Is Weight Gain an Unavoidable Consequence of Insulin Therapy?

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Abstract

Weight gain is often a significant concern among patients with type 2 diabetes. Patients using long-acting insulin analogs, particularly insulin detemir, often have decreased weight gain and sometimes even weight loss following treatment, as well as a reduced incidence of hypoglycemia. These benefits may be due in part to the more predictable action profiles associated with long-acting insulin analogs, as compared with the older basal formulations that are based on human insulin. In this review, the properties of basal insulin analogs will be considered as they relate to weight gain, and several strategies to more effectively manage the problem of insulin-associated weight gain will be discussed.

CONFLICT OF INTEREST

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ABBREVIATIONS

A1C = glycosylated hemoglobin;
GLP-1 = glucagon-like peptide-1;
OAD = oral antidiabetes drug

INTRODUCTION

The prevalence of type 2 diabetes is increasing rapidly in the United States, and along with this trend, we are observing an emerging epidemic of obesity ([1]). The implications of these statistics are rather alarming when one considers the increased potential for premature morbidity and mortality as a result of chronic complications associated with diabetes along with cardiovascular risks related to both diabetes and obesity ([2,3]). Several large studies have determined that maintaining strict glycaemic control is associated with reduced risk of micro- and macrovascular complications of diabetes ([4,5,6,7]). As a result, the American Diabetes Association and American Association of Clinical Endocrinologists have suggested guidelines for achieving target glycosylated hemoglobin (A1C) levels of <7.0% and ≤6.5%, respectively, to maintain optimal glycemic control and reduce the risk of developing complications ([8,9]). Unfortunately, the substantial health benefits associated with intensive glycemic control, in terms of reduced risk for complications, have in general proven to come at the expense of increased risk of hypoglycemia as well as weight gain ([4,10,11,12]).

In type 1 diabetes the body is incapable of producing the hormone insulin that is needed to regulate the uptake of glucose into cells to provide energy. Type 2 diabetes is a heterogeneous disease, characterized by both insulin resistance and a gradual decrease in pancreatic □-cell function and thus, insulin secretory capacity ([13,14]). Owing to the progressive nature of type 2 diabetes, diet and exercise or combinations of oral agents often are unable to sustain glycemic control in the long term. Data from the United Kingdom Prospective Diabetes Study (UKPDS) revealed that after 3 years, only about 50% of patients on monotherapy with diet, sulfonylurea, or insulin were able to achieve an A1C of less than 7%, and after 9 years, only about 25% were able to achieve this goal ([15]). As a result of the progressive nature of type 2 diabetes, most patients will eventually require treatment with insulin to achieve optimal glucose control ([12]).

Excess weight gain has been considered one of the primary adverse effects for patients treated with insulin therapy ([16,17,18,19]). The amount of weight gain observed may increase as more intensive insulin treatment programs are utilized. As found in the Diabetes Control and Complications Trial

(DCCT), patients who were treated with intensive insulin therapy gained 4.75 kg more than patients on conventional therapy ([10]). In a smaller study, among 14 patients with type 2 diabetes, treated with an intensive insulin program over 6 months, there was an increase in body weight from 93.5 (± 5.8) to 102.2 (± 6.8) kg (P<0.001) ([20]). Weight gain associated with insulin therapy is believed to be primarily due to the anabolic effects of insulin, an increase in appetite, and reduction of glycosuria ([18,21]).

The involvement of weight effects progresses differently between people with type 1 compared to those with type 2 diabetes. People with type 1 diabetes are less often overweight initially, however, studies have been done showing that as glycemic control increases, weight gain also increases ([22,23]). Many patients with type 2 diabetes are already overweight when diagnosed, as there seems to be a correlation between obesity and progression to type 2 diabetes ([24]). Because of this, and the fact that many patients with type 2 diabetes are initiated to insulin therapy through the use of a basal insulin analog, this review pays special attention to recent developments relating to long-acting insulin analog safety profiles and their weight-related implications for patients with type 2 diabetes. Nevertheless, weight gain is an extremely troublesome side effect for people with both types of diabetes because it can increase insulin resistance and the risk of cardiovascular disease ([24,25,26]).

MAJOR CAUSES OF WEIGHT GAIN IN DIABETES

Many patients with type 2 diabetes are overweight before being diagnosed. Initiation of therapy, either with oral agents or insulin treatment, can lead to improved glycemic control while at the same time leading to weight gain ([23,27]). Several factors are associated with weight gain and more intensive therapy: failure to compensate for calories no longer being lost through glycosuria, intake of extra calories to treat more frequent episodes of hypoglycemia, repletion of body water due to periods of poor glucose control, and habitual overeating ([25,28,29]). Overall, increased caloric intake leads to weight gain and increased insulin resistance, which then exacerbates the progression of diabetes ([30,31]).

Hunger is a symptom of hypoglycemia, which in many cases can lead to overeating ([32]). A patient's fear of hypoglycemia can also lead to insufficient use of insulin or chronic overeating in order to try to prevent hypoglycemic episodes ([32]). This so-called “defensive snacking” can be a habit for many people with diabetes as they try to control or prevent hypoglycemic episodes ([33]).

INSULIN AND HYPOGLYCEMIA

Treatment with insulin carries a greater risk of hypoglycemia than other diabetes treatments because it so effectively lowers glucose levels ([34]). However, as human insulin formulations have relatively variable and unpredictable onsets, peaks, and durations of action, the timing of insulin administration is often difficult to coordinate with mealtimes and other elements of a patient's daily routine ([16,17,35]). For example, human insulin has an onset of action between 30 and 60 min with an accompanying peak of action of 2 to 4 hours. The range of NPH insulin's onset may extend from 1 to 3 hours with peak activity occurring between 5 and 7 hours post-injection ([35]). Hypoglycemia can be a problem unless the insulin injections are timed appropriately to mealtimes. In particular, human basal insulins are most troublesome in this respect, owing to the potential for overlapping action with short-acting insulins used at mealtimes in basal-bolus therapy ([35]). Taking the appropriate dose of insulin but then skipping a meal or decreasing the expected caloric intake also contributes to the incidence of hypoglycemia in people with diabetes.

The insulin analogs were developed in order to control some of the more unpredictable aspects of human insulin action. Rapid-acting insulin analogs have a very fast onset of action allowing for dosing closer to mealtimes ([36]). Also, as the basal insulin analogs have a flatter, more extended profile of action that lasts close to 24 hours, they offer less variable changes in glucose levels, which can lead to decreased incidence of hypoglycemia ([37,38]).

INSULIN EFFECTS IN THE LIVER, PERIPHERAL TISSUES, AND BRAIN

The physiologic action of insulin takes place in several different organs. In addition to its effects in pancreatic tissue, insulin plays an important role in regulating endogenous glucose production in the liver ([39]). In people with diabetes, increased hepatic glucose production is related to insulin resistance in the liver ([31]). This leads to unrestricted gluconeogenesis and glycogenolysis with the effect of increased hepatic output, which is an important contributor to the incidence of hyperglycemia in people with type 2 diabetes ([31]). Basal insulin, either physiological or exogenous, is needed to mediate glucose uptake in the liver as well as in peripheral muscle and adipose tissue ([35,40]). However, in people without diabetes, the level of

endogenous insulin that reaches the periphery is decreased by about 50% after initially travelling through the liver ([25]). In patients with diabetes who are treated with exogenous insulin therapy, the amount of peripheral insulin present is increased over that of physiologic insulin, and the resulting uptake of excess energy is believed to contribute to fat stores and weight gain ([25]).

Insulin enters the brain from the circulation where it can interact with insulin receptors on neurons and acts to decrease energy intake ([41]). Infusion of insulin intravenously throughout the night has been shown to result in a dose-dependent decrease of feeding during the day in animal and human studies. This suggests that the uninterrupted presence of insulin in the circulation may allow the brain to act continuously to stimulate peripheral lipolysis and hypophagia ([42,43]). The hormones insulin and leptin have been shown to be intimately involved in this feedback mechanism to maintain a balance in the intake of food and body weight regulation ([44]).

It has been suggested that actions of the basal insulin analog, insulin detemir, in both the liver and brain, may contribute to the explanation of favorable weight characteristics that have been associated with its use. As insulin detemir is bound to albumin, it has easy access through the hepatic sinusoids, directly into the liver. This might lead to a preferential effect on the liver and relatively reduced effect in the periphery, which more closely approximates physiological insulin action as compared to the other basal insulin formulations, and could cause similar plasma glucose levels with less hypoglycemia and weight gain ([25,45]). In a study involving mice, insulin detemir was found to act faster and more predominantly in the brain, as measured by an altered pattern of insulin-receptor signalling, as compared with human insulin. This marked activation of insulin signalling in the brain may be involved in preventing overeating and weight gain ([46]).

STRATEGIES FOR WEIGHT CONTROL DURING INSULIN THERAPY

Because weight gain is a significant issue that contributes to progression of diabetes, identifying key strategies to minimize weight gain is an important aspect of treatment. Designing an appropriate protocol for using insulin therapy should take into consideration the timing of insulin dosing, the use of insulin analogs, and the additive effect of other treatments. One consideration for designing an insulin treatment program that takes into account weight effects involves the timing of insulin administration. For example, in initiating once-daily insulin therapy with human basal insulin (NPH), bedtime dosing has been shown to cause less weight gain than breakfast dosing ([47]). When a twice-daily dosing program for insulin detemir is used, the combination of morning dosing with pre-dinner dosing was found in one study to result in significantly less change in mean body weight than dosing in the morning and at bedtime, -0.6 kg versus 0.1 kg, respectively ([48]). As described in more detail below, using a long-acting insulin analog as basal insulin may be helpful in preventing weight gain due to their more physiologic profiles ([49,50]). In particular, treatment with insulin detemir has been shown to result in decreased weight gain, if not actual weight loss, that is maintained over extended time periods as compared to patients treated with NPH insulin ([51,52,53,54,55,56,57,58,59]).

LONG-ACTING INSULIN ANALOGS

Long-acting insulin analogs have many advantages over intermediate-acting human insulins, including a flatter and more predictable time-action profile. The action of NPH insulin involves dissolution of the protamine crystal structure from hexamers to dimers and monomers that can then be absorbed into the bloodstream. Variability associated with NPH insulin may be partially due to inadequate mixing before injection and also to unpredictability in the rate of the dissolution process ([60]). Reports indicate that the within-subject coefficient of variation ranges between 20% and 40% for NPH insulin ([61,62]).

For insulin glargine, structural modifications result in a shift in the isoelectric point, which then significantly decreases its solubility at physiologic pH ([63]). After injection into the subcutaneous tissue, insulin glargine forms precipitates that dissolve and enter the circulation without a definable peak of activity with nearly a 24-hour duration of action ([63,64]). Insulin detemir remains soluble after injection, and the addition of a fatty-acid chain allows increased self-association and binding to albumin, both of which result in delayed absorption. Insulin detemir also has a relatively flat time-action profile and a duration of action close to 24 hours ([37,65]). With no precipitation plus the ability to bind to albumin, which limits changes in the rate of insulin uptake, insulin detemir has low variability in absorption ([66,67,68,69,70]).

Less variable absorption translates to less variable action. Patients treated with insulin glargine have been shown to have lower day-to-day variation in blood glucose levels than those treated with NPH insulin ([59]). In studies in which

glucose levels are held constant (eg, glycemic clamp studies), lower within-subject variability has been shown with insulin detemir than with NPH insulin or insulin glargine ([71,72,73]). In clinical trials, significantly less intrapatient variability has been observed with insulin detemir than in patients treated with NPH insulin ([51,52,53,56,74,75]).

LONG-ACTING INSULIN ANALOGS REDUCE THE RISK OF HYPOGLYCEMIA

A key characteristic of the long-acting insulin analogs is their ability to more closely mimic the continuous, basal physiologic release of insulin. By decreasing their variability of action, the long-acting insulin analogs can provide more predictable blood glucose levels to patients, which may in turn reduce the risk of hypoglycemia ([76]). Several studies have shown decreased risk of overall hypoglycemia in patients treated with long-acting insulin analogs, insulin glargine ([77,78]), or insulin detemir ([52,53,57,79]) as compared with those treated with the intermediate-acting NPH insulin.

Of particular concern to individuals with diabetes are episodes of nocturnal hypoglycemia because symptoms are easily missed during sleep and progression to more severe hypoglycemic episodes can occur. Treatment with either insulin glargine ([58,77,78]) or insulin detemir ([52,53,56,57]) has also been shown to reduce the risk of nocturnal hypoglycemia as compared with patients treated with NPH insulin.

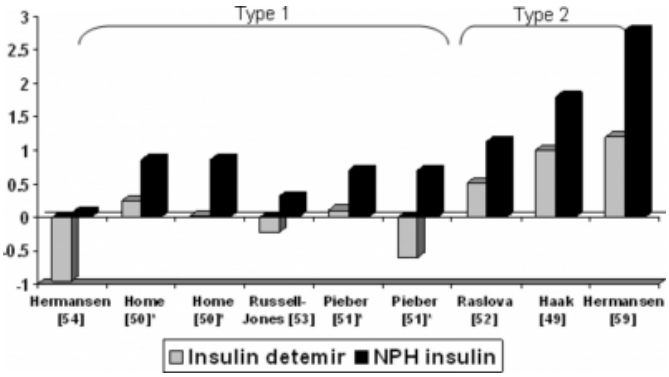
STUDIES ON WEIGHT EFFECTS OF LONG-ACTING INSULIN ANALOGS

For most patients diagnosed with type 2 diabetes, weight control is a particular concern. The long-acting insulin analogs, and in particular insulin detemir, have been shown to significantly decrease weight gain as compared to other basal insulin therapy ([21,25]). Patients treated with insulin glargine initially gain less weight than those treated with NPH insulin. In two different studies, the mean increases in body weight from baseline were 0.12 kg or 0.4 kg for insulin glargine compared with 0.54 kg or 1.4 kg for NPH insulin (P=0.034; P=0.0007) ([58,59]). However, in data collected after 1 year of treatment, patients treated with insulin glargine and NPH insulin had very similar gains in mean body weight (2.57 ± 0.23 kg and 2.34 ± 0.23 kg, respectively) ([77]).

The majority of the clinical trials conducted to date with insulin detemir show that patients gain significantly less weight or even experience weight loss compared with patients using NPH insulin (Fig. 1) ([51,52,53,56,57,80,81]) or insulin glargine ([82]).

Figure 1

Figure 1: Summary of Clinical Studies with Insulin Detemir Demonstrating Weight Changes. Data is taken from various clinical trials (,,,,,,). Mean body weight changes are adjusted for baseline. (*) Presented data represents two different dosing schedules of insulin detemir from the same study.



Less weight was gained by patients treated with insulin detemir (in the range of 0.6 to 1.6 kg) compared with patients treated with NPH insulin or insulin glargine ([51,52,53,56,57,82,83,84]). A few studies found that weight loss occurred in patients treated with insulin detemir as compared to their baseline mean body weight values. These studies showed changes in weight of -0.23, -0.95, and -0.6 kg with insulin detemir, along with treatment differences in comparison with NPH of -0.52, -1.01, and -1.3 kg, respectively ([52,56,85]). It should be mentioned that in the latter study only one of the two tested insulin detemir dosing regimens led to a mean body weight reduction (-0.6 kg for morning and before dinner dosing of detemir versus 0.1 kg for morning and bedtime dosing of detemir, and 0.7 kg for morning and bedtime dosing of NPH) ([52,56,85]). Of the studies performed to date, only trials with type 1 diabetes patients show actual weight loss with insulin detemir, while trials with either type 1 or type 2 diabetes patients have shown decreased weight gain.

One hypothesis suggests that the weight loss associated with insulin detemir treatment may be related to lower risk of hypoglycemia and a decreased need for “defensive, between-meal snacking” ([51]). More recently, a study was conducted to examine the correlation between the number of hypoglycemic events and weight gain in patients with type 2 diabetes. A statistically significant relationship was found for NPH but not for insulin detemir ([86]). Therefore, the beneficial weight effects associated with insulin detemir are not entirely linked to the incidence of hypoglycemia, and other possible mechanisms remain to be determined.

Regardless of the mechanism responsible for the observation of positive weight effects with insulin detemir, this brings hope for the future of people with diabetes as weight gain may no longer be an unavoidable outcome of insulin therapy.

BENEFICIAL WEIGHT EFFECTS ASSOCIATED WITH ADJUNCTIVE THERAPIES

Several different pharmacologic agents have been found to be useful in addition to insulin therapy. The additive effect of insulin on previous oral antidiabetes drug (OAD) treatments needs to be considered for maintaining glycemic control with minimal weight effects. It has been suggested that when progressing from oral therapy of diabetes to treatment with insulin, use of metformin should be continued. Treatment with metformin, in combination with insulin or alone, was found to decrease dietary intake and thus decrease weight gain in people with diabetes ([29,87]). The ability of metformin to maintain a stable weight or to facilitate modest weight loss seems to be a function of decreased feelings of hunger and appetite suppression ([87]).

An incretin mimetic, exenatide, has been approved that mimics the action of human glucagon-like peptide-1 (GLP-1), primarily its ability to stimulate insulin response and inhibit glucagon secretion ([88]). In several clinical trials, this drug resulted in significant weight loss compared with placebo controls while achieving beneficial A1C levels ([89,90,91]). Similarly, injectable GLP-1 has been found to be useful for treatment of diabetes as it decreases energy intake in patients with type 2 diabetes ([92]). Various stable analogs of GLP-1 have been studied, including liraglutide (NN2211), which has been used in several type 2 diabetes clinical trials and found to result in weight loss ([93,94,95,96]). A hormone that can be used with insulin for additional control is amylin, or the commercially developed synthetic analog pramlintide. This hormone also demonstrates a significant decrease in body weight during clinical trials of people with either type 1 or type 2 diabetes ([97,98]). Future studies are needed with all of these drugs to determine the long-term effects of reducing weight gain in patients with diabetes.

LIFESTYLE MODIFICATIONS FOR WEIGHT CONTROL IN TYPE 2 DIABETES PATIENTS USING INSULIN

For ideal diabetes management, a team of health-care professionals is necessary to provide a wide scope of health-related information in the best interest of the patient. This team can include physicians, nurse manager/educator/clinicians, dietitians, mental health professionals, or other specialists experienced in the care of people with diabetes ([28]). The team is responsible for helping the patient to monitor potential adverse effects (eg, weight gain) associated with more intensive insulin therapy. An individualized treatment plan for patients with diabetes can then be implemented based on a variety of individual factors including work or school schedules, family dynamics, personal preferences and motivation, and economic, cultural, and religious concerns ([28]).

Most importantly, as intensive therapy for diabetes often causes weight gain, several management strategies can be initiated: (1) reduce caloric intake by 200-400 kcal/day, (2) eliminate between meal snacks, (3) treat hypoglycemia with foods containing glucose, (4) teach flexibility in meal planning, and (5) initiate an exercise program but decrease insulin dose to account for extra exercise([17,28,31]). It is suggested that people with type 2 diabetes should engage in regular physical activity with a minimum expenditure of 1000 kcal/wk ([17,28,31]). The potential risk for exercise-related hypoglycemia can be addressed via self-monitoring blood glucose levels and then adjusting insulin doses or adding a carbohydrate supplement if needed. The recommended carbohydrate intake should increase within the range of 15-100 g/h for every 30-60 minutes of activity above normal ([17,28,31]), or the insulin dose should be decreased by about 30%-50% depending on the duration of physical activity ([17,28,31]).

While these strategies are designed with the best interests of the patient in mind, many patients do not follow these recommendations for healthy maintenance of their lifestyle while on insulin therapy. Owing to the inconveniences related to strict maintenance of a diet and exercise program, meals or opportunities for exercise are often skipped. In addition, patients often are not receiving adequate medical nutrition therapy to completely comprehend the complexities associated with regulating their dietary intake ([17,28,31]). Overall, treatment strategies to control weight gain should be closely monitored by a team of diabetes health-care professionals and the patient to incorporate their individual needs.

CONCLUSIONS

Type 2 diabetes is a progressive disease based on decreasing physiological insulin availability and increasing insulin resistance. Optimal glucose control has been established as a primary goal of diabetes treatment, and most patients with

type 2 diabetes will eventually require insulin in order to optimize their blood glucose levels. Weight control is also an essential aspect of effective long-term diabetes management. Although insulin therapy carries the risk of weight gain, with careful management of diabetes-related therapy, weight gain is not inevitable ([25]). A variety of lifestyle changes and targeted therapies are currently available to achieve the lowest possible weight change while maintaining adequate glycemic control. With education regarding the best types of therapy for individuals with diabetes, we can hope for overall improvements related to the optimization of glycemic control without the consequence of excessive weight gain. In the future, development of new and better treatments for diabetes should be targeted not only at improving glycemic control but decreasing adverse effects, such as weight gain.

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