Volume 1 – Issue 2

Canadian Diabetes & Endocrinology Today

ISSN 2817-4097
(English ed. online)

June 2023

The Editorial Board

Robyn Houlden
MD, FRCPC

Professor and Chair, Division of Endocrinology, Queen's University

Consultant, Adult Endocrinology, Kingston Health Sciences Centre

Diabetes Advisor, Canadian Optimal Medication Prescribing and Utilization Service, CADTH

Clinical Advisory Group, eConsult and eReferral, Ontario Ministry of Health

Chair, 2018 Clinical Practice Guidelines, Diabetes Canada

Jill Trinacty
BSc (Hons), MD, FRCPC, ABOM

Lecturer, University of Ottawa

Endocrinologist, LMC Ottawa, Bariatric Medical Institute, and Bruyère Continuing Care

Vice-Chair, Endocrinology & Metabolism, Ontario Medical Association

Sara Stafford
MDCM, FRCPC

Endocrinologist, Fraser River Endocrinology and Surrey Memorial Hospital

Clinical Teaching Site Lead, SMH Endocrinology, Fraser Health Division of Endocrinology

Clinical Assistant Professor, University of British Columbia

Professional Section Executive, Diabetes Canada

Medical Director, Carrier Sekani Family Services Mobile Diabetes Clinic

Table of Contents

Canadian Diabetes & Endocrinology Today is published 3 times per year in English and French.

To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, canadiandiabetesandendocrinologytoday.com.

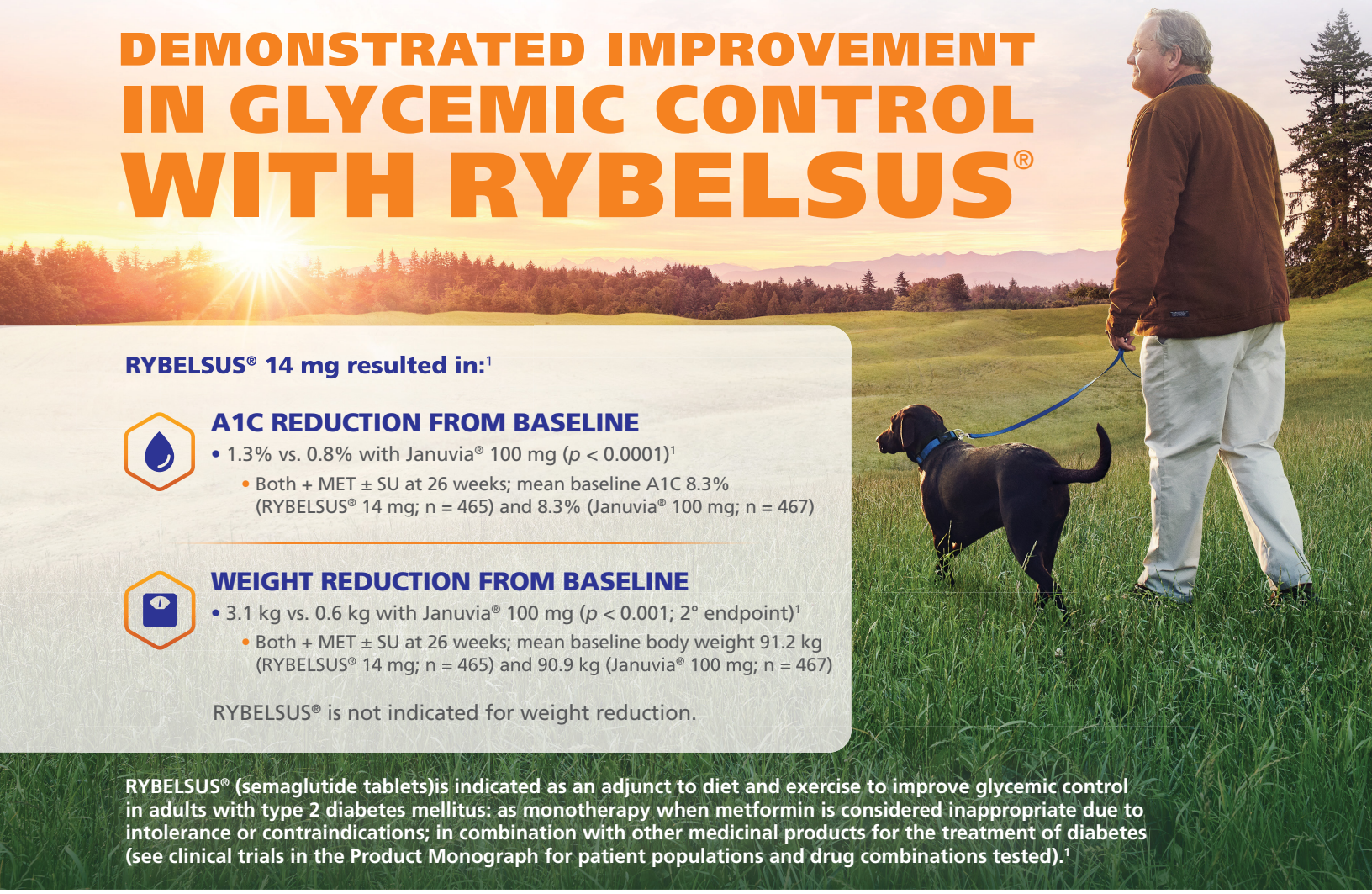
To subscribe to Canadian Diabetes & Endocrinology Today and more open access scientific specialty journals published by Catalytic Health, please visit catalytichealth.com/cdet.

The content of this journal qualifies for Section 2 (self-learning) CPD credits under the Royal College's Maintenance of Certification (MOC) program.

For more information on how journal articles can meet your CPD needs, please consult the Royal College's website. For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

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.

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

PrRYBELSUS® semaglutide tablets

Endocrinopathies Associated with Immune Checkpoint Inhibitors

Irena Druce, MD, MSc, FRCPC

About the Author

Dr. Irena Druce completed her studies, including a Masters' in Cellular and Molecular Medicine and her medical education, at the University of Ottawa. She practices in the community and as a part-time associate with The Ottawa Hospital. She is an assistant professor with the Department of Medicine at the University of Ottawa and has collaborated with medical oncology on research into endocrine side effects of immune checkpoint inhibitor therapy. Her other clinical interests include type 2 diabetes and transgender medicine.

Affiliations

Division of Endocrinology, Department of Medicine, University of Ottawa
Chronic Disease Program, The Ottawa Hospital Research Institute

Introduction

Immune checkpoint receptors are expressed by cells of the immune system and lead to reduced or absent function, which physiologically limits autoimmunity. These receptors are also exploited by malignant cells to maintain immune tolerance and evade destruction. Monoclonal antibodies targeting immune checkpoints have revolutionized oncology, with potential long-lasting clinical response, even in the setting of metastatic solid tumors. For example, in the past, metastatic melanoma signalled certain death; now, remission is possible.[1]

The primary targets of current pharmacotherapy are cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and the programmed cell death protein 1 (PD-1) and its ligand (PD-L1). Today, half of all patients with metastatic disease are eligible to receive immune checkpoint inhibitor (ICI) therapy. As of December 2021, there were eight approved agents available for 17 malignancies, and more than 1,000 clinical trials have been conducted to explore these agents in adjuvant and maintenance settings.[1,2]

The immune activation that underlies ICI therapy and the persistence of clinical response beyond the pharmacologic half-life also explain the toxicities that have been observed.[1] Immune-related adverse events (irAEs) from ICI therapy have been shown to occur in virtually every organ system. They manifest at varying times during treatment, sometimes occurring after its discontinuation. Interestingly, the presence of these adverse events (AEs) is related to the immune system's degree of self-tolerance and predicts patient response to this treatment modality.[3]

Endocrinopathies are some of the most common irAEs, occurring in 15–40% of patients; however, they have posed challenges for clinicians as they are difficult to diagnose due to diverse and non-specific manifestations.[1-4] In contrast to other irAEs, endocrinopathies do not respond to high-dose glucocorticoids and they are permanent. Steroid treatment has been shown to have no effect on the disease severity or the likelihood of resolution.[5,6] Fortunately, when diagnosed appropriately, ICI-associated endocrinopathies are easy to treat, do not necessitate treatment discontinuation, and have an excellent prognosis.[7]

ICI-Associated Hypophysitis

Hypophysitis is one of the more common and most life-threatening irAEs and can affect any, and often multiple, anterior pituitary cell lineages (**Figure 1**). ICI-associated diabetes insipidus (DI) resulting from antidiuretic hormone deficiency has been noted only in case reports. Hypophysitis is noted most frequently with CTLA-4 therapy (either alone or in combination with programmed cell death protein 1/ligand 1 [PD-1/L1]), seen in up to 10% of treated patients. It has also

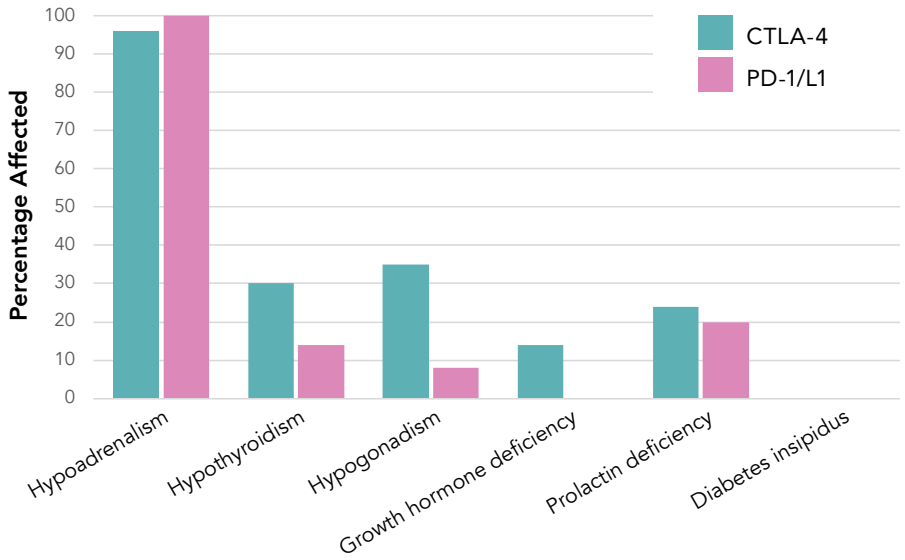


Figure 1: Percentage of patients presenting with deficiency in specific cell axes in ICI-associated hypophysitis. *Data adapted from Faje and Druce.*[8,9]

been shown to occur with PD-1/L1 monotherapy, although more rarely, with a reported incidence of 1–3% (Table 1). The clinical presentation differs based on the causative agent.

CTLA-4-associated hypophysitis occurs early in the treatment course, typically within 9–12 weeks, and most commonly causes concurrent central hypoadrenalism and central hypothyroidism. The underlying mechanism has been proposed to be a hypersensitivity type II reaction with lymphocytic infiltration into the pituitary gland noted on pathology. This is very similar to autoimmune hypophysitis which was a known, albeit rare, entity prior to the ICI-era.

Hypophysitis due to PD-1/L1 therapy occurs later in the treatment course, generally following 20 weeks, and almost universally affects adrenocorticotropic hormone (ACTH) secretion leading to hypoadrenalism; it rarely affects other cell lineages.[4,8,9] The mechanism for PD-1/L1-associated hypophysitis is not yet elucidated.

There is no consensus on asymptomatic screening for hypophysitis, more specifically ACTH deficiency, in ICI-treated patients. This may be due to the complexity of obtaining morning serum cortisol measurements, as well as correct interpretation while accounting for confounding by the frequent use of glucocorticoids in this population.[8] Some practitioners support routine screening in at least CTLA-4-containing regimens, based on the increased incidence; however, there are no clear guidelines concerning how to measure and interpret cortisol values. Debate exists, even among endocrinologists, regarding what cut-off values should be used for interpretation of serum cortisol.[9] Measuring ACTH is not practical due to the long turn-around time for this assay in most institutions.

ACTH deficiency is acutely life-threatening and its manifestations, namely malaise, nausea and hypotension are, unfortunately, common in patients receiving systemic therapy for cancer. Late diagnosis is a realistic possibility and it can have a profound impact on patient morbidity and mortality, supporting the implementation of asymptomatic screening.[4,9] Clinicians are encouraged to have a high index of suspicion for pituitary dysfunction, and should be aware of the need for this condition to be assessed and treated by oncologists and endocrinologists collaboratively.

In addition, imaging the pituitary gland in ICI-associated hypophysitis is not standard, as the presence of inflammation and stalk thickening on magnetic resonance imaging (MRI) does not predict the severity or course of the condition. Imaging should be considered if pituitary metastases are on the differential.[4,7]

ICI-associated hypophysitis is treated by replacing the target hormones, as with any other etiology of hypopituitarism. Priority should be given to replacing the adrenal and thyroid axes. Sex hormone replacement can be considered if the underlying disease has a reasonable prognosis, and growth hormone replacement therapy (GHRT) is contraindicated in the setting of active malignancy.[4,7,10]

ICI-Associated Thyroid Disease

Primary thyroid dysfunction is the most common endocrinopathy noted with ICI therapy and typically presents within six weeks of treatment. It can, however, occur at any time during therapy and these factors have led to screening serum thyroid stimulating hormone (TSH) as routine practice.[4] The incidence varies by treatment; the clinical data has shown 5% in CTLA-4 monotherapy, 10% in PD-1/L1 monotherapy, and up to 20% for patients treated with combination therapy.[4,11]

The most common presentation is destructive, painless thyroiditis, where transient hyperthyroidism leads to permanent hypothyroidism in virtually 70% of cases within approximately six weeks. This time course is more rapid than that of non-ICI-associated thyroiditis and is unaffected by the use of glucocorticoids. It is possible that the

Endocrinopathy	Incidence (%)			Onset (Median Weeks)		
	CTLA-4	*PD-1/L1*	*Combo*	*CTLA-4*	*PD-1/L1*	*Combo*
Hypophysitis	9%	1-3%	10.5%	9-12	26	9-12
Primary thyroid						
Thyroiditis	1-5%	5-10%	2-10%	6+	6+	6+
Hypothyroidism	2-5%	3-10%	5-23%	6+	6+	6+
Graves disease	-	-	-	-	-	-
Autoimmune diabetes	-	0.2-5%	0.6%	-	Within 15	-
Primary adrenal	0.3-2%	0.3-4%	1-3%	-	-	-

Table 1: Summary of incidence and timing of onset of ICI-associated endocrinopathies based on treatment regimen. *Data adapted from Wright and Barroso-Sousa.*[4,11]

incidence of self-limited thyroiditis is much higher as it is largely subclinical. Graves disease is rare and has been noted in case reports due to the presence of orbitopathy.[4]

There is no clinical utility in measuring thyroid-stimulating hormone (TSH)-receptor antibodies. Other anti-thyroid antibodies, such as anti-thyroid peroxidase and anti-thyroglobulin, are often absent in patients manifesting with ICI-associated thyroid dysfunction. In patients with pre-existing anti-thyroid antibodies, there is a higher risk to develop irAEs; however, there is no correlation with disease severity.[4,12] The pathophysiology of this endocrinopathy remains under study; however, the PD-1/L1 pathway is integral in T-cell function, which is linked to the pathophysiology of Hashimoto thyroiditis.[13]

Recommendations for monitoring and treatment of ICI-associated primary thyroid dysfunction are unanimous and clear: Free hormones should be measured where an abnormal TSH is noted, and levothyroxine therapy should be initiated when the TSH is >10mIU/mL at a standard dosing of 1.6 mcg/kg (less in the elderly and frail), followed by biochemical reassessment in six weeks.[4,7]

ICI-Associated Diabetes Mellitus

The next most notable ICI-associated endocrinopathy is autoimmune diabetes (ICI-DM). Its incidence is rare; it occurs in less than 0.2–5% of patients; however, its presentation can be dramatic with rapid autoimmune destruction of β-cells and up to 70% of patients presenting with fulminant ketoacidosis.[4] Due to its rapid presentation, screening with A1c may not be useful and random plasma or capillary blood glucose monitoring should be used for routine screening.[7] In a clinical trial, the majority of patients, over 70%, presented in the first three months of initiating ICI therapy; however, the latest presentation reported was 15 months.[14] Fewer than 50% of patients were noted to have islet-antibodies; however, the patients who had positive antibodies developed ICI-DM at an earlier point. More than 97% of cases of ICI-DM have been noted in patients on PD-1/L1 therapy and this pathway has been observed to be important to the development of diabetes mellitus in mouse models.[4] In addition, genetic factors are likely to contribute to the development of ICI-DM, with classic HLA haplotypes linked with classic type 1 diabetes (DR3-DQ2 and DR4-DQ8) being over-represented in ICI-DM, along with a strong association with ICI-DM and HLA-DR4.[15]

The administration of high-dose glucocorticoids has not been shown to provide any benefit in ICI-DM; this condition should be treated with subcutaneous insulin.[7] It should also be noted that the patient population requiring ICI therapy is at higher risk of developing pre-existing type 2 diabetes and the frequent use of glucocorticoids in this population may exacerbate glycemic control. Patients should be screened for pre-existing diabetes prior to initiating treatment.

Additional ICI-Associated Endocrinopathies

Other endocrinopathies are rare. Primary adrenal insufficiency has been noted to occur with an incidence of 0.2–0.5% and is rarely associated with the presence of anti-adrenal antibodies.[11] Hypoparathyroidism, DI and ACTH-dependent Cushing disease have been noted in case reports; however, the link to ICI therapy is questioned.[4] In these instances, causality is unimportant as, ultimately, the treatment is unaffected.

Where ICI therapy is making the biggest impact on endocrinologists is with the increased incidence of hypophysitis and autoimmune diabetes, which require expert diagnosis and treatment.

Summary

ICIs have ushered in a new era in cancer treatment, but they are still in their infancy. Most notably, the first ICI was FDA approved in recent years, in 2011. Extensive research is needed to elucidate the mechanisms that underly the irAEs so that patients can be properly diagnosed and treated. Future research may also allow the identification of high-risk patients requiring closer surveillance.

With regard to ICI-associated endocrinopathies, at this time, clinicians must rely on their clinical acumen and routine screening. A basic screening algorithm is proposed in Figure 2 and could be adapted to individual institutional needs. Asymptomatic screening should be most intense during treatment when the incidence of onset is highest. It is important to note that irAEs can occur after treatment discontinuation and clinical vigilance must persist. Patients with any prior exposure to ICI therapy should be identified in their medical record and should have biannual clinical review with targeted endocrine testing as indicated.

With ICI therapy, patients could potentially be cured of their malignancy, and the possibility exists that they could be discharged to their primary care providers (PCPs), who would then assume the responsibility for ongoing surveillance. Knowledge dissemination, a multidisciplinary approach and collaboration between specialists will be key on the path forward.

Prior to treatment	Serum/capillary glucose
	TSH
During treatment Q1–2 cycles	TSH
	Serum/capillary glucose
	Morning serum cortisol*
After treatment discontinuation	Clinical assessment every 6 months, investigations as clinically indicated

* *Consider for all patients but at minimum those exposed to CTLA-4 agents.*

Figure 2: Basic algorithm for screening of ICI-associated endocrinopathies.

Correspondence

Dr. Irena Druce
Email: idruce@toh.ca

Financial Disclosures

Speaking Honoraria: Abbott, Astra Zeneca, Boehringer Ingelheim, Janssen, Merck, Novo Nordisk, Sanofi
Consultancy Fees: Abbott, Lilly, Novo Nordisk, Sanofi

References

1. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol. 2022 Apr;19(4):254-67.
2. Esfahani K, Meti N, Miller WH, Hudson M. Adverse events associated with immune checkpoint inhibitor treatment for cancer. CMAJ. 2019 Jan 14;191(2):E40-6.
3. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer. 2019 Dec;7(1):1-1.
4. Wright JJ, Powers AC, Johnson DB. Endocrine toxicities of immune checkpoint inhibitors. Nat Rev Endocrinol. 2021 Jul;17(7):389-99.
5. Faje AT, Lawrence D, Flaherty K, Freedman C, Fadden R, Rubin K, Cohen J, Sullivan RJ. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. Cancer. 2018 Sep 15;124(18):3706-14.
6. Ma C, Hodi FS, Giobbie-Hurder A, Wang X, Zhou J, Zhang A, Zhou Y, Mao F, Angell TE, Andrews CP, Hu J. The Impact of High-Dose Glucocorticoids on the Outcome of Immune-Checkpoint Inhibitor–Related Thyroid DisordersManagement of ICI-Induced Thyroiditis. Cancer Immunol Res. 2019 Jul 1;7(7):1214-20.
7. Husebye ES, Castinetti F, Criseno S, Curigliano G, Decallonne B, Fleseriu M, Higham CE, Lupi I, Paschou SA, Toth M, van der Kooij M. Endocrine-related adverse conditions in patients receiving immune checkpoint inhibition: an ESE clinical practice guideline. Eur J Endocrinol. 2022 Dec;187(6):G1-21.
8. Faje A, Reynolds K, Zubiri L, Lawrence D, Cohen JV, Sullivan RJ, Nachtigall L, Tritos N. Hypophysitis secondary to nivolumab and pembrolizumab is a clinical entity distinct from ipilimumab-associated hypophysitis. Eur J Endocrinol. 2019 Sep;181(3):211-9.
9. Druce I, Tawagi K, Shaw JL, Ibrahim A, Lochnan H, Ong M. Routine Screening for Central and Primary Adrenal Insufficiency during Immune-Checkpoint Inhibitor Therapy: An Endocrinology Perspective for Oncologists. Curr Oncol. 2022 Jul 2;29(7):4665-77.
10. Girotra M, Hansen A, Farooki A, Byun DJ, Min L, Creelan BC, Callahan MK, Atkins MB, Sharon E, Antonia SJ, West P. The current understanding of the endocrine effects from immune checkpoint inhibitors and recommendations for management. JNCI Cancer Spectr. 2018 Jul;2(3):pky021..
11. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, Tolaney SM. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018 Feb 1;4(2):173-82.
12. Kobayashi T, Iwama S, Yasuda Y, Okada N, Tsunekawa T, Onoue T, Takagi H, Hagiwara D, Ito Y, Morishita Y, Goto M. Patients with antithyroid antibodies are prone to develop destructive thyroiditis by nivolumab: a prospective study. J Endocr Soc. 2018 Mar;2(3):241-51.
13. Zhan L, Feng HF, Liu HQ, Guo LT, Chen C, Yao XL, Sun SR. Immune checkpoint inhibitors-related thyroid dysfunction: epidemiology, clinical presentation, possible pathogenesis, and management. Front Endocrinol. 2021 Jun 10;12:649863.
14. Akturk HK, Kahramangil D, Sarwal A, Hoffecker L, Murad MH, Michels AW. Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. Diabet Med. 2019 Sep;36(9):1075-81.
15. Tsang VH, McGrath RT, Clifton-Bligh RJ, Scolyer RA, Jakrot V, Guminski AD, Long GV, Menzies AM. Checkpoint inhibitor–associated autoimmune diabetes is distinct from type 1 diabetes. J Clin Endocrinol Met. 2019 Nov;104(11):5499-506.

Future Role of Non-Insulin Antihyperglycemic Agents in the Management of Type 1 Diabetes Mellitus

Peter A. Senior, BMedSci (Hons), MBBS (Hons), PhD, FRCP(E), FRCP

About the Author

Dr. Peter A. Senior is the Director of the Alberta Diabetes Institute, the Charles A. Allard Chair in Diabetes Research and a Professor of Medicine at the University of Alberta. He has clinical appointments as the Medical Director of the Clinical Islet Transplant Program and staff endocrinologist for Alberta Health Services, in Edmonton, Canada. He completed his specialist training in Diabetes and Endocrinology at the University of Newcastle upon Tyne, in the UK, where he received his PhD in 2002. His clinical and research interests focus on type 1 diabetes, hypoglycemia, diabetic kidney disease and islet transplantation. In 2020, he received the Gerald Wong Service Award from Diabetes Canada. Dr. Senior currently serves as Chair of Diabetes Canada's Board of Directors and has previously served as Chair of Diabetes Canada's Clinical Practice Guidelines Steering Committee and its Professional Section.

Affiliations

Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta

Introduction

In contrast to current approaches to Type 2 diabetes (T2DM), the management of Type 1 diabetes (T1DM) continues to be glucocentric. This is understandable considering the substantial lifetime risk of potentially devastating microvascular complications associated with the disease. Consequently, advances in the management of T1DM have largely focused on enhanced insulin preparations, technologies for insulin delivery and blood glucose monitoring. However, despite the use of these therapeutic approaches, only 21% of adults (and fewer children) reach glycemic targets associated with a lower risk of microvascular complications[1] and life expectancy in patients with T1DM is 12 years shorter than that of the general population.[2] Cardiovascular and kidney disease, together with hypoglycemia, are the major causes of mortality in patients with T1DM.[3]

Significant morbidity and mortality are associated with T1DM, but also with its treatment. The adverse effects of insulin, causing hypoglycemia (which is often a key barrier to achieving glycemic targets) and body weight gain are well known to clinicians. Insufficient attention has been paid to the burden of diabetes self-management and the negative impact of the disease and its treatment on patients' quality of life.

Should practitioners consider a broader perspective on T1DM management with the objective of reducing microvascular and macrovascular risk, while simultaneously reducing the burden of T1DM and the adverse effects of therapy? Could using non-insulin antihyperglycemic agents (NIAHAs) as adjuncts to insulin assist practitioners in achieving this objective? (**Figure 1**). The potential utility of NIAHAs in the management of T1DM is discussed in this paper.

Metformin

Based on long experience and its effect as an insulin sensitizer, metformin has been used by many physicians in the management of T1DM, particularly in individuals with obesity and/or high insulin requirements. Treatment-associated gastrointestinal (GI) side effects have been common and persistence with therapy has been variable. A small number of randomized clinical

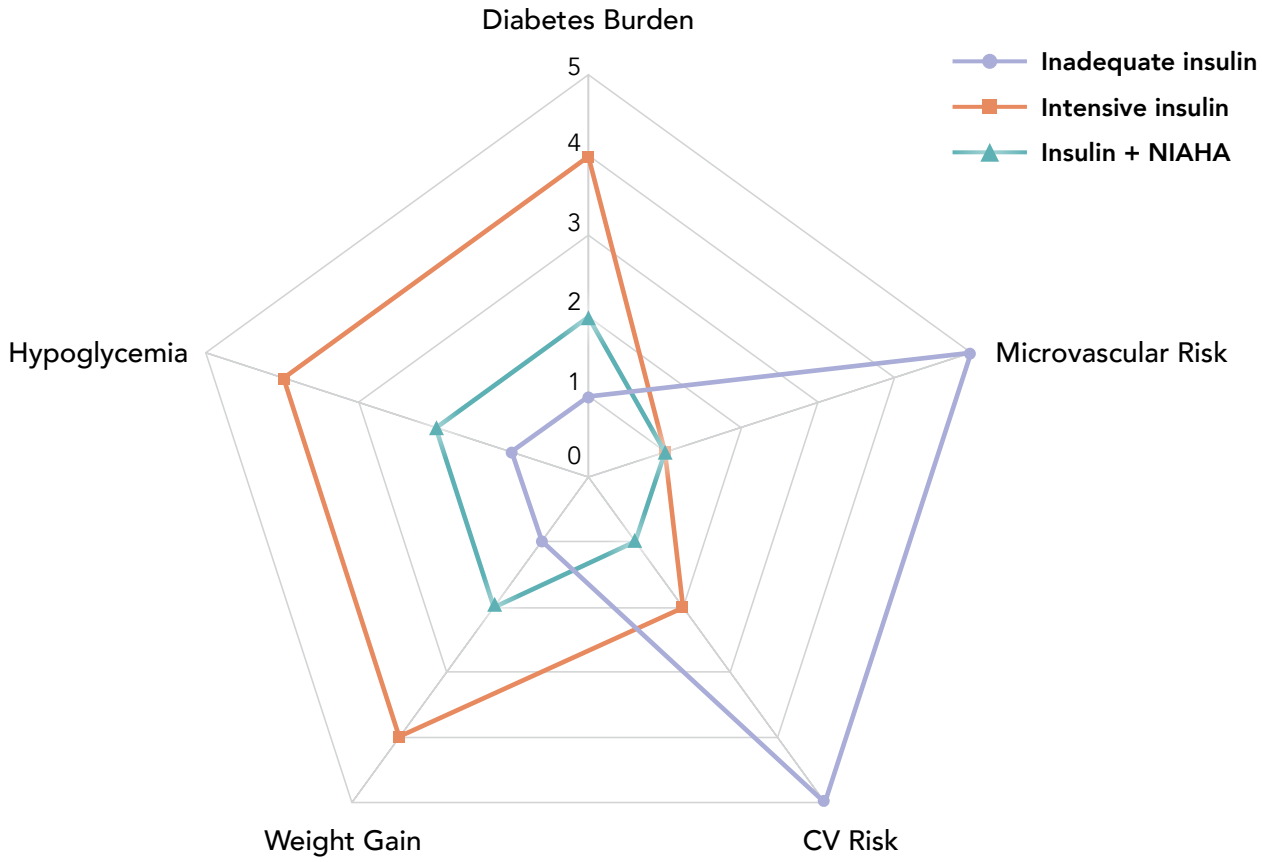


Figure 1: Hypothetical illustration of various approaches to T1DM management and their relative impact on microvascular and macrovascular systems; hypoglycemia risk; body weight gain; and diabetes burden. Inadequate insulin therapy with high A1c would be associated with high risk for microvascular and macrovascular complications, but low risk for body weight gain and hypoglycemia. Intensification of insulin therapy could reduce the risk of microvascular and macrovascular complications, but might be associated with increased disease burden, body weight gain, and risk for hypoglycemia. Adjunctive therapies (e.g., NIAHAs) which could help achieve glycemic targets without body weight gain, hypoglycemia or diabetes burden would be desirable.
Courtesy of Dr. Peter A. Senior.

trials investigating the utility of metformin in T1DM have demonstrated that metformin is associated with small, but statistically significant improvements in A1c, with lower insulin requirements, and body weight loss (Table 1).[4] The REMOVAL trial was a large, double blind, placebo-controlled clinical trial of metformin 1,000 mg bid administered to adults with T1DM >40 years of age for three years to evaluate whether or not it would slow the progression of carotid intima-media thickening (IMT).[5] Although no difference was seen in the primary outcome, maximal carotid IMT was lower with metformin. There were, however, significant reductions in body weight and low-density lipoprotein (LDL) cholesterol. Glomerular filtration rate (GFR) was stable with metformin vs a decline of 4 mL/min/1.73m^2 with placebo. There was no sustained difference in A1c or the insulin dose over three years.

GLP-1 Receptor Agonists (GLP-1RAs)

Although some of the glucose-lowering effects of incretin therapies in T2DM, mediated by enhancing glucose-dependent insulin secretion, should not apply in C-peptide negative individuals with Type 1 diabetes, other effects mediated by alteration in food intake, satiety and suppression of post-prandial glucagon levels have the potential to benefit individuals with T1DM. Furthermore, pre-clinical data suggesting an anti-apoptic effect of glucagon-like peptide (GLP) on beta cells has suggested the potential for glucagon-like peptide-1 receptor agonists (GLP-1RAs) to preserve beta cells in new-onset T1DM. However, two Phase 2 clinical trials of GLP-1RAs in new-onset T1DM showed no effect on beta cell preservation on their own but may have been helpful when combined

Agent/Class	Metformin[4,5]	GLP-1RA[9,10]	SGLT2i[13,14]
A1c	0.28% (ns)	-0.35–0.15%	0.37%
Insulin Requirements	-6.6 units	-5.5 to -1.2 units	-6.23 units
Body Weight	-1.2 kg	-3.6 kg to -4.9 kg	-2.54 kg
Blood Pressure		Short-term lowering	-2 to -4 mmHg
Hypoglycemia	=	Additional symptomatic events Severe hypoglycemia	=
CV Risk	LDL -0.13 Lower max cIMT	?	?lower LDL, triglycerides
Renal	+ 4 mL/min	No change[11]	To be tested
Other *(QoL, Variability)*		Improved TRIM-D score No difference in SF36[9,10] More TIR in pump trial[11]	Increased TIR, less variability
DKA	No increase	?Slight increase	Increases

Table 1: Impact of adjunct NIAHAs added to insulin vs placebo in clinical trials or meta-analyses on metabolic and other outcomes. *CV, cardiovascular; DKA, diabetic ketoacidosis; TRIM-D, Treatment-Related Impact Measures–Diabetes; QoL, quality of life; LDL, low-density lipoprotein; TIR, time-in-range.*
Courtesy of Dr. Peter A. Senior.

with anti-interleukin-21.[6,7] These studies were not designed to examine potential benefits for A1c or metabolic factors.

Subsequent to small, mechanistic studies of short-acting GLP-1RAs in T1DM,[8] two large clinical studies of liraglutide (0.6, 1.2, 1.8 mg/day) were conducted. One study had a treat-to-target design while the insulin dose was capped in the other study.[9,10] In both studies, liraglutide was associated with reductions in A1c, body weight and insulin dose; the effect was greater with the 1.2 mg and 1.8 mg doses (Table 1). In both studies, there were increased rates of symptomatic hypoglycemia with liraglutide, and higher rates of hyperglycemia with ketosis in subjects randomised to the 1.8 mg dose. There was no increase in nocturnal or severe hypoglycemia.[10] Sub-group analyses suggested that greater benefits may be seen in subjects with residual c-peptide.

Greater differences in A1c (-0.7%), body weight (-6.3 kg) and insulin dose (-8 units) were demonstrated in a smaller 26-week randomized, controlled clinical trial of liraglutide 1.8 mg in obese T1DM subjects using insulin pumps.[11] In this study, there was an increase in time-in-range and no increase in hypoglycemia. Treatment satisfaction as recorded in the Diabetes Treatment Satisfaction Questionnaire (DTSQc) increased to a greater extent with liraglutide than with placebo. No cases of diabetic ketoacidosis (DKA) were reported, nor any effect on GFR or albumin-to-creatinine ratio (ACR).

Sodium Glucose Transporter Inhibitors (SGLT2is)

Several SGLT2is have been evaluated in T1DM, including canagliflozin, dapagliflozin, empagliflozin and sotagliflozin. On the basis of Phase 3 clinical trials, dapagliflozin was licensed for use in T1DM in Europe, before its manufacturer voluntarily removed the indication late in 2021.[12] The U.S. Food and Drug Administration (FDA) did not approve an application for sotagliflozin to be licensed for use in T1DM.

A meta-analysis of randomized clinical trials of SGLT2is used as adjuncts to insulin in T1DM showed similar reductions in A1c and insulin dose to those with metformin and GLP-1RAs, with intermediate-level reductions in body weight (Table 1).[13] Reductions in blood pressure, LDL and triglyceride levels were also reported. Even in relatively small clinical studies, SGLT2is were clearly associated with an increased risk for DKA (2.5–5% in 26-week studies), albeit they were invariably associated with a precipitating factor, as well as with genital tract infections.[13] The EASE trials were able to reduce the risk of DKA by including a low-dose arm using empagliflozin at 2.5 mg daily. This resulted in lower efficacy for reductions in A1c and insulin dose, with no significant reduction in body weight versus 10 mg or 25 mg dosing.[14] SGLT2i use was also associated with more time in range and less glucose variability.[14,15]

Summary and Interpretation

There is clear evidence that the addition of NIAHAs can have beneficial effects for glycemic control, without the adverse effects of body weight gain and/or hypoglycemia, which would be expected with insulin. Their adverse effects (AEs) are generally predictable and manageable (GI AEs with metformin and GLP-1RAs; and genital infections with SGLT2is). The risks of DKA with SGLT2is are finite but significant and should prompt a pause, particularly because of the dissociation between hyperglycemia and ketosis. However, the question of why these agents have not been licensed for use in T1DM in Canada remains.

This may be due, in part, because of the current glucocentric focus, such that the reductions in HbA1c are perceived to be marginal and of limited clinical significance. However, a key oversight is to view the "small, incremental" reductions in body weight, insulin dose and A1c as independent parameters. Clearly, they are interdependent; however, the changes seen with the addition of NIAHAs run counter to what would normally be expected. An intervention that lowers A1c while reducing both body weight and insulin dose is surprising, but highly valued by patients. This may be reflected in the improvements in patient quality of life and treatment satisfaction observed in several clinical studies but has been most striking in terms of the strong preference of clinical trial participants to remain on active drug at the conclusion of clinical trials of NIAHAs—note that this is a personal observation.

Overall, there appears to be little or no increase in hypoglycemia with these NIAHAs. Given the nature of blinded trials, which may have included a treat-to-target design, it may be easier to avoid hypoglycemia with NIAHAs in clinical practice as there is no placebo, and proactive adjustments to insulin doses can be made.

Apart from the treatment effects on A1c is the desire to avoid complications and mortality. It is striking that metformin seems to have some cardiometabolic benefits that may be relevant to atherosclerosis. The trials of GLP-1RAs and SGLT2is have not been of sufficient duration to provide any clear information about their benefits. An extremely important question, however, is whether SGLT2i may have renal benefits in T1DM subjects with diabetic nephropathy. A Canadian-led study (SUGARNSALT) has been designed to answer that question.[16]

Conclusion

Patients with T1DM desire and deserve more than simply improved A1c. Mean blood glucose does not adequately reflect how people feel. Blood glucose variability, within and between days, is a major frustration and impediment which is better captured by continuous glucose monitoring (CGM). Therefore, it is intriguing that both GLP-1RAs and SGLT2is appear to be associated with more time in range and less glucose variability. Greater attention should be paid to evaluating patient preferences and quality of life in future studies of NIAHAs in T1DM, using more specific instruments and/or qualitative methods.

Practical Next Steps

Clinical trials provide important information about the safety and efficacy of new agents. Often, they are designed to be broadly generalizable, but this may overlook the fact that not all patients will benefit equally. Therefore, an individualized, patient-centred approach seems optimal from both an intellectual and inter-personal perspective. Selective use of NIAHAs in individuals struggling with weight gain, insulin resistance and/or difficulty reaching glycemic targets would be an obvious place to begin. Weighing the risks of DKA in individuals and providing education and tools for sick day management is important prior

to initiating an SGLT2i. Adopting these agents for a therapeutic trial, perhaps sequentially, could usefully inform shared decision-making, while access, coverage and side effects may limit therapeutic choices. While T1DM patients do not have a choice about whether or not to continue taking insulin, they can make choices about whether or not continuing to take an NIAHA is worth it to them, assuming that their physician administered it as a trial. While the Canadian Agency for Drugs and Technologies in Health (CADTH) states that "Marketing of off-label uses is prohibited," it also notes that "Off-label prescribing is allowed, and necessary in some cases."[17] NIAHAs are not licenced for use in T1DM; however, there is clear evidence from multiple clinical trials that they can deliver meaningful results. This supports careful and judicious off-label prescribing with the objective of delivering optimal care to individuals with T1DM.

Correspondence

Dr. Peter A. Senior
Email: psenior@ualberta.ca

Financial Disclosures

Investigator: DEPICT-2 and ADJUNCT-One (all fees to University of Alberta).

Honoraria/speaker fees: CPD Network, PPME, Humber River Hospital, Diabetes Canada.

Consulting fees: Bayer, Insulet, Novo Nordisk, Vertex, Viacyte.

References

1. Foster NC, Beck RW, Miller KM, Clements MA, Rickels MR, DiMeglio LA, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes technology & therapeutics. 2019 Feb;21(2):66–72.
2. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, Beaufort C de, et al. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol. 2022;10(10):741–60.
3. Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997–2010: a national Australian registry-based cohort study. Diabetologia. 2016 Jan 21;59(6):1177–85.
4. Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia. 2010;53(5):809–20.
5. Petrie JR, Chaturvedi N, Ford I, Brouwers MCGJ, Greenlaw N, Tillin T, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2017;5(8):597-609.
6. Pozzilli P, Bosi E, Cirkel D, Harris J, Leech N, Tinahones FJ, et al. Randomized 52-week Phase 2 Trial of Albiglutide Versus Placebo in Adult Patients With Newly Diagnosed Type 1 Diabetes. J Clin Endocrinol Metab. 2020 Mar 27;105(6):2066.
7. Herrath M von, Bain SC, Bode B, Clausen JO, Coppieters K, Gaysina L, et al. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Diabetes Endocrinol. 2021 Mar 1;9(4):212–24.
8. Albèr A, Brønden A, Knop FK. Short-acting glucagon-like peptide-1 receptor agonists as add-on to insulin therapy in type 1 diabetes: A review. Diabetes Obes Metabolism. 2017;19(7):915–25.
9. Mathieu C, Zinman B, Hemmingsson JU, Woo V, Colman P, Christiansen E, et al. Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. Diabetes Care. 2016 Oct;39(10):1702–10.
10. Ahrén B, Hirsch IB, Pieber TR, Mathieu C, Gómez-Peralta F, Hansen TK, et al. Efficacy and Safety of Liraglutide Added to Capped Insulin Treatment in Subjects With Type 1 Diabetes: The ADJUNCT TWO Randomized Trial. Diabetes Care. 2016;39(10):1693–701.
11. Dejgaard TF, Schmidt S, Frandsen CS, Vistisen D, Madsbad S, Andersen HU, et al. Liraglutide reduces hyperglycaemia and body weight in overweight, dysregulated insulin-pump-treated patients with type 1 diabetes: The Lira Pump trial—a randomized, double-blinded, placebo-controlled trial. Diabetes Obes Metabolism. 2020 Apr;22(4):492–500.
12. Mahase E. Type 1 diabetes drug was withdrawn because of a "commercial conflict of interest," charity argues. BMJ. 2022;376:o373.
13. Chen J, Fan F, Wang JY, Long Y, Gao CL, Stanton RC, et al. The efficacy and safety of SGLT2 inhibitors for adjunctive treatment of type 1 diabetes: a systematic review and meta-analysis. Sci Rep-uk. 2017;7(1):44128.
14. Rosenstock J, Marquard J, Laffel LM, Neubacher D, Kaspers S, Cherney DZ, et al. Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes: The EASE Trials. Diabetes Care. 2018 Dec;41(12):2560–9.
15. Mathieu C, Dandona P, Gillard P, Senior P, Hasslacher C, Araki E, et al. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 Study): 24-Week Results From a Randomized Controlled Trial. Diabetes Care. 2018 Sep;41(9):1938–46.
16. $2M Investment for Diabetic Kidney Disease Research [Internet]. 2021 Nov 25 [accessed 2023 Apr]. Available from: https://kidney.ca/News-Media/News/ALL/2M-Investment-for-Diabetic-Kidney-Disease-Research
17. Off-Label Use of Drugs: Questions and answers about the off-label use of drugs for health care providers. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). [accessed 2023 Apr]. Available from: https://www.cadth.ca/label-tools-professional-and-patient.

Management of Pediatric Type 2 Diabetes: A Practical Overview of Current Guidelines and Emerging Therapies

Sanjukta Basak, MDCM, FRCPC, MScCH (HPTE)

About the Author

Dr. Sanjukta Basak is a pediatric endocrinologist and clinical assistant professor at the University of British Columbia and BC Children's Hospital. She completed her medical degree at McGill University, followed by a Pediatric residency and Pediatric Endocrinology fellowship at the Hospital for Sick Children in Toronto. Sanjukta has a keen interest in medical education also has completed a Masters of Community Health with a focus on health practitioner and patient education at the University of Toronto. She is currently the Associate Pediatric Endocrinology Fellowship Program Director. She also serves as the clinical lead in the Pediatric Insulin Resistance and Type 2 Diabetes Program. As a member of the BC Children's Hospital Research Institute, her academic interests are in pediatric obesity, diabetes management, patient education, and health equity.

Affiliations

BC Children's Hospital, BC Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia

Introduction

Type 2 Diabetes Mellitus (T2DM) can no longer be considered an adult chronic disease. The diagnosis of pediatric T2DM is based on the laboratory criteria of fasting plasma glucose ≥7.0 mmol/L; 2-hour plasma glucose on a 75 g oral glucose tolerance test (OGTT) ≥11.1 mmol/L; random plasma glucose ≥11.1 mmol/L; or A1c ≥6.5% per Diabetes Canada.[1] It is important to note that these criteria are based on extrapolations from adult data, and have not been specifically validated in youth. The International Society for Pediatric and Adolescent Diabetes (ISPAD) adds that the diagnosis should not be made on these laboratory criteria alone, but should include symptoms of hyperglycemia and negative islet auto-antibodies.[2]

A Canadian national surveillance study of pediatric T2DM completed in 2010, has demonstrated a minimum incidence of youth-onset T2DM of 1.54 per 100,000 children per year with significant regional variation; the highest incidence was 12.45 per 100,000 children per year in Manitoba.[3] Youth-onset T2DM disproportionately affected Canadian children from high-risk ethnic groups, with 44% of new diagnoses occurring in the Indigenous, Asian, African and Caribbean populations.[3]

Over the past twenty years, youth-onset diabetes has been rising. In the United States, according to the SEARCH for Diabetes in Youth Study, there has been an annual increase of 7.1% observed across all age, sex, race and ethnic groups.[4] The COVID-19 pandemic has added further escalation in the incidence of youth-onset worsening disease severity at presentation.[5] New cases in the United States rose by 77.3% in the initial year following the COVID-19 pandemic, vs in the two years pre-pandemic. Furthermore, 21% of youth presented with diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome vs previous estimates of 9% pre-pandemic.[5] The SEARCH for Diabetes in Youth Group projects that the number of youths with T2DM will increase from 28,000 to 48,000 youth today, to 220,000 youth by 2060, with widening racial and ethnic disparities among youth with T2DM.[6]

Navigating the Heavy Burden of Youth-Onset T2DM

Several pivotal studies show that youth-onset T2DM has a more aggressive clinical course than adult-onset T2DM.

1. **The RISE consortium:** Pancreatic β-cell failure progresses more rapidly in youth than in adults despite early treatment with metformin and/or glargine.[7] Glycemic worsening occurred in 17.8% of youth vs 7.5% of adults within 12 months (P=0.008) and in 36% of youth vs 20% of adults within 21 months (P=0.002).[7]
2. **The TODAY study group:** Youth with T2DM develop microvascular and macrovascular complications with shorter disease duration than youth with T1DM and adults with T2DM.[8] With a mean diagnosis at age 13.3 ± 1.8 years, the cumulative incidence of any microvascular complication was 50% by 9 years and 80% by 15 years of disease duration. The cumulative incidence of hypertension was 67.5%; dyslipidemia was 51.6%; diabetic kidney disease was 54.8%; and peripheral neuropathy was 32.4%.[8] The prevalence of retinopathy increased from 13.7% to 51.0% between 5 years to 12 years of disease duration.[9] Risk factors for the development of complications included minority race or ethnic group, hyperglycemia, hypertension, and dyslipidemia.[8]
3. **The SEARCH group:** Microvascular and macrovascular complications are statistically higher in youth with T2DM versus those with T1DM: diabetic kidney disease (absolute difference [AD]: 14.0%); retinopathy (AD: 3.5%); peripheral neuropathy (AD: 9.2%); arterial stiffness (AD: 35.9%); and hypertension (AD: 11.5%).[10]
4. **The SEARCH group:** There remains high all-cause mortality among youth and young adults with T2DM beyond that which occurs in youth with T1DM, and the general population.[11]

Lessons from these studies suggest an urgent need for improvements in our approach to managing youth-onset T2DM.

Navigating Disease Management

Current pharmacologic management strategies are centered around a limited number of clinical studies: metformin,[12] glimepiride,[13] the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study,[14] the ELLIPSE trial of liraglutide,[15] meta-analysis of GLP-1RAs,[16] DINAMO,[17] and the pediatric arm of the Restoring Insulin SEcretion (RISE) Study.[18]

There are a number of challenges in procuring evidence-based data for the treatment of youth-onset T2DM, including the high cost of operating randomized, placebo-controlled trials; lack of inclusive patient engagement of ethnic minority groups; barriers in access to clinical trial sites; strict study entry criteria; and the high prevalence of psychosocial challenges that impact patient participation. Advocates in the field urge for the consideration and early adoption of off-label antidiabetic agents.[19]

Current guidelines from Diabetes Canada (2018),[1] ISPAD (2022)[2] and the American Diabetes Association (ADA) (2023)[20] have been developed based on the current literature and clinical expertise. The objective of youth-onset T2DM glycemic control is to achieve target A1c of <7%.[2,20] Lower A1c (<6.5%) can be targeted for select populations: (a) recently diagnosed patients to preserve their beta function; (b) youth who are able to achieve significant weight loss by lifestyle changes; and (c) youth managed on metformin only.[2,20]

Culturally sensitive, family-based lifestyle modification in a safe healthcare setting free of stigma, shame and blame is first-line treatment for T2DM. In selecting pharmacotherapy, it is critical to balance achieving optimal glycemic control (A1c <7%) and the prevention of complications with avoidance of over-insulinization and the prevention of weight gain.

Navigating Diabetes Education

Youth-onset T2DM is best managed by a multidisciplinary pediatric team with expertise in this cohort's unique dietary, exercise and psychological needs. The treatment team should ideally include a pediatric endocrinologist, certified diabetes educator, dietitian, psychologist, and/or social worker, and an exercise physiologist if resources permit.[2] Important considerations for diabetes education delivery include:

1. A family-centered approach that focuses on the family's involvement; sharing responsibility and self-management with family monitoring and support using nonjudgmental, motivational and supportive conversations;
2. Education using culturally appropriate material in the patient's/family's first language;
3. Interpreter services and workforce diversity to optimize communication;
4. Encouragement of self-management guided by the patient's/family's level of confidence and motivation;

5. Consideration of group education to assist with motivation and social networking;[22]
6. Consideration of hybrid in-person and virtual models of care to improve access to care for patients living in remote communities;[22,23]
7. Education content should also extend to schools to optimize support of diabetes management among youth.[2]

Pharmacotherapy

Initial management: metformin and insulin

Metformin is used as the first-line drug of choice in youth with A1c <8.5%, with minimal symptoms, and no ketosis or acidosis, at a starting dose of 500 mg/day, gradually increasing to 2,000 mg/day over four weeks in order to minimize potential gastrointestinal (GI) side effects. In youth with ketosis, A1c ≥8.5%, and no signs of acidosis, metformin paired with long-acting basal insulin (a starting dose of 0.25–0.5 units/kg) is often effective in attaining metabolic control, while minimizing excessive weight gain. The use of prandial fast-acting insulin is now reserved for youth with T2DM presenting in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) upon transition off intravenous (IV) continuous insulin infusion.

Data emerging from the TODAY study indicates that 90% of youth presenting with T2DM can be successfully weaned off insulin and treated with metformin alone.[8] Transition off insulin can usually be achieved over two-to-six weeks by reducing the insulin dose in 30–50% increments as the metformin dose is increased.[2,20]

Subsequent therapy

If the A1c target of <7.0% is not achieved within three-to-four months on metformin monotherapy, additional second-line agents should be considered (Table 1). While polypharmacy may not appear to be the optimal treatment approach in youth who struggle with compliance, it is the experience of many pediatric endocrinologists that patients and their families are motivated by the possibility of avoiding insulin.[19]

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA)

The most recent ADA and ISPAD guidelines recommend the consideration of GLP-1RAs if glycemic targets are not met with metformin monotherapy (with or without insulin) in children ≥10 years of age.[2,20] Diabetes Canada has not yet made this recommendation.[1] There was clear benefit in A1c reduction reported in the ELLIPSE trial assessing the safety and efficacy of liraglutide.[15] This was corroborated in a meta-analysis of seven studies of GLP-1RAs[16] and the AWARDS-PEDS study of dulaglutide.[24] Semaglutide was assessed for the treatment of obesity in the STEP TEENS trial; however no data was collected in those with youth-onset T2DM.[25] In adults with T2DM, GLP-1RAs have been demonstrated to be both cardio- and reno-protective, while such impact has yet to be assessed in youth. Given the previously stated data regarding severe complications in youth-onset T2DM, it is vital to consider early adoption of GLP-1RAs.

Health Canada has approved liraglutide for use in youth age >12 years, whereas semaglutide has not yet received this approval.

Sodium-glucose cotransporter-2 inhibitors (SGLT2is)

SGLT2is (dapagliflozin, empagliflozin and canagliflozin) are not yet Health Canada approved for youth-onset T2DM. Phase 3 results of a clinical trial of dapagliflozin in children and young adults with T2DM determined that dapagliflozin safely lowers glucose in this population (decreased A1c by 0.62% vs placebo).[26] Empagliflozin also showed clinically significant reductions in A1c of 0.84% vs placebo at 26 weeks of treatment; however, hypoglycemia was noted as an adverse event in 77% of participants.[17] These agents represent a potential treatment option for youth-onset T2DM.

Dipeptidyl peptidase 4 inhibitors (DPP4is)

DPP4is are not yet Health Canada approved for youth-onset T2DM. Systematic reviews and recent clinical trials of linagliptin do not show any advantage of DPP4is for glycemic improvement in youth-onset T2DM.[17,27]

Thiazolidinediones (TZDs)

TZDs are not yet Health Canada approved for youth-onset T2DM. The addition of TZD (rosiglitazone) to metformin decreased the risk for progression to insulin requirement by 23% in youth in the TODAY study.[14] This class of medication has been associated with a high risk of weight gain; this has limited its widespread off-label adoption in the pediatric population. Some experts report that it can be considered viable for patients who cannot tolerate metformin or for those for whom the cost of the newer agents is prohibitive.[19]

Combination medications

Tirzepatide is a dual GLP-1RA and glucose-dependent insulinotropic peptide (GIP) receptor agonist that has been shown to cause substantial weight loss in adults, with improvement in A1c of 1.07%.[28] An ongoing clinical trial is being conducted to demonstrate the

Class	Mechanism of action	Names and dosing	HbA1c impact	Impact on weight management	Cost
GLP-1RA	1. Increasing insulin secretion 2. Suppressing glucagon 3. Prolonging gastric emptying and promoting satiety	**Liraglutide** (1.8 mg SC daily)	ELLIPSE trial: reduction of 0.64% in HbA1c; 63.7% of patients in liraglutide group achieved HbA1c values <7.0%	ELLIPSE trial: mean difference of 1.3 kg after 26 weeks	High; variable coverage in Canada depending on province
		Semaglutide (1.0 mg SC daily)	No pediatric data available	STEP-TEENS trial: BMI from baseline to week 68 was -16.7% estimated difference; 73% had weight loss of 5% or more	
		Dulaglutide (0.75 or 1.5 mg SC weekly)	AWARDS-PEDS: reduced HbA1c by 0.9%	No significant change in body weight noted at 26 weeks of treatment	
		Exenatide (2 mg SC weekly)	Reduced HbA1c by 0.85%	No significant change in body weight noted at 24 weeks of treatment	
SGLT2i	Inhibits renal tubular reabsorption of glucose, leading to increased urinary glucose loss, reduction in serum glucose, and weight loss	**Canaglifozin** (100–300 mg/day) **Dapagliflozin** (10 mg/day) **Empagliflozin** (10–25 mg/day) **Ertugliflozin** (15 mg/day)	**Dapapgliflozin**: Reduced HbA1c by 0.5% at 24 weeks **Empagliflozin**: Reduced HbA1c by 0.85%	DINAMO trial: No impact on weight	Moderate
DPP4i	Inhibits the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1	**Linagliptin** (5 mg/day)	DINAMO trial: No impact on HbA1c	DINAMO trial: No impact on weight	Moderate
TZD	1. Binds to nuclear PPAR gamma, ubiquitous orphan steroid receptors abundant in adipocytes 2. Increases insulin sensitivity in muscle, adipose, and liver tissue	**Pioglitazone** (15 mg/day; can increase to 30 mg/day) 45 mg/day dose available	0.5–1.3% HbA1c reduction	Weight gain noted	Low to Moderate

Table 1: Summary of current pediatric literature in use of off-label second-line anti-hyperglycemic agents.
Adapted from ISPAD 2022 guidelines.

metabolic and weight reduction effects of tirzepatide in adolescents (National Library of Medicine, NCT number: NCT05260021).

Bariatric Surgery

Bariatric Surgery in the post-pubertal adolescent population can be an effective tool for the remission of T2DM.[2,20] Five years after bariatric surgery, adolescents were 1.27 times more likely to have remission of T2DM vs adults five years post-surgery.[29]

Nutrition

The involvement of a dietitian for initial T2DM education and subsequent management is key to achieving target glycemic control and working toward remission. Nutritional therapy should be aimed at youth and their family including all those involved in creating the child's food environment. A balanced approach is recommended; there are no data to support very low calorie, low carbohydrate or ketogenic diets, nor

intermittent fasting, in youth with T2DM. Diet modification should incorporate:[1,2,20]

1. Eliminating sugar-sweetened soft drinks and juices
2. Reducing the intake of foods made from refined, simple sugars and high-fructose corn syrup
3. Limiting intake of high-fat and/or calorie dense foods
4. Reducing the intake of processed, prepackaged and "convenience" foods
5. Understanding healthy portions sizes
6. Reducing meals eaten away from home and in fast food restaurants
7. Increasing vegetable and fruit intake
8. Replacing enriched white rice and white flour with brown rice and whole grains with a lower glycemic index to promote the gradual absorption of glucose with meals
9. Healthy parenting practices and promoting parental modelling of healthy eating habits, while avoiding an overly restrictive food intake
10. Encouraging healthy meal practices such as eating on schedule, in one place, preferably as a family unit, and with no other activity (use of computers or studying)
11. Use of educational materials on nutrition; healthy plate models that include ethnically diverse foods

Ongoing patient assessment for unhealthy eating habits is recommended given the increased risk for eating disorders in youth with T2DM.[30] It is advisable to incorporate the use of regular screening questions for all youth regardless of gender and BMI, in particular, in youth reporting body dissatisfaction; history of dieting; history of depression; poor glycemic control; missed clinical appointments; recurrent episodes of DKA; recurrent hypoglycemia secondary to intentional medication overdose; and dietary manipulation.[31]

Nutritional recommendations should also be provided under the practical lens of household food security, housing stability, access to fresh water, barriers to accessing fruits and vegetables due to climate change, and family financial resources.

Physical Activity

Regular daily physical activity is an integral part of all diabetes management plans for improving glycemic control, reducing cardiovascular (CV) risk factors, contributing to weight loss, and improving mental health. Youth are encouraged to target 60 minutes of moderate to vigorous physical activity daily, with strength training at least three days per week.[2] Key considerations for youth with T2DM include:

1. Promote physical activity as a family event, including daily efforts to increase body movement, such as using stairs instead of elevators, walking or cycling to school and shopping outings, and doing house and yard work
2. Encourage physical activity with positive reinforcement and avoid the use a punitive measure as a means to address the intake of high-fat and/or calorie dense foods
3. Reduce sedentary on-screen time to less than two hours per day

Physical activity targets should be specific, negotiated, enjoyable, and sensitive to family resources.[2] Clinical assessment of physical activity should include an understanding of the youth's community, physical environment and neighborhood walkability scores. There is also emerging data to suggest that technology-based interventions such as active video games can improve dyslipidemia and result in weight loss.[32] Effort should also be made to draw on cultural traditions when trying to promote physical fitness.[33] Recent publications have supported the use of Bhangra dancing, for example, to improve cardiovascular respiratory profiles, dyslipidemia and insulin resistance.[34]

Psychosocial Considerations

Psychosocial factors constitute a major challenge in implementing pharmacotherapy and lifestyle behaviour change in youth with T2DM.[4] Youth-onset T2DM disproportionately affects visible ethnic minorities living in poverty,[35] individuals in food insecure households,[36] and those exposed to structural racism.[37] Treatment recommendations should be individualized to consider the cultural, social, geographic and economic barriers to implementing behavioural change.

Youth with T2DM should be screened for psychological comorbidities including depression, anxiety, weight stigma, diabetes distress, and disordered eating at diagnosis and at regular follow-up intervals.[2,38] These factors can create a barrier to lifestyle modifications leading to sedentary lifestyles, disturbed sleep patterns, poor medication adherence, and excessive snacking. The selection of weight-neutral antidepressant medications is recommended when treating depression or other mental health conditions in adolescents with T2DM.[2]

This highlights the importance of the early inclusion of social worker support, the creation of pathways for accessing support groups, and psychologists.

Complications/ Comorbidities	Screening Test	Screening Interval	Initial Treatment
Hypertension	Blood pressure using appropriately sized cuff	At every visit	• Aim for weight loss • Diet: limitation of dietary salt to <2300 mg/day, initiate DASH diet • Increase physical activity to 1 hour daily • Start ACE inhibitor or ARB if no improvement within 6 months • Referral to pediatric nephrology as required
Dyslipidemia *(high plasma triglycerides, low HDL-C, and high LDL-C)*	Fasting lipid profile	Yearly, starting at 3 months after diagnosis	• Optimize HbA1c <7% • Diet: limit saturated fats, avoid trans fats, improve fiber intake, lower intake of simple sugars and sugar sweetened beverages, increase intake of omega-3 • Increase physical activity to 1 hour daily • Monitor lipid levels every 3–6 months • Start statins to lower LDL-C if no improvement after 6 months of dietary modification • Start fibrates to lower triglycerides if no improvement after 6 months of dietary modification
Nephropathy	Urine albumin to creatinine ratio (ACR)	Yearly, starting at diagnosis	• Elevated spot value occur secondary to contamination, exercise, smoking, menstruation, infection and orthostasis. • Document 2–3 a.m. urine ACR immediately after rising • Consultation with pediatric nephrology if persistently elevated ACR >30 mg/mmol
Retinopathy	Comprehensive eye examination with dilated pupils or retinal photography by optometrist or ophthalmologist	Yearly, starting at diagnosis	• Optimize HbA1c <7% • Ensure treatment of dyslipidemia and hypertension if present • Ongoing close follow-up with ophthalmologist
Neuropathy	Clinical history of symptoms (numbness, pain, cramps, and paresthesia); tests of vibration sense, light touch, and ankle reflexes	Yearly, starting at diagnosis	• Optimize HbA1c <7% • Ensure treatment of dyslipidemia, optimize HDL-C • Counsel on avoidance of smoking and smoking cessation (if applicable) • Referral to pediatric neurologist if symptomatic
NAFLD	ALT, AST	Yearly, starting at diagnosis	• Optimize HbA1c <7% • Consider optimizing diabetes medications; glitazones and GLP-1RA can improve liver enzymes • Consider need for liver ultrasound • Consult pediatric gastroenterologist if ALT and AST >3 times normal reference range over 6 months to exclude other causes of liver enzyme elevation via imaging and/or liver biopsy
OSA	Clinical history of snoring, sleep quality, apnea, morning headaches, daytime sleepiness	Yearly, starting at diagnosis	• Confirm diagnosis with referral to a sleep specialist for sleep study; nocturnal pulse oximetry can be an initial useful evaluation if there is limited access for a sleep study
PCOS	Clinical history of menstrual cycle irregularity and evidence of hyperandrogenism	Yearly at diagnosis in post-pubertal girls	• Optimize HbA1c <7% • Diet: engage in dietary changes towards weight loss • Increase physical activity to 1 hour daily • Start OCP to assist with menstrual irregularity and symptoms of hyperandrogenism as adjunctive therapy
Psychosocial Health	Clinical history of depression, disordered eating, food security, smoking, vaping, drugs, alcohol use, sexual activity, school support and family financial concerns	At every visit	• Engage regular follow-up and monitoring with social worker and mental health resources

Table 2: Navigating complications and comorbidities associated with youth onset T2D. *Courtesy of Dr. Sanjukta Basak.*

Navigating Additional Barriers to Management

Other factors unique to youth include pubertal insulin resistance, which often leads to prescribing large doses of insulin; this, in turn, promotes weight gain. In addition, the development of the adolescent brain is associated with compliance challenges. Often, youth with T2DM have multiple family members with T2DM and diabetes-related complications, creating additional logistical barriers as they manage multiple family appointments, and the added costs of diabetes medications and supplies. Youth may face additional challenges of caring for family members while trying to manage their own diabetes. Youth with diabetes may also present with additional comorbidities such as polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), hypertension, obstructive sleep apnea (OSA), and dyslipidemia, which can lead to further setbacks in coping with disease and quality of life burdens. From a financial perspective, there is a scarcity of Health Canada-approved medications for use in pediatric T2DM, leading to barriers in coverage by provincial healthcare plans and extended health care benefits.

Navigating Co-Morbidities Associated with Youth-Onset T2DM

Centralizing the care of T2DM patients and diabetes-related complications is the optimal approach for successful patient engagement and outcomes. As pediatric education centres evolve toward specialized pediatric T2DM clinics, it is critical to ensure that pathways for screening and investigation, as well as for the management of hypertension, dyslipidemia, nephropathy, retinopathy, NAFLD, OSA, PCOS, and referrals, are developed for efficient patient care (Table 2).

Conclusion

Youth-onset T2DM is clinically complex and aggressive, with a high burden of disease. Poor glycemic control and high rates of complications in youth-onset T2DM persist despite management with metformin and insulin. It is important to balance achieving optimal glycemic control (A1c <7%) with the prevention of complications from over-insulinization, and the prevention of weight gain. Limited Health Canada-approved tools exist for the treatment of pediatric T2DM. We need to consider safe, early adoption of off-label medications for this patient population.

Correspondence

Dr. Sanjukta Basak
Email: sanjukta.basak@cw.bc.ca

Financial Disclosures

Research Studies/Clinical Trials: Neurocrine Biosciences, Ultragenyx, Pfizer, Rhythm Pharmaceuticals

Speaking Honoraria: Canadian Diabetes & Endocrinology Today, Pfizer, Canadian Pediatric Endocrine Group Meeting, Eli Lily

Advisory Boards: Novo Nordisk Pediatric Expert Obesity National Advisory Board, Growth Hormone Pediatric Endocrinology National Advisory Board

References

1. Diabetes Canada Clinical Practice Guidelines Expert C, Panagiotopoulos C, Hadjiyannakis S, Henderson M. Type 2 Diabetes in children and adolescents. Can J Diabetes. 2018;42 Suppl 1:S247-S54.
2. Shah AS, Zeitler PS, Wong J, Pena AS, Wicklow B, Arslanian S, Chang N, Fu J, Dabadghao P, Pinhas-Hamiel O, Urakami T. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. Pediatric Diabetes. 2022 Nov;23(7):872-902.
3. Amed S, Dean HJ, Panagiotopoulos C, Sellers EA, Hadjiyannakis S, Laubscher TA, Dannenbaum D, Shah BR, Booth GL, Hamilton JK. Type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children: a prospective national surveillance study. Diabetes Care. 2010 Apr 1;33(4):786-91.
4. Rodriquez IM, O'Sullivan KL. Youth-Onset Type 2 Diabetes: Burden of Complications and Socioeconomic Cost. Current Diabetes Reports. 2023 Mar 24:1-9.
5. Magge SN, Wolf RM, Pyle L, Brown EA, Benavides VC, Bianco ME, Chao LC, Cymbaluk A, Balikcioglu PG, Halpin K, Hsia DS. The coronavirus disease 2019 pandemic is associated with a substantial rise in frequency and severity of presentation of youth-onset type 2 diabetes. The Journal of Pediatrics. 2022 Dec 1;251:51-9.
6. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, Lawrence JM, Liese AD, Liu LL, Mayer-Davis EJ, Rodriguez BL. Projections of type 1 and type 2 diabetes burden in the US population aged< 20 years through 2050: dynamic modeling of incidence, mortality, and population growth. Diabetes Care. 2012 Dec 1;35(12):2515-20.
7. RISE Consortium. Impact of insulin and metformin versus metformin alone on β-cell function in youth with impaired glucose tolerance or recently diagnosed type 2 diabetes. Diabetes Care. 2018;41(8):1717-25.
8. TODAY Study Group; Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, et al. Long-term complications in youth-onset type 2 diabetes. N Engl J Med. 2021;385(5):416-26.
9. TODAY Study Group. Development and progression of diabetic retinopathy in adolescents and young adults with type 2 diabetes: results from the TODAY study. Diabetes Care. 2021;45(5):1049-55.

10. Dabelea D, Stafford JM, Mayer-Davis EJ, D'Agostino R, Dolan L, Imperatore G, Linder B, Lawrence JM, Marcovina SM, Mottl AK, Black MH; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA. 2017 Feb 28;317(8):825-35.
11. Lawrence JM, Reynolds K, Saydah SH, Mottl A, Pihoker C, Dabelea D, Dolan L, Henkin L, Liese AD, Isom S, Divers J. Demographic correlates of short-term mortality among youth and young adults with youth-onset diabetes diagnosed from 2002 to 2015: the SEARCH for Diabetes in Youth Study. Diabetes Care. 2021 Dec 1;44(12):2691-8.
12. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. Diabetes Care. 2002 Jan 1;25(1):89-94.
13. Gottschalk M, Danne T, Vlajnic A, Cara JF. Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: a randomized, single-blind comparative study. Diabetes Care. 2007;30(4):790-4.
14. TODAY Study Group; Zeitler P, Epstein L, Grey M, Hirst K, Kaufman F, et al. Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. Pediatr Diabetes. 2007;8(2):74-87.
15. Tamborlane WV, Barrientos-Perez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med. 2019;381(7):637-46.
16. Chadda KR, Cheng TS, Ong KK. GLP-1 agonists for obesity and type 2 diabetes in children: Systematic review and meta-analysis. Obes Rev. 2021;22(6):e13177.
17. Laffel LM, Danne T, Klingensmith GJ, Tamborlane WV, Willi S, Zeitler P, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. Lancet Diabetes Endocrinol. 2023;11(3):169-81.
18. Sam S, Edelstein SL, Arslanian SA, Barengolts E, Buchanan TA, Caprio S, et al. Baseline Predictors of Glycemic Worsening in Youth and Adults With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes in the Restoring Insulin Secretion (RISE) Study. Diabetes Care. 2021;44(9):1938-47.
19. Kelsey MM, Zeitler PS, Nadeau KJ, Shah AS. Type 2 diabetes in youth: Rationale for use of off-label antidiabetic agents. Pediatr Diabetes. 2022;23(6):615-9.
20. American Diabetes Association Professional Practice Committee. 14. Children and adolescents: Standards of medical care in diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S208-S31.
21. Salama M, Biggs BK, Creo A, Prissel R, Al Nofal A, Kumar S. Adolescents with Type 2 Diabetes: Overcoming Barriers to Effective Weight Management. Diabetes, Metabolic Syndrome and Obesity. 2023 Dec 31:693-711.
22. Lee V. The experiences and views of children with type 2 diabetes and their families. Diabetes Care Child Young People. 2020;10:165.
23. Fung A, Irvine M, Ayub A, Ziabakhsh S, Amed S, Hursh BE. Evaluation of telephone and virtual visits for routine pediatric diabetes care during the COVID-19 pandemic. J Clin Transl Endocrinol. 2020;22:100238.
24. Arslanian SA, Hannon T, Zeitler P, Chao LC, Boucher-Berry C, Barrientos-Pérez M, Bismuth E, Dib S, Cho JI, Cox D. Once-weekly dulaglutide for the treatment of youths with type 2 diabetes. New England Journal of Medicine. 2022 Aug 4;387(5):433-43.
25. Weghuber D, Boberg K, Hesse D, Jeppesen OK, Sorrig R, Kelly AS, et al. Semaglutide treatment for obesity in teenagers: a plain language summary of the STEP TEENS research study. J Comp Eff Res. 2023;12(2):e220187.
26. Tamborlane WV, Laffel LM, Shehadeh N, Isganaitis E, Van Name M, Ratnayake J, et al. Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study. Lancet Diabetes Endocrinol. 2022;10(5):341-50.
27. Li X, Sun T, Du X, Xie X, Shi L. The efficacy and safety of dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists in pediatric patients with type 2 diabetes: a systematic review. J Pediatr Endocrinol Metab. 2022;35(12):1457-63.
28. Tang Y, Zhang L, Zeng Y, Wang X, Zhang M. Efficacy and safety of tirzepatide in patients with type 2 diabetes: A systematic review and meta-analysis. Front Pharmacol. 2022;13:1016639.
29. Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Brandt ML, Xanthakos SA, et al. Five-Year outcomes of gastric bypass in adolescents as compared with adults. N Engl J Med. 2019;380(22):2136-45.
30. Pinhas-Hamiel O, Levy-Shraga Y. Eating disorders in adolescents with type 2 and type 1 diabetes. Curr Diab Rep. 2013;13(2):289-97.
31. Racicka E, Brynska A. Eating Disorders in children and adolescents with Type 1 and Type 2 diabetes: prevalence, risk factors, warning signs. Psychiatr Pol. 2015;49(5):1017-24.
32. Ercelik ZE, Caglar S. Effectiveness of active video games in overweight and obese adolescents: a systematic review and meta-analysis of randomized controlled trials. Ann Pediatr Endocrinol Metab. 2022;27(2):98-104.
33. Tang TS, Mahmood B, Amed S, McKay H. Drawing on cultural traditions to improve cardiorespiratory fitness with South Asian children: a feasibility study. Child Obes. 2022;18(5):333-41.
34. Priya G, Grewal E. When the DHOL is beating, BHANGRA comes to the rescue! Indian J Endocrinol Metab. 2021;25(3):253-4.
35. Hawkes CP, Lipman TH. Racial disparities in pediatric Type 1 diabetes: yet another consequence of structural racism. Pediatrics. 2021;148(2).
36. Reid LA, Zheng S, Mendoza JA, Reboussin BA, Roberts AJ, Sauder KA, et al. Household food insecurity and fear of hypoglycemia in adolescents and young adults with diabetes and parents of youth with diabetes. Diabetes Care. 2023;46(2):262-9.
37. Egede LE, Campbell JA, Walker RJ, Linde S. Structural racism as an upstream social determinant of diabetes outcomes: a scoping review. Diabetes Care. 2023;46(4):667-77.
38. Gulley LD, Shomaker LB. Depression in youth-onset type 2 diabetes. Curr Diab Rep. 2020;20(10):51.

Resistance Exercise in the Context of Type 1 Diabetes

Jane E. Yardley, MSc, PhD

About the Author

Dr. Jane Yardley is an Associate Professor at the University of Alberta, a recipient of a Heart and Stroke Foundation Alberta New Investigator Award, and part of the Physical Activity and Diabetes Laboratory at the Alberta Diabetes Institute. Her research focuses on the impact of exercise on blood glucose levels in adults with type 1 diabetes, with projects focusing on resistance exercise and along with aspects of women's health. She is a co-author of the 2016 American Diabetes Association Position Statement on Diabetes and Exercise/Physical Activity.

Affiliations

Augustana Faculty, University of Alberta
Physical Activity and Diabetes Laboratory, Alberta Diabetes Institute
Women and Children's Health Research Institute

Introduction

Exercise and physical activity are associated with many benefits for individuals with type 1 diabetes (T1D), including increased longevity and a decrease in the incidence/severity of diabetes-related complications.[1,2] Unfortunately, these activities (and aerobic exercise in particular) also increase the risk of hypoglycemia and glycemic variability, both of which act as barriers to being more active in this population.[3] Resistance exercise is an often-overlooked activity, as historically it has been seen in training reserved for elite athletes. For individuals with T1D, it is associated with a multitude of benefits including a reduced risk of hypoglycemia during activity.[4,5] With improved insulin formulations and rapid increases in technology to manage T1D, people with this condition are living longer, healthier lives. This article describes the many reasons why resistance exercise should be a part of this longevity.

Benefits of Longer-Term Resistance Training

Resistance exercise is generally described as using muscular contraction against an external force. This force can be provided by body weight, resistance bands, weight-lifting machines or free weights. The benefits of resistance exercise in people without diabetes include increases in skeletal muscle mass, strength and endurance, improvements in insulin sensitivity, decreases in visceral fat, an enhancement of cardiovascular health (in particular through reductions in blood pressure), increases in bone mineral density, and an ameliorated lipid profile.[6] Most of these benefits are also seen in people with T1D, although recent evidence may suggest that performing resistance exercise may not lead to improvements in average blood glucose levels as measured by HbA1c.[4,7]

Acute Glycemic Effects of Resistance Exercise

Due to its reliance on blood glucose as a fuel source, aerobic exercise (activities involving repeated contractions of large muscle groups over extended periods of time, e.g. walking, swimming, cycling, etc.) relies on lipids and blood glucose to fuel activity. This selection of fuels produces large declines in blood glucose during aerobic activity in individuals with T1D, leading to a greater risk of hypoglycemia during activity. In contrast, higher intensity (anaerobic) activities, have a greater reliance on hepatic and muscular glycogen stores.[5] As a result, there is a tendency for smaller blood glucose declines during anaerobic activity, albeit with the potential for more post-exercise hypoglycemia.[5,8]

The acute glycemic effects of resistance exercise in people with T1D have only recently been examined.

In 2013, using a repeated measures design, Yardley et al showed that late afternoon resistance exercise produced a smaller decline in blood glucose levels than a comparable duration of moderate aerobic exercise performed at the same time of day in physically active individuals with T1D.[5] To the extent possible, the authors controlled for food intake (self-selected but repeated over three days of monitoring for each exercise session), insulin adjustments (self-reported) and background physical activity (measured by pedometer). While blood glucose decreased less during exercise, post-exercise continuous glucose monitoring revealed a greater amount of hypoglycemia overnight after resistance exercise, likely due to the replenishment of glycogen stores.[5]

Not long after this initial publication, Turner et al found an increase in blood glucose levels in individuals with T1D performing a similar resistance exercise protocol.[9] It has recently been shown that this difference can be attributed to the fact that participants in the Turner study were exercising after an overnight fast. Using a repeated measures design, Toghi-Eshghi and Yardley (2019) compared the response of a group of participants with T1D to an identical resistance exercise protocol performed once in the fed state (around 5 p.m.) and once in the fasted state (around 7 a.m.) to replicate the scenarios from the previous studies.[10] They found that intra-individual blood glucose was more likely to increase during fasted morning resistance exercise, while it decreased when the same protocol was performed later in the day.[10] As such, performing resistance exercise while fasted can be advised for individuals with T1D for whom the fear of hypoglycemia is a major barrier to being active. The physiology behind these blood glucose responses to fasted exercise are described in detail elsewhere.[11]

An additional glycemic benefit to performing resistance exercise is that it may slow or prevent large blood glucose declines during subsequent aerobic exercise. In a crossover study of afternoon exercise (protocols performed at 5 p.m.), participants with T1D experienced a delayed, and slower, decline in blood glucose levels during 45 minutes of aerobic exercise when it was performed after 45 minutes of resistance exercise.[12] Conversely, large blood glucose declines were immediately evident when aerobic exercise was performed first. As a result, if individuals with T1D approach a combined exercise session with blood glucose levels in a higher than desired range, performing aerobic exercise first may be beneficial. Conversely, if blood glucose levels are lower and there is a concern that hypoglycemia may occur, performing resistance exercise first may be the safest option.

It is also important to note that there may be sex-related differences in blood glucose responses to resistance exercise in people with T1D. A secondary analysis by Brockman et al showed that male participants had both a greater blood glucose decline during resistance exercise, and developed more hypoglycemia in the six hours following exercise.[16] However, the authors note that these differences may be due simply to differences in body composition (males tend to have more muscle mass than females) and the amount of work performed (males lifted more weight than females, even if it was of similar intensity relative to the participants' maximum lifting ability). A recent cross-sectional study also indicated that gender-related (behavioural) differences in glycemic management strategies around exercise are likely to exist for those with T1D and, as such, it is possible that the differences in blood glucose responses (in particular post-exercise), may be the result of different management strategies in women and men.[14]

Frailty Prevention

Due to recent improvements in insulin agents and diabetes technology, people with T1D are living longer, healthier lives. However, recent studies show that as they age, individuals with T1D lose muscle mass and quality faster than matched controls without diabetes.[15] There is also evidence to indicate that bone strength (whether due to bone density or bone quality) also decreases faster, thereby increasing the risk of fractures.[16] These two factors combined elevate the risk of frailty in older individuals with T1D. As such, it is essential for individuals with T1D to perform weight-bearing and resistance exercise throughout their lifespan to offset diabetes-related declines in strength, bone health and functional mobility.

While data from individuals with T1D are currently lacking, early adoption of these activities in those without diabetes, even in small doses, can lead to higher peak muscle strength/mass and higher bone density/quality, from which the eventual age-related declines will occur.[17,18] In people without diabetes, those who perform resistance exercise and high-impact activities tend to have a slower loss of muscle and bone with aging.[18] Studies of older adults show that it is still possible to gain strength by performing resistance exercise.[19] Further research is necessary to determine if these benefits are as pronounced in individuals with T1D.

Gaps in the Research

It is important to note that the research to date on the acute glycemic effects of resistance exercise in people with T1D has involved only one type of resistance exercise protocol—one that is designed to build muscle mass (performing 3 sets of 8 repetitions). Several types of resistance exercise protocols exist, each stimulating different physiological adaptations. High-volume, low-resistance protocols are designed to increase muscular endurance and are likely to have a greater contribution of aerobic metabolism. As such, they may be associated with greater blood glucose declines, but less post-exercise hypoglycemia. Very low-volume, high-resistance protocols favour neurological adaptations to produce more powerful muscular contractions. These activities may, therefore, be reliant to an even greater degree on glycogen as a fuel source. At this stage, however, potential glycemic responses are purely speculative.

There is also very little known about how differences in age, sex and physical fitness may affect blood glucose responses to resistance exercise. Research in individuals without T1D show that these physiological factors can affect fuel selection during different types of exercise.[20] Whether or not their effect is potent enough to influence blood glucose responses to resistance exercise in T1D (where synthetic insulin also plays a very dominant role) has not been fully elucidated.

Conclusion

Resistance exercise is associated with many health benefits for people with and without diabetes. With more predictable and smaller blood glucose changes during exercise, there is often less need for insulin adjustments prior to exercise and a lower need for carbohydrate supplementation when it is being practiced by those with T1D. The former is important for overcoming a barrier to exercise in those with unpredictable schedules, while the latter is important to those who are exercising for the purpose of weight maintenance or weight loss. Overall, for individuals with T1D, performing regular resistance exercise should be seen as a means to maintain overall health and physical function, thereby creating a higher quality of life with aging.

Correspondence

Dr. Jane E. Yardley
Email: jeyardle@ualberta.ca

Financial Disclosures

Speaker's fees: Abbott Diabetes Canada, Dexcom
In-kind support: Dexcom, LifeScan Canada

References

1. Moy CS, Songer TJ, LaPorte RE et al. Insulin-dependent diabetes mellitus, physical activity, and death. Am J Epidemiol. 1993;137:74-81.
2. Pongrac Barlovic D, Harjutsalo V, Groop PH. Exercise and nutrition in type 1 diabetes: Insights from the FinnDiane cohort. Front Endocrinol (Lausanne). 2022;13:1064185.
3. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care. 2008;31:2108-2109.
4. McCarthy O, Moser O, Eckstein ML et al. Resistance isn't futile: The physiological basis of the health effects of resistance exercise in individuals with type 1 diabetes. Front Endocrinol (Lausanne). 2019;10:507.
5. Yardley JE, Kenny GP, Perkins BA et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. Diabetes Care. 2013;36:537-542.
6. Westcott WL. Resistance training is medicine: effects of strength training on health. Curr Sports Med Rep. 2012;11:209-216.
7. Sigal RJ, Yardley JE, Perkins BA et al. The Resistance Exercise in Already Active Diabetic Individuals (READI) randomised clinical trial. J Clin Endocrinol Metab. 2022. In press.
8. Rempel M, Yardley JE, MacIntosh A et al. Vigorous intervals and hypoglycemia in type 1 diabetes: A randomized cross over trial. Sci Rep 2018;8:15879.
9. Turner D, Luzio S, Gray BJ et al. Impact of single and multiple sets of resistance exercise in type 1 diabetes. Scand J Med Sci Sports. 2015;25:e99-109.
10. Toghi-Eshghi SR, Yardley JE. Morning (fasting) vs afternoon resistance exercise in individuals with type 1 diabetes: A randomized crossover study. J Clin Endocrinol Metab. 2019;104:5217-5224.
11. Yardley JE. Reassessing the evidence: prandial state dictates glycaemic responses to exercise in individuals with type 1 diabetes to a greater extent than intensity. Diabetologia. 2022;65(12):1994-1999.
12. Yardley JE, Kenny GP, Perkins BA et al. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. Diabetes Care. 2012;35:669-75.
13. Brockman NK, Sigal RJ, Kenny GP, Riddell MC, Perkins BA, Yardley JE. Sex-related differences in blood glucose responses to resistance exercise in adults with type 1 diabetes: A secondary data analysis. Can J Diabetes. 2020;44:267-273 e1.
14. Prevost MS, Rabasa-Lhoret R, Talbo MK, Yardley JE, Curry EG, Brazeau AS. Gender differences in strategies to prevent physical activity-related hypoglycemia in patients with type 1 diabetes: A BETTER study. Diabetes Care. 2022;45:e51-e53.
15. Dial AG, Monaco CMF, Grafham GK, Patel TP, Tarnopolsky MA, Hawke TJ. Impaired function and altered morphology in the skeletal muscles of adult men and women with type 1 diabetes. J Clin Endocrinol Metab. 2021;106:2405-2422.
16. Vilaca T, Schini M, Harnan S et al. The risk of hip and non-vertebral fractures in type 1 and type 2 diabetes: A systematic review and meta-analysis update. Bone. 2020;137:115457.
17. Fyfe JJ, Hamilton DL, Daly RM. Minimal-dose resistance training for improving muscle mass, strength, and function: A narrative review of current evidence and practical considerations. Sports Med. 2022;52:463-79.
18. Cauley JA, Giangregorio L. Physical activity and skeletal health in adults. Lancet Diabetes Endocrinol. 2020;8:150-62.
19. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. Ageing Res Rev. 2010;9:226-237.
20. Yardley JE, Brockman NK, Bracken RM. Could age, sex and physical fitness affect blood glucose responses to exercise in type 1 diabetes? Front Endocrinol (Lausanne). 2018;9:674.

Looking for more?

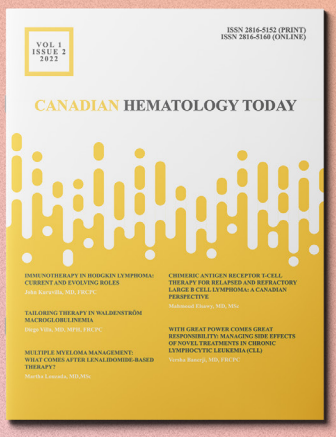
This journal is presented by Catalytic Health, publishers of open access scientific specialty journals. All articles appearing in this issue, as in all Catalytic Health journals, are available at no cost, and may be read and downloaded in their entirety from the journal's website.

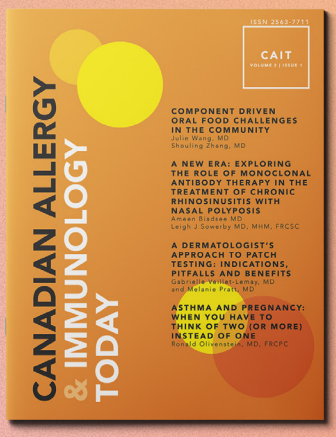
Each of Catalytic Health's peer-reviewed specialty journals was developed as a practical resource for Canadian practitioners, providing useful perspectives on the latest innovations in care and real-world insights on current clinical approaches to disease management in Canada.

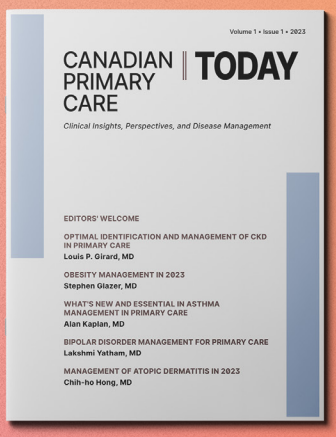
To learn more about Catalytic Health's scientific journals or to subscribe, please visit catalytichealth.com/subscribe.

catalytic health

communications • advertising • strategy







SCAN TO SUBSCRIBE

Improving Access to Endocrinologists through Provider-to-Provider eConsultations

Erin Keely, MD, FRCPC and Clare Liddy, MD, MSc, CCFP

About the Authors

Dr. Erin Keely is an Endocrinologist at the Ottawa Hospital and a Full Professor at the University of Ottawa's Department of Medicine. She is the co-founder of the Champlain BASE eConsult service and Co-Executive Director (specialist lead) of the Ontario eConsult Centre of Excellence.

Affiliations

The Ottawa Hospital; University of Ottawa

Dr. Clare Liddy is the Chair and a Full Professor at the University of Ottawa's Department of Family Medicine with a University of Ottawa Research Chair in eConsult and Primary Health Care Delivery. She is the co-founder of the Champlain BASE eConsult service and Co-Executive Director (primary care lead) of the Ontario eConsult Centre of Excellence.

Affiliations

The Ottawa Hospital; University of Ottawa

The Challenge of Patient Access to Specialty Healthcare

Access to specialty healthcare care remains a major issue for many Canadians.[1] Not only are wait times long, but other barriers contribute to inequitable access. These include the patient's ability to attend appointments (e.g. related to transportation difficulties and/or cost), and the ability of some patients to participate in an appointment (e.g. due to cognitive impairment, mobility challenges, loss of wages, or degree of comfort with a new provider).

Informal consultations between healthcare providers have always played a role in healthcare access. The "call a colleague" approach works well when a practitioner is able to contact a colleague by telephone and an established network of specialists exists; however, it is inefficient, does not facilitate record-keeping for medico-legal purposes and follow-up, and is not remunerated. One way to help address these obstacles is through inter-provider electronic consultations (eConsults).

Definition of an eConsult

An eConsult is a process whereby a physician or nurse practitioner engages in a secure, asynchronous, electronic dialogue with a specialist to manage non-urgent patient care, often without the need for a patient consultation with a specialist. There is no patient interaction, distinguishing it from a virtual patient visit in which the clinician would either have a call or a video session with a patient. The referring provider supplies the relevant clinical information which may include lab test results, images and medication history, and asks a specific clinical question. The responding clinician provides appropriate guidance in response to the information provided. As a general rule, specialists should decline to provide advice through an eConsult if they feel that the available information is inadequate or outside their scope of practice, or if an in-person patient consultation is needed to provide the appropriate advice.

eConsult services frequently allow back-and-forth dialogue allowing the specialist to gather additional

information from the requesting provider, and enable the requesting provider to seek clarification from the specialist. It is the responsibility of the requesting provider to decide if they will act on the advice provided by the specialist and to share the advice received with the patient. The information exchange between providers is documented and retrievable unlike telephone consultations.

Currently, there are two funded eConsult platforms available in Ontario (www.econsultontario.ca): The Champlain eConsult Building Access to Specialists through eConsultation (BASE™) service on the SharePoint platform, and the eConsult service on the Ontario Telemedicine Network (OTN) hub. More than 100,000 eConsults were responded to in the past year, by more than 120 different specialty services. Approximately 6% of these were directed to endocrinology.

eConsults are now recognized as a standard of practice by the Royal College of Physicians and Surgeons of Canada and the Canadian College of Family Practice. All of the Canadian provinces, with the exception of Saskatchewan and PEI, have developed and implemented multispecialty eConsult programs to some degree.

The Benefits of an eConsult

The utilization and impact of eConsults encompassing the four objectives of the Quadruple Aim outlined in Table 1 have been documented in multiple publications.[2]

In addition to shortening the time required to obtain specialist advice from several months in some situations to less than a week, the direct interaction between primary care providers and specialists has been shown to carry other benefits:

- Enhanced professional respect and collaboration;
- Prompted learning for primary care providers and specialists;
- Improved efficiency by avoiding "telephone tag";
- Improved documentation compared to that of other types of informal consultations.

Surveys of patients who have waited for an endocrinology referral and those who have had an eConsult conducted on their behalf also support the eConsult option.[3,4]

Primary care providers are generally appreciative of being able to access specialist advice through eConsults. However, some primary care providers have raised the issue of increased workload as the follow-up required transfers the responsibility from the specialist to the referring provider.[5] It is important to

Better Population Health
eConsult cuts response times from months to days (0.9 days median)
Two-thirds of cases did not require a face-to-face specialist referral
Exploration of specific populations (e.g. chronic pain patients, pharmacists) reveal high value of service
Improved Patient Experience
eConsult responds to previously articulated patient dissatisfaction with wait times
Interviews with patients reveal high satisfaction with eConsult's impact on access, care quality, and continuity of care
Lower Costs
Across specialty groups, the service cost is a weighted average of $47.35/case vs. $133.60/case for traditional referrals
Costs drop dramatically after the startup period, reaching ~$6.45/case by year 3
Further savings that account for societal costs are estimated at ~$11 per eConsult
Improved Provider Experience
PCPs rank eConsult as high/very high value in over 90% of cases
94% of specialists report eConsult improves communication with PCPs
eConsult provides a powerful teaching tool for PCPs
Exploring Policy/Implementation Issues
eConsult services remain relatively uncommon in Canada
Implementation of a successful service requires adherence to key steps
A number of legal and policy challenges must be addresses to support the full and effective implementation of eConsult services

Table 1: The evidence base for Champlain BASE.[2]

Subject area of clinical questions	Tran et al. *(n=464)*	Anderson et al. *(n=x)*	Wasfy et al. *(n=92)*
Thyroid	36%	44%	30%
Bone	15%	2%	29%
Diabetes	12%	10%	-
Reproduction	9%	11%	14%
Adrenal	6%	7%	18%
Other	12%	13%	8%

Table 2: Clinical questions asked through eConsult.

note that eConsult is designed to support primary care and that eConsult services can be integrated into the referral-consultation pathways.

Expectations of Specialists Participating in eConsult Services

Specialists who chose to participate in eConsult services must be committed to providing timely, high-quality responses to primary care provider inquiries.[7,8]

The key factors of a high-quality response include:

- Recommendations specific to the individual patient (when possible)
- Recommendations that are actionable/within the scope of the referring provider
- Details enabling the primary care provider to easily follow suggestions (e.g., medication dose/titration, resources for medical investigations)
- Educational clinical pearls (e.g., the rationale for the recommendations)
- Anticipatory guidance (e.g., next steps if recommendations are not effective, when to re-refer patients)
- Resources available in the community
- A professional/supportive communication style

Types of Questions Addressed to Endocrinologists through eConsult

Several clinical studies in various medical specialties have demonstrated that endocrinology is one of the specialties most commonly requested through eConsult services.[9-11] One retrospective study reviewing faxed referrals to an endocrinology tertiary care centre, suggested that 25% to 27% of referrals were potentially amenable to being answered through eConsult.[12]

Three clinical studies have investigated the types of clinical questions asked through eConsult (**Table 2**).[13-15]

In one study, the type of clinical question was also assessed; the results revealed these as drug treatment (33%), diagnosis (28%), more than one question (18%), and non-pharmacological management (14%).[13]

Two additional clinical studies have investigated the specific endocrine conditions of thyroid biopsies and osteoporosis.[15,16] A retrospective study of 302 thyroid fine needle biopsies where endocrinologists' input was received through eConsult showed that the biopsies with an eConsult had faster work-up times and similar concordance with clinical guidelines compared to patients seen in person.[15] In another study of veterans with a recent fracture, an eConsult note by a metabolic bone specialist sent to the primary care provider with specific recommendations for management showed a modest increase in prescribing rates of bisphosphonate, bone density studies, calcium/vitamin D.[16]

The Impact of Endocrinology eConsults on Requesting Primary Care Providers and Specialists

As part of the Champlain BASE eConsult service, before closing a case, requesting primary care providers complete a mandatory survey containing four questions (impact on need for referral; impact on course of action for the patient; educational value; and whether this topic should be included in a future Continuing Professional Development [CPD] event). These surveys have revealed that in Ontario, for cases directed to endocrinology, the referring PCP originally contemplated a referral but no longer felt it was needed in 44% of cases (i.e. referral was avoided). In 22% of cases, a referral was contemplated and was still needed; and in 31% of cases, a referral was not contemplated and was still not needed. In 3% of cases, a referral was originally not contemplated and will now be sent, thereby avoiding a delay in patient referral. This impact on the need for referrals was shown to be consistent with that in other medical specialties.

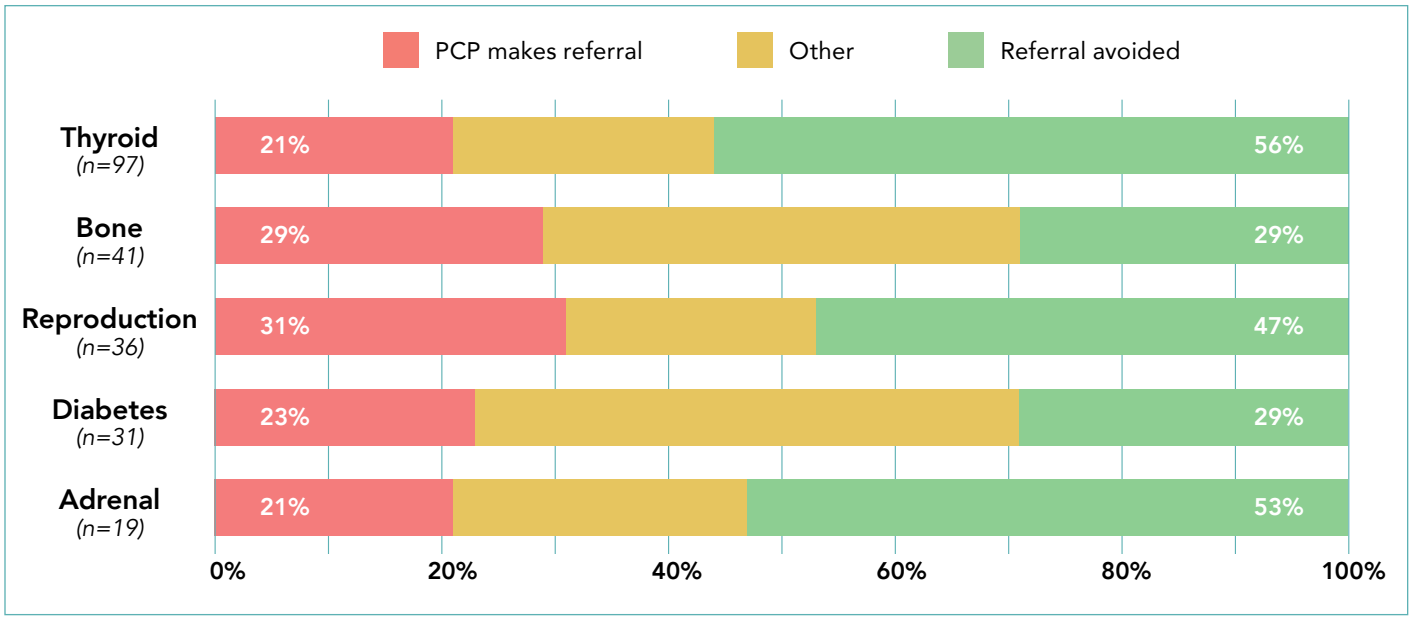


Figure 1: Referral rates according to medical specialty.

Referrals were avoided most frequently for thyroid and adrenal cases (Figure 1).

In 60% of cases, the requesting provider received a recommendation for a new or additional course of action, which confirms that the patient's treatment was directly affected by the eConsult advice received.[13] Requesting primary care providers ranked 93% of cases as having high educational value and suggested that 66% of cases were an important clinical problem to include in future CPD initiatives. For the Ontario eConsult services, the specialist provides a self-reported billing time record. In 48% of cases, the time billed was <10 minutes; in 34% it was 10–15 minutes; and in 16% it was >15 minutes. The time billed was lowest for thyroid, bone and diabetes questions.[13]

Summary

In light of the challenges involved in accessing specialty healthcare, as well as burnout within the primary care sector, it is important that specialists find innovative ways to support primary care by building their capacity and confidence in managing less complex conditions. Provider to-provider eConsults initiated by primary care have been shown to be highly acceptable and impactful in improving the care of patients with endocrinological problems in Ontario. eConsults provide support and education to requesting primary care providers, and empower them to confidently address clinical issues.

Correspondence

Dr. Erin Keely
Email: ekeely@toh.ca

Financial Disclosures

Drs. Keely and Liddy receive salary support from Ontario Health for their leadership role at the Ontario eConsult Centre of Excellence. Dr. Keely participates as a specialist in the Champlain BASE eConsult service.

References

1. Moir M, Barua B. Waiting your turn: Wait times for health care in Canada, 2022 Report. Fraser Institute. 2022 Dec 8 [accessed 2023 Apr 7]. Available from: fraserinstitute.org/categories/health-care-wait-times.
2. Champlain eConsult BASE™ [Internet]. Accessed 2023 Apr 7. Available from: www.champlainbaseeconsult.com.
3. Liddy C, Keely E. Using the quadruple aim framework to measure impact of heath technology implementation: a case study of eConsult. The Journal of the American Board of Family Medicine. 2018 May 1;31(3):445-55.
4. Joschko J, Liddy C, Moroz I, Reiche M, Crowe L, Afkham A, Keely E. Just a click away: exploring patients' perspectives on receiving care through the Champlain BASETM eConsult service. Family Practice. 2018 Feb;35(1):93-8. doi:10.1093/fampra/cmx073
5. Keely E, Traczyk L, Liddy C. Patients' perspectives on wait times and the referral-consultation process while attending a tertiary diabetes and endocrinology centre: is econsultation an acceptable option? Canadian Journal of Diabetes. 2015 Aug 1;39(4):325-9. doi: 10.1016/j.jcjd.2014.12.010
6. Lee M, Leonard C, Greene P, Kenney R, Whittington MD, Kirsh S, Ho PM, Sayre G, Simonetti J. Perspectives of VA primary care clinicians toward electronic consultation-related workload burden: a qualitative analysis. JAMA Network Open. 2020 Oct 1;3(10):e2018104.
7. Keely E, Liddy C. Specialist participation in e-consult and e-referral services: best practices. Telemedicine and e-Health. 2021 Jan 1;27(1):17-9. doi:10.1089/tmj.2020.0023
8. Tran C, Archibald D, Humphrey-Murto S, Liddy C, Keely E. What makes a high-quality electronic consultation (eConsult)? A nominal group study. Journal of Telemedicine and Telecare. 2020 May;26(4):239-47. doi:10.1177/1357633X18822885
9. Thompson MA, Fuhlbrigge AL, Pearson DW, Saxon DR, Oberst-Walsh LA, Thomas JF. Building eConsult (electronic consults) capability at an academic medical center to improve efficiencies in delivering specialty care. Journal of Primary Care & Community Health. 2021 Mar;12:21501327211005303.
10. Saxon DR, Kaboli PJ, Haraldsson B, Wilson C, Ohl M, Augustine MR. Growth of electronic consultations in the Veterans Health Administration. American Journal of Managed Care. 2021 Jan 1;27(1). doi:10.37765/ajmc.2021.88572
11. Kirsh S, Carey E, Aron DC, Cardenas O, Graham G, Jain R, Au DH, Tseng CL, Franklin H, Ho PM. Impact of a national specialty e-consultation implementation project on access. Am J Manag Care. 2015;21:e648-e654.14.
12. Pun N, Arnaout A, Tran C, Liddy C, Keely E. Comparing the content of traditional faxed consultations to eConsults within an academic endocrinology clinic. Journal of Clinical & Translational Endocrinology. 2021 Mar 1;24:100260. doi:10.1016/j.jcte.2021.100260
13. Tran CS, Liddy CE, Liu DM, Afkham A, Keely EJ. eConsults to endocrinologists improve access and change primary care provider behavior. Endocrine Practice. 2016 Oct 1;22(10):1145-50. doi:10.4158/E161321.OR
14. Anderson D, Porto A, Koppel J, Macri G, Wright M. Impact of endocrinology eConsults on access to endocrinology care for Medicaid patients. Telemedicine and e-Health. 2020 Nov 1;26(11):1383-90. doi:10.1089/tmj.2019.0238
15. Yoon SS, Wong DH, Wormwood JB, Reisman JI, Vimalananda VG. Impact of Electronic Consultation on Timeliness and Guideline Concordance of Workups Leading to Thyroid Nodule Fine-Needle Aspiration Biopsy. Endocrine Practice. 2021 Oct 1;27(10):1011-6. doi:10.1016/j.eprac.2021.03.008
16. Lee RH, Lyles KW, Pearson M, Barnard K, Colón-Emeric C. Osteoporosis screening and treatment among veterans with recent fracture after implementation of an electronic consult service. Calcified Tissue International. 2014 Jun;94:659-64.

Canadian Diabetes & Endocrinology Today
Science for the Real World

canadiandiabetesandendocrinologytoday.com

Canadian Diabetes & Endocrinology Today is published three times per year in English and in French (ISSN 2817-4100) under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) license by Catalytic Health in Toronto, Ontario, Canada.

ISSN 2817-4097
(English ed. online)