

University of Manitoba

**Lifestyle based remission in type 2 diabetes:
Implications for clinical practice**

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ABSTRACT

Type 2 diabetes is often thought of as a chronic and progressive disease. This paper evaluates three emerging methods of achieving remission of type 2 diabetes through dietary lifestyle interventions. These strategies have also highlighted the need for medication deprescribing guidelines. This paper reviews the efficacy, safety, adverse effects and implementation of very low energy diets, low-carbohydrate diets and intermittent fasting on type 2 diabetes. The very-low energy based on The Diabetes Remission Clinical Trial (DiRECT) demonstrated remission in 46% of participants after one year, with 74% taken off all anti-hyperglycemics. Low carbohydrate intake (<30g per day) in the Virta Health study demonstrated 83% of participants continuing to the one-year mark. Average HbA1c decreasing from 7.6 to 6.3 %, with an average weight loss of 13 kg. 94% of them reduced or eliminated insulin use. Intermittent fasting has been shown in literature to promote weight loss and glycemic control since the 1970's, however recent case studies show patients removed of 70+ units of insulin daily in 5-18 days. The conclusion is while there is not yet a consensus best way to achieve remission of type 2 diabetes, nor a guarantee that it will work for all patients, there may need not be one. Practitioners should have the knowledge to discuss a variety of potential options with patients and assist them with the medication deprescribing that may be necessary.

Key words:

Diabetes remission, very low energy diet, DiRECT Trial, low carbohydrate diet, Virta Health study, intermittent fasting, time restricted feeding, medication deprescribing in type 2 diabetes.

INTRODUCTION

This paper will focus on type 2 diabetes which accounts for over 90% of all diabetes cases worldwide (1). In Canada, by 2025 an estimated 5 million people will have Diabetes and over 6.4 million will fall under the classification of pre-diabetes. An estimated increase of 44% from years 2015-2025. With a health care expenditure increase of over 25% during this time (2).

Diabetes is commonly known as a chronic and progressive disease (3). However, remission of type 2 diabetes is possible. Bariatric surgery has demonstrated effectiveness in achieving diabetes remission in 30-80% of patients according to various studies (4–6). The drastic reduction in energy intake following bariatric surgery, leads to reduction in ectopic (intraorgan) body fat. This is thought to lead to restoration of insulin sensitivity in the liver and skeletal muscle, as well as normalization of insulin production by the pancreas (7). Unfortunately, bariatric surgery has a high financial cost to the individual and the health care system. There is also a higher risk of long term problems such as micronutrient deficiencies and post-surgical complications (8,9). Due to the large number of patients with diabetes it is not feasible to offer bariatric surgery to all those who could benefit from it. Therefore, this paper looks to focus on non-surgical means of achieving the same outcome through lifestyle interventions. This is necessary because despite improvements in pharmacotherapy, some reports suggest that less than 50% of patients with moderate to severe type 2 diabetes achieve and/or maintain therapeutic glycemic control levels. Additionally, in the ACCORD study, 10, 251 patients with type 2 diabetes, with a median starting HgbA1c of 8.1%, compared intensive pharmacological glucose lowering therapy (target of <6% HbA1c) to a standard therapy group targeting a level from 7.0 to 7.9%. Intensive pharmacotherapy as a comprehensive, customized, therapeutic strategy targeting glycated hemoglobin levels below 6.0% increased the rate of death from any cause after a mean of 3.5 years (10).

Specifically, it will focus on the lifestyle interventions intermittent fasting, very low energy (calorie) diets (VLED), and low carbohydrate diets. With the plethora of good and bad information available to patients online, there is no shortage “best” ways to achieve diabetes remission. Unfortunately, the scientific evidence on many of these methods are slim, and

therefore guidelines for clinicians to follow to support them are also limited. These are intensive lifestyle modifications that most medical practitioners are not educated on, but may inevitably be asked to medically supervise (11). Each of these remission strategies can be used by patients and health care practitioners like Physicians, Physician Assistants, and Nurse Practitioners, Dieticians and Diabetic Educators to assist motivated patients in reducing their medication requirements and potentially achieve remission. The goal of this paper is to outline these methods, discuss the efficacy of each, and provide practitioners options to offer their patients. Options that best fit their personal lifestyle and health goals. These interventions are important to update because current guidelines for weight and diabetes management often suggest following a DASH and/or Mediterranean diet. The new Canada food guide includes a visual guide that denotes portions of each food group that should constitute a given meal. This includes “healthy” carbohydrates as defined by low glycemic index, more whole foods and less processed choices. As well as increased fruit/vegetables while reducing refined sugar intake (12,13).

A 2016 study from Alberta focused on implementing the Canadian Diabetes Association (CDA) recommendations with the help of weekly health care led lifestyle change instruction. This study identified key barriers to diabetic control, including translating recommendations into operational plans such as food procurement, recipe selection, managing time to include food preparation, and budgeting/cost of recommended food choices. Methods included a current diet intake assessment, a weekly 1.5-2 hour meeting that utilized Social Cognitive Theory to guide behavior changes to incorporate CDA nutrition guidelines for 8 weeks (14).

The study participants were 39 males, 34 females and included >85% with more than high school education and >80% of people making >\$ 60,000 dollars per year. At baseline, average BMI was 32 kg/m², on average participant had T2DM for 9.1 years, and average HbA1C was

~8% +/- 1.8. All participants were deemed to have low physical activity of 5500 +/- 3500 steps per day. (14).

The study found significant improvements in A1c (-0.7%), BMI (-0.6 kg/m²) and lipids were maintained at six months. However, *no changes in hyperglycemia, hypertension and dyslipidemia medications were reported by participants after intervention* (14). Despite the changes in behavior, which follow current CDA recommendations, all participants failed to achieve remission of their diabetes. The current CDA dietary recommendations are likely not be sufficient for the treatment or remission of type 2 diabetes, and often much higher in carbohydrate than desired for many patients with diabetes.

The ultimate goal of this project is to review the existing literature on Very Low Energy (calorie) Diets (VLED), Low carbohydrate-high fat diets (LCHF), Intermittent fasting (IF) or time restricted feeding and type 2 diabetes. In order to provide practitioners with *guidance on how to best assist patients who want to remove medications and manage their diabetes a part of lifestyle intervention focused on type 2 diabetes remission*. This will assist practitioners in discussing the available evidence around remission methods with their patients. At this time there are many unknowns in relations to long term efficacy, adherence and consequences of VLED, intermittent fasting, and very low carbohydrate diets but as a part of a healthy lifestyle they may surrogate outcome measures of type 2 diabetes at least short term.

LITERATURE SEARCH

A literature search for English language publications was conducted using PudMed, and Google scholar for this narrative review. Keywords included “type 2 diabetes” plus “remission”, “reversal”, “intermittent fasting”, “low energy diet”, “low carb diet”, “time restricted feeding”, “prolonged fasts”, “medication deprescribing”, “medication adjustments”, “deprescribing”, “Insulin secretion”, “Liver fat”, “Pancreatic fat”.

“macronutrient composition” plus “obesity”, “weight loss”, “insulin resistance”, “type 2 diabetes”

“Mechanism of” plus “insulin resistance”, “endothelial damage”, “low carb diets”

“gluconeogenesis in fasting”, “gluconeogenesis with low carb intake”, “NAFLD”

“Deprescribing” plus “Ramadan”, “very low energy”, “low carb”, “intermittent fasting”, “time restricted feeding”. The searches were filtered and only human studies which were: randomized clinical trials, meta-analyses, case studies were reviewed. Many articles were accessed via references within articles or from references that stemmed from previous research.

We also reviewed the Canadian Diabetes Association guidelines, American Diabetes Association guidelines

NUTRITION INTERVENTIONS

1.) Very Low Energy Diets (VLED)

Background

VLED traditionally target a >1000 calorie per day energy deficit (often ~ 800 kcal per day ingested). Formulas contain all essential nutrients to prevent vitamin, mineral and electrolyte deficiencies. Weight loss from VLED is significantly correlated to decrease in fasting glucose, improved insulin sensitivity, and lowering of HbA1c (15). Significantly lowered energy intake (<800 kcals/day) has been shown to lower plasma glucose and insulin concentrations prior to altering body weight (16). From a mechanistic standpoint the remission of type 2 diabetes has been proposed to be dependent on the reduction of hepatic and pancreatic fat accumulations (17). VLED have been shown to reduce hepatic triglyceride production and improve insulin sensitivity by reduction in visceral adipose tissue and resolution of non-alcoholic fatty liver disease (NAFLD) (18). Resolution of Intraabdominal/visceral fat has been shown to improve insulin sensitivity over loss of peripheral/skeletal adipose tissue (19). Reduction of visceral adipose can

restore first phase insulin response. During a very low calorie diet, liver fat rapidly decreases and hepatic insulin sensitivity normalizes within 7 days (16). The pancreas can regain lost function over the next 8 weeks. This is consistently seen in people who have had dysfunction for less than 10 years (17).

The Diabetes Remission Clinical Trial (DiRECT)

There is no current primary care nutrition strategy looking to achieve remission of type 2 diabetes. DiRECT, a pragmatic cluster randomized trial aimed to test a weight loss program targeting of ≥ 15 kg at 12 months, delivered within routine primary care utilizing a VLED (20). It encompassed 49 primary care practices in Scotland and England. It followed a diet/formulation made by CounterWeight, (diet management company in the UK). The Counterweight-pro 800 weight loss guide consists of 3 phases. Phase 1 consists of prepackaged/powdered meal replacements added to water, a daily multivitamin and 30 mins of light exercise daily. This phase is to be done for 12-20 weeks or until a BMI of 23 kg/m^2 is achieved. Phase 2 is a 6-week food reintroduction focusing on healthy, proper food choices based on Diabetes UK recommendations. At this stage additional calories are added or subtracted to maintain desired weight. The recommended diet at the end of the Counterweight program follows a regime very similar to that of the CFG. 45-65% daily calories from Carbohydrates, 20-35% from lipids, and 10-35% protein based on plate/portion model (12).

In the DiRECT, the treatment group of clinics utilized the weight management program that involved total diet replacement of 825-853 kcal/day for 3-5 months. Followed by 2-8 weeks of food reintroduction. Participants received structured, long term weight loss maintenance coaching for the rest of 1 year. The control group was to follow the existing best practice care guidelines. Primary outcomes were weight loss of >15 kg, remission of diabetes, defined at

HbA1c of less than 6.5% after minimum 2 months off all diabetic medications, from baseline to 12 months (20).

There were 149 participants in each group. In the treatment group, weight loss of ≥ 15 kg occurred in 24% (36 people) and none of the control group. Diabetes remission was achieved by 46% (68/149 people) in intervention group, 4% (6/149 people) of control group at the end of one year (20). The results were such that there are now multiple companies offering Total Diet Replacement programs in Europe. At 12 months, 109 (74%) of 149 participants in the intervention group were taking no antidiabetic medications (mean HbA1c 6.4%) compared with 27 (18%) of 148 participants in the control group (mean HbA1c 7.2%). Mean number of prescribed medications decreased in intervention group, increased in control (20).

Efficacy and Safety Surpass Bariatric Surgery

VLED have been shown to be effective in the short term, with normalized cholesterol, triglycerides, fasting glucose and insulin blood levels. It has also been shown to reduce blood pressure and chronic inflammation related to aging and unhealthy lifestyle as reflected by lower circulating CRP and TNF- α levels (21). The DiRECT trial had very few adverse effects associated with the VLED. 7/157 patients reported adverse events. There were no deaths and only 1 patient had biliary colic/abdominal pain that was deemed related to the intervention. Biliary tract issues have been correlated with rapid weight loss in other studies and pose a risk factor for any patient attempting a VLED (16). The primary side effects associated with rapid weight loss are electrolyte imbalances, malnutrition, dehydration and gall stones. This study showing the rate of such is much lower than once estimated if done correctly and in the presence of a qualified medical practitioner. Other adverse effects like headache, sensitivity to cold, dizziness and constipation were mild to moderate, dissipated over time and in the vast majority were eliminated during the food reintroduction phase (20). The DiRECT trial has proven the

benefits of bariatric surgery are mimicked in VLED and the positive change associated to visceral fat and B cell function. Quality of life as rated by physical and psychological well-being increased as a result of the weight loss achieved. This was true for both successful participants as well as those who did not achieve full remission. This in mind, to implement such a plan in a primary care setting could allow for diabetes remission and/or a starting point for other interventions to improved health.

Limitations and Cost

The DiRECT Trial did not accept patients currently receiving insulin therapy. This is a downfall, given that insulin therapy makes up a high number of diabetics in Manitoba and Canada. Those of which may benefit from an intense dietary intervention to achieve remission. However, as many bariatric surgery patients are on insulin and anti-hyperglycemics prior to surgery this barrier can be overcome and medications deprescribed. Adherence to the designed program was very promising. Less than 25% of the population dropped out of participation. Given the results, close follow up and motivation allowed for 74% to wean off diabetic medications and 68% stopped all hypertensive medications (20).

Cost is another potential barrier for patients. An estimated cost of \$65-90 (British Pounds) per week for pre-packaged formulas (9,24). One study showed an average of \$861 pounds was the cost to the patient during phase 1. Each bariatric surgery is estimated to cost on average \$15,000-20,000 CAD (23). While a funding model exists for patients to undergo bariatric surgery, one does not exist to undertake intensive dietary/lifestyle management programs. More work is needed to estimate true costs or savings of VLED programs for the treatment of type 2 diabetes, as the programs could save money via cost savings achieved through deprescribing and/or reduction in costly diabetic complications.

Long Term Maintenance of Weight Loss

Estimates of up to 50% of people that partake in VLED regain that weight in less than 5 years (18). For this reason, low and VLED are not regularly included in weight management guidelines. However, meta-analysis showed a mean weight below baseline after 2 years. With a substantial number of people able to maintain ≥ 15 kg loss 18–36 months after a VLED when the structured food-reintroduction program is part of the intervention (20,24). The DiRECT trial has a model of food reintroduction and education to attempt and mitigate the weight regain. Routine medical care visits and dietary advice which may include strategies discussed in the following sections could assist in this weight management process.

Medication Deprescribing in VLED

Key Points for Deprescribing Across All Interventions

1. Medications that are at highest risk of causing hypoglycemia are short acting insulin, sulfonylureas and meglitinides. They increase insulin production independent of carbohydrate intake. Therefore, should be eliminated first and/or changed to oral anti-hyperglycemic with lower risk of hypoglycemia before starting a lifestyle intervention protocol (25,26).
2. Basal insulin should be closely monitored and discontinued next. 3-4 blood glucose tests per day is recommended during weaning period due to moderate-high risk of hypoglycemia (27). Tracking fasting and postprandial levels for 2-4 weeks prior to dietary intervention may not be required but considered in patient deemed poorly controlled (28).
3. Risk of hypoglycemia is main concern during any lifestyle-based remission protocol. Erring on side of under dosing insulin may cause glucose to be above target range. However, dietary interventions may promptly allow glucose to normalize (27).
4. 1st line agent to continue and maximize is Metformin. With low hypoglycemic effect and extended benefit profile it may be continued indefinitely unless side effect profile discourages continuation or remission is achieved (26).

5. 2nd line agents recommended in addition to metformin and/or when removing insulinogenic agents mentioned above are GLP-1 analogues and DPP-4 inhibitors (26). SGLT-2 inhibitors may be considered but keep in mind they do carry risk (albeit low) of euglycemic ketoacidosis (27).

6. Signs and symptoms of hyperglycemia and hypoglycemia should be explained to patient and medication adjustments or emergency hypoglycemic protocols initiated if needed.

Table 1: Medication Adjustments and Deprescribing in VLED. All recommendations based on day 1 of diet intervention.

Class of Medication	Agents	Dose	Risk of Hypoglycemia	Duration of Action	Recommended Dose Adjustment with VLED	Check Blood Glucose/day	Comment
Postprandial - Bolus/rapid and short acting Insulins	Lispro (humalog) Aspart (novorapid) Glulisine (Apidra) Humulin-R Novolin geToronto	variable	high	rapid - <3 hours	Best controlled with basal insulin and oral hyperglycemics that reduce risk of hypoglycemia. Hold if <40 g Carbs in meal or If >40 g carbs - Dose based on net carb content of meal (1 Unit per 10-15 g carbs) and monitor frequently	4+	Studies on VLED and bariatric surgery showed rapid decrease in post-prandial insulin requirements. When deprescribing its critical to heir on the side of slightly high as opposed to low. If in doubt, stop fast acting insulin. Switch to oral hyperglycemic with reduced risk of hypoglycemia. Metformin then DPP-4 inhib. or GLP-1 receptor analogues. Avoid Sulfonylureas and Meglitinides. Recommendations based on Day 1 of diet
Combination Insulins	70/30 - Humulin 75/25 - Humalog 75% insulin Lispro suspension and 25% Lispro long acting. 50/50 - Humalog Mix 50% short acting 50% long acting.	variable	high based on short acting component	rapid - <3 hours in addition to long acting basal component	Recommend long acting insulin for daily treatment and follow suggestion for basal insulin. When no longer needed or dose is minimal, consider switch to oral hyperglycemics that do not cause hypoglycemia.	4+	If possible, substitutions should be made to entirely long acting basal insulins to prevent hypoglycemic events (see next row) Recommendations are guidelines and do not substitute for clinical judgement.

Basal Insulin - take at same time as normal	Glargine (Basaglar, Lantus) Determir (Levemir) Degludec (Tresiba)	variable A1c <8% 0.1-0.2 U/kg A1c >8% 0.2-0.3 U/kg	high	~24 hours	Start with 50-66% of daily dose. <u>At next dose:</u> If Fasting BG <2.2 mmol decrease 40%. Fasting BG <3.9 mmol decrease 30%. Fasting BG 4.0-6.66 mmol decrease 10-20%. Fasting BG 6.66-9.99 mmol continue dose. Fasting BG 10-14 mmol may continue dose if fasting glucose is trending down or increase 10% now.	4+	Critical to test glucose 3-4 times daily while adjustments are being made. Insulin may change quickly depending on patient's adherence to selected plan and hypoglycemic awareness. Heir on the side of reducing insulin too much. Long term benefit of VLED outweighs short term risk of hypoglycemia. In some cases bariatric patients have been completely removed of insulin use prior to discharge after surgery. Patients with insulin pump should start with basal rate decrease minimum 10% lower. Glucose should be checked every 2 hours minimum.
Intermediate-acting (NPH) - take at same time	Humulin-N Novolin ge NPH			typically, twice daily dosing			
Sulfonylureas	Glyburide (Diabeta), Gliclizide (Diamicron), Glimepiride (Amaryl)	N/A	High	16-36 hrs	discontinue		Due to high risk of hypoglycemia should be discontinued prior to VLED diet. Do not use in conjunction with Basal insulin
Meglitinides (non-sulfonylurea insulin secretagogue)	Nateglinide Repaglinide	N/A	moderate-High	4-6 hrs	discontinue		Normally taken prior to meal. Consider switch to oral anti-hyperglycemic with decreased risk of hypoglycemia (DPP-4 inhibitor or GLP-1 receptor analogue)
Biguanides	Metformin	500 mg - 2500 mg divided BID with meals	Low	12-24 hrs	none	2-4/day	Rarely causes hypoglycemia, has beneficial effect. May titrate up to decrease side effects that occur at higher doses. Discontinue last and if glucose well controlled. Maximize metformin to side effect free level before increasing or adding another agent.
DPP-4 inhibitors	Saxagliptin Sitagliptin	2.5, 5 mg tabs up to 5mg OD 25, 50, 100 mg tabs up to 100 mg OD	low	~24 hrs	none - may decrease dose by 20-50% when AM fasting glucose	2-4/day	Due to inhibition of glucagon, associated with hypoglycemia when fasting >16 hrs. If intermittent fasting during VLED, hold.

	Alogliptin Linagliptin	6.25, 12.5, up to 25 mg OD 5 mg OD			<6.66 mmol. Continue dose while fasting glucose 6.67-10 mmol. Increase dose 20-50% if AM fasting glucose >10 mmol >3 times per 1 week.		To be taken again prior to breaking fast. Alternative: GLP-1 receptor analogues do not have insulinotropic effect <4 mmol. If SC option is tolerated. May considering adding DPP-4 inhibitor if fasting glucose >10 mmol and metformin maximized or prior high risk anti-hyperglycemic discontinued. Discontinue after insulin/sulfonylureas were stopped and fasting blood glucose was consistently under 5.55 mmol
SGLT-2 Inhibitors	Dapagliflozin Empagliflozin Canagliflozin Ertugliflozin	5-10 mg OD 10, 25 mg OD 100 mg up to 300 mg OD 5 mg up to 15 mg OD	low	12-24 hours	Decrease dose 20-50% once fasting glucose <10 mmol for 3 days. Decrease dose ~50% if fasting glucose <6.66 mmol for 3 days or one time glucose <4.0 mmol or symptoms of hypoglycemia May continue current or increase dose during food reintroduction phase to prevent weight gain and insulin desensitization or if fasting glucose >9.99.	2-4/day	Benefit of weight loss in all modalities. Enhances urinary glucose excretion and may act as osmotic agent. Ensure adequate hydration during any modality due to osmotic effect of glucose. May continue as a part of VLED. Helps weight loss and expels glucose above renal threshold. For all modalities, discontinued after insulin/sulfonylureas were stopped and fasting blood glucose was consistently within desired range. No benefit to continuing and risk of euglycemic ketoacidosis.

GLP-1 Receptor Analogues - Subcutaneous - Daily	Liraglutide (Victoza) Lixisenatide Exenatide (Byetta) Albiglutide (Eperxan) Dulaglutide (Trulicity)	0.6 mg up to 1.8 mg daily 10mcg up to 20 mcg daily 5-10 mcg SC q12hr 30-50 mcg SC weekly 0.75-1.5 mg SC weekly	low	12-24 hours ~7 days	none - May decrease dose by 20-50% when AM fasting glucose <6.66 mmol for 3 days or <5.5 mmol once. Continue dose while fasting glucose 6.67-10 mmol. Increase dose 20-50% if AM fasting glucose >10 mmol >3 times per 1 week.	2-4/day	Risk of hypoglycemia very low. Safer than DPP-4 inhibitors as add on agent because it does not have same glucagon blocking response when blood glucose <4 mmol. However, only available in sub-cutaneous option. May discontinue after insulin/sulfonylureas were stopped and fasting, pre/post meal blood glucose was consistently under 5.55 mmol.
Alpha Glucosidase Inhibitors	Acarbose Miglitol	25 mg up to 100 mg with each meal containing carbohydrates	low/none	<4 hrs	discontinue as nutrients are limited and needed	2-4/day	May want to stop prior to VLED due to drastic reduction in energy. Majority of VLED formulas contain >45% carbohydrates. Risk for malnutrition and unwanted side effects.
Bile Acid Sequestrant	Colesevelam	1.875 g (3 tabs or 1/2 packet oral suspension) BID up to 3.75 g/day	low/none	~24	Continue daily. Maximize with fewest side effects	2-4/day	May continue until cholesterol levels are within appropriate range. Immediate reduction in dose is appropriate unless familial hypercholesterolemia is present as VLED will improve cholesterol levels.

Data is based on case studies, years of practitioner experience and randomized control trial recommendations for safe deprescribing based on frequent glucose checks and diligent practitioner assessment. See (20,25,26,28–34)

2.) Low Carbohydrate/Ketosis Diets

Background – Insulin Resistance

Type 2 diabetes is characterized by insulin resistance, which is seen clinically as elevated blood glucose and HbA1c levels (35). Insulin is a storage hormone, signaling the body to uptake glucose in the blood as a source of energy and/or store it in muscle tissue and liver as glycogen when glucose is in excess. Storage is not infinite and once the body’s limited capacity to store glucose as glycogen (mainly liver and skeletal muscle) has been exceeded, excess glucose in the liver is converted via de novo lipogenesis to triglycerides. Insulin signals lipoprotein lipase in the adipose tissue to pull the newly formed triglycerides out of the blood and into adipose. If production of triglycerides is higher than utilization and storage of these triglycerides, they can accumulate in the liver, skeletal muscle and pancreas (19,36–38).

Defining Low Carbohydrate. How Low is Low enough?

Low carbohydrate-high fat diets are an effective mean of reducing blood sugars and insulin production by the body (24,39). Replacing carbohydrates with fats has little to no insulin response by the body thus helps to improve insulin sensitivity (34). Numerous studies show restriction of carbs reduce postprandial, overall glucose concentrations, HbA1c and improve fasting glucose (40). Variations in degree of carbohydrate reduction and recommendations exist in the literature. Very low carbohydrate diet (VLCK) contains <30 g carbs/day (<10% total daily calorie intake) with no total kcal/day restriction and will achieve nutritional ketosis (26). Low carbohydrate (LCK) diets typically contain 30-50 g carbs/day with no total kcal/day restriction (34). Meta-analysis has shown that LCK produce a reduction in hunger that corresponds to decreased overall calorie consumption despite eating to satiety (40). Moderate carbohydrate diets contain >130 g carbs/day and make up 26-44% of total caloric intake per day. Diets considered high in carbohydrates are 45-65% daily caloric intake of energy (40). Canadian Diabetes Association continues to recommend no less than 130 g carbs/day and >45% carbs to make up total daily caloric intake (41).

Fastest decrease in serum insulin concentrations and insulin sensitization are seen in carbohydrate concentrations that make up <10% of the patients daily caloric intake (39). Less than 50 g carbohydrates will shift metabolism to utilize ketone bodies and fatty acids as primary energy source. This is known as nutritional ketosis (34).

Virta Health Study

The recent 2018 Virta Health study looked at low dietary carbohydrate intake (<30g/day) compared with an observational group undergoing current diabetic treatment guidelines against. The main outcomes were HbA1c, weight change and need for medicines after 1 year in adults with T2DM. One group followed the current model of care with regular follow up with a

physician/endocrinologist and dietician. The test group were cared for remotely by phone and app on an as needed basis, with in person visits if requested. Health coaches and doctors were available to track blood glucose, ketones, weight, diet changes electronically. Patients had access to blogs, telemedicine and on demand feedback via the app. The intent was comprehensive care to support patients to achieve ketosis while eating to satiety and ensuring compliance. The test group received cell connected weight scale, blood and ketone tester, BP cuff, web based/app software and access to telemedicine for advice and medication management (26).

Results and Adverse Effects

Showed 83% the initial 262 were enrolled at the 1year mark. On average, HbA1c declined from $7.6 \pm 0.09\%$ to $6.3 \pm 0.07\%$ and weight declined 13.8 ± 0.71 kg. Medications (not metformin) were continued in only $29.7 \pm 3.0\%$ of the group. Insulin was reduced or eliminated in 94%. Sulfonylureas were completely removed. Adverse effects were reported in 6/262 patients in the test group but were not found to be associated with the diet itself. Secondary outcomes showed CRP decreased by 39%, triglycerides declined by 24%, HDL-cholesterol increased 18% and LDL-cholesterol increased 10%. LDL:HDL ratio improved. Serum creatinine and liver enzymes (ALT, AST, and ALP) declined and apo-lipoprotein B was unchanged. The control group was reported to have no significant changes in biomarkers or medications at 1 year (26). This study shows the efficacy of a low carbohydrate diet on improved primary and secondary outcomes.

Feasibility and Implementation

As technology advances, this study presents the possibility to improve patient prognosis, reduce medication and decrease overall health care costs by use of apps and telehealth. Many such companies are commercially available. Including but not limited to Virta Health, Noom,

Omada, and Livongo. Each focusing on food logs, meal feedback and education. Some are able to actively track and recommend medication adjustments.

Resistance to Low Carbohydrate: Changing Conventional Thinking on Safety

The question is why is this intuitive diet option not widely utilized? In response to the Virta Health study, the American Diabetes Association (ADA) has now added a statement that indicates that low-carbohydrate eating plans may result in improved glycemia, reduce antihyperglycemic medications in people with T2DM (42). Low fat-high carbohydrate diets have been promoted as the heart healthy based on the idea that fat intake increases your risk for heart disease by raising LDL cholesterol. A meta-analysis of 17 low carb diet trials covering 1,140 obese patients found that low-carb diets neither increased nor decreased LDL cholesterol. Results showed low-carb diets were associated with decreases in body weight as well as improvements in other cardiovascular risk factors such as decreased triglycerides, fasting glucose, blood pressure, body mass index, abdominal circumference, plasma insulin and c-reactive protein, as well as an increase in HDL cholesterol (24).

Practitioner Advice and Low Carbohydrate Guidelines

Practitioners can educate patients to replace carbohydrates with healthy fat alternatives, which should include as many whole and unprocessed foods as possible. Understanding dietary habits, highly consumed food items, and using food diaries are effective ways to initiate this process. Simple, practical changes are the best way to facilitate the transition to low carb-high fat diets. For example: each meal should consist of protein, fat from natural sources like meat, eggs, nuts, fish/seafood, vegetables and fruits like avocado. Maximizing vegetable intake is critical. Understanding that frozen is not worse than fresh if availability is a barrier (43). Oils such as extra virgin olive oil are high in polyunsaturated and monounsaturated fats. Foods high in (saturated) fats have shown to have little effect on endothelial/vascular compromise in the

absence of hyperglycemia such as during a low carb diet. Chronic hyperglycemia combined with hyperlipidemia is thought to increase intravascular endothelia dysfunction via oxidative stress not seen in hyperlipemia alone (44). LowCarbUSA, recently (2019) released clinical guidelines for carbohydrate reduction. Included for practitioners and patients is resources and guides to which foods are appropriate to consume (34).

Procurement and Cost

Depending on geographical location, procurement and cost could be significant for the above-mentioned food sources. Local meats, vegetables and alternatives to suggested foods must be discussed and will vary depending on region.

Table 2: Medication Adjustments and Deprescribing in Low-Carbohydrate Diets

Class of Medication	Agents	Dose	Risk of Hypoglycemia	Duration of Action	Recommended Dose Adjustment with Low-Carb	Check Blood Glucose/day	Comment
Postprandial - Bolus/rapid and short acting Insulins	Lispro (humalog) Aspart (novorapid) Glulisine (Apidra) Humulin-R Novolin geToronto	variable	high	rapid - <3 hours	Hold if <40 g Carbs or If >40 g carbs - Dose based on net carb content of meal (1 Unit per 10-15 g carbs) and monitor frequently Best controlled with basal insulin and oral hyperglycemics that reduce risk of hypoglycemia.	4+	Virta Health maintained goal fasting, pre and post meal glucose of 6.66-9.99 mmol/L. Low carb decreases insulin release and need exogenous insulin support. If in doubt, stop fast acting insulin. Continue long acting insulin if fasting glucose remains >6.66 mmol/L. Do not Give insulin if <6.66 mmol/L Switch to oral hyperglycemic with reduced risk of hypoglycemia. Metformin then DPP-4 inhib. or GLP-1 receptor analogues. Avoid Sulfonylureas and Meglitinides. Recommendations based on Day 1 of diet

Combination Insulins	70/30 - Humulin 75/25 - Humalog 75%insulin Lispro suspension and 25% Lispro long acting. 50/50 - Humalog Mix 50% short acting 50% long acting.	variable	high based on short acting component	rapid - <3 hours in addition to long acting basal component	Risk of hypoglycemia too great. Switch to long acting once daily with short acting bolus and carb counting as above.	4+	If possible, substitutions should be made to entirely long acting basal insulins with to prevent hypoglycemic events (see next row). Goal of 6.66-9.99 mmol/L. Recommend switch to oral anti-hyperglycemic that do not cause hypoglycemia (GLP-1, DPP-4) as soon as possible. Use basal insulin alone if carbs <40 g per meal and insulin still required due to elevated fasting glucose >10 mmol as per below. Recommendations are guidelines and do not substitute for clinical judgement.
Basal Insulin - take at same time Intermediate-acting (NPH) - take at same time	Glargine (Basaglar, Lantus) Determir (Levemir) Degludec (Tresiba) Humulin-N Novolin ge NPH	variable A1c <8% 0.1-0.2 U/kg A1c >8% 0.2-0.3 U/kg	high	~24 hours typically twice daily dosing	<40 g reduce daily dose by 50% to start. 40-80 g reduce 25% to start 80-130g reduce 10% to start Prior to next dose: If Fasting BG <2.2 mmol decrease additional 40-50%. Fasting BG <3.9 mmol decrease additional 30-40%. Fasting BG 4.0-6.66 mmol decrease additional 10-20%. Fasting BG 6.66-9.99 mmol continue dose. Fasting BG 10-14 mmol may continue dose if fasting glucose is trending down or increase 10% now.	4+	Critical to test glucose 3-4 times daily while adjustments are being made. Goal of fasting, pre/post-meal glucose of 6.66-9.99 mmol/L. Insulin may change quickly depending on patient's adherence to selected plan and hypoglycemic awareness. Heir on the side of reducing insulin too much. Patient with insulin pump should start with basal rate decrease minimum 10% lower. Glucose should be checked every 2 hours minimum. Rate adjusted 10% increments to keep within 6.66-9.99 mmol/L range.
Sulfonylureas	Glyburide (Diabeta), Gliclizide (Diamicon),	N/A	High	16-36 hrs	discontinue		Due to high risk of hypoglycemia should be discontinued prior to Low carb diet.

	Glimepiride (Amaryl)						Do not use in conjunction with Basal insulin
Meglitinides (non-sulfonylurea insulin secretagogue)	Nateglinide, Repaglinide	N/A	moderate-High	4-6 hrs	discontinue		Normally taken prior to meal. If containing low/no carbohydrate it should be skipped or discontinued altogether prior to any plan.
Biguanides	Metformin	500 mg - 2500 mg divided BID with meals	Low	12-24 hrs	none	2-4/day	Rarely causes hypoglycemia, has beneficial effect. May discontinue if side effects are present and glucose well controlled. Maximize metformin to side effect free level before increasing or adding another agent.
DPP-4 inhibitors	Saxagliptin Sitagliptin Alogliptin Linagliptin	2.5, 5 mg tabs up to 5mg OD 25, 50, 100 mg tabs up to 100 mg OD 6.25, 12.5, up to 25 mg OD 5 mg OD	low	~24 hrs	none - may decrease dose by 20-50% when AM fasting glucose <6.66 mmol. Stop after fasting glucose consistently <5.55 mmol/L Continue dose while fasting glucose 6.67-10 mmol. Increase dose 20-50% if AM fasting glucose >10 mmol >3 times per 1 week.	2-4/day	May be continued on low-carb diet May consider adding DPP-4 inhibitor if fasting glucose >10 mmol and metformin maximized or prior high risk anti-hyperglycemic discontinued. Discontinue after insulin/sulfonylureas were stopped and fasting blood glucose was consistently under 5.55 mmol
SGLT-2 Inhibitors	Dapagliflozin Empagliflozin Canagliflozin Ertugliflozin	5-10 mg OD 10, 25 mg OD 100 mg up to 300 mg OD 5 mg up to 15 mg OD	low	12-24 hours	Decrease dose up to 20-50% once fasting glucose <10 mmol/L Discontinue once fasting, pre/post-meal glucose within goal range of 6.66-9.99 mmol/L	2-4/day	Virth Health and LowCarbUSA recommend discontinued SGLT2s after insulin/sulfonylureas because no benefit in very low carbohydrate context and risk of euglycemic ketoacidosis. Some benefit during initial days-weeks of low-carb. Recommend change/hold/decrease of agent if one-time glucose below 4 mmol or hypoglycemic symptoms.

GLP-1 Receptor Analogues - Subcutaneous - Daily SC – weekly	Liraglutide (Victoza)	0.6 mg up to 1.8 mg daily	low	12-24 hours	none - May decrease dose by 20-50% when AM fasting glucose <6.66 mmol for 3 days or <5.5 mmol once.	2-4/day	Risk of hypoglycemia very low. Safer than DPP-4 inhibitors as add on agent because it does not have same glucagon blocking response when blood glucose <4 mmol. However, only available in subcutaneous option. May discontinue after insulin/sulfonylureas were stopped and fasting blood glucose was consistently under 5.55 mmol.
	Lixisenatide	10mcg up to 20 mcg daily					
	Exenatide (Byetta)	5-10 mcg SC q12hr					
	Albiglutide (Eperxan)	30-50 mcg SC weekly		~7 days	Continue dose while fasting glucose 6.67-10 mmol. Increase dose 20-50% if AM fasting glucose >10 mmol >3 times per 1 week.		
	Dulaglutide (Trulicity)	0.75-1.5 mg SC weekly					
Alpha Glucosidase Inhibitors	Acarbose Miglitol	25 mg up to 100 mg with each meal containing carbohydrates	low/none	<4 hrs	skip or discontinue	2-4/day	Does not cause hypoglycemia but work by inhibiting carbohydrate absorption. Therefore, likely not needed during very low carbohydrate diet.
Bile Acid Sequestrant	Colesevelam	1.875 g (3 tabs or 1/2 packet oral suspension) BID or 3.75 g (6 tabs or full packet oral suspension) daily	low/none	~24	Continue daily. Maximize with fewest side effects	2-4/day	May continue until cholesterol levels are within appropriate range. Low carb will improve lipid panel on own. Immediate reduction in dose is appropriate unless familial hypercholesterolemia or other reason to continue is present.

Data is based on case studies, years of practitioner experience and randomized control trial recommendations for safe deprescribing based on frequent glucose checks and diligent practitioner assessment. See (20,25,34,26–33)

3.) Intermittent Fasting and Time Restricted Feeding

Background

Fasting is defined as the voluntary abstinence from caloric food or beverages for therapeutic, spiritual or political reasons (45). Conventional weight loss advice recommends strategies to reduce daily energy intake. Several studies have shown that a chronic reduction in energy/day, causes the basal metabolic rate (BMR) to respond with a corresponding reduction. Often when energy intake is increased back to prior baseline, BMR is unable to adapt as quickly as it had during the decreased energy period. Energy input is higher than output and leads to weight gain (46,47). This differs greatly from therapeutic Intermittent fasting (IF). Which is a period of

consuming zero energy for 12-48 hours or longer. The body adapts to periods of no energy intake by first using liver glycogen stores (starting ~4 hours post-prandial). As glycogen stores decrease, gluconeogenesis rate increases. Rate of gluconeogenesis is approximately the same as glycogenolysis at ~16 hours postprandial. Hepatic glycogen continues to deplete until approximately 48 hours. At this point, gluconeogenesis produces all required glucose to sustain basic metabolic functions (48).

The Physiological Effects of IF

Have been shown to be very different than that of prolonged daily caloric restriction. An 8-week weight loss study compared a control group that received calorie reduction of 400 calories per day (based on estimated energy requirements) to an alternate day fasting group (36 hour fasting protocol). The IF group ate *ad libitum* on feed days, and zero calories every other day. Macronutrient content was the same for both groups when feeding (55% carbohydrate, 15% protein and 30% fat). At the end of the 8 weeks, the energy deficit from baseline was -1178 \pm 51 kcal/day in the IF group. Despite feeding *ad libitum* the IF group consumed ~500 calories more per day than the restricted group. At the end of the 8 weeks, no adverse effects were reported, and 93% adherence was maintained. The relative percentage of weight loss was slightly higher in the IF group with this group have a significantly lowered fasting glucose concentrations. If fasting on a regular basis, the burning of glycogen stores and enhanced gluconeogenesis may promote re-sensitization to the presence of insulin (49). At a 24-week follow-up the daily calorie restriction group had regained +1.2 \pm 0.8 kg fat mass and +1.1 \pm 0.5 kg lean mass. The IF group had lost -0.4 \pm 0.8 kg fat mass while gaining +2.0 \pm 0.5 kg lean mass (50). Concluding that body composition changes were more favorable in the If group.

Metabolic Response to Prolonged Fasting

The suggested mechanism behind lean mass preservation is by sharply reducing insulin, noradrenaline rises to mobilize fat stores for energy. Growth hormone rises as well to maintain lean muscle and prevent its breakdown for energy (51). Interestingly, four days of continuous fasting showed metabolic rate increase by 12% (51).

Studies on medically supervised, prolonged fasts of 200+ days have been deemed safe and an effective means of reaching an ideal body weight (45,52). Reintroduction of food poses some risks but can be mitigated based on knowledge of re-feeding conditions and electrolyte abnormalities (52). Fasting studies may help to reduce blood pressure, levels of oxidative stress, decrease overall appetite and most importantly, decrease post-prandial insulin levels. In time, improving insulin sensitivity and B-cell function of the pancreas (53).

Observational studies suggest that bariatric surgery can rapidly improve glycemic control in patients with type 2 diabetes (8). The mechanism by which bariatric surgery can so drastically improve blood glucose is thought to be due to severe energy restriction. Often patients are weaned from medications and achieve glucose control even before drastic weight loss is achieved (9). The effects of intermittent fasting may work along the same lines without the potential complications, risks or cost of surgery (54).

Case Studies of IF and Medication Deprescribing

Three recently published case studies utilizing IF in T2DM showed great promise. All three males had long standing T2DM with individual comorbidities. Fasts were 24 hours long, 3 days per week where water, coffee, tea, bone broth and multivitamins are permitted during that 24 hours. Blood sugars were required four times daily with twice a week follow up until insulin was discontinued. All three patient were receiving at least 70 units of insulin per day at the start of the trials. Insulin was completely removed in 5-18 days for all three patients with no episodes of hypoglycemia reported. Subjectively they felt “excellent” during fasting days with blood sugars

consistently within 5-10 mmol/L. When they did eat, they followed a low carbohydrate diet of 20-50g per day, which controlled hunger and lead to a minimum 12% total weight loss between the three. By the time they reached their desired weight loss patient 1 was taking only Capagaflozin, patient 2 was free of all medications and patient 3 continued metformin only (27).

Fasting is a tool, that may be done by those of any financial standing and may save the patient the cost of medications, syringes and glucose test supplies. Educating patients on the benefits of fasting, following with close medical supervision and continuous education and support may lead to remission of disease (27).

Combining Therapeutic Lifestyle Based Remission Strategies

Fasting is a powerful dietary measure that can be used alone, or for maximal effect, in addition to a VLED or low carbohydrate diet. This amplifies the insulin desensitization process and can effectively wean patients off their medication in days-weeks (27). Cost and procurement are non-issues, and no barriers to geography exist with IF. It is important to counsel patients on appropriate ways to manage hunger. Techniques such as staying busy, hydrating well and continuing current physical activity regime are encouraged during fasting. Muscle mass is preserved as an evolutionary advantage. Only to be broken down for energy when body fat percentage gets dangerously low (55). Exercise utilizes muscle glycogen, which can speed up gluconeogenesis leading to more rapid lipolysis and faster induction of ketogenesis.

Additionally, light to moderate exercise during a fast signal the body to preserve lean mass and utilize fat stores for energy. This has been shown by McCue, M (2012), who showed during 70 days of alternate day fasts subjects decreased body weight by 6%. Overall fat mass decreased by 11% while lean muscle mass was preserved during this time (56).

Long Term Benefits and Emerging Evidence

Long-term benefits of fasting have not been fully elicited in human trials. That said, good evidence from epidemiologic studies, pilot interventional trials and various clinics across North America releasing case studies suggesting the benefits of fasting outweigh the potential harms in the average individual. However, each individual has different needs and careful observation, education and patient feedback are required prior to, during, and after any given fasting regimen. No universal template for medication adjustments exists. Much of our current guides for medication adjustments during IF come from practitioners who worked with patients undergoing religious fasts, such as during Ramadan. Practitioners must ensure patients are self-monitoring blood glucose levels frequently though out the day. It is also imperative that when in doubt, heir on the side of under-dosing medication. Hyperglycemia is more acceptable in the short term than hypoglycemic event (27).

Types of Fasts:

16:8 – Time Restricted Feeding (TRF)

16 hours of fasting with all caloric intake for the day condensed into an 8-hour window. The intention is not to achieve ketosis but to get many of the weight loss, fat burning benefits of fasting with minimal effect on the person’s life. It is safe to do with most medications (see table 3) and a good starting and/or maintenance protocol for individuals. Additionally, this time restriction could be extended to 18:6 or 20:4. The longer the fast, the more gluconeogenesis increases. A recent 8 week study comparing TRF of 8 hours to a typical 12 hour feeding period of the same meal composition and caloric intake showed a decrease in overall fat mass (16.4% vs 2.8), with improvements in insulin levels and fasting glucose (57). Caution should be taken that patients ensure they get adequate nutrients when they do feed (28).

24 - Hour fasts

Typically consists of eating one meal that day, permitting any medications that should be taken with food to be consumed. It can easily be fit into personal routines, as people fast during

the day then have family dinner or main meal when they choose. Nutrient deficiencies are very rare during this short duration. It is important to counsel patients to eat to satiety. As they are burning a lot of calories during fasting periods, eating to satiety ensures BMR remains elevated. This strategy is effective 2-3 days per week but can be done more frequently for more rapid effects. It has been shown to induce steady weight loss with minimal adverse effects (56).

The 5:2 Diet

Consists of 5 days of regular eating with 2 days (grouped together or spread apart) of <500 calories (females) and <600 calories (males). The same mechanisms seen in fasting are present to a lesser extent and benefits seen as long as calories are kept low enough (58). A 6-month randomized study of this nature compared 25% energy reduction in both groups. 7 days/week of 25% energy restriction per day based on estimated requirements to 25% energy restriction condensed into 2 days (<650 kcals/day) based on 5 days of no energy restriction. At the end of 6 months, weight loss was comparable in both groups, however greater improvements in fasting insulin and insulin resistance levels were seen in the intermittent fasting group (58). It was deemed effective for insulin resistant individuals and may be done until desired weight is achieved then fasting days less frequently (28). It is also a bridge to longer fasts. Given there is some caloric intake on fasting days may reduce risk of hypoglycemic events in high risk individuals undergoing medication deprescribing (34).

36-42 hour fasts

This protocol involves a full day of no caloric intake. Some protocols have included three per week until patients are off medications and/or desired weight is achieved, then fasting is shortened or made less frequent (27). As with all fasting examples, it is important to measure blood sugars 2-4 times per day to ensure medications are properly adjusted and avoid hypoglycemic as well as elevated blood sugar events (27).

Prolonged fasts – 48+ hours

Used for severe diabetes and/or morbid obesity or conditions that are more urgent and require drastic action. Patients can then transitioned to 36-42 hour fasts. This protocol must be well supervised. Medications will inevitably have to be adjusted. Due to the possibility of refeeding syndrome, if fasting >5 days, practitioners are advised to understand how to deal with this potential complication (59). This is a very rare and risk is greatly diminished by taking a daily multivitamin and ingesting bone broth or other such sources of minerals like phosphorous (52). Another counselling point for patients is “will I feel hungry all the time?”. The body follows a natural circadian rhythm. The hunger hormone ghrelin peaks and lowers throughout the day despite eating or not. In prolonged fasts it is maximal at 48 hours and then proceeds to drop from there (60).

Table 3. Medication Adjustments and Deprescribing in Intermittent Fasting Protocols

Class of Medication	Agents	Dose	Risk of Hypoglycemia and Duration of Action	Recommended Dose Adjustment with IF	Check Blood Glucose/day	Last Dose Prior to Fasting	Comment
Postprandial - Bolus/rapid and short acting Insulins	Lispro (humalog) Aspart (novorapid) Glulisine (Apidra) Humulin-R Novolin geToronto	variable	high rapid - <3 hours	Hold if not eating. On feeding days may resume carb counting at 1 unit per 10-15 g carbohydrates. Target 2-hr post-prandial glucose 6.66-9.99 mmol.	4+	only prior to carbohydrate containing meals. Dose appropriately by carb counting.	Not needed if not eating.
Combination Insulins	70/30 - Humulin 75/25 - Humalog 75%insulin Lispro suspension and 25% Lispro long acting. 50/50 - Humalog Mix 50% short acting 50% long acting.	variable	high based on short acting component rapid - <3 hours in addition to long acting basal component	hold dose if not eating due to rapid acting component. If basal insulin is required, long acting insulin is safer choice. Follow as per below.	4+	Basal insulin recommended as per below	Not recommended due to short acting component
Basal Insulin - take at same time	Glargine (Basaglar, Lantus) Determir (Levemir) Degludec	variable A1c <8% 0.1-0.2 U/kg A1c >8%	high ~24 hours	<20 hour fast start by taking basal insulin at same time. Starting with 25-33% of regular basal dose. If	4+	same time but at reduced dose. Monitor closely in order to make adjustments	Critical to test glucose 3-4 times daily while adjustments are being made. Insulin may change quickly depending on patient's adherence to selected plan and hypoglycemic awareness. Heir on

Intermediate-acting (NPH) - take at same time	(Tresiba) Humulin-N Novolin ge NPH	0.2-0.3 U/kg	typically twice daily dosing"	fasting glucose >10 mmol prior to breaking fast add 2 units or 10%. If 6.66-9.99 mmol continue normal dose. If <6.66 mmol decrease 2-4 units or 10-20%. If >20 hour - 25- 33% of regular dose for first 24 hours, then do not take or reduce dose if glucose between 8-10 mmol. If 10-14 mmol at ~24 hrs dose remains same. If 6.66-9.99 mmol decrease dose. If <6.66 decrease by additional 2-4 units or 10-25%. Decrease 10- 25% at start of next fast as glucose control improves. Prolonged fast - same as above. hold further basal insulin when one time glucose <5.5 mmol. Ramadan schedule when breaking fast or for those not low-carb/VLED on feeding days: <3.9mmol or symptoms - decrease 4U 3.9-5.0 mmol - reduce 2 U 5.0-7.2 mmol - same dose 7.2-11.0 mmol - same or incr. 2 U >11.1 mmol - Incr. 2-4 U		prior to fast and depending on length of fast. Studies have shown even 50% reduced dose on fasting days (<24hrs) resulted in hypoglycemic events.	the side of reducing insulin too much. Long term benefit of fasting outweighs short term risk of hypoglycemia. Patient with insulin pump should start with basal rate decrease minimum 10% lower. Glucose should be checked every 2 hours minimum.
Sulfonylureas	Glyburide (Diabeta), Gliclazide (Diamicron), Glimepiride (Amaryl)	N/A	High 16-36 hrs	discontinue		24-36 hrs	Due to high risk of hypoglycemia. May continue use on feeding days. Do not use in conjunction with Basal insulin
Meglitinides (non- sulfonylurea insulin secretagogue)	Nateglinide, Repaglinide	N/A	moderate- High 4-6 hrs	discontinue		Prior to last meal before fasting	Normally taken prior to meal. Consider switch to oral anti- hyperglycemic with decreased risk of hypoglycemia (DPP-4 inhibitor or GLP-1 receptor analogue)
Biguanides	Metformin	500 mg - 2500 mg divided	Low 12-24 hrs	none or skip on fasting days (if well controlled)	2-4/day	before last meal prior to onset (if well controlled)	Rarely causes hypoglycemia, has beneficial effect. May decrease dose if side effects are present.

		BID with meals					Discontinue last and if glucose well controlled. Maximize metformin to side effect free level before increasing or adding another agent.
DPP-4 inhibitors	Saxagliptin Sitagliptin Alogliptin Linagliptin	2.5, 5 mg tabs up to 5mg OD 25, 50, 100 mg tabs up to 100 mg OD 6.25, 12.5, up to 25 mg OD 5 mg OD	low ~24 hrs	skip dose if >20 hr fast - no added benefit. Low risk but associated with occasional hypoglycemic event. <20 hr fast - may decrease dose by 20-50% when AM fasting glucose <6.66 mmol. Continue dose while fasting glucose 6.67-10 mmol. Increase dose 20-50% if AM fasting glucose >10 mmol >3 times per 1 week prior to breaking fast.	2-4/day	24 hrs	Due to inhibition of glucagon, associated with hypoglycemia when fasting >16 hrs. To be taken on feeding days only. Alternative: GLP-1 receptor analogues do not have insulinotropic effect <4 mmol. If SC option is tolerated. May considering adding DPP-4 inhibitor if fasting glucose >10 mmol and metformin maximized or prior high risk anti-hyperglycemic discontinued. Discontinue after insulin/sulfonylureas were stopped and fasting blood glucose was consistently under 5.55 mmol
SGLT-2 Inhibitors	Dapagliflozin Empagliflozin Canagliflozin Ertugliflozin	5-10 mg OD 10, 25 mg OD 100 mg up to 300 mg OD 5 mg up to 15 mg OD	low 12-24 hours	>48 hour fast - stop at ~48 hour mark to prevent euglycemic ketoacidosis or when one time glucose <6.66 mmol/L. >20 hour fast - may continue . Hold dose if low carb intake (<50 g) on feeding days or fasting glucose prior to fast <6.66 mmol. Discontinue if fasting glucose <5.5 mmol prior to fast. <20 hour fast - prior to fast: Continue withing goal range >6.67 mmol. Hold or ~50% dose if fasting glucose <6.66 mmol.	2-4/day	24 hrs	Benefit of weight loss in all modalities. Enhances urinary glucose excretion and may act as osmotic agent. Ensure adequate hydration during any modality due to osmotic effect of glucose. May continue as a part of intermittent fasting on feeding days. Helps weight loss and expells glucose above renal threshold. For all modalities, discontinued after insulin/sulfonylureas were stopped and fasting blood glucose was consistently within desired range. No benefit to continuing and risk of euglycemic ketoacidosis.
GLP-1 Receptor Analogues Subcut Daily/weekly	Liraglutide (Victoza) Lixisenatide	0.6 mg up to 1.8 mg daily 10mcg up to 20 mcg daily 5-10 mcg	low "12-24 hours	For Lixisenatide only - skip dose if >20 hr fast. Liraglutide should be continued <20 hr fast -	2-4/day	24 hrs	Risk of hypoglycemia very low. Safer than DPP-4 inhibitors as add on agent because it does not have same glucagon blocking response when blood glucose <4 mmol. However, only available in sub-cutaneous option.

	Exenatide (Byetta) Albiglutide (Eperxan) Dulaglutide (Trulicity)	SC q12hr 30-50 mcg SC weekly 0.75-1.5 mg SC weekly	~7 days"	continue. May decrease dose by 20-50% when AM fasting glucose <6.66 mmol for 3 days. Continue dose while fasting glucose 6.67-10 mmol. Increase dose 20-50% on feeding days if AM fasting glucose >10 mmol >3 times per 1 week.			May discontinue after insulin/sulfonylureas were stopped and fasting blood glucose was consistently under 5.55 mmol.
Alpha Glucosidase Inhibitors	Acarbose Miglitol	25 mg up to 100 mg with each meal containin g carbohydrates	low/none <4 hrs	skip and resume during feeding when carbs are part of meal	2-4/day	before last meal	Taken with meals containing carbohydrates >30 g only.
Bile Acid Sequestrant	Colesevelam	1.875 g (3 tabs or 1/2 packet oral suspension) BID or 3.75 g daily	low/none ~24	Continue daily. Maximize with fewest side effects	2-4/day	continuous	May continue until cholesterol levels are within appropriate range if primary indication is cholesterol control.

Data is based on case studies, years of practitioner experience and randomized control trial recommendations for safe deprescribing based on frequent glucose checks and diligent practitioner assessment (20,25,34,26–33).

DISCUSSION

T2DM continues to be a growing worldwide epidemic of disease burden and health care cost (2). While these treatment options may not be for everyone or every setting, this has proved to be an area of study that practitioners need to know how to address. Having options to treat non-medically through diet and lifestyle interventions remains first line treatment for T2DM. Having a knowledge of these methods allows practitioners to safely implement diet and medication changes for their patients. Lots of information on these lifestyle programs is out there, and the motivated patients will inevitably ask their practitioner for further answers or support. Some people will go looking for other ways to alter their disease course when conventional treatments are not working for them. Others may not know about these lifestyle-based strategies but may be

good candidates for them. In both examples, it is necessary for the current and next generation of practitioners to be informed on these methods in order to best serve their patients.

Areas of consensus in guidelines

Weight management:

T2DM is associated with obesity and insulin resistance. Weight loss is linked to improved glycemic control, blood pressure and lipid profile. Ultimately reducing the complications of disease. Diet and exercise being the forefront of these interventions (41,42). The best methods of each highly variable and debated but both deemed essential and achievable in a variety of ways.

Energy Balance:

First line lifestyle interventions recommend reduced energy intake through portion control. Recommended diets are high in whole, unprocessed foods with reduction in added sugar and high glycemic index items (41,42). This has been shown to have benefits on hormones such as ghrelin, leptin and hunger satiety and are part of ongoing support in reducing overall energy intake (13,34,61).

Foods to avoid:

Reduction of refined grains and sugars (especially sugar sweetened drinks). Low glycemic carbohydrates such as high fiber, legumes and whole grain options are better to control glucose/insulin spikes. Diets high in vegetables are widely recommended. Trans fat and high sodium intake are continued to be discouraged due to cardiovascular risk (41,42).

Areas of uncertainty in guidelines

Dietary patterns and “healthy foods”

Many guidelines such as Canada’s Food Guide and the Dietary Guidelines for Americans suggest variety and nutrient dense diets high in vegetables, fruit, whole grains, legumes, nuts, and dairy products such as yogurt and low-fat milk. But some dietary approaches (eg, low carbohydrate diets) restrict fruits in particular due to fructose content and effect on liver metabolism (34). Whole grains and legumes have high starch content and increase insulin

secretion. Those with diabetes, have impaired glucose metabolism. Many suggest the insulin reducing effects of avoiding these foods are beneficial in achieving disease remission. Despite the benefits of micronutrient, phytochemical, and fiber content of fruit/legumes (26).

The Mediterranean diet is deemed safe and appropriate for management of type 2 diabetes. Questions arise about alternatives to such plans if cost, attainability and quality cannot be achieved (2,13,42,62).

Difficulties in setting guidelines for deprescribing

The dietary interventions outlined in this paper are newer and show promising effects (20,26,27,40,63). However, deprescribing medication methods are confined to practitioner preference, years of experience, and not widely published. Each individual patient is different both in response to medication as well as dietary intervention undertaken. Guidelines exist for increasing and adding on medications because T2DM is widely considered progressive. Diligence in tracking glucose and providing rapid response to patients may be required to prevent hypo and hyperglycemic events. Variability also exists in these studies in regard to how information is transmitted (office visits vs application and/or telehealth) (20,25,34,26–33).

Remission of type 2 diabetes through diet

Remission of type 2 diabetes is defined as glucose levels lower than the diagnostic level for diabetes in the absence of medications for hyperglycemia for a period of time at least one year) (17,64). Ongoing, long term data does not exist. However, data looks promising to suggest these methods can help to achieve the desired weight loss. At this point a transition and maintenance period to more sustainable form of eating may allow for remission to be achieved (20). With continued education and follow up with practitioner, good glycemic control and reduction in medications may be feasible. Low energy diets in the presence of bariatric surgery are a comparable and proven remission (5,8,9,24). Low carb diets have plenty of case studies and

anecdotal evidence in mainstream media but minimal long-term data. Fasting has proven effective in studies less than one year (33,50). It has long been practiced in religious practice such as Ramadan (63). Longer term randomized control trials are needed to assess adherence, effectiveness, physiological changes and feasibility in type 2 diabetics when used on a consistent basis. However, the predominant role of energy deficit versus macronutrient composition of the diet in achieving remission is still controversial.

Future research:

Comparison of very low calorie, low carb, IF in long term settings is underway. Effectiveness and feasibility need to be assessed in type 2 diabetes populations specifically. Consensus needs to be made on safety and adherence long term.

Uncertainty surrounding nuts, fruits, legumes, plant oils, low fat versus high fat dairy, and diet quantity and quality will vary but consensus on alternatives for staple food items will have to be determined.

Testing deprescribing protocols is important to patient safety. More data needs to be published on methods of doing so in existing and upcoming trials to aid practitioners in doing so themselves.

Investment in medical education to train medical students, PA's and NP's in the available lifestyle interventions, including nutrition education and meal timing in regard to disease prevention and overall well-being.

CONCLUSION

Evidence suggests that current management of type 2 diabetes is poorly achieved in many presenting individuals. Despite the challenges of nutritional research, considerable evidence suggests alternatives to current guidelines. While there is no consensus on the best method, there

may not need be one. These interventions may be helpful to medical practitioners and provide options for patients to achieve remission their type 2 diabetes. Weight loss continues to be the cornerstone of lifestyle interventions. Any option to achieve such results is beneficial to disease progression and outcomes. All medication changes and dosing should be closely monitored by the practitioner. This can be safely done with a basic understanding of the mechanism and how to safely taper these drugs during a given regimen.

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