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PRACTICAL IMPLEMENTATION OF DIABETES CANADA GUIDELINE UPDATES FOR TYPE 2 DIABETES MANAGEMENT IN PRIMARY CARE

Introduction

Type 2 diabetes (T2DM) is a growing global health epidemic identified by the World Health Organization (WHO) as a major public health challenge of the 21st century.[1] By 2050, it is estimated that 1.31 billion people worldwide could be living with T2DM.[1] Across Canada, T2DM affects >9% of our population (i.e., >3.6 million individuals), and age-adjusted prevalence is also increasing at an alarming rate averaging 3.3% per year.[2] More than 90% of people living with diabetes have T2DM, and most of these individuals are cared for in the primary care setting. With rising rates of obesity and metabolic risk factors, along with an aging Canadian population, the burden of T2DM facing primary care is only expected to increase over time.

T2DM care is complex, tailored to the individual, and rapidly advancing. A May 2023 survey commissioned by Diabetes Canada estimated that over one-third of family practitioners' time is spent treating diabetes, and that most healthcare providers find T2DM challenging to treat.[3] The Diabetes Canada Clinical Practice Guidelines (DCAN CPG) provides useful and practical guidance on T2DM management. It has recently shifted its update structure from a comprehensive overhaul every five years, to a select few focused chapter updates each year in recognition of the rapidly shifting body of evidence. More recently, updated chapters of the DCAN CPG include a Pharmacologic Glycemic Management of Type 2 Diabetes in Adults chapter in 2020; Blood Glucose Monitoring in Adults and Children with Diabetes chapter in 2021; Remission of Type 2 Diabetes special article in 2022; and Hypoglycemia in Adults chapter and Position Statement on DIY Automated Insulin Delivery special article in 2023. The purpose of this review is to provide a pragmatic overview of these recent chapter updates and to highlight priorities for T2DM management in primary care.

Priority #1: Screening at-risk individuals, individualizing treatment targets, and delivering person-centred care

It is estimated that over 1.2 million Canadians live with undiagnosed T2DM.[4] Untreated and suboptimally treated T2DM are associated with significant comorbidities and increased risks of microvascular and macrovascular complications.[5] Screening for prediabetes and T2DM by fasting plasma glucose (FPG) or hemoglobin A1c (HbA1c) is therefore recommended every three years by Diabetes Canada guidelines for anyone over the age of 40 or at high risk for T2DM using a risk calculator such as CANRISK.[6,7] Earlier screening should also be considered for people with additional risk factors such as a first-degree relative with T2DM; high-risk ethnicity (e.g., African, Arab, Asian, Hispanic, Indigenous, or South Asian); history of gestational diabetes mellitus (GDM); or those at very high risk based on a risk calculator.[6]

Once a diagnosis of T2DM is established, the choice of initial and subsequent management strategies and targets of glycemic control should be individualized based on patient characteristics; the presence of established atherosclerotic cardiovascular (CV) disease or renal disease; the presence of CV risk factors; medication cost and coverage considerations; and the patient's preference.[8] While for most adults with T2DM it is recommended to target HbA1c ≤7.0%, in select individuals at low risk of hypoglycemia based on class of medications utilized and other characteristics, it is reasonable to target HbA1c ≤6.5% to reduce the risk of chronic kidney disease and retinopathy.[9] A higher HbA1c target should be considered with HbA1c 7.1%-8.0% for individuals who are functionally dependent, and HbA1c 7.1%-8.5% for individuals with recurrent, severe hypoglycemia, especially if accompanied by hypoglycemia unawareness, limited life expectancy, or in the frail elderly with dementia.[9]

In the 2022 Diabetes Canada Special Article on Remission of Type 2 Diabetes, the above individualized HbA1c targets have been expanded to include the option of T2DM remission.[10] Remission is defined as achieving the following HbA1c ranges without any antihyperglycemic medications for ≥3 months, with remission to prediabetes defined as HbA1c 6.0%-6.4% and remission to normoglycemia defined as HbA1c <6.0%.[10] The ideal candidate for whom remission is an option is a person with a diagnosis of T2DM <6 years; with overweight or obesity; without significant eating or mental health disorders; without microvascular or macrovascular complications of T2DM; and who is inclined and able to engage in sustained weight loss by either bariatric surgery, a low-calorie total dietary/meal replacement diet, or a structured exercise program combined with a calorie-restricted diet.[10] Once remission is achieved, HBA1c should continue to be performed every six months to assess the persistence of remission and monitor for relapse.[10] The User's Guide accompanying this special

article provides practical examples of commercially available low-calorie meal replacement options and a checklist clinicians can use to guide discussions and shared decision-making with patients.[11]

Priority #2: Optimizing pharmacotherapy to prevent complications and improve outcomes

Newer antihyperglycemic agents approved and available for use in Canada, including sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP1-RAs), have been shown to have CV benefits in people living with T2DM in CV outcome trials. In recognition of this rapidly advancing body of evidence, Diabetes Canada published a 2020 Chapter Update on Pharmacologic Glycemic Management of Type 2 Diabetes in Adults.[8] In this chapter update, the selection and adjustment of antihyperglycemic pharmacotherapy shifted away from a glucocentric approach aimed at meeting HBA1c targets to a more holistic approach. It recommended that the choice of antihyperglycemic medications be individualized according to a multitude of factors including degree of hyperglycemia; efficacy of agents for reducing T2DM complications and blood glucose; medication effects on the risk of hypoglycemia; body weight; concomitant medical conditions; the ability to adhere to the regimen; affordability of medications; and patient values and preferences.[8]

For instance, in people living with T2DM who have established atherosclerotic cardiovascular disease (ASCVD), either an SGLT2i or a GLP1-RA should be added to reduce major adverse cardiovascular events (MACE), and an SGLT2i be added to reduce hospitalization for heart failure and progression of nephropathy.[8] In people living with T2DM and chronic kidney disease (CKD), an SGLT2i is recommended to reduce the risk of progression of nephropathy, hospitalization for heart failure (HHF), and MACE, and GLP1-RA can be considered to reduce MACE.[8] Last, in people without ASCVD but age >60 with at least two CV risk factors, a GLP1-RA (dulaglutide, liraglutide, or subcutaneous semaglutide) should be considered to reduce MACE, and an SGLT2i (dapagliflozin or canagliflozin) should be considered to reduce HHF and progression of nephropathy.[8]

Oral semaglutide was notably not named in the chapter update as having comparable CV benefits as the injectable GLP1-RA options. This is because while oral semaglutide demonstrated CV safety in the PIONEER-6 trial compared to placebo, the trial was not designed to demonstrate superiority; this will be examined further in the upcoming SOUL trial.[12,13] As of March 2023, the once weekly injectable glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 co-agonist tirzepatide has also received Health Canada indication for use to improve glycemic control for the treatment of adults living with T2DM. The SURPASS trials have shown superiority of tirzepatide vs placebo, subcutaneous semaglutide, and insulin glargine in glycemic lowering and weight loss in this population. The upcoming SURPASS-CVOT will shed light on whether or not it carries the same CV benefit as GLP1-RA therapy.[14,15]

When using SGLT2i, there are several management considerations. First, although empagliflozin and canagliflozin each have two doses available, the lower dose is sufficient for most patients. This is because the cardiorenal benefits are not different between the two doses and often the lower dose is the only one studied in dedicated renal trials (e.g., CREDENCE and EMPA-KIDNEY.)[16,17] The dose response curve is also rather flat and a higher dose generally has only a small effect in further reduction in blood glucose. The exception to this rule is dapagliflozin, as 10 mg PO daily was the demonstrated cardiorenal protective dose used in the DAPA-HF and DAPA-CKD trials.[18,19] Second, although renal protective effects persist at low estimated glomerular filtration rate (eGFR) ranges, glycemic-lowering effects are blunted once eGFR is below 45. As such, although SGLT2i should still be initiated for cardiorenal protection in patients with eGFR <45 (canagliflozin 100 mg daily can be initiated for eGFR >30, dapagliflozin 10 mg daily can be initiated for eGFR >25, and empagliflozin 10 mg daily can be initiated for eGFR >20), additional glycemic control agents should be considered to reach HbA1c targets.[16,17,19] Last, due to the associated risks of diabetic ketoacidosis, patients should be counselled to temporarily withhold SGLT2i use during acute illnesses associated with risk for dehydration and prior to major surgical procedures for at least 48-72 hours.[8]

When it comes to using GLP1-RA therapy, there are also several management pearls. All GLP1-RA medications have the potential to cause gastrointestinal side effects, with nausea (25%-60%), vomiting (5%-15%) and diarrhea being the most common in clinical trials leading to discontinuation.[20] To minimize these side effects, all GLP1-RA medications are initiated at a low dose and titrated according to product monographs. Up-titration can be slowed to reduce the severity and frequency of side effects. Patients should also be counselled that these effects are transient and usually resolve with time, and on lifestyle management strategies that improve side effects including eating smaller meals, eating more slowly, stop eating prior to feeling full, and avoidance of fatty and spicy foods.[21] Last, GLP1-RAs are contraindicated in pregnancy and breastfeeding. Women of reproductive age being prescribed these medications should receive counselling on reliable contraception while taking them and advised to switch to alternative non-teratogenic options prior to planned pregnancy.

Priority #3: Promoting safety in T2DM care across the lifespan

Throughout the lifespan of a person living with T2DM, there are several important safety considerations to

address, including hypoglycemia and mental health. As primary care physicians provide comprehensive and longitudinal care, they are also uniquely positioned to be aware of important checkpoints for intervention in a patient's life that impact their T2DM management, such as family planning and preconception counselling for reproductive age women, and functional decline and deprescribing in the elderly.[22]

Hypoglycemia can occur in individuals treated with insulin or insulin secretagogues, and if occurring frequently, poses significant long-term health risks to the patient. The latest 2023 Diabetes Canada Chapter Update on Hypoglycemia in Adults defined severity of hypoglycemia not only by glucose levels but also severity of the associated symptoms.[23] While level 1 (glucose 3.0 mmol/L -3.9 mmol/L accompanied by autonomic symptoms) and level 2 (glucose <3.0 mmol/L accompanied by neuroglycopenic symptoms without significant impact on mental status) can be recognized and treated by the individual experiencing hypoglycemia, level 3 is defined as hypoglycemia of any degree that requires external assistance to treat.[23] Frequent hypoglycemia predisposes individuals to impaired awareness of hypoglycemia, which occurs when the threshold for development of autonomic warning symptoms is close to, or lower than, the threshold for neuroglycopenic symptoms.[23] Effective strategies to reduce hypoglycemia include psychoeducational training of patients and support persons in recognizing and reducing hypoglycemia; prescribing glucagon (intranasal, intramuscular or subcutaneous) and teaching family members on administration technique; transition to pharmacotherapies that reduce the risk of hypoglycemia (e.g., discontinue insulin and secretagogues in favour of incretin-based pharmacotherapy, consider second-generation basal insulin analogues insulin glargine-300 and degludec over insulin NPH, glargine-100, and detemir to reduce nocturnal hypoglycemia); and the use of continuous glucose monitoring (CGM) to identify episodes of hypoglycemia.[23]

Living with T2DM comes with significant mental and emotional burdens, and research has identified three T2DM-specific psychological syndromes.[24] Diabetes distress (DD) refers to the negative emotional burden of self-management related to living with T2DM. Psychological insulin resistance is the strong negative response from people with T2DM to the recommendation from healthcare providers that they should start insulin. Fear of hypoglycemia, usually a result of traumatic experiences of serious or nocturnal hypoglycemia, often results in patients adopting compensatory hyperglycemia as a prevention strategy for future hypoglycemia events.[24] All of these are underrecognized barriers to T2DM care and, if left unaddressed, can significantly impact the patient's ability to achieve glycemic targets, prevent complications, and achieve overall quality of life.[24] The 2023 Chapter Update on Diabetes and Mental Health provides detailed recommendations on the screening and management of mental health comorbidities in people living with T2DM, and how to differentiate DD from major depressive disorder.[24]

As the diagnosis of T2DM becomes increasingly common in younger age groups, the prevalence of pre-existing T2DM in pregnancy has also increased steadily over the past decade.[25] Among women with pre-existing T2DM, preconception care is known to improve maternal and fetal outcomes, and therefore it is paramount that women of reproductive age living with T2DM receive preconception counselling as part of healthcare visits for disease management. The Diabetes in Pregnancy chapter of the 2018 Diabetes Canada CPG outlines key components to preconception care.[25] This involves patient education about the importance of optimizing glycemic control prior to pregnancy, as hyperglycemia is teratogenic and increases risk of congenital anomalies in the first trimester.[25] Most antihyperglycemic medications (except metformin, insulin and glyburide), renal protective antihypertensives (e.g., angiotensin-converting-enzyme inhibitors and angiotensin-2 receptor blockers), as well as statins, are contraindicated in pregnancy.[25]. Patients treated with these medications must be counselled on the importance of reliable contraception or be transitioned to pregnancy-safe alternatives prior to conception.[25] Microvascular complications such as retinopathy and nephropathy can also worsen in pregnancy. Women with pre-existing T2DM should undergo retinopathy screening by a vision care specialist preconception, in the first trimester, and within the first year postpartum.[25] Nephropathy screening should be completed preconception, and women with albuminuria or CKD should be followed closely in pregnancy for the development of hypertension and preeclampsia.[25] Regarding T2DM management in older adults, care should be individualized taking into account the existence of other comorbidities and frailty. In functionally independent older people living with T2DM, who have life expectancy of >10 years, Diabetes Canada guidelines recommend following the same glycemic, blood pressure and lipid targets as younger people with T2DM.[26] However, in the older person with T2DM and multiple comorbidities or frailty, the priority should shift to strictly preventing hypoglycemia by transitioning patients off of antihyperglycemic agents that increase the risk of hypoglycemia in favour of alternatives with less risk of hypoglycemia (e.g., incretin-based therapies in place of sulfonylureas, modified-release gliclazide in place of shorter-acting glyburide, and the second-generation basal insulins, insulin glargine-300 or degludec in place of insulin NPH, detemir, or glargine-100).[26] In older adults on insulin or with impaired awareness of hypoglycemia, continuous glucose monitoring devices can be considered to assist with glucose monitoring and identification of hypoglycemia. Polypharmacy is common in older

adults living with T2DM, and deprescribing should be considered, especially in individuals with limited life expectancy, to reduce complexity of therapy, unwanted side effects and drug-drug interactions.[26]

Conclusion

T2DM is an increasingly prevalent and complex problem facing primary care physicians. With an abundance of effective pharmacotherapy agents coming to market, the approach to T2DM management needs be more holistic than glucocentric. Pharmacotherapy selection should also be tailored to the individual with factors such as presence of complications and comorbidities, body weight, cost and coverage, and patient preference taken into consideration during shared decision-making. The DCAN CPG chapters are an up-to-date, comprehensive yet succinct, and user-friendly resource available to guide clinicians navigating through this increasingly complex landscape.

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Financial Disclosures

Dr. Jennifer Fu: None declared.

Dr. Jeremy Gilbert: Speaking, Honoraria/Advisory Board consultations: Amgen, Abbott, AstraZeneca, Dexcom, Eli Lilly, Boehringer, Janssen, Novartis, Novo Nordisk, Sanofi, HLS therapeutics, Pfizer, GSK

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