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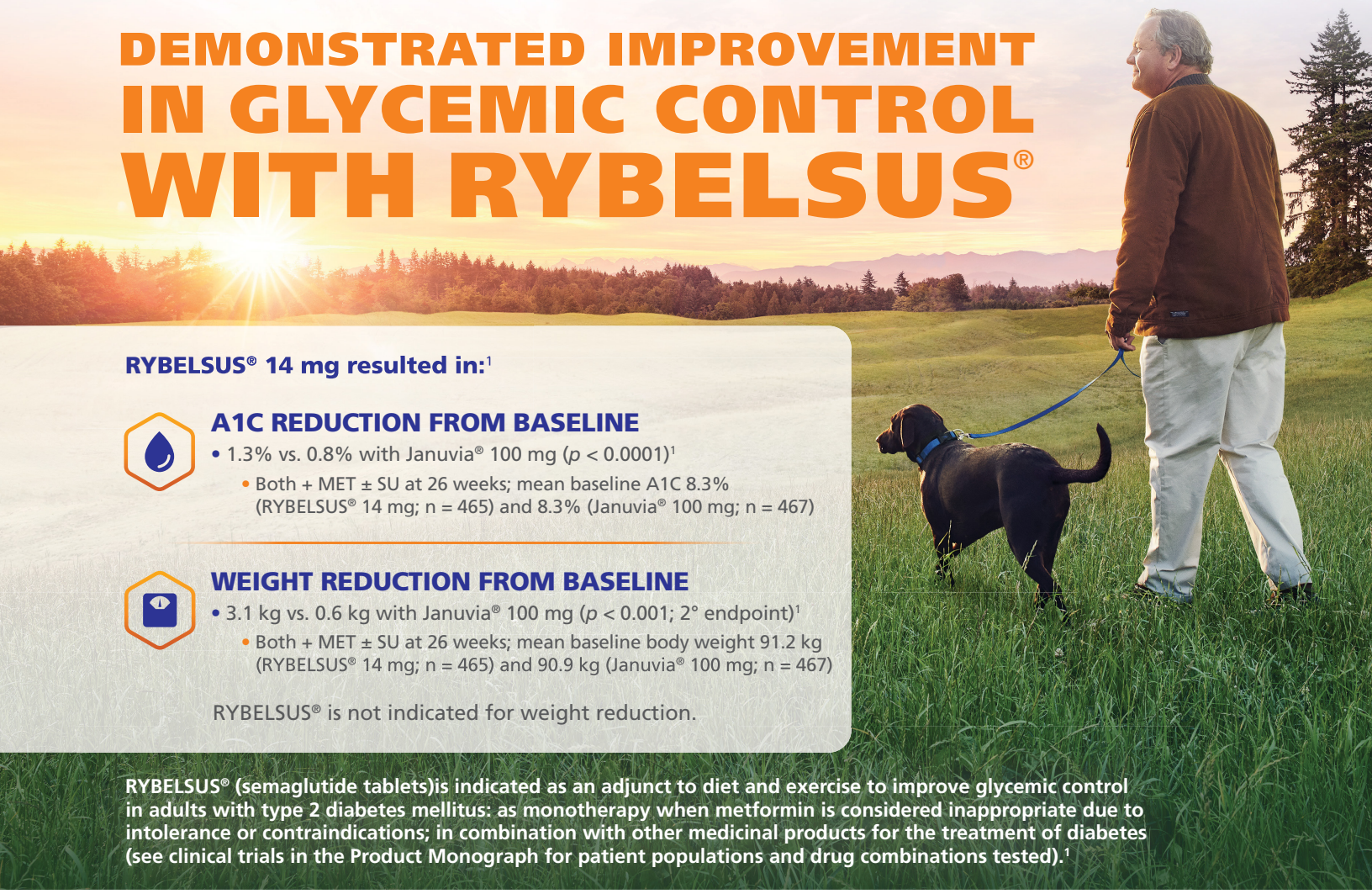
THE FIRST AND ONLY ORAL GLP-1 RA*

DEMONSTRATED IMPROVEMENT IN GLYCEMIC CONTROL WITH RYBELSUS®



RYBELSUS® 14 mg resulted in:[1]

A1C REDUCTION FROM BASELINE

- 1.3% vs. 0.8% with Januvia® 100 mg ($p < 0.0001$)[1]
  - Both + MET ± SU at 26 weeks; mean baseline A1C 8.3% (RYBELSUS® 14 mg; n = 465) and 8.3% (Januvia® 100 mg; n = 467)

WEIGHT REDUCTION FROM BASELINE

- 3.1 kg vs. 0.6 kg with Januvia® 100 mg ($p < 0.001$; 2° endpoint)[1]
  - Both + MET ± SU at 26 weeks; mean baseline body weight 91.2 kg (RYBELSUS® 14 mg; n = 465) and 90.9 kg (Januvia® 100 mg; n = 467)

RYBELSUS® is not indicated for weight reduction.

RYBELSUS® (semaglutide tablets)is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: as monotherapy when metformin is considered inappropriate due to intolerance or contraindications; in combination with other medicinal products for the treatment of diabetes (see clinical trials in the Product Monograph for patient populations and drug combinations tested).[1]

Clinical use:
RYBELSUS® is not indicated for use in type1 diabetes or for the treatment of diabetic ketoacidosis. RYBELSUS® is not indicated for use in pediatric patients. Greater sensitivity of some older individuals cannot be ruled out. Therapeutic experience in patients ≥ 75 years of age is limited.

Contraindications:
- Hypersensitivity to RYBELSUS® or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container
- Personal or family history of medullary thyroid carcinoma (MTC), or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- Pregnancy or breastfeeding

Most serious warnings and precautions:
Risk of thyroid C-cell tumours: In both genders of rats and mice, semaglutide caused treatment-dependent thyroid C-cell tumours at clinically relevant exposures. It is unknown whether semaglutide causes thyroid C-cell tumours in humans. Patients should be counselled regarding the risk and symptoms of thyroid tumours.

Relevant warnings and precautions:
- Hypoglycemia with concomitant use of insulin secretagogues or insulin
- Driving and operating machinery
- CV effects: increased heart rate; PR interval prolongation
- Pancreatitis
- Hypersensitivity
- Diabetic retinopathy: In patients with history of disease, monitor for worsening
- Renal insufficiency: Severe GI adverse reactions warrant monitoring of renal function; acute renal failure and worsening of chronic renal failure have been reported
- Fertility
- Hepatic impairment

For more information:
Please consult the Product Monograph at RYBELSUSPM-E.ca for more information relating to adverse reactions, drug interactions, and dosing information, which have not been discussed in this advertisement.

The Product Monograph is also available by calling us at 1-800-465-4334.

Scan this QR code or visit Rybelsus.ca to watch a video on RYBELSUS® and learn about helpful resources for you and your patients!

* Comparative clinical significance has not been established. Adapted from the RYBELSUS® Product Monograph;[1] Rosenstock J, et al., 2019,[2] see below for study design (PIONEER 3).
CV, cardiovascular; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SU, sulfonylurea.

References: 1. RYBELSUS® (semaglutide tablets) Product Monograph. Novo Nordisk Canada Inc., March 30, 2020.
2. Rosenstock J, et al. Effect of additional oral semaglutide versus sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: The PIONEER 3 randomized clinical trial. *JAMA.* 2019.

A 78-week, double-blind trial to compare the efficacy and safety of RYBELSUS® vs. Januvia®. A total of 1864 patients with type 2 diabetes were randomized to RYBELSUS® 3 mg (n = 466), RYBELSUS® 7 mg (n = 465), RYBELSUS® 14 mg (n = 465), or sitagliptin 100 mg (n = 467) once daily, all in combination with metformin alone or metformin and sulfonylurea. The primary endpoint was change in A1C from baseline to week 26.

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PrRYBELSUS® semaglutide tablets

How to apply the Canadian Obesity Clinical Practice Guidelines to people with type 2 diabetes

Sue D. Pedersen, MD, FRCPC, DABOM

About the Author

Dr. Sue Pedersen is a Specialist in Endocrinology & Metabolism and a certified American Board of Obesity Medicine (ABOM) diplomate. She completed her training as an endocrinologist at the University of Calgary in 2005 and has a busy endocrinology practice at the C-ENDO Diabetes & Endocrinology Clinic in Calgary. She is the lead author on the pharmacotherapy chapter of the 2020 and 2022 Canadian Obesity Clinical Practice Guidelines, and a member of the Expert Committee for the 2018 Diabetes Canada guidelines as a co-author of the Weight Management chapter. She is a principal investigator for several studies of diabetes and obesity pharmacotherapy, and a co-author of many of the resultant publications. She has a public information website for healthcare providers and patients about obesity and diabetes (www.drsue.ca).

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Approximately 90% of people with type 2 diabetes (T2D) have overweight or obesity. Thus, weight management is a highly relevant clinical issue in this patient population. However, studies of obesity treatment in people with T2D consistently show that people with T2D lose less weight than people who do not have diabetes. There are many reasons why weight loss can be more difficult to achieve for people with diabetes.

Some medications can cause weight gain, as can cessation of hyperglycemia-associated glucosuria with acquisition of glucose control. Complications of DM can limit physical activity. Hypoglycemia can lead to weight gain, not only because treatment of hypoglycemia requires the ingestion of carbohydrates, but also because some patients may consume more calories than necessary to prevent hypoglycemia ('defensive snacking') or engage in a compensatory increase in food consumption due to fear of hypoglycemia. The stress and burden of diabetes can also lead to emotional eating. Furthermore, insulin resistance is often cited as making weight loss more challenging, though the mechanisms at play here are poorly understood.

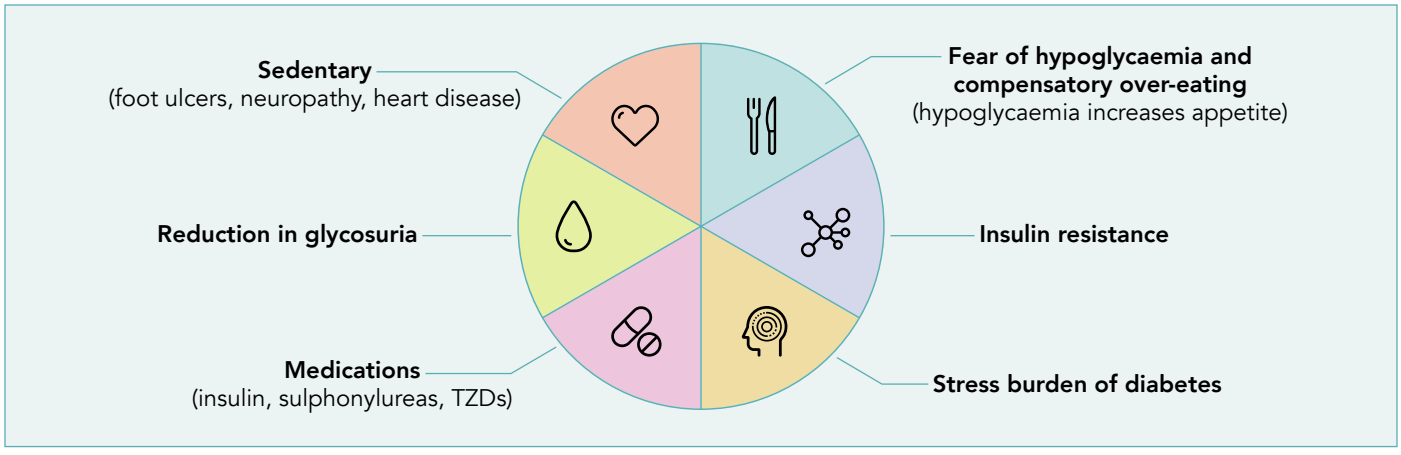

Figure 1: Reasons weight loss can be more difficult to achieve in people with diabetes[1,2,3,4]

Weight loss is associated with improvement in various comorbidities related to obesity, including glycemia. Among individuals with prediabetes, one kilogram of weight loss is associated with a 16% relative risk reduction in the development of T2D.[5] An approximate 15% weight loss from baseline with lifestyle intervention can lead to remission of T2D,[6] especially when the duration of diabetes is short. While these data for lifestyle interventions are encouraging, the vast majority of people who lose weight with the help of lifestyle intervention are not able to maintain the weight loss over the long term due to natural biology which drives weight regain through increase in ghrelin, reduction in satiety hormones, and a reduction in resting energy expenditure.[7] Another challenge is that these interventions may be difficult to implement in real-world clinical practice.

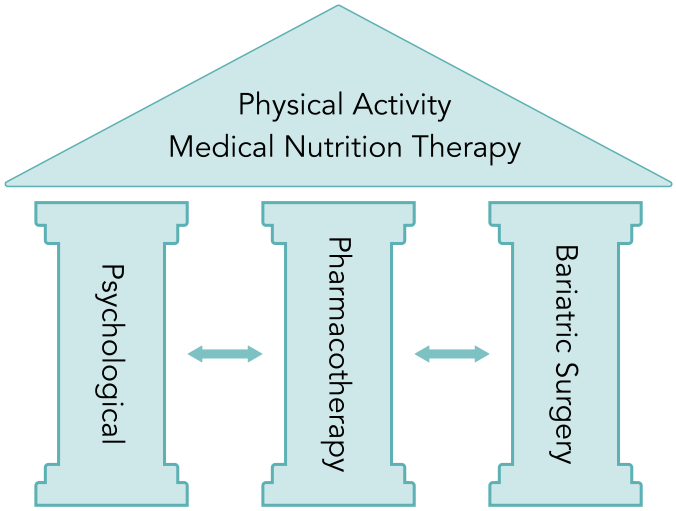

Figure 2: Three pillars of obesity management that support medical nutrition therapy & physical activity.

So what do the Canadian obesity guidelines recommend for people with T2D?

The three pillars of obesity management that support medical nutrition therapy and physical activity are psychological support, pharmacotherapy, and/or bariatric surgery (Figure 2).

The Canadian obesity guidelines recommend choosing therapy from these pillars as appropriate for each patient. Lifestyle approaches, which include medical nutrition therapy and physical activity, are not sufficient interventions in and of themselves; rather, the pillars of treatment facilitate adherence to healthier lifestyles.[8]

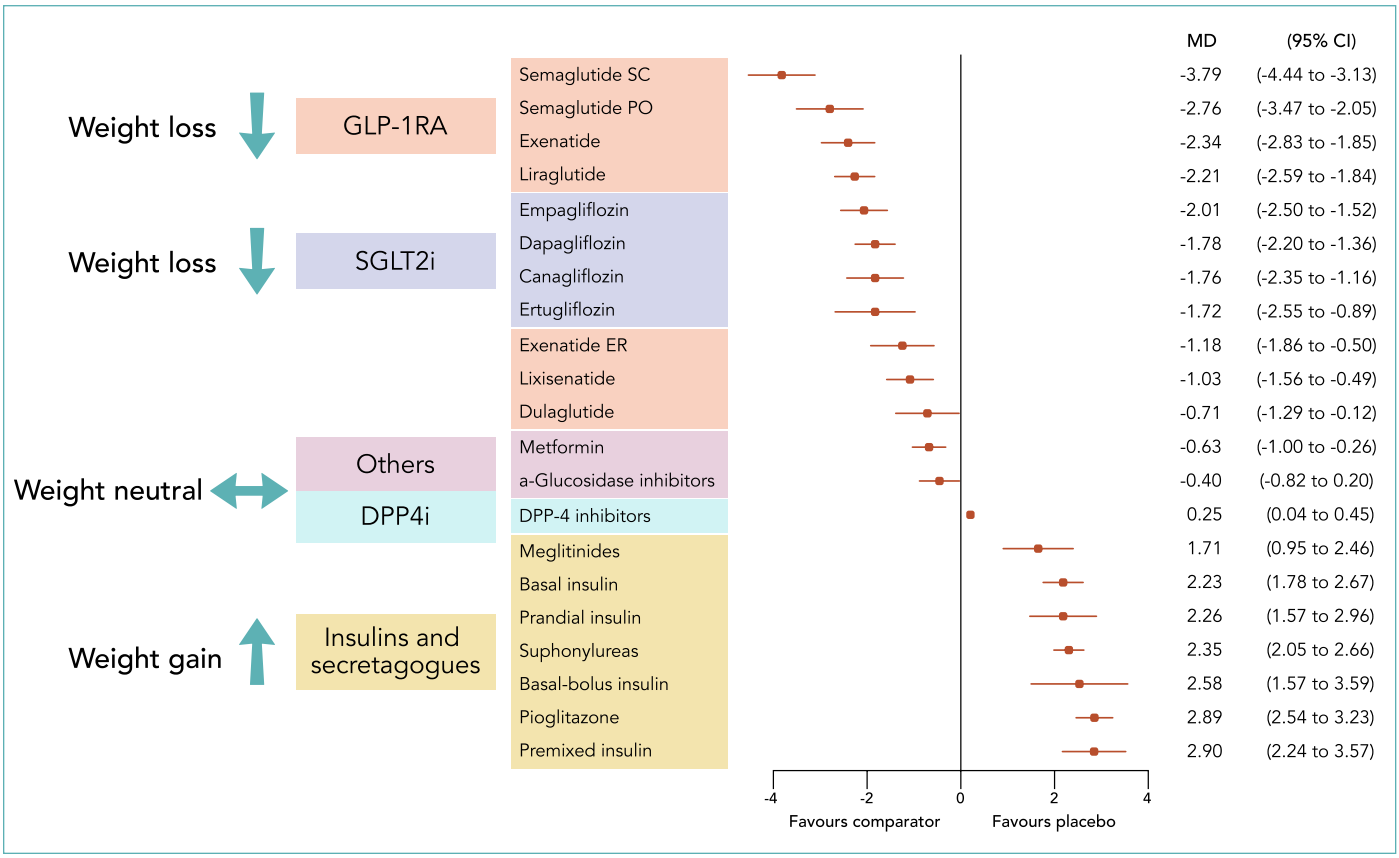

Figure 3: Effects of glucose-lowering agents on body weight: network meta-analysis of 394 trials.
Adapted from Kakotrichi P et al.[13]

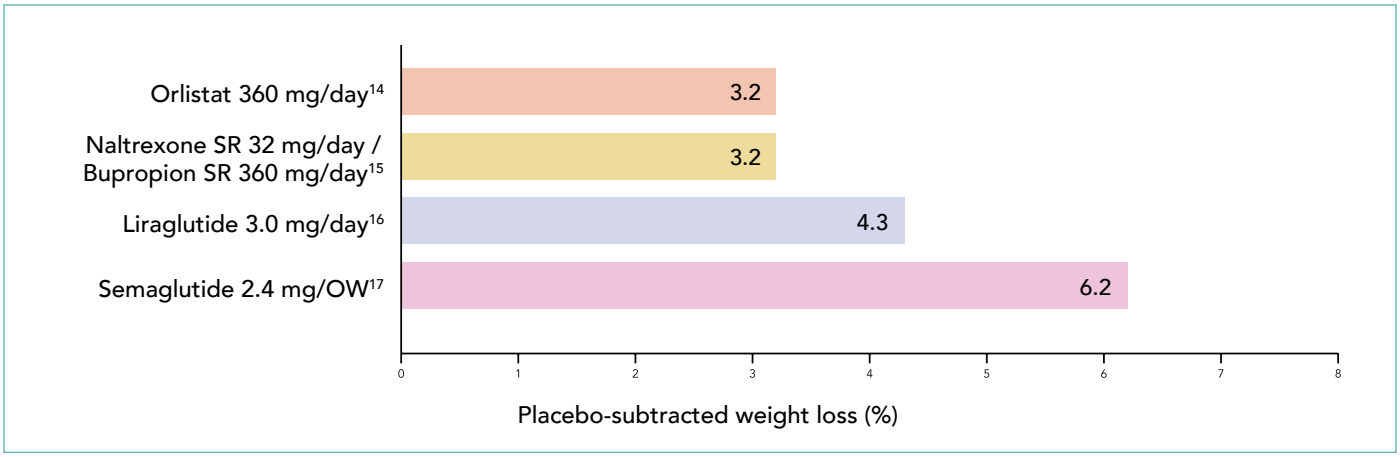

Figure 4: Efficacy of approved obesity pharmacotherapy in people with type 2 diabetes. All treatment differences for obesity pharmacotherapy were significant, p<0.001 vs. placebo.[14,15,16,17]
SW: Sustained Relase; OW: Once Weekly

Medical Nutrition Therapy

There are numerous nutritional approaches that can improve glycemia with or without a small amount of weight loss.[9] These approaches include following the Mediterranean dietary pattern, a vegetarian diet, low glycemic index, a DASH (Dietary Approaches to Stop Hypertension) diet, and the inclusion of pulses (e.g. beans), vegetables, and nuts as part of one's routine nutritional consumption. It is recommended that nutrition plans should be personalized to ensure that they meet individual values and preferences and are safe, effective, nutritionally adequate, culturally acceptable, and affordable for long-term adherence. It is recommended to consider intensive lifestyle interventions that target a 7–15% weight loss to increase the likelihood of remission of T2D.[9]

Physical Activity

Meta-analyses have consistently shown improvements in Hemoglobin A1c (A1c) following structured or supervised aerobic and/or resistance exercise training in people with T2D, even in the absence of weight loss.[10] Numerous studies have demonstrated that exercise with or without dietary interventions can reduce the risk of type 2 diabetes by 38–58% among people with prediabetes.[11]

Pharmacotherapy

According to the Obesity Canada guidelines, when choosing the most appropriate medications for glycemic control, the effect of glucose-lowering pharmacotherapy on weight should be considered.[12] GLP-1 receptor agonists and sodium/glucose cotransporter 2 (SGLT2) inhibitors are associated with weight loss in addition to improving glycemic control. Other agents such as metformin, DPP-4 inhibitors, and acarbose are typically weight-neutral. Insulin, insulin secretagogues, and thiazolidinediones (TZDs) are associated with weight gain. As GLP-1 receptor agonists and SGLT2 inhibitors address the coincident goals of weight loss, glycemic control, and cardiorenal protection, they should be prioritized for the treatment of T2D.

When used in conjunction with health behaviour changes, obesity pharmacotherapy can facilitate weight management, improve glycemic control, and reduce the need for other glucose-lowering medication for people with T2D and a BMI ≥ 27 kg/m2.[12]

Figure 4 illustrates the placebo-subtracted weight loss efficacy of approved obesity pharmacotherapies in people with T2D. This depiction illustrates an indirect treatment comparison and is not from head-to-head trials. Readers should note that patients differ in terms of background glucose lowering medication, the duration of their T2D, and other important demographic and disease-related factors.

Orlistat is a pancreatic lipase inhibitor, inhibiting the absorption of ingested fat and thereby creating a caloric deficit. A meta-analysis of patients with T2D and obesity found that patients treated for 6 or 12 months with 120 mg orlistat t.i.d. had significantly greater reduction in A1c compared with placebo (0.74% vs. 0.31%, respectively).[18] The average weight loss in the orlistat group was 3.8kg compared to a loss of 1.4kg for patients in the placebo arm. The primary reason for improvement in glycemic control with orlistat is weight loss.

Liraglutide is a GLP-1 receptor agonist that acts centrally to improve satiation and satiety and reduce

hunger, with a transient effect to decrease gastric emptying.[19,20] Liraglutide is approved for T2D at a dose of 1.2 mg or 1.8 mg daily, with near-maximal efficacy for A1c lowering at the 1.8 mg dose. It is approved for long-term obesity management at a dose of 3.0 mg daily for people with or without T2D. In people with obesity and T2DM managed with 0-3 oral agents, the SCALE randomized clinical trial found that in conjunction with health behaviour change, liraglutide 3.0 mg reduced weight by -6.0%, vs -4.7% with liraglutide 1.8 mg and -2.0% with placebo at 56 weeks.[21] A1c was reduced by 1.3% in the liraglutide 3.0 mg group, 1.1% in the liraglutide 1.8 mg group, and 0.3% in those receiving placebo.

Naltrexone/bupropion is approved for obesity management as a combination tablet, which works by inducing satiety centrally and reducing cravings.[22] Used along with health behaviour changes in adults with a BMI of 27–45 kg/m^2 and T2D managed with oral agents or diet, naltrexone/bupropion-treated patients achieved a 5% weight reduction from baseline, compared with 1.8% with placebo, and achieved a 0.5% greater reduction in HbA1c vs placebo. The change in A1c was correlated with the change in body weight.

Semaglutide is a GLP-1 receptor agonist that acts centrally to improve satiation and satiety, reduce hunger, and reduce cravings.[23] Semaglutide is approved for treatment of T2D at a dose of 0.5 mg, 1.0 mg, or 2.0 mg weekly, with near-maximal therapeutic efficacy for A1c lowering at the 1.0 mg dose. Semaglutide is approved in Canada for long-term obesity management at a dose of 2.4 mg weekly, in people with or without T2D. Among people with overweight or obesity and who have T2D managed with oral agents or health behaviours alone, semaglutide 2.4mg with health behaviour modification resulted in a superior weight loss of 9.6% at 68 weeks, compared to a loss of 7.0% with semaglutide 1.0 mg and 3.4% with placebo. Reduction in A1c was 1.6% with semaglutide 2.4 mg, 1.5% with semaglutide 1.0 mg, and 0.4% with placebo.

Bariatric Surgery

Bariatric surgery can be considered for people with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with T2D, to induce control and remission of T2D in combination with best medical management, over best medical management alone.[24] Bariatric surgery should also be considered in patients with poorly controlled T2D and Class I obesity (BMI between 30 and 35 kg/m^2)[10] despite optimal medical management. Remission rates of diabetes at three years have been reported at 79% and 95% in Roux-en-Y gastric bypass and duodenal switch groups, respectively, compared to no response with

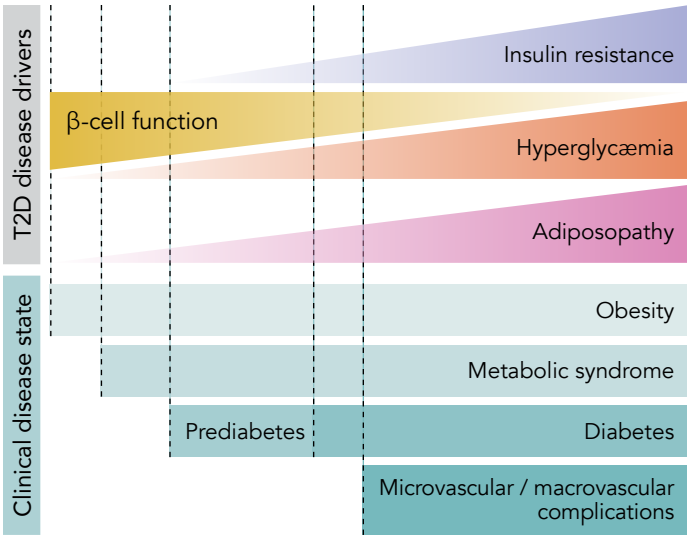

Figure 5: Obesity management disrupts type 2 diabetes progression.[28]

medical intervention alone. Long-term outcome data from a randomized controlled trial found that 29% of patients who underwent Roux-en-Y gastric bypass and 23% who underwent sleeve gastrectomy maintained A1c levels of 6.0% or lower at 5 years, with or without the use of diabetes medications, compared to 5% of patients who underwent intensive medical therapy alone.[25] Predictors of diabetes remission include higher preoperative serum C-peptide, younger age, shorter duration of diabetes, and lack of need of insulin therapy preoperatively.[26] In people who experience diabetes remission, it is important that routine screening for diabetes continues lifelong, as recurrence of diabetes is common.

Treating obesity earlier disrupts the natural history of T2D

Weight gain, central adiposity, and insulin resistance, which ultimately lead to hyperglycemia, are typically present decades before a diagnosis of T2D. As shown in Figure 5, treatment in the early years of obesity provides the opportunity to prevent comorbidities related to excess adiposity. At the stage where metabolic syndrome has developed, treatment of obesity is targeted towards resolution of metabolic syndrome and prevention of prediabetes. During the prediabetes stage, potential outcomes of obesity management include remission of prediabetes and prevention of T2D, whereas if the same intervention is started after the onset of T2D, goals of treatment center on glycemic control or perhaps T2D remission. Once diabetes-related complications have developed, the focus is on treating or preventing progression of

those complications, in addition to glycemic control.

While there are important benefits to treating obesity across the continuum, by treating obesity earlier, we have the potential to disrupt the natural history of T2D. As such, a focus on weight management must start as early as possible in the continuum of metabolic disease.

As most patients with T2D will benefit from having a primary weight-centric approach to diabetes management, the 2022 ADA/EASD guidelines have been updated to prioritize weight management alongside glycemic control and cardiorenal protection in their diabetes pharmacotherapy algorithm[27]—an important addition to the treatment paradigm!

Clinical Pearls

- When any weight management treatment modality is initiated in a person with T2D, it is important to consider any needed reduction in insulin or secretagogues for avoidance of hypoglycemia.
- As weight decreases, reduction in other medications (eg. hypertension medications, thyroid hormone treatment for hypothyroidism) may be required, and these parameters should be monitored.
- For any patient who experiences remission of T2D or prediabetes with any treatment modality, it is essential that glycemic control is re-evaluated regularly to screen for recurrence.

Financial Disclosures

Honoraria: Abbott, AstraZeneca, Bausch, Bayer, Boehringer, Dexcom, HLS, Janssen, Lilly, Novo Nordisk, Merck, Pfizer, Sanofi

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Consideration of cannabinoids in the treatment of Diabetic Peripheral Neuropathic Pain

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About the Author

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Introduction

Diabetic Peripheral Neuropathic Pain (DPNP) is a leading complication of diabetes that can have marked impacts on quality of life,[1] may lead to increased depressive symptoms,[2] and can be difficult to treat due to medication side effects.[3] As a result, there has been growing interest in exploring adjunctive treatment options for chronic neuropathic pain, including medical cannabinoids. While the pathogenesis of DPNP is not fully understood, there is evidence that persistent hyperglycemia contributes to a number of processes leading to vascular damage, increased oxidative stress, and release of free radicals and pro-inflammatory molecules[4,5]—all of which may lead to DPNP symptoms, including pain.

Cannabinoids and the Endocannabinoid System

The endocannabinoid system (ECS) is ubiquitous in the human body and has been linked to a range of system pathways, including those implicated in seizures, mood, nausea, sleep, and pain. Cannabinoid receptors, such as the CB1 receptor, are highly present in the central nervous system where they are the most common form of G-protein coupled receptor, as well as the peripheral nervous system where they are commonly found at sympathetic nerve terminals.[6] Both the location and density of receptors make the ECS an interesting potential therapeutic target for treating neuropathic pain.

The Cannabis sativa plant is the best-known source of cannabinoid chemicals, including the two most common: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has a longstanding tradition in various cultures of medicinal and spiritual use, and more broadly as a recreational substance with psychoactive effects. Adverse effects may include tachycardia, hypotension, fatigue, changes in appetite, anxiety, psychosis, and impaired judgement and coordination. CBD itself does not have recreational psychoactive effects and has recently been promoted as having a wide range of potential clinical uses, including anti-inflammatory and antioxidant properties.[7]

While CBD is generally well tolerated, some common side effects may include fatigue or sedation, diarrhea, and changes in appetite or weight.[8] Both THC and CBD are metabolized by the cytochrome P450, leading to consideration of potential drug interactions.

Medical Cannabinoids in Canada

In Canada, medical cannabinoids can be divided into prescription-based and authorization-based (Table 1). Cannabis has been officially legal in Canada

Prescription-based	THC:CBD content	Health Canada approved application
Nabilone	Synthetic THC available in 0.25mg, 0.5mg and 1 mg capsules	Chemotherapy-induced nausea and vomiting
Nabiximols	Plant-derived oromucosal spray with 2.7 mg THC and 2.5 mg CBD per spray	MS-related spasticity, secondarily for adjunctive symptomatic treatment of neuropathic pain in MS; cancer-related pain
Authorization-based	**THC:CBD content**	**Health Canada approved application**
Herbal cannabis, including gel capsules, edible oils, topical oils, vape products	Variable ratios. Common oil formats include: • CBD dominant 1:20 • Balanced 1:1 • THC dominant 20:0	None; medical cannabis is regulated, but has no specific approved application

Table 1: Legal forms of medical cannabinoids in Canada

for medical purposes since 2001, and for recreational use since 2018.

Prescription-based medical cannabinoids are those that have a drug identification number (DIN), require a prescription, and are dispensed at a pharmacy. These products undergo Health Canada's drug approval process.

Authorization-based products are covered by the Cannabis Act, but do not have a DIN and therefore cannot be prescribed but are instead authorized. The patient is then registered with a licensed producer (a company legally licensed to produce and sell plant-derived medical cannabis products). The products are ordered online and delivered directly to the patient via the postal system. These products may include dried herbal products intended for combustion and inhalational use, vape products, oils intended for ingestion or topical application, gel capsules, and a variety of edible products, and are regulated by Health Canada but not specifically approved for any indication. Due to the wide heterogeneity of strains and products, coupled with historic regulatory and legal restrictions, there is a paucity of randomized controlled clinical trials using medical cannabinoids.

Medical Cannabinoids and Neuropathic Pain

Historically, cannabinoids have not routinely been recommended for the treatment of neuropathic pain due issues of legality, lack of evidence or concerns about risk of use. Within the last decade there have been multiple organizations and societies that have reviewed the evolving literature and have published updated guidelines positioning cannabinoids as a third-line treatment for chronic neuropathic pain (Table 2).

Organization	Cannabinoid Role
Canadian Pain Society, 2014[9]	3rd line
European Pain Federation (EFIC), 2018[10]	3rd line
German Pain Society, 2019[11]	3rd line
International Society for the Study of Pain (IASP) French Chapter, 2020[12]	Inconclusive due to lack of high-quality evidence.
American Academy of Neurology, 2022[13]	Limited comment on nabilone: "probably more likely than placebo to improve pain."

Table 2: Summary of international societies/organizations and their recent cannabinoid recommendations for neuropathic pain

The reviews leading to these updated guidelines generally assessed a small pool of existing higher-quality clinical studies, often with the use of prescription-based medical cannabinoids. While there is a wealth of animal-based studies showing promising cannabinoid efficacy for neuropathic pain, there remain a limited number of human clinical studies. Below is a summary of several recent studies not captured in some of the earlier reviews.

- A small trial of 17 patients with chronic lumbar radicular pain was published in 2018 that randomized the patients to receive either THC-based oil or placebo oil. The THC group experienced a statistically significant improvement in perceived pain.[14]
- A small trial of 29 patients with peripheral neuropathy was published in 2020 and randomized patients to CBD-based topical oil or placebo with crossover possible at 4 weeks. The CBD group demonstrated statistically significant reductions in intense and sharp pain, but not in deep pain. No adverse effects were experienced during the study period.[15]
- Two real-world reviews of the German Pain e-Registry resulted in publications in 2019 and 2022:
  - A 12-week open-label, real-world review of 800 patients treated with a balanced THC:CBD oromucosal spray as an adjunctive treatment for refractory and severe chronic pain. The conclusion was that the treatment was well tolerated and effective, particularly for neuropathic pain.[16]
  - A retrospective real-world comparison of the effectiveness of an oral THC-based treatment versus a balanced THC:CBD based oromucosal treatment with 337 patients in each arm. The study concluded that both were effective, but that the balanced THC:CBD appeared to be more effective and better tolerated.[17]

Undoubtedly a need remains for larger high-quality studies that can address gaps in knowledge relating to efficacy, strain/product selection, patient selection, dosing, and long-term safety.

Practical Considerations for Authorizing

The decision to move forward with cannabinoid-based treatment (prescriptions or authorizations) should be made on a patient-by-patient basis with shared decision making and consideration of patients' personal health characteristics, potential medication interactions, adverse effect risks, and severity of symptoms and response to initial treatments, as well as clinician comfort and expertise.

Authorization

The two components required for a patient to order medical cannabis products are the authorization provided by the clinician and the patient registering directly with a licensed producer. The authorization must include the patient's name and date of birth; the quantity of dried herbal cannabis equivalent per day (which is treated as a monthly quota for ordering purposes); the duration of the authorization (up to a maximum of 12 months) and the clinician's name, medical license number, business address, and signature. Many provincial regulatory bodies recommend including a THC limit on authorizations.

Titration

Historically, titration of medical cannabis has been clinician-dependent, but as clinical experience and research in this area have evolved, there has been a growing move toward expert, research-informed consensus guidelines. An example of these are the recently published recommendations for the dosing of medical cannabis to treat chronic pain which were developed by an international team via a modified Delphi method.[18] This has been modified to provide simple step-wise dosing considerations (Figure 1).

Delivery Options

Historically, only dried herbal cannabis products were available for legal sale in Canada. Over time, there have been the development and approval of a wide range of products including topical options, edibles and orally ingested oils or capsules, and vapes. While pharmacokinetic and pharmacodynamic data is not routinely available for each product, there are some general considerations with each option (Table 3).

Delivery Options
Topical creams and oils are becoming an increasingly viable option and may help reduce systemic side effects. A historical concern has been that the lipophilic nature of cannabinoids reduces transdermal absorption and cost-effectiveness.
Orally ingested oils or gel capsules are commonly recommended for chronic symptoms due to their ease of dosing and longer duration of action. They are also more accessible to patients who do not have a history of smoking or vaping.
Inhalational options such as smoking or vaping allow for rapid absorption and easy titration by patients, but shorter duration and higher fluctuations in blood cannabinoid levels. While an option for certain patients, notably with acute pain flares requiring rapid treatment, they are less frequently recommended in the context of chronic symptoms. Smoking and other combustion methods are not recommended due to health risks.

Table 3: General considerations for various delivery mechanisms

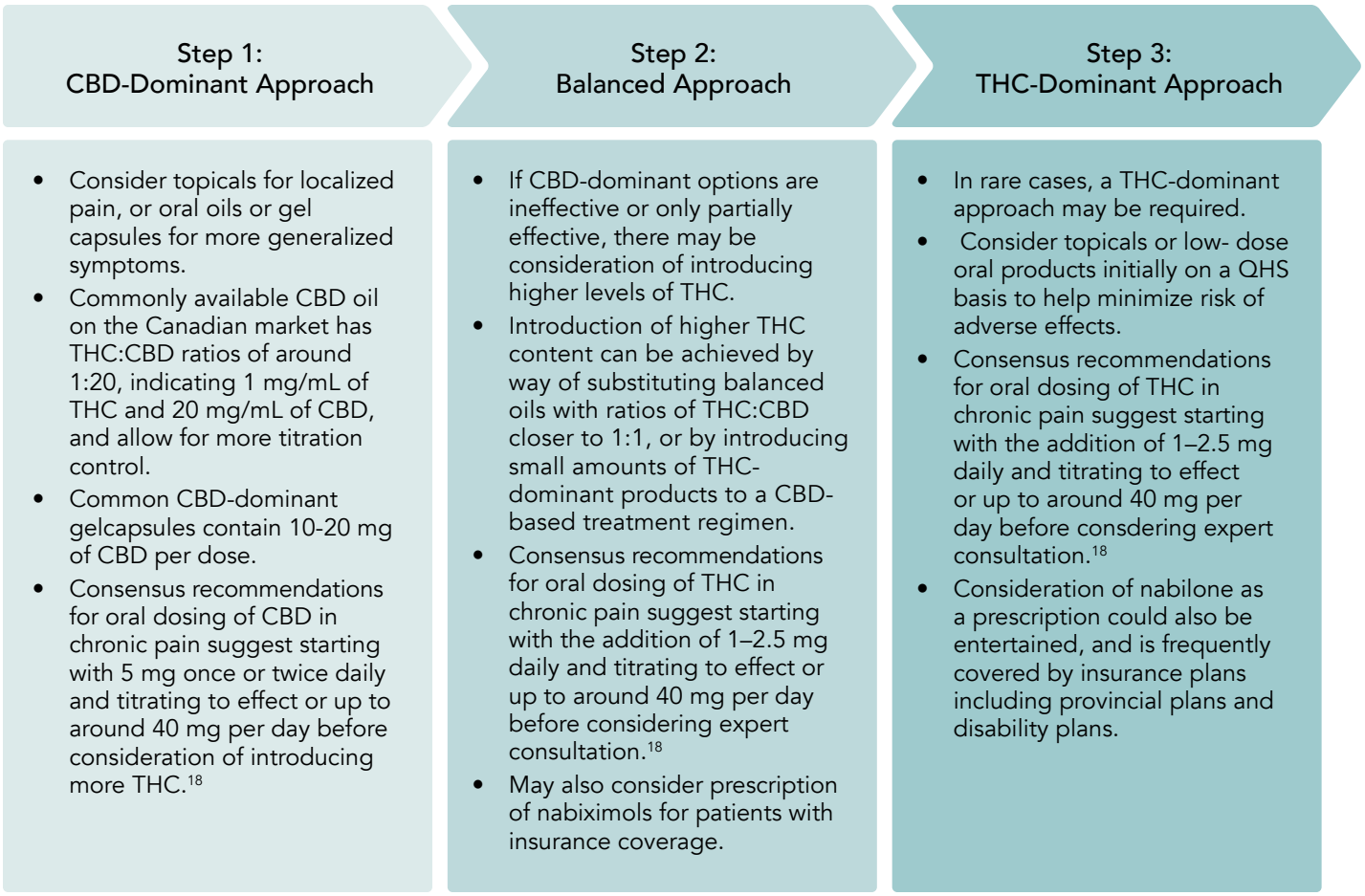

Figure 1: Step-wise dosing considerations (Modified from Bhaskar et al 2021)

Summary

Medical cannabinoids represent an important adjunctive option for patients experiencing persistent and troubling symptoms of DPNP, and increasingly are listed as a third-line treatment option for neuropathic pain. Both prescription and authorized products are available in Canada, although currently, CBD-dominant options are only available via authorization. Further research is required to more clearly elucidate optimal delivery options, strains and THC:CBD ratios, dosing, and long-term safety data.

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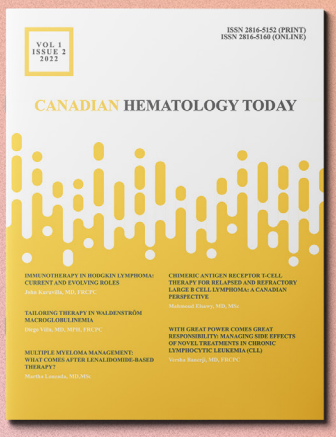

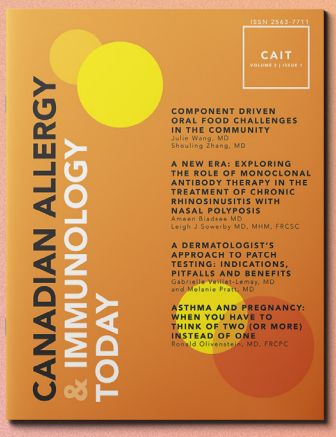

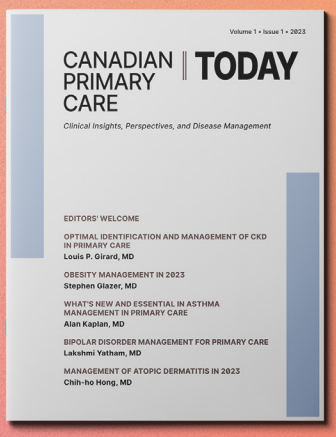

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Type 2 diabetes remission: An overview

Akshay Jain, MD, FRCPC, FACE, CCD, ECNU, DABOM

About the Author

Dr. Akshay Jain is the first Canadian physician to be triple board-certified by the American Boards in Endocrinology, Internal Medicine and Obesity Medicine. He is the only Canadian to have won the AACE Rising Star in Endocrinology Award (2022) and to feature on Medscape's list of 25 Top Rising Stars of Medicine (2020). He practices in Surrey, BC and is a Clinical Instructor in the Division of Endocrinology at the University of British Columbia. He is fluent in 6 languages: English, Hindi, Gujarati, Marathi, Marwari and Urdu. In 2022, he won the Top 25 Canadian Immigrant Award.

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Introduction

In my practice, one of the most common questions I encounter with my type 2 diabetes (T2D) patients is, "How can I get rid of this disease?" The primary focus of practitioners' discussion regarding T2D is the chronicity and irreversibility of the condition. Recently, however, new hope is emerging concerning remission of diabetes with the increasing amount of evidence-based data available.

The need for remission

Diabetes is one of the most expensive conditions to manage in the medical arena. The global burden of diabetes-associated medical costs is predicted to be $1,028 billion by 2030 and $1,054 billion by 2045.[1]

Diabetes is currently the 15th most common cause of decreased life expectancy;[2] socioeconomically disadvantaged and high-risk populations are more adversely affected than the general population.[3]

Diabetes occurs in millions of Canadians; according to the most recent data, approximately 10% of Canadian adults live with diagnosed diabetes. Furthermore, when combined with undiagnosed diabetes and prediabetes, prevalence increases to approximately 30%.[4] The cost of managing diabetes includes both direct costs (including cost of medications, testing supplies, visits to healthcare providers) and indirect costs (including loss of workdays; diminished productivity at work; reduced productivity among the unemployed, diabetes-related disability causing unemployment; and premature deaths attributed to diabetes as a result of workforce loss). The above does not even include the ramifications to mental health that arise as a result of the diagnosis, as well as the ongoing management of a chronic condition such as diabetes. Clearly, therefore, remission of diabetes can have profound benefits from a bio-psycho-socio-economic perspective.

Definition of remission

According to the most recent Diabetes Canada Clinical Practice Guidelines (CPG) type 2 diabetes remission is defined as achieving specified glycated hemoglobin (A1c) thresholds without the use of any antihyperglycemic medication for a minimum of 3 months. Remission to prediabetes is defined as A1C between 6.0% and 6.4%; remission to normal glucose concentrations is defined as A1C <6.0%.[5]

It is important to note that, although there are modalities such as islet cell transplant for type 1 diabetes, this article will focus on remission of type 2 diabetes, which is more clearly established within a growing body of scientific evidence.

Who can achieve remission?

The United Kingdom Prospective Diabetes Study (UKPDS) suggested that at the time of T2D diagnosis,

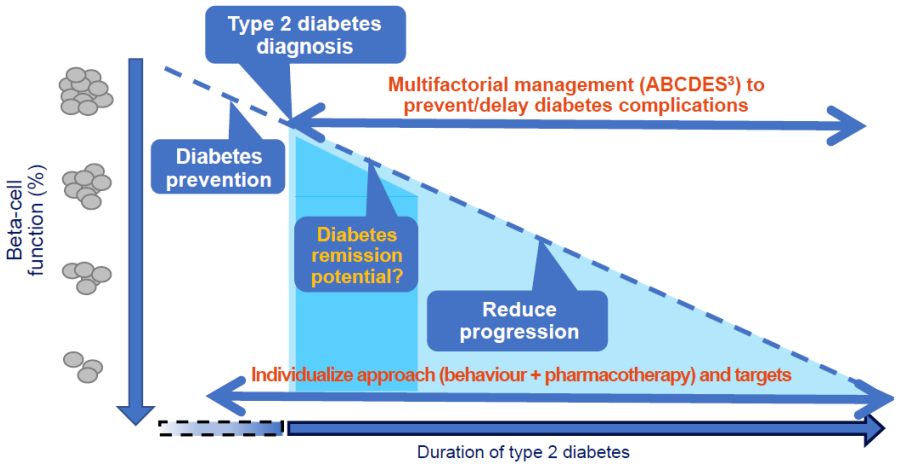

Figure 1: Potential goals and approaches for Type 2 Diabetes
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the β-cell function of an individual has diminished to approximately 50%.[6] Subsequently, decline of β-cell function occurs at the rate of about 4% to 7% per year.[7] The likelihood of achieving remission is highest in individuals who have received a recent diagnosis of diabetes, and is inversely proportionate to the number of years since diagnosis. Similarly, those individuals on few antihyperglycemic agents, at low doses, achieving good glycemic control are more likely to experience remission than individuals on very high doses of insulin/multiple antihyperglycemic agents. The CPG states that remission may be considered for individuals with T2D who are interested in attempting remission; do not have significant eating or mental health disorders; do not have a compelling indication for antihyperglycemic agent(s) for renal or cardiovascular benefit; and are able to participate in health-related behavioural interventions (caloric restriction leading to weight loss, exercise training) with or without bariatric surgery.[5]

How remission is achieved

The succinct response to the vital question, "How is remission achieved?" is, primarily through healthy weight loss. However, this may not be easily accomplished. Of the various CPG recommendations for diabetes remission, only 2 achieve Grade A Level 1A status, both of which entail weight loss: bariatric surgery for those in whom it is appropriate, and a low-calorie diet leading to weight loss with or without large increase in physical activity.[5]

Bariatric surgery

An abundance of data supports the fact that bariatric surgery leads to significant improvement in glycemic control, with favourable results in both ensuing weight loss following surgery and weight-independent effects including: activation of gastrointestinal hormones that influence insulin secretion; altering the rate and site of nutrient delivery; augmentation of gut-brain crosstalk concerning food preferences and behaviour; and modification of bile acids and bacteria that influence peripheral insulin sensitivity and glycemic control.[8]

The CPG recommend bariatric surgery for individuals with diabetes and a BMI ≥ 35. However, the current bariatric surgery guidelines by the American Society for Metabolic and Bariatric Surgery (ASMBS) recommend surgery for individuals with metabolic disease and a BMI of 30–34.9 kg/m^2. More importantly, the guidelines recommend reconsideration of BMI thresholds in individuals of Asian origin, such that individuals with a BMI of 27.5 kg/m^2 should be offered metabolic and bariatric surgery.[9]

Low calorie diets

The majority of the data examining calorie-restrictive nutritional intake by behavioural intervention has been limited as there has been a paucity of robust, randomized control trials (RCTs) specifically investigating diabetes remission as a predefined primary outcome.

However, the results of four key RCTs (DiRECT, DIADEM-I, U-TURN and LookAHEAD) have been instrumental in proposing the following: low-calorie (800 to 850 kcal/day) diets with meal replacement products for a period of three to five months, aimed at achieving >15 kg body weight loss; followed by structured food reintroduction and increased physical activity for weight loss maintenance. This applies to nonpregnant adults with a BMI between 27 and 45 kg/m^2; T2D duration of <6 years, A1C <12% and not using insulin.[5] A recent position statement from Diabetes Canada recognizes that low-carbohydrate food patterns support weight loss, improve the ability to reach glycemic targets and/or attenuate the potential use of anti-hyperglycemic therapies.

In order to limit the risk of weight relapse, it is recommended that a personalized dietary plan is formulated for each T2D patient with the help of a registered dietitian. The likelihood of diabetes remission is directly proportionate to the degree of weight loss. The data on weight loss in excess of 15 kg is particularly robust. The DiRECT trial, in particular, was very practical

in its design, with intervention occurring at a primary care level. Patients adhered to an approximately 850 kcal/day meal replacement plan for up to 20 weeks, followed by a 2- to 8-week food reintroduction phase and then a weight loss maintenance phase that included instructions to increase physical activity. Nearly 46% of individuals were able to achieve and maintain remission at the one-year mark; 35.6% maintained remission at the two-year mark. Among those who achieved remission, followed by relapse, there was a strong correlation with weight regain.[10]

Clinical investigations to establish remission of type 2 diabetes

In light of the fact that the definition of remission is based predominantly on A1c parameters, monitoring A1c is critical to establish remission. If A1c is deemed unreliable, experts suggest using secondary criteria, which may include: meeting fasting plasma glucose (FPG) thresholds on two separate occasions (FPG ≤6 mmol/L for remission to normal glucose levels; or 6.1 to 6.9 mmol/L for remission to prediabetes). The alternative is meeting both oral glucose tolerance test (OGTT) thresholds (both FPG [as above] and 2hPG ≤7.7 mmol/L for remission to normal glucose levels or 7.8 to 11.0 mmol/L for remission to prediabetes). It is recommended that remission laboratory testing (A1c or, if A1c is deemed unreliable, FPG/2-hour OGTT) be performed at three and six months following cessation of any antihyperglycemic therapy.

After remission criteria have been met, testing to evaluate for persistence of remission vs relapse should be performed at least every six months.[5]

Remission vs reversal

From my perspective, it is crucial to impress upon individuals with diabetes that remission is not synonymous with diabetes reversal. The latter often implies finality, suggesting that recurrence cannot take place. However, if there is worsening of metabolic health, a relapse of T2D can potentially take place. Therefore, emphasizing this fact will help motivate individuals to continue with maintenance of the lifestyle changes that led to the occurrence of remission.

Additional diabetes management approaches

Clearly, weight loss is one of the most fundamental aspects of diabetes remission. Based on epidemiological data, it is estimated that virtually 80% of people with diabetes are living with obesity or overweight.[11] Practitioners' evolving understanding of obesity has contributed to the realization that, in addition to the foundational lifestyle modifications required (nutrition modification and physical activity), three pillars of obesity management exist: psychological, bariatric surgery and pharmacotherapy.[12] Pharmacotherapy is particularly important in the context of diabetes remission. Considering the fact that obesity is a chronic disease, most individuals with obesity who are on pharmacotherapy for weight management will require it over the long term. Discontinuation of these medications is often associated with weight regain.

Many of the approved therapies for the management of obesity (including lipase inhibitors, GLP-1 receptor agonists) are also approved for the management of T2D; however, the doses may be different from each other in some instances.

At the time of this article's development, the U.S. FDA is evaluating the possible approval of GIP/GLP-1 receptor co-agonist therapy (already approved for the management of T2D) for the management of obesity. As the treatment for obesity is long-term, individuals on these agents may not meet the definition of diabetes remission, despite their A1C being well within the range of normoglycemia, and their target weight having been achieved. Additional guidance is needed concerning how to characterize patients who previously had T2D, are receiving obesity pharmacotherapy with adequate weight loss, and have normoglycemia. At this point, it is not a certainty that these patients can be considered as having undergone diabetes remission.

Conclusion

The previously unimaginable concept of T2D remission is now within reach for at least some individuals with the condition. It is extremely important that this therapeutic objective be considered in order to reduce the bio-psycho-socio-economic ramifications of this increasingly prevalent condition. Current data suggests that remission of diabetes might be a distinct possibility in individuals with relatively recent onset of diagnosis; with A1C <12%; and in those who are able to participate in either surgical and/or health behavioural modification to achieve sustained weight loss of >15 kg.

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The use of biosimilar insulins in 2023

Sarah Monsonego, MD, FRCPC

About the Author

Dr. Sarah Monsonego is originally from Montreal and obtained her medical degree at McGill University. She completed her Internal Medicine residency in 2017 at the University of Ottawa and remained in Ottawa for her residency in Endocrinology & Metabolism, which she completed in 2020. After her residency, Dr. Monsonego relocated to Toronto and currently practices as a community Endocrinologist doing both ambulatory and hospital work. Her practice focuses on general endocrinology, and she has a keen interest in type 2 diabetes and obesity, as well as diabetes in pregnancy.

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Introduction

A biosimilar is a drug that is highly similar to a biologic drug and has been shown to have no clinically meaningful difference from its originator drug despite minor differences in clinically inactive components. In light of the increasing rates of diabetes and costs to the Canadian healthcare system, the use of biosimilar insulins is intended to increase the affordability of biologics. This article will review the available biosimilars approved in Canada (Table 1), safety and efficacy studies, and the advantages and potential concerns regarding the switch to biosimilar insulins.

Background

The history and development of insulin are continuously evolving. From the initial discovery of insulin in 1921, several milestones have marked its progress, including the use of recombinant technology to enable production of large amounts of insulin in 1977.[1]

This synthetic version of insulin was termed "human insulin" to distinguish it from insulin derived from animal sources. Subsequent landmarks include the development of rapid-acting insulin in the 1990s, followed by the long-acting form of insulin in the early 2000s. Technology to develop insulin at a commercial level has continued to evolve, and the first biosimilar insulin, insulin glargine, was approved in Canada in 2015.

Biologic drugs are large molecules derived from living organisms and are produced using biotechnology.[2] Once the patent for a biologic drug expires, manufacturers may produce a newer version of the drug called a biosimilar. Biosimilars are often mistaken for generic drugs, however, they differ from generics in several ways. Due to the complexities of their manufacturing process, the molecular structure of a biosimilar is not identical to its reference biologic drug, whereas generic drugs contain identical medical ingredients.

The cost savings for biosimilars are somewhat less than those of a generic drug as their cost of development is higher. Prior to authorization, Health Canada must evaluate whether the biosimilar drug is highly similar to its reference drug, as well as ensure that clinical trials demonstrate comparable efficacy and safety.[3] The approval process is stricter than that required for generic drugs, but it is less complex than the process required for the approval of a novel drug.

An important solution to rising healthcare costs

In Canada, diabetes is the leading cause of blindness, end-stage renal disease, heart disease, stroke, and amputations. There are approximately 11 million people living with prediabetes or diabetes in Canada and the cost of to the national health care system is approximately $3 billion annually.[3] Fortunately, biologic drugs such as insulin are more

Insulin Molecule	Reference Brand (Manufacturer)	Biosimilar Insulin (Manufacturer)

Insulin glargine 100 u/mL	**Lantus**® (Sanofi)
	• 10 mL vials
	• 3 mL prefilled disposable pen 3 mL: Lantus® SoloSTAR®
	• 3 mL cartridges: should only be used with
	  • JuniorSTAR® (0.5 unit dose increments)
	  • ClikSTAR®
	  • AllStar Pro™
	• Also available in 300 u/mL concentration as Toujeo® SoloSTAR® and DoubleSTAR®
		Basaglar® (Eli Lilly)
		• Available only in 100 u/mL concentration
		• 3 mL cartridges
		• 3 mL prefilled KwikPens®
		
		Semglee® (Mylan)
		• Available only in 100 u/mL concentration
		• 3 mL prefilled disposable pens

Insulin lispro 100 u/mL	**Humalog**® (Eli Lilly) • 10 mL vials • 3 mL vials • 3 mL prefilled disposable KwikPen® • 3 mL cartridges • Junior KwikPen (0.5 unit dose increments), 3 mL prefilled pen • Also available as Humalog 200 u/mL KwikPen® (3 mL prefilled pen)	**Admelog**® (Sanofi) • Available only in 100 u/mL concentration • 10 mL vials • 3 mL cartridges • 3 mL disposable prefilled SoloSTAR® pen
Insulin aspart 100 u/mL	**NovoRapid**® (Novo Nordisk) • 10 mL vials • 3 mL Penfill® cartridges • NovoRapid® FlexTouch® 3 mL disposable pens	**Trurapi**® (Sanofi) • Trurapi® SoloSTAR® disposable pens • 3 mL cartridges • Trurapi® cartridges should be used only with the following pens: • JuniorSTAR® (0.5 unit dose increments) • AllStar PRO® (1 unit dose increments) **Kirsty**® (Mylan) • 10 mL vials • 3 mL disposable prefilled pen

Table 1: Available biosimilar insulins approved in Canada.

readily available than in the past, however, their cost has become a major concern. The availability of newer versions of a biologics allows for more competition, thereby lowering their cost. Not only will access to biosimilars increase affordability for biologic drugs for patients; when made accessible on a larger scale they would help reduce the financial burden on the Canadian healthcare system and provide opportunity to maximize healthcare resources.

Certain provinces have developed a switching policy to expand the use of biosimilar insulins; Ontario will become the seventh Canadian province to adopt this policy in the near future. Public formularies are beginning to cover biosimilar insulins instead of their reference biologic drugs which, in turn, impacts some private insurance plans. The Ontario Drug Benefit (ODB) program is one of the largest public drug plans in Canada. Biosimilars Canada predicts that implementing a switching policy in Ontario would result in a cost savings of approximately 160 million dollars annually.[4]

Biosimilar insulins are equally safe and effective

Health Canada implements similar regulatory standards as those of other biologic drugs when authorizing a biosimilar drug. In 2010, Health Canada approved the first biosimilar safety and efficacy pathway.[2] The process is initiated with extensive structural and functional studies followed by human clinical studies. As a general note, the pathway focuses on analytical characterization (in vitro studies); however, there are fewer clinical studies comparing biosimilars to their reference biologic drugs.[5] Clinical study programs and specific data requirements differ according to the individual product. Biosimilar

Study	Study type	Patient characteristics	Sample size	Primary endpoint	Primary outcome
ELEMENT 1[6]	Prospective, open label, parallel trial	Type 1 DM with HbA1C <11%, treated with basal bolus	N=267 Lantus® N=268 Basaglar®	Change in HbA1C at 24 weeks	Basaglar® was non-inferior to Lantus® in terms of the change in HbA1c from baseline to 24 weeks
ELEMENT 2[7]	Randomized, double-blind trial	Type 2 DM insulin-naïve, or previously on Lantus® on ≥2 OADs and A1C <11%	N=380 Lantus® N=376 Basaglar®		
SORELLA 1[8]	Randomized, open-label parallel arm	Adult type 1 DM in combination with insulin glargine	N=253 Admelog® N=254 Humalog®	Change in HbA1c at Week 26	Admelog® was non-inferior to Humalog® in terms of the change in HbA1c from baseline to 26 weeks
SORELLA 2[9]	Randomized open-label, multicenter, 2-arm parallel study	Adult type 2 DM in combination with insulin glargine	N= 253 Admelog® N= 252 Humalog®		
GEMELLI 1[10]	Randomized, open-label parallel arm	Adult type 1 or type 2 DM in combination with insulin glargine	N=296 NovoRapid® N=301 Trurapi®	Change in HbA1c at Week 26	Trurapi® was non-inferior to NovoRapid® in terms of the change in HbA1c from baseline to 26 weeks
INSTRIDE 1[11]	Open-label, randomized, multicentre, parallel-group	Adult type 1 DM in combination with insulin lispro	N=278 Lantus® N=280 Semglee®	Change in HbA1c at Week 24	Semglee® was non-inferior to Lantus® in terms of HbA1C reduction at 24 weeks
INSTRIDE 2[12]	Open-label, randomized, multicentre, parallel-group	Adult type 2 DM in combination with insulin lispro	N=283 Lantus® N=277 Semglee®	Change in HbA1c at Week 24	

Table 2: Safety and efficacy studies.

authorization is based on the entirety of evidence given to Health Canada including comparative structural and functional as well as clinical studies. Health authorities can choose to mandate or reject certain studies in order to establish biosimilar efficacy on a case-by-case basis.

Once authorized, biosimilars are issued a unique Drug Identification Number (DIN). Health Canada monitors the safety of biosimilars by conducting post-marketing surveillance studies and monitoring for adverse reaction reports. Despite their approval by Health Canada, biosimilars are not considered equivalent to their reference drug and their interchangeability varies according to province. Interchangeability of a drug refers to the ability of a pharmacist to change one drug to another without the intervention of the prescriber.[2] In randomized clinical trials, biosimilar insulins demonstrated similar efficacy and safety to their reference insulin in both patients with type 1 and type 2 diabetes (Table 2).[6-14]

Clinical outcomes were measured in terms of change in A1C from baseline, and no significant difference between the two drugs was observed. Subgroup analyses also demonstrated comparable glycemic control and safety when switching from a reference to a biologic insulin.[6-14] The risk of hypoglycemia, immunogenicity and other adverse reactions with biosimilars was comparable to that of their refence insulins. When exposed to a biologic drug, there is a theoretical risk of an immune system response and the development of antibodies which may have the ability to reduce the drug's efficacy. In reality, the presence of antibodies has no actual clinical impact; however, it is still important to note and requires

monitoring. Studies that demonstrate no anticipated clinically meaningful differences in immunogenicity are required. Health Canada also requires a 'Risk Management Plan' by manufacturers for monitoring once a biosimilar has been authorized which includes strict pharmacovigilance parameters. In a systematic review of biosimilar insulin vs reference insulins, all of the drugs studied demonstrated a similar proportion of patients developing antibodies between the biosimilar and reference groups.[15,16]

Clinical considerations and practical guidelines

The product monographs of biosimilars state similar indications to those of their reference insulins. This is supported by the clinical studies cited above (Table 2). However, there is insufficient data on special sub-populations including pregnant women and the pediatric population.[3] Biosimilar insulins have demonstrated comparable safety in insulin pumps,[17] but currently only Admelog® (Sanofi, Bridgewater, New Jersey) is available in vial format for pumps in Canada, whereas the use of Trurapi® (Sanofi, Bridgewater, New Jersey) is not yet indicated in pump form.

Theoretical concerns regarding safety and immunogenicity exist because of the small difference in the structure of the biosimilar molecule. Despite favourable studies demonstrating comparable efficacy and safety, there may be hesitation among physicians and patients when switching to a biosimilar. The uncertainty of biosimilars as non-identical molecules are limiting their extensive use.[18] In response to this, increasing awareness regarding biosimilar insulins among patients and providers can help reduce misconceptions, increase prescribers' comfort level, and enable patients in their treatment decisions.[19]

Diabetes Canada supports biosimilar insulins as the first treatment option for insulin-naïve patients when a cost advantage is present. However, they do not recommend mandatory switching policies initiated at the governmental level. Switching to a biosimilar insulin should be a joint decision made between the patient and their healthcare provider.[3] Diabetes Canada recommends supporting patients who are at risk of increased lability in their glycemic control with a change in their insulin. There is evidence in the literature that altering an effective treatment plan can be disruptive to patients, causing psychological impact. Clinical studies have demonstrated that the nocebo effect (when negative expectations of the patient regarding a treatment causes the treatment to have a more negative effect than it otherwise would have) can impact a patient's perspective of a drug and its outcomes. Patients may associate non-specific symptoms with the new drug which may lead to a perceived lack of efficacy, resulting in higher rates of discontinuing the medication.[19] Therefore, prior to switching to a biosimilar insulin, it is important for prescribers to discuss the topic of switching with the patient, and to provide support and counselling to allow for a positive transition.

When switching insulins, glucose levels should be carefully monitored. In theory, dosing and titration of insulin is the same when initiating or switching to a biosimilar insulin. Any adverse reaction to a biosimilar insulin should be reported for post-marketing surveillance to take place.

Use of the device should be reviewed prior to switching a patient to a biosimilar (e.g., prefilled pens vs cartridges). Biosimilar insulin devices are available in the manufacturer's format, rather than that of its reference insulin. Patients may have a preference in the type of device used, which can affect their level of comfort in its use.

Additionally, prescribing and dispensing errors are more likely to occur when there is increased availability of various versions of an insulin. Prescribing brand name products is important in order to avoid automatic substitution or confusion on the part of dispensing pharmacists.[20]

Summary

Biosimilar insulins are similar but not identical to their reference insulin and are not necessarily interchangeable. Safety and efficacy studies have demonstrated that they are comparable to their reference insulin and that their dosing regimens are identical. Biosimilars provide improved patient access and affordability to biologic therapy. Many provincial payers have initiated biosimilar policies in order to increase the use of biosimilar insulins and reduce healthcare costs. Involuntary switching to a biosimilar can impact the patient's perspective of their glycemic control. Therefore, awareness of biosimilars, and effective conversations to address individual patients' needs are essential.

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Addressing NAFLD as a type 2 diabetes complication using the emerging paradigms in diagnostic and management techniques

Harpreet S. Bajaj, MD, MPH, FACE

About the Author

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Introduction

Several critical epidemiological facts underscore the urgent need to address non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes (T2D):

1. NAFLD is the most common liver disease in Canada, affecting approximately one in four Canadians[1,2]
2. NAFLD is projected to become the number one leading indication for liver transplant by 2025[3]
3. Individuals with T2D are at the greatest risk of liver disease progression in NAFLD; T2D is the main predictor of NAFLD-related liver fibrosis and mortality[4,5]

To put this into clinical perspective, consider the following fictitious case: A 45-year-old teetotaler, Caucasian woman with T2D and a body mass index (BMI) of 32 kg/m^2, with no microvascular or macrovascular complications, was incidentally found to have "fatty liver" on abdominal ultrasound. ALT and AST were both within normal range. She was recommended to lose weight and control A1C. Twelve years later, she developed hematemesis and liver biopsy confirmed end-stage liver cirrhosis, with hepatocellular carcinoma. She was scheduled to undergo a liver transplant at age 59.

Despite the three established facts presented above and an abundance of cases similar to the one presented here, currently NAFLD is not being addressed during routine diabetes care as a complication of T2D. The primary reasons for this surprising clinical omission are:

1. NAFLD does not fit into the classical picture of the microvascular or macrovascular complications of T2D that are traditionally taught in undergraduate medical, residency, and continuing professional programs.
2. Early stages of NAFLD are asymptomatic (silent), with normal levels of liver enzymes and other liver function tests. Most cases are clinically diagnosed at a late stage of fibrosis, cirrhosis, or hepatocellular carcinoma.
3. Liver biopsy, the gold standard method of NAFLD diagnosis, is invasive, may not be readily accessible to all patients, and has several limitations.

4. Non-invasive methods to diagnose NAFLD, such as biomarker testing and imaging modalities, are evolving and screening algorithms are not yet standardized.
5. Most non-invasive screening methods for NAFLD are not easily accessed by Canadians, as they are either restricted or not covered by provincial health plans.
6. No guideline recommendations currently exist in Canada for screening of NAFLD in T2D.
7. No pharmacologic treatment is approved by Health Canada for NAFLD.
8. The majority of Canadian physicians and allied health care professionals have insufficient clinical knowledge about NAFLD.[6]

The changing paradigms

Fortunately, the majority of the above described clinical challenges are being resolved. Medical societies worldwide are now recommending systematic screening of NAFLD for individuals with T2D as an approach that has been demonstrated to be cost-effective.[7-10] Simultaneously, there is a growing consensus on non-invasive algorithms for NAFLD screening, coupled with recent positive outcome results from therapeutics directed at NAFLD.

Below are some of the most pertinent clinical background features of NAFLD in T2D (pathophysiology, terminology, epidemiology, diagnostics, and treatment) of which health care providers, including endocrinologists and other diabetes specialists, should be aware.

Definition, pathophysiology and terminology of NAFLD

NAFLD is defined as the accumulation of hepatic fat (steatosis) in ≥5% of hepatocytes in the absence of excessive alcohol consumption (<20 g/day for women and <30 g/day for men). NAFLD is characterized by fat accumulation in the liver, which can subsequently cause inflammation and fibrosis (scarring), leading to irreversible damage, cirrhosis, and eventually hepatocellular carcinoma. In addition to life-threatening hepatic events, NAFLD is associated with an increased risk of cardiovascular disease, extrahepatic cancers and renal disease.[7,9]

NAFLD is a progressive disease that encompasses two distinct histologic entities:

1. Nonalcoholic fatty liver (NAFL): Signified by a relatively benign histology; characterized by hepatic steatosis without evidence of hepatocellular injury.
2. Nonalcoholic steatohepatitis (NASH): A more serious process defined by steatosis accompanied by lobular inflammation and hepatocyte ballooning (cell death), without or with fibrosis (stages F1-F4 on liver biopsy).

Evolving diagnostic and therapeutic inter-disciplinary clinical care pathways

Figure 1 describes a roadmap for the diagnosis of NAFLD in T2D, emphasizing the need for an inter-disciplinary approach that places the chief onus of case finding on primary care and diabetes care teams. Referral to hepatology (or gastroenterology, depending on local access/options) should be considered for diagnostic challenges or for screening and managing liver complications in individuals at high risk for NASH.

Within the primary care and diabetes care teams, FIB-4 (Fibrosis Index based on 4 factors: age, AST, ALT and platelet count) calculation can be integrated into electronic medical records (EMRs) to screen and categorize individual as being at low, intermediate or high risk for NASH (available at www.hepatitisc.uw.edu/page/clinical-calculators/fib-4).

For those with intermediate risk on FIB-4, Vibration Controlled Transient Elastography (VCTE e.g., FibroScan®) performed in community diagnostic or hepatology centres may be utilized as a second step to further evaluate the risk of NASH. Low-risk liver stiffness is often considered for those individuals with VCTE <8 kPa, while those with VCTE ≥12 kPa are likely to have high-risk liver stiffness for NASH fibrosis.

As no pharmacotherapy is approved by Health Canada for NAFLD or NASH, health behavioural changes with emphasis on weight loss[11] and avoidance of alcohol remain the cornerstones of clinical management. Selected individuals with NAFLD together with T2D and high BMI may benefit from bariatric surgery.[12]

Certain antihyperglycemic medications, including glucagon-like peptide 1 receptor agonists (GLP-1RAs),[13] sodium-glucose co-transporter-2 (SGLT2) inhibitors,[14,15] and pioglitazone,[16] have demonstrated randomized clinical trial (RCT) evidence of reversal of liver steatosis and reduction of progression of fibrosis. However, no effect of these diabetes medications on reversing fibrosis has been observed in these short-term studies.

Recently, interim analyses from two large, randomized trials with NASH-targeted therapies—one with obeticholic acid[17] (a semi-synthetic bile acid analog) and another with resmetirom (a liver-directed selective thyroid hormone receptor agonist)—have reported positive results on the primary endpoint of

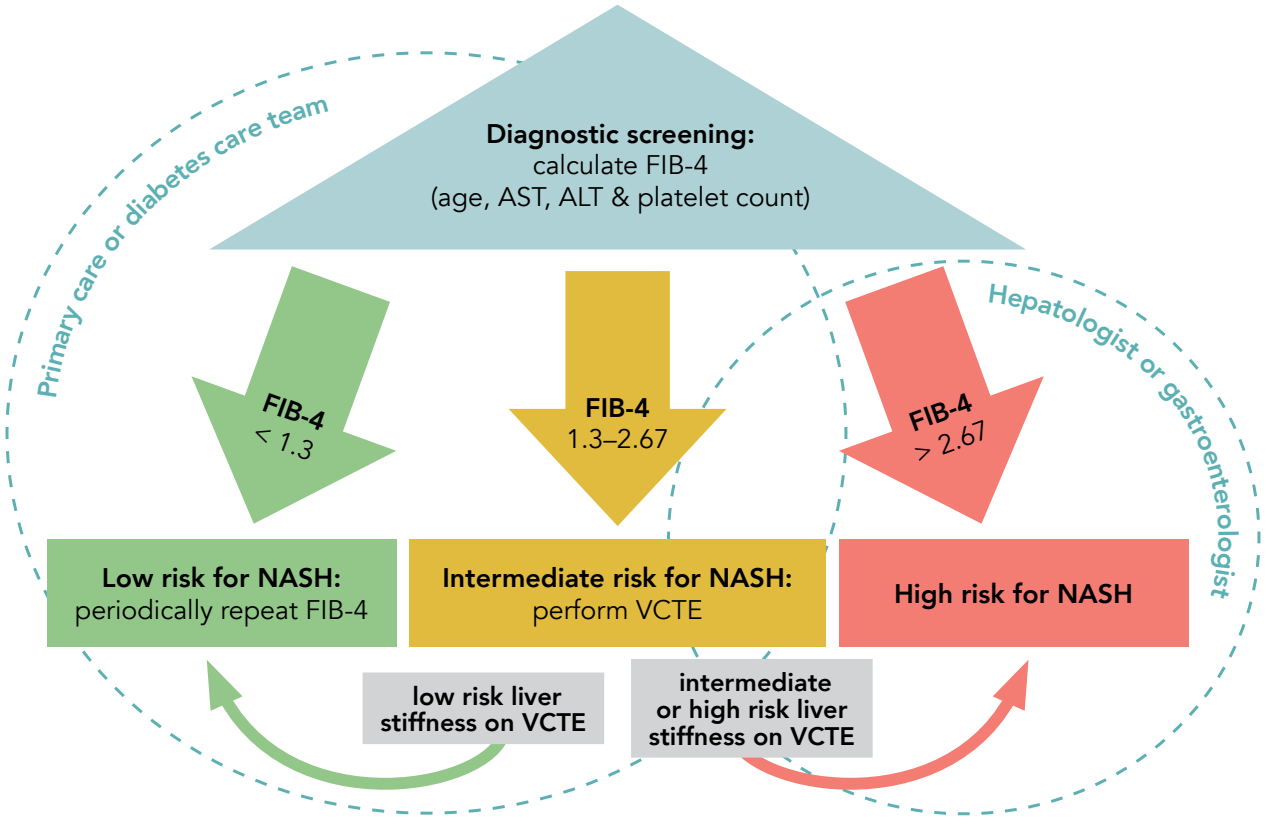

Figure 1: Interdisciplinary pathway for integration of NAFLD screening in clinical practice for individuals with type 2 diabetes. **FIB-4**: Fibrosis Index Based on 4 Factors; **ALT**: alanine transaminase; **AST**: aspartate transaminase; **VCTE**: vibration controlled transient elastography.
Courtesy of Harpreet Bajaj, MD

fibrosis improvement (≥1 stage) with no worsening of NASH. These positive outcome results may lead to regulatory approval of these and other new classes of NASH therapeutics in the near future.

Summary

NAFLD is a prevalent, yet undiagnosed complication of T2D. Non-invasive diagnostic testing methods and consensus concerning NASH screening algorithms are rapidly evolving. It is anticipated that biomarker testing, the FIB-4 index, for example, may soon become the standard of care for NAFLD screening in individuals with T2D, similar to the utility of urinary albumin-creatinine ratio for nephropathy screening. Large randomized trials with NASH therapeutics, including antihyperglycemic medications and liver-targeted therapies, are underway and offer hope for regulatory approval of treatment options in the near future. Canada-wide, collaborative educational efforts are urgently needed to fill the existing clinical care gaps so that healthcare professionals can begin to evaluate and manage NAFLD as a common non-microvascular, non-macrovascular complication of T2D.

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