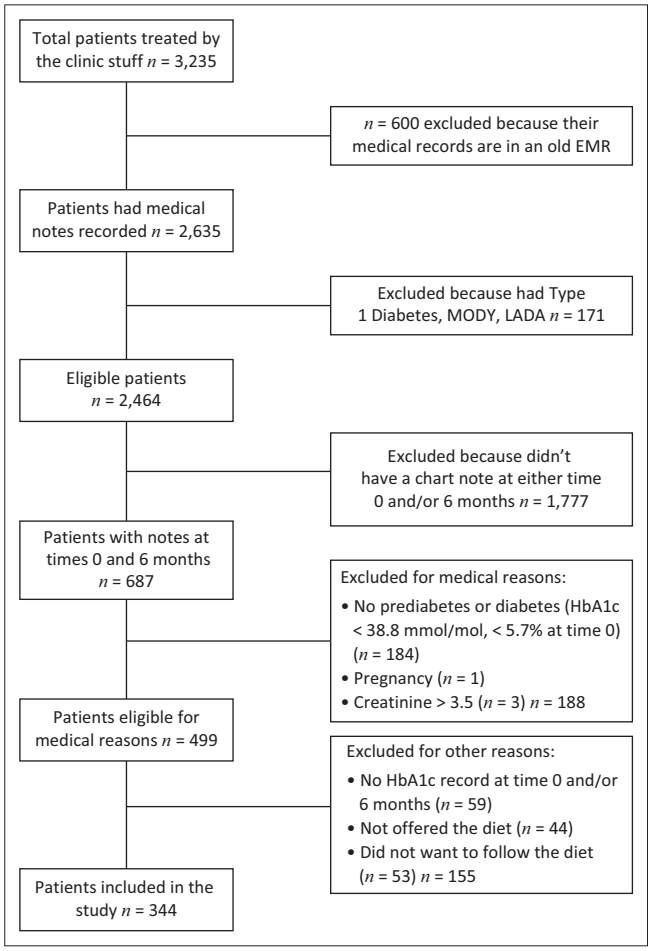

FIGURE 1: Flowchart showing the recruitment process of the total number of patients observed in the Glandt Center for Diabetes Care.

All the patients in the cohort had an appointment with an endocrinologist who presented the idea of using a very low carb diet as the main therapy for T2D. The diet was also offered to concomitantly treat other symptoms of metabolic syndrome such as obesity, high blood pressure, high blood triglycerides and low high-density lipoproteins (HDL). Educational material (see Online Appendix 1) was provided. When the patient agreed to start the dietary intervention, medications were adjusted as necessary, similar to the protocol delineated in Cucuzzella et al.[20] Insulin administration was adjusted accordingly to individual needs to avoid hypoglycaemia. All sulfonylurea and meglitinide medications were stopped from the first visit. SGLT-2 inhibitors were stopped or adjusted at the beginning of treatment in order to decrease the risk of euglycemic diabetic ketoacidosis (DKA).[21] If SGLT-2 inhibitors were continued, patients were told to take half the dose every other day and to check ketones. Blood pressure medications were also adjusted, as blood pressure can decrease as lifestyle changes are implemented.[22] Patients had blood pressure and weight measured at this visit and after 6 months.

Lifestyle or dietary treatment

Within the first week of the baseline meeting with the endocrinologist, the patient met with a dietician who provided an individualised dietary treatment plan, which in all cases consisted of a maximum of 20 g – 50 g net carbohydrates per day. A brochure with the dietary guidelines was given to the patients (see Supplementary files). Patients then met with the dietician and/or physician on average every 2 months before the 6-month visit.

Blood laboratory analysis

Patients had blood tests that included serum glucose, haemoglobin A1c (HbA1c), triglycerides, total cholesterol, low-density lipoprotein (LDL)-cholesterol, HDL-cholesterol, creatinine, alanine transaminase (ALT), creatinine before the first visit and at 6 months again. Every patient had to have at least a baseline and 6-month HbA1c to be included in the cohort of the audit.

Statistical analysis

The results of our analysis are reported as median with an interquartile range (IQR). Tests for significant differences between the patients at time 0 and after 6 months were performed using paired two-tailed student's *t*-test. Statistical analysis was performed using Python with NumPy and SciPy libraries. Data are expressed as mean ± standard error of the mean (SEM). $P < 0.05$ was considered statistically significant.

Ethical considerations

This article reports an internal audit, rather than a study, and hence it does not require an ethics committee review.

Results

Our cohort included a total of 344 patients (Table 1). The average age for the whole group was 62 and the average time with T2D or prediabetes was 12.3 years. Of these, 244 had T2D, that is, HbA1c was 48 mmol/mol (6.5%) or above, and 100 patients had prediabetes with an HbA1c ranging from 39 mmol/mol (5.7%) to 47 mmol/mol (6.4%).

In the entire cohort, 78 patients (22.6%) had a history of a cardiac event and 48 patients (14%) reported symptoms of diabetic peripheral neuropathy.

For the T2D group of 244 patients, the median age was 64 years, with a median duration of diabetes of 12 years. Eighty-seven (35.7%) patients were females. The baseline median (IQR) HbA1c was 59.5 mmol/mol (51.9, 72.7) (7.6%) and decreased to 45.3 mmol/mol (39.8, 42.1) (6.3%) after 6 months, $p < 0.001$. The majority of patients, 96.3%, had an improvement in their HbA1c (Figure 2).

In the T2D group median (IQR), weight was reduced from 89.5 (78.2, 102.1) kg to 83 (72.1, 93.5) kg. Median (IQR) systolic BP decreased from 142 mm Hg (131, 150) to 129 mm Hg (121, 137), $p < 0.001$ and diastolic blood pressure decreased from 80 mm Hg (73, 90) to 75.5 mm Hg (71, 82). Median (IQR) triglycerides decreased from 170 mg/dL (113, 243) to 120 mg/dL (88, 159), $p < 0.001$. Median (IQR) HDL increased from 42 mg/dL (35, 50) to 47.5 mg/dL (41, 54), $p < 0.001$.

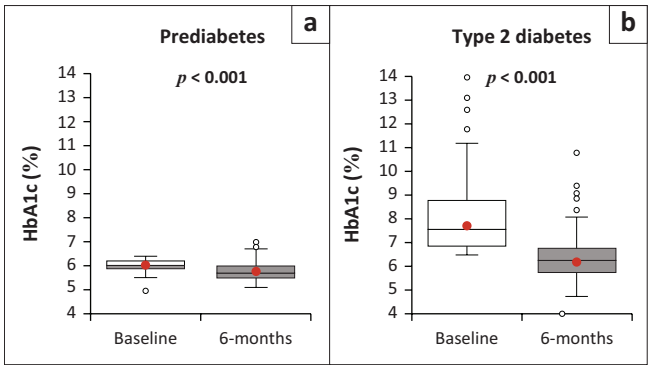

FIGURE 2: Baseline and 6-month follow-up haemoglobin A1c (HbA1c) in patients with (a) prediabetes (5.7% < HbA1c > 6.5%) and (b) type 2 diabetes (HbA1c > 6.5%). Data are presented in Whisker plots.

TABLE 1: Statistical analysis of demographic and cardiometabolic variables measured at baseline and after 6 months follow-up.

Measurements	*N*	%	Baseline	IQR	6 months	IQR	*P*
Patients with type 2 diabetes (244)							
Age (years)	244	100	64	56, 70	-	-	-
Gender (females/males)	87/157	36/64	-	-	-	-	-
Years of diabetes, median	244	100	12	5, 20	-	-	-
Weight (Kg)	227	93	89.5	78.2, 102.1	83	72.1, 93.5	< 0.001
Haemoglobin A1c (HbA1c) (mmol/mol)	244	100	59.5	51.9, 72.7	45.3	39.8, 42.1	< 0.001
Blood pressure (systolic) (mm Hg)	145	59.4	142	131, 150	129	121, 137	< 0.001
Blood pressure (diastolic) (mm Hg)	144	59	80	73, 90	75.5	71, 82	< 0.001
Low-density lipoproteins (LDL) (mg/dL)	114	47	87	66.5, 120.5	94	69, 127	< 0.05
High-density lipoproteins (HDL) (mg/dL)	136	56	42	35, 50	47.5	41, 54	< 0.05
Triglycerides (TG) (mg/dL)	136	56	170	113, 243	120	88, 159	< 0.001
TG/HDL	136	56	3.8	2.2.6.4	2.5	1.6, 3.9	< 0.001
Creatinine (mg/dL)	123	50	0.9	0.7, 1.0	0.8	0.7, 1.0	0.079
Alanine transaminase (ALT) (U/L)	61	25	28	20, 40	20	16, 27	< 0.001
Patients with prediabetes (100)							
Age (years)	100	100	63.5	55, 70	-	-	-
Gender (females/males)	53/47	53/47	-	-	-	-	-
Years of prediabetes, median	100	100	5.5	3, 13.5	-	-	-
Weight (Kg)	90	90	87.1	75.7, 97.7	81.4	71.3, 91.7	< 0.001
Haemoglobin A1c HbA1c (mmol/mol)	100	100	42	41, 44.2	38.7	36.6, 42	< 0.001
Blood pressure (systolic) (mm Hg)	53	53	139	126, 147	128	120, 135	< 0.001
Blood pressure (diastolic) (mm Hg)	53	53	83	76, 88	78	72, 84	< 0.001
Low-density lipoproteins (LDL) (mg/dL)	53	53	101	81, 133	116	84, 145	0.089
High-density lipoproteins (HDL) (mg/dL)	57	57	47	37, 55	52	43, 59	< 0.001
Triglycerides (TG) (mg/dL)	57	57	123	93, 197	97	74, 146	< 0.001
TG/HDL	57	57	2.7	1.8, 4.4	1.8	1.3, 2.9	< 0.001
Creatinine (mg/dL)	51	51	0.8	0.7, 0.9	0.7	0.7, 0.9	< 0.05
Alanine transaminase (ALT) (U/L)	32	32	25	18.5, 38	20	16, 25	< 0.05

The results are shown as median (IQR) unless otherwise stated.

Median (IQR) LDL increased from 87 mg/dL (66.5, 120.5) to 94 mg/dL (69, 127), $p < 0.018$. Median (IQR) ALT was 28 mg/dL (20, 40), and it decreased to 20 (16, 27), $p < 0.001$. Median (IQR) creatinine was 0.9 mg/dL (0.7, 1.0) and decreased to 0.8 mg/dL (0.7, 1.0), $p = 0.079$.

For the prediabetes group of 100 patients, the median age was 63.5 years, with an average duration of 5.5 years. Fifty-three (53%) were female. The baseline median (IQR) HbA1c was 42 mmol/mol (41, 44.2) (6%) and decreased to 38.7 mmol/mol (36.6, 42) (5.7%) after 6 months, $p < 0.001$ (Figure 2). Eighty-four percent of patients had an improvement in their HbA1c.

In the prediabetes group, median (IQR) weight was reduced from 87.1 (75.7, 97.7) kg to 81.4 (71.3, 91.7) kg. Median (IQR) systolic BP decreased from 139 mm Hg (126, 147) to 128 mm Hg (120, 135), $p < 0.001$, and diastolic blood pressure decreased from 83 mm Hg (76, 88) to 78 mm Hg (72, 84). Median (IQR) triglycerides decreased from 123 mg/dL (93, 197) to 97 mg/dL (74, 146), $p < 0.001$. Median (IQR) HDL increased from 47 mg/dL (37, 55) to 52 mg/dL (43, 59), $p < 0.001$. Median (IQR) LDL increased from 101 mg/dL (81, 133) to 116 mg/dL (84, 145), $p < 0.089$. Median (IQR) ALT was 25 mg/dL (18.5, 38) and it decreased to 20 mg/dL (16, 25), $p = 0.004$. Median (IQR) creatinine was 0.8 mg/dL (0.7, 0.9) and decreased to 0.7 mg/dL (0.7, 0.9), $p = 0.047$.

Seventy-eight patients were taking insulin at the beginning of the treatment. Of these, only 16 patients were taking insulin by 6 months, that is, 79% of patients were able to stop insulin. Of these 16 patients who were still on insulin at 6 months, the average insulin dose decreased from 55 to 15 units per day, a decrease of 72% (Figure 3). The patients who were not able to get off insulin had on average a longer duration of diabetes (24.9 years) versus those who were able to stop insulin (19.9 years). Of the 78 patients that were able to stop injecting insulin, 20 patients had a GLP-1 agonist medication added to their treatment.

The number of patients taking metformin increased from 203 (59%) to 223 (64.8%). The number of patients on GLP-1 agonists treatment increased from 79 patients (23%) at the beginning of the treatment to 122 patients (35.4%) after 6 months. The number of patients on SGLT-2 inhibitors decreased from 77 (22.3%) to 45 (13.1%). The number of patients who were taking DPP-4 inhibitors decreased from 76 (22%) to 64 (18.6%). The number of patients taking thiazolidinediones increased from 14 (4.1%) to 18 (5.2%). All 37 patients who were taking sulfonylureas or meglitinides stopped taking these medications (Table 2).

Fifty-three percent of patients were taking statins at the beginning of treatment. Three patients had statins added to their medication regimen, while two patients stopped taking statins during the 6-month observation period.

Discussion

This article presents real-world data from a cohort of 344 patients who adhered to a very low carbohydrate programme for 6 months under the guidance of a treating endocrinologist in a specialty clinic. The total cohort comprised patients who had T2D or prediabetes for an average of 12 years. In this type of population, diabetes is considered a progressive disease, and medications are usually added to prevent its deterioration.[23]

The analysis of this cohort demonstrated that both patients with T2D and prediabetes significantly improved glucose

TABLE 2: Breakdown of the medication regimen for all patients at baseline and after 6-month follow-up.

Meds for the entire cohort	Baseline	6-months
Metformin	203	223
SGLT2 inhibitors	77	45
Insulin	78	16
GLP-1	79	122
DPP4 inhibitors	76	64
Thiazolidinediones	14	18
Sulfonylureas	20	0
Metiglinides	17	0

SGLT2, Sodium-glucose co-transporter-2; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase IV.

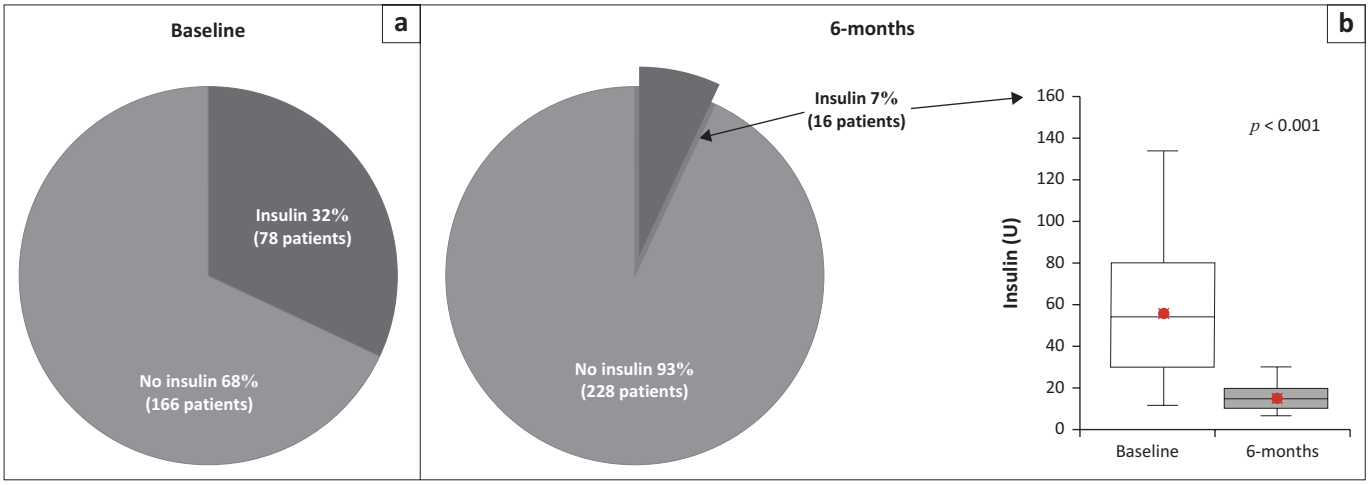

FIGURE 3: (a) Type 2 diabetes pie chart; baseline and 6-month follow-up percentage of patients taking insulin. (b) Insulin dosage in patients who continued taking insulin after 6 months was significantly lower.

control. Out of the 244 patients in the cohort with T2D, 93% showed improvement, a very encouraging finding, given that diabetes control in the United States is declining.[24] Even more encouraging is the finding that of the 78 patients taking insulin, 62 patients were able to stop insulin completely by 6 months, while improving their glucose control.

The treatment of T2D has been glucocentric, focusing mainly on treating the symptom of hyperglycaemia. We have understood that the root cause of T2D is insulin resistance, and hence, we must treat both insulin resistance and glucose levels in order to have improvements in the entire metabolic picture. Studies through the years have shown that it matters how glucose levels are lowered. If the glucose levels are lowered by increasing insulin levels, endogenously by using sulfonylureas or meglitinides or exogenously with insulin injections, this leads to increased insulin resistance and inadvertently increases morbidity.[25,26,27]

On the other hand, when medications lower glucose, while lowering insulin resistance, such as GLP-1 agonists or SGLT-2 inhibitors, then studies show a reduction in CV events and even mortality.[28,29,30] In our medical practice, the aim has been to both simultaneously normalise glucose and decrease insulin resistance. The use of the VLCKD has demonstrated its effectiveness as a powerful tool to reach this objective.[1]

When necessary, particularly in patients with a long duration of diabetes, drugs such as metformin, GLP-1 agonists and SGLT-2 inhibitors were combined with the VLCKD, as an intervention that lowers glucose while lowering insulin resistance.

When patients presented to the clinic on a regimen that included sulfonylureas or meglitinides at the beginning of the treatment, the medications were stopped right away because they increase insulin resistance. They also increase the risk of hypoglycaemia and lead to increased inflammation in the pancreas.[31,32] For those taking insulin, the dose was also titrated down as tolerated because of safety concerns to avoid hypoglycaemia when starting the diet and, again, to decrease insulin resistance and improve metabolic syndrome.[20]

This internal audit has shown that the components of the metabolic syndrome improved significantly. There was an average weight loss of 7.2%, which is a good proxy for waist circumference.[33]

The significant reduction in the circulating triglycerides and significant rise in HDL led to an improved triglycerides to HDL ratio. Previous studies showed that a ratio of triglycerides to HDL-cholesterol (TG/HDL-c) of more than 3 is a reliable marker for insulin resistance[34] and is associated with an atherogenic lipid profile and a risk for the development of coronary disease.[35] In this audit, the median of the TG/HDL ratio decreased from 3.6 to 2.4. This suggests that in this cohort, the quality of LDL improved and shifted from an atherogenic phenotype to a less dangerous type of cholesterol.[36] Both systolic and diastolic blood pressure improved as well.

Often there is a fear that VLCKDs worsen kidney function but randomised controlled trials have not shown this to be the case,[37] and our audit also confirms its safety, as creatinine levels were similar in the T2D group and significantly decreased in the prediabetes group after 6 months, as compared to time 0.

The very low carbohydrate diet has been shown to be the most effective means of improving fatty liver.[38] As insulin levels drop, fat is able to be used for energy. The first place where the fat is oxidised is the ectopic fat, for example, in the liver.[39] We do not have specific data on fatty liver, but we do show that ALT decreased significantly by 6 months, which does correlate with an improvement in fatty liver.

An interesting point can be gleaned from our data. It was estimated in a UK National Diabetes Audit that both patients with type 1 diabetes and T2D each year with a HbA1c > 58 mmol/mol (7.5%) lose around 100 life days.[40] In our cohort, 135 patients (39.2%) had a HbA1c of more than 58 mmol/mol (7.5%), with an average of 74.9 mmol/mol (9%). Out of these 135 patients, 117 (86.7%) were able to decrease their HbA1c to below 58 mmol/mol (7.5%), to an average of 45 mmol/mol (6.3%). This suggests that these patients, if they persist, may see an advantage in longevity.

Some patients experienced side effects, particularly flu-like symptoms when starting the diet. In all cases, the symptoms were transient and were mitigated or avoided by increasing hydration and adding salt to the diet. There were two cases of maculopapular rashes, which resolved on their own and one case of kidney stones in someone with a prior history of kidney stones. In this cohort, there were two cases of euglycemic DKA, one in 2015 and the other in 2016, both of which happened in combination with an SGLT-2 inhibitor. One patient was treated temporarily with insulin and fluids at home. The second patient required hospitalisation and was treated with fluids and insulin. In both cases, the patients continued with the diet, but with cessation of the SGLT-2 inhibitor. These two cases of euglycemic DKA occurred, as the first case reports of euglycemic DKA were published.

With increasing use of SGLT-2 inhibitors, guidance suggests that they should be stopped when adopting a low carbohydrate diet.[20] In our audit, SGLT-2 inhibitors were still prescribed in very insulin-resistant patients in combination with the diet, but only with the patient's full awareness of the risks of DKA. Patients received comprehensive education regarding the associated risks and were required to acknowledge their understanding of these risks in writing within their medical charts. Additionally, they were instructed to purchase a ketone metre for periodic monitoring and in case of any adverse symptoms. In most cases, the dose prescribed is half of the minimum standard dose, and it is to be taken every other day (e.g. empagliflozin 5 mg every other

day). Patients were also instructed on the importance of maintaining hydration.

Audits of this nature offer various strengths, including the ability to assess effectiveness in a large number of people. They also provide a reflection of real-world effectiveness, making them more representative than tightly controlled trials. There are, however, a number of limitations to this work. A limitation of these data is that ketone levels are not consistently documented during all office visits. In certain instances, although the visit note indicated the patient's diet compliance based on clinic-conducted ketone checks, these levels were not recorded in the patient's chart. Conversely, in some cases, ketone levels were not measured, and compliance was presumed based on the patient's self-reporting. This hinders our capacity to definitively ascertain the patient's adherence to the diet. Another limitation is the relatively short duration of the audit. Given the powerful temptations in our environment to eat carbohydrates, this will need to be tested over time. However, we have seen from previous studies that a low carbohydrate diet is sustainable.[1,41] How sustainable the diet is may be in large part a function of how much support the patients receive from the medical establishment.[42]

Our audit is the first to look at the use of a VLCKD in patients who have an average duration of T2D for 12 years. Determining the precise contribution of medications versus dietary changes to our results proves challenging; however, we assert the diet's significant role based on established evidence of the benefits of VLCKD in T2D treatment.[43] This audit demonstrates that a VLCKD can improve glycaemic control while concurrently reducing the need for diabetes medications. It offers a potent tool capable of reversing the progression of T2D, even among individuals with a prolonged history of the disease.

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Competing interests

M.G. has an equity interest in OwnaHealth and Eatsane. S.B. has equity interest in OwnaHealth. N.Y.A. and D.U. have no conflict of interest.

Authors' contributions

M.G. contributed with the treatment of the patients, the analysis of the results and the writing of the original draft. N.Y.A. was responsible for the software and analysis of the data. S.B. contributed with the investigation, analysis and visualisation of the data. D.U. contributed to the conceptualisation, writing of the draft and methodology.

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Data availability

Data may be obtained from a third party and are not publicly available. The anonymised (de-identified participant data) are on an Excel Spreadsheet held by the corresponding author, M.G., on behalf of the Glandt Center for Diabetes Care.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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