Canadian Diabetes & Endocrinology Today

Volume 3 – Issue 1

ISSN 2817-4089 (PRINT)
ISSN 2817-4097 (ONLINE)

Spring 2025

Editorial Board

Table of Contents

Canadian Diabetes & Endocrinology Today is published 3 times per year.

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 world's FIRST and ONLY single molecule GIP/GLP-1 receptor agonist[1,2]*

Pr mounjaro®
(tirzepatide) injection

DISCOVER MOUNJARO

to help them rise to the challenge of glycemic control

FOR ONCE-WEEKLY TREATMENT OF ADULT PATIENTS WITH T2D

Mounjaro (tirzepatide injection) is indicated for once-weekly administration as an adjunct to diet and exercise to improve glycemic control for the treatment of adult patients with type 2 diabetes mellitus.[1]

- As **monotherapy** when metformin is inappropriate due to contraindication or intolerance.
- In **combination with:**
  - metformin, or
  - metformin and a sulfonylurea, or
  - metformin and a sodium-glucose cotransporter 2 inhibitor (SGLT2i), or
  - basal insulin with or without metformin

REVIEW THE DATA

Scan here or visit mounjaro.ca† for Mounjaro vs. Ozempic® head-to-head efficacy data

MOUNJARO IS NOW AVAILABLE IN A
MULTI-DOSE, PREFILLED KWIKPEN®

Comprehensive and enhanced financial assistance available for eligible patients with T2D.
For more information, talk to your sales representative or contact the Eli Lilly Customer Response Centre (1-888-545-5972).

Please consult the Product Monograph at http://pi.lilly.com/ca/mounjaro-ca-pm.pdf for more information relating to contraindications, warnings (including benzyl alcohol in KwikPen), precautions, adverse reactions, interactions, dosing, and conditions of clinical use which have not been discussed in this piece. The Product Monograph is also available by calling us at 1-888-545-5972.

GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; T2D=type 2 diabetes
* Comparative clinical significance has not been established.
† The landing page of mounjaro.ca is open to the general public. To access healthcare provider-directed information, you will need to log in. Patients will require a DIN to access patient-directed information.

References: 1. Current Mounjaro Product Monograph. Eli Lilly Canada Inc. **2.** Data on File (First & Only). April 9, 2024.

doi.org/10.58931/cdet.2025.3135

About the Author

Alyse Goldberg, MD

Dr. Alyse Goldberg practices as a consultant Endocrinologist at fertility centres in Toronto, as well as a part of the Women's and Babies team at Sunnybrook Health Sciences Centre managing patients with gestational diabetes. She is a member of the International PCOS Network that authored the 2023 International Evidence based Guidelines for Assessment and Management of PCOS. She focuses on care of patients with polycystic ovarian syndrome as well as pregestational metabolic optimization.

Affiliations: Division of Endocrinology, University of Toronto

Polycystic ovary syndrome (PCOS) is a heterogeneous complex endocrine disorder characterized by oligo-ovulation, insulin resistance, and hyperandrogenism. Treatment should be individualized based on each patient's symptoms and reproductive goals. Unfortunately, there is no pharmacologic medication that simultaneously promotes ovulation, improves metabolic health, and reduces clinical hyperandrogenism. Metformin is a well accepted, evidence-based pharmacologic therapy that targets the insulin resistance pathway and improves ovulatory frequency, but it has limited effects on clinical hyperandrogenism as well as poor tolerability for some patients. The growing interest in complementary therapies has highlighted the need for more tolerable and 'non-pharmacologic' treatment options. Inositol, a naturally occurring compound, has gained attention as a promising therapeutic agent for managing PCOS. This review aims to support shared decision-making between clinicians and patients by exploring the roll of inositol as a complementary therapy for PCOS management.

Addressing Inositol Use in PCOS Management

Alyse Goldberg, MD

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by hyperandrogenism, reproductive dysfunction, and insulin resistance. It is diagnosed by meeting 2 of the 3 Rotterdam criteria (hyperandrogenism, oligomenorrhea, and polycystic ovarian morphology).[1] However, as PCOS is a heterogenous condition that presents with a variety of symptoms of concern, therapy requires individualization. Current non-pharmacologic and pharmacologic therapeutic regimens aim to prevent complications such as endometrial hyperplasia and metabolic syndrome, while also managing symptoms of hyperandrogenism and oligo-ovulation/oligomenorrhea. These regimens may include targeting the insulin resistance pathway with lifestyle optimization and medications such as metformin to increase ovulation frequency or establishing endometrial protection with progesterone-containing

medications or combined estrogen and progesterone contraceptives. Anti-androgens may be used as an adjuvant therapy to combined oral contraceptive pills to target clinical symptoms of hirsutism or acne. Unfortunately, there is currently no pharmacologic medication that simultaneously promotes natural ovulation, improves metabolic health, and reduces clinical hyperandrogenism. Metformin is considered the gold standard pharmacologic therapy for targeting the insulin resistance pathway and has been shown to improve ovulatory frequency even in those without biochemical evidence of insulin resistance. However, it is not a perfect solution. Metformin is not efficacious in improving clinical hyperandrogenism,[1] and importantly, is associated with gastrointestinal side effects that limit achieving a therapeutic dose.

In this reproductive age population, many individuals may feel inadequately treated by available evidence-based therapies and may be targeted online with marketing for potential alternative therapies. Consequently, there is a growing interest in complementary therapies to improve health outcomes in PCOS.[2] Inositol, particularly in its forms of myoinositol isomer (MI) and D-chiro-inositol (DCI), has emerged as a promising therapeutic agent for managing PCOS symptoms. While there is a concern that this population may be vulnerable to marketing of costly, non-evidence-based therapies, empowering our patients to explore additional symptom management strategies can inspire greater motivation to adopt beneficial lifestyle changes, such as improved nutrition and regular activity, which are essential for living with PCOS. Thus, increasing our knowledge regarding popular supplements that may be "trending" may enhance our therapeutic relationships with our patients.

Inositol

Inositol, a sugar alcohol found naturally in plants and animals, was previously labelled as Vitamin B-8.[2] However, it is now known to be naturally present in foods such as fruits, beans, grains, and nuts. It has been touted as a supplement for PCOS and is available at health food stores and online in various forms, such as a white powder to dissolve in water, or in gel capsules. It is sold as either MI alone, DCI alone, MI+DCI combination, or with a variety of additives such as folic acid.

Myoinositol is the most abundant stereo-isomer of inositol in the human body. It plays various biological roles as a second messenger, including promoting glucose uptake in insulin transduction pathways, as well as in follicle-stimulating hormone (FSH)-mediated pathways affecting proliferation and maturation of granulosa cells in the ovary. Insulin stimulates the conversion of MI to DCI, which controls glycogen synthesis and insulin-induced androgen synthesis as well as cellular glucose uptake.

Hyperinsulinemia in the setting of PCOS may increase ovarian "epimerase" activity, leading to increased DCI synthesis. This adjustment alters the ratio of MI to DCI, favouring a higher DCI level and a lower than optimal MI level. This change is thought to contribute to the pathophysiology of PCOS by impairing insulin signalling and exacerbating hyperandrogenism.[3]

Inositol supplementation for PCOS has been suggested to improve insulin signalling pathways, leading to improved glucose metabolism, lower insulin levels, and potentially modest reductions in body mass index (BMI).[4] Its roll in FSH signalling may contribute to improved menstrual cycle regulation and ovarian function (thus reducing ovarian testosterone). By reducing insulin, inositol may improve sex hormone-binding globulin (SHBG) levels and support the physiological MI:DCI ratio, thereby facilitating the conversion of androgens to estrogen.

Guidelines

As part of the 2023 evidence-based PCOS guidelines,[1] the evaluation of inositol as a therapeutic option for PCOS was reviewed in section 4.7. The systematic review included 29 randomized controlled trials (RCTs) and 19 of these were included in the meta-analysis to determine recommendations. Ten studies had high risk of bias, 16 had a low or moderate risk, and 3 had an unclear risk of bias. The interventions and comparators were heterogeneous, which has led to concerns related to misinformation, and potential conflict of interest in the studies that support use of inositol. Since these supplements come at high financial cost, we need to ensure that evidence-based information is guiding their use.

As part of the recommendations in the guidelines, women taking inositol are encouraged to "advise their health professional[1]" if they are using complementary therapies. However, clinicians who refer to the guidelines will note the recommendation that "Specific types, doses or combinations of inositol cannot currently be recommended for adults and adolescents

with PCOS, due to a lack of quality evidence" (section 4.7.[4]).[1] Thus, how can we, as clinicians, adopt an evidence-based approach when the evidence does not meet the standards of clinical practice guidelines? Further, as a supplement rather than a medication, there are fewer clear regulations for commercially available products and less oversight regarding consistency within or between products and doses.

Therefore, the goal of this review is to complement these recommendations and inform shared decision-making with our patients who seek complementary therapy with inositol. As a medical community, we want to arm a vulnerable population with unbiased information to assist in navigating marketing campaigns of potentially expensive therapies with unclear benefits.

Described Effects of Inositol in PCOS

Metabolic Outcomes

Unfer et al. (2017) conducted a meta-analysis of 9 RCTs involving 496 participants with PCOS. Among the participants, 249 were in the control group and 247 received MI alone or combined with DI. The doses used were MI ranging from 1.1-4 g and/or DI ranging from 27.6-2400 mg/day over a period of 2 to 24 weeks. Their findings demonstrated that MI supplementation significantly decreased homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin levels. This effect was most apparent after 24 weeks of administration, suggesting that improvements in metabolic outcomes may be time dependent. More recently, Greff et al.[5] found a significant reduction in BMI[5] (mean difference 0.45 kg/m^2), glucose levels (MD = -3.14; CI: -5.75, -0.54), and insulin values (MD = -2081.05, CI: -2745.32, -1416.78) compared with placebo in their meta-analysis. However, the authors acknowledged the presence of moderate and high risk of bias in some of these domains.

Hyperandrogenism

Inositol appears to play a role in the regulation of androgens. However, its effects on serum testosterone, androstenedione, and SHBG are inconsistent, depending on the dose of MI versus DI used. These results have been inconsistent across different meta analyses.[3,5] Despite these variances, as summarized in the 2023 guidelines, even if there may be biochemical improvement in androgens, no difference in hirsutism has been observed.[1]

Reproductive Outcomes

Pundir et al. conducted a meta-analysis that included 10 RCTs with 600 women with PCOS. The participants were treated with MI (doses ranging from 1.2-4 g), DI (doses ranging from 600-1200 mg), or placebo or metformin for 2 to 24 weeks. The study found that inositol improved ovulation rates and increased menstrual cycle frequency, but evidence for pregnancy, miscarriage, and live birth rates is lacking.

Additional proposed benefits of inositol are related to its role in advanced reproductive therapy. MI plays a potential role in FSH sensitivity and has been associated with reduced recombinant FSH dosing and fewer stimulation days needed during ovarian stimulation for in vitro fertilization (IVF).[6] Further, MI supplementation may improve the quality of oocytes and embryos in women undergoing IVF and intracytoplasmic sperm injection (ICSI) procedures, reducing the risk of hyperstimulation and potentially increasing the rates of successful pregnancies.[7]

Regarding its utility during pregnancy, a Cochrane review evaluated the potential of MI use to reduce gestational diabetes mellitus (GDM).[8] The authors concluded antenatal dietary supplementation with MI during pregnancy may reduce the incidence of GDM, hypertensive disorders of pregnancy, and preterm birth. However, they provided the caveat that current evidence is based on small studies that were not powered to detect differences in outcomes such as perinatal mortality, serious infant morbidity, and long-term implications.

Comparison to Metformin

Metformin has been considered the gold standard insulin sensitizer for managing PCOS. It has evidence to improve oligo-ovulation, prevent the progression of dysglycemia, and improve anthropometric measurements.[1] However, it may induce gastrointestinal side effects that prevent patients from reaching the therapeutic dose. The current literature comparing MI to metformin has a risk of bias[1] and still yielded results that were considered 'low certainty evidence' for all outcomes. Nonetheless, the meta-analysis conducted by Greff et al.,[5] found that inositol

showed non-inferiority compared to metformin in terms of improving cycle regularity.

Metformin has been rigorously studied and is currently recommended over inositol for improving central adiposity and cycle regularity if it is well tolerated.[1] However, inositol may serve as a "weaker" version of metformin for those who cannot tolerate it. It should be noted that some individuals report mild side effects from MI including nausea, dizziness, headaches, and gastrointestinal discomfort.[9]

Limitations

Dosing

Further research is necessary to establish optimal dosing regimens and long-term safety profiles for inositol. Over the past 10+ years, varying dosing regimens of MI powder have been studied and summarized.[6] The authors concluded that a dose of 4 g of MI with DCI at a ratio of 40:1 (MI:DI) is supported by many preclinical and clinical studies for targeting ovulation. They also highlighted that this consistency is not found in all supplements on the market. Further, the addition of other macro or microelements lack scientific rationale. However, an alternative "expert opinion" publication proposed that there may be a rationale for alternative ratios targeting fertility and pregnancy outcomes.[10]

It should be noted that when taken in gel capsule form, there may be improved gastrointestinal absorption, allowing for a reduction in dose by one-third compared to the powder form, with one published study suggesting an equivalent dose of 0.6 g MI in capsule form to 2 g MI in powder form.[11]

Varied Efficacy

As with most therapies, not all individuals will experience improvements in the targeted outcomes. One consideration is that specific phenotypes of PCOS may benefit more from inositol than others. However, it has been suggested that rather than focusing on phenotypes that would benefit, those with higher BMI or more significant insulin resistance may not experience as much benefit from inositol therapy as those without these co-morbidities.[12] No specific cut offs for these or any other co-morbidities have been provided to guide who would or would not be a good candidate for inositol therapy.

Summary

Inositol supplementation remains an accessible and potentially beneficial complementary therapy for patients. Ongoing research will be essential to fully elucidate its mechanisms of action, optimize treatment protocols, and identify those who would benefit most from these supplements. Regulation of products is needed to confidently integrate inositol into standard care practices for PCOS. As clinicians, we should consider therapeutic goals when counselling those interested in using inositol. Evidence supports targeting ovulatory frequency. However, the metabolic benefits are less clear. There have been observations of reduced fasting insulin and slight reductions in BMI without clear clinical implications. Importantly, there is limited observed changes to clinical hyperandrogenism.

Another concern is that there are no standardized dosing regimens. However, using 2 g of MI:DI powder at a 40:1 ratio twice daily appears to be the most acceptable approach. Lastly, the ideal duration of use and the implications of long-term use have not been determined.

Tips for counselling patients interested in trying inositol

- Emphasize lifestyle optimization and healthy behaviours as part of holistic care for PCOS.
- Have a therapeutic target in mind when starting therapies (e.g., menstrual frequency) and counsel patients that if insufficient, alternative pharmaceuticals are available (e.g., endometrial protection with progesterone or a combined oral contraceptive).
- Although some small studies have demonstrated a reduction in insulin parameters or androgens, these findings may not translate to clinically noted benefits.
- Anticipate that inositol is costly and unlikely to be covered by private or public insurance providers.
- Acknowledge that there may be inconsistencies between brands and within brands, as Health Canada does not regulate most inositol supplements.
- The dosing regimens and duration of therapy have not been established, and the long-term safety has not been adequately studied, raising concerns about potential unknown risks associated with prolonged use.

Correspondence

Alyse Goldberg, MD
Email: alyse.goldberg@utoronto.ca

Financial Disclosures

A.G.: Speaker Honoraria: Biosyent, EMD Serono

References

1. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Pitonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023;189(2):G43-G64. doi:10.1093/ejendo/lvad096
2. Alesi S, Ee C, Moran LJ, Rao V, Mousa A. Nutritional supplements and complementary therapies in polycystic ovary syndrome. Adv Nutr Bethesda Md. 2022;13(4):1243-1266. doi:10.1093/advances/nmab141
3. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with PCOS: a systematic review of randomized controlled trials. Int J Endocrinol. 2016;2016:1-12. doi:10.1155/2016/1849162
4. Dason ES, Koshkina O, Chan C, Sobel M. Diagnosis and management of polycystic ovarian syndrome [published correction appears in CMAJ. 2024 Mar 3;196(8):E269. doi: 10.1503/cmaj.240216.] [published correction appears in CMAJ. 2024 Mar 17;196(10):E351. doi: 10.1503/cmaj.240303.]. CMAJ. 2024;196(3):E85-E94. Published 2024 Jan 28. doi:10.1503/cmaj.231251
5. Greff D, Juhász AE, Váncsa S, Varadi A, Sipos Z, Szinte J, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2023;21(1):10. doi:10.1186/s12958-023-01055-z
6. Roseff S, Montenegro M. Inositol treatment for PCOS should be science-based and not arbitrary. Int J Endocrinol. 2020;2020:1-8. doi:10.1155/2020/6461254
7. Etrusco A, Laganà AS, Chiantera V, Buzzaccarini G, Unfer V. Myo-inositol in assisted reproductive technology from bench to bedside. Trends Endocrinol Metab. 2024;35(1):74-83. doi:10.1016/j.tem.2023.09.005
8. Motuhifonua SK, Lin L, Alsweiler J, Crawford TJ, Crowther CA. Antenatal dietary supplementation with myo-inositol for preventing gestational diabetes. Cochrane Database Syst Rev. 2023;2023(2):CD011507. doi:10.1002/14651858.CD011507.pub3
9. Dhaliwal J. Comparing metformin, inositol, and lifestyle modifications to improve symptomatology of polycystic ovary syndrome (PCOS): a research protocol. Undergrad Res Nat Clin Sci Technol URNCST J. 2022;6(11):1-8. doi:10.26685/urncst.409
10. Facchinetti F, Appetecchia M, Aragona C, Bevilacqua A, Bezerra Espinola MS, Bizzarri M, et al. Experts' opinion on inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes mellitus: a further help for human reproduction and beyond. Expert Opin Drug Metab Toxicol. 2020;16(3):255-274. doi:10.1080/17425255.2020.1737675
11. Carlomagno G, De Grazia S, Unfer V, Manna F. Myo-inositol in a new pharmaceutical form: a step forward to a broader clinical use. Expert Opin Drug Deliv. 2012;9(3):267-271. doi:10.1517/17425247.2012.662953
12. Kamenov Z, Gateva A, Dinicola S, Unfer V. Comparing the efficacy of myo-inositol plus α-lactalbumin vs. myo-inositol alone on reproductive and metabolic disturbances of polycystic ovary syndrome. Metabolites. 2023;13(6):717. doi:10.3390/metabo13060717

doi.org/10.58931/cdet.2025.3136

About the Author

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

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

Affiliations: Division of Endocrinology, Department of Medicine, University of British Columbia, Vancouver, BC
TLC Diabetes and Endocrinology, Surrey, BC

Diabetes Remission: Where are We Now?

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

Introduction

Type 2 diabetes (T2D) poses a substantial global health burden. In 2023, we published an overview on the remission of T2D. Since then, additional long-term data has emerged regarding the outcomes associated with T2D remission, highlighting the importance of revisiting this topic. This article synthesizes findings from the landmark Diabetes Remission Clinical Trial (DiRECT), its 5-year follow-up, and recent studies exploring the enduring benefits of both short-term and sustained remission.

Overview of the DiRECT Trial[1]

The DiRECT trial, a randomized controlled trial conducted in the UK, investigated the efficacy of intensive weight management in achieving T2D remission. The study enrolled 298 participants who had been diagnosed with T2D within the preceding 6 years and had a body mass index between 27 and 45 kg/m^2. Participants were randomly assigned to either an intervention group, receiving a very low-calorie diet followed by structured dietary support for 1 year, or a control group, receiving standard diabetes care. All patients were managed in a primary care setting.

Results of the DiRECT Trial

The initial 12-month results, published in 2017, demonstrated a significant remission rate of 46% (68 participants) in the intervention group, defined as an HbA1c below 6.5% without the use of glucose-lowering medication. In contrast, only 4% (6 participants) in the control group achieved remission.

Five-Year Follow-Up Findings[2]

After sharing the 2-year results with all participants, UK National Health Service data were collected annually until year five. This included data from the remaining intervention participants who received low-intensity dietary support, intervention withdrawals, and the original randomly allocated groups. The primary outcome

was remission of T2D. Based on the findings established in the DiRECT trial, which showed that sustained weight loss was the dominant driver of remission, this assumption was carried forward into the extension study.

After 2 years, all intervention participants still in the trial (101 [68%] of 149) were approached to receive low-intensity support for a further 3 years. Of these, 95 (94%) had consented to continue and were allocated to the DiRECT extension group, while 54 participants were allocated to the non-extension group, where the intervention was withdrawn (**Figure 1**). At the 5-year time point, DiRECT extension participants (n=85) lost an average of 6.1 kg, with 11 (13%) in remission (**Figure 2**). Compared with the non-extension group, DiRECT extension participants had more visits with HbA1c <6.5% (36% vs 17%, p=0.0004), without glucose-lowering medication (62% vs 30%, p<0.0001), and in remission (34% vs 12%, p<0.0001).

The 5-year follow-up, as reported in the *Lancet Diabetes & Endocrinology* publication, presents a nuanced picture of sustained remission. Notably, the original intervention group demonstrated a higher remission rate compared to the original control group. Specifically, 27% of the original intervention group were in remission at 5 years, compared to 4% of the original control group (p<0.0001). Of those in remission at year 2, 26% remained in remission at year 5.

Long-Term Benefits of Remission: Insights from Recent Research

In addition to the DiRECT trial, 2 additional studies[3,4] have evaluated the long-term outcomes observed in individuals who achieve remission, even if only for a brief period of time. Key findings from these studies highlight several significant advantages. Short-term remission was correlated with significant reductions in cardiovascular risk factors, including blood pressure and improved lipid profiles, suggesting lasting cardioprotective effects. Additionally, transient remission led to sustained improvements in glucose metabolism and insulin sensitivity, extending beyond the remission period. Participants who experienced remission reported an enhanced quality of life, improved mental health, reduced diabetes-related distress, and higher levels of physical activity. Evidence also suggests that even a brief remission may promote beneficial changes in pancreatic beta-cell function, contributing to improved long-term metabolic health. Furthermore, the potential for reduced healthcare costs associated with managing diabetes complications during and after remission underscores the economic benefits of investing in effective weight management programs.

Challenges Associated with Achieving and Maintaining Remission

Although the benefits of T2D remission are well-known, achieving remission is difficult for many individuals and maintaining ongoing remission is even more difficult (**Figure 3**). Key factors associated with the recurrence of T2D include the following.

1. Weight Regain

Weight regain is influenced by several factors. Physiological adaptations play a significant role, as the body's natural tendency to defend against weight loss can lead to metabolic adaptations that promote weight regain. These adaptations include alterations in appetite-regulating hormones and a reduction in the basal metabolic rate. This factor was notable, as observed in the DiRECT trial follow ups. Additionally, sustaining long-term lifestyle changes, such as dietary modifications and increased physical activity, is difficult for many individuals. Social, economic, and psychological factors can also contribute to weight regain. Furthermore, very low-calorie diets such as those used in the DiRECT study are extremely restrictive, making it challenging for most individuals to adhere to nutritionally depletive diets.

2. Beta-Cell Function

Beta-cell function can progressively decline.[5] Even with remission, underlying beta-cell dysfunction may persist. Over time, this can lead to a gradual decline in beta-cell function and subsequent relapse. The degree to which beta-cell function can be recovered is still under investigation. However, it is known that the longer the duration following a T2D diagnosis, the higher the likelihood of beta-cell dysfunction.

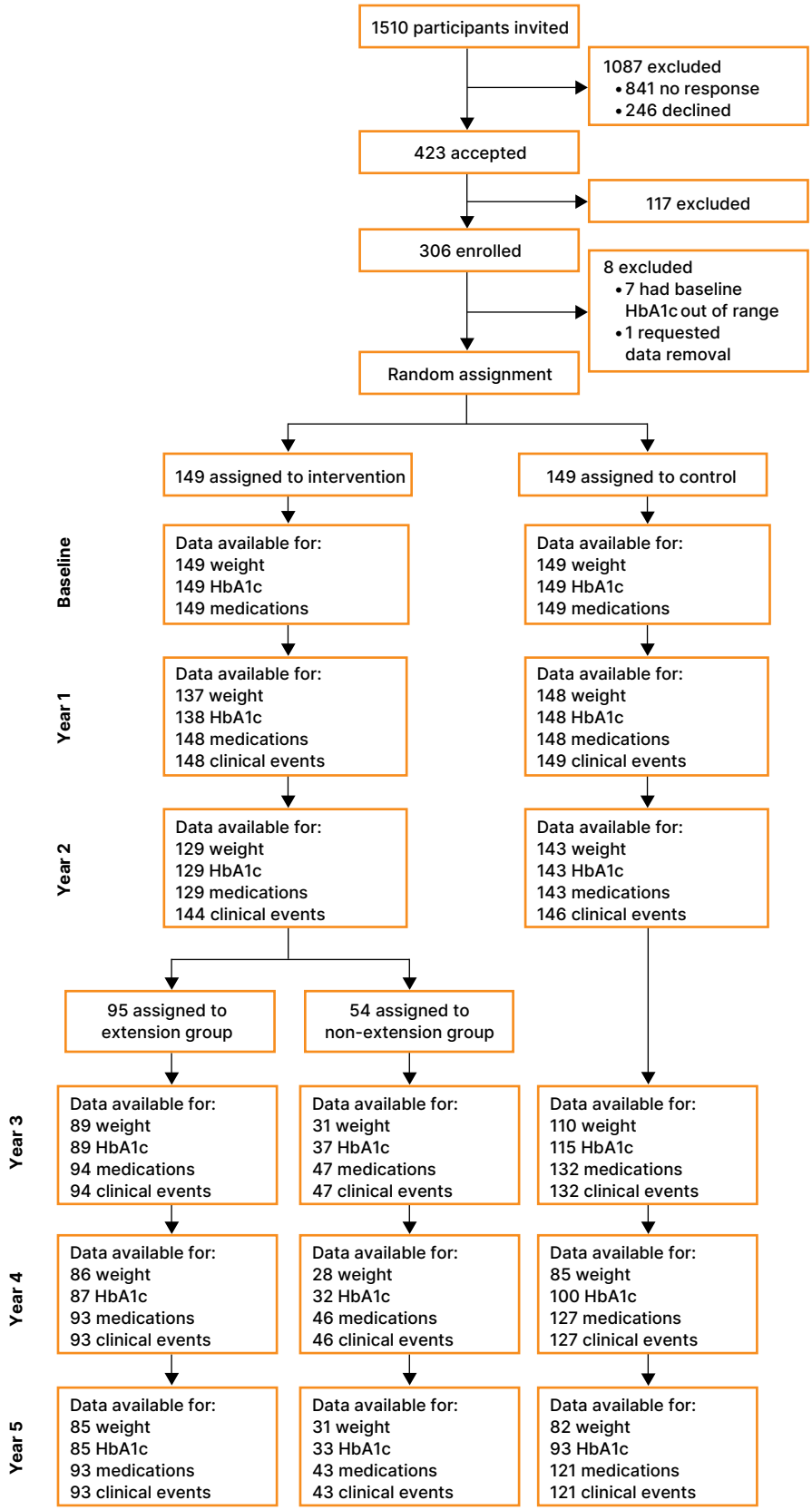


Figure 1. Overview of the DiRECT trial; *adapted from Lean ME et al., 2024.*

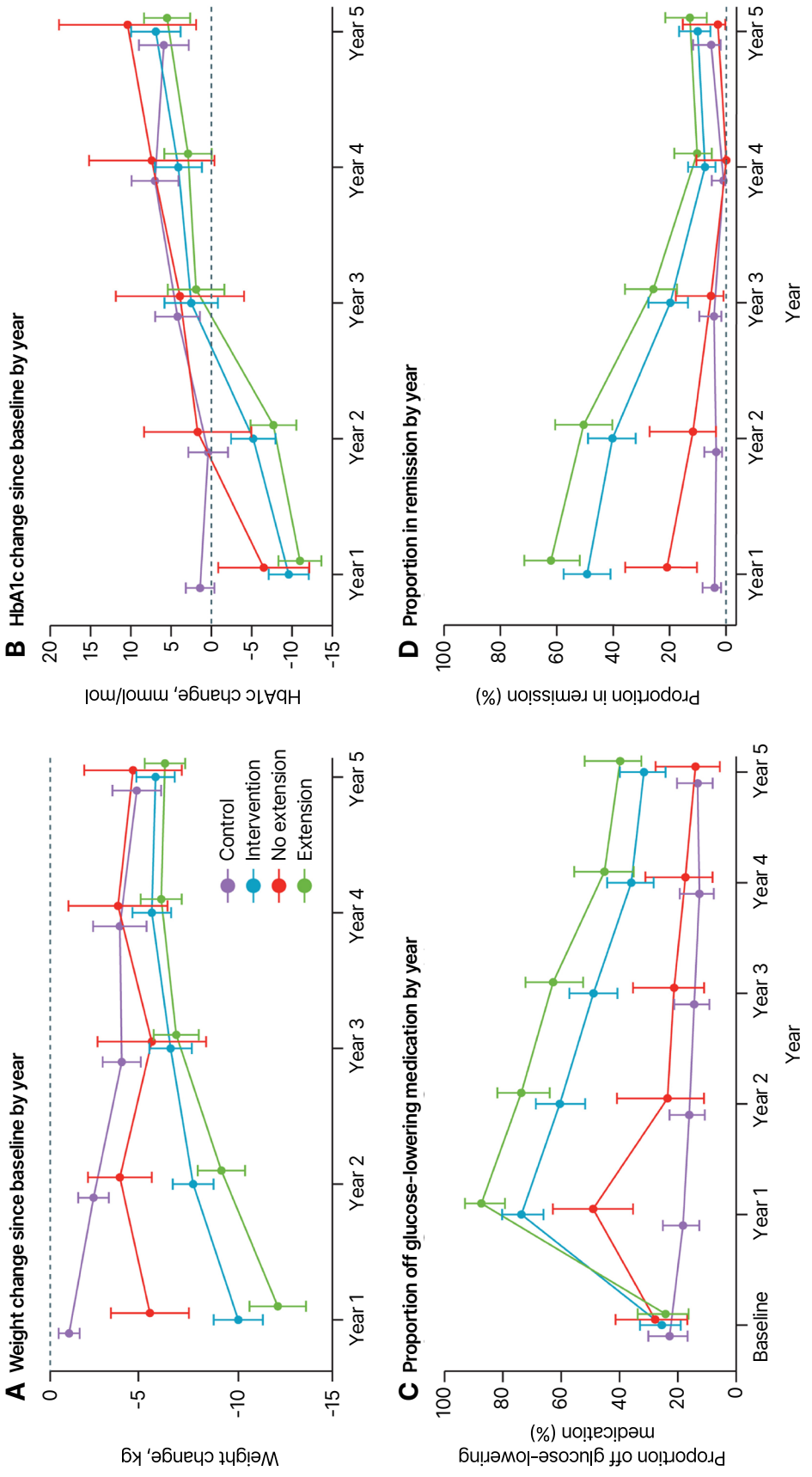


Figure 2. Mean weight in kg (**A**) HbA1c in mmol/mol (**B**) changes since baseline, proportions of those off all glucose-lowering medications (**C**) and in remission each year (**D**); *adapted from Lean ME et al., 2024.*

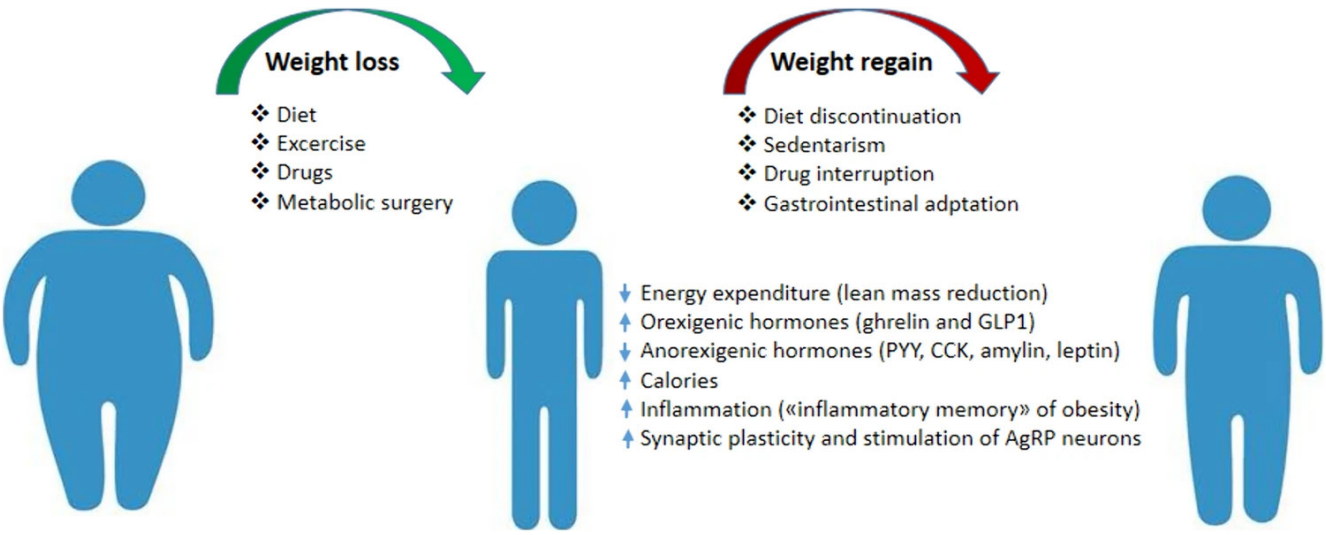


Figure 3. Pathophysiology of weight regain; *adapted from Capoccia D, et al., 2024.*

3. Psychological and Behavioural Factors[6]

Psychological and behavioural factors play an important role in maintaining long-term adherence to lifestyle changes. Sustained motivation and support are essential for individuals to continue with healthy habits. However, psychological factors, such as stress, depression, and anxiety, can hinder adherence. Over time, individuals may gradually revert to previous behaviours, leading to weight gain, thereby contributing to recurrence of diabetes.

4. Lack of Long-Term Support

Healthcare systems may not always provide adequate long-term support for individuals in remission. This can include limited access to dietary counselling, behavioural therapy, and ongoing monitoring. In the current Canadian healthcare system, this is particularly important as there are no provincial-funded programs that offer long-term support with registered dietitians, behavioural health coaches, kinesiologists, and other key healthcare team members to assist with ongoing, targeted maintenance of remission using an individualized approach. Additionally, a lack of social support from family and friends can also make it difficult to maintain lifestyle changes.

5. Individual Variability

T2D is a heterogeneous disease, and individuals respond differently to interventions. Factors such as the duration of diabetes, the severity of insulin resistance, and genetic predisposition can influence the likelihood of achieving long-term remission.

By understanding these challenges, healthcare professionals can develop more effective strategies to support individuals in achieving and maintaining T2D remission.

Implications for Diabetes Management

The findings from the DiRECT trial and its 5-year follow-up, along with the long-term data from the LOOK AHEAD study, have significant implications for T2D management.

- ***Emphasis on Intensive Lifestyle Interventions.*** These studies reinforce the efficacy of intensive lifestyle interventions, particularly those involving significant weight loss, in achieving diabetes remission for those who are willing and able to incorporate these interventions. The 5-year follow-up data reinforces the need for long-term support to maintain remission.
- ***Importance of Ongoing Support.*** Sustaining remission necessitates continuous support and reinforcement of healthy lifestyle behaviours. The 5-year data shows the importance of long-term support and demonstrates how a lack of long-term support negatively impacts remission rates. Healthcare systems must provide accessible resources and counselling.
- ***Personalized Care Plans.*** Tailoring interventions to suit individual preferences and challenges is crucial for optimizing outcomes, given the heterogeneity in responses to treatment.
- ***Integration of Mental Health Support.*** Recognizing the psychological benefits of remission and integrating mental health support into diabetes management programs can enhance adherence and overall well-being.
- ***Addressing Insurance and Clinical Practice Gaps.*** There is a pressing need for insurance companies to develop policies regarding the impact of remission on premiums. Additionally, clear clinical guidelines are required to define appropriate blood pressure and lipid targets for individuals in remission, which address uncertainties about their cardiovascular risk.

Key Considerations

- Remission is not a cure, and ongoing monitoring is essential.
- A multidisciplinary approach, involving healthcare professionals, dietitians, and behavioural therapists, is crucial for long-term success.
- Further research is needed to identify predictors of long-term remission and develop effective maintenance strategies.

Conclusion

The findings from the DiRECT trial indicate that, despite a disappointing decline in remission rates over five years, the intervention group achieved a mean weight loss of 6.1 kg, which is significantly better than typical outcomes in conventional T2D care. In comparison, the LOOK AHEAD trial reported only 11% of participants had achieved remission at year one and 7% achieved remission at year four, highlighting the relative success of the DiRECT trial in maintaining weight loss and achieving remission compared to other interventions.

Achieving and maintaining T2D remission presents a significant challenge. However, the benefits are substantial, including enhanced quality of life, improved cardiovascular health, and potential economic advantages. Ongoing research and the implementation of evidence-based strategies are essential for optimizing diabetes management and improving patient outcomes.

Correspondence

Akshay Jain, MD, FRCPC, FACE, CCD, ECNU, DABIM, DABOM
Email: oxyjain@gmail.com

Financial Disclosures

A.J.: Grants/Research Support: Abbott, Amgen, Astra Zeneca, Eli Lilly, Novo Nordisk, Sanofi; **Speakers Bureau/Honoraria:** Abbott, Abbvie, AstraZeneca, Amgen, Antibody, Bausch Healthcare, Bayer, Boehringer Ingelheim, Care to Know, CCRN, Connected in Motion, CPD Network, Dexcom, Diabetes Canada, Eisai, Eli Lilly, Embecta, EOCI, GSK, HLS Therapeutics, Insulet, Janssen, Liv, Master Clinician Alliance, MDBriefcase, Merck, Medtronic, Moderna, Novartis, Novo Nordisk, NP Circle, Obesity Canada, Partners in Progressive Medical Education, Pfizer, Sanofi, Six Degrees, Timed Right, Unik, WebMD; **Consulting Fees:** Abbott, AstraZeneca, Amgen, Bausch Healthcare, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, Embecta, Endocrine Society, Gilead Sciences, GSK, HLS Therapeutics, Industrii, Insulet, Janssen, Medtronic, Novartis, Novo Nordisk, Partners in Progressive Medical Education, PocketPills, Roche, Sandoz, Takeda, Ypsomed

References

1. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-551. doi:10.1016/S0140-6736(17)33102-1.
2. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. 5-year follow-up of the randomised diabetes remission clinical trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study. Lancet Diabetes Endocrinol. 2024 Jun;12(6):e17. doi: 10.1016/S2213-8587(24)00128-1. Erratum in Lancet Diabetes Endocrinol. 2024;12(4):233-246. doi:10.1016/S2213-8587(23)00385-6
3. Gregg EW, Chen H, Bancks M, Manalac R, Maruthur N, Munshi M, . et al. Impact of remission from type 2 diabetes on long-term health outcomes: findings from the Look AHEAD study. Diabetologia. 2024;67(3):459-469. doi:10.1007/s00125-023-06048-6
4. Dambha-Miller H, Hounkpatin HO, Stuart B, Farmer A, Griffin S. Type 2 diabetes remission trajectories and variation in risk of diabetes complications: A population-based cohort study. PLOS ONE 18(8):e0290791 doi:10.1371/journal.pone.0290791
5. Retnakaran R, Kashyap SR, Gerstein HC, Aroda VR. Contemporary clinical perspectives on targeting remission of type 2 diabetes. J Clin Endocrinol Metab. 2024;109(5):1179-1188. doi:10.1210/clinem/dgad746
6. Aksoy AN, Abayomi J, Relph N, Butler T. Physiological and psychological determinants of long-term diet-induced type 2 diabetes (T2DM) remission: a narrative review. Obes Rev. 2024;25(6):e13733. doi: 10.1111/obr.13733

doi.org/10.58931/cdet.2025.3137

About the Author

Ronald M. Goldenberg, MD, FRCPC, FACE

Dr. Ronald Goldenberg is a consultant endocrinologist emeritus affiliated with LMC Diabetes & Endocrinology in Vaughan, Ontario. Dr. Goldenberg has been an investigator in a wide array of clinical trials in the areas of diabetes, hypertension, obesity, and dyslipidemia. He has been actively involved in Continuing Medical Education for over 3 decades, with a strong focus on translating evidence-based medicine into practical patient care. Dr. Goldenberg was a councillor on the Diabetes Canada Clinical & Scientific Section Executive Committee from 2010 to 2016. He was a member of the Steering Committee and an author for the *2013 CDA Clinical Practice Guidelines*, lead author of the *CDA March 2016 Interim Update* and co-author of the *November 2016 Interim Update on the Pharmacologic Management of Type 2 Diabetes*. He was on the Executive Committee and an author for the 2018 Diabetes Canada CPGs. He was the 2021 recipient of the Diabetes Canada Gerald S. Wong Service Award.

Affiliations: Consultant Endocrinologist Emeritus
LMC Diabetes & Endocrinology, Vaughan, Ontario, Canada

Glucagon-like Peptide-1 Receptor Agonists and Thyroid Cancer: Myth or Reality?

Ronald M. Goldenberg, MD, FRCPC, FACE

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are being used increasingly for the management of type 2 diabetes mellitus (T2DM) or obesity because of their association with robust glucose lowering, weight loss, and cardiorenal benefits.[1] The association between GLP-1RA treatments and thyroid cancer has been a topic of discussion since their early development with the understanding that GLP-1 receptors are present on rodent thyroid parafollicular cells (C-cells), and that GLP-1RAs can cause an increase in calcitonin, and both C-cell hyperplasia and medullary thyroid carcinoma (MTC).[2] This data from rodent studies has led to GLP-1RAs being contraindicated in patients with a personal or family history of MTC or with multiple endocrine neoplasia syndrome type 2.[1]

Despite this contraindication, the human relevance of GLP-1RA induced MTC in rodents has not been proven. Normal or hyperplastic C-cells in humans may not express the GLP-1 receptor, and studies of human MTCs have shown variable expression of the GLP-1 receptor.[3,4] Studies have shown conflicting evidence regarding the expression of the GLP-1 receptor in human papillary thyroid cancer (PTC) cell lines: however, GLP-1RAs did not have significant effects on the proliferation of PTC cells.[4,5]

Because of the data that potentially links GLP-1RAs to an increased risk of thyroid cancer, clinical studies in humans are important in addressing this issue. I will review the relevant data from human studies that have analyzed

the potential link between GLP-1RA treatment and thyroid cancer, including pharmacovigilance and observational studies as well as randomized controlled trials (RCTs).

Pharmacovigilance Studies

Pharmacovigilance databases can be used to analyze spontaneous reports of adverse events in drug treated individuals. Such studies have been conducted for reports of thyroid cancer possibly related to GLP-1RAs. An analysis of the European pharmacovigilance database (EudraVigilance) reviewed all reports of thyroid cancer with GLP-1RAs from their initial marketing through to January 2020. Disproportionality was observed for GLP-1RAs and thyroid cancer as well as MTC, with proportional reporting ratios (PRRs) of 14.4 (95% confidence interval [CI] 11.8–17.4) and 221.5 (95% CI 155.7-315.1), respectively.[6] The Food and Drug Administration Adverse Event Reporting System (FAERS) data from 2004 to 2021 were used for a disproportionality analysis to assess the relationship between GLP-1RAs and all types of neoplasms. This analysis revealed a significant PRR ($p<0.001$) between GLP-1RA and thyroid cancer (PRR 6.89), MTC (PRR 27.43), and PTC (PRR 8.68).[7] Finally, an analysis of the World Health Organization's pharmacovigilance database (VigiBAse) showed signals of disproportionality with GLP-1RA for thyroid cancer (PRR 30.5, 95% CI 25.1–37.2) and for MTC (PRR 28.7, 95% CI 16.1–51.1).[8]

Although pharmacovigilance studies suggest disproportionality with GLP-1RAs and thyroid cancer, these analyses cannot be used to prove causality. Furthermore, selection bias may relate to increased reporting of thyroid cancer in GLP-1RA treated individuals due to the known potential relationship between GLP-1RAs and thyroid cancer (notoriety bias). Detection bias is also likely due to greater surveillance for thyroid cancer in GLP-1RA treated individuals or perhaps weight loss related to GLP-1RA treatment makes thyroid nodules more apparent.

Observational Studies

Figure 1 summarizes the main results of 8 observational studies that have explored the link between GLP-1RAs and thyroid cancer. Using commercial health insurance claims data in the USA (Normative Health Information), Dore et al. reported the results of a retrospective cohort study with propensity matching comparing initiators of exenatide to initiators of metformin or glyburide between 2005 and 2009 with up to 1 year of follow-up. The incidence of thyroid cancer was 37/32,822 (0.1%) amongst the exenatide group and 26/32,842 (0.1%) in the metformin/glyburide group (relative risk [RR] 1.4, 95% CI 0.8–2.4).[9] In another retrospective cohort study using 2 administrative databases in the USA, the median follow-up was 1 year. This study compared 33,629 users of exenatide to 49,317 propensity-score matched users of other antidiabetic drugs (OADs). The incidence rates of thyroid cancer were 0.62 events and 0.44 events per 1,000 patient-years in the exenatide and OAD groups, respectively (hazard ratio [HR] 1.46, 95% CI 0.98–2.19). Results of a time-dependent analysis by duration of treatment or cumulative dose were similar.[10] In 2021, Funch et al. reported findings from a prospective cohort study using data drawn from a US health plan (Optum), comparing propensity score matched initiators of liraglutide versus OADs. Amongst 34,707 individuals treated with liraglutide or OADs (excluding exenatide), who were followed for a median of 1.4 years, the incidence of thyroid cancer was significantly increased in the liraglutide group, with 41 cases compared to 24 cases amongst OAD users (RR 1.70, 95% CI 1.03–2.81).[11] Wang et al. performed a retrospective analysis of a large electronic heath database in the USA (Explorys) and compared 64,230 users of GLP-1RAs to 619,340 users of metformin. Within 5 years of starting medication, GLP-1RA was associated with a significantly higher incident risk of thyroid cancer (adjusted odds ratio [OR] 1.65, 95% CI 1.31–2.05).[12] A nested case-control study by Bezin et al. used the French national health care insurance system database and compared 2,562 individuals with T2DM and thyroid cancer to 45,184 control subjects with T2DM. Current use of GLP-1RA was 8.1% in case subjects and 6.0% in control subjects (HR 1.46, 95% CI 1.23–1.74). Similarly significant results were shown for MTC (15.5% of all thyroid cancer cases), with current GLP-1RA use of 8.8% in case subjects and 5.9% in control subjects (HR 1.76, 95% CI 1.16–2.69). In a cumulative exposure model, use of GLP-1RA for 1–3 years or >3 years was associated with an increased risk of thyroid cancer and use of GLP-1RA for 1–3 years was associated with an increased risk of MTC.[8] A population-based cohort study using claims data from the *Korean National Health Insurance Database*

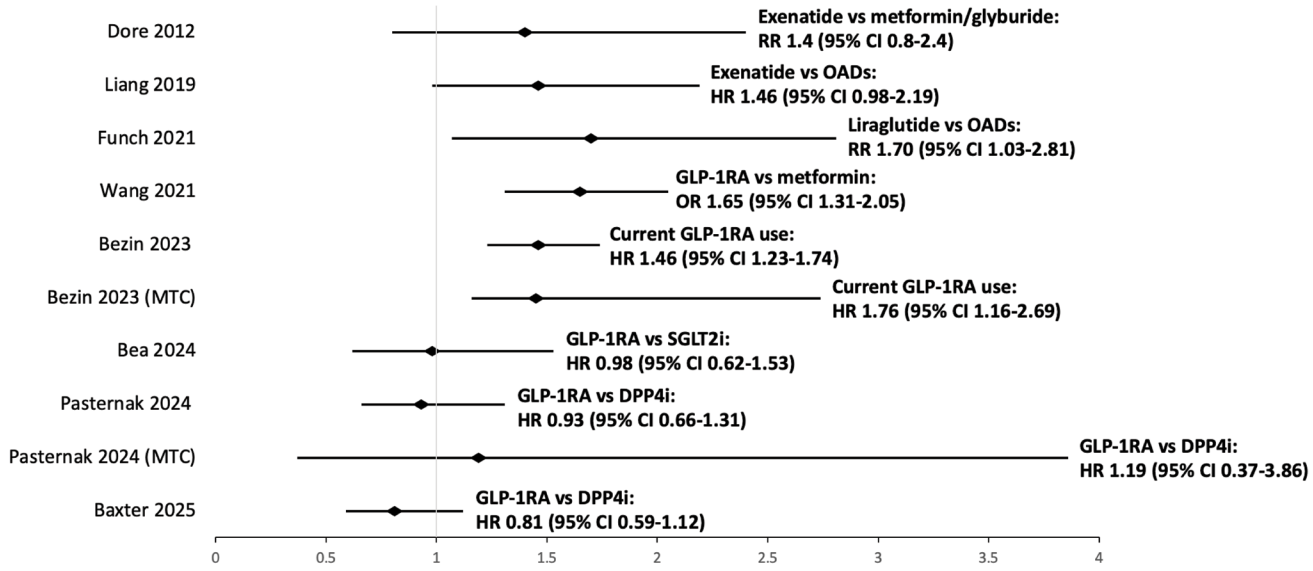


Figure 1. Summary of primary results from observational studies of GLP-1RAs and thyroid cancer; *courtesy of Ronald M. Goldenberg, MD, FRCPC, FACE*.

Except for the Bezin study, data shown for each study compares thyroid cancer risk (or MTC risk where indicated) with GLP-1RA treatment vs comparator. The Bezin study data compares current GLP-1RA use in thyroid cancer cases (or MTC where indicated) to control cases.

Abbreviations: GLP-1RA: glucagon-like peptide-1 receptor agonist, **MTC:** medullary thyroid carcinoma, **RR:** relative risk, **HR:** hazard ratio; **OR:** odds ratio, **CI:** confidence interval, **OADs:** other antidiabetic drugs, **SGLT2i:** sodium-glucose cotransporter-2 inhibitors, **DPP4i:** dipeptidyl peptidase 4 inhibitors.

compared 18,863 new users of GLP-1RAs to 325,307 new users of sodium-glucose cotransporter-2 inhibitors (SGLT2i) after propensity score weighting. The hazard ratio for thyroid cancer for GLP-1RAs vs SGLT2is was 0.98 (95% CI 0.62-1.53).[13] Pasternak et al. investigated the association of GLP-1RAs with an increased risk of thyroid cancer in a Scandinavian retrospective cohort study using an active-active comparator new user design with propensity score weighting. In the primary analysis that compared 145,410 GLP-1RA users to 291,667 dipeptidyl peptidase 4 (DPP4) inhibitor users, after a mean follow-up time of approximately 4–5 years, the incidence rates were 1.33 and 1.46 events per 10,000 person-years, respectively (HR 0.93, 95% CI 0.66-1.31). The hazard ratio for MTC was 1.19 (95% CI 0.37-3.86). In an additional analysis comparing GLP-1RA use to SGLT2i use, the hazard ratio for thyroid cancer was 1.16 (95% CI 0.65-2.05).[14] Finally, in the most robust observational study thus far, Baxter et al. performed a pooled international cohort study using databases from six countries, including Canada. Patients with T2DM were studied from 2007 to 2023, and 98,147 GLP-1RA users with a median follow-up of 1.8 to 3.0 years were compared to 99,870 DPP4 inhibitor users using propensity score weighting. GLP-1RA use was not associated with an increased risk of thyroid cancer (adjusted HR 0.81, 95% CI 0.59–1.12).[15]

Results of the observational studies are inconsistent, with the studies by Funch, Wang, and Bezin each demonstrating a statistically significant increase in GLP-1RA-associated thyroid cancer, while 5 other studies did not show significance and had variable effect sizes (**Figure 1**). However, these observational studies have limitations that make conclusions impossible, including the potential for unmeasured or residual confounding (e.g., family history, obesity, radiation exposure), detection bias, and time-related bias. Relatively short follow-up times may also be a limiting factor in observational studies of drug-induced cancer risk. In fact, the onset of thyroid cancer after only one-to-three years[8] or five years[12] of GLP-1RA exposure suggests that residual confounding or

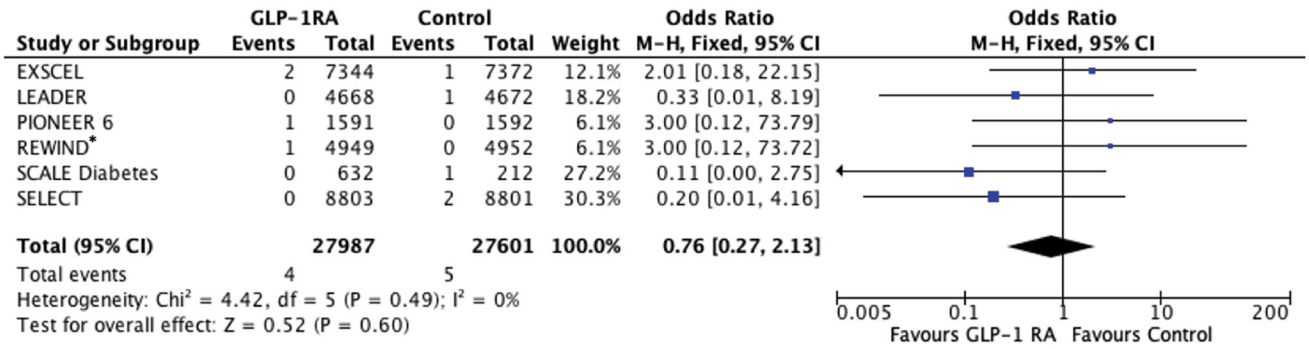


Figure 2. Meta-analysis of GLP-1RA randomized controlled trials and risk of medullary thyroid cancer; *courtesy of Ronald M, Goldenberg, MD, FRCPC, FACE*.

***The case shown in REWIND had C-cell hyperplasia and not medullary thyroid carcinoma.

Abbreviations: GLP-1RA: glucagon-like peptide-1 receptor agonist, **M-H:** Mantel–Haenszel, **CI:** confidence interval.

detection bias was present. A further limitation of the Bezin study regarding an increased risk of MTC relates to the definition of MTC that may have led to overestimation of this diagnosis, perhaps explaining the 15.5% prevalence of MTC amongst all thyroid cancer cases despite the fact that MTC should typically be observed in approximately 3% of thyroid cancer cases.[16]

Randomized Controlled Trials

It is well established that RCTs do not have the limitations or biases seen in observational studies and hence are useful in the assessment of important safety concerns such as GLP-1RA related thyroid cancer. A recent meta-analysis included all RCTs of at least 52 weeks duration that compared a European Medicines Agency approved GLP-1RA to any comparator.[17] A fixed-effect analysis of 26 trials that reported at least one incident case of thyroid cancer reported a statistically significant increase in thyroid cancer (OR 1.52, 95% CI 1.01–2.29; p=0.04). Thyroid cancer incidence was low, with only 86 cases of thyroid cancer amongst 69,909 patients. The small number of thyroid cancer cases accounted for a low fragility index, suggesting that only one additional case of thyroid cancer in the comparator arm would lead to a statistically insignificant result. In random-effect and continuity correction analyses the result was no longer significant.[17]

The potential association between GLP-1RAs and MTC has also been studied in RCTs. In large GLP-1RA outcome trials, there was no difference in calcitonin concentrations or the proportion of individuals with clinically concerning calcitonin elevations between GLP-1RA and placebo.[18,19] Cases of MTC in the GLP-1RA trials were extremely rare. In an updated meta-analysis performed by this author for this review, only six trials reported at least one case of MTC,[20-25] with 4 cases out of 27,987 individuals in the GLP-1RA arms and 5 cases out of 27,601 individuals in the comparator arms (OR 0.76, 95% CI 0.27–2.13; p=0.60) (**Figure 2**). The low incidence of MTC in the RCTs is consistent with the low incidence rate of MTC in the US population of 0.225 per 100,000 person-years.[26]

The RCTs have not proven an association between GLP-1RAs and thyroid cancer. Case numbers are relatively small with high fragility, resulting in inconclusive results.

Conclusion

The totality of evidence from pharmacovigilance, observational, and randomized controlled studies has not conclusively demonstrated a link between increased thyroid cancer and GLP-1RA treatment in humans. Although rodent studies have demonstrated an increased risk of MTC, the data in humans remains uncertain. A safety committee of the European Medicines Agency has suggested that the current evidence does not support a link between the use of GLP-1RAs in humans and thyroid cancer.[27]

Clinicians should continue prescribing GLP-1RAs for the management of T2DM or obesity when indicated as the proven benefits outweigh the unproven risk of thyroid cancer.

Correspondence

R.G.: Ronald M. Goldenberg, MD, FRCPC, FACE
Email: ronaldgoldenberg@gmail.com

Financial Disclosures

Research Support and/or Personal Fees: Eli Lilly, Novo Nordisk and Sanofi.

References

1. Shah BR, Bajaj HS, Butalia S, Dasgupta K, Eurich DT, Jain R, et al. Pharmacologic glycemic management of type 2 diabetes in adults---2024 update. Can J Diabetes. 2024;48(7):415-424. doi:10.1016/j.jcjd.2024.08.002
2. Bjerre Knudsen L, Madsen LW, Andersen S, Almholt K, de Boer AS, Drucker DJ, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology. 2010;151(4):1473-1486. doi:10.1210/en.2009-1272
3. Song Y, Zhou M, Cao Y, Qi J, Geng J, Liu X. Expression of GLP-1 receptor and CD26 in human thyroid C-cells: the association of thyroid C-cell tumorigenesis with incretin-based medicine. Oncol Lett. 2017;13(4):2684-2690. doi:10.3892/ol.2017.5752
4. Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Mod Pathol. 2015;28(3):391-402. doi:10.1038/modpathol.2014.113
5. He L, Zhang S, Zhang X, Liu R, Guan H, Zhang H. Effects of insulin analogs and glucagon-like peptide-1 receptor agonists on proliferation and cellular energy metabolism in papillary thyroid cancer. Onco Targets Ther. 2017;10:5621-5631. doi:10.2147/ott.S150701
6. Mali G, Ahuja V, Dubey K. Glucagon-like peptide-1 analogues and thyroid cancer: an analysis of cases reported in the European pharmacovigilance database. J Clin Pharm Ther. 2021;46(1):99-105. doi:10.1111/jcpt.13259
7. Yang Z, Lv Y, Yu M, Mei M, Xiang L, Zhao S, et al. GLP-1 receptor agonist-associated tumor adverse events: a real-world study from 2004 to 2021 based on FAERS. Front Pharmacol. 2022;13:925377. doi:10.3389/fphar.2022.925377
8. Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care. 2023;46(2):384-390. doi:10.2337/dc22-1148
9. Dore DD, Seeger JD, Chan KA. Incidence of health insurance claims for thyroid neoplasm and pancreatic malignancy in association with exenatide: signal refinement using active safety surveillance. Ther Adv Drug Saf. 2012;3(4):157-164. doi:10.1177/2042098612446473
10. Liang C, Bertoia ML, Ding Y, Clifford CR, Qiao Q, Gagne JJ, et al. Exenatide use and incidence of pancreatic and thyroid cancer: a retrospective cohort study. Diabetes Obes Metab. 2019;21(4):1037-1042. doi:10.1111/dom.13597
11. Funch D, Mortimer K, Ziyadeh NJ, J DS, Zhou L, Ng E, et al. Risk of thyroid cancer associated with use of liraglutide and other antidiabetic drugs in a US commercially insured population. Diabetes Metab Syndr Obes. 2021;14:2619-2629. doi:10.2147/dmso.S305496
12. Wang J, Kim CH. Differential risk of cancer associated with glucagon-like peptide-1 receptor agonists: analysis of real-world databases. Endocr Res. 2022;47(1):18-25. doi:10.1080/07435800.2021.1955255
13. Bea S, Son H, Bae JH, Cho SW, Shin JY, Cho YM. Risk of thyroid cancer associated with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: a population-based cohort study. Diabetes Obes Metab. 2024;26(1):108-117. doi:10.1111/dom.15292
14. Pasternak B, Wintzell V, Hviid A, Eliasson B, Gudbjörnsdottir S, Jonasson C, et al. Glucagon-like peptide 1 receptor agonist use and risk of thyroid cancer: Scandinavian cohort study. BMJ. 2024;385:e078225. doi:10.1136/bmj-2023-078225
15. Baxter SM, Lund LC, Andersen JH, Brix TH, Hegedüs L, Hsieh MH, Su CT, Cheng MC, Chang ZC, Lai EC, Hussain S, Chu C, Gomes T, Antoniou T, Eskander A, Bouck Z, Tadrous M, Bea S, Choi EY, Shin JY, Modig K, Talbäck M, Ljung R, Gulseth HL, Karlstad Ø, Hicks B, Pottegård A. Glucagon-Like Peptide 1 Receptor Agonists and Risk of Thyroid Cancer: An International Multisite Cohort Study. Thyroid. 2025 Jan;35(1):69-78. doi: 10.1089/thy.2024.0387.
16. Goldenberg RM, Jain AB. Comment on Bezin et al. GLP-1 receptor agonists and the risk of thyroid cancer. Diabetes Care 2023;46:384-390. Diabetes Care. 2023;46(5):e117. doi:10.2337/dc22-2300
17. Silverii GA, Monami M, Gallo M, Ragni A, Prattichizzo F, Renzelli V, et al. Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: a systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2024;26(3):891-900. doi:10.1111/dom.15382

18. Hegedüs L, Sherman SI, Tuttle RM, von Scholten BJ, Rasmussen S, Karsbøl JD, et al. No evidence of increase in calcitonin concentrations or development of c-cell malignancy in response to liraglutide for up to 5 years in the LEADER trial. Diabetes Care. 2018;41(3):620-622. doi:10.2337/dc17-1956
19. Bethel MA, Patel RA, Thompson VP, Merrill P, Reed SD, Li Y, et al. Changes in serum calcitonin concentrations, incidence of medullary thyroid carcinoma, and impact of routine calcitonin concentration monitoring in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL). Diabetes Care. 2019;42(6):1075-1080. doi:10.2337/dc18-2028
20. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917
21. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827
22. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841-851. doi:10.1056/NEJMoa1901118
23. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-130. doi:10.1016/s0140-6736(19)31149-3
24. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, et al. Efficacy of Liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. Jama. 2015;314(7):687-699. doi:10.1001/jama.2015.9676
25. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
26. Tao Z, Deng X, Guo B, Ding Z, Fan Y. Subgroup analysis of steadily increased trends in medullary thyroid carcinoma incidence and mortality in the USA, 2000-2020: a population-based retrospective cohort study. Endocr Relat Cancer. 2024;31(5). doi:10.1530/erc-23-0319
27. European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 23-26 October 2023 [Internet]. [Accessed December 30, 2024]. Available from: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-23-26-october-2023.

About the Author

Phelopater Sedrak, MD

Dr. Phelopater Sedrak is an internal medicine resident at the University of Toronto, where he also completed his medical school education. His academic interests are in novel therapies for heart failure and the promotion of health equity in inpatient practices. Dr. Sedrak is actively involved in teaching and mentoring medical students across various stages of their training. He also has an interest in advancing the point of care ultrasound curriculum. He has received multiple awards for clinical excellence in patient care at the undergraduate medical level.

Affiliations: Department of Internal Medicine, University of Toronto, Toronto, Ontario, Canada

About the Author

Kim A. Connelly, MBBS, PhD

Dr. Kim Connelly is a Cardiologist and Scientist who is both nationally recognized as an expert in echocardiography, cardiovascular MRI and the impact of diabetes upon cardiac function and ventricular remodeling. Dr. Connelly runs a basic research laboratory at the Keenan Research Centre at St. Michael's Hospital where he focuses upon basic mechanisms of disease – primarily around the role of pathological extracellular matrix accumulation with a focus upon integrin biology and translating discoveries into therapies in humans. He is a member of the editorial board of various journals such as The Canadian Journal of Cardiology and Cardiovascular Diabetology. He has received funding from the Heart and Stroke Foundation Canada, CIHR, Canadian Foundation of Innovation, Ministry of Ontario and industry sources, totally >$5 million as principal investigator. As a co-investigator, he has been part of >$20 million in funding, from the Ministry of Ontario, HSF, CIHR, CFI and industry sources. Dr. Connelly has been recognized for his contributions to science by being awarded a HSF clinician scientist award, a CIHR New Investigator Award, an Early Researcher Award from the Ministry of Ontario, the SC Verma award and the Insulin 100 emerging leader award to celebrate 100 years since the discovery of insulin at University of Toronto, as well as Canadian Cardiovascular Congress YIA 2012. He is past chair of the Canadian Cardiovascular guideline and was chair of the macrovascular complication section for Diabetes Canada CPG 2018. Dr. Kim Connelly is the executive director of the Keenan Research Centre for Biomedical Science and holds the Keenan Chair in Research Leadership, and is the head of the Division of Cardiology, St. Michael's hospital, Toronto.

Affiliations: Executive Director, Keenan Research Centre for Biomedical Science, Unity Health
Keenan Chair in Research Leadership
Associate Professor of Medicine, University of Toronto

doi.org/10.58931/cdet.2025.3138

The Role of GLP-1R and GIPR Agonism in Heart Failure

Phelopater Sedrak, MD
Kim A. Connelly, MBBS, PhD

Take Home Messages

- GLP-1RA and GLP-1R/GIPR dual agonism is safe and beneficial for patients with HF across the LVEF spectrum, but especially in obesity-related HFpEF.
- Semaglutide has shown favourable outcomes in both the STEP-HFpEF and STEP-HFpEF DM trials, while tirzepatide has demonstrated favourable outcomes in the SUMMIT trial.
- The proposed mechanism for GLP-RA in HF is through the promotion of favourable reverse cardiac remodelling and the reduction of inflammation.

Introduction

Heart failure (HF) is a clinical syndrome characterized by signs and symptoms of structural and functional cardiac abnormalities. It is corroborated by elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and objective evidence of pulmonary or systemic congestion. More than 100,000 Canadians are diagnosed with HF annually. For years, HF has been classified based on left ventricular ejection fraction (LVEF). HF with reduced ejection fraction (HFrEF) refers to symptomatic HF with an LVEF <40%. However, if the LVEF is >50%, this is known as HF with preserved ejection fraction (HFpEF). In HFpEF, obesity is commonly implicated in the disease pathophysiology, and is present in up to 80% of people with this condition.[1-3] Obesity contributes to concentric heart remodelling through mechanisms such as insulin resistance, diabetes, hyperlipidemia, visceral adipose tissue expansion, and myocardial steatosis.[1] Additionally, obesity leads to a pro-inflammatory state which affects the vasculature and visceral organs.[2] Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, have shown promise in weight reduction across multiple Phase 3 clinical trials. Agents combining GLP-1RA and glucose-dependent insulinotropic peptide receptor (GIPR) agonism, such as tirzepatide, have also contributed to clinically significant weight loss. As such, their impact in addressing obesity-related HFpEF is under investigation.[1] This paper reviews the data on GLP-1RAs and tirzepatide in patients with HF across the LVEF spectrum, with a particular focus on those with HFpEF.

Evidence from Earlier Trials: Are GLP-1RAs safe in Heart Failure?

Concerns were raised about the use of GLP-1RAs in the context of HF. The Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial was the first to raise safety concerns associated with the use of liraglutide in patients with type 2 diabetes mellitus (T2DM) and HF. FIGHT, a Phase 2 trial, randomized 300 participants to receive either liraglutide or placebo. There were no significant differences between the groups in the primary end point, which included the number of deaths, re-hospitalization for HF, or the composite of death or re-hospitalization for HF. Although the effect was not statistically significant, the authors commented that the rates of HF re-hospitalization were higher in the liraglutide group.[4] The Liraglutide on Left Ventricular Function (LIVE) study was a randomized, placebo-controlled trial that investigated the effects of liraglutide in participants with HF and an LVEF <45%. The

primary outcome they measured was the change in LVEF, with secondary outcomes including changes in plasma NT-proBNP levels. Liraglutide was associated with an increase in heart rate by 6 beats per minute compared to placebo.[5] As a result, a publication in 2020 included the following: "The uncertainty regarding the effect of GLP-1RAs in patients with HFrEF suggested in the smaller LIVE and FIGHT trials, coupled with the pharmacodynamic profile of GLP-1RAs including some plausibly pernicious secondary effects, raise concerns about their use in patients with HFrEF. These concerns make it incumbent to have dedicated randomized trials powered to properly assess clinical outcomes with the use of GLP-1RAs in patients with T2DM who have American College of Cardiology/American Heart Association stage C HF to firmly establish the risk/benefit ratio in these patients".[6]

A meta-analysis of seven cardiovascular outcomes trials on GLP-1RAs presented a pooled analysis of this class of drugs on cardiovascular (CV), kidney, and safety outcomes.[7] Across all trials, the prevalence of a history of HF in trial participants ranged from 9% to 24%, with an average prevalence of 17%. On average, 79% of study participants had established cardiovascular disease. This study has demonstrated the positive impact of GLP-1RAs, showing a 12% reduction in all-cause mortality (hazard ratio [HR] 0.88, p=0.001), a 9% reduction in hospital admissions for HF (HR 0.91, p=0.028), and a 17% improvement in composite kidney outcomes (HR 0.83, p<0.001).[7] This meta-analysis included a larger number of participants than the earlier FIGHT and LIVE trials, and commented that GLP-1RAs have an acceptable safety profile. Thus, in the broad population of HF patients included in this study, there was no signal for harm and a signal for potential benefit. However, further validation of this association requires dedicated trials to investigate these agents in HF patients.

Semaglutide Heart Failure Clinical Trials

The STEP-HFpEF trial included 529 participants with an LVEF >45% and a body mass index (BMI) of at least 30. They were followed for a duration of 52 weeks. The study compared 2.4 mg of semaglutide with a placebo and found a statistically significant difference in the 2 primary end points: the change in the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and the percentage change in body weight. Additionally, there was a 21.5 meter improvement in the 6-minute walk distance (6MWD) and a reduction in C-reactive protein (CRP) levels.[8] The STEP-HFpEF DM trial had a similar design and measured outcomes. It included 616 participants, all of whom had T2DM. Semaglutide showed similar improvements in the KCCQ-CSS scores and 6MWD, along with reductions in body weight and CRP levels.[9] However, the rate of treatment discontinuation was higher in the semaglutide group in both trials, owing mainly to gastrointestinal events. Overall, the trials demonstrated that semaglutide significantly improved HF-related symptoms, physical limitations, and exercise function while promoting weight reduction.[10]

Tirzepatide Heart Failure Clinical Trial

The recently published SUMMIT trial investigated tirzepatide in patients with HFpEF and a BMI >30. This international, double-blind study randomized 731 participants to receive up to 15 mg of tirzepatide or a placebo. The primary outcome was a hierarchical composite of death from any cause including adjudicated death from CV causes or a worsening HF event resulting in hospitalization, the use of intravenous drugs in an urgent care setting, or the intensification of oral diuretic therapy. In addition, changes in the KCCQ-CSS score, the 6MWD, body weight, and CRP levels were taken into account. At 52 weeks of follow-up, the trial demonstrated that tirzepatide significantly reduced the risk of CV death or worsening HF compared to placebo. Specifically, worsening HF events occurred in 8.0% of tirzepatide-treated patients versus 14.2% in the placebo group. In addition, similar to semaglutide, tirzepatide resulted in a greater improvement in KCCQ-CSS scores, 6MWD, body weight reduction, and CRP levels compared to the placebo.[11] **Table 1** presents a summary of the trial design for these dedicated HF trials.

Contemporary Studies of GLP-1RA/GIPR Agonists Across the Spectrum of Heart Failure

In 2017, the EXSCEL trial investigated the effects of once-weekly exenatide in 14,752 patients with T2DM. While the primary outcome was the three-component major adverse cardiovascular event (3P-MACE), the study also evaluated worsening HF, hospitalization for HF

Trial	Inclusion Criteria	Participants	Outcomes
STEP-HFpEF (semaglutide)	LVEF >45% BMI >30	529	Δ in KCCQ-CCS; Δ in body weight; 6MWD; CRP level
STEP-HFpEF DM (semaglutide)	LVEF >45% BMI >30 HbA1c 6.5%–10%	616	Δ in KCCQ-CCS; Δ in body weight; 6MWD; CRP level
SUMMIT (tirzepatide)	LVEF >50% BMI >30	731	Death from CV causes; worsening HF event; Δ in KCCQ-CCS; Δ in body weight; 6MWD; CRP level

Table 1. The inclusion criteria and measured outcomes in the dedicated HF trials for semaglutide and tirzepatide.[8-11]

Abbreviations: 6MWD: 6-minute walk distance; **BMI:** body mass index, **CRP:** C-reactive protein, **DM:** diabetes mellites, **CV:** cardiovascular, **HF:** heart failure, **HFpEF:** heart failure with preserved ejection fraction, **KCCQ-CCS:** *Kansas City Cardiomyopathy Questionnaire* clinical summary score, **LVEF:** left ventricular ejection fraction.

(HHF), and death from CV causes.[12] Similarly, the SELECT trial assessed a composite HF endpoint, which included death from CV causes, hospitalization, or an urgent medical visit for HF, in 17,604 participants with obesity but without T2DM.[13] In a prespecified analysis of the SELECT trial, over 4,000 patients with atherosclerotic cardiovascular disease (ASCVD) were found to have a history of HF at enrolment. The benefits observed with semaglutide did not differ in patients with HFpEF compared with HFrEF.[14] These efficacy findings were in contrast to earlier studies suggesting that the use of GLP-1RAs in HF may be ineffective or even harmful.[4-6] In July, 2024, the FLOW trial reported on HF outcomes in 3,533 participants with T2DM and chronic kidney disease comparing semaglutide to a placebo.[15] A meta-analysis that combined results from these three trials, in addition to STEP-HFpEF, STEP-HFpEF DM, and SUMMIT, showed the benefit of GLP-1RAs and tirzepatide in reducing worsening HF events across the LVEF spectrum, with acceptable safety outcomes.[16-17] A summary of the timeline of the trials is presented in **Table 2**.

The Proposed Mechanisms of GLP-1RAs and GLP-1RA/GIPR Agonists in Heart Failure

The echocardiographic sub-study of the STEP-HFpEF clinical trial program found that semaglutide led to a reduction in left atrial (LA) volume and right ventricular dimensions, both of which are critical markers of adverse remodelling in HFpEF.[18] Additionally, semaglutide improved E-wave velocity, E/A ratio, and E/e' ratio, indicating enhanced diastolic relaxation and reduced left ventricular (LV) filling pressures. The observed correlation between greater weight loss and reductions in LA volume suggests that the primary driver behind the cardiac benefits of semaglutide in HFpEF may be its ability to reverse obesity-related cardiac structural abnormalities. These benefits were accompanied by reductions in CRP levels and NT-proBNP, suggesting an anti-inflammatory and congestion-relieving effect. The impact of semaglutide on promoting significant weight loss therefore contributes to its cardiac benefits by reducing ventricular strain, systemic inflammation, and myocardial stiffness.[18]

The SUMMIT trial and its secondary analyses have provided compelling evidence that tirzepatide improves cardiac structure and function by reducing LV mass, para-cardiac adipose tissue, and circulatory overload.[19-20] Cardiac magnetic resonance imaging demonstrated a significant reduction in LV mass with tirzepatide, which correlated with weight loss and improvements in waist circumference and blood pressure.[19] This suggests that the effect of tirzepatide on cardiac remodelling may be mediated through a combination of direct myocardial unloading and systemic metabolic improvements. Furthermore, tirzepatide decreased paracardiac adipose tissue, which is a known contributor to myocardial inflammation and fibrosis in obesity-related HFpEF. Beyond structural changes, tirzepatide also addressed hemodynamic

Study	Year	Outcome
FIGHT	2016	Liraglutide was associated with a higher rate of HF rehospitalization.
LIVE	2016	Liraglutide was associated with a 6 bpm increase in heart rate.
EXSCEL	2017	A meta-analysis of these 6 trials demonstrated the safety and benefit of GLP-1RAs and tirzepatide in participants with HF across the LVEF spectrum, but especially in patients with obesity-related HFpEF.
STEP-HFpEF	2023	
SELECT	2023	
STEP-HFpEF DM	2024	
FLOW	2024	
SUMMIT	2025	

Table 2. Early concerns and the cumulative evidence on GLP-1R and GIPR agonism in participants with HF.[4-5,12-17]

Abbreviations: bpm: beats per minute, **GLP-1RA:** glucagon-like peptide-1 receptor agonists, **GIPR:** glucose-dependent insulinotropic peptide receptor, **HF:** heart failure, **HFpEF:** heart failure with preserved ejection fraction, **LVEF:** left ventricular ejection fraction.

abnormalities characteristic of HFpEF. The secondary analysis of the SUMMIT trial showed that tirzepatide reduced circulatory volume expansion, lowered systolic blood pressure, and decreased systemic inflammation, as evidenced by reductions in CRP and troponin T levels.[20] Additionally, the improvement in the estimated glomerular filtration rate and the reduction in urine albumin-to-creatinine ratio suggest that tirzepatide confers renal protective effects, which may further contribute to favourable hemodynamic modulation.[20]

These findings highlight the potential of both agents as disease-modifying therapies in obesity-related HFpEF, targeting both myocardial remodelling and systemic congestion, as shown in **Figure 1**. Collectively, these effects correlate with improvements in symptoms, tolerance of exertion, and quality of life.

New and Ongoing Trials

The SOUL trial was a randomized, double-blind, parallel-group, placebo-controlled cardiovascular outcomes superiority trial involving patients with T2DM and established ASCVD.[21] In this trial, 23% of the patients had prevalent HF. The participants were randomized to receive either once-daily oral semaglutide up to 14 mg or a placebo, in addition to standard care. A notable aspect of this study was that 49% of the participants received a sodium-glucose cotransporter-2 inhibitor (SGLT2-i) at some point during the trial. On March 29, 2025, the study reported on the time to the first occurrence of MACE and a composite kidney outcome.[22] There was a statistically significant reduction in 3P-MACE among participants treated with oral semaglutide versus a placebo. However, the differences in the secondary outcomes, which included major kidney disease events and three-point composite for heart failure events (death from CV causes, an urgent visit for HF, or HHF) were not significant.[22] This suggests that patients with HF already receiving an SGLT2-i would benefit from GLP-1RA therapy, with additional efficacy in terms of 3P-MACE.

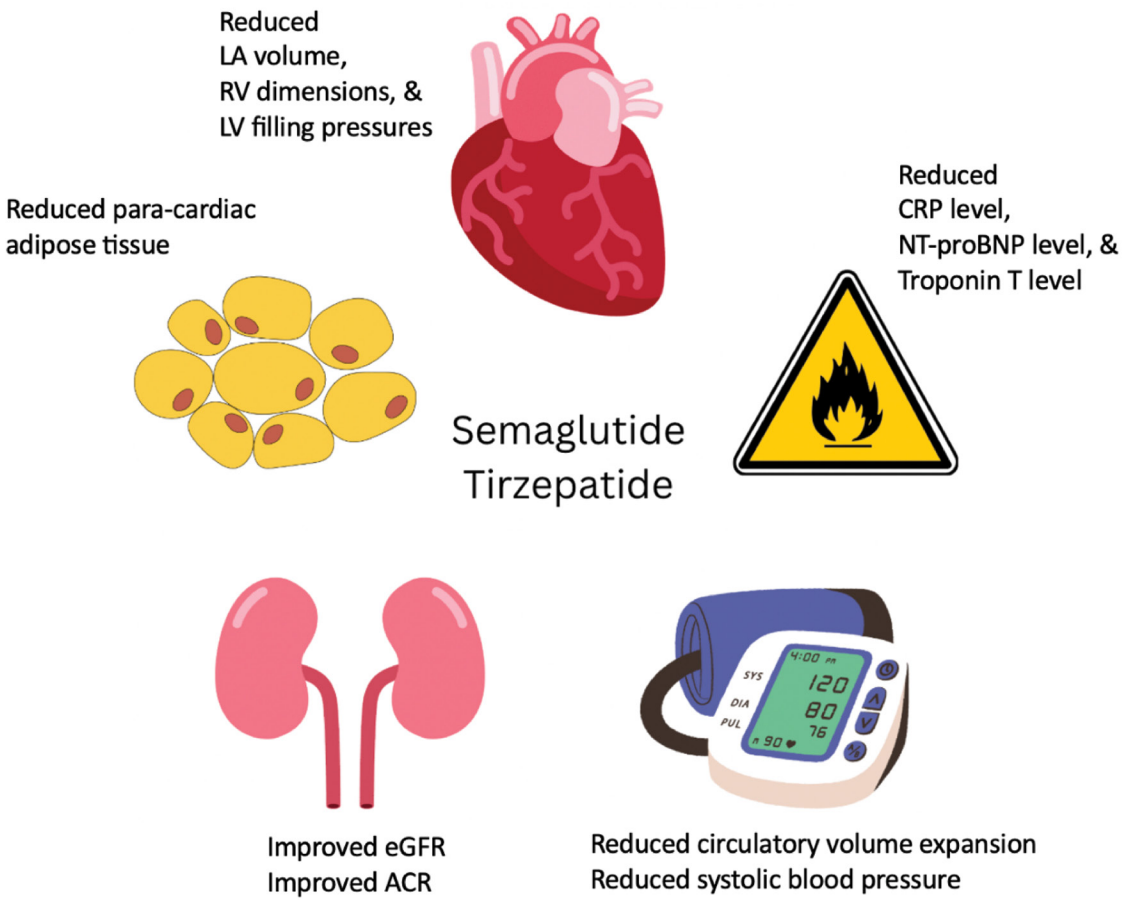


Figure 1. The proposed mechanisms by which semaglutide and tirzepatide contribute to improved HF outcomes; *courtesy of Phelopater Sedrak, MD and Kim Connelly, MBBS, PhD.*

Abbreviations: ACR: albumin-creatinine ratio, **CRP:** C-reactive protein, **eGFR:** estimated glomerular filtration rate, **LA:** left atrial, **LV:** left ventricular, **NT-proBNP:** N-terminal pro-B-type natriuretic peptide, **RV:** right ventricular.

Regarding ongoing trials, SURMOUNT-MMO is a Phase 3 randomized, placebo-controlled study designed to evaluate the impact of tirzepatide on reducing morbidity and mortality in adults with obesity. The study started on October 11, 2022, and is expected to conclude in October, 2027. The primary objective is to assess whether tirzepatide can effectively reduce the incidence of MACE in people with ASCVD or those at high-risk for primary prevention who are living with obesity but do not have diabetes. The SURPASS-CVOT is a Phase 3 randomized, active controlled study designed to evaluate the CV safety and efficacy of tirzepatide compared to dulaglutide in adults with T2DM and established ASCVD. The primary endpoint is the time to the first occurrence of MACE. The primary analysis aims to demonstrate that tirzepatide is not inferior to dulaglutide by establishing an upper confidence limit of less than 1.05 for the HR, which would also confirm its superiority to a putative placebo. The trial is fully recruited and ongoing.

Conclusion

Medical management of HF has seen significant advances in recent decades, including most recently with the introduction of SGLT-2i agents. The recent data unequivocally removes any concerns of harm regarding the safety of GLP-1RA monotherapy or GLP-1RA and GIPR agonism. Furthermore, these agents have shown clear improvements in quality of life, functional status, and a reduction in HF admissions across the LVEF spectrum. This effect is observed in patients already receiving standard therapies for HF and demonstrates the additive effect of these agents. Current Canadian guidelines focus on the use of these agents in patients with HF and known T2DM, have/are overweight or obesity, and have ASCVD or multiple risk factors for ASCVD.[23] The proposed mechanisms include promoting favourable cardiac remodelling, and reducing inflammation and congestion. Ongoing trials continue to measure HF outcomes in various populations, which will allow for the integration of these agents into standard care.

Correspondence

Phelopater Sedrak, MD
Email: phelopater.sedrak@mail.utoronto.ca

Financial Disclosures

P.S.: None declared.
K.A.C.: Dr. Connelly is listed as an inventor on a patent application by Boehringer Ingelheim on the use of dipeptidyl peptidase-4 inhibitors in heart failure; **Research Grants:** AstraZeneca, Servier, and Boehringer Ingelheim; **Travel Funding:** Boehringer Ingelheim; **Honoraria/Advisory Boards:** Servier, Merck, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Ferring, Novo Nordisk, Novartis, and Janssen. Dr, Connelly holds the Keenan Chair in Research Leadership.

References

1. Cimino G, Vaduganathan M, Lombardi CM, Pagnesi M, Vizzardi E, Tomasoni D, et al. Obesity, heart failure with preserved ejection fraction, and the role of glucagon-like peptide-1 receptor agonists. ESC heart failure. 2024;11(2):649-661. doi:10.1002/ehf2.14560
2. Borlaug BA, Jensen MD, Kitzman DW, Lam CS, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res. 2023;118(18):3434-3450. doi:10.1093/cvr/cvac120
3. Obokata M, Reddy YN, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation. 2017;136(1):6-19. doi:10.1161/CIRCULATIONAHA.116.026807
4. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2016;316(5):500-508. doi:10.1001/jama.2016.10260
5. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)—a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail. 2017;19(1):69-77. doi:10.1002/ejhf.657
6. Khan MS, Fonarow GC, McGuire DK, Hernandez AF, Vaduganathan M, Rosenstock J, et al. Glucagon-like peptide 1 receptor agonists and heart failure: the need for further evidence generation and practice guidelines optimization. Circulation. 2020;142(12):1205-1218. doi:10.1161/CIRCULATIONAHA.120.045888
7. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. [published correction appears in Lancet Diabetes Endocrinol. 2020 Mar;8(3):e2. doi: 10.1016/S2213-8587(20)30037-1.]. Lancet Diabetes Endocrinol. 2019;7(10):776-785. doi:10.1016/S2213-8587(19)30249-9

8. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023;389(12):1069-1084. doi:10.1056/NEJMoa230696 .
9. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med. 2024;390(15):1394-1407. doi:10.1056/NEJMoa2313917
10. Butler J, Shah SJ, Petrie MC, Borlaug BA, Abildstrøm SZ, Davies MJ, et al. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. Lancet. 2024;403(10437):1635-1648. doi:10.1016/S0140-6736(24)00469-0
11. Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med. 2025;392(5):427-437. doi:10.1056/NEJMoa2410027
12. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228-1239. doi:10.1056/NEJMoa1612917
13. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
14. Deanfield J, Verma S, Scirica BM, Kahn SE, Emerson SS, Ryan D, et al. Semaglutide and cardiovascular outcomes in patients with obesity and prevalent heart failure: a prespecified analysis of the SELECT trial. Lancet. 2024;404(10454):773-786. doi:10.1016/S0140-6736(24)01498-3
15. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JF, Bakris G, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391(2):109-121. doi:10.1056/NEJMoa2403347
16. Waqas SA, Sohail MU, Saad M, Minhas AM, Greene SJ, Fudim M, et al. Efficacy of GLP-1 receptor agonists in patients with heart failure and mildly reduced or preserved ejection fraction: a systematic review and meta-analysis. J Card Fail. Published online February 22, 2025. doi:10.1016/j.cardfail.2025.01.022
17. Kosiborod MN, Deanfield J, Pratley R, Borlaug BA, Butler J, Davies MJ, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. Lancet. 2024;404(10456):949-961. doi:10.1016/S0140-6736(24)01643-X
18. Solomon SD, Ostrominski JW, Wang X, Shah SJ, Borlaug BA, Butler J, et al. Effect of semaglutide on cardiac structure and function in patients with obesity-related heart failure. [published correction appears in J Am Coll Cardiol. 2025 Mar 11;85(9):967-968. doi: 10.1016/j.jacc.2025.01.010.]. J Am Coll Cardiol. 2024;84(17):1587-1602. doi:10.1016/j.jacc.2024.08.021
19. Kramer CM, Borlaug BA, Zile MR, Ruff D, DiMaria JM, Menon V, et al. Tirzepatide reduces LV mass and paracardiac adipose tissue in obesity-related heart failure: SUMMIT CMR substudy J Am Coll Cardiol. 2025;85(7):699-706. doi:10.1016/j.jacc.2024.11.001
20. Borlaug BA, Zile MR, Kramer CM, Baum SJ, Hurt K, Litwin SE, et al. Effects of tirzepatide on circulatory overload and end-organ damage in heart failure with preserved ejection fraction and obesity: a secondary analysis of the SUMMIT trial. Nat Med. 2025;31(2):544-551. doi:10.1038/s41591-024-03374-z
21. McGuire DK, Busui RP, Deanfield J, Inzucchi SE, Mann JF, Marx N, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: Design and baseline characteristics of SOUL, a randomized trial. Diabetes Obes Metab. 2023;25(7):1932-1941. doi:10.1111/dom.15058
22. McGuire DK, Marx N, Mulvagh SL, Deanfield JE, Inzucchi SE, Pop-Busui R, et al. Oral semaglutide and cardiovascular outcomes in high-risk type 2 diabetes. N Engl J Med. 2025;382(13):1234-1245. doi:10.1056/NEJMoa2501006
23. Mancini GJ, O'Meara E, Zieroth S, Bernier M, Cheng AY, Cherney DZ, et al. 2022 Canadian Cardiovascular Society guideline for use of GLP-1 receptor agonists and SGLT2 inhibitors for cardiorenal risk reduction in adults. [published correction appears in Can J Cardiol. 2022 Dec;38(12):1979. doi: 10.1016/j.cjca.2022.10.008.]. Can J Cardiol. 2022;38(8):1153-1167. doi:10.1016/j.cjca.2022.04.029

doi.org/10.58931/cdet.2025.3139

About the Author

Irena Druce, MD, FRCPC, MSc

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 is the recipient of the 2024 Jeff Tunbul Health Advocacy Award. Her areas of clinical interest include type 2 diabetes, endocrine toxicities of immune checkpoint inhibitor therapy and transgender health.

Affiliations: Division of Endocrinology and Metabolism, Department of Medicine, University of Ottawa
Inflammation & Chronic Disease Program, The Ottawa Hospital Research Institute

GLP-1 Receptor Agonist Use in Pregnancy

Irena Druce, MD, FRCPC, MSc

Introduction

As of 2018 data, 30–60% of reproductive-aged women in Canada were affected by overweight (body mass index [BMI] 25.9–29.9) and obesity (BMI >30.0), and these rates are increasing.[1] Obesity during pregnancy is associated with higher rates of preeclampsia, gestational diabetes, macrosomia, stillbirth, post-term pregnancy, and increased caesarean delivery rates.[2] Obesity is also associated with higher rates of diabetes, which has well-known consequences for pregnancy, and ovulatory dysfunction, which impacts fertility, such as in polycystic ovarian syndrome (PCOS). Addressing obesity and its associated metabolic impacts could have a profound effect on reproductive and fetal health.[3]

Since the 2000s, incretin-based therapies for diabetes and obesity have become the focus of research and clinical practice. Glucagon-like-peptide 1 (GLP-1), an endogenous incretin hormone secreted by intestinal L-cells in response to food intake, and its agonists, have been available for clinical use in Canada since the introduction of liraglutide in 2011. Recently, pharmacologic agonists of glucose-dependent insulinotropic polypeptide (GIP), an incretin synthesized in the K-cells of the duodenum and jejunum, have also become available. Dual agonism of these hormones is associated with more significant reductions in blood glucose and weight.[4] The currently available incretin-based therapies are listed in **Table 1**, and their physiologic effects are summarized in **Figure 1**.

Active research is underway on new molecules, for example agonists of amylin and glucagon, in various combinations with GLP-1 and GIP, to maximize clinical benefits. These combinations have shown weight loss effects rivalling those of metabolic surgery.[5] Considering their potential, this medication class has taken the world by storm. Canada's Drug Agency (CDA) found that expenditure on injectable semaglutide, under the brand-name Ozempic™, increased from $13.5 million in 2019 to $227 million in 2021, with 20% of the claims being for non-type 2 diabetes use.[6]

The metabolic improvements and weight loss achieved with incretin-based therapies are

Drug	Administration Route	Administration Frequency	Dose (*mg*)	Effect on A1c	Effect on Weight	Weight Loss Indication	CV Benefit
Exendin-based GLP1 Receptor Agonists							
Exenatide	SC	BID	5–10	↓↓	↓↓	No	No
Lixisenatide	SC	Daily	10–20	↓↓	↓	No	No
Human GLP1-based GLP1 Receptor Agonists							
Liraglutide	SC	Daily	0.6–1.8*	↓↓	↓↓↓	Yes	Yes
Dulaglutide	SC	Weekly	0.75–1.5	↓↓	↓↓	No	Yes
Semaglutide	SC	Weekly	0.25–2*	↓↓↓	↓↓↓	Yes	Yes
	Oral	Daily	3–14	↓↓↓	↓↓↓	No	Yes
Dual GLP1/G1P Receptor Agonists							
Tirzepatide	SC	Weekly	2.5–15	↓↓↓↓	↓↓↓↓	No	No

Table 1. Comparison among incretin-based therapies; *courtesy of Irena Druce, MD, FRCPC, MSc.*

*Doses indicated for weight loss are higher than those listed, all listed dosages are for the indication of glycemic management.

Abbreviations: BID: twice daily, **CV:** cardiovascular, **GIP:** glucose-dependent insulinotropic polypeptide, **GLP1:** glucagon-like peptide 1, **SC:** subcutaneous.

associated with improved fertility. While product monographs warn against use in pregnancy and lactation, conception while on these treatments is becoming more common.[3] Considering this increasing reality, this review aims to summarize what is currently known about GLP-1 and GIP agonists and their effects during pregnancy.

GLP-1 Effects on Reproduction and Fertility

Metabolic dysfunction associated with PCOS and type 2 diabetes results in menstrual irregularities from anovulation and infertility. GLP-1 action has been implicated in pituitary function; it was shown to increase serum luteinizing hormone (LH) in most functional studies, with GLP-1-related increases in gonadotropin-releasing hormone (GnRH) being the prime mechanism. An acute central administration of GLP-1 to female rats during the proestrous phase doubled the amplitude of the pre-ovulatory LH surge. This, in turn, influenced the estradiol and progesterone levels throughout the oestrous cycle and promoted an increased number of mature Graafian follicles.[8]

GLP-1 may also be associated with effects on other reproductive organs. It may have direct effects on the ovary, as GLP-1-receptor knockout mice exhibited a slight delay in the onset of puberty and a decreased number of ovarian follicles.[7] In animal models, insulin resistance has also been shown to affect the endometrium, leading to implantation failure, pregnancy loss, and defective placentation. In diabetic rats, exenatide administration led to decreased histologic degeneration and fibrosis in the endometrium, mainly by decreasing inflammation and antagonizing oxidative stress.[9]

One of the mainstays of PCOS management is weight reduction, which makes GLP-1 and GIP agonists attractive options. Currently none of the available therapies are indicated for PCOS;

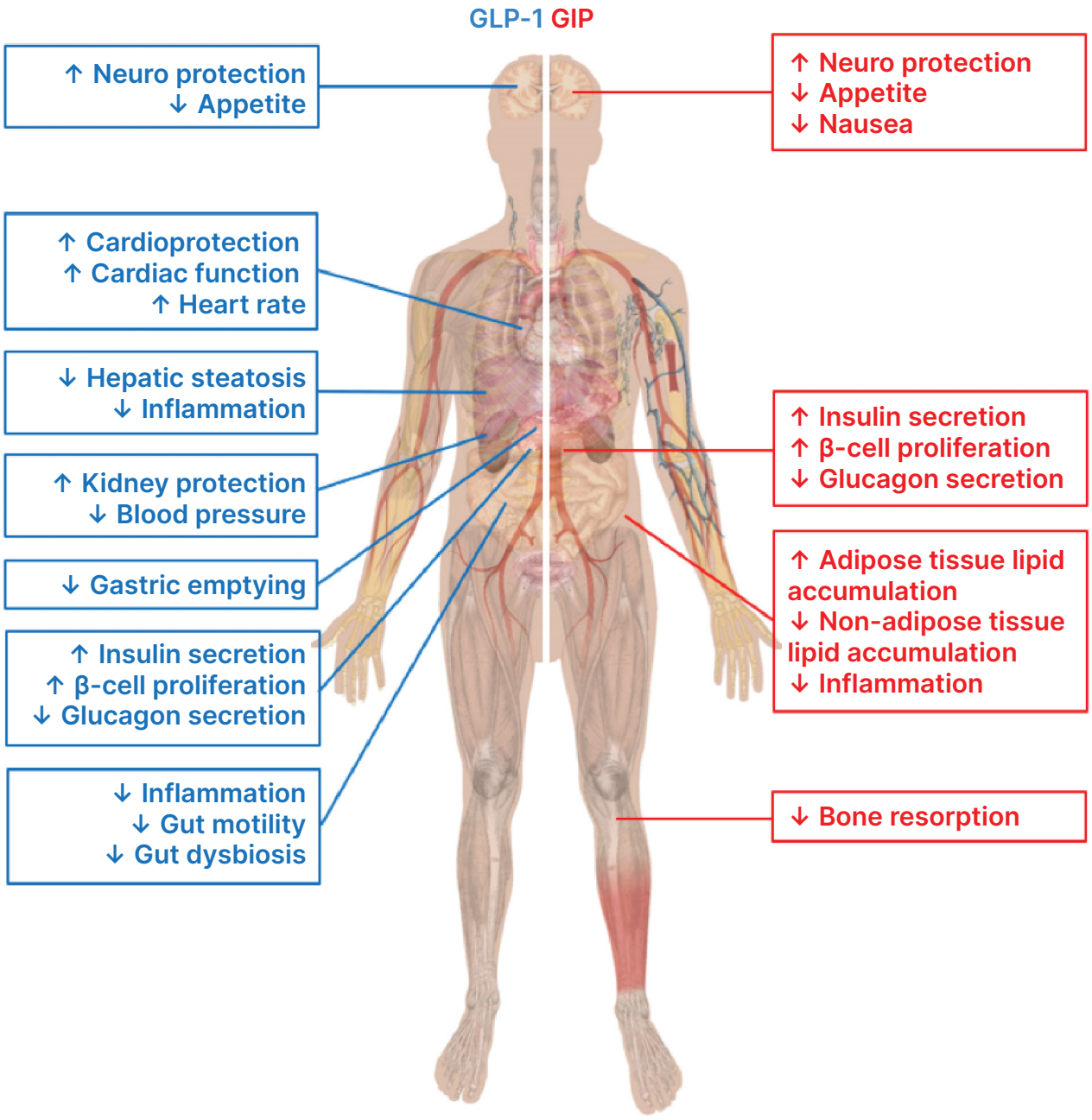


Figure 1. Summary of the biological actions of glucagon-like polypeptide 1 (GLP1-) and glucose-dependent insulinotropic peptide (GIP) receptor agonism; *adapted from Hammoud R. et al. Nat Rev Endocrinol. 2023; 169(4):201-16.*

however, numerous small studies have shown their benefits. Treatment of women with PCOS using GLP-1 led to reduced body weight, improved insulin sensitivity, decreased liver and visceral adiposity, and decreased androgen levels. Furthermore, trials comparing GLP-1 receptor agonists with metformin demonstrated improved menstrual regularity and ovulation rates in the GLP-1-treated group.[10] Another study showed that women with PCOS treated with GLP-1 experienced improved spontaneous pregnancy rates, although there was no discussion on the outcomes of the pregnancies or effects on the offspring.[11]

The use of GLP-1 receptor agonists for weight management is also endorsed by The Canadian Adult Obesity Practical Guidelines, citing benefits for many cardiovascular and metabolic parameters, including PCOS.[12]

GLP-1 in Pregnancy

Animal Data

Numerous studies in rats and rabbits have assessed the effects of high dose exposure to GLP-1 receptor agonists. At doses 0.8–11 times the levels of human exposure of the drug liraglutide, there was a reduction in fetal growth and early embryonic death. All GLP-1 receptor agonists are too large to pass through the placenta and were not found on the fetal side, indicating that the effects are exerted via impact on maternal food consumption and possibly placental effects.[3]

Mouse studies revealed that treating healthy pregnant mice with semaglutide resulted in lower maternal blood glucose levels. Even when these levels were restored with glucose infusion, the pups had lower birth weights. The placentas maintained their usual mass but had decreased architecture with alterations in placental blood supply, decreased capillary density, and decreased expression of the facilitative glucose transporter GLUT1.[13]

In a mouse model of placental ischemia and maternal hypertension, liraglutide administration resulted in lower blood pressure, improved renal function, and improved placental perfusion, however, the pups were still smaller in size compared to those from control pregnancies.[14]

Other abnormalities noted in animals who were exposed to GLP-1 receptor agonists were delayed ossification, skeletal variants, and visceral abnormalities.[3]

The picture is muddied by studies with contrasting results. When pregnant mice were administered exenin-4, the peptide found in Gila monster venom that shares homology with human GLP-1, and is the basis for drugs such as exenatide and lixisenatide, the pregnant mice gained more weight than controls, and the pups were also heavier prior to weaning.[15]

In the peripartum period, animal studies demonstrated a rapid upregulation of GLP-1 receptors in offspring, which correlated with improved surfactant production and lung function. When GLP-1 was administered to animals during lactation, the concentrations in milk compared to maternal serum were found to be <2.5% for exenatide, 8.3–33% for semaglutide, and 50% for liraglutide, with liraglutide being the smallest GLP-1 receptor agonist.[16]

Human Pregnancies

Various case reports have described the outcomes of unintentional GLP-1 use in early pregnancy, with exposure lasting up to 17 weeks of gestation. Among the seven pregnancies presented, all deliveries occurred after 37 weeks, with one elective cesarean section mentioned. One birth defect, an atrial septal defect, was noted, which resolved by the age of three years. There was one case of shoulder dystocia due to fetal macrosomia. Whether the increased fetal birth weight was due to drug exposure, or the underlying condition for which the drug was prescribed, cannot be proven.[3]

Another case report described a woman who intentionally used liraglutide throughout her entire pregnancy to manage difficult-to-control diabetes. She had an uncomplicated pregnancy and delivery via elective cesarean section at 39 weeks. The concentration of liraglutide was assessed in maternal blood and the umbilical vein 3.5 hours after the last dose was administered. However, the concentration of drug in the umbilical vein was below the sensitivity of the assay.[17]

A recent observational population-based cohort study looked at trends in the use of antidiabetic medications in pregnancy and the associated risks of congenital malformations compared to insulin. The study examined over 50,000 pregnancies from six countries, with 8.3% (n = 938) exposed to GLP-1 receptor agonists, mainly for the treatment of obesity and PCOS. They concluded that there was no elevated risk of major congenital malformations based on adjusted relative risks. In line with prescribing

practices, the study noted an increased use of GLP-1 receptor agonists during pregnancy in the US over time.[18]

Dao and colleagues conducted an observational, multicenter prospective cohort study based on six databases of the European Network of Teratology Information Services. They assessed three groups of approximately 160 patients; patients exposed to GLP-1 receptor agonists in the first trimester, and patients with diabetes and with overweight and obesity, without any GLP-1 exposure. In the GLP-1-treated group, the median exposure was five weeks and three congenital malformations were noted, though they were thought to be unrelated to the medication. After adjusting for maternal age, parity, and number of medications, the GLP-1 group had the same rate of congenital malformations as the diabetes group (2.6% vs. 2.3%). The highest rate of malformations was noted in the overweight and obesity group at 3.9%.[19]

None of the recent studies discussed the link between GLP-1 exposure and fetal or birth weight. Interestingly, a study looking at obese pregnancies noted that compared to controls, women with obesity had higher levels of endogenous GLP-1, which correlated with large for gestational age (LGA) infants. Higher GLP-1 expression was also noted in the umbilical cord blood of LGA infants.[20] Elevated fasting GLP-1 levels have been noted in obese children and adolescents, although data in adults is conflicting.[21] It is not possible to compare the effects of endogenous GLP-1 to pharmacologic agonists that have been molecularly altered, and clearly more research in this domain is needed.

Effects on Hormonal Contraception

With very rare exceptions, data on GLP-1 and GIP agonist exposure intrapartum comes from unintended pregnancies while on the medication. Currently, the generally accepted guidance is to discontinue GLP-1 receptor agonists prior to conception (1-2 months before, depending on the agent) and during lactation due to the limited evidence. What may add another level of complexity to the story is that data is emerging which suggests that these medications may impact the effectiveness of oral hormonal contraception, which is the second most commonly used contraceptive option in Canada.[22]

Data from Eli Lilly's clinical trials found that among over 5,000 treated patients, there were six pregnancies in those treated with the dual GLP-1/GIP receptor agonist tirzepatide, five of whom were using hormonal contraception at the time of the study. A review found that the use of the concomitantly administered tirzepatide with an oral hormonal contraceptive showed a statistically significant reduction in area under the plasma drug concentration-time curve, maximum concentration, and time to reach maximum plasma concentration for the contraceptive. Similar assessments of GLP-1 monoagonists did not show a statistically or clinically significant difference in the impact of the agents on oral hormonal contraceptives. The postulated mechanism is that tirzepatide is associated with a faster dose escalation and a greater slowing of gastric emptying, which may impact the absorption of oral medications such as contraceptives.[23]

In view of these findings, the manufacturer of tirzepatide recommends that individuals taking oral contraceptives use a barrier method of contraception for 4 weeks after starting the medication or increasing the dose. Until further data is available, the possible impacts of these novel agents on contraceptive effectiveness need to be communicated to patients as part of our counselling around their use in pregnancy.

Conclusions

The benefits of GLP-1 receptor agonist therapy continue to expand and there is potential for this medication class to improve fertility and pregnancy outcomes via reductions in weight, blood glucose, and insulin resistance. However, data specifically on the use of these medications in pregnancy is unfortunately still limited. Therefore, all relevant clinical guidelines still recommend cessation of GLP-1 and GIP receptor agonists prior to conception and during lactation.

A fundamental issue is the ongoing exclusion of pregnant women from clinical trials. Relevant agencies are calling for an end to this practice, stating that the active exclusion of pregnant patients from clinical research is unethical. However, as the majority of clinical trials are industry-led, it is unlikely that we will see such a bold step forward in the near future.

Clinicians should be reassured that, despite animal studies demonstrating possible negative impacts of GLP-1 exposure on birth weight and possible increased birth defects, human data (from largely accidental exposure) has thus far been quite reassuring. Hopefully, we will continue to gather post-marketing evidence demonstrating safety. At a minimum, this data

will allow clinicians to counsel and reassure their patients who will inadvertently become pregnant while on incretin therapy. For some practitioners, this knowledge could also bolster clinical courage to consider these therapies in women wishing to conceive while managing obesity, diabetes, and metabolic disease.

Correspondence

Irena Druce, MD, FRCPC, MSc
Email: idruce@toh.ca

Financial Disclosures

I.D.: Speaking Honoraria: Abbott, Astra Zeneca, Amgen, Bayer, Boehringer Ingelheim, CCRN, CPD Network, Dexcom, Eli Lilly, HLS Therapeutics, Janssen, Merck, Novo Nordisk, Sanofi; **Consultancy Fees:** Abbott, Amgen, Bayer, Dexcom, Eli Lilly, Novo Nordisk, Sanofi

References

1. Statistics Canada. Overweight and Obese Adults, 2018: Statistics Canada; 2018 [updated 2019, cited March 10, 2025]. Available from: https://www150.statcan.gc.ca/n1/pub/82-625-x/2019001/article/00005-eng.htm
2. Mission JF, Marshall NE, Caughey AB. Pregnancy risks associated with obesity. Obstet Gynecol Clin North Am. 2015;42(2):335-353. doi:10.1016/j.ogc.2015.01.008
3. Drummond RF, Seif KE, Reece EA. Glucagon-like peptide-1 receptor agonist use in pregnancy: a review. Am J Obstet Gynecol. 2025;232(1):17-25. doi:10.1016/j.ajog.2024.08.024
4. Drucker DJ, Holst JJ. The expanding incretin universe: from basic biology to clinical translation. Diabetologia. 2023;66(10):1765-1779. doi:10.1007/s00125-023-05906-7
5. Jastreboff AM, Kaplan LM, Frias JP, Wu Q, Du Y, Gurbuz S, et al. Triple-hormone-receptor agonist retatrutide for obesity - a phase 2 trial. N Engl J Med. 2023;389(6):514-526. doi:10.1056/NEJMoa2301972
6. Vaanabouathong C, Crotty C, Le K, Eurich D, Dyrda P. CADTH health technology review: current utilization patterns of glucagon-like peptide-1 receptor agonists. Canadian Journal of Health Technologies. 2022;2(9):1-50.
7. Jensterle M, Janez A, Fliers E, DeVries JH, Vrtacnik-Bokal E, Siegelaar SE. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. Hum Reprod Update. 2019;25(4):504-517. doi:10.1093/humupd/dmz019
8. Outeirino-Iglesias V, Romani-Perez M, Gonzalez-Matias LC, Vigo E, Mallo F. GLP-1 increases preovulatory lh source and the number of mature follicles, as well as synchronizing the onset of puberty in female rats. Endocrinology. 2015;156(11):4226-4237. doi:10.1210/en.2014-1978
9. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015;31(3):196-201. doi:10.3109/09513590.2014.975686

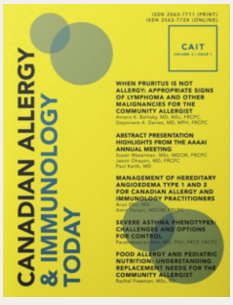
10. Szczesnowicz A, Szeliga A, Niwczyk O, Bala G, Meczekalski B. Do GLP-1 analogs have a place in the treatment of PCOS? New insights and promising therapies. J Clin Med. 2023;12(18):5915. doi:10.3390/jcm12185915
11. Siamashvili M, Davis SN. Update on the effects of GLP-1 receptor agonists for the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2021;14(9):1081-1089. doi:10.1080/17512433.2021.1933433
12. Pedersen SD, Manjoo P, Wharton S. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy for Obesity Management. Available from: https://obesitycanada.ca/guidelines/pharmacotherapy.
13. Qiao L, Lu C, Zang T, Dzyuba B, Shao J. Maternal GLP-1 receptor activation inhibits fetal growth. Am J Physiol Endocrinol Metab. 2024;326(3):E268-E276. doi:10.1152/ajpendo.00361.2023
14. Younes ST, Maeda KJ, Sasser J, Ryan MJ. The glucagon-like peptide 1 receptor agonist liraglutide attenuates placental ischemia-induced hypertension. Am J Physiol Heart Circ Physiol. 2020;318(1):H72-H77. doi:10.1152/ajpheart.00486.2019
15. Graham DL, Madkour HS, Noble BL, Schatschneider C, Stanwood GD. Long-term functional alterations following prenatal GLP-1R activation. Neurotoxicol Teratol. 2021;87:106984. doi:10.1016/j.ntt.2021.106984
16. Price SAL, Nankervis A. Considering the use of GLP-1 receptor agonists in women with obesity prior to pregnancy: a narrative review. Arch Gynecol Obstet. 2025. doi:10.1007/s00404-024-07849-9
17. Ivanisevic M, Herman M, Horvaticek M, Vucic Lovrencic M, Delmis J. Pregnancy outcome and liraglutide levels in serum and umbilical vein blood of a woman with type 2 diabetes. A case report. Gynaecol Perinatol. 2018;27(3-4):70-72.
18. Cesta CE, Rotem R, Bateman BT, Chodick G, Cohen JM, Furu K, et al. Safety of GLP-1 receptor agonists and other second-line antidiabetics in early pregnancy. JAMA Intern Med. 2024;184(2):144-152. doi:10.1001/jamainternmed.2023.6663
19. Dao K, Shechtman S, Weber-Schoendorfer C, Diav-Citrin O, Murad RH, Berlin M, et al. Use of GLP1 receptor agonists in early pregnancy and reproductive safety: a multicentre, observational, prospective cohort study based on the databases of six Teratology Information Services. BMJ Open. 2024;14(4):e083550. doi:10.1136/bmjopen-2023-083550
20. Dumolt JH, Rosario FJ, Kramer AC, Horwitz S, Powell TL, Jansson T. Maternal glucagon-like peptide-1 is positively associated with fetal growth in pregnancies complicated with obesity. Clin Sci (Lond). 2023;137(8):663-678. doi:10.1042/CS20220890
21. Kubota S, Yabe D. Elevation of Fasting GLP-1 Levels in Child and Adolescent Obesity: Friend or Foe? J Clin Endocrinol Metab. 2021;106(9):e3778-e3780. doi:10.1210/clinem/dgab301
22. Chapter 1 Contraception in Canada. J Obstet Gynaecol Can. 2015;37(10 Suppl):S5-S12. doi:10.1016/S1701-2163(16)39370-7
23. Skelley JW, Swearengin K, York AL, Glover LH. The impact of tirzepatide and glucagon-like peptide 1 receptor agonists on oral hormonal contraception. J Am Pharm Assoc (2003). 2024;64(1):204-211 e204. doi:10.1016/j.japh.2023.10.037

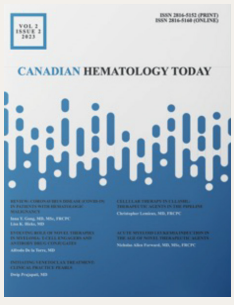
catalytic health
communications • advertising • strategy

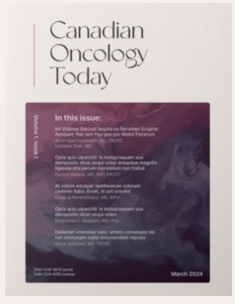
15 years

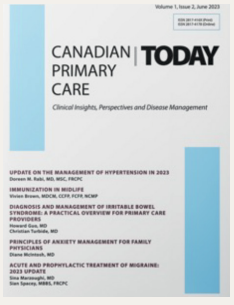
Medical minds gather here.

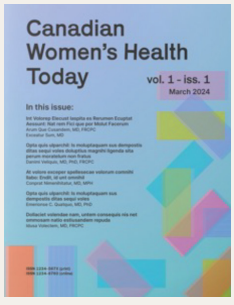
As the largest independent medical publisher in Canada, our peer-reviewed open access scientific journals are a practical resource for Canadian healthcare practitioners. We currently publish specialty journals in the areas of allergy & immunology, dermatology, hematology, ophthalmology, diabetes & endocrinology, gastroenterology, primary care, women's health, rheumatology, oncology, respirology and our press is constantly growing with new titles planned for 2025.











canadiandiabetesandendocrinologytoday.com

Canadian Diabetes & Endocrinology Today is published three times per year (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.

Register for future digital and print issues by visiting us at catalytichealth.com/cdet

Looking for more?
All back issues are available online at canadiandiabetesandendocrinologytoday.com