Type 2 diabetes and the management of hyperglycaemia

About the Reviewer

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Professor Krebs is an Endocrinologist with a particular interest in obesity and diabetes. He trained in Endocrinology at Wellington Hospital in New Zealand and then did his doctorate with the Medical Research Council - Human Nutrition Research unit in Cambridge, England. His thesis was on the impact of dietary factors on obesity and insulin resistance. Professor Krebs returned to New Zealand in 2002 to take up a consultant Endocrinology post at Wellington Hospital, and was Clinical Leader of Endocrinology and Diabetes at Capital and Coast District Health Board. He heads the research group and is Professor with the University of Otago, and former Director of the Clinical Research Diploma at Victoria University - which he established. As well as clinical and teaching activities, Professor Krebs maintains active research interests in the area of obesity and diabetes, with a particular focus on the association between obesity and type 2 diabetes, both from an aetiology and management perspective, with a focus on nutritional aspects, bariatric surgery and diabetes service delivery.

Abbreviations used in this review:
ADA = American Diabetes Association
ASCVD = atherosclerotic cardiovascular disease
CKD = chronic kidney disease
DPP4 = dipeptidyl peptidase-4
EASD = European Association for the Study of Diabetes
GI = gastrointestinal
GLP-1 = glucagon-like peptide-1 receptor
HbA1c = glycated haemoglobin
HF = heart failure
MACE = major adverse cardiovascular events
SGLT2 = sodium-glucose co-transporter 2
T2DM = type 2 diabetes mellitus
TZDs = thiazolidinediones

This article is intended as an educational resource for healthcare professionals, particularly those in the primary care clinical setting. The review presents relevant background information on the impact of hyperglycaemia in persons with type 2 diabetes mellitus (T2DM) and focuses on pharmacologic management strategies as recommended in New Zealand guidelines as well as those more recently published by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). This review is sponsored by an educational grant from Sanofi.

Introduction

Type 2 diabetes mellitus (T2DM) is a long-term metabolic disorder characterised by high levels of blood glucose resulting from deficiencies in insulin secretion and/or action.[1,2] Diabetes increases the risk of damage to the heart, brain, eyes, kidneys, nerves, blood vessels and many other body systems.

As in other developed countries, T2DM is one of New Zealand's fastest-growing long-term conditions.[3,4] The prevalence of T2DM in New Zealand is estimated to be around 6%, and it is almost twice as prevalent in Maori, or people of South Asian ethnicity, and over three times more prevalent in Pacific Islanders, compared with the rest of the New Zealand population.[5] Although T2DM is more prevalent in people aged over 55 years,[5] the increase of T2DM in children, adolescents and young adults is concerning. Individuals who develop T2DM early in life have significantly higher rates of complications, morbidity and mortality than when T2DM is diagnosed later in life.[6-9]

The rising prevalence of T2DM in New Zealand represents the "perfect storm" which has resulted from a combination of determining factors including the obesogenic environment, an increasingly sedentary lifestyle, energy dense diets, better detection of cases through increased screening, and the changing demographics of our nation (including its ethnic composition and population ageing).[3,4]

In New Zealand, chronic, long-term conditions such as diabetes are contributing to rising healthcare costs,[3,10-12] with people with T2DM increasingly requiring access to secondary and tertiary health services, especially for the treatment of diabetes-related complications. The long-term effects of diabetes is likely to place a burden on society as a whole as an increasing number of people may not be able to continue working as they did prior to the onset of their diabetes. The cost of this loss of productivity has been estimated as being more than direct healthcare costs.[3]

Guidelines and targets for the management of type 2 diabetes mellitus

In New Zealand, the Ministry of Health has published guidelines for the management of T2DM (2011),[13] the content of which is also available in the New Zealand Primary Care Handbook (2012).[14] More recent international guidelines on the management of T2DM have also been released (October, 2018) by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).[15]

In line with the New Zealand guidelines,[13,14] the new ADA/EASD guidelines emphasise that the goals of treatment for T2DM are to prevent or delay complications and maintain the individual's quality of life.[15] Improving glycaemic control is only one of several goals for people with T2DM, and targets for managing cardiovascular risk factors such as blood pressure and lipid levels have also been set.[3,13,14,16] This review will focus on the management of hyperglycaemia within primary care, a setting that is generally considered *'the medical home'* for people with diabetes.[3,17]

Treatment targets

Glycaemic targets are primarily assessed by measuring glycated haemoglobin (HbA1c) levels.[15] New Zealand guidelines recommend an HbA1c target of 50–55 mmol/mol (6.7–7.2%).[13] Importantly, glycaemic targets should be negotiated with individual patients using a shared decision making approach, with healthcare providers prioritising the delivery of patient-centred care.[13,15] Any HbA1c target should reflect an agreement between patient and doctor.[18,19] HbA1c targets and glucose-lowering therapies should therefore be individualised, taking into consideration where possible the patient's preferences, needs, cultural background and values. Both patients and their healthcare professional(s) should work toward this target within an agreed time frame.[19]

When good glycaemic control is achieved, there are substantial and enduring reductions in the onset and progression of microvascular complications.[15] The impact of glycaemic control on macrovascular complications is complex and less clear.[15] This is largely because the benefits of intensive glucose control emerge slowly. In addition, many confounding variables may be involved in preventing macrovascular complications.[15,20,21] Nevertheless, it is clear that T2DM confers a substantial independent risk of the individual having atherosclerotic cardiovascular disease (ASCVD).[15] HbA1c levels outside targets have been shown to be predictors of acute myocardial infarction and stroke.[22] Outcomes from highly controlled studies like the UKPDS and Steno 2 indicate that targeting cardiovascular risk factors including glucose, lipids and HbA1c improves cardiovascular outcomes.[20, 21] However, the benefits of achieving HbA1c targets need to be balanced against the potential harms, such as increased weight gain or hypoglycaemia.[13] Studies have indicated that there is an increased risk of cardiovascular mortality with intensive glycaemic control in people with T2DM;[23,24] this outcome has largely been linked to the increase in hypoglycaemia.[25]

Clinical inertia

The failure to initiate or intensify therapy when indicated or a failure to act despite recognition of the problem has become known as 'clinical inertia'.[26-28] Resistance to initiating or intensification of therapy can exist when adding or intensifying oral anti-hyperglycaemic agents,[29] or when initiating or intensifying insulin therapy.[30,31] Clinical inertia appears to be particularly problematic when insulin initiation is being considered.[32,33] Since the reasons for clinical inertia are multifactorial, with physician-, patient- and healthcare system-related factors all contributing,[14,30,31,34,35] a multifaceted approach to overcoming it is needed.[36] Importantly, any attempt to overcome clinical inertia must be tailored to the individual, and be mindful of their diabetes duration, the presence of co-morbidities, life expectancy, social circumstances and their personal beliefs and priorities.

Self-management education and support

In order to achieve HbA1c targets, people with diabetes should receive high-quality structured self-management education that is tailored to their individual and cultural needs.[13,15,16] Individuals with T2DM and their families/whanau should be informed of, and provided with, support services and resources that are appropriate and locally available.[3,16,37,38] Individuals with T2DM can be directed to further self-help, evidence-based websites such as the Diabetes New Zealand website: www.diabetes.org.nz.

Important topics for patient education include the side effects of intensive therapy (e.g. weight gain, hypoglycaemia), managing injections and insulin dose adjustments.[31] In particular, it is important that patients are helped to understand their insulin regimen and are encouraged to take an active role during the initiation of insulin.[13,16]

EXPERT COMMENT

The rates of T2DM are alarming in NZ, particularly for Pacific, Indian and Maori, who have significantly greater prevalence, younger ages of onset and greater risk of micro- and macrovascular complications than European New Zealanders. Interventions at a personal and public health level to target those with pre-diabetes must be a priority for the NZ health-system. Recent evidence shows that in those with early T2DM, intensive lifestyle intervention which results in significant weight loss, can reverse the metabolic consequences of obesity. Efforts to integrate this into routine primary care practice are needed. However, that is not the focus of this article. Here is a contemporary commentary and guideline to the medications used for glucose management of those with T2DM. Important aspects of this are the need to avoid clinical inertia, for which we are all guilty, and also to recognise the need for quality structured and ongoing programmes to assist people with diabetes to self-manage. Both are vitally important to the effectiveness of any plan to manage hyperglycaemia.

Glucose-lowering treatments
Lifestyle interventions

Lifestyle interventions (e.g. exercise, dietary changes) should be part of the initial therapy from the time of diagnosis of T2DM and should be co-therapy for individuals who also require glucose-lowering medications (**Figure 1**).[13,15,16,39] The recently published DIRECT trial illustrated that a professionally supported intensive weight management programme, conducted within the primary healthcare setting, enabled almost half of the participants to achieve remission to a non-diabetic state and came off antidiabetic drugs.[39] International guidelines advise that lifestyle management should be part of the ongoing discussion with people with T2DM at each visit.[15]
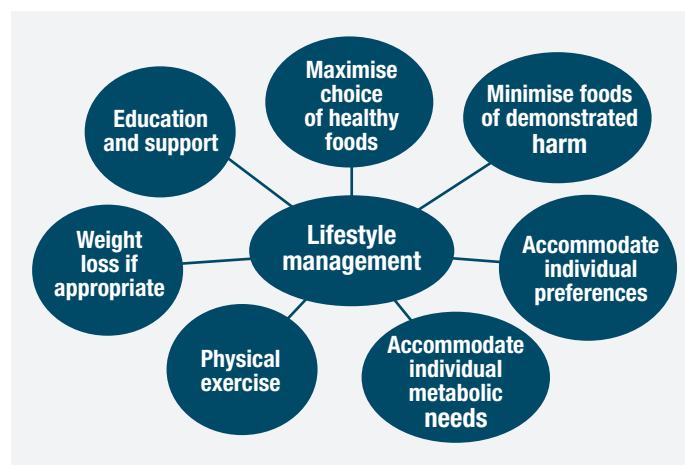

Figure 1. Lifestyle management in individuals with T2DM[15]

Glucose-lowering medications

Glucose-lowering medications registered and funded in New Zealand are presented in **Table 1**[13] and include metformin, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor (GLP-1) agonists, dipeptidyl peptidase-4 (DPP4) inhibitors, sulphonylureas, thiazolidinediones (TZDs), α-glucosidase inhibitors and insulin. Currently, two classes of drugs which are mentioned in the recommendations in the recent ADA/EASD guidelines, namely SGLT2 inhibitors, and GLP1 agonists, are not funded by PHARMAC (**Table 1**). Of the basal insulins, only the long-acting insulin analogue insulin glargine and the intermediate-acting human isophane insulin are currently funded by PHARMAC (**Table 1**).

This section reviews these medications, focusing on their glucose lowering efficacy and tolerability profile. The various glucose-lowering agents are associated with different advantages and disadvantages **(Tables 2 and 3)**. Of note, the insulins if given in adequate doses have the most potential to lower HbA1c (by approximately 22 mmol/mol; 2% or more if the starting HbA1c is very high).[15] With regard to the impact on weight, the acarbose and DPP4 inhibitors are weight neutral, the GLP-1 agonists encourage progressive weight loss sustained over many years of use, while metformin and SGLT-2 inhibitors are also associated with modest weight loss. Sulphonylureas and insulin are associated with weight gain. While insulin and sulphonylureas can increase the risk of hypoglycaemia, there is a lower risk of hypoglycaemia with SGLT2 inhibitors, GLP-1 agonists, DPP4 inhibitors, acarbose or thiazolidinediones.[15]

Table 1. Registered and funded antidiabetic medication (November 2018)

Registered with Medsafe	Funded by PHARMAC
• **Metformin**	• **Metformin**

• **Sulphonylureas**
  - Gliclazide
  - Glipizide
  - Glibenclamide
	• **Sulphonylureas**
	  - Gliclazide
	  - Glipizide
	  - Glibenclamide

• **Thiazolidinediones**
  - Pioglitazone
	• **Thiazolidinediones**
	  - Pioglitazone

• **α-Glucosidase inhibitor**
  - Acarbose
	• **α-Glucosidase inhibitor**
	  - Acarbose

• **DPP4 inhibitors**
  - Sitagliptin
  - Saxagliptin
  - Vildagliptin
	• **DPP4 inhibitors**
	  - Vildagliptin

• **SGLT2 inhibitors**
  - Dapagliflozin
  - Canagliflozin
  - Empagliflozin	

• **GLP1 analogues/agonists**
  - Exenatide (immediate release and modified release)
  - Lixisenatide	

• **Insulins**
Rapid-acting
  - Insulin aspart
  - Insulin glulisine
  - Insulin lispro
  - Human neutral insulin
Intermediate-acting
  - Insulin isophane
Long-acting
  - Insulin detemir
  - Insulin glargine 100 IU/mL
  - Insulin glargine 300 IU/mL
Premixed insulins
  - Insulin aspart with insulin aspart protamine
  - Insulin neutral with insulin isophane
  - Insulin lispro with insulin lispro protamine
	• **Insulins**
	Rapid-acting
	  - Insulin aspart
	  - Insulin glulisine
	  - Insulin lispro
	  - Human neutral insulin
	Intermediate-acting
	  - Insulin isophane
	Long acting
	  - Insulin glargine (100 IU/mL)
	
	Premixed insulins
	  - Insulin aspart with insulin aspart protamine
	  - Insulin neutral with insulin isophane
	  - Insulin lispro with insulin lispro protamine

DPP4 = dipeptidyl peptidase-4; GLP1 = glucagon-like peptide-1; SGLT2 = sodium-glucose co-transporter 2.

Biguanides

Metformin (**Table 2**) is an effective oral medication that is associated with a very minimal risk of hypoglycaemia when used as monotherapy, and the potential for some weight loss.[13,15] Rare instances of lactic acidosis have occurred, usually in people with severe illness or acute kidney injury. Consequently, it is recommended that metformin is temporarily discontinued if the person is severely ill, vomiting, or dehydrated. Metformin can lower serum vitamin B_{12} levels,[40] and so periodic monitoring and supplementation is generally advised if levels are deficient or in those with anaemia or neuropathy.[15] Because metformin is renally cleared, special caution should be exercised in situations where renal function may become impaired, with doses being reduced as renal function declines.[41,42] Metformin is contraindicated in individuals with renal failure (creatinine clearance <15 mL/min).[41] Given the favourable efficacy and tolerability profile of metformin, clinical trial evidence of reduced micro- and macrovascular complications, metformin's long history of safety, metformin's probable favourable effects on risk of various cancers, along with its low cost, guidelines recommend metformin as a first-line glucose-lowering agent for most people with T2DM.[13,15]

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

These oral agents reduce plasma glucose levels by enhancing the urinary excretion of glucose (**Table 2**).[15,43,44] In people with normal renal function, these agents effectively lower blood glucose levels.[45] SGLT2 inhibitors are associated with a reduction in weight and blood pressure and they do not increase the risk of hypoglycaemia when used alone or with metformin.[45] Importantly, dapaglifozin, empagliflozin and canagliflozin have cardiac and renal benefits in people with established or at high risk of ASCVD.[15,46-49] In the large EMPA-REG OUTCOME trial in 7,020 patients with T2DM and CVD, the absolute risk reduction for the primary composite end point of nonfatal MI, nonfatal stroke, and cardiovascular (CV) death was 1.6% in favour of empagliflozin versus placebo.[46] In the DECLARE–TIMI 58 trial in 17,160 patients with T2DM who had or were at risk for ASCVD, dapagliflozin versus placebo lowered the rate of CV death or hospitalisation for heart failure (4.9% vs 5.8%; hazard ratio 0.83; 95% CI 0.73, 0.95; p=0.005).[49] The recent guidelines now recommend that, in people with T2DM who have established ASCVD, SGLT2 inhibitors with proven cardiovascular benefit should be part of the glycaemic management.[15]

Generally, SGLT2 inhibitors are well tolerated, with the most common adverse events being genital mycotic infections and increased urination.[50] Rare cases of diabetic ketoacidosis have been reported when people with T2DM were treated with SGLT2 inhibitors;[51] recent international guidelines recommend that these agents be used with caution and appropriate patient education.[15] These agents have also been associated with an increased risk of acute kidney injury, dehydration, and orthostatic hypotension; and so caution is also advised when SGLT2 inhibitors are used in combination with diuretics and/or angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers.[15]

Glucagon-like peptide-1 receptor (GLP-1) agonists

GLP-1 is a hormone released from the lower small bowel in response to food, and it stimulates insulin release, suppresses raised glucagon, slows gastric emptying and induces satiety.[15] GLP-1 agonists (**Table 2**) stimulate the GLP-1 receptor thus increasing insulin secretion and reducing glucagon secretion.[15] In addition they also have an effect on other organs including the brain and gastrointestinal system resulting in reduced appetite and decreased gastric emptying, and thus these agents encourage weight loss.[52] Importantly, the stimulation of insulin release is glucose dependent and switches off as glucose concentrations fall[53] and so GLP-1 agonist monotherapy is not associated with an increased risk of hypoglycaemia. Liraglutide has been associated with improved cardiovascular outcomes in people with T2DM.[54]

Nausea, vomiting, and diarrhoea are the most commonly reported adverse events associated with GLP-1 receptor agonists, although these events tend to diminish over time.[15] Despite early concerns, GLP-1 receptor agonists do not seem to be associated with an increased risk of pancreatitis, pancreatic cancer, or bone disease.[15,55,56]

Dipeptidyl peptidase-4 (DPP4) inhibitors

These oral agents (**Table 2**) reduce the activity of the enzyme which inactivates GLP-1, increasing endogenous levels of GLP-1 and allowing improved and more prolonged GLP-1 action.[15] Consequently, insulin secretion is increased and glucagon secretion is decreased.[15] DPP4 inhibitors effectively lower blood glucose levels,[57] and are generally well tolerated, with a neutral effect on weight and a minimal risk of hypoglycaemia when used as monotherapy.[58] There is a 50% increased risk of hypoglycaemia if a DPP4 inhibitor is added to sulfonylurea therapy.[59]

A rare, but increased risk of pancreatitis and musculoskeletal side effects have been reported with DPP4 use.[60,61]

Table 2: Summary of main characteristics of glucose-lowering agents (other than insulin)[13,15,41,47-71]

Drug class	Example available in NZ	Route of administration	Main mechanism of action	Advantages	Disadvantages	HbA1c lowering efficacy
Biguanide	Metformin	Oral	↓ Hepatic glucose production	No hypoglycaemia Low cost Extensive history of use PHARMAC funded	GI symptoms Vitamin B12 deficiency Use with caution or dose adjustment for patients with CKD Rare lactic acidosis Contraindicated with renal failure	High
SGLT2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin	Oral	↓ Glucose reabsorption by the kidney, increasing glycosuria	No hypoglycaemia ↓ Weight ↓ Blood pressure ↓ MACE, HF, CKD with some agents	Genital infections Urinary tract infections Polyuria Volume depletion/hypotension Dizziness Dose adjustment/avoidance for renal disease Rare ketoacidosis Not PHARMAC funded	High to intermediate [depending on kidney function]
GLP-1 agonists	Exenatide Lixisenatide	By injection	Stimulate GLP-1 receptor ↑ Insulin secretion ↓ Glucagon secretion ↑ Satiety	Glucose-dependent No hypoglycaemia ↓ Postprandial glucose excursions Improves cardiovascular risk factors including reducing weight ↓ Albuminuria with some agents ↓ MACE with some agents	GI side effects ↑ Heart rate Training requirements Clinical inertia Dose adjustment/avoidance in renal disease Not PHARMAC funded	High
DPP4 inhibitors	Sitagliptin Saxagliptin Vildagliptin	Oral	↑ Insulin secretion ↓ Glucagon secretion ↑ Satiety	Glucose-dependent No hypoglycaemia Weight neutral Well tolerated	Rare ↑ risk of musculoskeletal side effects Dose adjustment/avoidance for renal disease depending on agent Only vildagliptin is PHARMAC funded	Intermediate
TZDs	Pioglitazone	Oral	↑ Insulin sensitivity by activating the peroxisome proliferator-activated receptor γ	Low risk of hypoglycaemia Durability ↑ HDL-C ↓ Triacylglycerols PHARMAC funded	↑ Weight Oedema/heart failure Bone loss ↑ Bone fractures ↑?Bladder cancer	High
Sulphonyl-ureas	Gliclazide Glipizide Gliben-clamide	Oral	↑ Insulin secretion	Extensive experience ↓ Microvascular risk PHARMAC funded	Hypoglycaemia ↑ Weight Uncertain cardiovascular safety Dose adjustment/avoidance for renal disease High rate of secondary failure	High
α -Glucosidase inhibitors	Acarbose	Oral	Slows carbohydrate digestion/absorption	Low risk for hypoglycaemia ↓ Postprandial glucose excursions Non-systemic mechanism of action PHARMAC funded	GI adverse events Frequent dosing schedule Dose adjustment/avoidance for renal disease	Intermediate to low

Glucose-lowering efficacy of drugs assessed by change in HbA1c;
high = 11–22 mmol/mol (1–2%); intermediate = 6–11 mmol/mol (0.5–1.5%); low = 6 mmol/mol (0.5%).

Thiazolidinediones (TZDs)

These oral agents increase insulin sensitivity and have an established efficacy in lowering blood glucose levels in persons with T2DM (**Table 2**).[15,62] Safety concerns have been associated with this class of agent, including fluid retention and congestive heart failure,[63,64] increased weight,[65] bone loss and fracture,[66] and possibly bladder cancer.[67] Lower-dose TZDs mitigate weight gain and fluid retention, but the broader benefits and harms of low-dose TZD therapy have not been evaluated.[15]

Sulfonylureas

These oral medications (**Table 2**) lower blood glucose by stimulating insulin secretion from pancreatic β-cells.[15,68] They are inexpensive and effective in people with T2DM, but their use has been associated with risks of hypoglycaemia and weight gain.[68] However, the weight gain associated with sulfonylureas is relatively low in large cohort studies and the incidence of severe hypoglycaemia is lower than with insulin.[69] Large, multicentre, randomised controlled trials have demonstrated the microvascular benefits of sulphonylureas, a reduction in the incidence or worsening of nephropathy and retinopathy, and no increase in all-cause mortality. Whether these benefits are directly the result of sulphonylurea therapy and not an overall glucose-lowering effect is unclear.[69] The safety profile of the individual sulphonylureas appears to differ. Glibenclamide is associated with a higher risk of hypoglycaemia than other sulphonylureas including glipizide or gliclazide.[69] Caution is advised for people at high risk of hypoglycaemia, such as older individuals and those with chronic kidney disease (CKD).[15]

α-Glucosidase inhibitors

Acarbose (**Table 2**) slows carbohydrate digestion and absorption, and effectively lowers post-prandial glucose excursions.[70] α-Glucosidase inhibitors are associated with a low risk of hypoglycaemia, but gastrointestinal side effects are very common with these agents and limit their acceptability and therefore use.[15,71]

Insulin

Various formulations of insulin are available with differing durations of action (**Table 3**). Insulin has the advantage over other glucose-lowering medications in that it can lower blood glucose levels and HbA1c in a dose-dependent manner to almost any glycaemic target which is higher than that reported with other agents (**Table 2**).[15] The main limitation in the HbA1c reducing capacity of insulin is the increasing frequency of hypoglycaemia. Older formulations of insulin have been associated with a reduction in microvascular complications and with all-cause mortality and diabetes-related death when used over the longer term.[20] Aside from the risk of hypoglycaemia, insulin use is also associated with weight gain, the need for insulin to be injected, the need to titrate the dosage to ensure optimal efficacy, and the need for glucose monitoring.[72]

Basal insulin

These insulins are intended to cover the basal metabolic insulin requirements.[15] The different intermediate- and long-acting basal insulins have different timings of onset, durations of action, and risks of hypoglycaemia (**Table 3**).[15,73] Insulin isophane (also called neutral protamine Hagedorn insulin [NPH]) is an intermediate-acting insulin that can be injected once or twice daily, with a maximal effect at 4 to 6 hours. Long-acting insulin analogues include insulin degludec, insulin glargine and insulin detemir.[73] Insulin glargine 100 IU/mL and insulin detemir have a longer duration of action, a more consistent glucose-lowering effect and less prominent concentration peaks than insulin isophane.[15,73] Insulin glargine 100 IU/mL and insulin degludec have physiological profiles that more closely resemble endogenous basal insulin, with a more evenly distributed, predictable and prolonged time-action profile and improved within-patient variability in their glucose-lowering effect.[73] A new long-acting formulation of insulin glargine containing 300 IU/mL is available that has more stable and smoother-pharmacokinetic and pharmacodynamic profiles than the older formulation of insulin glargine 100 IU/mL.[74,75] In real-world studies, a change to insulin glargine 300 IU/mL was associated with an improvement in glycaemic control, and no weight gain in patients switched from other basal insulins,[76] and an incidence of hypoglycaemia that was lower than that with other basal insulins.[77] The long-acting insulin analogues are associated with a modestly lower absolute risk of hypoglycaemia than the intermediate-acting human isophane insulin.[73,78-81]

Other insulins

Short- and rapid-acting insulin formulations which are administered at mealtime are commonly used in addition to basal insulin therapy in people with T2DM who are not meeting glycaemic targets (**Table 3**).[15] The rapid-acting insulin analogues are generally associated with a lower risk of hypoglycaemia than human neutral insulin.[15] Premixed formulations of human and analogue insulins are available (**Table 3**), but they tend to be associated with an increased risk of hypoglycaemia compared with basal insulin alone.[15] Pre-mixed formulations combine insulins with different onset and duration of action, usually a fixed ratio of short-acting and intermediate-acting forms of insulin, designed to be given either once or twice a day. Premixed insulin can be considered where a person already taking insulin has consistently high blood glucose levels following meals, and where HbA1c targets are not being met.[13] Some people may prefer pre-mixed insulins as they help reduce the number of daily injections.

EXPERT COMMENT

It used to be relatively simple to know what to do for people with T2DM. Lifestyle advice, metformin, then sulphonylureas, then insulin. However, the management of hyperglycaemia in 2019 is now much more complex. We now have multiple agents available with different mechanisms of action, targeting different defects in metabolism or novel strategies to reduce glucose. Each has their strengths and weaknesses, different side effects and very relevant in NZ, different funding. It is important for clinicians to become familiar with the properties of these newer agents in order to be able to discuss them with people with diabetes, and tailor their therapy for best outcomes. Whilst it is great to now have access to a funded DPPIV inhibitor, and many people will get significant benefit from this, the most excitement in the diabetes world currently is the evidence for major cardiovascular and renal benefits of the SGLT-2 inhibitors and GLP-1 agonists.

Insulin is the ultimate hypoglycaemic agent in the toolkit for managing glucose in diabetes. Since its discovery early last century, there have been many evolutions of the insulin preparations available for clinical use. After many years of animal insulin preparations we then got human insulin, and now we have modified human insulins with differing properties that either enhance or delay absorption from a subcutaneous injection site. These modern analogue insulins enable us to tailor an insulin regimen for any individual. It is important to realise that no one size fits all when it comes to insulin therapy. Whilst we have reasonably standardised approaches to initiation of insulin, it is important that clinicians design a regimen which addresses the specific hyperglycaemic profile and pattern of each individual. For some, this is once daily basal insulin, for others it is obvious that mealtime insulin is required. It is also critical to work with a person to design a regimen which is acceptable and achievable for them. For example, that may mean that premixed insulin is more appropriate than a basal bolus regimen even if it doesn't achieve tight control. Unlike other hypoglycaemic agents, we are reasonably well off in NZ for funded insulin options. With the exception of insulin detemir, insulin degludec and insulin glargine 300 IU/mL, we have the full range of insulins available and funded.

Table 3. Summary of main characteristics of insulins[15]

Insulins	Example available in NZ	Route of administration	Main mechanism of action	Advantages	Disadvantages	HbA1c lowering efficacy
Long acting (basal)	Insulin detemir Insulin glargine 100 IU/mL Insulin glargine 300 IU/mL	Injection	Activates insulin receptor ↑ Glucose disposal ↓ Glucose production	Theoretical unlimited efficacy Insulin glargine fully funded by PHARMAC	Hypoglycaemia ↑ Weight Training requirements Clinical inertia Frequent dose adjustment for optimal efficacy	Very high
Intermediate acting (basal)	Insulin isophane (NPH insulin)	Injection	Activates insulin receptor ↑ Glucose disposal ↓ Glucose production	Theoretical unlimited efficacy PHARMAC funded	Hypoglycaemia ↑ Weight Training requirements Clinical inertia Often given twice daily Frequent dose adjustment for optimal efficacy	Very high
Rapid acting	Insulin aspart Insulin lispro Insulin glulisine	Injection	Activates insulin receptor ↑ Glucose disposal ↓ Glucose production	Theoretical unlimited efficacy ↓ Postprandial glucose PHARMAC funded	Hypoglycaemia ↑ Weight Training requirements Clinical inertia Often multiple daily injections Frequent dose adjustment for optimal efficacy	Very high
Short acting	Human neutral insulin	Injection	Activates insulin receptor ↑ Glucose disposal ↓ Glucose production	Theoretically unlimited efficacy ↓ Postprandial glucose PHARMAC funded	Hypoglycaemia ↑ Weight Training requirements Clinical inertia Often multiple daily injections Frequent dose adjustment for optimal efficacy	Very high
Biphasic insulins	Insulin neutral with insulin isophane Insulin lispro with insulin lispro protamine Insulin aspart with insulin aspart protamine	Injection	Activates insulin receptor ↑ Glucose disposal ↓ Glucose production	Theoretically unlimited efficacy Provide both an immediate-release component and a prolonged-duration component Fewer injections than basal/bolus before every meal PHARMAC funded	Hypoglycaemia ↑ Weight Training requirements Clinical inertia Frequent dose adjustment for optimal efficacy	Very high

Medication selection for lowering blood glucose

Both New Zealand and the new ADA/EASD guidelines emphasise that any glycaemic treatment target, as well as considering the preferences and goals of the person with diabetes, should assess the risk of adverse effects of therapy (e.g. hypoglycaemia and weight gain), and the person's characteristics (such as their frailty and comorbid conditions).[13,15]

The new ADA/EASD guidelines have taken into consideration the effect of specific medications on mortality, heart failure and progression of renal disease in individuals with established ASCVD.[15] Consequently, the new guidelines recommend that a history of ASCVD or CKD is considered very early in the process of treatment selection.[15] Similarly, New Zealand guidelines emphasise the early identification of individuals at high risk of diabetes-related complications, so that they can be treated accordingly.[13]

Given the favourable efficacy and tolerability profile of metformin, along with its low cost, both recent international and New Zealand guidelines recommend metformin as a first-line glucose-lowering agent for most people with T2DM.[13,15]

The choice of glucose-lowering medication to be added to metformin should depend on the individual's preference and clinical characteristics, such as the presence of established ASCVD and other comorbidities such as heart failure or CKD.[15] Other important considerations include the risk for specific adverse medication effects, particularly hypoglycaemia and weight gain, as well as the safety, tolerability, and cost of any particular agent.[13,15] A stepwise approach to adding glucose-lowering medication is usually preferred to initial combination therapy.[15]

Similarly, the new ADA/EASD guidelines note that the impact of medication side effects on comorbidities, as well as the burden of treatment and cost, should be considered when intensifying treatment beyond dual therapy to maintain glycaemic targets.[15] In people with long-standing diabetes and multiple co-morbidities such as renal impairment, neuropathy and ischaemic heart disease, intensive blood glucose control can be harmful and can increase mortality[20] or may present with unusual symptoms (e.g. unrecognized hypoglycaemia causing acute confusion in an elderly person).[13,42,82]

The new ADA/EASD guidelines also provided recommendations for people with T2DM and co-morbidities with recommendations that:

- For people with established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists which have proven cardiovascular benefit should form part of glycaemic management.[15]
- For people with CKD, with or without cardiovascular disease, an SGLT2 inhibitor proven to reduce CKD progression should be use, or if contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression.[15]

In people on oral medication who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are recommended over insulin in the first instance by the new ADA/EASD guidelines.[15] Insulin is recommended for people with extreme and symptomatic hyperglycaemia.[15] These guidelines recommend that if additional glucose lowering is required, despite therapy with a long-acting GLP-1 receptor agonist, the addition of basal insulin is a reasonable option. An alternative, well-established option is to add insulin to oral medication regimens and this is the course of action recommended by the current New Zealand guidelines.[13] Using basal insulin combined with oral medications is very effective in reducing HbA1c, and associated with less hypoglycaemia and weight increase than combinations using premixed insulin formulations or prandial insulin.[15] Both human isophane insulin and long-acting insulin analogues effectively lower fasting glucose levels. However, basal analogue formulations are associated with a reduced risk of hypoglycaemia, particularly overnight, when titrated to the same fasting glucose target as human isophane insulin.[78, 81, 83]

The new ADA/EASD guidelines recommend that treatment should be intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin for individuals with T2DM who are unable to maintain glycaemic targets on basal insulin in combination with oral medications.[15]

Conclusions

The management of hyperglycaemia in people with T2DM is complicated by the wide variety of glucose-lowering medications available. The available medications target different defects in the physiology of individuals with T2DM, and have different effects on hypoglycaemia and body weight and they may not all require the same level of blood glucose monitoring. Not all classes of medications are currently funded by PHARMAC.

Decisions on the choice of glucose-lowering medication must be patient centred and should include an early assessment of individual's risk of diabetes-related complications. Any medication chosen, should be accompanied by efforts to improve lifestyle interventions (e.g. diet and exercise). While metformin remains the initial choice, other glucose-lowering medications must be based on patient comorbidities and preferences. All insulin regimens should be tailored to the needs of the individual with T2DM. When insulin is initiated, basal insulin analogues represent a suitable choice given their association with a relative low risk of hypoglycaemia and weight gain. In some instances, it may be more appropriate to use short-acting mealtime insulins in addition to, or instead of, basal insulin.

CONCLUDING COMMENTS

The release of the 2018 EASD/ADA guideline marks a major turning point in the status of New Zealand in modern medical management of T2DM. For the first time, we no longer have open access to funded medication which is specifically recommended as second-line therapy in a treatment algorithm. The main cause of premature mortality in people with T2DM is cardiovascular disease and a major cause of morbidity is renal failure. There is now high-quality evidence from large randomised controlled trials that both SGLT-2 inhibitors and GLP-1 agonists reduce the risk of both of these. Yet despite this, and despite applications for funding being considered by PHARMAC over the last 10 years, we still do not have funded access to either class of drugs. These new guidelines should be promoted to all clinicians in New Zealand, yet the concern is that because of funding constraints we will see increasing disparities in outcomes.

TAKE-HOME MESSAGES

- A wide variety of glucose-lowering medications are available, with the different classes targeting different aspects of the defective metabolism of people with T2DM
- The various glucose-lowering agents have different abilities to lower HbA1c, with insulin being the most effective
- The different glucose-lowering agents have differing effects on hypoglycaemia and body weight
- The choice of glucose-lowering medications must be based on the person's comorbidities and preferences
- Metformin is the recommended initial medication for treating people with T2DM
- SGLT-2 inhibitors or GLP-1 analogues, although not currently funded, should be considered as second-line therapy where the person has ASCVD or CKD
- When adding insulin to oral medications, basal insulin analogues such as NPH or insulin glargine are suitable options to consider as the first insulin to start

RESOURCES FOR PRIMARY CARE

NZ Primary Care Handbook 2012 https://www.health.govt.nz/system/files/documents/publications/nz-primary-care-handbook-2012.pdf

Guidance on the Management of Type 2 Diabetes 2011
http://www.moh.govt.nz/notebook/nbbooks.nsf/0/60306295DECB0BC6CC257A4F000FC0CB/$file/NZGG-management-of-type-2-diabetes-web.pdf

ADA/EASD consensus report (2018) on the management of hyperglycaemia in type 2 diabetes.
http://care.diabetesjournals.org/content/41/12/2669

Living well with diabetes: a plan for people at high risk of or living with diabetes 2015–2020. https://www.health.govt.nz/system/files/documents/publications/living-well-with-diabetes-oct15.pdf

Quality Standards for Diabetes Care Toolkit 2014. https://www.health.govt.nz/publication/quality-standards-diabetes-care-toolkit-2014

Diabetes New Zealand website http://www.diabetes.org.nz.

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