Can J Diabetes 39 (2015) S148–S154

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Impact of Current and Emerging Glucose-Lowering Drugs on Body Weight in Type 2 Diabetes

David C.W. Lau MD, PhD, FRCPC [a,*], Hwee Teoh PhD [b]

[a] *Departments of Medicine, Biochemistry and Molecular Biology, Julia McFarlane Diabetes Research Centre and Libin Cardiovascular Institute of Alberta, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada*

[b] *Divisions of Endocrinology & Metabolism and Cardiac Surgery, Keenan Research Centre for Biomedical Science and the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada*

ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form
25 September 2015
Accepted 25 September 2015

Keywords:
glucose-lowering drugs
dipeptidyl peptidase-4 inhibitors
glucagon-like-peptide-1 agonists
insulin/insulin secretagogues
sodium-glucose cotransporter-2 inhibitors

ABSTRACT

Type 2 diabetes is a progressive disease, and most people with diabetes will eventually require adjunctive pharmacotherapy to optimize their glycemic control. As the majority of people with type 2 diabetes are overweight or obese, weight management is an essential component of diabetes management to improve their overall health and quality of life. Many of the currently available glucose-lowering drugs are associated with weight gain, which makes it challenging for both prescribing clinicians and patients. The 2015 Canadian Diabetes Association Clinical Practice Guidelines interim update on the pharmacologic management of type 2 diabetes recommend individualization of therapy and glycemic targets. Clinicians should take into consideration not only the drug's efficacy and safety profiles but also its propensity for causing hypoglycemia and weight gain. Given that the number of glucose-lowering drugs is expanding rapidly, a better understanding of the impacts of current and emerging therapies on body weight will serve as a useful guide. Metformin remains the first-line drug after diet and exercise therapy. The next add-on agent could be selected from the incretin or sodium-glucose cotransporter-2 inhibitor class because these drugs rarely cause hypoglycemia and may lead to modest weight loss. When insulin therapy is considered, choosing a basal insulin that is associated with less nocturnal hypoglycemia and weight gain is recommended. Emerging therapies using combination therapy of an incretin-sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide-1 agonist-basal insulin hold promise to achieve robust glycemic control with weight loss and low risk for hypoglycemia.

Mots clés :
hypoglycémiants
inhibiteurs de la dipeptidyl peptidase–4
agonistes des récepteurs du GLP–1 (*glucagon-like peptide–1*)
insuline/sécrétagogues de l'insuline
inhibiteurs du cotransporteur sodium-glucose de type 2

RÉSUMÉ

Le diabète de type 2 est une maladie évolutive pour laquelle la plupart des personnes diabétiques auront éventuellement besoin d'une pharmacothérapie en complément du régime alimentaire et de l'exercice pour optimiser leur maîtrise de la glycémie et du métabolisme. La majorité des personnes souffrant du diabète de type 2 ont un excès de poids ou sont obèses. Par conséquent, la prise en charge du poids constitue une composante essentielle de la prise en charge du diabète pour améliorer leur santé globale et leur qualité de vie. Plusieurs des hypoglycémiants actuellement disponibles sont associés à un gain de poids, qui complique la prise en charge par les cliniciens prescripteurs et les patients. L'actualisation provisoire des lignes directrices de pratique clinique 2015 sur la prise en charge pharmacologique du diabète de type 2 de l'Association canadienne du diabète recommande l'individualisation du traitement et des cibles glycémiques. Les cliniciens devraient prendre en considération non seulement les profils d'efficacité et d'innocuité des médicaments, mais également sa propension à provoquer une hypoglycémie et un gain de poids. Étant donné que le nombre d'hypoglycémiants augmente rapidement, une meilleure compréhension des répercussions des traitements actuels et émergents sur le poids corporel sera utile. La metformine demeure le médicament de première intention lorsque le régime alimentaire et l'exercice ne parviennent pas à maîtriser la glycémie. Le médicament d'appoint suivant pourrait être sélectionné dans la classe des incrétines ou des inhibiteurs du cotransporteur sodium-glucose de type 2 (SGLT2) puisque

* Address for correspondence: David C.W. Lau, MD, PhD, FRCPC, Departments of Medicine, Biochemistry and Molecular Biology, Julia McFarlane Diabetes Research Centre and Libin Cardiovascular Institute of Alberta, University of Calgary Cumming School of Medicine, G82-3330 Hospital Drive NW, Calgary, Alberta T2N 4N1, Canada.
E-mail address: dcwlau@ucalgary.ca

1499-2671
http://dx.doi.org/10.1016/j.jcjd.2015.09.090

ces médicaments provoquent rarement une hypoglycémie et qu'ils peuvent entraîner une perte de poids modeste. Lorsque l'insulinothérapie est envisagée, il est recommandé de choisir l'insuline basale dont l'hypoglycémie nocturne et la perte de poids qui y sont associées sont moindres. Les traitements émergents reposant sur la combinaison incrétine-inhibiteur du SGLT2 ou agoniste des récepteurs du GLP–1 (*glucagon-like peptide–1*)–insuline basale promettent d'atteindre une maîtrise fiable de la glycémie en plus d'entraîner une perte de poids et de présenter un faible risque d'hypoglycémie.

Introduction

In Canada, diabetes rates have doubled over the past decade, with 2.4 million adults (6.8%) living with diabetes in 2009, and the number is projected to reach 3.7 million by 2019 (1). If improperly managed, diabetes can lead to many devastating complications, such as heart disease, stroke, blindness, kidney failure and limb amputations, which can significantly reduce the quality of life and life expectancy. Type 2 diabetes is a chronic disease characterized by insulin resistance and progressive beta-cell failure. The overall goal in the treatment of people with diabetes is to restore, optimize and maintain their quality of life by keeping the blood sugar as close to normal levels as possible and within target ranges that will prevent or delay the development of the serious small- and large-blood-vessel complications of diabetes. The cornerstone in its management is nutrition therapy along with regular physical activity. The majority of people with type 2 diabetes are overweight or obese, so weight loss is recommended to achieve and maintain healthy body weights. The Look AHEAD (Action for Health in Diabetes) trial demonstrated that intensive health-behaviour modification for modest weight loss provided many benefits. They included improved glycemic control; reduction in the need for, number and cost of medications required to manage and achieve blood glucose and blood pressure targets; improvements in mobility, sleep apnea, urinary incontinence and quality of life; as well as fewer hospitalizations and reductions in long-term health care costs (2). When intervention through health-behaviour modifications fails to achieve adequate euglycemia, pharmacotherapy is necessary for a vast majority of people with type 2 diabetes. The number of glucose-lowering drugs has skyrocketed over the years and, as a result, the management of type 2 diabetes at the primary care level has become increasingly complex and challenging. The 2013 evidence-based Canadian Diabetes Association (CDA) Clinical Practice Guidelines (CPGs) emphasized the individualization of glycemic targets, with the vast majority of people with diabetes continuing to target glycated hemoglobin (A1C) levels of ≤7.0% while providing guidance on when more or less stringent targets should be considered (3). The CDA CPGs also recommended that the choice of glucose-lowering drugs should take into consideration the following factors: the degree of hyperglycemia, the effectiveness in reducing diabetes complications, the safety and tolerability of the medications and patients' preferences and costs. They provided an algorithm for the pharmacologic management of type 2 diabetes, with emphasis on individualization of choice of agents, and they included 2 important adverse side effects that might impact the overall management: the effect of the drug on the risk for hypoglycemia and its effect on body weight. Because hypoglycemia can be associated with serious clinical sequelae, including worsening cardiovascular disease outcomes, the caution concerning avoiding the risk for hypoglycemia is fairly obvious, especially if it is severe. On the other hand, although many glucose-lowering drugs induce weight gain to varying degrees, and that may compromise overall diabetes management, this adverse side effect is often neglected. The recent change in the landscape of glucose-lowering agents has prompted the CDA CPGs expert panel to publish an interim 2015 update on the pharmacologic management of type 2 diabetes (4).

Review Methods

The purpose of this timely review is to focus on the impact of current and emerging glucose-lowering therapies on body weight. Relevant articles published between 2000 and June 2015 were identified through PubMed, Embase, Google Scholar and Cochrane Library searches using the search terms *oral hypoglycemic drugs*, *antihyperglycemic drugs*, *pharmacotherapy* and *type 2 diabetes*.

Benefits of Modest Weight Loss

In the Look AHEAD trial, intensive lifestyle intervention at the end of a median follow-up period of 9.6 years was associated with a 6.0% reduction in body weight compared with 3.5% in the control group and was accompanied by a greater A1C level reduction of 0.22% (2). Weight loss in people with type 2 diabetes is beneficial not only in improving glycemic and metabolic control but may also improve quality of life and reduce the risk for cardiovascular disease (5).

Although weight loss is recommended for the prevention and management of type 2 diabetes, there are significant barriers to, as well as clinical inertia and therapeutic nihilism, helping patients with type 2 diabetes to manage their body weight more proactively. People with type 2 diabetes experience greater difficulty with weight loss than individuals without diabetes for several reasons. In insulin-resistant states, skeletal muscle and liver are the predominant organs responsible for glucose disposal. Hyperinsulinemia promotes triglyceride synthesis and storage while inhibiting lipolysis in adipocytes, resulting in an expansion of adipose tissue. People with diabetes may live more sedentary lifestyles and be less physically active. Weight regain can result from the compensatory response to hormonal and metabolic changes following initial weight loss, when orexigenic mediators that stimulate appetite persist for an extended period. Importantly, and as will be discussed, many of the commonly used glucose-lowering drugs are associated with weight gain, rendering weight management even more challenging.

Glucose-Lowering Drugs Associated with Weight Gain

Prandial, biphasic and basal insulins

Insulin and insulin secretagogues contribute directly to weight gain through their modes of action in reducing hyperglycemia. Both classes of drugs lower blood glucose by promoting glucose uptake by the target cells (mainly muscle and fat) and decreasing glucosuria, thereby retaining more glucose calories in the body, leading to weight gain. Insulin is an anabolic hormone that promotes glycogen, protein and lipid synthesis and inhibits proteolysis and lipolysis. It also exerts a central effect on appetite regulation, but such action may be somewhat impaired in individuals with type 2 diabetes. Insulin-induced hypoglycemia also stimulates appetite, but some people with type 2 diabetes overcompensate by consuming calories to treat and prevent hypoglycemia. Not all insulin preparations, however, have the same propensity to cause hypoglycemia and, consequently, weight gain. In the Treating To Target in Type 2

Diabetes (4-T) trial, which compared glycemic efficacy, weight fluctuations and hypoglycemic events using 3 different insulin preparations in 708 participants who were suboptimally controlled with metformin and sulfonylurea, basal and prandial insulin therapies demonstrated superior A1C-level control relative to the biphasic insulin-based regimen (6). Notably, the mean weight gain and the frequency of hypoglycemia were significantly lower in those who received basal insulin treatment (3.6 kg) compared to the prandial (6.4 kg) and biphasic (5.7 kg) insulin groups (6) (Table 1). During the 6-year Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, which investigated whether normalizing fasting hyperglycemia with insulin would reduce cardiovascular events in people with or at risk for type 2 diabetes, glargine insulin was associated with a placebo-subtracted weight gain of 2.1 kg (7). Among the basal insulins, insulin detemir appears to be associated with less weight gain than glargine or NPH insulins (8,9). Detemir insulin was associated with ~0.2 body mass index (BMI) unit less weight gain compared with glargine insulin (9). One possible explanation is reduced food intake compared to those taking NPH insulin, as reported in a 32-week randomized cross-over study of subjects with type 1 diabetes (10). Because of the differential effects of insulin on body weight, the 2015 U.S. Endocrine Society Clinical Practice Guidelines on the Pharmacological Management of Obesity recommends that basal insulin should be prioritized over other insulin therapy, when indicated, and that combination therapy with weight loss-associated glucose-lowering medications should be considered to help counteract some of the insulin-related weight gain (11).

Insulin secretagogues

Insulin secretagogues can cause weight gain via many of the same mechanisms that are triggered by insulin therapy. The magnitude of weight gain appears to correlate with the propensity of these agents to cause hypoglycemia.

Sulfonylureas are insulin secretagogues and are the second most widely prescribed class of glucose-lowering drugs after metformin. There are 3 generations of sulfonylureas; each succeeding generation is purported to have better glycemic efficacy and improved safety. In the landmark United Kingdom Prospective Diabetes Study, subjects randomized to insulin therapy gained about 4 kg more than those taking conventional therapy during the 10-year study, whereas those who took sulfonylureas gained about half as much weight—2.6 kg for the first-generation chlorpropamide-treated group and 1.7 kg for the second-generation glibenclamide-treated group (12). The second-generation glyburide was associated with a 1.6 kg weight gain in the A Diabetes Outcome Progression Trial (ADOPT) trial, which compared glycemic durability among monotherapy with glyburide, metformin and rosiglitazone, a thiazolidinedione, over a 4-year period (13). When used as an active comparator, the third-generation glimepiride (8 mg) was associated with a~1.12 kg weight gain in a 52-week efficacy clinical trial comparing liraglutide and glimepiride monotherapy (14). A recent systematic review and meta-analysis indicated that weight gain occurs with the following sulfonylureas: glyburide (2.6 kg), glipizide (2.2 kg), glimepiride (2.1 kg) and gliclazide (1.8 kg) (15) (Table 1). Sulfonylureas have been

Table 1
Impact of glucose-lowering agents on body weight

Drug class	Mode of action on body weight	Impact on body weight
Drugs associated with weight gain		
Insulins	Insulin promotes fat storage, inhibits lipolysis, leading to	
Prandial	increased body fat mass	+6.4 kg (6)
Biphasic	Central effect of insulin on appetite regulation, which	+5.7 kg (6)
Basal (detemir)	may be impaired in type 2 diabetes	+3.6 kg (6); –0.2 BMI units less than glargine (9)
Glargine	Decreased glucosuria resulting in more glucose calories	+2.1 kg (7)
NPH	reabsorbed	+7 kg (12); +0.2 BMI units more than detemir (9)
	Overcorrection or prevention of hypoglycemia with food	
Sulfonylureas	Overcorrection or prevention of hypoglycemia with food	
First generation (chlorpropamide 500 mg QD)		+5.5 kg (15)
Second-generation (glyburide 5 to 10 mg BID)		+2.6 kg (15)
Third-generation (glimeperide 4 to 8 mg QD)		+1.1-2.1 kg (15)
(gliclazide MR 30 to 60 mg QD)		+1.8 kg (15)
Meglitinides	Overcorrection or prevention of hypoglycemia with food	+0.3 kg (15)
Repaglinide (0.5 to 4 mg TID)		
Nateglinide (60 to 180 mg TID)		
Thiazolidinediones (TZDs)	Increase total body fat, with redistribution from visceral	
Rosiglitazone (4 to 8 mg QD)	to subcutaneous	+4.8 kg (13)
Pioglitazone (15 to 30 mg QD)	Increased fluid retention	+2.6 kg (15)
Drugs associated with weight neutrality		
Alpha-glucosidase inhibitors	Decreased carbohydrate digestion and absorption with	–0.4–1.8 kg (15, 39)
Acarbose (50 to 100 mg TID)	less caloric intake	
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Decreased food intake and fat absorption	–0.4 kg (39)
Sitagliptin (25 to 100 mg QD)		+0.55 kg (15)
Saxagliptin (2.5 to 5 mg QD)		
Linagliptin (5 mg QD)		
Alogliptin (10 mg QD)		
Drugs associated with weight loss		
Lipase inhibitor	Decreased fat digestion and absorption, with 30% less fat	–1.9 kg (1.9%) (22)
Orlistat (120 mg TID)	calorie intake	
Biguanides	Inhibits hepatic glucose production, but also has effect	–1.1 kg (15)
Metformin	on muscle insulin sensitivity	
	Nausea	
GLP-1 receptor agonists	Reduced gastric emptying	–2.8 kg (15, 24)
Exenatide (10 μg sc BID)	Central inhibitory effect on appetite and food intake	–2.8 kg (14)
Liraglutide (0.6 to 1.8 mg sc QD)		–3.2 kg (14)
Sodium-glucose cotransporter-2 inhibitors	Decreased glucose calories through increased glucosuria	(25,26,40)
Canagliflozin (100 to 300 mg QD)		–2.3–3.3 kg (27)
Dapagliflozin (5 to 10 mg QD)		–1.8–2.4 kg
Empagliflozin (25 to 50 mg QD)		–2.3–2.5 kg

on the market for a long time and are widely used because of extensive clinical trial data demonstrating good glucose-lowering efficacy and low cost.

Meglitinides are short-acting insulin secretagogues compared with sulfonylureas. However, they have profiles similar to those of sulfonylureas with respect to hypoglycemia and weight gain.

Thiazolidinediones

The insulin-sensitizer thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor gamma receptor agonists that enhance the insulin sensitivity of muscle and fat by increasing adiponectin secretion in these tissues. Thiazolidinediones stimulate preadipocyte maturation and formation of smaller adipocytes that are more insulin sensitive as well as shifts in fat distribution from visceral to subcutaneous depots. This class of drugs increases total body fat as well as fluid retention, so some people with type 2 diabetes gain fairly significant weight when taking TZDs. The mean weight gain with rosiglitazone was 4.8 kg in the ADOPT trial, compared with a loss of 2.9 kg with metformin over the 4-year study period (13). The concerns linking rosiglitazone to increased cardiovascular events, though not clinically proven, prompted the U.S. Food and Drug Administration to place a black-box warning on the drug and to develop guidance for the subsequent approval of new glucose-lowering drugs for type 2 diabetes. All new glucose-lowering medications are now mandated to demonstrate cardiovascular safety in their clinical trials prior to approval, and long-term postmarketing clinical trials are required to demonstrate cardiovascular safety. Although both rosiglitazone and pioglitazone are powerful glucose-lowering drugs, their pleiotropic effects have been linked to increased adverse side effects, notably congestive heart failure, vertebral fractures in women and rare cases of macula edema. The use of TZDs has fallen dramatically over the years, and they are now seldom prescribed in primary care.

Glucose-lowering drugs associated with some weight loss

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors decrease carbohydrate digestion and absorption in the gastrointestinal tract and thereby lower blood glucose by decreasing postprandial hyperglycemia (16). Data from meta-analyses suggest that acarbose is associated with small but significant decreases in body weight (15). However, its use is limited because of its modest glucose-lowering efficacy of ~0.5% and the associated unpleasant gastrointestinal side effects of flatulence, abdominal pain and diarrhea.

Dipeptidyl peptidase-4 inhibitors

Under normal physiologic conditions, dipeptidyl peptidase-4 (DPP-4) inhibitors cleave and inactivate glucagon-like peptide-1 (GLP-1). In people with type 2 diabetes, DPP-4 inhibitors stimulate endogenous insulin production by prolonging the actions of endogenous GLP-1. These drugs do not cause hypoglycemia and are reported to be either weight neutral or associated with modest weight loss in a number of clinical trials. In a 1-year open-labelled, head-to-head comparison with liraglutide, sitagliptin was associated with a weight loss of 1.2 kg at 52 weeks from baseline, compared with 2.8 and 3.7 kg with liraglutide at 1.2 and 1.8 mg, respectively (17). The corresponding A1C level reduction was 0.88% with sitagliptin and 1.3% and 1.5% with liraglutide 1.2 and 1.8 mg. Systematic reviews and network meta-analysis of DPP-4 inhibitors show comparable efficacies and weight-change effects among the 4 gliptins that are currently available in Canada (sitagliptin, saxagliptin, linagliptin and alogliptin) (18). DPP-4 inhibitors have gained popularity because of their efficacy, low risk for hypoglycemia, weight neutrality or modest weight loss and low incidence of side effects. Three large cardiovascular safety trials that were conducted in accordance with the FDA guidance, TIMI-SAVOR, EXAMINE and TECOS, have demonstrated no increased signals in cardiovascular mortality compared to other glucose-lowering drug therapies (19,20).

Biguanides

Metformin is the most widely prescribed antihyperglycemic agent globally and is recommended by most diabetes CPGs as the first-line therapy after health-behaviour modification. It is a weak insulin sensitizer that acts mainly in the liver to inhibit hepatic glucose production, but it also enhances muscle insulin sensitivity. Its glucose-lowering efficacy is comparable to that of other oral agents commonly used to treat type 2 diabetes. The pooled results of a meta-analysis of 31 trials, with 4570 participants followed for 8267 patient-years, showed that metformin reduced BMI by 5.3% when compared with placebo or no treatment (21). Its modest effect on weight loss of 1 to 2 kg (1% to 2%) is possibly due to the effect on decreased appetite and possibly to the gastrointestinal side effects of nausea and diarrhea. Metformin is generally safe and well tolerated, and the gastrointestinal symptoms tend to decline over time.

Glucose-lowering drugs associated with weight loss

Orlistat

Orlistat is the only medication approved by Health Canada for long-term weight management and for the glycemic treatment of type 2 diabetes. It is an intestinal lipase inhibitor that results in a modest weight loss of 1.9% (1.9 kg) by reducing dietary fat digestion and absorption by about 30% and decreases A1C levels by about 0.5% (22,23). Postulated mechanisms of the glucose-lowering benefits may include improvements of insulin sensitivity, slower and incomplete digestion of dietary fat, reduction of postprandial plasma nonesterified fatty acids, decreased visceral adipose tissue and stimulation of glucagon-like peptide-1 secretion in the lower small intestine (23). Despite its dual benefits in weight loss and glycemic control, orlistat is seldom prescribed by primary care practitioners because of its undesirable gastrointestinal side effects of flatulence, abdominal pain, oily stools and diarrhea.

Glucagon-like peptide-1 receptors agonists

The injectable glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved as second- or third-line add-on therapy for individuals with type 2 diabetes. Unlike DPP-4 inhibitors, GLP-1 RAs raise the gut-derived GLP-1 incretin hormone to pharmacologic levels which, in turn, exert a central inhibitory effect on appetite and food intake (24). GLP-1 RAs reduce A1C levels by 1.2% to 1.5% by stimulating insulin and suppressing glucagon secretion, and they were associated with an average weight loss of 2.8 kg in a meta-analysis of 25 clinical trials (24). Liraglutide is a long-acting acylated analog of human GLP-1, whereas exenatide is a GLP-1 mimetic derived from Gila monster lizard saliva. In a 26-week head-to-head comparison of liraglutide (1.8 mg daily) and exenatide (10 μg twice daily), liraglutide treatment showed better glycemic efficacy (–1.12% vs. –0.79%) and greater weight loss than exenatide (–3.24 kg vs. –2.87 kg), with similar adverse side-effect profiles. Two other GLP-1 RAs, once-weekly albiglutide and dulaglutide, which are approved in the United States, will soon become available in Canada. Both agents have comparable glycemic efficacy but less weight reduction when compared against liraglutide. Adverse side effects of GLP-1 RAs include nausea, abdominal pain and diarrhea, which tend to diminish with time. Extensive use of this class of drugs is limited by the cost and lack of coverage by provincial formulary, daily subcutaneous injections and lower tolerability.

Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the newest class of oral glucose-lowering agents approved in Canada. They lower

blood glucose levels by reducing glucose reabsorption, thereby augmenting glucosuria, a novel insulin-independent mechanism of glucose lowering that does not cause hypoglycemia (25). There are 3 SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) that are currently available in Canada and their A1C-level-lowering efficacies vary between 0.7% and –0.9% (26,27). SGLT2 inhibitors increase glucose excretion and, consequently, fewer calories are being reabsorbed, culminating in a sustained weight loss of about 2 kg in long-term studies up to 2 years (25,27,28). Although the sustained weight loss is attributed largely to loss of calories resulting from glucosuria, recent studies suggest that compensatory overeating occurs with long-term drug use, which appears to attenuate the weight loss achieved (25). SGLT2 inhibitors are the first class of oral glucose-lowering agents that are associated with modest but sustained weight loss, and they can be used in monotherapy or combination therapy with any of the other available glucose-lowering agents. SGLT2 inhibitors also reduce blood pressure by 4.5 mm Hg. SGLT2 inhibitors are not recommended in patients with estimated glomerular filtration rates (eGFRs) less than 60 mL/min because of decreased efficacy. Adverse side effects include increased risk for mycotic infections in the genitourinary tract, hypotension and rare cases of ketoacidosis with mild hyperglycemia (27,28).

Emerging pharmacotherapies for type 2 diabetes and body weight

A number of exciting new glucose-lowering drugs are under development and in various phases of clinical trials. Some of these have recently been approved in the United States and Europe but are not yet available in Canada (Table 2).

Novel long-acting insulins

A new long-acting insulin analogue, glargine U300, has just arrived in Canada. This is the same glargine molecule that is 3 times more concentrated than the original glargine. However, it has different pharmacokinetic and pharmacodynamic profiles and has slower absorption. Clinical trial data showed comparable efficacy with glargine but with less nocturnal hypoglycemia and less weight gain of about 0.26 kg (29).

Degludec, an ultralong-acting basal insulin currently available in Europe, is associated with less nocturnal hypoglycemia in a meta-analysis of 7 clinical trials (30). It is unclear whether degludec has any weight advantage over other basal insulins, but it is feasible that less hypoglycemia may be linked to less weight gain because of less compensation with food.

GLP-I RA-basal insulin combination

There has been increasing interest in the concept of combining a GLP-1 RA with a basal insulin because this approach could provide robust glucose-lowering capability with low risk for hypoglycemia or weight gain. A meta-analysis of 15 randomized clinical trials indicated that such a combination yields an improved A1C level reduction of 0.44% and an impressive weight loss of 3.22 kg compared to other glucose-lowering therapies (31).

Several fixed combinations of novel GLP-I RAs and basal insulin are currently in phase 2 and phase 3 trials, and an example is degludec insulin combined with liraglutide (iDegLira) in a single injection. It has the potential benefit of achieving better glycemic control with lower fasting and postprandial hyperglycemia and reduced risk for hypoglycemia coupled with weight loss. The 1-year Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes (DUAL I) trial compared the effect of adding iDegLira, insulin degludec or liraglutide to the medications of patients with type 2 diabetes whose levels had been poorly controlled by metformin±pioglitazone. At week 52, more patients receiving iDegLira treatment achieved A1C levels of <7%, with 37% lower insulin doses, less hypoglycemia and greater decreases in body weight (2.89 kg) than patients treated with degludec insulin alone (32).

Timed-release bromocryptine

Timed-release bromocryptine is a sympatholytic D2-dopamine agonist that has been approved in the United States for the treatment of type 2 diabetes. Bromocryptine is unique in that it does not have a specific receptor that mediates its action on glucose and lipid metabolism. It acts by resetting the dopaminergic and sympathetic tones within the central nervous system (33). Phase 3 trials of monotherapy and in combination with other oral glucose-lowering drugs demonstrated 0.6% to 0.7% A1C levels without affecting body weight (33).

Table 2
Emerging pharmacotherapies for type 2 diabetes and impact on glycemia and body weight

Drug class	Benefits	A1C reduction	Impact on body weight
Short-acting bromocryptine	Reduces plasma glucose, triglycerides and free fatty acids	–0.6 to 0.7%	Weight neutral (33)
Pramlintide		–0.33%	–2.3 kg (15, 34)
Long-acting GLP1 RAs	Weekly injections	0.78%	–0.2 kg (placebo-subtracted) (35)
Albiglutide	Daily injections	0.8%	Less weight loss than exenatide (41)
Lixisenatide	Weekly injections		
Semaglutide (under development)			
Oral GLP1 RAs	Better adherence with oral formulation	?	?
Long-acting basal insulins	Less hypoglycemia with less weight gain	Similar to glargine insulin, 1% to 2%	
Glargine U300		Similar to basal insulin, 1% to 2%	–0.26 kg compared with glargine (29)
Degludec	Hepatoselective with less effect on body fat		–0.62 kg vs. biphasic (42)
PEGylated insulin			–1.9 kg (43)
Insulin-GLP1 RAs	Reduce fasting and prandial hyperglycemia, with lower insulin dose and weight loss	–0.44%	–3.22 kg (31)
Degludec/liraglutide fixed combination (iDegLira)		1.8% compared with 1.4% with degludec alone	–2.8 kg compared to degludec alone (32)
Lixisenatide/glargine (LixiLan)		–0.4% (placebo-subtracted)	–1.3 kg (placebo-subtracted) (44)
DPP-4 inhibitor–SGLT2 inhibitor	More effective glycemic control	1.5%	–2.1 kg (saxagliptin-subtracted) (36)
Dapagliflozin/saxagliptin 10 mg/5 mg QD)		1.1% to 1.2%	–2.4 to 2.9 kg (linagliptin-subtracted) (37)
Empagliflozin/linagliptin (10 to 25 mg/mg QD)			
GLP1 RA–SGLT2 inhibitor	Better glycemic control and greater weight loss	?	Greater weight loss than either drugs alone

A1C, glycated hemoglobin; *DPP-4,* dipeptidyl peptidase-4; *GLP1 RA,* glucagon-like peptide-1 receptor agonist; *SGLT2,* sodium-glucose cotransporter 2.

Pramlintide

Pramlintide is a synthetic analogue of human amylin that lowers postprandial hyperglycemia. It is currently available in the United States but not in Canada or Europe. Amylin is a neuroendocrine peptide hormone that is cosecreted with insulin by pancreatic beta-cells in response to meals. Its anorexigenic properties are mediated centrally and peripherally by delayed gastric emptying. Subcutaneous pramlintide administration is associated with a modest reduction in A1C levels by 0.4% and weight loss (~2.3 kg) (34).

Long-acting GLP-1 RAs

Weekly GLP-1 RAs have the potential benefit of reducing A1C levels and body weight with fewer injections, which might enhance patient adherence. Albiglutide is a weekly GLP-1 RA that has recently been approved in the United States. It reduces A1C levels by 0.9% and a minimal placebo-subtracted body weight loss of 0.2 kg in a 2-year randomized clinical trial comparing albiglutide to sitagliptin, glimepiride or placebo in patients with type 2 diabetes not controlled on metformin therapy (35). Semaglutide is another long-acting weekly GLP-1 RAs currently undergoing phase 2 and phase 3 trial evaluation.

Combination therapy with fixed-dose DPP-4 inhibitor and SGLT2 inhibitor

In patients not controlled by health-behaviour modification and/or metformin, the addition of a DPP-4 inhibitor and an SGLT2 inhibitor may offer better glycemic control through the complementary modes of action of these drugs than either drug class alone. It can be reasoned that this combination might have more favourable efficacy and safety profiles of currently available combination therapies, with low risk for hypoglycemia or weight gain. Combination therapy with dapagliflozin/saxagliptin for 24 weeks reduced A1C levels by 1.5% from a baseline of 8.9%, vs. 1.2% for dapagliflozin and 0.9% for saxagliptin alone. Corresponding weight loss was 2.1 kg for the combination, 2.4 kg for dapagliflozin and none for saxagliptin alone (36). Similar results have also been reported with an empagliflozin/linagliptin combination in a 52-week randomized clinical trial in patients not controlled with metformin alone (37). These 2 fixed-dose combination pills showed superior A1C level reduction (1.1% to 1.2%) from baseline A1C levels of ~8% and greater weight loss (2.7 to 3.1 kg) than empagliflozin (–0.66% A1C level reduction and weight loss of 2.9 kg) or linagliptin (–0.7% A1C level reduction and weight loss of 0.3 kg) alone (37).

Another possible combination therapy is GLP-1 RAs and SGLT2 inhibitors, which have the advantage of greater weight loss while improving glycemic control without hypoglycemia.

Recently, a new monomeric peptide "triagonist" has been developed for the management of obesity and type 2 diabetes. This novel compound simultaneously targets 3 key metabolically related peptide hormone receptors, resulting in improved glycemic control and weight loss, as well as reversing hepatic steatosis in rodent models (38). The 3 receptors involved are glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and glucagon. Glucagon is thought to inhibit the secretion of orexin A, thereby increasing energy expenditure while reducing food intake, leading to weight loss. The diabetogenic effect of glucagon can be counteracted by stimulating the receptors of the 2 incretin hormones. The discovery of such a triagonist represents a new paradigm for new drug development that could drastically alter the management of overweight and obese people with type 2 diabetes (38).

Conclusions

Health-behaviour modification remains the cornerstone for the treatment of, type 2 diabetes, but pharmacotherapy is often necessary as an adjunct to optimize glycemic and metabolic control so as to improve quality of life and to prevent or delay the complications of diabetes. With rapid advances in new knowledge of the pathophysiology of type 2 diabetes, the number of glucose-lowering drugs has expanded dramatically over the years. The management of type 2 diabetes has become increasingly complex and challenging. The 2013 evidence-based CDA CPGs emphasized the importance of individualizing therapy by choosing the proper glucose-lowering drug that is best suited for each patient. Because the majority of people with type 2 diabetes are already overweight or obese, weight management is an integral component of the overall treatment strategy and should be regularly reinforced. Moreover, choosing glucose-lowering drugs that are associated with weight loss is preferable to using those that are weight neutral or associated with weight gain. The 2015 United States Endocrine Society Clinical Practice Guidelines on the Pharmacological Management of Obesity recommend that physicians should pay greater attention in choosing glucose-lowering drugs with favourable effects on body weight and, whenever possible, avoid drugs that promote weight gain (11). The 2015 CDA CPGs interim update also reinforced the importance of choosing glucose-lowering drugs that are associated with low risk for hypoglycemia and weight loss (4). We now have more choices of glucose-lowering drugs that enable clinicians to help their patients to achieve concomitantly their glycemic targets and healthier body weights. Metformin is clearly the first-line agent when health-behaviour modification fails to maintain glycemic control. The next add-on agent after metformin could be selected from the incretin class or the SGLT2 inhibitors; these drugs rarely cause hypoglycemia and may lead to modest weight loss. When insulin therapy is considered, it would be advisable to choose a basal insulin that is associated with less nocturnal hypoglycemia and weight gain. Emerging therapies using combination therapy of a DPP-4 inhibitor and an SGLT2 inhibitor or a GLP-1 RA-basal insulin hold promise for achieving robust glycemic control with weight loss and low risk for hypoglycemia.

Author Disclosures

Dr. Lau has received research support or honouraria from Amgen, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Merck, Novo Nordisk Canada Inc., Roche, Sanofi and Valeant; Dr. Teoh has no conflicts of interest to declare.

Author Contributions

David C.W. Lau planned and drafted the manuscript; David C.W. Lau and Hwee Teoh revised the manuscript.

References

1. Public Health Agency of Canada. Diabetes in Canada: Facts and figures from a public health perspective. Ottawa, Canada: Public Health Agency of Canada, 2011.
2. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–54.
3. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic management of type 2 diabetes. Can J Diabetes 2013;37(Suppl. 1):S61–8.
4. Harper W, Clement M, Goldenberg R, et al. Policies, guidelines and consensus statements: Pharmacologic management of type 2 diabetes: 2015 interim update. Can J Diabetes 2015;39:250–2.
5. Lau DCW, Teoh H. Benefits of modest weight loss on the management of type 2 diabetes mellitus. Can J Diabetes 2013;37:128–34.
6. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009;361:1736–47.
7. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–28.

8. Lau DCW. Diabetes and weight management. Prim Care Diabetes 2010;4(Suppl. 1):24–30.
9. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: A meta-analysis. Diabetes Res Clin Pract 2008;81:184–9.
10. Zachariah S, Sheldon B, Shojaee-Moradie F, et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care 2011;34:1487–91.
11. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015;100:342–62.
12. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.
13. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.
14. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473–81.
15. Domecq JP, Prutsky G, Leppin A, et al. Drugs commonly associated with weight change: A systematic review and meta-analysis. J Clin Endocrinol Metab 2015;100:363–70.
16. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). Diabetes Care 1999;22:960–4.
17. Pratley R, Nauck M, Bailey T, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: A randomised, parallel-group, open-label trial. Int J Clin Pract 2011;65:397–407.
18. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: Systematic review and meta-analysis. BMJ 2012;344:e1369.
19. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet 2008;383:17.
20. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42.
21. Salpeter SR, Buckley NS, Kahn JA, et al. Meta-analysis: Metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008;121:149–57, e2.
22. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes: A 1-year randomized double-blind study. Diabetes Care 1998;21:1288–94.
23. Jacob S, Rabbia M, Meier MK, et al. Orlistat 120 mg improves glycaemic control in type 2 diabetic patients with or without concurrent weight loss. Diabetes Obes Metab 2009;11:361–71.
24. Vilsbøll T, Christensen M, Junker AE, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: Systematic review and meta-analyses of randomised controlled trials. BMJ 2012;344:d7771.
25. Scheen A. Pharmacodynamics: Efficacy and safety of sodium–glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015;75:33–59.
26. Hasan FM, Alsahli M, Gerich JE. SGLT2 inhibitors in the treatment of type 2 diabetes. Diabetes Res Clin Pract 2014;104:297–322.
27. Yang X-P, Lai D, Zhong X-Y, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: Systematic review and meta-analysis. Eur J Clin Pharmacol 2014;70:1149–58.
28. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: A systematic review and meta-analysis. Ann Intern Med 2013;159:262–74.
29. Bolli GB, DeVries JH. New long-acting insulin analogs: From clamp studies to clinical practice. Diabetes Care 2015;38:541–3.
30. Russell-Jones D, Gall MA, Niemeyer M, et al. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: A meta-analysis of seven clinical trials. Nutr Metab Cardiovasc Dis 2015;25:898–905.
31. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: A systematic review and meta-analysis. Lancet 2014;384:2228–34.
32. Gough SCL, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: Results of a 26-week extension to a 26-week main trial. Diabetes Obes Metab 2015;17:965–73.
33. DeFronzo RA. Bromocriptine: A sympatholytic, D2-dopamine agonist for the treatment of type 2 diabetes. Diabetes Care 2011;34:789–94.
34. Aronne L, Fujioka K, Aroda V, et al. Progressive reduction in body weight after treatment with the amylin analog pramlintide in obese subjects: A phase 2, randomized, placebo-controlled, dose-escalation study. J Clin Endocrinol Metab 2007;92:2977–83.
35. Ahrén B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 2014;37:2141–8.
36. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: A randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015;38:376–83.
37. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015;38:384–93.
38. Finan B, Yang B, Ottaway N, et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. Nat Med 2015;21:27–36.
39. Liu S-C, Tu Y-K, Chien M-N, et al. Effect of antidiabetic agents added to metformin on glycemic control, hypoglycemia and weight change in patients with type 2 diabetes: A network meta-analysis. Diabetes Obes Metab 2012;14:810–20.
40. Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;2.
41. Rosenstock J, Raccah D, Korányi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: A 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care 2013;36:2945–51.
42. Fulcher GR, Christiansen JS, Bantwal G, et al. Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: A phase 3a, randomized, treat-to-target trial. Diabetes Care 2014;37:2084–90.
43. Caparrotta TM, Evans M. PEGylated insulin lispro (LY2605541): A new basal insulin analogue. Diabetes Obes Metab 2014;16:388–95.
44. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: A 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care 2013;36:2489–96.