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Risk Stratification to Improve Care and Outcomes in Diabetic Kidney Disease

Navdeep Tangri, MD, PhD

About the Author

Dr. Navdeep Tangri, MD, PhD, is working on a clinical research program that is also translational, focusing on the improvement of clinical decision making for patients with advanced chronic kidney disease. He developed and validated the Kidney Failure Risk Equation (KFRE) to predict the need for dialysis in patients with chronic kidney disease, and is currently engaged in multiple validation and implementation exercises to increase the uptake of the KFRE.

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Introduction

Chronic kidney disease (CKD) is a global public health problem that affects one in eight Canadians, and nearly one in two with Type 2 diabetes (T2DM).[1-3] It is widely recognized as a potent risk factor for cardiovascular (CV) outcomes, all-cause mortality, and progression to kidney failure requiring dialysis or transplant.[4,5] End stage kidney disease is catastrophic for patients and families, but for most individuals who are identified as having high-risk CKD, progression is now preventable in this new era of guideline-directed medical therapy.[6-9]

This review will summarize a new paradigm for diagnosis, staging, and management of CKD, that is centered around risk of progression rather than kidney function (eGFR or serum creatinine alone).[8,9] We will describe the heterogeneity in the progression of kidney disease, as well as the clinical utility and usability of accurate risk prediction tools that can be used today in Canadian clinical practice.

CKD – Epidemiology and Variability in Risk of Progression

CKD is defined as loss of kidney function (eGFR < 60 mL/min/1.73m^2), or evidence of kidney damage (urine albumin to creatinine ratio > 3 mg/mmol) or imaging abnormalities), and a confirmation that these changes have been present for at least 3 months.[10] Longitudinal studies from healthy community-based populations suggest that most adults lose about 1 mL/min/1.73m^2 of kidney function after the age of 40.[11] In the general population, the prevalence of CKD is below 5% in younger adults (< 50 years of age), but rises to 35% in older adults (> 80 years of age).[12]

In adults with T2DM, the prevalence of CKD is much higher, and T2DM is the leading cause of kidney failure in Canada.[3,13] Studies from national health surveys in the United States indicate that 26% of adults with T2DM < 65 years of age had concomitant CKD, and this rose to 59% in those

older than 65.[14] In Canada, a study in primary care practices focusing on later stages of CKD (G3-G5) found an overall prevalence of 7.4% in the general population, but this rose to 27% in those with T2DM and hypertension.[1] These findings highlight the importance of screening with eGFR and urine ACR in all adults with diabetes (Type 1 and Type 2) on an annual basis.

It is important to note that while CKD is common, kidney failure requiring dialysis remains an uncommon event. Since 2018, there has been a plateau in the overall incidence in Canada, and 6,000 patients start dialysis or receive a transplant annually, at a rate of 200 per million persons.[15] Of these, approximately 3,000 are adults with T2DM, and more than 50% of new dialysis patients have T2DM as a cause of CKD or a comorbid condition.[15]

The gap in rates (140,000 per one million for prevalent CKD, and 766 per one million for incident dialysis) reflect the heterogeneity in disease progression, as well as the poor survival once patients reach renal replacement therapy.[15,16] It is likely that a minority of patients with CKD/diabetic kidney disease (DKD) are high-risk and drive the majority of kidney failure outcomes, while most patients progress slowly, and have competing CV events and do not ever reach kidney failure. As such, accurate risk stratification to identify these high-risk individuals early in the course of disease can be highly effective in preventing both kidney failure and CV events.[17]

Clinical Practice Guideline Recommendations

The Kidney Disease Improving Global Outcomes Guidelines (KDIGO) are the gold standard for guiding treatment for adults with CKD, and are typically endorsed by the Canadian nephrology community. The most recent update to the guidelines was released in March 2024, and acknowledges the importance of staging and risk prediction in determining optimal treatment for patients with CKD.

Staging for CKD requires testing for both eGFR and albuminuria, and patients are staged along a heatmap **(Figure 1)**. The heatmap represents relative

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

Figure 1. KDIGO heatmap of increasing risk of developing CKD through decreasing glomerular filtration rate (GFR) and increasing and persistent albuminuria.[10]

risks for progression of kidney disease, CV events, acute kidney injury, and all-cause mortality.[10] While the heatmap represents a major advance over the eGFR-only staging system for CKD, there is considerable variation in absolute risk even within a single heatmap box. In fact, two individuals who are green or red can have up to an 80-fold variability in their risk of disease progression.[8] Therefore, risk prediction equations that estimate the absolute risk for each individual person are needed, available and recommended by the KDIGO clinical practice guidelines.

Risk Prediction Tools for Later Stages of CKD (G3-G5)

In adults with more advanced CKD (eGFR <60 mL/min/1.73m^2), the kidney failure risk equation (KFRE) is the most widely used and validated tool to predict CKD progression.[18] The equation was originally developed and validated in Canada (Ontario and British Columbia), and has subsequently been validated in more than 30 countries and two million individuals.[19] The KFRE is easy to calculate using freely available web sites (kidneyfailurerisk.com), electronic medical record integrations (Oscar Pro, Input Health), and through automatic reporting by medical laboratories (Alphalabs, Lifelabs) **(Figure 2)**.

In Ontario, Manitoba, and Alberta, the KFRE is used to determine the need for nephrology referral or interdisciplinary care, in combination with eGFR and urine ACR based criteria. Physicians who provide care for adults with CKD Stage G3+ should calculate the KFRE and can use it to guide referral to nephrology care as well as provide counselling for patients on their risk of dialysis. Studies comparing patient and provider perspectives on risk prediction have consistently shown that the KFRE is more accurate than nephrologists, and that patients value knowing their risk, as it improves their engagement and participation in shared decision-making.[20-23]

Risk Prediction Tools that Enable Early Intervention (G1-G3)

The treatment landscape for patients with CKD and DKD has changed dramatically in the last 10 years. From 2000-2015, patients with DKD were only treated with renin angiotensin aldosterone inhibitors (RAASi), and high-risk patients lost kidney function at 5-7 mL/min/1.73m^2/year even with optimal treatment. Since that time, landmark trials of SGLT2 inhibitor therapy,[24,25] followed by two large-randomized trials of finerenone, a nonsteroidal mineralocorticoid receptor antagonist (ns-MRA)[26] have shown that the progression of CKD can be reduced by up to 60% compared to RAASi therapy alone.[27] Furthermore, even high-risk patients can achieve a substantial reduction in eGFR slope to less than 3 mL/min/1.73m^2/year. Recently, top line data from the FLOW trial (semaglutide) was also released, confirming an additional 24% reduction in kidney disease progression and CV events in patients with DKD, further adding to the importance of a pillar-based approach for slowing CKD progression.[28]

In the current diagnostic and treatment paradigm, patients are unrecognized as having CKD until eGFR is typically <45 mL/min/1.73m^2, leading to a narrow window for intervention, and an increased risk of adverse effects and treatment discontinuation. Risk prediction tools that identify high-risk individuals for multi-drug therapy, early in the course of disease,

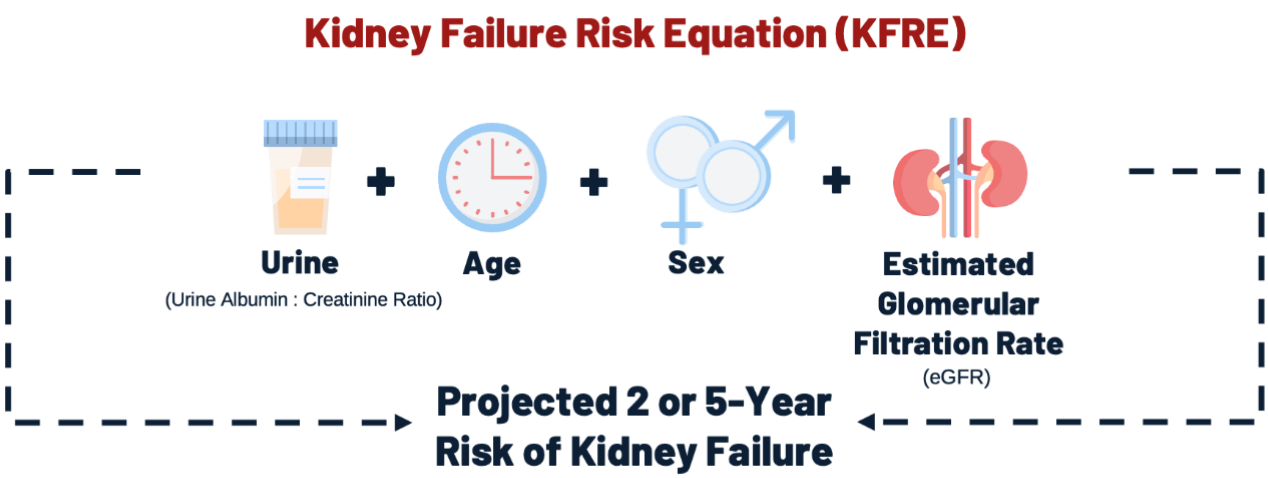

Figure 2. Summary of the key variables within the four- and eight-variable kidney failure risk equations.[18]

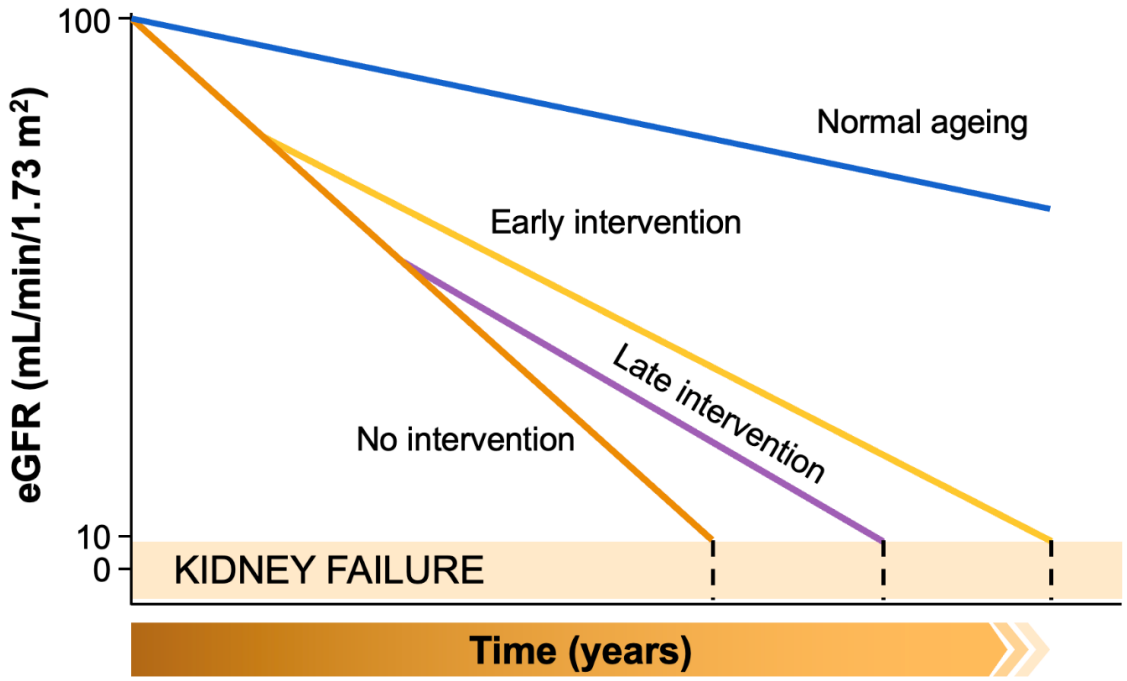

Figure 3. Display of the significant effect of early identification treatment onset for CKD; Adapted from Alexiuk & Tangri.[29]

when eGFR is preserved, can change how care is delivered **(Figure 3)**. These tools are now accurate and accessible, and have been rigorously validated in multiple countries and healthcare settings. In this section of the review, we will highlight two models that can be used to identify high-risk individuals with early stages of CKD.

CKD-PC eGFR Decline Model

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) represents a group of multidisciplinary scientists who collaborate to develop and validate risk prediction tools for patients with CKD. In 2023, the CKD-PC investigators developed a new model to predict 40% decline in eGFR in patients with or without T2DM, and preserved kidney function.[8] These models, along with other CKD-PC models are available for use at www.ckdpcrisk.org

The CKD-PC models used rigorous methods and were developed and validated in 1.6 million individuals across 43 cohorts and 23 countries. The model uses routinely available data on demographics, laboratory variables, medications, and comorbid conditions to predict progression of kidney disease in adults with preserved eGFR. A list of the variables included in the models and the performance characteristics (AUC 0.77 in adults with T2DM) of these models are summarized in **Table 1**. It is important to note that these models are tied to actionable clinical thresholds and decisions. The authors recommend RAASi and SGLT2i therapy for patients at >1% risk of progression in 2-3 years, and multi-drug therapy for those at >5 % risk at 3 years.

Klinrisk Models

The Klinrisk models take a novel artificial intelligence/machine learning-based approach to risk prediction in patients with early stages of disease.[9] These models were developed in Canada and have subsequently been validated in multinational clinical trials, as well as in a recently presented study of 4.6 million U.S. adults with or without CKD at baseline. Similar to the CKD-PC models, the Klinrisk models are equally effective in adults with or without T2DM, and predict 40% decline in eGFR or kidney failure.

There are some important differences in the models and their implementation. The Klinrisk models are machine learning-based, and use laboratory data only, and therefore do not require information on comorbid conditions, medication or blood pressure. They are also highly accurate, with AUC ranging from 0.84-0.88 in development and external validation. In Canada, these models are available through Lifelabs Inc. as a patient paid test, and are accompanied by clinical decision support that aligns

	CKD-PC T2DM[8]	Klinrisk[9]
Variables	• Age (20-80 years) • Sex • eGFR • UACR • Systolic Blood Pressure • Antihypertensive Medication Use • Heart Failure • Coronary Heart Disease • Atrial Fibrillation • BMI • Smoking History • T2DM Medication • Hemoglobin HbA1c	• Age • Sex • eGFR • UACR • Random Glucose • Blood Urea (BUN) • Sodium • Potassium • ALT • Alkaline Phosphatase • Bilirubin • Albumin • ACR • Complete Blood Count • Calcium • Magnesium • Chloride • Phosphate • Bicarbonate
Population	N = 1.6 million from 43 cohorts, globally	N = 77,196 (study cohort) N = 4.6 million (validation)
Outcome	3-year probability of 40% decline in eGFR	2- and 5-year probability of 40% decline in eGFR
AUROC	0.77	0.84–0.88

Table 1. Summary of risk prediction models for early-stage CKD; courtesy of Navdeep Tangri, MD, PhD

with both KDIGO clinical practice guidelines and provincial criteria for referral to nephrology.

These models are therefore also actionable, and can be used in clinical practice today to facilitate early intervention in adults with T2DM.

Summary and Conclusions

CKD is common in patients with T2DM, but has a heterogeneous course. Risk prediction can transform the management of DKD by helping clinicians identify high-risk patients early when intervention is most effective. When high-risk patients receive guideline-directed medical therapy early, dialysis is entirely preventable. Our approach to DKD must include measurement of risk.

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Role of Continuous Glucose Monitoring in Non-Insulin-Requiring Type 2 Diabetes

Ronnie Aronson, MD, FRCPC

About the Author

Ronnie Aronson is an Endocrinologist and the founder of LMC Diabetes and Endocrinology (LMC), a practice groups of more than 60 Endocrinologists, providing care to over 45,000 people with diabetes, supported by diabetes educators, pharmacists, chiropodists and optometrists. Dr. Aronson's own research focus has centred on individuals who struggle to achieve optimal diabetes health outcomes. He has led projects that have defined their barriers, validated new devices, and developed novel tools and strategies to overcome these barriers. He has served as Principal Investigator in over 300 clinical trials in diabetes and its complications.

Affiliations: Chief Medical Officer, LMC Diabetes & Endocrinology

Introduction

Effective management of diabetes has always been contingent on our awareness of patients' glucose levels. There has been a slow evolution in glucose-measurement technology over the last century. Benedict's copper reagent test for urinary glucose became available in 1908, followed by the colorimetric technology of Dextrostix, patented in 1963 by Miles Laboratories Inc., and the electrochemical process of ExacTech introduced by Medisense in 1987, as examples.

Continuous glucose monitoring (CGM) systems have evolved more rapidly with a well-established evidence base documenting their value in individuals using insulin. Their potential impact among individuals with type 2 diabetes (T2D) who are not using insulin has been the subject of a series of studies in the past few years, culminating most recently in a key Canadian randomized controlled trial, the IMMEDIATE study.[1]

Reviewing first the major trials that used real-time CGM (rtCGM), we find a number of prospective trials that had initially explored mixed populations with T2D, where a significant proportion were non-insulin requiring. A Korean study of four hospital-based clinics, reported on 57 individuals with T2D, most not using insulin therapy (n=48).[2] Participants were randomized to a monthly series of 3-day Guardian RT wears, in comparison to continued self-monitor blood glucose (SMBG) alone, and showed a greater hemoglobin A1c (HbA1c) reduction of 0.7% (p=0.004) over the 3-month trial.

Also in 2008, a smaller pilot study (n=25) by a group of French hospital-based clinics found a similar trend of HbA1c reduction (0.3%, not statistically significant), following a single 48-hour wear of the GlucoDay CGM combined with physician counseling.[3]

In 2011, the Walter Reed Health Care System was the setting for a randomized controlled trial (RCT) comparing an early-generation Dexcom product, the SEVEN, to SMBG alone.[4] Among 100

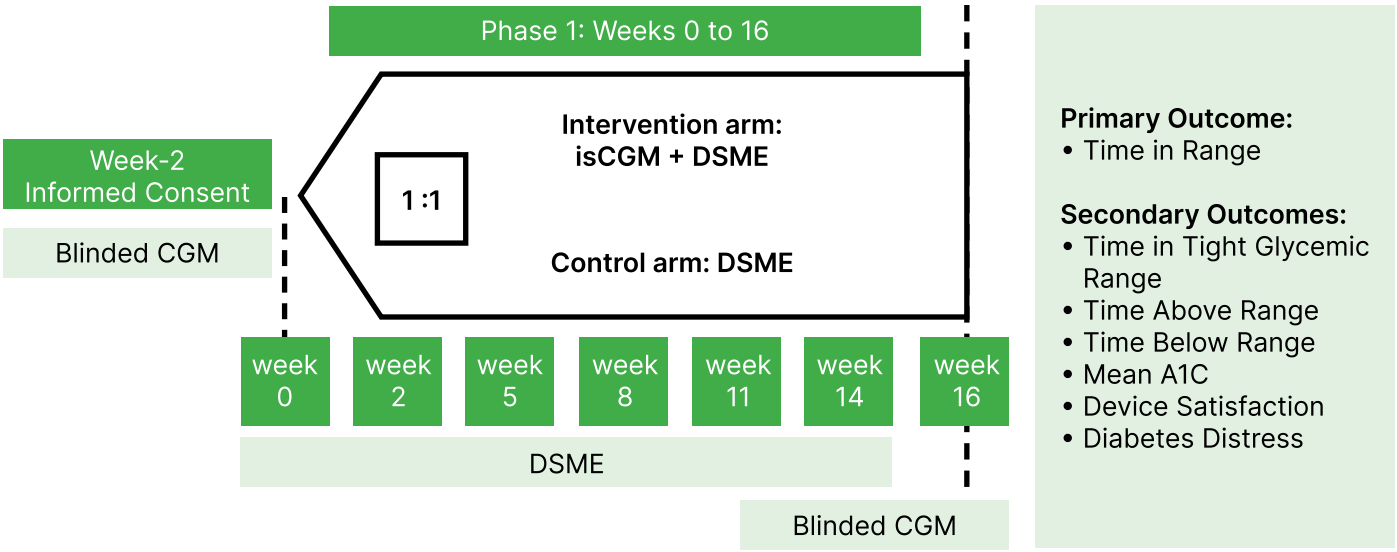


Figure 1: IMMEDIATE Study Design; courtesy of Ronnie Aronson, MD, FRCPC
Abbr: isCGM: intermittently scanned continuous glucose monitoring;
DSME: diabetes self-management education

randomized individuals with T2D, two-thirds were not insulin-requiring. Participants that wore CGM intermittently for four cycles showed a greater HbA1c reduction of 0.5% vs those continuing SMBG.

Most recently, the International Diabetes Center in Minnesota specifically compared CGM to frequent and structured SMBG[5] and found a trend to benefit with a non-significant 0.3% HbA1c difference between groups. The trial was comprised of subjects with uncontrolled T2D (A1c ≥7.0%) between the ages of 18 and 75 and who were being treated with one of the following three common therapies: **1.** sulfonylurea (SU) ± metformin (SU group), **2.** incretin (DPP4 inhibitor or GLP-1 agonist) ± metformin (incretin group), or **3.** insulin± metformin (insulin group).

The impact of rtCGM among individuals who were exclusively not insulin-requiring has been studied in only three trials, each using an episodic-wear approach.

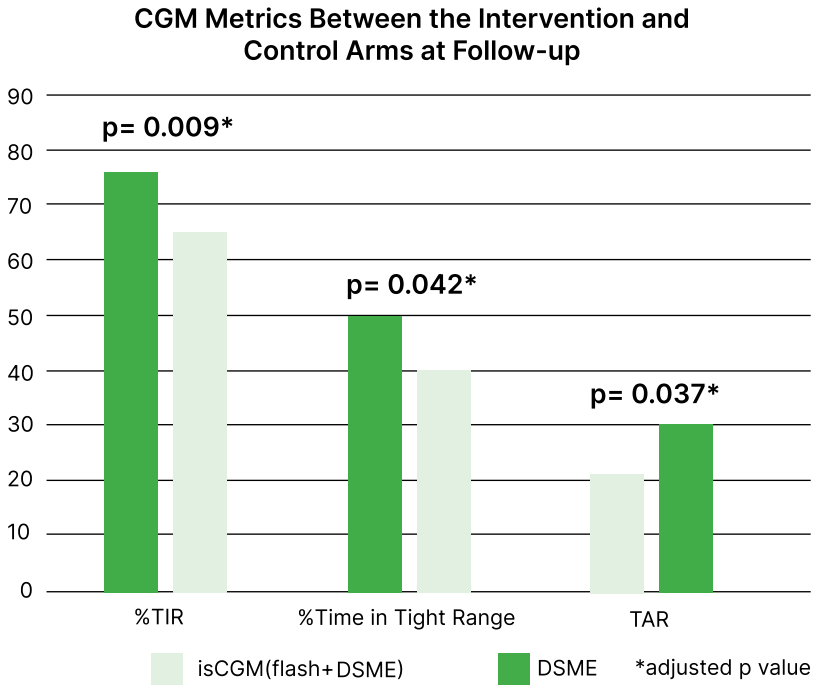
The Glycemic Excursion Management (GEM) initiative at the University of Virginia used the Dexcom G4 in one of its studies, along with considerable individualized specialist counselling.[6] In a randomized, controlled study of only 30 individuals, researchers found that using a Dexcom G4 along with extensive physician interaction was associated with a greater HbA1c reduction by 1.1% vs continued self-monitoring. Two subsequent trials used a similar design of episodic CGM versus SMBG. The COMMITED study found a non-significant trend to HbA1c reduction (0.2%) vs continued SMBG using the Dexcom G6 in three 10-day cycles.[7] A Korean study found a significantly larger HbA1c reduction of 0.7% ($p < 0.02$) using the Guardian Connect in three 7-day cycles.[8]

As with real-time CGM, intermittent-scanned CGM technology (isCGM) has been studied in both mixed populations with T2D and those not on insulin. Among mixed-population studies, the large, recently reported PDF trial in Seoul, South Korea, randomized 126 participants with T2D, of which 72.5% did not use insulin, to Freestyle Libre vs continued SMBG.[9] At 12 weeks, the researchers found a between-group difference in HbA1c of 0.5% in favour of CGM ($p<0.001$).

Studies of isCGM specifically in non-insulin-using individuals include several retrospective studies and real-world-evidence reports, all of which consistently show a benefit of CGM use on glycemic control. Three prospective trials in this population have also been published. In Japan, a group of five hospital-based practices randomized 100 individuals to 12 weeks of isCGM – in this case, Freestyle Libre – versus continued SMBG and found an HbA1c reduction of 0.3% versus that of the SMBG group that reached statistical significance at the end of the pre-planned 24-week extended period of observation.[10]

An uncontrolled, prospective pilot study led by William Polonsky in San Diego involving 35 non-insulin-requiring individuals with T2D showed an increase in time in range (TIR) of 19% (55–74%) over 3 months using isCGM with Freestyle Libre[11] with extensive personalized diabetes education.

To more definitively assess the efficacy of isCGM in adults with T2D using non-insulin therapies, a group of Canadian community-based diabetes clinics initiated the IMMEDIATE study.[12] The trial,



As compared to the DSME arm, at 16 weeks of follow-up the intervention arm had:

- Significantly greater mean TIR by 9.9% (2.4 hours)
- Significantly greater time in the tight glycaemic range by 8.5% (2.0 hours)
- Significantly less TAR by 8.1% (1.9 hours)

Figure 2: IMMEDIATE Study Results; courtesy of Ronnie Aronson, MD, FRCPC
Abbr: TIR: time in range; TAR; time above range

across six sites, used a randomized, controlled, open-label design. Participants were randomized to either 16 weeks of isCGM (Freestyle Libre) or continued daily SMBG, in a 1:1 ratio, stratified by use of glucagon-like peptide-1 receptor agonists (GLP-1 RA) **(Figure 1)**.

Outcome data in IMMEDIATE were based on 2-week periods of blinded CGM-wear at baseline and at 16 weeks. Because of potential confounding by individualized diabetes self-management education (DSME) on outcomes, we sought to control for that variable by providing a structured curriculum to all participants, with equal time provided to each group. Inclusion criteria were adults with T2D of more than 6 months duration and an HbA1c >7.5% who were taking more than one non-insulin antihyperglycemic therapy. All participants had no prior CGM use. TIR was the primary outcome, adjusted for baseline glycemic control. Secondary outcomes included HbA1c and several other CGM outcomes, such as time in tight glycemic range.

The study enrolled 116 participants, of which 63.8% were male, with a mean age of 58.4 years, with a BMI of 29.9 kg/m^2 and having a duration of diabetes of 10 years. Participants were using a mean of 2.4 antihyperglycemic agents, with nearly all using metformin. Approximately 30% were using GLP-1 RAs and approximately 39% were taking SGLT2 inhibitors.

The primary outcome of TIR was significantly higher in the CGM group at 76.3% vs the SMBG group at 65.6% (adjusted difference of 9.9%, p<0.001), indicating nearly 2.4 hours daily of additional TIR for this group **(Figure 2)**. Time in tight glycemic range (3.9 - 7.8 mmol/L) was higher by 8.5% (p = 0.04) and time above range was lower by 8.1% for the CGM group (p = 0.04) **(Figure 2)**.

In the IMMEDIATE trial, as in previous studies, HbA1c showed a greater improvement in the CGM group, in this case showing a difference of 0.3% (p<0.05). Hypoglycemia, whether measured by time below range or as clinical hypoglycemia events, was minimal and not different between groups. There were no events of severe hypoglycemia. TIR outcomes were not altered when stratified by mean number of therapies, GLP-1 RA use, diabetes duration, or isCGM scanning frequency. There was a greater treatment effect among participants with a baseline HbA1C above 9%. These individuals gained 20.4% of time in range, which translates to a mean of 4.9 hours per day.

Most patient-reported outcome measures improved equally in both groups over the course of the study, including important measures such as diabetes distress, which has sometimes increased among individuals adopting greater self-monitoring of any type. An exception was the Glucose Monitoring Satisfaction Survey (GMSS) mean score, which improved in the CGM arm and was unchanged among self-monitoring patients.

Finally, the IMMEDIATE trial showed that there was no change in mean number of therapies per person, nor adherence, as measured by the Adherence to Refills and Medications–Diabetes (ARMS-D) scale. There were also no significant differences in final weight or waist circumferences, although mean weight did decline by 1.4kg in the CGM group with no change in the SMBG group.

Two recent meta-analyses support the IMMEDIATE findings. One study of 26 RCTs in T2D demonstrated a significant HbA1c improvement with CGM versus self-monitoring mean difference 0.19%; [95% CI 0.04, 0.34]).[12] The advantage was even greater with isCGM (mean difference 0.31%; [95% CI 0.17, 0.46]) and results were similar for populations using or not using insulin. A second meta-analysis explored six RCTs that focused on non-insulin-using individuals and found an HbA1c reduction advantage of 0.31% (95%CI 0.21, 0.42), TIR gain of 8.6% (95%CI 4.54, 12.71) and improved treatment satisfaction.[13]

Historically, the value of glucose self-monitoring for non-insulin-users with T2D has been challenging to demonstrate convincingly. As more expensive and complex systems such as continuous glucose monitoring gain popularity in all populations with diabetes, understanding their value in non-insulin-users becomes even more germane. The accumulating evidence of research over the past decade indicates that both rtCGM and isCGM are both more effective at glycemic control than conventional self-monitoring alone, even among individuals not using insulin therapy.

How is CGM use in non-insulin users contributing to the improved glycemic control seen in these studies? Such individuals, after all, aren't adjusting their therapy many times a day, as insulin users do. The studies also indicated no overall change in the mean dose, or number or type of non-insulin therapies used. Interestingly, as seen in the GEM study, even intermittent CGM use may have glycemic control benefit, when supported with sufficient diabetes self-management education.[5] Of note, isCGM studies (including IMMEDIATE) did not find a relationship between number of scans per day and the resulting glycemic benefit. Among insulin users, scanning frequency is usually associated with outcome, most likely because the more frequent awareness of glucose level leads to real-time dosing changes. However, in the case of non-insulin-users a different mechanism may be in play. Episodic scanning may contribute to a glycemic benefit through the pathway of larger behaviour change, such as subtle changes to medication adherence not detectable through, for example, the ARMS-D scale in IMMEDIATE, or through improved dietary and lifestyle choices.

Finally, we might consider the degree of the potential benefit of increased TIR and reduced HbA1c to non-insulin-users. IMMEDIATE achieved a nearly 10% gain in TIR (and an additional HbA1c reduction of 0.3%) versus self-monitoring. In general, a gain of 5% in mean TIR has been considered clinically meaningful. Further, as with most interventions in diabetes, those with poor glycemic control derived even greater benefit.

Summary

An accumulating body of evidence, culminating in the recent IMMEDIATE randomized, controlled trial, has confirmed the value of continuous glucose monitoring technology for individuals with T2D who are not using insulin if they have been unable to achieve control with prior measures. Future research into these approaches for non-insulin-users will provide additional insights into mechanism and help build the body of data on optimal application for inclusion in future updates of clinical practice guidelines.

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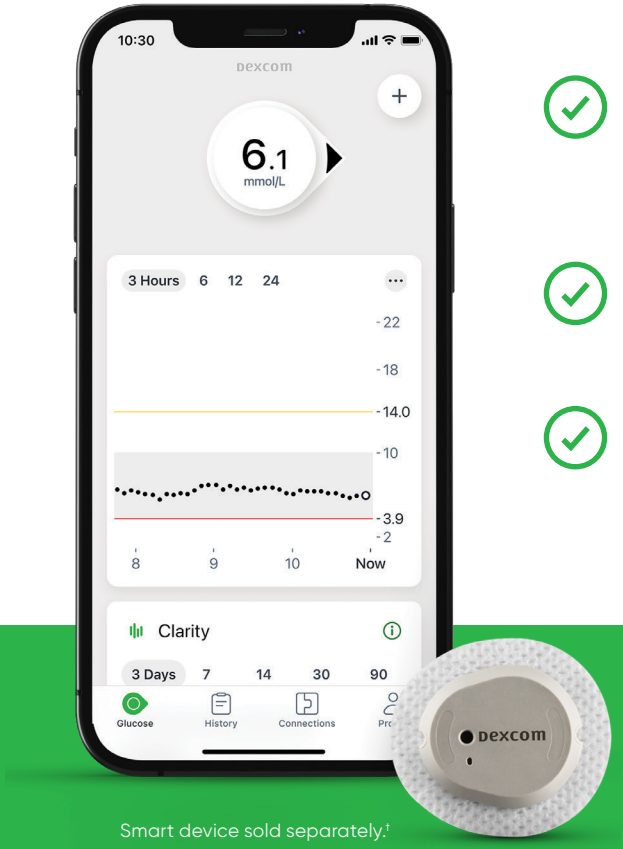

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‡ Retrospective, real-world observational analysis of the Canadian LMC Diabetes Registry using the medical records of 143 consenting CGM-naïve adults with type 1 diabetes (T1D) in each rtCGM- and isCGM-matched cohorts. To be eligible, people must have had: diagnosis of T1D >12 months, baseline A1C ≥7.0%, and 1 or more completed HbA1c measurements 6 months prior and 6-12 months post-index date.
§ Based on data from Dexcom CGM users in the U.S.

1 Dexcom, data on file, 2023. 2 Beck RW, et al. *JAMA*. 2017;317(4):371-378. 3 Beck RW, et al. *Ann Intern Med*. 2017;167(6):365-374. 4 Martens T, et al. *JAMA*. 2021;325(22):2262-2272. 5 Laffel LM, et al. *JAMA*. 2020;323(23):2388-2396. 6 Welsh JB, et al. *J Diabetes Sci Technol*. 2022:19322968221099879. 7 Brown RE, et al. *Diabetic Medicine*. 2022;39:e14937. 8 Dexcom G7 CGM System User Guide, 2023. 9 Dexcom, U.S. data on file, 2022.

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From the Bottom Up: Foot Care in Diabetes and the Role of the Endocrinologist

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About the Author

Dr. Daniel Shafran is a specialist in Internal Medicine and co-founder of the Edmonton Diabetes & High Risk Foot Clinic. He completed medical school at the University of Calgary, residency at the University of Toronto, and a fellowship in General Internal Medicine at the University of Alberta. He is a Staff Physician at the Royal Alexandra Hospital's Diabetic Foot Clinic and attends on the Internal Medicine wards at the Misericordia Hospital. At the Edmonton Diabetes & High Risk Foot Clinic, he has gathered internal medicine, endocrinology, wound care nurses, foot care nurses, mental health professionals, dieticians, pharmacists, diabetes educators, and insulin pump trainers to work collaboratively under one roof to provide comprehensive care to Albertans living with diabetes.

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Introduction

Diabetic foot ulcers (DFUs) are a common, serious, and costly complication of diabetes. By some estimates, up to a third of people living with diabetes (PWDs) will develop a DFU in their lifetime.[1] The 5-year mortality rate in patients with a DFU is approximately 30%, and the mortality rate can be as high as 70% in patients with an above the foot amputation.[2] In Canada, hospital admissions for DFUs are 25% more expensive than other common costly conditions such as heart failure and pneumonia, and this is prior to accounting for additional costs associated with treatment of DFUs, such as outpatient antibiotics, rehabilitation, prosthetics, therapeutic footwear, and continuing care.[3] Endocrinologists and other diabetes specialists are well positioned to identify patients at high risk of developing DFUs. By providing early or preventive treatment for DFUs, there is perhaps nothing more impactful that one can do to improve the quality of life of patients living with diabetes.[4]

Understanding Diabetic Foot Problems

Diabetic neuropathy impacts motor, sensory, and autonomic nerves, which can act together to create conditions in which a DFU can develop. Motor neuropathy leads to foot deformity and biomechanical abnormalities; sensory neuropathy reduces patients' protective sensation; and autonomic neuropathy alters the local homeostatic response, resulting in abnormal moisture or dryness of the skin.[2] Neuropathy therefore provides ideal conditions for callus formation, which, left untreated, and subject to chronic, repetitive impact, may induce the formation of a DFU.

There are also age, body habitus-related, and financial challenges, common in PWDs, that impair patients' ability to examine or care for their feet: reduced flexibility or increased abdominal obesity

may prevent one from being able to adequately inspect their own feet; reduced vision, whether from age-related vision loss or retinopathy, may reduce the utility of such an exam; attempts to trim one's own toenails (if one is able to reach his or her toes) may result in inadvertent self-inflicted injury of the nail bed. Financial constraints prevent some patients from purchasing updated, properly-fitted footwear or obtaining professional foot care.

Screening for Sensory Neuropathy

Endocrinologists are well placed to screen for and discuss the risks of diabetic foot disease with their patients as part of providing comprehensive diabetes care. Diabetes Canada and the International Working Group for the Diabetic Foot (IWGDF) recommend annual foot exams for most patients, and exams at more frequent intervals for patients at higher risk.[5,6] A review of the risk factors that place a patient at higher risk of developing a DFU is helpful: they are peripheral neuropathy, history of ulcer or amputation, structural foot deformity, limited joint mobility, peripheral arterial disease, microvascular complications, increased hemoglobin A1c (HbA1c), and onychomycosis.

Screening for sensory neuropathy is a quick and straightforward process. The IWGDF suggests the use of either a monofilament or tuning fork as adequate to assess for the loss of protective sensation. Loss of sensation to a Semmes-Weinstein 10g monofilament is the strongest predictor of risk for developing a DFU, conferring a relative risk of 2.5 to 7.9.[7] Monofilament testing need only be performed at three sites on each foot[6] **(Figure 1)**.

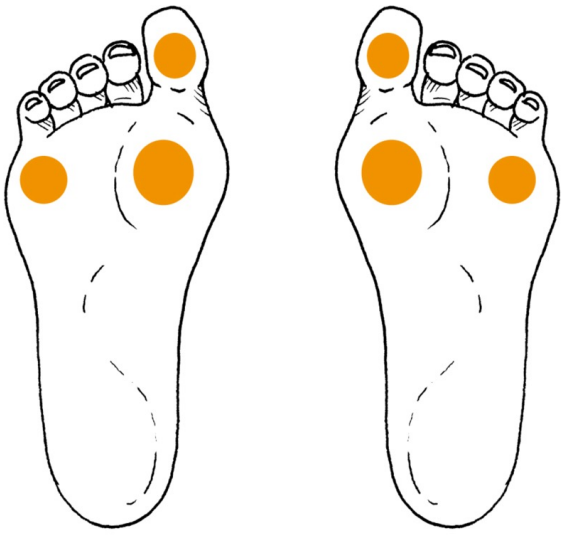

Figure 1. Testing sites for loss of protective sensation using a 10g Semmes-Weinstein monofilament. Source: IWDGF[6]

Despite the fact that testing for neuropathy is quick and inexpensive, some studies have shown that screening is only performed in a third of PWDs.[8] Few screening tests exist in clinical practice for such life-altering diagnoses that are as quick, inexpensive, and noninvasive as neuropathy screening; therefore, it should be performed at every initial diabetes consult and, as mentioned above, at least annually thereafter.

If You Discover a Diabetic Foot Ulcer

While most diabetes specialists are not expected to manage DFUs, all should be equipped to provide initial advice to a patient discovered to have a DFU, and to understand the importance of making an immediate referral to an appropriate specialty clinic. Initial treatment of a DFU requires addressing five areas: off-loading, wound debridement, wound dressings, treating infection, and perfusion.[9] Upon discovery of a DFU on the plantar aspect of the foot, diabetes specialists should instruct the patient to offload the foot as much as possible. Offloading can be supported with the use of off-loading devices such as a knee walker, crutches, walker, or wheelchair, wherever possible. Wounds on the lateral or dorsal aspect of the foot are often a result of ill-fitting footwear. Inspection of the patient's footwear can often confirm this and a quick fix—new footwear—can be recommended.

If a DFU shows signs of infection, antibiotics should be prescribed, though the ideal first-line empiric agent varies upon the nature of the infection. Mild infections without complicating features (such as receipt of recent antibiotics) can be treated with first generation cephalosporins. More severe infections should be treated with broad-spectrum antibiotics such as amoxicillin/clavulanate. Patients with a history of drug-resistant pathogens should receive appropriately-targeted antimicrobial therapy. Patients with evidence of severe infection or ischemia, gangrene, abscess, or hemodynamic changes should be directed to the nearest emergency department to receive urgent surgical consultation.[10] For a patient discovered to have a DFU, an immediate referral to a dedicated multidisciplinary high risk foot care team is essential. These teams must be able to offer regular debridement of nonviable tissue and the surrounding callus, select and apply appropriate wound dressings, treat infections or refer the patient to a specialist in infectious diseases, and workup and manage peripheral arterial disease. These teams may also include, or work closely with, orthopedic surgeons, vascular surgeons, interventional radiologists, podiatrists, podiatric surgeons, orthopedic

technicians, specialist nurses, and pedorthists/orthotists.[9] Indeed, multidisciplinary care teams have been shown to reduce the risk of major amputation compared to usual care.[11]

Prevention and Avoiding Recurrence

Due to the high risk of recurrence of DFUs, patients with a history of DFU should not be considered healed or cured but should instead be considered "in remission". The recurrence rate of a DFU at one year is 42%, and at five years is 65%.[1] Therefore, it is more likely than not that patients who have had a DFU will develop another one in the future. Patients should be counselled on three practices that may reduce their risk of developing a first or recurrent DFU. First, patients should perform daily foot inspections, or have someone else perform these inspections for them if they are unable to.[6] This facilitates the discovery of pre-ulcerative lesions, such as calluses, before they become wounds, and increases the likelihood that open wounds are treated earlier. Second, PWDs should be instructed to seek care from a foot care specialist if they discover corns, calluses, ingrown toenails, splinters, or other wounds; they should not treat these themselves.[5] Patients with a history of DFU are at the highest risk of ulceration, and should receive lifelong ulcer prevention from a foot care professional at regular intervals to ensure early and safe callus removal.[6] Third, the use of therapeutic footwear (which may include custom shoes, orthotics, or both) reduces the risk of ulceration by half.[12] All patients with a loss of protective sensation on the foot should wear footwear anytime their feet touch the ground—indoors or out.

Emerging Technologies and Innovations

While much of modern DFU treatment is the application of basic principles such as debridement and offloading, new technologies show promise in reducing the incidence of DFUs and expediting their resolution. Intelligent insoles, equipped with multiple temperature and pressure sensors which are remotely monitored, are now commercially available. One such intelligent insole, manufactured by a Canadian company, showed a 71% reduction in ulcer incidence in a small study.[13] Extracorporeal shockwave therapy (ESWT), initially used for nephrolithiasis and now commonly used by physiotherapists for several musculoskeletal ailments, has been approved by the FDA for the treatment of neuropathic DFUs, based on randomized trials that showed over 10% more wounds had completely healed by 20 and 24 weeks with the use of ESWT compared to sham therapy.[14] Other treatments, such as topical oxygen therapy, placenta-derived products, topical fibrin and leucocyte platelet patches, sucrose octasulfate dressings, and hyperbaric oxygen have modest evidence to support their use, and though they may be considered as adjunctive treatments in non-healing ulcers,[6] their use is not widespread.

Conclusion

DFUs pose a significant threat to the quality of life and mortality of PWDs. Endocrinologists and other diabetes specialists can and should play a critical role in the screening, prevention, and where necessary, initial management of DFUs. Screening patients for loss of protective sensation—and indeed, for active wounds, which may exist unbeknownst to the patient with neuropathy—is often overlooked but of critical importance in identifying and treating DFUs. Patients found to have an ulcer require prompt referral to a specialized care team, and anyone with a history of ulceration requires lifelong preventative foot care and therapeutic footwear to reduce the very high likelihood of recurrence. While emerging technologies to assist with this challenge are being evaluated, the mainstay of treating DFUs remains a strict focus on basic principles, such as offloading and debridement of the wound, treating incident infections, and ensuring adequate perfusion. Endocrinologists and other diabetes specialists stand on the front line in the fight against DFUs and should play a pivotal role in the early detection and prevention of DFUs to enhance the overall well-being of individuals with diabetes.

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Diabetes Management at Time of Childbirth

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Introduction

Dynamic changes occur in glucose handling as well as insulin sensitivity and pharmacokinetics at the time of childbirth in pregnancies complicated by diabetes. The unpredictable timing and nature of labour and childbirth contribute to intrapartum glycemic challenges. Furthermore, there is a lack of high-quality evidence in the literature to guide glycemic targets and management in the intrapartum period.[1] This lack of high-quality evidence contributes to the controversies about optimum intrapartum glycaemic targets, and results in wide variations between hospital protocols for intrapartum glucose monitoring and management. Despite these controversies, women with diabetes, particularly those with type 1 diabetes, are vulnerable for the development of hypoglycemia and/or diabetic ketoacidosis if their intrapartum glycemia is not appropriately managed.

An in-depth discussion of the timing of delivery in women with diabetes in pregnancy is beyond the scope of this article. Briefly, communication between diabetes and obstetrical care providers is encouraged to develop an individualized plan for the optimum timing of childbirth for women experiencing diabetes in pregnancy. This plan should be based on the glycemia achieved in pregnancy, the type of diabetes, and other risk factors for stillbirth such as maternal age, smoking status, the presence of retinopathy and fetal monitoring findings.[2-4]

What Intrapartum Glycemic Target Should We Strive For?

In theory, avoidance of hyperglycemia at time of labour and childbirth reduces the risk of neonatal hypoglycemia by reducing maternal glucose transferred to the fetus, and resultant glucose induced fetal hyperinsulinemia, which contributes to fetal overgrowth and neonatal hypoglycemia. However, the existing evidence to support this theory is conflicting.[1] There is increasing recognition of the contribution of maternal hyperglycemia in the second and third trimester of pregnancy to the risk for neonatal hypoglycemia. This has led groups to debate the relative contribution of intrapartum

hyperglycemia to the development of neonatal hypoglycemia and to question the risk/benefit ratio of striving for tight glycemic targets of 4.0 to 7.0 mmol/L, as recommended by guidelines. Tight glycemia at the time of childbirth has been challenging to achieve with our traditional modalities of insulin delivery. Glycemic management challenges during childbirth are generally more pronounced among women living with type 1 diabetes in pregnancy compared to those with type 2 or gestational diabetes. One large retrospective study found that over one third of women with type 1 diabetes experienced intrapartum hypoglycemia, defined as a least one recorded capillary or venous glucose level of <3.5 mmol/L.[5] The proportion of women with type 2 or gestational diabetes with intrapartum hypoglycemia in this study was 14% and 2.4%, respectively.[5] This study did not find a significant association between in-target intrapartum glycemia and neonatal hypoglycemia after adjustment for neonatal factors such as prematurity. A higher intrapartum glycemic target range of 5.0 to 8.0 mmol/L has been proposed by some experts to reduce intrapartum maternal hypoglycemia.[6]

Preparation for Glycemic Management Prior to Childbirth

Peripartum considerations should be discussed with women with diabetes in pregnancy well before childbirth. Women should receive instruction about which diabetes supplies they should bring to the hospital. It is particularly important for women who use insulin pump therapy to bring extra insulin pump supplies with them for their hospitalization, which should include batteries or a charging cord, insulin pump cartridges, and infusions sets.

The day prior to induction/cervical ripening, the usual diabetes management including glucose testing, insulin, and metformin should continue as usual, with an exception for those using degludec insulin. Postpartum hypoglycemia is a risk for women using long duration insulin (degludec) in pregnancy. In order to prevent challenges with postpartum hypoglycemia, consideration should be given to switching from degludec insulin to a basal insulin that is shorter acting well in advance of anticipated childbirth. Alternatively, a reduction in the degludec insulin dose to be 30% to 50% less than the preconception degludec insulin dose starting two to three days in advance of a scheduled caesarean birth could be considered, which acknowledges that hyperglycemia requiring correction with rapid-acting insulin boluses may occur prior to childbirth.

Additional points of discussion to help prepare women with diabetes for childbirth are provided in **Table 1**.

✔	Discuss and develop a plan well in advance of anticipated childbirth
✔	Adjust very long-acting insulin prior to childbirth if it is being used
✔	Retinal assessment, when indicated, since this may influence the mode or method of childbirth
✔	Who/what supports are available during labour and the postpartum period
✔	Food intake during labour
✔	Personal desire to self-manage the insulin pump at the time of childbirth: Is there is a birth partner that is skilled in providing assistance with the insulin pump?
✔	Resources for hospital staff regarding insulin pump therapy in hospital to ensure they understand that if the insulin pump stops, basal insulin must be replaced within 2 hours to prevent the onset of diabetic ketoacidosis (example: To learn more, click here.
✔	Need to bring home diabetes supplies to hospital
✔	Review glucose monitoring type and frequency
✔	Provide recommendations for postpartum insulin dosing based on pre-pregnancy insulin dosing or diabetes agents: Reduce the insulin dose to be 20%-30% less than used in pre-pregnancy or to 50% of that used in late pregnancy if the former is unknown
✔	Postpartum diabetes follow-up plan: who, when, and how
✔	Avoidance of glucocorticoids for postpartum nausea prevention

Table 1: Planning checklist for childbirth in women with diabetes in pregnancy; courtesy of Lois E. Donovan, MD, FRCPC

Intrapartum Glucose Monitoring: Frequency and Type

The frequency of intrapartum glucose monitoring should be based on the type of diabetes, how it has been managed during pregnancy, and how it is being managed in the intrapartum period. When intravenous (IV) insulin therapy is used, hourly capillary glucose testing is required. Women who present for delivery with in-target glycemia using lifestyle measures alone require much less frequent monitoring. The experience of the author is that no further glucose monitoring is required for such women once in-target glycemia is documented at presentation for childbirth. Further glucose monitoring can be safely discontinued without negative consequences[5] provided no new concerns arise such as the need for glucocorticoid therapy.

Women using continuous glucose monitoring (CGM) should be informed that since CGM glucose levels lag behind capillary glucose monitoring by as much as 20 minutes, hospital policies usually require CGM to be supplemented with capillary glucose monitoring, and that capillary glucose monitoring is a requirement when IV insulin therapy is used. CGM sensors should be situated away from a potential operative site or unipolar diathermy pads because of the potential for electrical conduction.

When is Intravenous Insulin Required?

Once in active labour, if the glucose level is above 7–8 mmol/L for two consecutive hours in the absence of carbohydrate ingestion, insulin is traditionally initiated or continued depending on the clinical situation. Women with type 1 diabetes who are on a regimen of multiple daily insulin injections are generally switched to IV insulin at the onset of active labour. Many women with type 2 or gestational diabetes, even if they are using multiple daily doses of insulin during pregnancy, maintain in-target glycemia levels without the need for insulin during labour.

Close communication with the obstetrical team is required since the optimum glycemic management strategy will depend on the timing and mode of delivery, and if or when oral intake is permitted or tolerated. Nausea and vomiting are common occurrences during labour. Especially in the setting of type 1 diabetes, or when antenatal glucocorticoids have been recently administered, there should be a low threshold for assessing additional signs or symptoms of diabetic ketoacidosis (DKA), and to send lab work to screen for the possibility of DKA even in the setting of euglycemia, since 50% of DKA in pregnancy is euglycemic.[7]

The night prior to an elective caesarean birth, women taking intermediate acting insulin can take their usual evening intermediate-acting insulin dose or decrease their dose by 20%, depending on the clinical scenario and type of intermediate acting insulin. Those using degludec insulin should have insulin adjustments as outlined above in the days-to-months prior to delivery. An IV insulin infusion can be started the morning of a caesarean section if the glycemic level is above target or if there will be a delay in the timing of caesarian birth or anticipated return to subcutaneous insulin, owing to postoperative nausea and vomiting. Although the use of glucocorticoid therapy to prevent postoperative nausea and vomiting is gaining popularity amongst anesthesiologists, this practice should be avoided in women with diabetes in pregnancy because of the potential for this therapy to cause DKA.

IV delivery of insulin has traditionally been endorsed for women with diabetes during active labour because of the unpredictability of the timing of childbirth and the quick "on/off" duration of action when insulin is administered intravenously compared to subcutaneous delivery of insulin. Protocols used to guide the administration of IV insulin vary from centre to centre and are based on site-dependent hospital formularies and policies. Most centres initiate and vary the IV insulin dose based on total daily insulin requirements late in pregnancy and adjust infusion rates based on capillary blood glucose results. An infusion containing a 5% to 10% dextrose is administered with the insulin infusion to avoid hypoglycemia and ketosis. After delivery of the placenta, the IV insulin infusion should usually be decreased by 50% for women with type 1 diabetes and usually stopped for those with gestational or type 2 diabetes.

Insulin Pump Use for Intrapartum Insulin Delivery

Women living with diabetes that predates pregnancy are often very interested in maintaining control of their glucose management during the intrapartum period. Studies have shown the safety of continued nonautomated and automated ("closed-loop") insulin pump therapy in the intrapartum period.[8-11] This is provided that pain medications or exhaustion do not impair the ability of her or her birth partner, who is familiar with the operation of the insulin pump, to manage her pump effectively. Qualitative studies have highlighted women's

confidence and desire to continue automated insulin delivery at the time of childbirth to make their childbirth experience more enjoyable.[9-11] Furthermore, automated insulin delivery appears to be a promising option to reduce maternal hypoglycemia at the time of childbirth and in the postpartum period.[9-12] Regardless of whether women choose continued use of their insulin pump during labour and childbirth, postpartum insulin doses should be programmed into the pump beforehand for subsequent activation. Drever and Feig have previously outlined recommendations for nonautomated pump adjustments during labour and delivery,[8] which are summarized in **Table 2**, along with additional recommendations for insulin pump setting adjustments for automated insulin pump use.[10,11]

Postpartum

There is a dramatic decrease in insulin resistance immediately following the delivery of the placenta that results in a reduction of approximately 50–60% in postpartum insulin dosing in the setting of type 1 diabetes and may completely eliminate the need for insulin among women with type 2 diabetes in pregnancy. Because predicting postpartum insulin doses for women with type 1 diabetes can be challenging, there are risks postpartum of severe hypoglycemia and DKA. Postpartum insulin doses should be discussed by women and their primary diabetes team prior to delivery. A copy of this plan should be entered into the health record and be provided to the woman in advance of childbirth. Women using IV insulin should continue using it until it is safe to transition to either multiple daily injections or their insulin pump. Hourly capillary glucose testing should be maintained until after the woman is transitioned off of IV insulin and back to subcutaneous insulin. This should be clearly indicated in the hospital orders. Women using degludec insulin may need to skip the first postpartum day dose depending on how the degludec insulin was adjusted prior to childbirth as discussed above. Prior to hospital discharge, postpartum insulin dosing should be reviewed daily with the diabetes team with the goal of reducing the risk of hypoglycemia. Women with type 1 diabetes have indicated their need for ongoing close follow up in the early postpartum weeks.[13] As a result, the author recommends outpatient phone follow up for women with type 1 diabetes within a week of childbirth to support their need for insulin titration during this challenging period.

If intrapartum IV insulin was used for women with type 2 or gestational diabetes it should be stopped once the placenta is delivered. The frequency of capillary glucose monitoring for women with gestational diabetes prior to hospital discharge should be guided by how great the concerns are for persistent diabetes immediately postpartum as well as the potential obstacles to follow up for oral glucose tolerance testing postpartum. The plan for postpartum glucose testing for women with gestational diabetes, and diabetes management for women with type 2 diabetes, and with whom follow up is being provided (i.e. primary care or diabetes care providers) should be clearly communicated with the woman and her primary care provider. Postnatal prevention strategies to mitigate the risk of future development of diabetes and cardiometabolic disease should be discussed.

All women with diabetes in pregnancy should be informed of the benefits of breastfeeding, effective contraception, and the importance of planning for the next pregnancy should they desire another pregnancy.[14] Although it has become common to recommend a snack with breastfeeding to prevent hypoglycemia with breastfeeding in women on insulin, this is generally not required, especially among women skilled in carbohydrate counting and insulin adjustment who have appropriately reduced postpartum insulin dosing.[15]

Conclusions

Labour and childbirth present unique challenges in the management of diabetes. While protocols should be available to guide healthcare providers, clinical scenarios, personal preference, and experiences are unique; therefore, care must be individualized. Women who are able and willing can safely continue using the insulin pump during labour and vaginal or caesarean childbirth, however, IV insulin therapy should be discussed and used if necessary. Postpartum insulin dosing requirements must be considered prior to the onset of labour since there is a steep reduction in insulin resistance postpartum that drastically reduces the insulin dose requirements postpartum.

Well before childbirth
Enter and save, but do not activate, a profile for postpartum insulin pump settings that results in an insulin dose of approximately 20–30% less than the dose required preconception or approximately 50% less than the dose required in late pregnancy.[10] Note: certain insulin pumps will allow for multiple basal rate settings only (Medtronic™, Omnipod™) while other insulin pumps will allow entry of multiple profiles that include basal rates, insulin to carbohydrate ratios, and insulin sensitivity factors (Tandem™).
Educate women and their birth partners on the available resources and responsibilities for safe insulin pump therapy use in hospital. To learn more, click here.
Reinforce the importance of bringing extra pump supplies to the hospital.
Prior to childbirth
The insulin pump, infusion set, and CGM should be situated away from a potential operative site.
A Teflon insulin infusion cannula is a potential option to address this hypothetical risk of electrical conduction when used close to unipolar diathermy.
During labour
If the patient is not able to manage her insulin pump because of confusion or illness, call in the hospital diabetes management team to start an IV insulin drip, and only stop the insulin pump once the IV insulin drip is running. If capillary blood glucose is greater than 8 mmol/L for 2 consecutive hours while the patient is in active labour, notify the doctor to discuss glucose management with the patient.
Nonautomated insulin pumps: • If the blood glucose level is <4.0 mmol/L, decrease the basal insulin rate by 30%–50%. • If the blood glucose level is ≤3.7 mmol/L or the patient is symptomatic, treat the low blood glucose level as per hypoglycemia orders. • If the blood glucose level is ≥6 mmol/L, administer a correction insulin bolus.
Automated ("closed-loop") insulin delivery pumps: • Increase the insulin pump target glucose level if glucose is below the target glucose range. • Decrease the insulin pump target glucose level if possible if glucose is above the target level for 2 consecutive hours.
Prior to delivery activate postpartum insulin pump settings: • Non-automated insulin pumps: 1 to 2 hours prior to caesarean section or at the start of pushing. • Automated insulin delivery: Just prior to caesarean section or at the start of pushing.
Postpartum
If IV insulin is started and the insulin pump is stopped during labour, continue IV insulin until 2 hours after the insulin pump is restarted.
Relax glycemic targets to 5–10 mmol/L postpartum.
Increase the insulin pump target glucose setting if the glucose level is running too low postpartum.
If using CGM, personalize but consider relaxing high glucose alarms.

Table 2: Recommendations for insulin pump use at the time of labour and childbirth; adapted from Drever et al.[8]

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Diabetes and Osteoporosis

Timothy John O'Leary, MD, FRCPC

About the Author

Dr. Timothy O'Leary received his medical degree from Queen's University, Kingston, Ontario in 1981. He trained in Internal Medicine in Toronto followed by an Endocrinology residency in the Ottawa/Kingston Program. He was an Assistant Professor at the University of Ottawa from 1985 to 2014 with a special interest in disorders of bone and mineral metabolism. Dr. O'Leary is currently in private endocrine practice with LMC Healthcare Ottawa.

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Introduction

As part of our care of patients with diabetes, we monitor target organs for damage. We routinely screen for microvascular and macrovascular complications. In my opinion, the awareness of bones as a target organ of diabetes will improve the care that we provide to patients. Patients with both Type 1 (T1DM) and Type 2 (T2DM) are at increased risk of fractures. This will become a larger issue in the future as the prevalence of diabetes is rising and individuals with diabetes are living longer. In addition to skeletal factors, diabetes and its complications can increase fractures by increasing the patient's propensity to fall. This can be due to neuropathy, visual impairment and hypoglycemia. However, there are some differences between the characteristics of bone disease between patients with T1DM and T2DM.

T1DM Diabetes and Fractures

Patients with T1DM have an increased risk of almost all types of fractures starting in childhood. Beginning at age 40, both men and women with T1DM have an increased hip fracture risk.[1] Studies show a 4-6-fold increase in hip fractures compared to age-matched non-diabetic controls.[2] This very high incidence of hip fractures is particular to T1DM and is not well understood. While bone mineral density (BMD) is slightly lower in T1DM, this is not sufficient to explain the much higher risk of fractures. This suggests that there are bone quality issues in addition to the lower bone density. Risk factors for fractures in patient with T1DM include longer duration of diabetes, female sex, poor glycemic control, and microvascular complications.[2] Furthermore, T1DM patients have increased morbidity and mortality from their fractures.[9]

T2DM and Fractures

With T2DM, the duration of diabetes is a very important factor for fractures. Patients with prediabetes are not at a higher risk of fracture. By 10 years of diabetes, there is a 40% increase in the risk of hip fracture.[3] Paradoxically, BMD is higher in patients with Type 2 diabetes.[4] This indicates a bone quality issue. It also means that uncorrected BMD or FRAX will underestimate fracture risk.[11] Risk factors for fractures in patients with T2DM include older age, lower BMD, lower body mass index (BMI) and diabetic complications.[3] Insulin use is also a risk factor for

fractures but it may just be a surrogate for other risks like duration of diabetes, complications, and hypoglycemia. Insulin is anabolic for the bone and increases density.

Is BMD Measurement Predictive of Fractures in T2DM?

BMD by dual energy x-ray absorptiometry DEXA at the hip and at the lumbar spine is our standard way of assessing fracture risk. However, we have stated that T2DM patients have higher bone densities but have more fractures.[11] Individuals with T1DM have lower bone densities but their fracture risk is higher than predicted from their bone density. BMD is useful for assessing fracture risk in patients with diabetes, but a correction to properly estimate the must be applied. If one subtracts 0.05 from the T-score of patients with more than 10 years of diabetes, the risk is better approximated.[2] For example, a T-score of -2.0 in a patient with T2DM would have the fracture risk of a T-score of -2.5 in a person without diabetes. This correction can be used with T1DM but there is less supporting data. Some DEXA machines can provide a Trabecular Bone Score in addition to BMD. This is a measurement of bone texture at the lumbar spine. Trabecular Bone Score averages lower in patient with T2DM and is more predictive of fracture risk.[13]

Is FRAX a Useful Tool for Patients With T2DM?

Similar to BMD, the FRAX underestimates fracture risk in patient with diabetes.[14] The FRAX calculator is available online here at no charge. One inputs patient information and receives the 10-year risk of major fractures and hip fractures. In general, a risk for major fracture of ≥20% or hip fracture of ≥3% indicates the need for osteoporosis drug therapy. Unfortunately, the free version does not provide a check box for diabetes. Various corrections have been advocated. One can subtract 0.5 from the T-score, check the box for rheumatoid arthritis or check the box for secondary osteoporosis.[15] In general, these adjustments should only be done for patients with a 10-year history of diabetes.[12] The latest version of FRAX (www.FraxPlus.org) does allow corrections of the risk by the presence of diabetes and the duration of diabetes. If the DEXA machine you use provides a Trabecular Bone Score, you can add this in to FraxPlus for a more accurate prediction of risk. The use of FraxPlus does require a fee.

Bone Quality and Diabetes

The traditional method of assessing bone quality was a bone biopsy to demonstrate microarchitecture and turnover. This is difficult for the patient and doctor, and not commonly done in clinical practice. Some advanced centres have High Resolution Peripheral Quantitative Computer Tomography. This is a small CT scanner that can examine an arm or a leg and provides resolution down to 60 microns. Studies show more cortical porosity in patients with T1DM and T2DM.[5] These microscopic holes weaken the bone. They may represent microvascular disease of the bone. These cortical pores are more common in diabetics with microvascular disease in the eyes and kidneys. Another mechanism for reduction in bone quality is advanced glycation end products (AGE's). This process is utilized with hemoglobin A1c (HbA1c) measurement. Proteins become glycated with exposure to glucose. When AGE's form on the T1DM collagen fibers, the bone becomes weaker and less flexible. The osteoclasts are less able to metabolize the bone. Bone resorption and bone formation decrease leading to a low turnover state; bone strength decreases.

The Effect of Diabetes Medication on BMD and Fractures

Several classes of medications for diabetes have been shown to affect BMD and fractures **(Table 1)**. Some studies with metformin show a lower risk of fractures while others suggest that it is neutral.[7] Sulphonylureas and insulin may slightly increase the risk of fractures but this could be due to hypoglycemia and falls as these agents do not decrease BMD. Thiazolidinediones (rosiglitazone and pioglitazone) have the most clearly documented negative effects on bone.[7] As PPAR gamma agonists, thiazolidinediones favour mesenchymal stem cell differentiation into adipocytes rather than osteoblasts.[6] DPP-4 and GLP-1 agonists appear to be neutral for bone.[2] The skeletal effects of SGLT-2 inhibitors are less clear and evolving. Some studies with canagliflozin (CANVAS) suggest a decrease in hip BMD and increased fractures.[2] However, a large meta-analysis and post-marketing surveillance trials have failed to show increased fractures in patients on SGLT-2 inhibitors.[8] The benefits of SGLT-2 inhibitors generally outweigh the risks to the skeleton.

Medication	BMD	Fracture Risk
Metformin	Neutral or increase	Neutral or decrease
Sulphonylureas	Neutral	Neutral or Increase
Insulin	Neutral	Neutral or Increase
Thiazolidinediones	Decrease	Increase
DPP-4 Inhibitors	Neutral or increase	Neutral or decrease
GLP-1 Agonists	Neutral or increase	Neutral or decrease
SGLT-2 Inhibitors	Neutral or decrease	Neutral

Table 1. The effect of medications for T2DM on BMD and fractures; courtesy of Timothy John O'Leary, MD, FRCPC

Does Improving HbA1c Decrease Fractures?

Improving HbA1c most likely decreases fractures, but this is difficult to study. The Accord Trial, which compared a standard control group with a mean A1c of 7.5%, with an intensive control group with an HbA1c of 6.5% did not show a difference in fractures over the four years of the trial.[19] However, both arms were under fairly good control. Epidemiological studies suggest that fracture risk increases when the HbA1c exceeds 8.5%.[19] We have many reasons for attempting to achieve good diabetic control and it should also improve bone health.

How Should We Treat Osteoporosis in Diabetic Patients?

In general, we should follow the same guidelines as we do for patients without diabetes. We are unlikely to see prospective randomized controlled trials of osteoporosis medications in patients with diabetes that are large enough and long enough to demonstrate a fracture reduction. Subgroup analysis of diabetic patients in studies of osteoporosis medications show trends of BMD and fractures to suggest a similar response to nondiabetics. In the FIT study, women were randomized to alendronate or placebo for three years. Diabetic women assigned to alendronate had a similar increase in spine and hip density as non-diabetic women on alendronate.[16] There is observational data showing that diabetic patients receiving raloxifene or bisphosphonates have a similar reduction in fracture to non-diabetic patients on these medications.[17] The FREEDOM Trial of denosumab showed improvement in BMD and fewer fractures in the subgroup with T2DM.[18]

Summary

Patients with both T1DM and T2DM are at increased risk of fractures. Hip fracture incidence is particularly high in patients with T1DM. The fracture risk exceeds the prediction from BMD and FRAX for both T1DM and T2DM, suggesting bone quality issues. Leading theories about the cause of the bone quality issues include increased cortical porosity and advanced glycolation end products. Aside from thiazolidinediones (rosiglitazone and pioglitazone), treatments for diabetes do not have a major effect on fractures. BMD and FRAX are useful for assessing fracture risk although corrections need to be applied to prevent underestimation of fracture risk. Diabetes patients can be treated with the medications approved for osteoporosis in patients without diabetes.

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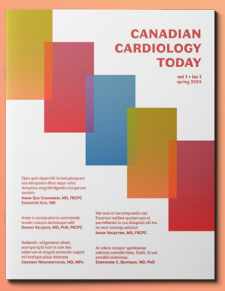

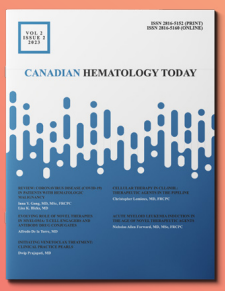

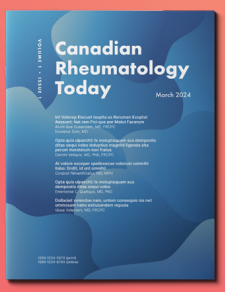

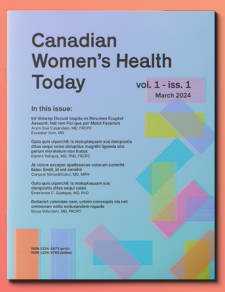

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