Volume 1 – Issue 3

Canadian Diabetes & Endocrinology Today

ISSN 2817-4097
(English ed. online)

October 2023

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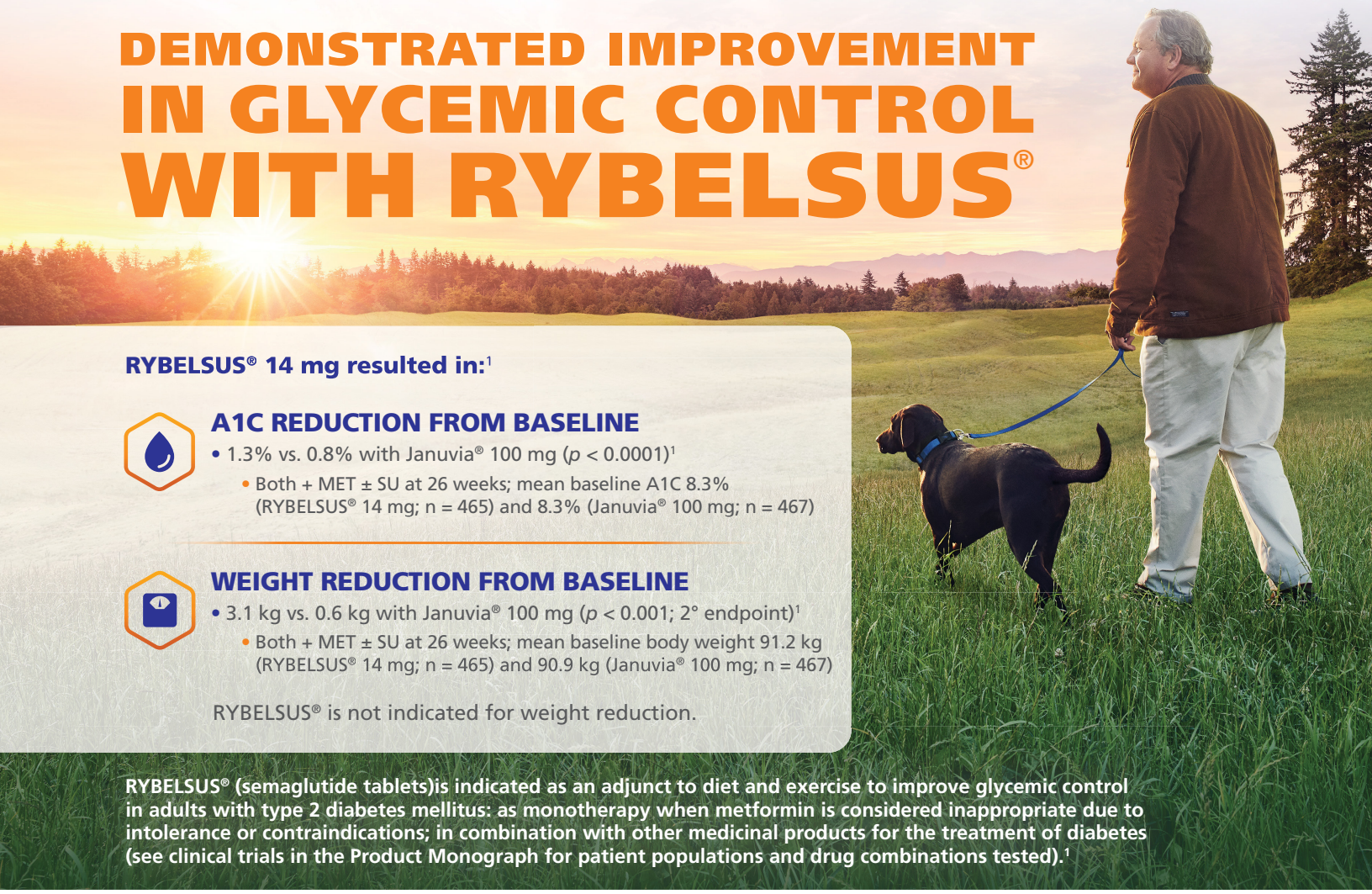

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CV, cardiovascular; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SU, sulfonylurea.

References: 1. RYBELSUS® (semaglutide tablets) Product Monograph. Novo Nordisk Canada Inc., March 30, 2020.
2. Rosenstock J, et al. Effect of additional oral semaglutide versus sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: The PIONEER 3 randomized clinical trial. *JAMA.* 2019.

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Lipoprotein (a) in Cardiovascular Risk Assessment and Management in Diabetes Mellitus

Gordon A. Francis, MDCM, FRCPC, FAHA

About the Author

Dr. Gordon Francis joined the Division of Endocrinology and Metabolism and Department of Medicine at the University of British Columbia in 2007 as a professor. He is an investigator in the Centre for Heart Lung Innovation and Providence Health Care Research Institute, and from 2007 to 2020, was director of the Prevention Clinic, both based at St. Paul's Hospital. His laboratory has done pioneering research showing the major role of cholesterol build up in artery smooth muscle cells in the development of atherosclerosis, the cause of most heart attacks and strokes. His laboratory is also studying the role of smooth muscle cells in development of cerebral amyloid angiopathy in Alzheimer's and other forms of dementia. Dr. Francis completed a BSc in Biochemistry at Simon Fraser University, medical school at McGill University, internal medicine and endocrinology residencies at the University of British Columbia and University of Alberta, and a senior research fellowship at the University of Washington. In addition to research and clinical work, he is involved in the development of national guidelines for the diagnosis and management of lipid abnormalities to prevent cardiovascular disease.

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Introduction

Lipoprotein (a) [Lp(a)] is an independent and genetically-determined risk factor for coronary heart disease (CHD) and stroke that is not changed by alterations in lifestyle factors. It is now recommended by Canadian and other national lipid guidelines to be measured once in a person's lifetime as part of overall assessment for cardiovascular risk, along with family history; presence of hypercholesterolemia; Type 2 diabetes (T2DM); hypertension; and smoking. The presence of elevated Lp(a) confers additional risk to the already high cardiovascular risk in individuals with T2DM. This review summarizes the nature and association of Lp(a) with elevated cardiovascular disease (CVD) risk; the increased cardiovascular risk in individuals with T2DM; potential therapies to lower Lp(a); whether or not to measure Lp(a); and recommendations on how to respond to the finding of elevated Lp(a) in a patient with T2DM.

Lp(a): Definition and Importance

Lp(a) is a lipoprotein molecule that is not reported along with the standard lipid profile. It consists of an LDL-like particle with an additional protein, apolipoprotein(a) [apo(a)] bound to apolipoprotein B of LDL by a disulfide bond (**Figure 1**).

Genetic variants in the LPA locus that regulate Lp(a) levels have been shown by Mendelian randomization studies to clearly associate with CHD risk, thereby strongly suggesting a causal association between Lp(a) and CVD.[1,2] Increased CVD risk with elevated Lp(a) is independent of the low density lipoprotein cholesterol (LDL-C) level and other major CVD risk factors,[3] and is thought to increase CVD risk by mechanisms including increased atherogenesis, inflammation and thrombosis.[4] Levels of Lp(a) >500 mg/L (>100 nmol/L) are found in approximately 20% of individuals of European and South Asian descent, 40% of African American individuals, and 10% of East Asian

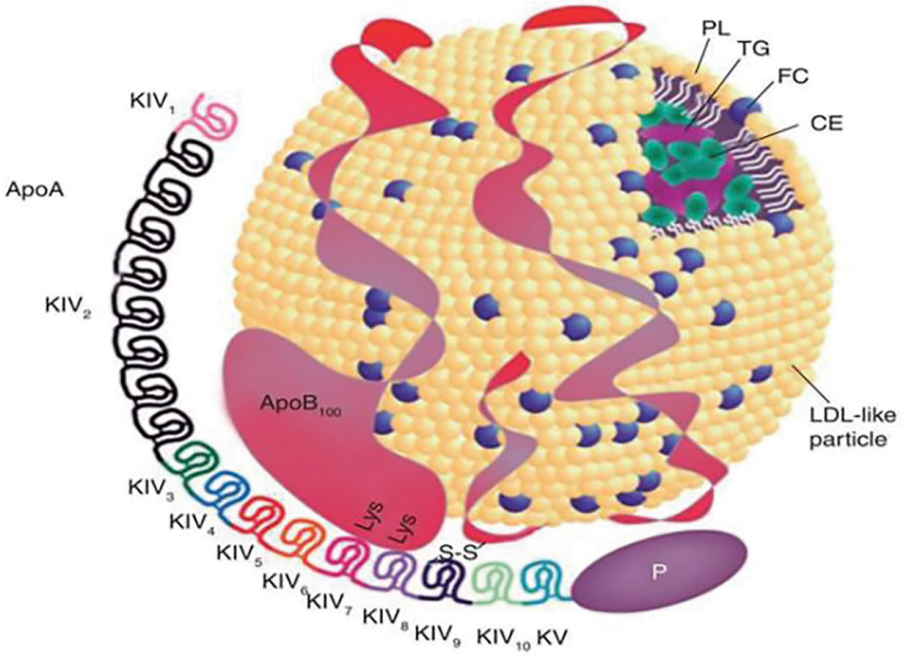

Figure 1. Lipoprotein (a); *courtesy of Gordon A. Francis, MD.*

individuals.[5,6] High Lp(a) is thus an extremely common CVD risk factor. Levels of Lp(a) are almost entirely genetically determined, (i.e., do not significantly vary by by changes in lifestyle including diet, exercise and weight change, and are not lowered by the use of standard lipid medications such as statins or ezetimibe.) *As a result, Lp(a) can be measured once in a person's lifetime, and does not need to be repeated* unless the individual is taking agents such as PCSK9 inhibitors or in the case of expected upcoming therapies that are capable of lowering Lp(a), as described below.

Based on the very strong correlation of Lp(a) level with CVD risk independent of other major coronary risk factors, and the standardization of Lp(a) clinical assays, since 2019 in the European Atherosclerosis Guidelines and since 2021 in the Canadian Lipid Guidelines, it has been recommended that all adults have Lp(a) measured once in their lifetime as part of routine cardiovascular risk assessment.[7,8] Measurement of Lp(a) can take place when an individual has their lipid profile measured for the first time in their lives,[8] or at any time thereafter.

Consideration that Lp(a) may be the reason for premature vascular events or a contributor to recurrent vascular events should be given when a patient suffers a premature coronary event or stroke in the absence of other obvious risk factors such as hypercholesterolemia, smoking, diabetes, or hypertension, or when a secondary prevention patient has recurrent events despite otherwise good control of background risk factors including achievement of recommended LDL-C targets. In such cases, elevated Lp(a) is very frequently the explanation for a patient's premature or recurrent vascular event.

Increased Cardiovascular Risk in T2DM with Elevated Lp(a)

The presence of T2DM confers markedly increased risk of cardiovascular disease even in the absence of elevated Lp(a). Men and women with T2DM have the same cardiovascular risk at age 45 as individuals without T2DM at age 70, demonstrating the profound effect diabetes has on cardiovascular age.[9] The reasons for such high cardiovascular risk in T2DM are not fully understood. However, they comprise dyslipidemia including the presence of small, dense LDL and increased remnant lipoprotein cholesterol due to impaired lipoprotein metabolism, chronic inflammation, hypercoagulability, and the effects of hyperglycemia on endothelial cell and other cell functions.[10,11]

Elevated Lp(a) has been shown to increase CVD risk in individuals with T2DM to a greater extent than in those without the disease, and to increase risk to a greater extent in individuals with T2DM vs those with T2DM and normal Lp(a).[12] The presence of CVD was found to be increased in individuals with T2DM and elevated Lp(a) vs those with T2DM and no Lp(a) elevation with an odds ratio for coronary artery disease (CAD) of 1.6.[13] Data from the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) study found the highest Lp(a)-associated CVD risk in individuals with T2DM compared to those without T2DM (HR for major coronary events 1.31 and for CVD 1.22 with T2DM vs 1.15 and 1.13 without T2DM, respectively).[14] Another multicentre study compared individuals with prediabetes or T2DM to individuals with normal glucose metabolism. The results showed that with Lp(a) >500 mg/dL (100 nmol/L), prediabetes conferred a 2.7-fold increased risk and T2DM a 3.5-fold increase in cardiovascular events vs individuals with normal glucose and the same level of elevated Lp(a).[15] The Atherosclerosis Risk in Communities (ARIC) Study with 15-year follow-up found that with

Lp(a) >500 mg/dl, risk of an incident CVD event was increased in the presence of prediabetes (HR 1.35) or T2DM (HR 1.42) vs individuals with normal fasting glucose.[16] The combined evidence indicates that elevated Lp(a) is a major risk enhancer for CVD in individuals with prediabetes or T2DM. At this time, the relationship of elevated Lp(a) with CVD risk in individuals with T1DM is less clear.[12]

In addition to increasing macrovascular risk in T2DM, elevated Lp(a) is also associated with a higher risk of microvascular complications including neuropathy and nephropathy, indicating that high Lp(a) is a general biomarker of increased risk of complications in T2DM.[17]

Novel Therapies to Lower Lp(a)

Improvement in lifestyle measures or T2DM control do not lower Lp(a), nor do T2DM medications or commonly-used lipid-lowering medications including statins or ezetimibe. The PCSK9 inhibitors evolocumab and alirocumab can reduce Lp(a) levels up to 25%. The reduction in cardiovascular outcomes with PCKS9 inhibitors may be related, in part, to their ability to lower Lp(a), independent of lowering of LDL-C.[18,19] Novel agents that can lower Lp(a) very effectively, including antisense oligonucleotides and those that silence RNA against apo(a), are currently being tested in robust cardiovascular outcome trials to determine the additional benefit of lowering Lp(a) on a background of effective LDL-C-lowering therapy. These trials are expected to report outcomes in the next 3–4 years.[20] These trials are expected to have large cohorts of patients with T2DM to allow subanalysis of these agents' benefits in T2DM. The elevated CVD risk conferred by elevated Lp(a) in T2DM suggests that individuals with T2DM could potentially benefit proportionally more from these agents than individuals with elevated Lp(a) but without T2DM.

It has been estimated that the amount of Lp(a) lowering required to achieve the same cardiovascular benefit as lowering LDL-C by 1 mmol/L is ~1000 mg/L or 214 nmol/L.[21] That suggests that if Lp(a)-lowering treatments are shown to add to the cardiovascular protection achieved with current LDL-lowering therapies, those individuals with the highest baseline Lp(a) levels will be the most likely to benefit. Several reports have found an association between very low levels of Lp(a) and increased risk of developing T2DM (summarized in Ward et al).[12] Whether there could be increased risk of developing T2DM with the use of Lp(a)-lowering drugs remains to be determined from ongoing clinical trials.

Should Lp(a) be Measured in Patients with T2DM?

Canadian and other international guidelines for the assessment and management of dyslipidemia now recommend measuring an individual's Lp(a) level once in a lifetime as part of overall cardiovascular risk assessment. The Canadian lipid guidelines recommend measuring Lp(a) at the same time as the first lipid profile measurement.[8] It is recommended that all individuals have Lp(a) measured even in the absence yet of agents that lower Lp(a) very effectively, to identify those at highest risk, and to reduce other modifiable risk factors as much as possible. While this guideline has been in place for two years, it is anticipated that it will take considerable time for general practitioners and specialists to become more aware of the risk of elevated Lp(a) and the need to measure it routinely. Attendance at a consultation for T2DM or at a specialty diabetes clinic provides an opportunity for Lp(a) measurement to be instituted as a routine policy, if it has not already been measured, given that it may not be measured in other settings.

Course of Action for Elevated Lp(a)

The current approach to finding elevated Lp(a) is to do a thorough review of all other major risk factors (hypercholesterolemia; smoking; T2DM; hypertension; family history of premature coronary disease or stroke), work to control the modifiable factors, and possibly performing vascular imaging such as carotid ultrasound or coronary calcium score to identify plaque. A shared decision-making process with the patient regarding whether or not to institute statin therapy should then occur based on all these factors. Statins have been shown to significantly reduce the CVD risk associated with elevated Lp(a), even though they do not lower Lp(a).[22] Given the significantly worse CVD and microvascular outcomes in people with T2DM who also have high Lp(a), a finding of elevated Lp(a) in a patient with T2DM should stress the need to institute effective statin +/− other LDL-C-lowering therapy possibly sooner than current recommendations regarding the timing of statin initiation in diabetes (T2DM or T1DM over age 40, or over age 30 with more than 15 years of diabetes, or the presence of any microvascular complications).[8] Although PCSK9 inhibitors can lower Lp(a) by up to 25%, elevated Lp(a) in the absence or presence of T2DM is not yet a provincially-funded indication for PCSK9 inhibitors unless the patient also has familial

hypercholesterolemia. Patients with documented symptomatic or subclinical ischemic vascular disease and with or without T2DM who do not achieve recommended lipid targets despite maximally-tolerated statin therapy plus ezetimibe may qualify for PCSK9 inhibitor treatment if they carry private insurance.

Lipid targets for all individuals with the statin-indicated definition of diabetes are LDL-C <2.0 mmol/L, nonHDL-C <2.6 mmol/L, and apoB <0.8 g/L. In the presence of any known cardiovascular disease, including subclinical disease found on a vascular imaging study, or in the presence of Lp(a) >100 nmol/L (500 mg/L), the lipid targets should be LDL-C <1.8 mmol/L, non-HDL-C <2.4 mmol/L, or apoB <0.7 g/L. In patients with T2DM who are resistant to taking statin therapy, the additional finding of elevated Lp(a), which will be present in approximately 20% of patients with T2DM as in the general population, provides another opportunity and rationale to convey the huge benefit of initiating lipid-lowering therapy in T2DM.

Conclusion

Lp(a) is a genetically determined factor known to be elevated in ~20% of the population including patients with T2DM. It is a major risk enhancer for cardiovascular disease, including adding significantly to the already high cardiovascular risk associated with T2DM. Lp(a) is recommended to be measured once in a lifetime as an integral part of overall CVD risk assessment. An office or specialty diabetes clinic consultation represents an excellent opportunity to screen for elevated Lp(a) if it has not yet been performed, and to further tailor cardiovascular disease preventive measures for patients with T2DM.

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Financial Disclosures

None declared.

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Approach to the Management of Thyroid Eye Disease

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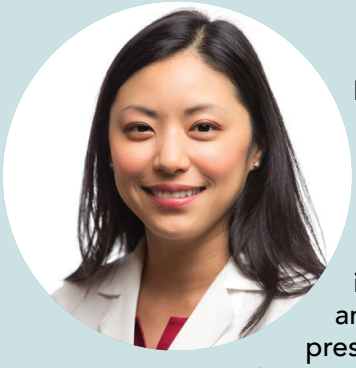

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Introduction

Thyroid Eye Disease (TED), also known as Graves' orbitopathy, is an autoimmune condition characterized by inflammation of the extraocular muscles, orbital fat and periocular tissues.[1] As the most common orbital disease worldwide, its prevalence is estimated to be between 0.5%–2% and it disproportionately affects females 4:1.[2] Although the majority of TED cases occur in patients with Graves' disease (80%–90%), it can also be seen with patients with Hashimoto's thyroiditis (10%), euthyroid individuals (5%–10%) and thyroid cancer.[3] At the time of initial Graves' disease diagnosis, 25% of patients have clinically detectable orbital involvement that is often mild.[4] The natural history of TED typically consists of an initial active inflammatory period lasting 6–36 months, which then plateaus and is followed by a quiescent fibrotic phase with stabilization of disease.[5]

Clinical Phenotypes

Similar to the wide range in duration of the disease, the clinical manifestation of TED can also be highly variable with no single pathognomonic diagnostic finding. The most commonly observed and often early sign is lid retraction (38%–90%) followed by von Graefe's sign (36%–80%).[6] Von Graefe's sign is a dynamic finding described as upper eyelid lag as the eye tracks a moving object downward, and is distinct from lid lag which is a static finding and occurs less frequently in TED. Proptosis (exophthalmos) (60%) and restriction in extraocular mobility (40%) are the most commonly seen orbital signs. On neuroimaging, extraocular muscles (EOM) can show enlargement and inflammation, with the order of involvement starting with inferior rectus, followed by medial rectus, superior rectus, and finally lateral rectus. Fat expansion can also be noted on neuroimaging. The combination of EOM enlargement and fat expansion produces compression at the orbital apex causing compression optic neuropathy, leading to vision loss. Less commonly, significant fat expansion alone can lead to severe proptosis and stretching of the optic nerve leading to optic neuropathy. Other inflammatory periocular changes can include edema and/or erythema of the lid, conjunctiva (chemosis and injection), caruncle, and plica. The patient can experience excessive tearing or dry eye symptoms as part of direct meibomian gland dysfunction (MGD) or lagophthalmos (incomplete closure of the eye) from lid retraction.

Diagnosis and Disease Grading

The heterogeneity of TED findings can make diagnosis difficult at times, especially in mild cases. In 1994, Bartley and Gorman proposed a diagnostic criterion for TED including eyelid retraction with one of these characteristics: thyroid dysfunction or regulation (antibodies), exophthalmos; optic nerve dysfunction, or EOM involvement, after exclusion of other orbital diseases. In cases where no lid retraction is noted, thyroid dysfunction or regulation must be present.[7] More recently, the North American Society of Academic Orbital Surgeons (NASAOS) proposed that the diagnostic criteria include serological evidence of autoimmune thyroid disease, clinical features in the orbit and eyelid consistent of TED, and imaging findings of fusiform, tendon-sparing enlargement of ≥1 extraocular muscle. Serum markers can include thyroid stimulating antibody (TSAb) and thyroid blocking antibodies (TBAbs) including anti-thyroid peroxidase antibody (TPOAb), TSH receptor antibody (TSHRAb), and thyroglobulin antibody (TGAb).

Dysthyroid optic neuropathy can also be difficult to identify, as no single clinical sign is completely reliable. Generally, optic nerve function is assessed with visual acuity; colour vision; presence of disc edema; relative afferent pupillary defect; absence of spontaneous venous pulsations; and abnormal visual fields.[8]

Neuroimaging may be use for diagnosis and to facilitate management. CT of orbits can facilitate surgical planning, and MR imaging can potentially

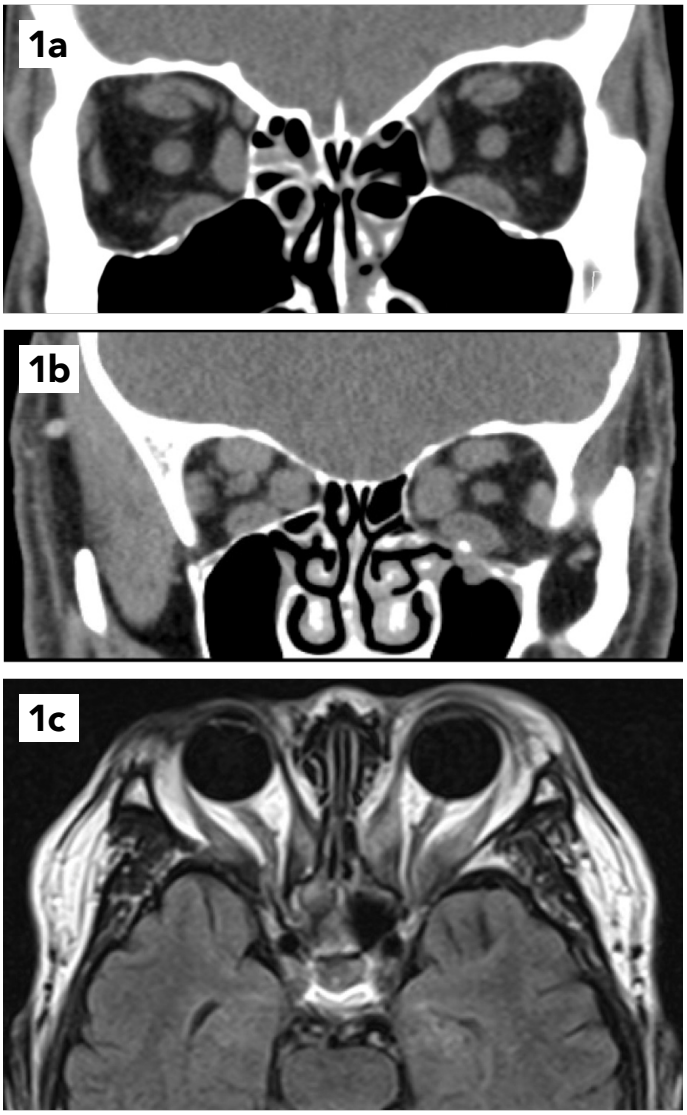

Figure 1. A. Coronal CT without contrast showing bilateral enlargement of the inferior rectus, medial rectus and superior rectus-levator complex with sparing of lateral rectus. No apical crowding. **B.** Coronal CT without contrast showing apical crowding. **C.** Axial MRI T2 flair showing enlargement of bilateral medial and lateral rectus with tendon sparing and enhancement indicating inflammation with the muscles. Neuroimaging used for diagnosis; *courtesy of Sabrina Yu, MD & Vivian T. Yin, MD.*

help delineate active inflammation in extraocular muscles (**Figure 1**). It is recommended that all Graves' disease patients be screened for TED at each visit and connected to ophthalmology early, with urgency of referral dependent on clinical presentation.[9]

In addition to the challenges of diagnosis, the variable course of the disease makes disease grading necessary in order to manage TED patients based on best evidence. There are two types of TED classifications based on the severity or activity of disease. The Clinical Activity Score (CAS) and vision, inflammation, strabismus, and appearance score (VISA)2 evaluate disease activity (**Table 1**). In contrast, the European Group on Graves' Orbitopathy (EUGOGO) classifies disease severity broadly into mild (<2 mm lid retraction; mild soft tissue involvement; <3 mm exophthalmos; transient/no diplopia); moderate-to-severe (lid retraction >2 mm; moderate/severe soft tissue involvement; exophthalmos >3 mm; diplopia), and sight-threatening (dysthyroid optic neuropathy and/or corneal breakdown).[10] As with all grading systems, none is perfect for all scenarios. The choice of grading system is dependent on purpose and ease of use; however, the key factor is consistency in order to track patients over time.

Conventional Treatments

Traditionally, the management of TED is dependent on the severity of disease. However, in all patients with TED, it is important to optimize modifiable risk factors. Smoking is the strongest modifiable risk factor. Smoking shows a dosage-dependant correlation with the development of proptosis and diplopia, disease progression and reduced efficacy of treatment.[11] Euthyroid status should be established and maintained early, as both hypothyroidism and hyperthyroidism have been shown to exacerbate TED.[10] However, in some studies radioactive iodine treatment has been shown to worsen and increase the risk of developing TED in patients with Grave's disease.[12] Consideration for prophylaxis corticosteroid treatment should be discussed with the patient and managed in conjunction with an ophthalmologist.

In patients with mild disease, supportive management includes artificial tears and ointments for dry eye, and prisms or ocular occlusion for diplopia.[9] In a randomized, controlled trial (RCT) from the European Group on Graves' Orbitopathy, selenium was shown to improve quality of life (QOL), eyelid aperture and soft tissue involvement compared to pentoxyphilline.[13] However, it remains unclear if supplementation is effective in populations that are not deficient in selenium, as is the case in North America.

In moderate-to-severe disease, glucocorticoids have historically been the mainstay of treatment to suppress orbital inflammation. In recent years, the use of intravenous methylprednisolone (IVMP) has become more common, as it has been shown to achieve more rapid improvement without the same degree of side effects than longer-term oral steroid use.[10] The recommended regimen is a total dose of 4.5 g IVMP divided as 0.5 g weekly for six weeks, then 0.25 g weekly for a further six weeks.[14] An individualized approach should be adopted in determining when to discontinue steroids or switch to another agent, although generally IVMP pulse should not continue beyond 12 weeks.[9] In the treatment of optic neuropathy, urgent decompression and high-dose IVMP (1,000–15,000 mg/kg) is advised.[15] Orbital injection of triamcinolone for the treatment of TED is controversial. Some studies have shown benefit in decreasing orbital congestion[16] and lid retraction;[17] however, there is risk of retinal embolic phenomenon with orbital injection.[18] Furthermore, real-life clinical response has not been as promising as the results seen in the literature.

The use of orbital radiation in treating TED remains variable. Although it is well tolerated, multiple systematic meta-analyses have reached varying conclusions regarding its efficacy.[19,20] Radiation can be considered in the early, active phase of the disease and appears most beneficial for dysthyroid optic neuropathy, periocular inflammatory changes and progressive diplopia.[21] The optimal dose and fractionation schedule is unclear, with 20 Gy over two weeks commonly administered, although alternatively lower-dose 1 Gy per week over 20 weeks may be equally effective.[22] Radiotherapy should be avoided in Type 2 diabetics to prevent retinopathy, and in patients < 35 for secondary malignancy risk. Radiotherapy has only been studied with oral steroids to date and there is no published data to date on its efficacy in combination with intravenous glucocorticoids. Currently, two multicentre RCTs are underway to compare the efficacy of combined radiotherapy and IVMP vs monotherapy IVMP, in both early progressive TED and dysthyroid optic neuropathy (thyroideyedisease.org).

Additional surgical intervention for rehabilitation purposes occurs on an elective basis once the disease is in the quiet phase, with a staged approach to address proptosis first with orbital decompression, then ocular misalignment with strabismus surgery, and lastly, eyelid retraction repair with levator-muller recession.[9]

Immunomodulatory Therapies

In recent years, there has been a proliferation of new therapies for modifying the course of TED. The first

	Grade	Subjective	Objective
VISA	Vision /1	Visual acuity Colour	Best correct visual acuity (BCVA) HRR colour test Optic nerve edema/pallor
	Inflammation /10	Retrobulbar ache Lid swelling Diurnal variation	Caruncle edema Chemosis Conjunctival injection Lid erythema Lid edema
	Strabismus /3	Diplopia Head turn/tilt	> 45° = 0 30–35° = 1 15–30° = 2 < 15° = 3
	Appearance /3	Lid stare Lid sensitivity Bulging eye Tearing Ocular irritation	Lid retraction, scleral show, lagophthalmos, exophthalmos, corneal erosion/ulcer, SLK, IOP primary, and upgaze

	Points	Parameters
CAS *inactive if < 3* *active if ≥ 3*	1	Spontaneous retrobulbar pain
	1	Pain on attempted upgaze or downgaze
	1	Eyelid erythema
	1	Eyelid edema
	1	Conjunctival hyperemia
	1	Conjunctival chemosis
	1	Inflammation of caruncle or plica
Follow-Up	1	Increase of > 2 mm proptosis
	1	Decrease of extraocular movement in any direction ≥ 5°
	1	Decrease of visual acuity > 1 Snellen line

	Severity	Description
EUGOGO	Mild	< 2 mm lid retraction Mild soft tissue involvement > 3 mm exophthalmos Transient/no diplopia Corneal exposure responsive to lubrication
	Moderate-to-Severe	≥ 2 mm lid retraction Moderate-severe soft tissue involvement ≥ 3 mm exophthalmos Diplopia
	Impaired function	Dysthyroid optic neuropathy Corneal breakdown

s	Class	Description
NO SPECS	0	No physical signs or symptoms
	I	Only signs, no symptoms (lid retraction)
	II	Soft tissue involvement (conjunctival/caruncle injection and chemosis, eyelid erythema, edema)
	III	Proptosis
	IV	Extraocular muscle signs
	V	Corneal involvement
	VI	Sight loss (optic nerve involvement)

Table 1. Four thyroid eye disease scoring systems. VISA grades both disease activity and severity. CAS measures disease activity. EUGOGO and NOSPECS classify disease severity; *courtesy of Dr. Sabrina Yu & Dr. Vivian T. Yin.*

Agent	Company	Mechanism of action	Route	Phase	Country Sites
Batoclimab (IMVT-401)	Immunovant	Anti-neonatal Fc receptor monoclonal antibody	SC	III	US, Belgium, Hungary, Latvia, Spain
VRDN-001	Viridian	Monoclonal antibody, IGF-1R inhibitor	IV	II/III	Canada Italy, Netherlands, UK, US
Linsitinib	Sling Therapeutic	Small molecule IGF-1R inhibitor	PO	II/III	Canada, Italy, Spain, UK, US

Table 2. Ongoing clinical trials in drug therapy for thyroid eye disease; *courtesy of Dr. Sabrina Yu & Dr. Vivian T. Yin.*

on the market in the United States was teprotumumab, a monoclonal antibody that binds to and inhibits the IGF-1 receptor, blocking signalling in the autoimmune activation of orbital fibroblasts.[23] It was approved by the FDA in January 2020 for the treatment of active moderate-to-severe TED. In a pooled RCT from two centres, there was a mean improvement in proptosis of 3 mm vs <0.5 mm, with 62% of patients achieving disease inactivation (CAS ≤1) at 24 weeks following every three-week infusion. Response at 72-week follow-up was maintained.[24] Real-world data indicates that this therapy may be effective in a more diverse population than was studied in the initial clinical trials, including patients with chronic thyroid orbitopathy[25] and dysthyroid optic neuropathy.[26] However, a small percentage of patients may require a second course of treatment.[27,28] Although teprotumumab is currently not Health Canada approved, clinical trials for a Phase 3 study will include Canadian sites. In addition, other candidate drugs targeting similar pathway are ongoing in Canada (**Table 2**).

Another emerging immunomodulatory agent for the treatment of TED is tocilizumab, a monoclonal antibody that blocks the interleukin-6 receptor. A multicentre RCT in Spain reported impressive findings of nearly ten-fold greater odds of CAS reduction of ≥2 points in steroid-resistant patients,[29] with subsequent consistent real-world data showing inactivation in 74% of treated patients.[30] Tocilizumab is Health Canada approved for use in rheumatoid arthritis, giant cell arteritis and juvenile idiopathic arthritis, and costs 20–30 times less than teprotumumab. Most surprisingly, early data from the Université de Montréal shows efficacy in the reversal of optic neuropathy in patients not amendable for decompression, in addition to 91% achieving CAS ≤1 at last follow-up (unpublished data).

Additionally, several adjunct and alternative agents have been studied in TED. The recent EUGOGO guidelines recommended combination therapy of IVMP and mycophenolate as first-line therapy; however, there are inconsistent findings from RCTs to conclude its impact.[9] No benefit was observed with azathioprine, and there is inconclusive evidence on rituximab in treating TED.[9]

Conclusion

TED can be a challenging and complex disease to evaluate and manage. Glucocorticoids continue to be the conventional mainstay for treating moderate-to-severe TED. However, a number of new molecules targeting TED pathways may alter the treatment of TED to focus on disease modification at an earlier stage.

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Financial Disclosures

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S.Y.: None declared.

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The Role of Plant-Based Diets in the Management of Type 2 Diabetes

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Background

A whole food plant-based (WFPB) diet is generally defined as a diet rich in fruits, vegetables, whole grains, legumes, nuts and seeds, and herbs and spices. Many define a WFPB diet as being exclusively plant-based with no animal products, excluding all red meat, poultry, fish, eggs, and dairy products. Other sources define it as a plant-forward dietary pattern that may still include small amounts of meat, eggs or dairy. A WFPB dietary pattern focuses on unprocessed plant foods, while avoiding processed foods containing refined grains, refined oils and added sugars. **Figure 1** depicts an example of a balanced WFPB meal.

On a practical level, it is important to distinguish a WFPB diet from a vegan diet, which eliminates all animal products but may include processed vegan foods (e.g., plant-based meats, pastries and fried foods). However, in the scientific literature, the term "vegan" is often used, and at times it is difficult to assess the amount of processed food included in diets of vegans included in observational studies. This paper will focus primarily on the evidence for an exclusively WFPB dietary pattern in the prevention and management of Type 2 diabetes mellitus (T2DM) and obesity. However, given certain limitations in the literature, some data on vegan diets and plant-rich but not exclusively plant-based diets will also be included.

The Dietitians of Canada and the American Dietetic Society have jointly stated that well-planned vegetarian and vegan diets can be healthful and appropriate for all life stages, highlighting the reduced risk of excess weight, cardiovascular disease, hypertension, and T2DM with these dietary pattern.[1] Vegetarian and vegan diets are identified in the Diabetes Canada Guidelines as one of several dietary patterns that have evidence for improved glycemic control, lipid profile and body weight in individuals with T2DM.[2]

T2DM Prevention

Observational data exists demonstrating that WFPB dietary patterns are associated with lower incidence and prevalence of T2DM. The Adventist Health Study-2 evaluated T2DM prevalence in relation to various types of dietary patterns: vegan, lacto-ovo vegetarian, pesco-vegetarian, semi-vegetarian, and non-vegetarian. Both body mass index (BMI) and risk of T2DM increased progressively with dietary patterns containing more animal products. Even after adjusting for BMI, vegan and lacto-ovo vegetarian diets were associated with a 0.51 (95% [CI 0.40–0.66]) and 0.54 (95% [CI 0.49–0.60]) odds ratio respectively for T2DM vs non-vegetarians.[3]

Similarly, Satija et al used food frequency questionnaire data from three large prospective cohort studies

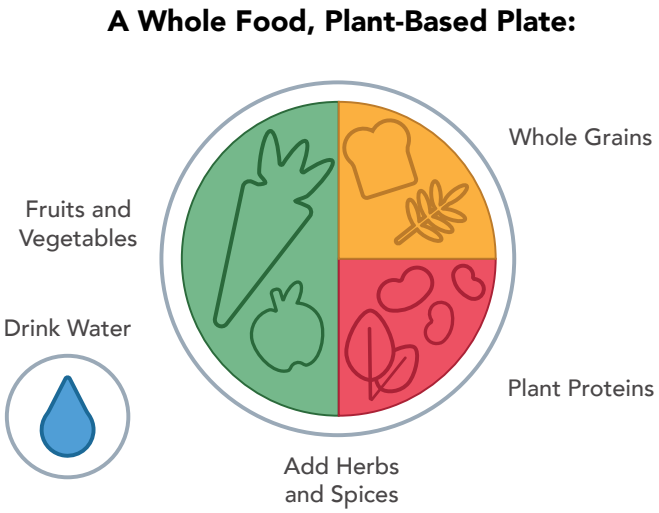

Figure 1. A fibre-filled, nutrient-dense antioxidant-rich plate for every meal; *courtesy of Dr. Heidi Dutton.*

(Nurses' Health Study, Nurses' Health Study 2 and Health Professionals Follow-Up Study) to create multiple dietary indexes including a healthy plant-based diet index in which all animal foods, and less healthy plant foods such as refined grains, along with fruit juice and sweets, received lower scores vs unrefined plant foods.[4] After adjusting for BMI and other T2DM risk factors, higher scores on the healthy plant-based diet index were associated with a reduced risk of T2DM with a hazard ratio of 0.66 (95% [CI 0.61-0.72]). Findings from these large cohort studies therefore suggest that diets rich in whole plant foods confer a lower risk of development of T2DM.

T2DM Management

Limited randomized controlled trials have been performed to evaluate the effect of a fully WFPB dietary pattern on glycemic control in patients with T2DM. In one study, Barnard et al randomized patients with T2DM to either the American Diabetes Association (ADA) diet or to a low-fat WFPB (vegan) diet consisting of vegetables, fruits, whole grains, and legumes. In the intention-to-treat analysis, HbA1c and body weight decreased by 0.96% and 6.5 kg respectively in the vegan group, and by 0.56% and 3.1 kg respectively in the ADA group (P=0.089 for HbA1c and P<0.001 for body weight). In individuals whose T2DM medications did not change during the trial, HbA1c fell by 1.23% in the vegan group and by 0.38% in the ADA group (P<0.001). Therefore, while both groups experienced glycemic control and weight loss benefit, the improvements appeared to be greater in the vegan group.[5] A systematic review and meta-analysis of six controlled trials of vegetarian and vegan dietary interventions in T2DM found that these diets are associated with significant improvement in HbA1c (pooled reduction of 0.39%).[6]

A recent non-randomized crossover trial evaluated a WFPB diet and a Dietary Approaches to Stop Hypertension (DASH) diet on insulin dose changes in 15 patients with T2DM managed with insulin (mean dose of 90 units/day).[7] The DASH diet is rich in whole plant foods but it is not exclusively plant-based. Participants completed seven days of the DASH diet, followed by seven days of the WFPB diet and subsequently seven days of the DASH diet again. Following the DASH diet week 1, the total daily dose (TDD) of insulin dropped by 24%; following the WFPB week, the TDD of insulin dropped by a total of 39% vs baseline; following the DASH diet week 2, insulin dosing increased 15% from the WFPB week. HOMA-IR decreased by 49% from baseline at the end of the WFPB week. Average daily blood glucose measured by continuous glucose monitoring improved by 22–24% from baseline across the three intervention weeks. Although the study was small and of short duration, this highlights that improvements in glycemic control and insulin requirements can occur rapidly with a shift toward a more WFPB dietary pattern.

Mechanisms for Improving Glycemic Control with a WFPB diet

A WFPB diet improves insulin resistance and glycemic control in T2DM via multiple mechanisms. Increased dietary fat intake is well-known to increase insulin resistance via increased intramyocellular lipid storage and lipotoxicity.[8] In particular, this is seen with high intake of saturated fat,[9] and animal products are the main source of saturated fat in human diets. In one small study, vegan subjects matched by BMI to omnivores were found to consume a similar percentage of dietary fat intake, but less saturated fat and more polyunsaturated fat. In addition, they demonstrated less intramyoceullar lipid storage and better beta cell function.[10]

The high fibre content of a WFPB diet also plays a role in the prevention and management of T2DM. Higher fibre content in a meal reduces postprandial blood glucose response and promotes satiety.[11] Furthermore, fermentation of dietary fibre via gut bacteria in the large intestine produces short chain fatty acids which have important metabolic health modulating effects, such as reduced postprandial glucose response and increased GLP-1 levels.[12] WFPB diets are also low in advanced glycation end products (AGEs) and trimethylamine

N-oxide, both of which are thought to play a role in the pathogenesis of T2DM, and are found in high levels in meat (AGEs are particularly high when meat is broiled, grilled or roasted at high temperatures).[13] Thus, WFPB dietary patterns are potentially protective against T2DM via multiple mechanisms.

Obesity Management and the WFPB Diet

Numerous different dietary patterns have been shown effective for weight loss, with no one dietary pattern recognized as being superior.[14] However, evidence certainly exists that a WFPB dietary pattern can promote weight loss. The BROAD study randomized overweight and obese individuals to either a low-fat (7%-15% total energy from fat) WFPB dietary intervention or standard care.[15] The intervention group utilized a group educational format and, notably, did not include any exercise interventions or restrict caloric intake. At six months, mean BMI reduction in the WFPB group was 4.4 kg/m2 vs 0.4 kg/m2 in the standard care group (P<00001). Another randomized crossover trial assigned overweight adults to a Mediterranean or low-fat (10% total energy from fat) vegan diet for 16 weeks, followed by return to baseline for four weeks and subsequently the opposite diet for 16 weeks.[16] Overall net weight changes were 0 kg on the Mediterranean diet vs -6.0 kg on the vegan diet (P<0.001). This trial did not prescribe any caloric restriction or exercise changes to participants.

A WFPB diet is thought to aid in weight loss partially because of the low-calorie density of most whole plant foods. Including more plant foods with higher water content and lower calorie density has been shown to promote weight loss and improve satiety.[17] A small, randomized crossover trial showed that compared to a low carbohydrate diet high in animal products, a low fat WFPB dietary pattern resulted in an average 689 +/- 73 kcal/d less energy intake when participants were allowed to eat ad libitum.[18] Thus, a WFPB dietary pattern, particularly when low in fat, can allow some patients who are pursuing weight loss to eat to satiety without the need to track calorie intake.

The WFPB Diet and Planetary Health

Mitigating climate change is another important reason to guide patients toward a more WFPB dietary pattern. Worsening planetary health affects the individual health of our patients on a daily basis, via increased respiratory illness, extreme temperatures and displacement due to events such as flooding and forest fires.[19] In 2020, The EAT Lancet Commission released a report highlighting evidence-based dietary recommendations designed to be beneficial for human health while also optimizing planetary health and sustainable food production. This commission assembled 18 co-authors from 16 countries with expertise in the areas of agriculture, sustainability, political science and human health. The recommended dietary pattern is largely plant-based emphasizing whole plant foods, with flexibility to include very modest amounts of fish, dairy and meat, with red meat largely excluded.[20] The Commission projects that this large dietary shift would allow the planet to sustainably feed an estimated population of 10 billion by 2050; however, consuming even marginally more dairy and red meat than what the report recommends will make this objective unattainable.

Clinical Pearls
✓ In a real-world setting, some patients may find a given diet more sustainable if small amounts of animal products continue to be included
✓ If patients follow a 100% WFPB or primarily WFPB dietary pattern, Vitamin B12 supplementation is necessary, particularly for patients taking metformin. Vitamin B12 levels should be monitored • For non-pregnant adults <65 years old, the recommended dose is 50 mcg daily or 2000 mcg weekly of cyanocobalamin[21]
✓ A WFPB dietary pattern is intended to be a delicious and enjoyable way of eating. The following websites contain numerous free WFPB recipes and resources to help patients get started: • https://www.forksoverknives.com/ • https://nutritionstudies.org/recipes/ • https://www.pcrm.org/news/news-releases/21-day-vegan-kickstart-program-launches-new-website-and-phone-app • https://www.pcrm.org/good-nutrition/healthy-communities (contains resources specific to non-Caucasian communities)
✓ WFPB eating does not need to be costly. Staples such as dried legumes, whole grains and frozen vegetables are affordable options at the grocery store
✓ Patients with established T2DM may still need to avoid or limit high glycemic index whole plant foods (tropical fruits, whole grain breads/pasta, potatoes) even while following a WFPB diet, as these may cause blood glucose elevation
✓ Patients transitioning to an exclusively WFPB dietary pattern can benefit from counselling with a registered dietitian experienced in this area, to ensure adequate intake of nutrients such as iron, calcium and Vitamin B12

Conclusion

Well-planned WFPB diets can provide adequate nutrients and show evidence for both T2DM prevention and improvement in glycemic control for individuals living with T2DM. With a transition to this dietary pattern some patients may experience rapid improvements in glycemic control, necessitating careful blood glucose monitoring and adjustments of T2DM pharmacotherapy that can cause hypoglycemia. A WFPB dietary pattern can also promote weight loss, primarily via reduced caloric intake that occurs due to the relatively low-calorie density of whole plant foods. In addition, a WFPB dietary pattern is recommended for improving planetary health, as human health and planetary health are inextricably linked.

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Financial Disclosures

None declared.

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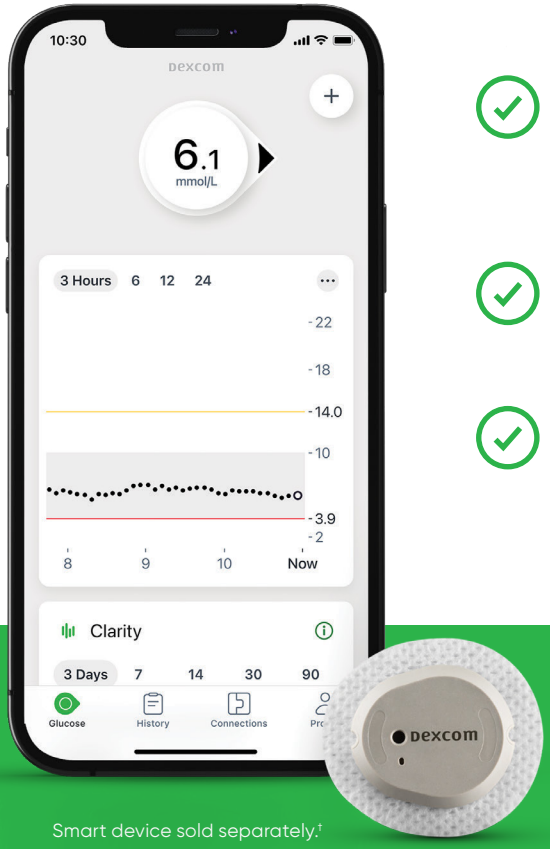

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§ Based on data from Dexcom CGM users in the U.S.

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.

G7

Glucagon-like Peptide-1 Receptor Agonist Treatment in Type 1 Diabetes: A Review of Current Evidence and Rationale for Use

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About the Author

Dr. Michael Tsoukas is an Associate Professor of Medicine, Division of Endocrinology at the McGill University Health Centre and Clinician Investigator of the Research Institute of McGill and Hygea Medical Clinic. He completed his residency training at Tuft's University and subsequently trained in Endocrinology at McGill University. He later pursued a post-graduate research fellowship in diabetes and obesity at Harvard University (Beth Israel Deaconess Medical Center), with a focus on GLP-1 receptor pharmacotherapy, brain signaling, and enterohormone treatments. Further training involved pathophysiological regulation of novel molecules such as SGLT-2 inhibitors and GLP-1 receptor agonists important in energy homeostasis, diabetes, and obesity.

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Introduction

Type 1 diabetes (T1D) is characterized by a progressive decline of insulin production due to a marked destruction of pancreatic β cells. Intensive insulin therapy is the pillar of T1D management. More recently, continuous glucose monitoring devices, closed-loop systems (CLS) and smarter connected insulin pen systems have all significantly helped individuals to improve glycemic control. However, despite these advances, more than three-quarters of the adult T1D population does not achieve recommended glycemic targets.[1] In addition, aggressive insulin intensification potentiates weight gain and the risk of recurrent hypoglycemic events. Recent significant increase in rates of obesity has also led to a sharp increase in T1D patients who concurrently have adiposity-based chronic disease, increasing their insulin resistance and predisposition for cardiovascular events.[2] While insulin will remain the basis of T1D management, there is an unmet need for individualized adjunctive therapeutic approaches focusing on the prevention of diabetic complications in addition to glycemic control. One such adjunctive therapy currently being explored in T1D are the glucagon-like peptide-1 receptor agonists (GLP-1RAs), a popular and robust approach in Type 2 diabetes (T2D) to mimic the natural endogenous GLP-1 incretin. This brief review will focus on the rationale and existing evidence for the use of GLP-1RAs in the management of T1D.

Background and Rationale

GLP-1RAs are well recognized for exerting multifaceted effects through activation of the widely dispersed GLP-1 receptor.[3] Data has shown predominant expression in the pancreatic islet cells, hypothalamus area of the central nervous system, and gastrointestinal (GI) tract.[4] This class of medication, commercially available since 2005, has been rigorously studied in the T2D population. In most cardiovascular outcome trials for T2D, GLP-1RAs have demonstrated profound reductions in major adverse cardiovascular events in atherosclerotic disease, all of which were independent of glycemic improvement.[4] In sub-group analyses, renal protective effects were also likely linked to reductions in albuminuria,[5] and certain GLP-1 mimetics have demonstrated improvements in non-alcoholic steatohepatitis, with reductions in liver enzymes and hepatic lipid accumulation.[6] Additionally, GLP-1RAs are routinely used in the pharmacotherapy of obesity due to their positive effects on the satiety

and food perception centres of the hypothalamus, and the slowing of gastric emptying.[7]

With the wealth of evidence of GLP-1RA in T2D and obesity management, the logical approach would be the use of these agents in T1D patient subgroups. Indeed, off-label use as adjunctive therapy to insulin is becoming increasingly common in practice. However, what are the potential beneficial mechanisms in a T1D population, and are there any evidence-based studies to support their use.

Potential Beneficial Properties for T1D

The complete benefits of GLP-1RAs in T1D are not fully elucidated; as a result, controversy exists over their off-label use. However, four main properties of GLP-1RAs have been proposed as having potential beneficial action in T1D (**Figure 1**).

1. Weight Loss Properties

Contrary to established perceptions, obesity is equally prevalent in the T1D population as it is in the general population.[8] Weight loss in T1D subgroups improves insulin resistance and can lower the total daily requirements of insulin. Two studies using liraglutide have been conducted in patients with T1D and overweight/obesity. One six-month trial demonstrated significant weight loss with thermogenesis and increased lipid oxidation as the main weight loss mechanisms.[9] Another study in a T1D cohort showed significant placebo-adjusted benefits with liraglutide on prolonged satiety, as well as decreased food consumption and food desire following standardized meal tests.[10] Insulin requirements are decreased with weight loss and, by association, cardiometabolic disease progression is potentially mitigated.

2. Suppression of Glucagon-mediated Gluconeogenesis

GLP-1RAs may offer glycemic improvement via their anti-glucagon property. The glucagonostatic effect exerted is important for potential efficacy in T1D given that the insulinotropic effect is less pertinent to individuals with inadequate β-cell function.[3] Two studies have demonstrated continued endogenous GLP-1 secretion following the ingestion of mixed meals in individuals with T1D, irrespective of residual β-cell function.[11,12] One probable pathway includes paracrine inhibition of α-cells, whereby GLP-1 receptor activation of δ-cells of the pancreas stimulates somatostatin release, which inhibits glucagon-stimulated increase in gluconeogenesis.[13] In doing so, improved glycemic control in target range with less hyperglycemia range, blood glucoses can potentially be achieved.

3. Inhibition of Gastric Emptying

Gastric emptying is a complex phenomenon in the T1D population, complicated by neuropathy, enterohormonal changes, modified neurotransmitters, and glycemia levels.[3] In some cases, gastric motility may be increased causing diarrhea, while in most cases motility is slowed causing gastroparesis. Authors of the EDIC trial observed altered gastric emptying in 47% of participants, most of which was asymptomatic.[14] This suggests that nearly half of the T1D population is affected by underlying GI autonomic neuropathy. These alterations affect post-prandial glycemia levels significantly. In T1D adolescents and young adults, one study (n=8) demonstrated delayed gastric emptying five hours postprandially with short-acting exenatide that was associated with reduced glucose excursions.[15] A longer trial in overweight people without diabetes

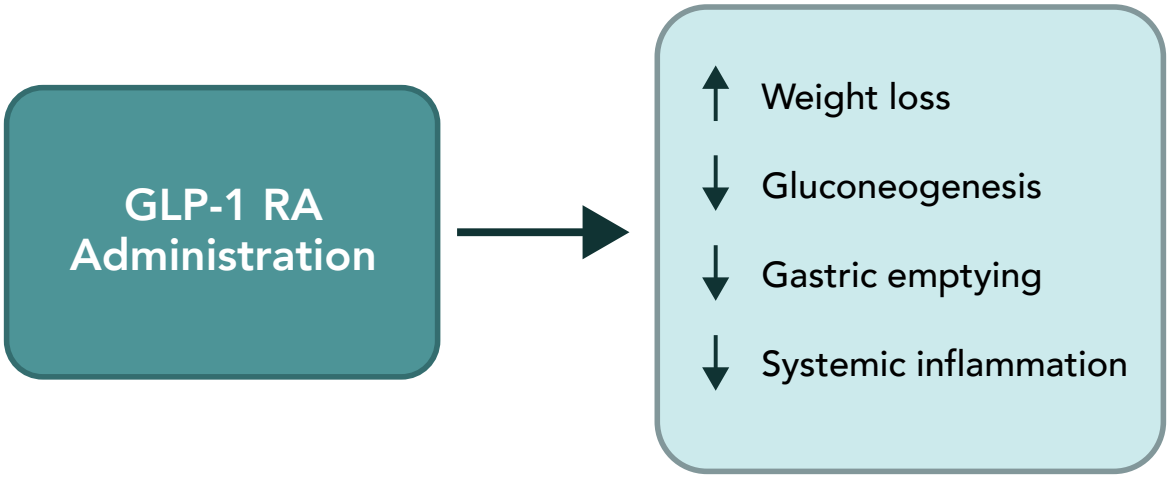

Figure 1. Potential beneficial mechanisms of GLP-1RAs in T1D; *courtesy of Dr. Michael A. Tsoukas.*

reported a marked reduction in gastric emptying and postprandial glycemia after eight weeks with once-weekly exenatide 2.0 mg.[16]

It is also known that acute changes in blood glucose concentration, both hyperglycemia and hypoglycemia, have a marked, reversible effect on gut motility.[17] Overall, the benefits of GLP-1RAs reflect improved post-prandial glycemic levels with less risk of glucose excursions. Finally, GI mechanoreceptors in gastroparesis relay a message of satiety to the brain, thereby also decreasing food intake which may, in turn, indirectly improve glycemic control.

4. Anti-inflammatory Properties

Systemic inflammation is well known to increase insulin resistance.[1819] Liraglutide treatment is reported to decrease levels of pro-inflammatory TNF-α and IL-6 as well as macrophage activation while increasing levels of the anti-inflammatory adiponectin.[20] Furthermore, high-sensitivity CRP and serum markers of endothelial function such as P-selectin, ICAM and VCAM have also been shown to improve with GLP-1 RA administration.[21] GLP-1RAs thus help with reducing inflammation which may have beneficial effects on glycemic control and atherosclerotic disease prevention.

T1D Clinical Studies Using GLP-1RAs

The majority of clinical studies examining GLP-1RAs in T1D have focused on examining the safety and efficacy of short-acting agents such as twice-daily exenatide and daily liraglutide, each as adjunct-to-insulin therapy for T1D in both multiple daily injection (MDI) and continuous subcutaneous insulin infusion (CSII) cohorts.[3]

Published evidence consistently demonstrates weight loss, decreases in total daily insulin requirements, and modest improvements in glycemic control with the use of GLP-1RAs. Of note, data on the more recent commercially available GLP-1RAs, such as semaglutide and dulaglutide, and dual co-agonists such as tirzepatide, have not yet been published; however, studies are in progress.

a) Exenatide

The use of short-acting exenatide in two clinical trials did not yield any significant HbA1c-lowering benefit nor improved time in range (3.9–10.0 mmol/L) vs placebo.[22,23] In the MAGIC trial, the authors noted an insignificant change in HbA1c from baseline, suggesting no clear HbA1c-lowering benefit with exenatide.[23] Furthermore, C-peptide levels did not differ among groups. However, a significant reduction in body weight and total daily insulin needs with no increased risk of hypoglycemia was reported.[22]

b) Liraglutide

i. MDI-only cohorts

The most robust MDI-only trial intervention was the Lira-1 trial which investigated daily liraglutide 1.8 mg in an overweight, sub-optimally controlled T1D population.[24] The primary outcome revealed a significant decrease of 0.4% HbA1c early in the study, while, by the end-of-trial period, no statistical significance was demonstrated. Interestingly, there was a marked reduction in body weight and total daily insulin requirements in the liraglutide-treated group, but no changes in glycemic variability or blood pressure. Furthermore, there were fewer reported hypoglycemic events vs placebo.

ii. Mixed MDI and CSII cohorts

Several clinical studies have examined liraglutide in a mixed MDI and CSII population. In a two-way trial using liraglutide in T1D adults with overweight and obesity, the authors reported a non-significant treatment effect of 0.29% HbA1c reduction from baseline.[9] Of note, the intervention group experienced a significant within-group HbA1c reduction of 0.41%, suggesting an overall underpowered intervention. Other findings included reductions in body weight which uniquely were further characterized by dual-energy X-ray absorptiometry and magnetic resonance imaging of total body fat mass and distribution. At present, the ADJUNCT program comprises the two largest double-blind, randomized, placebo-controlled trials to have investigated once-daily liraglutide as adjunct-to-insulin therapy for T1D.[25,26] Three different doses of daily liraglutide were analyzed in the ADJUNCT ONE study in 1,389 T1D adults over one year.[25] There was a dose-dependent decrease in HbA1c with all three doses, as well as a significant reduction in total body weight. The subsequent ADJUNCT TWO study examined liraglutide treatment tested on top of individualized capped insulin dosing in 831 participants. Compared to ADJUNCT ONE, the findings showed a similar body weight reduction but a more meaningful dose-dependent HbA1c-lowering effect with a decrease of 0.35% for the 1.8 mg dose.[26]

iii. CSII and Closed-Loop system studies

Only limited preliminary studies have explored the possibility of combining GLP-1 RA with Closed-Loop System (CLS) technology as an adjunctive hormonal therapy. Using a randomized, double-blind parallel

Author (year) and n sample size	Insulin Administration Modality	Comparator/ Intervention	Primary Endpoints	Additional Outcomes and Comments
Johansen et al.[23] (2020) n=105	MDI only cohort	Exenatide 10 µg tid vs placebo	HbA1c -0.1% (P=0.36)	• No run-in period • Double-blinded study
Dejgaard et al.[24] (2016) n=100	MDI only cohort	Liraglutide 1.8 mg daily vs placebo	HbA1c -0.2% (P=0.18)	• Reduced bolus insulin intake 5.8 units/day (P=0.023) • Double-blinded
Mathieu et al.[25] (2016) n=1389	2.5% MDI 27.5% CSII	Liraglutide 0.6 mg vs 1.2 mg vs 1.8 mg daily vs placebo	HbA1c -0.2% (P=0.0019)	• Increased hypogylcemic events • Significant body weight loss (-2.2 kg to -4.9 kg) • Decrease in total daily insulin requirements: 9 units/day (P<0.01)
Ahren et al.[26] (2016) n=831	74.5% MDI 25.5% CSII	Liraglutide 0.6 mg vs 1.2 mg vs 1.8 mg daily with use of capped insulin vs placebo	HbA1c -0.35% (P<0.0001)	• Significant body weight loss (-2.3 kg to -4.9 kg)
Ghanim et al.[9] (2020) n=64	31% MDI 69% CSII	Liraglutide 1.8 mg daily vs placebo	HbA1c -0.29% (P=0.1)	• Decrease in bolus insulin requirements: 4.0 units/day (P=0.021) • Significant body weight loss 4.2 kg (P=0.002)
Dejgaard et al.[27] (2020) n=44	CSII only cohort	Liraglutide 1.8 mg daily vs placebo	HbA1c -0.7% (P<0.001)	• Decrease in total insulin requirements: 7.7 units/day (P=0.008) • No run-in period

Table 1. Summary of selected trials examining GLP-1RAs in T1D. MDI: multiple daily injection insulin; CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; *courtesy of Dr. Michael A. Tsoukas.*

design, the Lira Pump trial is the only trial to date that has examined liraglutide administration in a population of CSII-treated, overweight T1D adults.[27] Change from baseline in HbA1c after 26 weeks was the most profound statistically-significant, placebo-corrected reduction (-0.6% as early as 13 weeks, and -0.7% by end of study). Furthermore, significant improvements were noted for body weight loss, glucose time in target ranges and total daily insulin requirements. The study was limited by a smaller sample size of (n=44); however a robust study design including adjustments for insulin sensitivity factors, carbohydrate ratios and basal rate modification was performed at the onset of treatment.

Table 1 shows a brief summary of findings from selected major interventional clinical trials.

Conclusion

While off-label use of GLP-1RAs as adjunctive therapy to insulin in T1D is becoming more common in practice, evidence of HbA1c reduction supporting its use is limited. Nonetheless, the current clinical evidence base does consistently demonstrate:

a) an indisputable weight loss effect, improving underlying adiposopathy of T1D, especially in view of the growing population with overweight/obesity; b) decreases in insulin requirements/total daily dosing for most study populations; and c) glycemic benefits in HbA1c lowering of approximately 0.5% reduction, although the improvement observed with placebo often diluted the treatment effect.[3] The proposed beneficial mechanistic effects of GLP-1RAs on gluconeogenesis suppression, delayed gastric emptying and anti-inflammation, also favour their use. Furthermore, clinical trials have examined the safety and efficacy of short-acting agents such as twice-daily exenatide and daily liraglutide as adjunct-to-insulin therapy for T1D in both MDI and CSII cohorts. However, no published data currently exists for more novel GLP-1RAs and dual co-agonists available commercially and used regularly in practice for T2DM patients.

As global diabetes treatment strategies increasingly prioritize cardiometabolic disease prevention and weight loss, the high value of these molecules would be of potential benefit in T1D patients with overweight/obesity and those with high-risk/pre-existing cardiovascular and renal disease. However, dedicated cardiovascular outcomes studies in T1D would bridge the knowledge gap and potentially reveal therapeutic potential. Other T1D subgroups, such as patients with advanced insulin delivery devices experiencing labile blood sugars and high rates of hypoglycemia may benefit from these molecules as well. Despite off-label use in practice, further work is needed to redirect GLP-1RAs as an indicated adjunctive therapy for an individualized treatment approach for T1D.

Acknowledgement:

We gratefully acknowledge Alessandra Kobayati, PhD for her substantial original conceptualization and detailed review analysis of the topic. These invaluable contributions were instrumental in the creation of this article.

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Financial Disclosures

Speaker honoraria: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, and NovoNordisk.

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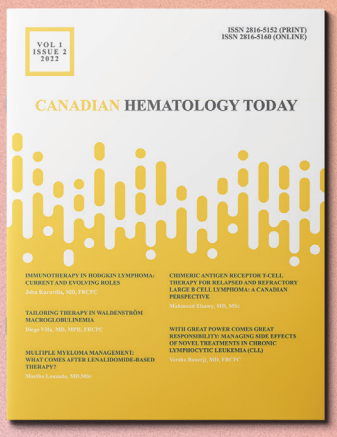

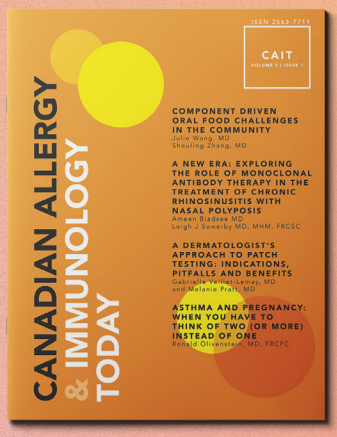

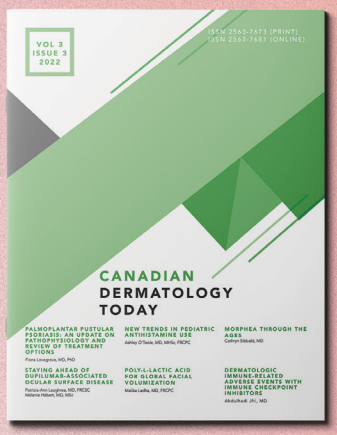

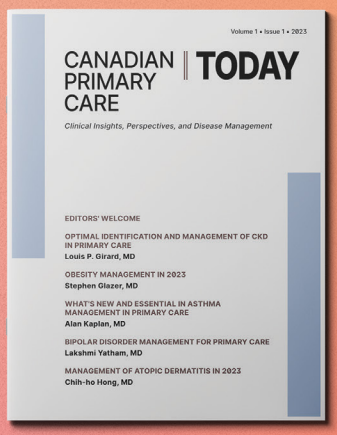

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Judith Atkin is a white settler to Turtle Island (Canada), with a very colonial past from Sri Lanka, South Africa and England. Walking alongside Indigenous community members both as a home care nurse and as a diabetes educator for the past 20 odd years has given her insight into the resourcefulness and resilience of Indigenous peoples as they negotiate the societal and health challenges of the results of residential school, racism and past and on-going colonialism. It is her honour and privilege to live and work amongst families of the Coast Salish and Nuu Chah Nulth Nations on their unceded lands of southern Vancouver Island.

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Case Report: A First Nation Man's Journey with Severe Insulin Resistance Syndrome

David B. Miller, MD; Susan Schaefer, RN, CDE; Judith Atkin, RN, CDE

Introduction

James (a pseudonym) was born in the 1940s near Vancouver Island, British Columbia, to a Coast Salish family. His schooling was the imposed residential school system whereby Indigenous children were removed from their homes and communities and sent to schools in communities far away. His siblings attended various residential schools, so during his three years at such schools he saw them only in the summer time. His treatment during his schooling fostered a deep distrust of physicians and nurses. In addition he lost much of his native language and culture during this time. He graduated from Queen Elizabeth (High) School in North Surrey, British Columbia, where he was the only Indigenous student. James attended Vancouver Vocational School before returning to Vancouver Island to work as a band manager for his First Nation community. He married Mary (a pseudonym) and together they raised four children. Today he works as an Elder in Residence with post-secondary institutions on Vancouver Island.

Diagnosis and Treatment

James was diagnosed with pre-Type 2 diabetes (T2DM) in November of 2006 and was treated with metformin. He remembers being told not to eat either salt or sugar, and that his diagnosis resurrected his feelings of distrust. The authors met James in December of 2008. His T2DM had suddenly changed. Two months earlier, while taking metformin, he had an HbA1c of 6.0%. He presented to a local hospital with classic symptoms of hyperglycemia, a random blood glucose of 28.7 mmol/L and an HbA1c of 11.4%. His medications at the time were metformin, atorvastatin, clopidogrel, felodipine, and quinapril. Treatment with insulin was initiated and he continued on his metformin, but his T2DM proved quite resistant to insulin up to 250 units per day, on a basal-bolus schedule.

James' history at that time was notable for the concurrent presentation of Guillain-Barré Syndrome and focal segmental glomerular sclerosis approximately 15 years earlier. He had spent close to six months in hospital at that time and retains a tracheostomy scar on his neck. When he presented with insulin resistance he had a stable eGFR of 65 mL/min/1.73m^2. In addition, he had an active urine sediment with with hyaline and granular casts in his urine and proteinuria, which had also been stable for many years. He weighed 75 kg (having unintentionally lost approximately 35 kg in the previous eight months) and had a BMI of 23 kg/m^2. The first clue to his diagnosis was an antinuclear antibodies test (ANA) which was strongly positive, with a titer of 1:640, with a homogenous and chromosomal pattern. Subsequently, his double stranded DNA was also positive. He had none of the cutaneous or rheumatologic issues normally associated with lupus. At this point the authors suspected that James had type B severe insulin resistance and consulted with Dr. Philip Gorden at the National Institutes of Health (NIH) in Bethesda, Maryland, a recognized expert in insulin resistance syndromes. From the onset, Dr. Gorden and his research team were very interested and engaged in James' care. At that time they were treating patients with type B with rituximab, cyclophosphamide and pulse corticosteroids,[1] and the same combination therapy was administered to James.

National Institutes of Health

In March of 2009, three months after his diagnosis, James and Mary travelled to the National Institutes of Health (NIH) to meet with Dr. Gorden and his team. They had never previously travelled outside of British Columbia. James recalls being fearful but with Mary's encouragement to trust his care team, proceeded to Bethesda. All travel and care expenses were paid for by the NIH. Mary was able to stay in an adjacent guest building and visit James daily during his three-week stay. During that time he received cyclophosphamide 100 mg daily, two cycles of pulse dexamethasone (40 mg daily x 4 days), and two dose of rituximab (each 1000 mg IV). The complete protocol is described by Malek et al.[1] In addition, the patient was administered Humulin R U-500, approximately 1,000 units per day in divided doses. While at the NIH, James was examined by clinicians in seven different disciplines/care teams; he estimated that he met with more than 30 specialists. He was repeatedly examined, shared his story multiple times and was invited to share his story at their Grand Rounds. When asked about these experiences he recounted his earlier distrust of doctors and nurses but

that through this journey he "learned to trust" again, relying on Mary for support.

Upon James' return from the NIH, the authors were able to continue his therapy with U-500 insulin. At the time U-500 had to be ordered through the Health Canada Special Access Program; it was available only in 20 mL vials and had to be administered in a syringe. In the early months of 2009, James reached his peak insulin dose—1800 units/day—administered in four injections—400 units (0.8 mL) before breakfast, 500 units (1.0 mL) before lunch, 500 units before dinner, and 400 units before bedtime. His HbA1c reached a peak of 13.0% around that time, despite the very large doses of insulin. There was frequent communication between the care team at the NIH and the care team in British Columbia.

In July of 2009, James and Mary returned to the NIH for the second and final time. Another round of multiple specialist visits took place and James was administered another two doses of 1,000 mg IV rituximab. His insulin doses were being tapered and his HbA1c had already begun to lower but remained quite high. He was receiving approximately 1,000 units per day of insulin and his HbA1c was 10%. By August of 2009, five months after his first trip to the NIH, James ceased the insulin and had normal blood sugars. His HbA1c normalized a couple of months later.

The Relapse

In late 2010 into early 2011 there was a steady rise in James' blood glucose despite no obvious changes in diet, exercise or medications. There was a discussion between NIH and the authors as to whether this was "just" his T2DM returning or his severe insulin resistance recurring. The conclusion was that this was a recurrence of his severe insulin resistance, the first such case the NIH had seen with this treatment protocol. On this occasion James was treated with cyclophosphamide and two pulses of dexamethasone. His insulin requirements peaked at "only" 1,100 units/day and he ceased insulin by April 2011. Other than peri-operatively, he has not needed insulin for the subsequent 12 years. At times he was treated with metformin and/or linagliptin with positive glycemic effect.

Type B Severe Insulin Resistance Syndrome

The syndrome was first described by Flier et al in 1975.[2] The underlying pathophysiology is that of anti-insulin receptor antibodies blocking insulin's ability to dock with the receptor. Patients with this syndrome require massive doses of insulin and suffer dramatic weight loss (in distinction to obesity-related insulin resistance); women will manifest hyperandrogenism,[3] which might be confused with obesity-related polycystic ovarian syndrome (PCOS). Acanthosis nigricans, common in other insulin resistance states, can be widespread.[4] Typically there is an associated rheumatologic illness with a wide range of auto-antibodies. The first descriptive case series from the NIH was published in 2002 and described 24 patients seen over a 28-year period; clearly it is quite rare.[5] In a subsequent treatment-related publication in 2010[1] which cited James' case, 14 patients were described with mixed connective tissue disease and five with systemic lupus erythematosus. The remaining six did not have a clear diagnosis but had positive titers including ANA, extractable nuclear antigen (ENA), and double-stranded DNA (ds-DNA). In addition to James, 12 of the 14 patients were female; 11 were African-American and two were Hispanic. At the time of publication in 2002, all of the patients were in remission; their anti-insulin receptor antibodies were measured in the laboratory of Dr. Robert Semple in the Department of Clinical Biochemistry, Cambridge University (UK). At the time of the NIH publication in 2010, James had among the highest antibody titers.

A subsequent publication in 2018[6] described 22 patients (again including James) treated with rituximab, high-dose pulsed steroids and cyclophosphamide until remission, followed by maintenance therapy with azathioprine. In this, study James' 1,800 units of insulin per day was average in the group. James was one of three patients who had had a relapse before responding to a second treatment course. All of the described and treated patients were alive at the time of the 2018 publication after a median follow-up to 72 months (six years). To date, James is the only Indigenous individual seen by the NIH with this severe insulin resistance syndrome (personal communication, Elaine Cochran to David Miller, April 2023).

The NIH group has authored publications regarding the use of U-500 insulin in patients with insulin resistance.[7] This treatment is typically reserved for patients receiving in excess of 2 units/ kg/day. It is now commercially available in Canada in pre-loaded pen format and manufactured by Eli-Lilly as Entuzity™.

Conclusion

James required coronary artery bypass grafting in 2014 and recovered well from the procedure. Hemodialysis was initiated in 2022. He last regularly took insulin in 2011.

James' wife Mary passed away in 2015. James lives with some of his children and grandchildren near where he was born and grew up (other than his forced trips to residential schools) on Vancouver Island.

We wanted to tell this story for a few reasons. The first, and most important, was to pay respect to James and the story-telling tradition in which he lives. His distrust of doctors and nurses dating back to his residential school experience could have been a barrier to the excellent treatment he received. With the support of his family and community, this distrust was lessened. The second reason is to raise awareness of this rare, but now treatable, form of diabetes. Finally, James and his British Columbia treatment team have nothing but gratitude and respect for his NIH-based team. What started with an email to the NIH led to this story.

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Financial support

None declared.

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ISSN 2817-4097
(English ed. online)