Canadian Diabetes & Endocrinology Today

Volume 3 – Issue 2

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

Summer 2025

Editorial Board

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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.

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* Comparative clinical significance is unknown.
† This landing page is open to the general public.
‡ Comparative clinical significance not established.
BMI, body mass index; CVD, cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

References: 1. Novo Nordisk Canada Inc. Data on file. 2025. **2.** Novo Nordisk Canada Inc. Wegovy® Product Monograph. April 8, 2025. **3.** IQVIA Inc. Xponent Data (MAR2024 to FEB2025). 2025. **4.** Novo Nordisk Canada Inc. Ozempic® Product Monograph. January 29, 2025. **5.** Novo Nordisk Canada Inc. RYBELSUS® Product Monograph. January 22, 2025. **6.** Novo Nordisk Canada Inc. Awiqli® Product Monograph. March 12, 2024.

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CA25SEMO00093E

doi.org/10.58931/cdet.2025.3240

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Autoantibodies in Type 1 Diabetes

Robyn Houlden, MD, FRCPC

Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by progressive destruction of pancreatic β cells. This process is mediated by both cellular (T lymphocyte) and humoral (autoantibody) immune responses. Although T cells play a central pathogenic role, autoantibodies are the earliest detectable markers of β cell autoimmunity and are instrumental in diagnosing and predicting disease progression.[1] Although T1D develops on a background of genetic risk, most individuals with genetic risk never develop type 1 diabetes. In contrast, virtually all individuals with 2 or more islet autoantibodies eventually develop type 1 diabetes.[2]

Major Islet Autoantibodies in T1D

Several well-characterized islet autoantibodies serve as key markers of T1D, and include[3]

- **Glutamic acid decarboxylase autoantibody (GAD 65 Ab, GADA)** – targets the GAD enzyme.
- **Insulin autoantibody (IAA)** – directed against insulin.
- **Insulinoma antigen-2 autoantibody (IA-2A) (also called islet cell autoantigen 512 [ICA512])** – directed against a tyrosine phosphatase-like protein.
- **Zinc transporter 8 autoantibody (ZnT8A)** – targets the ZnT8 protein on β cells.

Key features of these autoantibodies are summarized in **Table 1**. Measurement of all four autoantibodies is recommended with screening.[4] The prevalence of islet autoantibodies varies by ethnicity and region. For example, studies in India and China show lower frequencies of GADA of ~31 to 41%. ZnT8A and IA-2A frequencies are lower as well.[5] Specific HLA class II haplotypes influence susceptibility and prevalence of certain autoantibodies. For example, GADA is strongly associated with DR3-DQ2.5, and IAA and IA-2A are associated with DR4-DQ8.[6]

Risk Prediction and Disease Progression

The appearance of one or more islet autoantibodies typically precedes the clinical onset of T1D by months to years. The presence of multiple islet autoantibodies significantly increases the probability of progression. In a Diabetes TrialNet study of more than 2,300 older children and young adults (median age 16.2 years) who had a relative with T1D and also had multiple autoantibodies, 35% of individuals with normal glucose tolerance and 70% of those with abnormal glucose tolerance progressed to clinical T1D within five years, while others progressed over a longer time period.[7] A longitudinal cohort study, the Diabetes Autoimmunity Study in the Young (DAISY), followed 2,547 children with a high-risk HLA genotype (HLA-DR3/4) or a first-degree relative with T1D. Children with persistent IAA progressed more rapidly to clinical T1D: 100% progressed by 5.6 years, versus 63% in those with fluctuating IAA levels by 10 years.[8]

Clinical Applications of Islet Autoantibodies

In Latent Autoimmune Diabetes in Adults (LADA), autoantibodies can help distinguish from type 2 diabetes.[9] GADA, ICA, IA 2A, and ZnT8A may all be positive. GADA is especially prevalent in adult-onset autoimmune cases. However, it is important to recognize that approximately 5% of people with T1D are negative for the 4 major islet autoantibodies.[10] This is referred to as seronegative T1D, and may be caused by low autoantibody levels or novel antigens not covered by standard antibody panels.

Autoantibodies can also be used to stage individuals with T1D. A recent 2024 American Diabetes Association Consensus paper identified the following stages[11] **(Table 2)**:

- **At risk (pre-Stage 1):** Individuals have a single islet autoantibody or transient single autoantibody. They have normoglycemia and a normal A1C. They are asymptomatic.
- **Stage 1 diabetes (pre-clinical disease):** Individuals have ≥2 islet autoantibodies. They are asymptomatic and have normal glucose tolerance, but they have impaired C-peptide

Autoantibody	Approximate Prevalence at Diagnosis	Comments
GAD65 antibody (GADA)	~70–80%	Most common in adolescents and adults; less frequent in very young children. Strong association with slower progression.
Insulin autoantibody (IAA)	~40–60% overall; >70% in young children (<5 years)	Often the first autoantibody to appear in childhood. Frequency falls with increasing age at onset. It is present in 90% in children progressing to T1D before age 5 and drops to 40–50% in those older than 15. IAA must be measured within 2 weeks of beginning treatment with insulin. After that point, antibodies may be produced in response to exogenously administered insulin.
IA-2 antibody (IA-2A)	~50–70%	More frequent in children/teens; associated with rapid progression and higher risk of diabetic ketoacidosis (DKA).
Zinc transporter 8 antibody (ZnT8A)	~60–80%	Detected in both children and adults; adds diagnostic sensitivity, especially if GADA/IAA/IA-2A are absent.

Table 1. Major islet autoantibodies in T1D*; courtesy of Robyn Houlden, MD, FRCPC*

secretion compared with autoantibody-negative individuals. First-phase or early insulin secretion is impaired in response to intravenous or oral glucose administration; however, fasting insulin levels remain normal. This stage carries an approximate 70% risk of progression to Stage 3 T1D within 10 years and approaches a 100% risk over time.

- **Stage 2 diabetes (pre-clinical disease):** Individuals have ≥2 islet autoantibodies and dysglycemia or glucose intolerance. Individuals are asymptomatic. Impaired early phase insulin secretion results in increasing postprandial glucose values. Fasting glucose and A1C levels typically remain in the normal range.
- **Stage 3 diabetes (clinical disease):** Individuals have ≥1 islet autoantibody and meet diagnostic criteria for diabetes. Individuals are typically symptomatic. Most individuals continue to have significant insulin secretion, although the degree of preserved secretion varies. As a result, C-peptide is often not helpful at the time of diagnosis for distinguishing between T1D and T2D. Autoantibodies may disappear over time.[12]

Rationale for Screening for Diabetes-related Autoantibodies

Screening for islet autoantibodies, followed by appropriate metabolic monitoring, may reduce the likelihood of individuals presenting with severe hyperglycemia or diabetic ketoacidosis (DKA) with Stage 3 T1D. In high-income countries (North American, Western Europe, Australia), around 20 to 30% of children and adolescents with new onset of T1D present in DKA.[13] In adults, the rate is lower (typically 10 to 15%), since symptom recognition tends to be faster.[14] In low- and middle-income countries, rates can be much higher, often 40 to 80%, due to limited awareness and delayed access to care. Some sub-Saharan African studies report DKA in 70 to 80% of new diagnoses.[15] Several screening and monitoring programs have shown a significant decrease in the percentage of individuals presenting with DKA.[16]

Screening may also create an opportunity to provide early support and diabetes education allowing more time to accept a diagnosis of T1D.[17] Finally, screening and monitoring may facilitate access to disease-modifying therapy or clinical trials. For example, the anti-CD3 antibody teplizumab has been approved by Health Canada to delay progression from Stage 2 to Stage 3 T1D with a median delay of approximately 2 years.[18]

Whom to Screen

Two approaches to screening have been used in research and clinical settings.

Population-based screening initiatives such as the Fr1da study in Bavaria (Germany) and the Autoimmunity Screening for Kids (ASK) program in

Stage of TID	Islet Autoantibody Status	Glycemic Status
At risk (pre-stage T1D)	Single autoantibody or transient single autoantibody	Normoglycemia
Stage 1 T1D (presymptomatic)	≥2 autoantibodies	Normoglycemia
Stage 2 T1D (presymptomatic)	≥2 autoantibodies	Glucose intolerance or dysglycemia*
Stage 3 TID	≥1 autoantibody	Persistent hyperglycemia**

Table 2. Stages of T1D*; courtesy of Robyn Houlden, MD, FRCPC*

*2024 American Diabetes Association (ADA) Consensus Guidelines define as at least two of the following or meeting the same single criteria at two time points within 12 months: fasting plasma glucose 5.6–6.9 mmol/L; 120-min Oral Glucose Tolerance Test (OGTT) 7.8–11.0 mmol/L: OGTT values >11.1 mmol/L at 30, 60, and 90 min; A1C 5.7–6.4% or longitudinal > 10% increase in A1C from the first measurement with stage 2 T1D; capillary blood glucose (CGM) values >7.8 mmol/L for 10% of time over 10 days' continuous wear and confirmed by at least one other non-CGM glucose measurement test listed

** ADA Consensus Guidelines define as measured and confirmed by one or more of the following: one random venous glucose > 11.1 mmol/L with overt symptoms; 120-min OGTT >11.1 mmol/L and/or two random venous glucose >11.1 mmol/L and/or fasting plasma glucose >7 mmol/L and/or A1C >6.5%; CGM values >7.8 mmol/L for 20% of time over 10 days' continuous wear and confirmed by at least one other non-CGM glucose measurement test listed

Colorado, USA have shown the practical benefits of offering islet autoantibody testing to the general pediatric population. The Fr1da Study screened >90,000 children aged 2 to 5 years during routine pediatric visits.[19] The prevalence of multiple islet autoantibodies was ~0.3%. Children identified with presymptomatic T1D were enrolled in structured monitoring programs with regular glucose tolerance testing and education for the families. At clinical diagnosis, only ~5% of screened children presented with DKA compared with ~20 to 40% in unscreened children in the same region. They also had lower A1C and higher residual C-peptide, suggesting milder disease onset and better preserved β-cell function.

The ASK program targeted children aged 2 to 17 years, and offered islet autoantibody testing regardless of family history.[20] Around 1.7% of participants tested positive for ≥2 autoantibodies, similar to expected population prevalence. Families who receive positive results were offered close monitoring and education. ASK demonstrated high acceptability and demonstrated families valued early risk information. Children identified at risk who later developed Stage 3 T1D had substantially lower rates of DKA than those diagnosed without prior screening.

Family-based screening programs focus on first- and second-degree relatives of people with T1D through the age of 45 years. Antibody testing is most important during early childhood, as the rate of progression from multiple autoantibodies to clinical disease is more rapid in younger individuals. The most notable program is TrialNet Pathway to Prevention.[21] TrialNet has screened over 250,000 relatives worldwide, identifying many at presymptomatic stages. Relatives identified as autoantibody-positive are monitored regularly, significantly lowering the risk of DKA at diagnosis and allowing timely intervention. The 2025 ADA Standards of Care in Diabetes recommend that autoantibody-based screening for presymptomatic T1D should be offered to those with a family history of T1D or otherwise known elevated genetic risk.[22] In Canada, individuals with a relative with T1D can undergo autoantibody screening free of charge through Diabetes TrialNet (**https://www.trialnet.org/**) and Autoimmune Type 1 Diabetes Early Detection Program (**https://www.revvity.com/ca-en/category/autoimmune-type-1-diabetes-early-detection-program**).

Family-based programs maximize efficiency by focusing on high-risk groups, making them cost-effective and easier to integrate into existing healthcare systems. Population-based programs reach the majority of children who will eventually develop T1D, since ~85 to 90% of new diagnoses occur in those without a family history.[23] Although more resource-intensive, they are the only way to systematically identify this large group at risk. Both models have demonstrated that screening and follow-up substantially reduces the frequency and severity of DKA at onset, allow earlier initiation of insulin in a planned and less traumatic setting, and open the door to preventive therapies. **(Table 3)**

Monitoring of Islet Autoantibody Positive Individuals

The 2024 ADA Consensus Guidelines for monitoring islet autoantibody positive adults recommends the following management of single islet antibody positive adults[11]:

- Confirm persistent positivity with a second test
- Ensure other islet autoantibodies are negative.
- Annual metabolic monitoring may be considered if additional risk factors are present:
  - o First-degree relative with T1D
  - o Elevated genetic risk
  - o Dysglycemia (e.g., impaired fasting glucose or glucose tolerance)
  - o History of stress-induced hyperglycaemia
- If no additional risk factors, suggest monitoring every 3 years, similar to T2D at-risk adults.

The Consensus Guidelines recommend the following management of multiple autoantibody positive adults:

- Educate individuals on the importance of ongoing monitoring to prevent DKA.
- Provide written instructions with emergency contacts for symptoms of T1D or hyperglycemia.
- Confirm persistent multiple islet autoantibodies status with second test
- If confirmation is not possible, a single positive test for multiple islet autoantibodies is enough to initiate metabolic monitoring.
- If a previously multiple islet autoantibodies adult reverts to single or negative, continue monitoring.
- Provide self-monitoring of blood glucose tools for use during illness or symptoms.
- Monitor A1C annually. Adjust frequency based on age, autoantibody profile and glycemic trends

- If normoglycemia persists for 5+ years, monitoring every 2 years may be sufficient.

The ADA Consensus Guidelines provide detailed information on recommended monitoring for children and adolescents and readers are encouraged to refer to these when caring for this age group.[11]

Feature	Family-Based Screening (e.g., TrialNet)	Population-Based Screening (e.g., Fr1da, ASK)
Target group	First- and second-degree relatives of individuals with T1D	All children in a defined population, regardless of family history
Risk enrichment	~15-fold higher risk than general population	Includes majority of children who will develop T1D (85–90% of cases occur without family history)
Yield of multiple autoantibodies (≥2)	~3–5% of screened relatives	~0.3–0.5% of screened general children
Number needed to screen (NNS) to detect ≥2 IAb	Lower (more efficient due to enriched risk)	Higher (requires large-scale testing)
Major programs	TrialNet Pathway to Prevention (international, >250,000 relatives screened)	Fr1da (Germany) – >90,000 children screened; ASK (Colorado, USA) – 25,000+ screened and ongoing
Clinical outcomes at diagnosis	Lower diabetic ketoacidosis (DKA) rates compared to background population; diagnosis often anticipated	Dramatic reduction in DKA (e.g., 5% in Fr1da vs ~20–40% unscreened); lower A1C, higher C-peptide at onset
Access to monitoring and prevention	Structured follow-up; direct pipeline to prevention trials	Monitoring and education offered; enables access to prevention if therapy is available
Advantages	Cost-efficient, high-yield, lower resource burden; strong research infrastructure	Captures the majority of future T1D cases; population-wide health equity (doesn't miss those without family history)
Limitations	Misses ~85–90% of future T1D cases (no family history)	More resource-intensive; requires coordination with public health, schools, or primary care; cost-effectiveness still under study
Health system implications	Easier to implement in research or specialized settings; lower upfront costs	Potentially transformative for early diagnosis at the population level, but needs scalable infrastructure and funding

Table 3. Family-Based vs Population-Based Screening Programs in T1D*; courtesy of Robyn Houlden, MD, FRCPC*

Conclusion

Islet autoantibodies are important biomarkers used to identify individuals at risk of developing T1D. These autoantibodies target proteins found in the insulin-producing beta cells of the pancreas, signaling an autoimmune response. Screening for multiple islet autoantibodies, including GADA, IAA, IA-2, and ZnT8, can help detect early immune activity before clinical symptoms appear. The presence of two or more autoantibodies significantly increases the risk of progression to T1D. Early identification through autoantibody screening enables closer monitoring and reduces the risk of DKA and hyperglycemia with Stage 3 T1D. Screening may also create an opportunity to provide early support and diabetes education allowing more time to accept a diagnosis of T1D; and facilitate access to disease-modifying therapy or prevention trials. Family-based screening and population-based screening approaches have demonstrated clinical benefits. Guidelines are available to inform monitoring of single and multiple islet antibody positive individuals.

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Financial Disclosures

R.H.: Speakers Bureau/Honoraria: Abbott, Boehringer Ingelheim, CPD Network, Eli Lilly, Sanofi, Aventis **Consulting Fees:** Abbott, Eli Lilly

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Reference: Current Mounjaro Product Monograph. Eli Lilly Canada Inc.

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doi.org/10.58931/cdet.2025.3241

Current and Emerging Treatments For the Management of Hypoparathyroidism

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Abstract

Chronic hypoparathyroidism is a rare endocrine disorder marked by parathyroid hormone (PTH) deficiency, leading to hypocalcemia and its associated complications. Conventional therapy with oral calcium and active vitamin D fails to address the hormonal deficit and poses risks such as hypercalciuria and nephrocalcinosis. Recent advances in PTH replacement therapy have shifted the treatment paradigm. Palopegteriparatide, a long-acting prodrug of PTH (1–34), is now U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved, demonstrating effective calcium homeostasis, reduced reliance on conventional therapy, and potential renal benefits. Discontinuation of rhPTH (1–84) has accelerated interest in emerging alternatives such as eneboparatide, calcilytics (e.g., encaleret), MBX2109, and oral PTH1 receptor agonists. These novel therapies target PTH signalling through diverse mechanisms—offering injectable and oral options with improved safety, efficacy, and quality-of-life outcomes. This review synthesizes current evidence on approved and investigational treatments, underscoring their mechanisms, clinical impacts, and roles in personalized care for chronic hypoparathyroidism.

Introduction

Hypoparathyroidism is a rare endocrine disorder characterized by insufficient secretion of PTH, leading to hypocalcemia, hyperphosphatemia, and impaired calcium homeostasis. Conventional therapy with oral calcium salts and activated vitamin D does not address the underlying hormonal deficiency and is associated with complications such as hypercalciuria, nephrocalcinosis, and ectopic calcification. Studies have shown that patients receiving PTH replacement therapies, including PTH (1–34) and recombinant human (rh) PTH (1–84) have demonstrated improvements in biochemical control, urinary calcium excretion, bone turnover, and quality-of-life. However, PTH (1–34) is not approved for the indication of treating hypoparathyroidism and the discontinuation of rhPTH (1–84) manufacturing has created an urgent need for alternative PTH replacement therapies. Palopegteriparatide is a once daily PTH injectable that has received FDA and EMA approval for the treatment of hypoparathyroidism. Patients treated with palopegteriparatide have demonstrated eucalcaemia, decreased requirements for conventional therapy, and improvements in renal function. Other emerging therapies for hypoparathyroidism include eneboparatide, MBX 2109, oral PTH1 receptor agonists, and calcilytics. This paper reviews current evidence and evolving therapies for the treatment of chronic hypoparathyroidism, highlighting their mechanisms of action, clinical efficacy, and potential to address unmet therapeutic needs.

Conventional Treatment

Conventional treatment for hypoparathyroidism includes oral calcium salts and activated vitamin D to maintain serum calcium levels at or just below the lower limit of normal in nonpregnant individuals.[1] The aim is to alleviate hypocalcemia symptoms without overtreatment, as excess calcium and activated vitamin D can increase urinary calcium loss and raise phosphate levels, raising the risk of ectopic calcification.[1] Recommended calcium supplements include calcium carbonate (40% elemental calcium), which requires food for absorption, and calcium citrate (21% elemental calcium), which can be taken without meals.[2]

Activated forms of vitamin D, such as calcitriol or alfacalcidol, are used to enhance

calcium and phosphate absorption from the gastrointestinal tract.[1,2] Calcitriol is the more potent of the two, and both require close monitoring. Regular assessments of serum calcium, phosphate, urinary calcium, and 25-hydroxyvitamin D are essential to avoid complications such as hyperphosphatemia or hypercalciuria. The target 25-hydroxyvitamin D level is 75–125 nmol/L, with supplementation using ergocalciferol or cholecalciferol if needed.[1,2]

Magnesium levels should be normalized since hypomagnesemia as well as hypermagnesemia may cause hypoparathyroidism. Thiazide diuretics may reduce urinary calcium in select patient populations, though they should be avoided in those with autosomal dominant hypocalcemia types 1 and 2 (ADH1, ADH2), or adrenal insufficiency.[1,2] Patients initiated on thiazides need to be counselled on their associated increased risk of skin cancer.[1,2]

PTH replacement therapy offers an alternative to conventional therapy–its indications are listed in **Table 1**.

Intolerance to conventional therapy
Malabsorption issues impeding absorption of conventional therapy
Persistent electrolyte disturbances despite conventional therapy
Complications (e.g., nephrocalcinosis, renal impairment) to conventional therapy
Impaired quality-of-life on conventional therapy
Cognitive symptoms related to hypoparathyroidism

Table 1. Indications for Parathyroid Hormone Replacement Therapy in Hypoparathyroidism[2]*; courtesy of Sarah Khan, MD, FRCPC and Aliya Khan, MD, FRCPC, FACP, FACE, FASBMR*

PTH (1–34) and rhPTH(1–84)

PTH replacement was first explored in 1929 and has since evolved into a potential therapy for chronic hypoparathyroidism.[2] PTH (1–34) consists of 34-amino acids and is the biologically active peptide fragment of the full-length PTH (1–84) molecule. Both PTH (1–34) and rhPTH (1–84) have been studied as treatments for hypoparathyroidism.[2] PTH (1–34) normalizes serum calcium, lowers urinary calcium, and enhances phosphate excretion, with administration via infusion pump delivery offering more stable calcium levels and reduced dosing compared to injections. Currently, PTH (1–34) is used off-label and is not approved for the indication of hypoparathyroidism, despite its demonstrated effectiveness. rhPTH (1–84), with a 3-hour half-life, can be administered as a once daily injection.[2] The REPLACE study, a phase 3 trial, randomized patients with chronic hypoparathyroidism to receive rhPTH (1–84) or placebo for 24 weeks. The study showed that patients receiving rhPTH (1–84) exhibited reductions in calcium and calcitriol supplementation, improved serum calcium and phosphate balance, and enhanced quality-of-life.[2] Although the REPLACE study did not demonstrate a significant decline in renal calcium excretion among patients receiving rhPTH (1–84), a subsequent open-label study spanning over 8 years demonstrated reductions in urinary calcium excretion. Long-term studies showed increases in bone mineral density (BMD) at the lumbar spine and hip, with stable values at the femoral neck and decreased values at the one-third radial site, which were consistent with the known PTH effects to increase cortical porosity and endosteal resorption.[2] Despite its FDA approval, rhPTH (1–84) was globally discontinued in 2024 due to manufacturing issues.

Palopegteriparatide (TransCon PTH, Yorvipath)

Palopegteriparatide, also known as TransCon PTH, has received regulatory approval in both North America and Europe for treating chronic hypoparathyroidism.[2] It is a modified version of PTH (1–34) that is bound to a polyethylene glycol (PEG) molecule through a cleavable linker. This structural design prolongs its half-life to approximately 60 hours, allowing sustained PTH activity.[3] Once administered, the linker is cleaved at physiological pH and temperature conditions, releasing active PTH (1–34), while the PEG fragment is eliminated through the kidneys.[3]

Data from phase II and III studies has demonstrated that palopegteriparatide is effective in achieving normal calcium levels and in reducing both urinary calcium excretion and serum phosphate levels compared to placebo.[4-6] The phase III PaTHway trial enrolled 84 participants with chronic hypoparathyroidism who were on stable doses of conventional therapy. At week 26,

93% of individuals receiving palopegteriparatide achieved stable calcium levels without the need for conventional therapy.[6] Patients in the palopegteriparatide group also had significant improvements in quality-of-life as well as normalized urinary calcium.[6] Additionally, a post hoc analysis demonstrated that patients on palopegteriparatide for one year had an estimated glomerular filtration rate (eGFR) improvement of 9.3 mL/min/1.73 m^2.[2,7] While these results suggest the possibility of renal benefits, further studies are needed to confirm these outcomes.[7]

The 3-year results from the phase II PaTH Forward trial were recently published.[8] This trial began with a 4-week randomized double-blind placebo-controlled study followed by an ongoing 210-week open-label extension period.[8] During the initial 4-week double-blind phase, the primary end point was the percentage of participants who met all the following criteria: normal serum calcium levels, achieved independence from active vitamin D supplementation, required less than or equal to 1000 mg of oral calcium per day, and either normal urinary calcium excretion or a 50% decrease from baseline.[8] By week 162 of the trial, 91% of patients on palopegteriparatide achieved the above stated criteria. At week 62, patients on treatment maintained 24-hour urinary calcium excretion within the normal range. Palopegteriparatide treatment was associated with an initial rise in serum levels of bone turnover markers, with serum c-terminal telopeptide of type 1 collagen (CTX) levels peaking at week 12 and P1NP levels peaking at week 26.[8] These markers then declined and stabilized above baseline, establishing a new steady state that persisted through week 162. BMD T-scores remained within normal limits throughout the study period and stabilized after

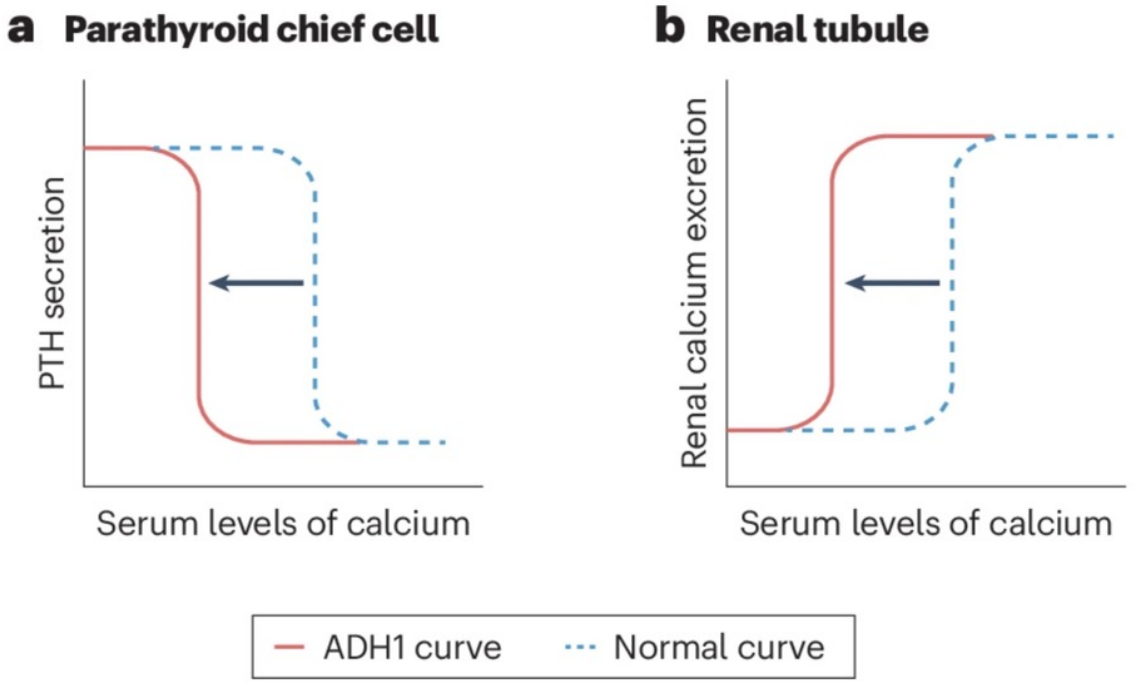

Figure 1. The Effect of ADH1 on PTH Secretion*; reproduced with permission from Khan et al.*[2]

The calcium–parathyroid hormone (PTH) secretion curve shows how PTH secretion changes as calcium levels in the blood vary. Normally, elevated calcium levels activate the calcium-sensing receptor (CaSR), leading to decreases in PTH secretion, and vice versa. In autosomal dominant hypocalcaemia type 1 (ADH1), activating mutations in the CaSR-encoding gene (CASR) leads to increased calcium sensitivity in CaSR. As a result, PTH secretion is suppressed even when calcium levels are within the normal range. This leads to a leftward shift in the serum calcium–PTH secretion curve. This means that lower concentrations of calcium are required to trigger a reduction in PTH secretion in patients with ADH1 compared with healthy individuals. In the kidney, the curve is also shifted to the left, as CaSR is more sensitive to the effects of serum concentrations of calcium, and urine calcium losses are increased compared with individuals without ADH1. Calcilytic agents work by normalizing CaSR sensitivity to calcium, leading to a shift of the curve toward normal. Through this mechanism, calcilytics increase serum PTH levels and decrease urinary calcium losses in patients with ADH1.

the initial 26 weeks of treatment. Z-scores, which were elevated at baseline due to chronic hypoparathyroidism, gradually trended toward values consistent with age- and sex-matched norms and remained above zero at week 162.[8]

Results from the phase 3 PaTHway trial up to week 52 have now been published.[9] The study assessed a multi-component efficacy endpoint, which measured the proportion of participants who maintained eucalcaemia while simultaneously achieving independence from calcium and active vitamin D supplementation. Among those receiving TransCon PTH, 81% met this composite endpoint, with 95% attaining independence from standard therapy.[9] At baseline, all participants exhibited elevated T-scores and Z-scores, indicating increased bone density secondary to hypoparathyroidism. In the palopegteriparatide group, BMD decreased relative to baseline over the initial 26 weeks but subsequently stabilized between weeks 26 and 52.[9] This early BMD decline paralleled increases in bone turnover markers. After 26 weeks, these markers gradually decreased toward normal reference values for sex and menopausal status, aligning with attenuated BMD losses through week 52.[9] These findings are consistent with observations reported at week 110 in the phase II PaTH Forward trial. Collectively, the 52-week data suggest a temporal progression toward a new skeletal equilibrium that more closely resembles age-appropriate bone turnover with ongoing palopegteriparatide therapy in patients with hypoparathyroidism.

Ongoing studies are evaluating the long-term efficacy and skeletal effects of palopegteriparatide. The recommended initial dose of palopegteriparatide is 18 mcg once daily, with subsequent uptitration to achieve eucalcaemia, accompanied by a gradual reduction in conventional therapy. Phase III clinical trials investigating the long-term impact of palopegteriparatide are ongoing.

Emerging Therapies

i) Long-acting PTH/ PTHrP (1–36) Analogue (Eneboparatide, AZP-3601)

Eneboparatide is a synthetic novel 36-amino acid analogue of PTH/PTHrP, designed to bind with a strong affinity to the PTH1 receptor in its R0 conformation. This receptor interaction enables multiple cycles of G-protein mediated signalling and a sustained pharmacodynamic profile despite a short pharmacokinetic profile.[2] Administered as a once-daily injection, eneboparatide has demonstrated in animal studies the ability to maintain prolonged G-protein mediated signalling and improved serum calcium levels over a 24 hour period despite its short half-life of less than 1 hour.[10,11] The phase II open-label study of eneboparatide enrolled 28 patients who were divided into two cohorts: Cohort 1 (n=12) received a starting dose of 20 µg/day, titrated up to 60 µg/day and Cohort 2 (n=16) received a starting dose of 10 µg/day, titrated up to 80 µg/day.[12] Both cohorts received eneboparatide for 3 months, during which conventional therapy was gradually reduced as eneboparatide doses were increased. After 3 months of treatment, 88% of patients achieved independence from conventional therapy while maintaining albumin-adjusted serum calcium within the target range. Patients on treatment experienced a significant reduction in urinary calcium, a benefit that was maintained during the extension phase. Additionally, a mean increase in eGFR of 6 mL/min/1.73 m^2 from baseline was noted.[12] Bone health indicators, including mean BMD, T-scores, Z-scores, and trabecular bone scores remained stable during the treatment period. No serious adverse effects were reported.[12] Eneboparatide is currently in the phase III clinical trial stage, with its optimal dose yet to be determined.

ii) Calcilytics

Individuals with autosomal hypocalcemia type 1 have a gain of function mutation in the calcium-sensing receptor gene (CaSR) which leads to an increase in the sensitivity of CaSR to serum calcium in both the parathyroid gland and kidneys.[2] The increased sensitivity in the parathyroid gland leads to decreased PTH secretion at low-normal serum calcium concentrations leading to hypocalcemia. At the renal level, increased sensitivity of the CaSR leads to increased renal calcium excretion.[2] Calcilytics, which are CaSR antagonists, work by decreasing the receptor's sensitivity to serum calcium. They restore the CaSR's sensitivity to calcium, thereby helping to normalize PTH synthesis and secretion, as well as urine calcium excretion in ADH.[2] **See Figure 1 for further details on the effect of ADH1 on PTH secretion.**

A phase IIb open-label trial evaluated the efficacy of encaleret, an oral calcilytic agent, in 13 individuals diagnosed with ADH1.[13] Encaleret was administered twice daily, with the dosage

adjusted to maintain albumin-corrected serum calcium within the normal range.[13] Over the 24-week treatment period, participants achieved normalized serum calcium levels, reduced 24-hour urinary calcium excretion, and exhibited increases in circulating PTH and 1,25-dihydroxyvitamin D levels[13]. Concurrently, serum phosphate levels declined relative to baseline.[13] As expected with elevated PTH, bone turnover markers showed an upward trend. While changes in BMD over this short duration were minimal, extended follow-up is necessary to determine encaleret's long-term skeletal impact. The eGFR remained stable and within normal limits, and there were no observed changes in the frequency or severity of nephrocalcinosis or nephrolithiasis on renal ultrasound.[13] Importantly, no serious adverse events were reported.[13] Encaleret is currently undergoing evaluation in a phase III clinical trial for the treatment of ADH1.

NPSP795, also referred to as SHP635, is a calcilytic compound assessed in a small proof-of-concept study involving five participants. Treatment with NPSP795 led to elevated PTH levels while maintaining stable ionized calcium concentrations, even as conventional therapy was gradually withdrawn, relative to baseline measurements prior to initiation. To mitigate the risk of fasting-related hypocalcemia, all participants received bedtime calcium supplementation throughout the study. The physiological response to NPSP795 was found to be dose-dependent.[14]

Quinazolinone-based calcilytics (ATF936 and AXT914) have been investigated in animal studies for the treatment of ADH1.[15] They offer an alternative to amino alcohol based calcilytics (i.e., encaleret, NPSP795) which are not effective for all ADH-1 causing mutations. In vitro and in vivo experiments using murine models demonstrated that ATF936 and AXT914 bind to the CaSR transmembrane domain, overlapping with the binding site used by amino alcohol calcilytics. In vivo, AXT914 significantly increased plasma PTH and albumin-adjusted calcium levels. No adverse effects or changes in phosphate, magnesium, or renal function were observed.[15] These findings support AXT914 as a promising targeted therapy for ADH1.

iii) MBX 2109: PTH Peptide Prodrug

MBX 2109 is a novel PTH peptide long-acting prodrug designed for once-weekly dosing due to its extended half-life of 184–213 hours.[16] Structurally, it is a 35-amino acid peptide incorporating the first 32 amino acids of human PTH with three modifications: two amino acids (Sar0, D-Lys–1) at the N-terminus and one (Lys33) at the C-terminus.[16] Both termini are bound to fatty acids that inactivate the molecule and promote albumin binding. Under physiological conditions, the fatty acid–linked N-terminal dipeptide is gradually cleaved, converting the prodrug into active PTH (1–32).[16]

A phase 1 randomized, double-blind, placebo-controlled study assessed the safety and tolerability of MBX 2109 in 40 healthy adults aged 21–60.[16] Participants discontinued calcium and vitamin D supplementation and received either MBX 2109 or placebo once weekly for 4 weeks. Treatment-emergent adverse events (TEAEs) were reported in 50–88% of MBX 2109 recipients versus 25% in the placebo group, with injection site reactions being the most common. No serious TEAEs occurred.[16] MBX 2109 produced dose-dependent increases in serum calcium and CTx levels, while reducing endogenous PTH. P1NP and bone-specific alkaline phosphatase (BSAP) initially declined but returned to baseline by week 4.[16] However, the study's limitations include a small sample size of healthy participants, necessitating further trials in hypoparathyroid populations.[16]

iv) Oral PTH-1 Receptor Agonist

Oral small molecule therapies may offer an alternative to both conventional treatments and injectable PTH replacement.[17] Activation of the PTH1 receptor (PTH1R) promotes calcium reabsorption and phosphate excretion from the kidneys and stimulates bone turnover by mobilizing calcium from the skeleton. SP-1462 is a selective oral PTH1R agonist that activates these pathways.[17] In vitro studies using human renal proximal epithelial cells and osteoblast-like cells (Saos-2) showed that SP-1462, similar to PTH, modulates gene expression related to transport, immunity, matrix remodelling, Wnt signalling, and bone metabolism.[17] In a rat model of surgical thyroparathyroidectomy, a single dose of SP-1805 (a related compound) increased serum calcium in a dose-dependent manner, with effects comparable to injectable PTH.[17] These findings suggest that oral PTH1R agonists can mimic the biological actions of PTH and may serve as a non-injectable option for hypoparathyroidism.[17] SP-1462 has now progressed to phase 1 clinical trials in healthy volunteers in Australia.

Conclusion

Management of chronic hypoparathyroidism is advancing beyond conventional therapies due to their inability to correct the underlying PTH deficiency and their association with long-term complications such as hypercalciuria and nephrocalcinosis. Palopegteriparatide, now approved by both the FDA and EMA for the indication of treating hypoparathyroidism, offers a long-acting, physiologic PTH replacement. It has demonstrated efficacy in normalizing calcium levels, improving renal outcomes, and reducing treatment burden. Eneboparatide is showing promising results as an emerging treatment for hypoparathyroidism and is currently in phase 3 clinical trials. Calcilytics, particularly encaleret, are being actively investigated as treatment options for ADH1, with encaleret having advanced to the phase 3 clinical trial stage. MBX2109 provides a once-weekly alternative for PTH replacement injectables, while oral PTH receptor agonists support the development of oral replacement strategies. As long-term data mature, these therapies may support more personalized, effective, and safer management strategies, ultimately improving outcomes and quality-of-life for individuals living with hypoparathyroidism.

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Financial Disclosures

S.K.: Honoraria/Advisory board: Amgen Pharmaceuticals, Sandoz Pharmaceuticals;
Co-investigator for trials funded by: Calcilytix, Ultragenyx and Ascendis.
A.K.: Research funding: Ascendis, Amolyt, Takeda, Chugai

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doi.org/10.58931/cdet.2025.3242

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Vaccinating Your Adult Diabetic Patient: What Vaccines Would You Recommend?

Wayne Ghesquiere, MD, FRCPC

Introduction

Adults with diabetes (type 1 or type 2) are at substantially higher risk of infections and complications from vaccine-preventable diseases. As a result, persons with diabetes experience higher rates of serious illnesses such as influenza, pneumonia, and other infections. Epidemiological studies show that during flu epidemics, persons with diabetes are hospitalized at much higher rates and are more likely to suffer serious complications (e.g., myocardial infarction, heart failure, stroke) than their non-diabetic peers. Globally, diabetes is one of the most common comorbidities among patients with severe COVID-19. In short, diabetes—especially when poorly controlled or long-standing—is a risk factor for viral, bacterial, and fungal infections. People with diabetes are more likely to be hospitalized or die from illnesses such as influenza, pneumonia, and COVID-19. Clinicians should understand that diabetes itself impairs immunity, making timely immunization critical. Notably, the Canadian Immunization Guide confirms that there is no evidence suggesting that vaccines adversely affect blood glucose control.

General Immunization Recommendations for Diabetes

Canadian guidelines emphasize that patients with diabetes should receive all age-appropriate routine immunizations, along with any additional vaccines indicated for chronic disease. Both the Canadian Immunization Guide and Diabetes Canada advise that “routine immunization, including annual influenza vaccine, is important for persons with endocrine (e.g., diabetes) and other metabolic disorders.” In other words, adults with diabetes require the same vaccines as other healthy adults (e.g., childhood series, tetanus/diphtheria/pertussis, measles, mumps, and rubella (MMR), varicella, human papillomavirus (HPV), hepatitis A and B when indicated), with an extra focus on vaccines that prevent against respiratory and invasive infections. In general, persons with diabetes may have a reduced response

to vaccines, making vaccination early in the disease course, ideally before complications or immunosuppression develop especially important. In Canada, the National Advisory Committee on Immunization (NACI) considers people with diabetes "at increased risk of complications" and recommends that they should be immunized according to both standard and high-risk schedules. Diabetes Canada guidelines likewise advise annual flu and pneumococcal vaccination for all adult diabetics.

Key point: At every diabetes-related visit, clinicians must review immunization status, ensuring both routine vaccines (MMR, varicella, tetanus, diphtheria, and acellular pertussis [Tdap], HPV, among others), as well as disease-specific vaccines are up-to-date, (see below). A recent Canadian study revealed that although most adults think they are fully immunized, fewer than 10% have received all recommended adult vaccines. Given this gap, proactive vaccine review is strongly recommended.

Influenza (Flu) Vaccination

Recommendation: All diabetic adults should receive an annual influenza vaccine before each flu season. Influenza causes more severe disease in those with diabetes. Canadian data show that those with diabetes have markedly higher rates of hospitalization for influenza/pneumonia and related cardiac events than those without diabetes. Diabetic patients hospitalized with flu have worse outcomes, and flu vaccination reduces these risks dramatically. For example, Diabetes Canada notes that flu vaccinations can reduce hospitalizations by ~40% in high-risk populations. Meta-analyses involving mixed-age cohorts (including persons with diabetes) confirm that vaccination lowers influenza-related mortality and hospitalization in adults.

The Canadian Immunization Guide explicitly lists diabetes among the conditions warranting annual flu vaccine NACI recommends the inactivated flu vaccine for all individuals aged ≥6 months, with particular emphasis on those with chronic illnesses (including diabetes) or those aged ≥60 years. In Canada, most immunization programs offer quadrivalent inactivated flu vaccines free to people with diabetes each fall. There are no diabetes-specific contraindications, apart from the usual precautions (e.g., anaphylaxis to vaccine components). Flu vaccines are safe for persons with diabetes and do not destabilize blood glucose levels. (For patients with severe egg allergies, egg-free formulations are available).

Clinical tip: Administer the flu vaccine early (e.g., October) to allow immunity before peak flu activity. When possible, consider co-administering it with other indicated vaccines during the same visit. NACI notes that COVID-19 and influenza vaccines may be given concurrently with no loss of efficacy.

Pneumococcal Vaccination

Pneumococcal disease risk: Public health guidance highlights that people with chronic illnesses (e.g., diabetes) are at a significantly increased risk for invasive pneumococcal infections. Persons with diabetes are hospitalized for pneumonia at significantly higher rates than those without diabetes, making immunization against *Streptococcus pneumoniae* essential. Pneumococcal vaccination has been shown to dramatically reduce severe outcomes; prior vaccination in adults is linked to lower mortality and fewer complications in cases of community-acquired pneumonia. Diabetes Canada guidelines state that persons with diabetes are "encouraged" to receive pneumococcal vaccination, noting that their risk profile is similar to other high-risk chronic diseases.

Recommendations in Canada: NACI's recent guidance (2024) explicitly includes diabetes as a chronic condition warranting pneumococcal conjugate vaccination (PCV). For example, one NACI statement lists "diabetes mellitus, particularly in those over 50 years" as a high-risk group that should receive high-valency PCV. Current Canadian practice generally involves:

- PCV followed by PPSV23: Adults with diabetes and other chronic conditions are recommended to receive one dose of a pneumococcal conjugate vaccine, either (PCV15 or PCV20), followed by one dose of the 23-valent polysaccharide vaccine (PPSV23) at least 8 weeks later. For example, a healthy 60-year-old with diabetes would receive one dose of PCV15 (Vaxneuvance) or PCV20 (Prevnar 20), followed by PPSV23 after at least 8 weeks. These higher-valency conjugate vaccines are now preferred because of their broader strain coverage and ability to induce immunologic memory. If PCV13 was previously administered,

updated guidance recommends giving PCV15/20 after one year.)

- Revaccination: Adults with diabetes who previously received PPSV23 before age 65 should receive one booster dose of PPSV23 at age 65 or older, provided that at least 5 years have passed since the previous dose. Those aged ≥65 years with diabetes are also candidates for PCV (either PCV15/20 alone or followed by PPSV23) if they have not previously received a conjugate vaccine. In short, diabetic adults aged 19–64 years receive at least one PPSV23, with a second dose at age ≥65. Diabetic adults aged ≥65 should receive a dose of PCV (now PCV15/20 or the new Pneu-C-21) in addition to PPSV23 for optimal protection.
- New conjugate vaccines: Recent NACI statements (2023–2024) incorporate the latest vaccines in Canada. Both 15-valent and 20-valent PCVs (Vaxneuvance, Prevnar-20) are now authorized, and a 21-valent PCV (Pneu-C-21) was approved in late 2024. NACI recommends these higher-valency PCVs for high-risk adults, including diabetic adults. For example, an adult diabetic who is recommended for pneumococcal vaccine should first be offered Pneu-C-21 (or PCV20/15 if Pneu-C-21 is not available), followed by PPSV23. These newer vaccines extend protection against more serotypes and may become the standard of care for adults with diabetes in provincial programs.

Key point: In practice, clinicians should ensure that all diabetic patients have received at least one pneumococcal vaccine during adulthood. If a patient has missed this, the immunization should be scheduled promptly. A helpful approach is to administer PCV15 or PCV20 first (as they provide broader coverage), followed later by PPSV23. This strategy has been shown in other immunocompromised adult populations to improve immune response

COVID-19 Vaccination

Adults with diabetes were prioritized for COVID-19 vaccination early in the pandemic because of their heightened risk of severe illness. The Public Health Agency of Canada (via NACI) lists “diabetes mellitus and other metabolic diseases” as underlying conditions that place people in a high-risk category for severe outcomes from COVID-19. Data consistently show that people living with diabetes, especially if aged ≥50 or with complications, are more likely to be hospitalized or die from COVID-19.

Recommendations: All patients with diabetes should receive the full COVID-19 vaccine series and stay up-to-date with booster doses, similar to the general population. NACI strongly recommends mRNA-based primary series and booster doses for everyone aged ≥6 months, with added emphasis on those with chronic conditions including diabetes. In fact, recent Canadian guidance advises that people at higher risk (adults aged 65 and older, and those with chronic illness) receive an updated COVID-19 vaccine each fall. The updated fall-2024 vaccines target the latest Omicron subvariants and are formulated as bivalent or monovalent mRNA vaccines. Diabetic patients, similar to others ≥65 or with comorbidities, can receive any authorized formulation (Pfizer or Moderna) and should follow NACI’s timing recommendations, generally one year after last dose or infection or fall booster.

- Concurrent administration: COVID-19 vaccines can be administered at the same time as other adult vaccines (e.g., flu) for added convenience.
- Safety: As with other vaccines, COVID-19 vaccines do not affect blood glucose control and have been shown to reduce severe outcomes in people with diabetes.

Herpes Zoster (Shingles) Vaccine

Varicella-zoster reactivation (shingles) is more common and often more severe in individuals with impaired immunity. One in three adults will develop shingles during their lifetime. While advancing age is the main risk factor (with two-thirds of cases occurring in those aged ≥50), diabetes also plays a contributing role. Evidence shows that diabetes is frequently accompanied by diminished cell-mediated immunity, and diabetic patients exhibit lower varicella zoster virus-specific T-cell responses than non-diabetic individuals. Some studies have also reported an association between diabetes and increased herpes zoster incidence.

Recommendations: All diabetic adults aged 50 and older should receive the recombinant zoster vaccine (RZV, Shingrix) as per NACI guidelines. The Canadian Immunization Guide explicitly recommends two doses of RZV, administered 2–6 months apart for everyone aged ≥50. Even patients who have previously had shingles or received the older live zoster

vaccine are advised to receive RZV once. Because immunity may wane more quickly for adults with diabetes, completing the series is important. Some provinces publicly fund RZV for those in their 60s, while others provide coverage for adults aged 50 and older with diabetes via private insurance or out-of-pocket payment. NACI now strongly recommends that individuals aged 18 and older who are or will become immunocompromised receive two doses of RZV to prevent herpes zoster and its associated complications.

Key Point: Diabetic patients should be counselled on shingles vaccination as they approach age 50. It markedly reduces the risk and severity of shingles and postherpetic neuralgia, conditions which can otherwise be quite debilitating in older adults. For patients with diabetes aged 18–49, the shingles vaccine may be considered based on shared clinical decision-making.

Respiratory Syncytial Virus Vaccine

Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infections in older adults and those with chronic illnesses. In 2023, Canada approved its first RSV vaccines for adults

Practical Recommendations for Clinicians

- Review immunizations at each visit. Use checklists or electronic reminders to ensure each diabetic adult has received the recommended vaccines for their age and risk group. Verify that flu vaccines are administered annually, and pneumococcal vaccines are scheduled appropriately. A patient-held vaccine card or provincial immunization registry can support accurate tracking and documentation.
- Educate on risks and benefits. Emphasize that vaccines are both safe and crucial. Dispel myths by noting, for example, that flu and COVID-19 vaccines cannot worsen diabetes and in fact are shown to prevent hospitalizations. Highlight that <10% of adults are fully up-to-date with all recommended vaccines, making catch-up immunization a common part of care.
- Bundle vaccinations. Whenever possible, administer multiple vaccines during the same visit to improve coverage and convenience (e.g., pairing flu and COVID-19 vaccines, or flu and pneumococcal vaccines during the appropriate season). NACI affirms that co-administration of adult vaccines is acceptable.
- Monitor and follow-up. For multi-dose vaccines (COVID-19, RZV, hepatitis B), ensure patients complete the full series. Set reminders for follow-up doses (e.g., the second RZV dose should be administered 2–6 months after the first).
- Leverage primary care/pharmacy. Many patients with diabetes visit pharmacies regularly for insulin or supplies, making pharmacists well-positioned to check immunization status and administer vaccines. When available, use community programs (e.g., “Vaccination Clinics for Adults with Diabetes”).
- Address barriers. Some patients may feel hesitant about vaccines due to fear of needles or a belief that they are not at risk. Use concrete evidence (e.g., “Your risk of pneumonia is as high as someone with COPD if you have diabetes”) to motivate them. Also address financial concerns by noting that most provinces cover flu/pneumococcal vaccines for high-risk adults, and many provide coverage for shingles and COVID-19 boosters.
- Coordinate with specialists. Immunization should be reinforced by all members of the care team, including endocrinologists, diabetes educators, and primary care providers. For hospitalized patients with diabetes, an inpatient vaccine program can capture missed opportunities.

In summary, vaccination is a vital part of diabetes care in Canada. It reduces the risk of serious morbidity and mortality from infections to which persons with diabetes are particularly vulnerable. Both Diabetes Canada and NACI stress that persons with diabetes should be fully immunized according to the general schedules and receive the additional recommended vaccines shown below. By following current Canadian guidelines and evidence-based practices, clinicians can greatly improve outcomes for their diabetic patients by preventing vaccine-preventable diseases.

aged 60 and older. NACI now regards diabetes as a "clinically significant chronic condition" warranting RSV immunization. The vaccines (Arexvy®, Abrysvo®) are single-dose regimens that have shown high efficacy (82–95% in clinical trials) in preventing RSV-related pneumonia and bronchiolitis in older adults.

Recommendation: All diabetic adults aged 60 and older should be offered the RSV vaccine, ideally before the RSV season in the fall. This is especially important for those with diabetes who have lung or heart disease, though NACI lists diabetes itself as an indication for immunization. Given that RSV may exacerbate chronic conditions such as chronic obstructive pulmonary disease (COPD) and diabetes, vaccination can help reduce hospitalizations in this vulnerable group. At present, there is no specific recommendation for adults with diabetes under 60 who do not have other risk factors.

Other Routine Vaccines

In addition to the above, people living with diabetes should not neglect standard adult vaccines. Key points include:

- Tetanus and Diphtheria (Td)/Tdap: Ensure Td boosters are administered every 10 years. In particular, adults aged 19 and older should receive a one-time dose of Tdap to provide protection against pertussis, followed by Td boosters every decade. (While a single dose of Tdap is also recommended during each pregnancy, this falls outside the scope of routine adult diabetes care).
- MMR and Varicella: Adults with diabetes who have never had chickenpox or MMR infection, or did not receive the childhood vaccination series, should be tested for immunity and immunized if needed. These are live vaccines typically administered in childhood, but catch-up vaccination in adulthood is safe for those who are not immune. (Live vaccines should only be avoided in individuals with significant immunosuppression).
- Hepatitis. Hepatitis A: Not routinely indicated for individuals with diabetes unless there are additional risk factors (e.g., travel to endemic regions, liver disease, being a man who has sex with men, injection drug use). Hepatitis B: Serologic testing is recommended. If a patient's Hepatitis B surface antibody level is negative or below the cutoff for immunity, hepatitis B vaccination is advised.
- HPV: The HPV vaccine is recommended for all individuals with diabetes up to age 26 who have not completed the vaccine series. For adults aged 27–45 with diabetes, vaccination may be considered based on shared clinical decision-making, particularly if they are at ongoing risk

Recommended Vaccines for Adults with Diabetes: (according to NACI/Diabetes Canada)
• Annual Influenza (inactivated): annually each fall.
• COVID-19 (mRNA): full series plus boosters (with emphasis on receiving the updated fall booster).
• Pneumococcal: one dose PCV15 or PCV20 followed by PPSV23 at least 8 weeks later. Revaccinate with PPSV23 at age ≥65 if indicated.
• Shingles (RZV): two doses 2–6 months apart for adults aged ≥50.
• Tdap/Td: one dose of Tdap after age 19 (if not administered in adulthood), then Td booster every 10 years thereafter.
• RSV: one dose for all adults aged 60 and over (diabetes is an indication).
• Other vaccines as needed: MMR, varicella, hepatitis A & B, HPV, and others per routine adult immunization guidelines.

Sources: Canadian Immunization Guide (NACI) chapters and updates; Diabetes Canada guidelines; peer-reviewed studies on infection risk in diabetes; and patient-focused resources summarizing Canadian recommendations. The evidence is clear that staying up-to-date on these vaccines is a key preventive strategy in diabetes management.

for new HPV exposure. Diabetes itself is not a contraindication to HPV vaccination, and immunogenicity studies show that individuals with diabetes mount a strong immune response. Completing the full series—two doses if started before age 15, or three doses if started at age 15 or older—is essential for long-term protection.

- Meningococcal: Routine meningococcal vaccination is not required for adults with diabetes unless they have asplenia or risks associated with travel/study.
- Travel Vaccines: Diabetic patients planning travel should be advised to visit a travel and immunization clinic. Vaccines (e.g., yellow fever, typhoid, among others), may be recommended. It is important to note that immune responses to some vaccines may be slightly reduced in individuals with diabetes.

Case Presentation

A 45-year-old male patient with insulin dependent diabetes presents to you seeking advice on improving his blood glucose control. He expresses concern about his deteriorating overall health. He reports that he has likely not received any vaccinations since childhood. Question: Which vaccines would you recommend for this patient?

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Financial Disclosures

W.G.: None declared.

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doi.org/10.58931/cdet.2025.3243

Thyroid Nodules: Reducing Overdiagnosis and Investigations

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Introduction

Thyroid nodules (TN) are incredibly common, with approximately 5% of the population presenting with palpable TN.[1] However, the widespread utilization of sensitive imaging techniques over the past few decades has led to a rapid increase in their prevalence.[2] Notwithstanding the clinically palpable TN, the rate of incidental nodules picked up on imaging studies varies remarkably with the underlying imaging modality. For instance, the prevalence of TNs on computed tomography (CT) scans of the neck is reported to be 16.5%,[3] FDG-PET to be 2%[1] and on neck ultrasounds (US) well over 50%.[3] The prevalence of TN is higher in females and increases with age, and while there has been little change in the overall reported incidence of palpable TNs, the rising prevalence can be almost exclusively attributed to the expanded use of imaging, particularly the widespread availability of sensitive US. It is estimated that over 60% of the population may have at least one TN.[1]

The Dark Side of Enhanced Diagnosis

Despite the overall low risk of malignancy in most TN thyroid nodules (~5%),[4] it is the exclusion of cancer that remains the over-riding concern for both patients and care providers. This strategy has led to the inevitable cascade of further investigations and the resulting enhanced case finding of subclinical thyroid malignancies.

Such an approach can have a lasting negative impact on patients as they undergo workup. In a study of 2,834 patients undergoing thyroid US, those diagnosed with TN experienced psychological distress and sleep disturbances compared with those without nodules.[5] Their distress and sleep quality further worsened after undergoing fine needle aspirate biopsy. In a qualitative study interviewing patients undergoing surgery for either confirmed thyroid cancer or indeterminate results, both groups expressed similar anxiety and a sense of urgency to have surgery to "get it out".[6] Even with indeterminate results, patients experience fear, worry, and a sense of major disruption to their lives. Regardless of whether the final pathology is malignant or benign, patients undergoing total thyroidectomy develop worsening fatigue post-operatively, with an odds ratio of 10.4 for developing asthenia (chronic fatigue syndrome) compared with those who undergo thyroid lobectomy.[7] These findings underscore the importance of careful consideration and patient-centred discussions when deciding on treatment for TN.

Thyroid Cancer in Thyroid Nodules – Putting Things in Perspective

The incidence of thyroid cancer has mirrored the rising incidence of TNs in developed countries. A Canadian study[8] reported a 5-to 6-fold increase in thyroid cancer diagnoses over the past four decades despite no change in the overall mortality. A recent study from Korea also showed a 15-fold increase in detection of thyroid cancer in the population from 1993 to 2011, which was directly attributable to increased use of screening US in asymptomatic patients,[9] while mortality rates remained stable. Another nationwide Korean study[10] attributed over 97% of the increase in incidence of thyroid cancer cases from 1999 to 2008 to the increased detection of small thyroid cancers with a 100% 5-year survival rate. Thyroid cancers detected through over diagnosis are estimated to account for 70–80% of cases in women and 45% of cases in men in many developed countries.[9] Furthermore, subclinical thyroid cancer is found in 6–35% of autopsies, with a stable prevalence across the age groups, further highlighting that not all thyroid cancers that are treated impact morbidity or mortality.[11] In fact, recent Canadian guidelines provide a robust framework for otherwise low recurrence risk thyroid cancer, indicating that certain patients, may only need active surveillance as the risk of

mortality and recurrence is very low.[12] Overall, the available evidence supports the need for de-emphasizing aggressive management of these small incidental cancers. Future studies should explore strategies to mitigate the fear of underdiagnosis among both patients and clinicians.

Tackling Inappropriate Thyroid Imaging

As discussed in the previous section, it is evident that the imaging studies such as sensitive US, account for the rising incidence of benign and malignant TNs. When adequately used, thyroid US is an excellent imaging modality to assess the anatomy of the thyroid gland; however there is consistent evidence from the literature that up to one-third of these scans do not have a sound basis for the request and include vague indications such as choking sensation or swallowing difficulties.[13] Indeed, a previous study conducted at our own centre reported that approximately 19% of scans were performed with no clear indication.[14] Furthermore, rates of US requests have continued to increase annually by as much as 20% with no clear strategy to minimize inappropriate thyroid US requests.[13]

For incidentally detected TN noted on CT or MRI, the American College of Radiology (ACR) recommends further clarification with thyroid US only for nodules that are >1.5 cm in size in patients >35 years and nodules that are >1 cm in those <35 years.[15] The risk of malignancy in nodules smaller than 1 cm identified on CT scans is very low, estimated at 0.1% (confidence interval [CI] 0–0.8) compared to 11.7% (CI 3.9–19.4) for nodules over 1 cm, and 24.9% (CI 0–52.7) for those exceeding 1.5 cm.[3] Despite this, guidelines[16,17] suggest performing US to further characterize any nodule detected on other imaging, regardless of size. Given that over 30% of thyroid US are requested following incidental findings on other imaging studies,[18] having clearer guidance and unified cutoffs for these thyroid incidentalomas may assist in decreasing over-investigation of TN.

While strategies to curb unnecessary thyroid US may vary by region, a tantalizing option is to enhance the integration of artificial intelligence (AI) in vetting US requests. A recent study reported that an AI based algorithm could evaluate the appropriateness for thyroid US referrals with a high level of accuracy.[19] To date, no published studies have evaluated effective interventions to address this important issue. Though restricting access to neck US is neither feasible nor advisable, regional audits on the inappropriate US requests could help identify problem areas and support developing tailored strategies to be put in place.

Reducing Thyroid Nodule Related Investigations

Once a functioning nodule has been excluded, further TN investigations are guided by sonographic features. The introduction of risk scores, such as the ACR Thyroid Imaging Reporting and Data System (TIRADS) system,[20] has improved standardization of nodule management. However, a Canadian retrospective review conducted before the implementation of ACR TIRADS revealed that 71% of US reports did not include the dominant nodule's three-dimensional size, 68% omitted echogenicity, and 46% did not provide an estimate for the risk of malignancy/recommendation for biopsy.[21] While multiple risk stratification systems exist, including the American Thyroid Association (ATA) guidelines, European Thyroid Imaging and Reporting Data System (EU-TIRADS), and the Korean Thyroid Association/Korean Society of Thyroid Radiology Guidelines (K-TIRADS), the ACR TIRADS has the highest size thresholds for biopsy resulting in 19.9–46.5% reduction in unnecessary fine needle aspirate biopsies (FNAB) compared to other scoring systems.[22] Regardless of the risk scoring system chosen, standardized implementation has been shown to significantly improve the quality of US reports and the classification reporting rates compared with radiology groups that do not adopt a systematic approach.[23] Developing standardized reporting forms through local consensus and education, providing reminders at the point of care, and conducting audits with feedback are viable strategies to improve the adoption of risk scoring systems. These efforts could help decrease the number of thyroid biopsies performed while increasing the rates of malignancy or intermediate cytology findings.[24]

Though FNABs are useful and accurate when benign or malignant results are reported, with false negative or positive rates <3%, at least 20% of FNABs result in indeterminate results. These indeterminate nodules have varying risk of malignancy that can be institution dependent but are most often benign and there is no consensus on management. A recent meta-analysis surmised that repeating FNAB can yield a more definitive

result in up to two-thirds of patients (50% benign, 15% malignant)[25]. Multiple thyroid nodule guidelines also recommend considering molecular testing[16,17] for indeterminate TNs. Molecular testing is used much more widely in the United States and is becoming available in Canada. There are several commercially available molecular tests which examine a variety of somatic mutations, gene expression profiles, and microRNA-based classifiers, each offering different positive and negative predictive values.[16] Publicly funded molecular testing has been implemented in both Alberta and Quebec. In Quebec, recent academic centres using Thyroseq v3 have demonstrated a benign call rate of 72.6% and found the test to be cost effective.[26] However, their analysis included non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in the "malignant" category and assumed that most Bethesda III and IV nodules measuring 1-4 cm would undergo diagnostic lobectomy, an approach that may not reflect standard practice in other centres. Unfortunately, it is still unclear whether molecular testing impacts rates of thyroid surgery. A recent large database analysis of patients in the United States who had undergone thyroid FNAB showed a steady trend of decreases in thyroidectomy surgeries after the release of the 2015 ATA guidelines. Notably, this decline was not impacted by molecular testing.[27] Regions with low adoption of molecular testing showed no differences in thyroidectomy rates compared with high testing adoption areas. In fact, low-adoption states appeared to have greater decline in thyroidectomy rates, likely reflecting the overall trend of more conservative management of low-risk thyroid cancers. Perhaps developing more nuanced decision-making nomograms that incorporate results from both molecular testing and clinical variables may enhance the accuracy of selecting surgical candidates.[28]

Conclusion

Overdiagnosis of TN is a growing worldwide concern, posing potential harm to both the healthcare system and patients. To address this, multi-targeted strategies need to be adopted, which should include reducing inappropriate US requests and minimizing subsequent investigations. Above all, engaging patients in a clear discussion in advance about the pros and cons of imaging including the possibility of incidental findings, will help them in making informed decisions.

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Financial Disclosures

V.M.: None declared.
S.I.: None declared.

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