Expert Opinion

Diabetes medications and body weight

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Tight diabetes control sometimes comes with a price: weight gain and hypoglycemia. Two of the three major recent trials that looked at the relationship between intensive diabetes control and cardiovascular events reported significant weight gain among the intensively treated groups. There is a growing concern that the weight gain induced by most diabetes medications diminishes their clinical benefits. On the other hand, there is a claim that treating diabetes with medications that are weight neutral or induces weight loss or less weight gain while minimizing those that increase body weight may emerge as the future direction for treating overweight and obese patients with diabetes. This review clarifies the weight effect of each of the currently available diabetes medications, and explains the mechanism of action behind this effect. Despite the great variability among reviewed clinical trials, the currently available evidence is quite sufficient to demonstrate the change in body weight in association with most of the currently available medications. This review also provides some guidelines on using diabetes medications during weight management programs.

Keywords: diabetes, diabetes medications, insulin, oral antidiabetic medications, weight gain, weight loss, weight management, Why WAIT program

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1. Introduction

Weight reduction is fundamental for diabetes management in overweight and obese patients with diabetes. It was found to be associated with increased insulin sensitivity [1] and has potential to lower blood pressure [2], serum total cholesterol and triglycerides [3] and to reduce markers of inflammation, coagulation and endothelial dysfunction [1,4,5]. Consequently, weight reduction may be beneficial in reducing cardiovascular risk [6]. Several trials, including bariatric surgical studies [4,6,7], showed that diabetes control is significantly better after weight reduction and patients with diabetes frequently use fewer medications after weight loss [8,9]. However, diabetes medications have variable effect on body weight. Some of them induce significant weight gain while others are either weight neutral, cause weight loss or are associated with less weight gain. Recently, the number of adjuvant diabetes medications that predominantly induce weight loss and improve glycemic control is increasing. The purpose of this review is to clarify the effect of each of the currently available diabetes medications on body weight, and to explain the possible mechanism of that effect.

2. Metformin

Metformin is one of the oldest diabetes medications. It is frequently chosen for being generic, well tolerated and for not causing hypoglycemia. It has an advantage of being a weight neutral medication. Furthermore, metformin is the only oral antidiabetic drug that was proven to reduce cardiovascular risk [10]. Physicians, in

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general, are comfortable with metformin selection as their first-line therapy for most overweight and obese patients with diabetes type 2. This choice is supported by many therapeutic guidelines, such as the most recent consensus statement of the American Diabetes Association [11,12]. Metformin improves blood glucose by increasing hepatic and muscle insulin sensitivity, reducing hepatic glucose production, activating AMPK and increasing glucagon like peptide-1 (GLP-1) serum level.

Several randomized studies showed that metformin has neutral effect on body weight [13-15]. Two other smaller non-randomized studies showed that metformin induces significant weight loss in patients with type 2 diabetes of different ethnicities [16,17]. In the UK Prospective Diabetes Study (UKPDS) [10], metformin did not change body weight after 3 years of continuous use. Patients on metformin gained less weight after 6 [18] and 10 years [19] of follow-up in comparison to sulfonylureas (SUs) and insulin. Addition of metformin to maximum dose of SU therapy in 591 type 2 patients with poor glycemic control did not induce significant weight gain in that study population [19].

Although the exact mechanism of action of metformin on body weight is not clearly understood, it was found that it decreases caloric intake [20]. One study showed that 88% of the metformin-induced weight loss was owing to reduction of adipose tissue, particularly visceral fat [16]. The effect of metformin on GLP-1 and dipeptidyl peptidase-4 (DPP-4) inhibitor is controversial. Green and colleagues [21] demonstrated that metformin is an inhibitor of DPP4. However, another trial showed no effect of metformin on DPP4 and hence increased GLP1 levels might be related to increased production [22]. The old claims that metformin-induced weight loss is simply related to its gastrointestinal adverse events or owing to reduced intestinal absorption of carbohydrates have little credibility [23].

3. Sulfonylureas

Sulfonylureas are effective medications in controlling hyperglycemia. They stimulate insulin production from pancreatic beta-cells irrespective of the blood glucose level and thus may induce hypoglycemia. The most commonly used SUs in the US are glyburide, glipizide and glimepiride. All of them are generic and cheap. Outside the US, glibenclamide and gliclazide are more frequently used. Older SUs such as chloropropamide and acetohexamide are rarely used nowadays.

In general, SUs are known to induce weight gain; however, the amount of weight gain is variable according to the compound used and the duration of its exposure. The 3-year follow-up report of the UKPDS showed that glibenclamide and chloropropamide caused more weight gain in comparison to diet intervention [24]. Regardless of the initial response to diet, patients on SUs gain 5 kg (11 lbs) on an average over a 6-year period [18]. Most of this weight gain occurs during the first year of treatment with SUs [18]. On the other hand, glimepiride [25] and other once-daily SUs, such as extended-release glipizide [26] or gliclazide MR [27], are weight neutral at least for the first year. The GAME regimen (Glimepiride at night, pre-meal insulin Aspart and MEtformin) did not show weight gain during the first 3 months of therapy, but weight gradually increased after 1 year of treatment [28,29].

As monotherapy, SUs caused more weight gain than either metformin [30,31] or repaglinide [32] and also caused more weight gain when added to other diabetes medications [33,34]. However, the weight gain associated with SUs is similar to that caused by pioglitazone [33] and less than that caused by insulin [24].

Being insulinotropics, SUs cause weight gain by the same mechanism as insulin. However, at the same level of glycemic control, insulin induces more weight gain than SUs [24]. It is not known if SUs, through their effect on beta-cells, enhance amylin release. It would be of interest to know the weight effect of amylin versus insulin in response to SUs. Other possible mechanisms of weight gain in association with SUs may be related to increased food intake to compensate for hypoglycemia and/or 'defensive snacking' for fear of hypoglycemia. In the UKPDS study, 27.8% of patients treated with glibenclamide monotherapy had hypoglycemic episodes in comparison to 1.2% in those treated with diet only [10].

4. Meglitinides

Meglitinides are short-acting secretagogues that enhance insulin synthesis and release. Both repaglinide and nateglinide are used as monotherapy or in combination with metformin, thiazolidinediones (TZDs) or long-acting insulin.

Meglitinides induce weight gain whether used alone or in combination with either metformin [35], Neutral Protamine Hagedorn (NPH) insulin plus metformin or gliclazide [36,37] or in combination with TZDs [38,39]. In a head-to-head comparison over 1 year, repaglinide caused less weight gain than glyburide in pharmacotherapy naïve patients but the difference was non-significant [32].

Nateglinide in combination with metformin induced more weight gain than metformin used alone after 24 weeks of treatment [40]. This effect on body weight was not observed in another shorter study [41]. Nonetheless, a recently published meta-analysis confirmed that patients on nateglinide gained weight in comparison to metformin [42]. Given the insulin-inducing mechanism of action of meglitinides, it is not surprising that they induce weight gain in patients with diabetes.

5. Thiazolidinediones

Thiazolidinediones improve insulin sensitivity and promote differentiation of fat cells through their effect on Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) [43,44]. When PPAR-γ receptors are activated by a TZD, the expression of insulin-dependent glucose transporters, GLUT-4, is enhanced, followed by an up-regulation of genes involved in the transport and synthesis of fatty acids [45-47]. Their effect on glycemic control lasts longer than metformin and SUs [48].

Several randomized, double-blind placebo-controlled studies showed that TZDs cause considerable weight gain. In a 23-week randomized, double-blind clinical trial, pioglitazone used as monotherapy was associated with 1.35 kg weight gain in comparison to placebo -1.87 kg ($p < 0.001$) [49,50]. Weight gain was more prominent in patients on higher doses of TZDs and in patients with higher body mass index (BMI) at baseline. Similar effect on body weight was seen when pioglitazone was used in combination with metformin [51], SUs [52] or insulin [53].

The Diabetes Outcome Progression Trial (ADOPT) compared the efficacy of rosiglitazone, glyburide and metformin in recently diagnosed patients with type 2 diabetes [48]. Patients treated with rosiglitazone gained significantly more weight than those treated with either metformin or glyburide [48]. Over 4 years, the rosiglitazone arm gained in average 2.5 kg [48]. Although, their waist circumference also increased significantly, their waist-to-hip ratio did not change. Similar results were reported in several other trials that used rosiglitazone as monotherapy or in combination [47,54-57].

In a recent 56-week randomized clinical trial, pioglitazone induced similar weight gain to glyburide, but it resulted in lower incidence of hypoglycemia and cardiac events [33]. After 104 weeks of adding pioglitazone to oral antidiabetics (OADs) in poorly controlled patients with type 2 diabetes, an average 3 kg weight gain was observed [58]. Similar magnitude of change can be seen over shorter period when pioglitazone is added to insulin. In one study, pioglitazone added to insulin for 24 weeks induced ~ 3 kg of weight gain [59]. Thiazolidinediones only induced less weight gain when combined with metformin [54].

The mechanism of weight gain with TZDs is not totally clear. It could be related to enhanced differentiation of newer fat cells through their effect on PPAR-γ receptors in the adipose tissue [43,44]. In a randomized, double-blind placebo-controlled trial, pioglitazone increased subcutaneous but not visceral fat over 24 weeks of intervention [60]. By the end of the first 4 weeks, weight increased by 3.88 kg. Weight gain did not seem to reach a plateau after 6 months of therapy. Troglitazone, the first TZD, was known to decrease circulating leptin levels [61]. Leptin is a known anorexigenic hormone that suppresses the hypothalamic feeding centers.

6. Alpha-glucosidase inhibitors

These medications slow or limit intestinal absorption of carbohydrates. They are generally weak diabetes medications and their clinical use is limited, at least in the US, by their gastrointestinal adverse events.

The effect of alpha-glucosidase inhibitors on body weight is controversial. The Essen study [62] showed that acarbose was weight neutral after 24 weeks of intervention. Later, in the Essen II study, acarbose induced 0.8 kg of weight loss over 24 weeks of treatment [63]. The difference between the two studies is not completely understood. With longer follow-up, acarbose added to other diabetes medications resulted in a small but significant weight loss in comparison to placebo [64]. This weight loss was explained in part by the dose reduction of other OADs or insulin and by the energy loss owing to increased colonic fermentation. The UKPDS 44 randomized patients with type 2 diabetes who were already on several antidiabetic medications to either acarbose or placebo and followed them for 3 years. The results showed no major difference in body weight, but careful titration was recommended giving acarbose gastrointestinal adverse events [65]. Finally, a meta-analysis showed that acarbose significantly decreased the BMI, but its effect on body weight was not significant [66]. In conclusion, acarbose clinical trials showed mixed effects on body weight, but never weight gain.

The effect of miglitol on body weight in comparison to glibenclamide and placebo was tested in a 24-week randomized clinical trial [67]. In this trial, miglitol was shown to be weight neutral. However, in elderly patients with type 2 diabetes, miglitol reduced body weight in comparison to glyburide but the change was not statistically significant in comparison to placebo [26]. A systematic review confirmed the neutral effect of miglitol on body weight [68].

7. Insulin

Insulin, in most of its forms, has been associated with weight gain. Several mechanisms have been considered to be involved in the weight gain associated with insulin therapy. Insulin stimulates protein synthesis [69] and increases intracellular amino acid influx [70]. It also has a direct anabolic effect on both muscles [71] and adipose tissues [72]. Long-acting insulin creates a pattern of 24-h hyperinsulinemia, which stimulates lipogenesis and inhibits lipolysis. Fear of hypoglycemia, which is frequently compensated by preemptive increase of food intake, was also postulated as a possible cause of weight gain. However, food intake and weight gain did not correlate in patients with type 1 diabetes enrolled in the Diabetes Control and Complication Trail (DCCT) [73]. Meanwhile, few patients freely eat knowing that hyperglycemia could be averted by insulin. Other researchers did not find such relationship [72]. On the other hand, prolonged insulin exposure increases leptin serum level, which is frequently nullified by leptin resistance [74].

It is estimated that 50% of insulin-induced weight gain is seen during the first 3 months of its use [75]. Weight gain usually continues at a slower pace beyond the first year, even with extensive dietary and behavioral modifications [65]. In the DCCT, 25% of the participants in the intensively treated arm reached the obesity range with an average BMI of 31 kg/m^2, an increase of 6.8 kg/m^2 from baseline after 6.5 years of follow-up [76]. In the UKPDS 13, participants treated with insulin had an average weight gain of 4.8 kg compared with participants treated with diet alone over a 3-year period [10]. All participants in this study received dietary counseling before and during the study. After 10 years of

follow-up, insulin had the greatest effect on body weight, with a mean increase of 4 kg [24].

Although some forms of insulin may cause less weight gain than others, the timing of insulin injection and the regimen used may impact the amount of weight gain. For example NPH insulin, given in a single evening dose in combination with OADs, induced less weight gain than four other regimens that included NPH insulin [77]. Similarly, combining bedtime NPH insulin with SUs has less impact on body weight than combining it with pre-meal short-acting insulin [78].

Nichols and colleagues [68] studied retrospectively the impact of adding a second hypoglycemic medication to an established first medication for 1 year in a large sample of type 2 patients with diabetes. Addition of NPH insulin resulted in an average weight gain of 3.3 kg/year. Insulin added to SUs results in an average weight gain of 3 kg. Patient treated with metformin lost in average 1.3 kg before adding insulin. The addition of insulin to metformin resulted in an average 4 kg weight gain. The retrospective nature of this study did not account for all other variables that might play a role in weight gain [79].

7.1 Glargine insulin

Insulin glargine is one of the most widely prescribed long-acting insulins. Similar to most other insulin preparations, glargine insulin induces weight gain. In comparison to NPH insulin, glargine insulin induced significantly less weight gain in patients with type 1 diabetes after 16 weeks of intervention [80]. Similar observation was seen in patients with type 2 diabetes after 28 weeks of intervention [81]. However, the difference between the two insulin formulations was not seen after 52 weeks of intervention [82]. Other trials showed no difference between both insulins after shorter duration of 24 [83] and 36 weeks [84]. Many of the previous studies showed that glargine insulin did not induce weight gain during the first 4 weeks of its use and that most of the weight gain was seen with longer duration of use.

7.2 Detemir insulin

Detemir is a long-acting insulin that induces less weight gain than other insulin preparations. In a large trial of > 10,000 participants with type 1 and type 2 diabetes, body weight did not change significantly from baseline after 14.5 weeks of its use [85]. In a 52-week randomized, open-label, multinational trial, detemir induced less weight gain in comparison to glargine insulin [86]. Similarly, detemir insulin induced less weight gain in comparison to NPH insulin after 24 weeks of intervention [77]. Interestingly, small amount of weight loss was seen in patients with type 2 diabetes with BMI > 35 kg/m$^{2.}$ The average weight loss was 0.5 kg [87]. Other trials in type 1 diabetes showed that detemir insulin was weight-neutral in comparison to NPH insulin after 6 and 12 months of intervention [88,89].

The reason(s) for the detemir weight neutrality is not clear. In comparison to NPH, detemir caused less hypo-glycemic episodes [90] and hence reduced defense eating or overcorrection [91]. Detemir insulin was also shown to have a high signaling level in the hypothalamic tissue of experimental animals. Its lipophilic characteristics and ability to cross the blood brain barrier differentiate it from other insulins [92]. It is not clear if this central access has any relation to its effect on body weight.

7.3 Insulin lispro

Insulin lispro is short-acting insulin with duration of action significantly shorter than regular insulin. However, it induces similar weight gain to regular insulin in both type 1 [93] and type 2 diabetics [94]. On the other hand, insulin lispro as single agent induced less weight gain when compared to glibenclamide in an open-label study of 26-week duration. In this study, insulin lispro was associated with a 0.7 kg weight loss in comparison to a 0.3 kg weight gain with glibenclamide [95]. Insulin lispro in a mixed combination with the long-acting form (75/25) induced an average of 1 kg of weight gain in comparison to glyburide, which induced an average of -0.85 kg of weight loss in an elderly population in the age range of 60 – 80 years [96]. In comparison to glargine insulin, 75/25 insulin added to metformin resulted in more weight gain over a 16-week period. Insulin lispro mix induced a weight gain of 2.3 kg in comparison to 1.6 kg weight gain with glargine insulin [97].

7.4 Insulin aspart

Insulin aspart is short-acting insulin that causes weight gain. When used as monotherapy, it caused an average of 0.4 kg of weight gain after 10 weeks of treatment [98]. This effect was also seen after its long-term use for 2 years [99]. Insulin aspart in combination with its long-acting form (70/30) induced more weight gain in comparison to glargine insulin after 28 weeks of intervention. More hypoglycemic episodes occurred with the mixed insulin; that may explain the excess weight gain [100]. When insulin aspart was used as monotherapy, it induced less weight gain than when it was combined with TZDs or SUs [101].

7.5 Insulin glulisine

Similar to the other two short-acting insulins, insulin glulisine induced weight gain similar to regular insulin when both were injected pre-meal [102]. However, in patients with type 1 diabetes, post-meal injection of insulin glulisine was shown to induce less weight gain than pre-meal regular insulin [103]. Further comparisons in randomized trials are needed to explore the effect of insulin glulisine on body weight when it is injected after meals in both type 1 and type 2 diabetics.

8. Pramlintide

Pramlintide is an amylin analogue. It slows gastric emptying [104], suppresses postprandial glucagon secretion [105]

and reduces caloric intake through a central appetite-suppressing action [106]. Pramlintide was approved for use in combination with pre-prandial insulin to improve postprandial blood glucose levels. After 52 weeks of adding pramlintide to stable insulin therapy in a large sample of patients with type 2 diabetes, the pramlintide group lost significant amount of weight using 120 mcg dose before each meal [107]. Smaller doses did not show similar effect.

Similarly, patients with type 1 diabetes who were treated with pramlintide 60 mcg 3 or 4 times daily in combination with insulin showed an average of 1.3 kg weight loss versus 0.7 kg weight gain in the placebo group after 26 weeks of intervention [108].

Phase II studies have shown a potential anti-obesity effect of pramlintide when combined with leptin. Long-term trials investigating the role of pramlintide with or without leptin in treatment of obesity are continuing.

9. Exenatide

Exenatide is a GLP-1 analogue. It is currently used as adjuvant therapy to metformin, SUs or TZDs. It stimulates insulin production and secretion from pancreatic beta-cells and suppresses glucagon production from pancreatic alpha-cells. This glucose-dependent dual mechanism in addition to delaying gastric emptying improves postprandial blood glucose level. Exenatide also induces weight loss through central suppression of appetite. Three Phase III clinical trials labeled the 'AC2993: Diabetes Management for Improving Glucose Outcomes' (AMIGO) evaluated the effect of exenatide added to oral hypoglycemic therapy. Over 30 weeks, addition of exenatide to metformin, SUs or combination of both resulted in significant weight loss [109-111]. Weight reduction was more prominent with 10 mcg twice daily in comparison to 5 mcg twice daily. When exenatide was combined with metformin, it induced more weight loss than when it was combined with SUs. Open-label extension of the AMIGO trial showed progressive reduction in body weight with an average of -4.7 kg (-5.4, -4) after 2 years [112].

Adding exenatide to TZDs for 16 weeks resulted in 1.5 kg weight loss in comparison to placebo [113]. In comparison to glargine insulin added to OADs, participants on exenatide lost in average 1.8 kg and those on glargine insulin gained in average 1.8 kg after 26 weeks of follow-up [114]. A pooled *post hoc* analysis showed that exenatide added to OADs resulted in weight loss in most patients (73%, average 3 kg weight loss) when compared with insulin added to OADs (76%, average 3 kg weight gain) [115]. In the previous trials, a small percentage of patients on exenatide did not lose weight and some gained weight, while few others were not able to tolerate its side events. The link between the weight loss that follows exenatide use and the degree of diabetes control needs further evaluation. So far it is not clear if the improvement in glycemic control is consequent to weight loss or the two effects are entirely independent.

10. DPP-4 inhibitors

There are two approved DPP-4 inhibitors in the global market, sitagliptin and vildagliptin, with many others lined up for FDA approval. So far, sitagliptin is the only FDA-approved DPP-4 inhibitor in the US market. The mechanism of action of DPP-4 inhibitors involves an increase in GLP-1 concentrations by 2 – 3 times and subsequent enhancement of insulin secretion from beta-cells in response to food intake. However, this mechanism is debated as peripheral infusion of GLP-1 at concentrations similar to those resulting from DPP-4 inhibition did not improve glycemic control and raised the possibility that having GLP-1 peripherally may not produce the same glycemic effect as having the same concentration in the portal circulation [116].

Similar to exenatide, sitagliptin also improves postprandial blood glucose level through suppression of glucagon secretion. However, sitagliptin does not cause weight loss. Its effect on body weight was shown to be neutral in few studies. In a randomized, controlled study, Nauck and colleagues [117] studied the difference in body weight between adding sitagliptin or glipizide to a stable dose of metformin. After 52 weeks of follow-up, the sitagliptin group experienced -1.5 kg weight loss in comparison to 1.1 kg weight gain in the glipizide group. Similarly, adding sitagliptin to pioglitazone did not show any further weight gain in comparison to placebo after 24 weeks of intervention [118]. Sitagliptin stabilizes postprandial GLP-1 levels; hence its net effect is mostly preventive of weight gain rather than inductive of weight loss [119].

Vildagliptin was also shown to be weight neutral in two 24-week placebo-controlled randomized trials [120,121]. A more recent randomized, placebo-controlled European study showed that vildagliptin was associated with minimal weight loss (-0.5 kg) after 50 weeks of follow-up [122]. In a 104-week randomized trial versus metformin [123] or rosiglitazone [124], vildagliptin showed weight neutrality while metformin was associated with weight loss and rosiglitazone with weight gain.

11. Conclusion

Newer trends in managing diabetes are emerging with more emphasis on minimizing the negative effect of antidiabetic medications on body weight without compromising on glycemic control. Current efforts are continuing to include agents in combination that have effective hypoglycemic action without inducing weight gain. Clinicians have in their armamentarium several newer and effective medications with novel mechanisms of action and distinct weight-altering profiles. However, sound judgment is necessary to effectively use these resources within the scope of the current knowledge. Weight reduction that may result from combining such adjustments of antidiabetic medications with an appropriate lifestyle showed significant impact on several metabolic and cardiovascular parameters that may exceed the benefits from progressively adding those antidiabetic medications that have

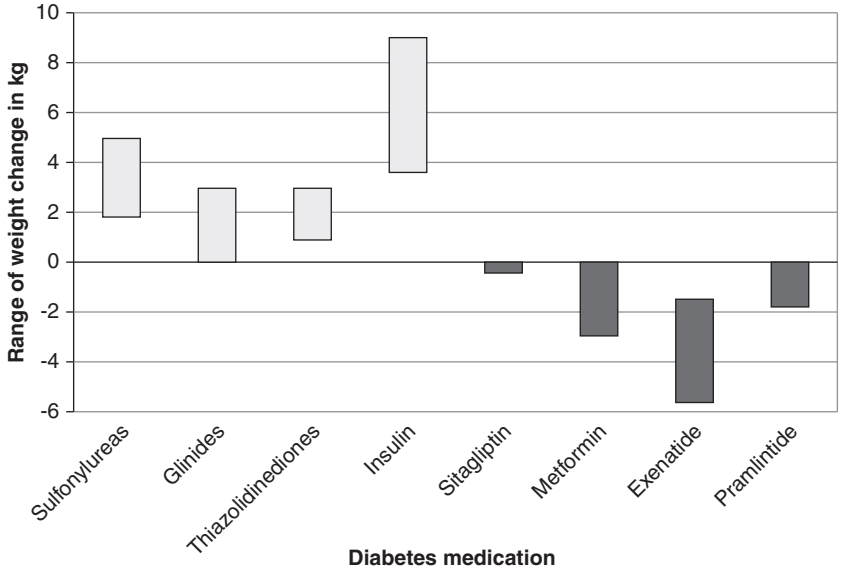

Figure 1. Range of weight change (in kilograms) in response to diabetes medications.

weight gain potentials. Further research is warranted to explain ways to conduct individualized therapy for patient with diabetes with the aim of reducing body weight while achieving the target glycemic control.

12. Expert opinion

Targeting body weight, as an alternative model to primarily targeting hemoglobin A1c, is emerging as a viable and potentially cost-effective approach to managing type 2 diabetes in clinical practice. Understanding the weight effect of each diabetes medication (**Figure 1** and **Table 1**) may help clinicians to wisely select the best combination that may help in achieving weight loss without compromising on diabetes control during weight management programs.

To enhance weight reduction, metformin should be initiated or increased unless there is a contraindication to its use. A maximal dose of 2,550 mg may be reached, as hypoglycemia rarely occurs. Sulfonylureas, in general, cause significant weight gain and should be reduced or eliminated during weight management. Reduction of caloric intake may also result in hypoglycemia in patients treated with SUs and may consequently retard further weight loss. If SUs are selected, extended-release formulations (glipizide XL or gliclazide MR) are preferred. Glimepride causes less weight gain in comparison to glyburide. Meglitinides, similar to SUs, are barriers to weight reduction in overweight and obese patients with diabetes. However, repaglinide induces less weight gain than glyburide. Meglitinides should be eliminated or their doses reduced during weight management. Thiazolidinediones are strong insulin sensitizers but they generally cause significant weight gain. Similar to metformin, they don't cause hypoglycemia. Their dose should be significantly reduced during weight management but there is no need to discontinue them for their long-lasting glycemic benefit. Sitagliptin is weight neutral and its use together with metformin is preferred during weight management.

If long-acting insulin is indicated, detemir insulin is preferred as it causes less weight gain than NPH and glargine insulin [14,15]. Short-acting insulin may be injected immediately after meals or within 20 min from the start of the meal. By administering the short-acting insulin after meals, patients had the opportunity to calculate the short-acting insulin dose based on the food that they actually consumed and not on the amount of food that they presumed to eat. This tactic minimizes the hypoglycemic risk and limits the consumption of the unneeded extra calories presumed to cover the pre-planned prandial insulin. Glulisine insulin is preferred in such scenario for being relatively quicker in its onset of action [13]. Exenatide and pramlintide are the only injectable medications that induce weight loss. Their use is encouraged during weight management. Maximal weight loss is seen when exenatide is used in combination with metformin. Our clinical experience showed that weight loss is maximal when exenatide is injected 1 h before meals.

In patients treated with pramlintide and prandial insulin, injecting the pramlintide before meals and the short-acting insulin immediately after meals was preferred. As appetite is frequently suppressed by pramlintide, patients usually eat much less than expected. Nausea is not common with pramlintide use in patients with type 2 diabetes in comparison to its use in patients with type 1 diabetes. Its use enables most patients to reduce prandial insulin dose and consequently enhance further weight reduction. Pramlintide is of particular importance for weight management in obese patients with type 1 diabetes. Although prevalence of obesity is not high in patients with

Table 1. Weight-specific effects of available classes of diabetes medications.

Medication	Weight effect	Remarks
Metformin	± ↓	
Sulfonylureas		5 kg weight gain over 6 years; most weight gain occurs in the first year
Glyburide	↑ ↑	
Glipizide	↑ ↑	
Glimepiride	± ↑	Weight increases gradually after the first year
Glipizide XL	± ↓	
Gliclazide MR	± ↓	
Glinides		
Nateglinide	↑	Causes less weight gain than glyburide
Repaglinide	↑	Weight gain is only seen on long-term use
Thiazolidinediones		Weight gain increases with increasing daily dose: 3 kg over 56 and 24 weeks when used with insulin
Pioglitazone	↑ ↑	
Rosiglitazone	↑ ↑	
Alpha-glucosidase inhibitors		Weight loss is seen on long-term use
Acarbose	± ↓	
Miglitol	± ↓	
DPP-4 inhibitor		
Sitagliptin	±	
Insulins		4.8 – 7.8 kg after 6 months to 3 years; more weight gain with intensive insulin therapy; 50% of weight gain is seen in the first 3 months
NPH	↑ ↑ ↑	Less weight gain if given as single evening dose is association with oral antidiabetic medications
Glargine	↑ ↑ ↑	3.3 kg/year; less weight gain than NPH on short-term, but similar after 1 year
Detemir	± ↑	No weight gain on short term; less weight gain than glargine insulin after 1 year
Aspart, Aspart 70/30	↑ ↑ ↑	0.4 – 2.6 kg weight gain after 6 – 10 weeks; 70/30 induces more weight gain than glargine insulin
Lispro, Lispro 75/25	↑ ↑ ↑	Weight gain similar to glyburide if used as single agent in combination with metformin, but more weight gain in elderly
Glulisine	↑ ↑ ↑	May cause weight loss if injected post-meal in type 1
Amylin analogue		
Pramlintide	↓ ↓	Weight loss is more significant with higher doses; weight regain occurs in type 1 after 1 year of use
GLP-1 receptor agonist		
Exenatide	↓ ↓	Weight loss is more significant with higher doses; weight loss is increased when combined with metformin

↑: Increased; ↓: Decreased.

Table 2. Use of diabetes medications during weight management.

Medications to be reduced (weight fury)	Medications to be added or increased (weight friendly)
Insulins	*Metformin*
NPH	*DPP-4 inhibitor*
Glargine	Sitagliptin
Aspart, Aspart 70/30	*Alpha-glucosidase inhibitors*
Lispro, Lispro 75/25	Acarbose
Glulisine (pre-meal)	Miglitol
	Amylin analogue
Sulfonylureas	Pramlintide
Glyburide	*GLP-1 receptor agonist*
Glipizide	Exenatide
Glimepiride	*Insulin*
Glinides	Detemir
Nateglinide	Glulisine (post-meal)
Repaglinide	
Thiazolidinediones	
Pioglitazone	
Rosiglitazone	

type 1 diabetes, it is of particular concern among young or middle-aged women who intentionally reduce their insulin intake to limit weight gain. Pramlintide use would allow them to reduce insulin dose without scarifying diabetes control. The central effect of pramlintide on appetite together with the concomitant reduction in insulin enhances weight loss.

This model of intervention was tested in clinical practice through the Weight Achievement and Intensive Treatment program (Why WAIT) at the Joslin Diabetes Center in Boston, Massachusetts, US [8,125]. This 12-week multidisciplinary program for weight control and intensive diabetes management was specifically designed for application in routine diabetes practice. This model was effective in improving key metabolic abnormalities seen in patients with diabetes with an extra benefit of reducing the dose and number of antidiabetic medications. In this program, diabetes medications were classified into two groups: those known to promote weight gain and those associated with weight loss or that are weight neutral or associated with minimal weight gain (**Table 2**). Without compromising diabetes control, medication regimens

were adjusted to facilitate weight loss by using more of the weight-friendly diabetes medications and reducing or eliminating those that promote weight gain. Participants treated with insulin and with good diabetes control (HbA1c < 7%) were advised to reduce their prandial insulin by ~ 20 – 30% at the start of the weight management program. Exenatide was frequently added to oral medications for its weight benefit, and pramlintide was frequently added to meal-time insulin for the same reason when appropriate. The average weight loss of 11.2 kg after 12 weeks of intervention was associated with significant reduction in HbA1c. Participants maintained an average 8.3 kg weight loss after 1 year and 8.5 kg at 18 months.

Declaration of interest

J Mitri reported no conflict of interest. O Hamdy is on the speaker bureau of Takeda Pharmaceutical North America, Novo-Nordisk, Merck Pharmaceutical, Inc., sanofi-aventis, Amylin Pharmaceutical and Eli-Lilly & Co. He is not receiving research support from any of these companies and is not consulting to any of them.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Hamdy O, Ledbury S, Mullooly C, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care 2003;26(7):2119-25
2. Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. Obes Res 2000;8(3):270-8
3. Metz JA, Stern JS, Kris-Etherton P, et al. A randomized trial of improved weight loss with a prepared meal plan in overweight and obese patients: impact on cardiovascular risk reduction. Arch Intern Med 2000;160(14):2150-8
4. Monzillo LU, Hamdy O, Horton ES, et al. Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. Obes Res 2003;11(9):1048-54
5. Ziccardi P, Nappo F, Giugliano G, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation 2002;105(7):804-9
6. Williams KV, Kelley DE. Metabolic consequences of weight loss on glucose metabolism and insulin action in type 2 diabetes. Diabetes Obes Metab 2000;2(3):121-9
7. Mumme DE, Mathiason MA, Kallies KJ, et al. Effect of laparoscopic Roux-en-Y gastric bypass surgery on hemoglobin A1c levels in diabetic patients: a matched-cohort analysis. Surg Obes Relat Dis 2009;5(1):4-10
8. Hamdy O, Carver C. The Why WAIT program: improving clinical outcomes through weight management in type 2 diabetes. Curr Diab Rep 2008;8(5):413-20
9. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 2009;122(3):248-56 e5
10. United Kingdom Prospective Diabetes Study (UKPDS). 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995;310(6972):83-8
11. Standards of medical care in diabetes–2009. Diabetes Care 2009;32(Suppl 1):S13-61
12. Rodbard HW, Blonde L, Braithwaite SS, et al. American association of clinical endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007;13(Suppl 1):1-68
13. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med 1995;333(9):541-9
14. Dornan TL, Heller SR, Peck GM, et al. Double-blind evaluation of efficacy and tolerability of metformin in NIDDM. Diabetes Care 1991;14(4):342-4
15. Rains SG, Wilson GA, Richmond W, et al. The effect of glibenclamide and metformin on serum lipoproteins in type 2 diabetes. Diabet Med 1988;5(7):653-8
16. Kurukulasuriya R, Banerji MA, Chaiken R, et al. Selective decrease in visceral fat is associated with weight loss during metformin treatment in African Americans with type 2 diabetes [abstract]. Diabetes 1999;48:A315
17. Stumvoll M, Nurjhan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995;333(9):550-4
18. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. United Kingdom Prospective Diabetes Study Group. Ann Intern Med 1998;128(3):165-75

•• **UKPDS is the largest clinical research study into diabetes ever conducted at the time**

19. UKPDS 28: a randomized trial of efficacy of early addition of metformin in ulfonylurea-treated type 2 diabetes. U.K. Prospective Diabetes Study Group. Diabetes Care 1998;21(1):87-92
20. Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. Obes Res 1998;6(1):47-53
21. Green BD, Irwin N, Duffy NA, et al. Inhibition of dipeptidyl peptidase-IV activity by metformin enhances the antidiabetic effects of glucagon-like peptide-1. Eur J Pharmacol 2006;547(1-3):192-9
22. Hinke SA, Kuhn-Wache K, Hoffmann T, et al. Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1. Biochem Biophys Res Commun 2002;291(5):1302-8
23. Berchtold P, Bolli P, Arbenz U, et al. Disturbance of intestinal absorption following metformin therapy (observations

on the mode of action of biguanides. Diabetologia 1969;5(6):405-12

24. 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(9131):837-53
25. Martin S, Kolb H, Beuth J, et al. Change in patients' body weight after 12 months of treatment with glimepiride or glibenclamide in Type 2 diabetes: a multicentre retrospective cohort study. Diabetologia 2003;46(12):1611-7
26. Johnston PS, Lebovitz HE, Coniff RF, et al. Advantages of alpha-glucosidase inhibition as monotherapy in elderly type 2 diabetic patients. J Clin Endocrinol Metab 1998;83(5):1515-22
27. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004;34(8):535-42
28. de Boer H, Jansen M, Koerts J, et al. Prevention of weight gain in type 2 diabetes requiring insulin treatment. Diabetes Obes Metab 2004;6(2):114-9
29. de Boer H, Keizers R, Jansen M, et al. Glycaemic control without weight gain in insulin requiring type 2 diabetes: 1-year results of the GAME regimen. Diabetes Obes Metab 2006;8(5):517-23
30. Campbell IW, Menzies DG, Chalmers J, et al. One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. Diabete Metab 1994;20(4):394-400
31. Hermann LS, Schersten B, Bitzen PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. Diabetes Care 1994;17(10):1100-9
32. Marbury T, Huang WC, Strange P, et al. Repaglinide versus glyburide: a one-year comparison trial. Diabetes Res Clin Pract 1999;43(3):155-66
33. Jain R, Osei K, Kupfer S, et al. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy 2006;26(10):1388-95
34. Lewitt MS, Yu VK, Rennie GC, et al. Effects of combined insulin-sulfonylurea therapy in type II patients. Diabetes Care 1989;12(6):379-83
35. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 1999;22(1):119-24
36. Furlong NJ, Hulme SA, O'Brien SV, et al. Repaglinide versus metformin in combination with bedtime NPH insulin in patients with type 2 diabetes established on insulin/metformin combination therapy. Diabetes Care 2002;25(10):1685-90
37. Furlong NJ, Hulme SA, O'Brien SV, et al. Comparison of repaglinide vs. gliclazide in combination with bedtime NPH insulin in patients with Type 2 diabetes inadequately controlled with oral hypoglycaemic agents. Diabet Med 2003;20(11):935-41
38. Jovanovic L, Hassman DR, Gooch B, et al. Treatment of type 2 diabetes with a combination regimen of repaglinide plus pioglitazone. Diabetes Res Clin Pract 2004;63(2):127-34
39. Raskin P, McGill J, Saad MF, et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. Diabet Med 2004;21(4):329-35
40. Marre M, Van Gaal L, Usadel KH, et al. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes Obes Metab 2002;4(3):177-86
41. Schatz H, Schoppel K, Lehwalder D, et al. Efficacy, tolerability and safety of nateglinide in combination with metformin. Results from a study under general practice conditions. Exp Clin Endocrinol Diabetes 2003;111(5):262-6
42. Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;(2):CD004654
43. Braissant O, Foufelle F, Scotto C, et al. Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. Endocrinology 1996;137(1):354-66
44. Gosset P, Charbonnier AS, Delerive P, et al. Peroxisome proliferator-activated receptor gamma activators affect the maturation of human monocyte-derived dendritic cells. Eur J Immunol 2001;31(10):2857-65
45. Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. J Clin Endocrinol Metab 2004;89(6):2563-8
46. Maeda N, Takahashi M, Funahashi T, et al. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 2001;50(9):2094-9
47. Phillips SA, Ciaraldi TP, Kong AP, et al. Modulation of circulating and adipose tissue adiponectin levels by antidiabetic therapy. Diabetes 2003;52(3):667-74
48. Viberti G, Kahn SE, Greene DA, et al. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care 2002;25(10):1737-43

•• **ADOPT is a pragmatic randomized trial comparing the role of three major oral antihyperglycemic medications in the treatment of diabetes.**

49. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 2000;23(11):1605-11
50. Rosenblatt S, Miskin B, Glazer NB, et al. The impact of pioglitazone on glycemic control and atherogenic dyslipidemia in patients with type 2 diabetes mellitus. Coron Artery Dis 2001;12(5):413-23
51. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. The Pioglitazone 027 Study Group. Clin Ther 2000;22(12):1395-409
52. Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Am J Med 2001;111(1):10-7
53. Davidson JA, Perez A, Zhang J. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. Diabetes Obes Metab 2006;8(2):164-74

54. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA 2000;283(13):1695-702

55. Dailey GE 3rd, Noor MA, Park JS, et al. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med 2004;116(4):223-9

56. Rosenstock J, Sugimoto D, Strange P, et al. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29(3):554-9

57. Home PD, Jones NP, Pocock SJ, et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabet Med 2007;24(6):626-34

58. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia 2005;48(6):1093-104

59. Davidson J, Vexiau P, Cucinotta D, et al. Biphasic insulin aspart 30: literature review of adverse events associated with treatment. Clin Ther 2005;27(Suppl B):S75-88

60. Smith SR, De Jonge L, Volaufova J, et al. Effect of pioglitazone on body composition and energy expenditure: a randomized controlled trial. Metabolism 2005;54(1):24-32

61. Shimizu H, Tsuchiya T, Sato N, et al. Troglitazone reduces plasma leptin concentration but increases hunger in NIDDM patients. Diabetes Care 1998;21(9):1470-4

62. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, glibenclamide, or placebo in NIDDM patients. The Essen Study. Diabetes Care 1994;17(6):561-6

63. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, metformin, or placebo in dietary-treated NIDDM patients: the Essen-II Study. Am J Med 1997;103(6):483-90

64. Wolever TM, Chiasson JL, Josse RG, et al. Small weight loss on long-term acarbose therapy with no change in dietary pattern or nutrient intake of individuals with non-insulin-dependent diabetes. Int J Obes Relat Metab Disord 1997;21(9):756-63

65. 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(6):960-4

66. van de Laar FA, Lucassen PL, Akkermans RP, et al. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005;28(1):154-63

67. Segal P, Feig PU, Schernthaner G, et al. The efficacy and safety of miglitol therapy compared with glibenclamide in patients with NIDDM inadequately controlled by diet alone. Diabetes Care 1997;20(5):687-91

68. Campbell LK, Baker DE, Campbell RK. Miglitol: assessment of its role in the treatment of patients with diabetes mellitus. Ann Pharmacother 2000;34(11):1291-301

69. Bark TH, McNurlan MA, Lang CH, et al. Increased protein synthesis after acute IGF-I or insulin infusion is localized to muscle in mice. Am J Physiol 1998;275(1 Pt 1):E118-23

70. Biolo G, Declan Fleming RY, Wolfe RR. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J Clin Invest 1995;95(2):811-9

71. Cederholm T, Sylven C, Esbjornsson-Liljedahl M, et al. Insulin treatment increases skeletal muscle fibre area in patients with diabetes mellitus type 2. Clin Physiol 2000;20(5):354-9

72. Jacob AN, Salinas K, Adams-Huet B, et al. Potential causes of weight gain in type 1 diabetes mellitus. Diabetes Obes Metab 2006;8(4):404-11

73. Weight gain associated with intensive therapy in the diabetes control and complications trial. The DCCT Research Group. Diabetes Care 1988;11(7):567-73

•• **DCCT is one of the largest type 1 diabetes studies at the time. It is important to know that one of the major side effects of intensive therapy is weight gain.**

74. Malmstrom R, Taskinen MR, Karonen SL, et al. Insulin increases plasma leptin concentrations in normal subjects and patients with NIDDM. Diabetologia 1996;39(8):993-6

75. Yki-Jarvinen H, Nikkila K, Makimattila S. Metformin prevents weight gain by reducing dietary intake during insulin therapy in patients with type 2 diabetes mellitus. Drugs 1999;58(Suppl 1):53-4; discussion 75-82

76. Purnell JQ, Hokanson JE, Marcovina SM, et al. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. Diabetes Control and Complications Trial. JAMA 1998;280(2):140-6

77. Yki-Jarvinen H, Kauppila M, Kujansuu E, et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1992;327(20):1426-33

78. Clauson P, Karlander S, Steen L, et al. Daytime glibenclamide and bedtime NPH insulin compared to intensive insulin treatment in secondary sulphonylurea failure: a 1-year follow-up. Diabet Med 1996;13(5):471-7

79. Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycaemic therapies. Diabetes Obes Metab 2007;9(1):96-102

80. Raskin P, Klaff L, Bergenstal R, et al. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care 2000;23(11):1666-71

81. Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001;24(4):631-6

82. Yki-Jarvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. Diabetes Care 2000;23(8):1130-6

83. Fritsche A, Schweitzer MA, Haring HU. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med 2003;138(12):952-9

84. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49(3):442-51

85. Meneghini LF, Rosenberg KH, Koenen C, et al. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. Diabetes Obes Metab 2007;9(3):418-27

86. Rosenstock J, Davies M, Home P, et al. Randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. Diabetologia 2008;51(3):408-16

•• **This is a head to head trial comparing the two long-acting insulins glargine and detemir.**

87. Raslova K, Tamer SC, Clauson P, et al. Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. Clin Drug Investig 2007;27(4):279-85

88. Russell-Jones D, Simpson R, Hylleberg B, et al. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther 2004;26(5):724-36

89. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. Diabetes Technol Ther 2004;6(5):579-88

90. Heller S. Weight gain during insulin therapy in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2004;65(Suppl 1):S23-7

91. Kolendorf K, Ross GP, Pavlic-Renar I, et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabet Med 2006;23(7):729-35

92. Hennige AM, Sartorius T, Tschritter O, et al. Tissue selectivity of insulin detemir action in vivo. Diabetologia 2006;49(6):1274-82

93. Raskin P, Holcombe JH, Tamborlane WV, et al. A comparison of insulin lispro and buffered regular human insulin administered via continuous subcutaneous insulin infusion pump. J Diabetes Complications 2001;15(6):295-300

94. Sargin H, Sargin M, Altuntas Y, et al. Comparison of lunch and bedtime NPH insulin plus mealtime insulin Lispro therapy with premeal regular insulin plus bedtime NPH insulin therapy in type 2 diabetes. Diabetes Res Clin Pract 2003;62(2):79-86

95. Forst T, Eriksson JW, Strotmann HJ, et al. Metabolic effects of mealtime insulin lispro in comparison to glibenclamide in early type 2 diabetes. Exp Clin Endocrinol Diabetes 2003;111(2):97-103

96. Herz M, Sun B, Milicevic Z, et al. Comparative efficacy of preprandial or postprandial Humalog Mix75/25 versus glyburide in patients 60 to 80 years of age with type 2 diabetes mellitus. Clin Ther 2002;24(1):73-86

97. Malone JK, Kerr LF, Campaigne BN, et al. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Ther 2004;26(12):2034-44

98. Warren ML, Conway MJ, Klaff LJ, et al. Postprandial versus preprandial dosing of biphasic insulin aspart in elderly type 2 diabetes patients. Diabetes Res Clin Pract 2004;66(1):23-9

99. Boehm BO, Vaz JA, Brondsted L, et al. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. Eur J Intern Med 2004;15(8):496-502

100. Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28(2):260-5

101. Raz I, Stranks S, Filipczak R, et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18-week, randomized, open-label study. Clin Ther 2005;27(9):1432-43

102. Dailey G, Rosenstock J, Moses RG, et al. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care 2004;27(10):2363-8

103. Garg S, Rosenstock J, Ways K. Optimized Basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with basal insulin glargine. Endocr Pract 2005;11(1):11-17

104. Kong MF, Stubbs TA, King P, et al. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. Diabetologia 1998;41(5):577-83

105. Fineman MS, Koda JE, Shen LZ, et al. The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. Metabolism 2002;51(5):636-41

106. Reda TK, Geliebter A, Pi-Sunyer FX. Amylin, Food Intake, and Obesity. Obesity Res 2002;10(10):1087-91

107. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2003;26(3):784-90

•• **A major randomized trial comparing the effect of pramlintide with placebo as adjunct to insulin in the treatment of type 2 diabetes.**

108. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004;21(11):1204-12

•• **A major randomized trial comparing the effect of pramlintide with placebo as adjunct to insulin in the treatment of type 1 diabetes.**

109. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28(5):1092-100

•• **It is a double blind randomized trial comparing the effectiveness of exenatide with placebo added to metformin leading to approval of exenatide as add-on therapy in to metformin in the treatment of type 2 diabetes.**

110. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control

over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27(11):2628-35

•• **It is a double-blind randomized trial comparing the effectiveness of exenatide with placebo added to sulfonylurea leading to approval of exenatide as add-on therapy to sulfonylurea in the treatment of type 2 diabetes.**

111. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28(5):1083-91

•• **It is a double-blind randomized trial comparing the effectiveness of exenatide with placebo added to sulfonylurea and metformin leading to approval of exenatide as add-on therapy to metformin and sulfonylurea in the treatment of type 2 diabetes.**

112. Buse JB, Klonoff DC, Nielsen LL, et al. Metabolic effects of two years of exenatide treatment on diabetes, obesity, and hepatic biomarkers in patients with type 2 diabetes: an interim analysis of data from the open-label, uncontrolled extension of three double-blind, placebo-controlled trials. Clin Ther 2007;29(1):139-53

•• **This is an extension study of three randomized trials exploring the effect of exenatide on diabetes and obesity in comparison to metformin, sulfonlyureas and their combination.**

113. Zinman B, Hoogwerf BJ, Duran Garcia S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2007;146(7):477-85

114. Barnett AH, Burger J, Johns D, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther 2007;29(11):2333-48

115. Glass LC, Qu Y, Lenox S, et al. Effects of exenatide versus insulin analogues on weight change in subjects with type 2 diabetes: a pooled post-hoc analysis. Curr Med Res Opin 2008;24(3):639-44

116. Vahl TP, Tauchi M, Durler TS, et al. Glucagon-like peptide-1 (GLP-1) receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. Endocrinology 2007;148(10):4965-73

117. Nauck MA, Meininger G, Sheng D, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007;9(2):194-205

118. Rosenstock J, Brazg R, Andryuk PJ, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2006;28(10):1556-68

119. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368(9548):1696-705

120. Dejager S, Razac S, Foley JE, et al. Vildagliptin in drug-naive patients with type 2 diabetes: a 24-week, double-blind, randomized, placebo-controlled, multiple-dose study. Horm Metab Res 2007;39(3):218-23

121. Pi-Sunyer FX, Schweizer A, Mills D, et al. Efficacy and tolerability of vildagliptin monotherapy in drug-naive patients with type 2 diabetes. Diabetes Res Clin Pract 2007;76(1):132-8

122. Scherbaum WA, Schweizer A, Mari A, et al. Efficacy and tolerability of vildagliptin in drug-naive patients with type 2 diabetes and mild hyperglycaemia*. Diabetes Obes Metab 2008;10(8):675-82

123. Goke B, Hershon K, Kerr D, et al. Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naive patients with type 2 diabetes: comparison with metformin. Horm Metab Res 2008;40(12):892-5

124. Rosenstock J, Niggli M, Maldonado-Lutomirsky M. Long-term 2-year safety and efficacy of vildagliptin compared with rosiglitazone in drug-naive patients with type 2 diabetes mellitus. Diabetes Obes Metab 2009;11(6):571-8

125. Hamdy O, Goebel-Fabbri A, Carver C, et al. Why WAIT program: a novel model for diabetes weight management in routine clinical practice. Obes Manage J 2008;4(4):176-83

•• **This study shows the short- and long-term results of diabetes weight management plan implemented in routine clinical practice.**

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