Insulin Treatment of Patients with Diabetes and the Problem of Weight Gain: What Do You Need to Know as a Diabetes Nurse Educator?

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Citation

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Abstract

Reducing hyperglycemia through effective diabetes management in patients with type 1 or type 2 diabetes can reduce progression or development of diabetic complications: this article examines the need for effective pharmacological therapy while minimizing the risk of weight gain, and the role of advanced practice nurses (APNs) in helping patients with these issues. Insulin therapy is effective, but its potential side effects, including excessive weight gain, can undermine treatment success through adverse physiological consequences and patient demotivation. Educational and practical steps can be taken and therapy choices made that can limit this problem. APNs, working closely with patients who have diabetes, with diabetes nurse educators and with dietitians, have a role to play in weight management. Education concerning medical nutritional therapy and physical activity contributes to the overall care of the patient and effective self-management of diabetes. APNs need to maintain an awareness of insulin options and of other emerging diabetes therapies.

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THE NEED FOR EFFECTIVE PHARMACOLOGICAL THERAPY IN PATIENTS WITH DIABETES

Optimal glycemic control is paramount in the treatment of diabetes. Well-known, large-scale studies such as the Diabetes Control and Complications Trial (DCCT) in patients with type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) or the Kumamoto study in patients with type 2 diabetes have conclusively shown that elevated levels of blood glucose are associated with the occurrence of microvascular complications, such as retinopathy and neuropathy ([1], [2], [3]). The DCCT was a prospective trial involving 1441 patients with type 1 diabetes randomized to either an intensive (three to four insulin injections/day or insulin pump) or conventional (one to two insulin injections/day) treatment protocol. Those in the intensive group achieved a better level of glycemic control than those in the conventional group (median HbA_{1c} 7.3% vs. 9.1%, respectively; $p < 0.001$), and this was associated with a reduction of development or progression of microvascular complications of up to 76% ([1]). In the Kumamoto trial ([2]) involving 110 patients with type 2 diabetes, a better level of metabolic control was achieved with intensified insulin treatment (three or more insulin injections: rapid-acting insulin at mealtimes and intermediate-acting insulin at bedtime) compared with conventional treatment (two intermediate-acting insulin injections daily), with respective mean HbA_{1c} values of 7.1% and 9.4% ($p < 0.001$). This improved control was associated with a reduction in risk for retinopathy of up to 76% over 6 years of treatment.

Data from the DCCT cohort subsequently reported by the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) researchers demonstrate that improved control achieved through intensive insulin therapy also has a positive and lasting impact on macrovascular outcomes in diabetes ([4]). Patients from the original DCCT cohort have been followed up for a mean 17 years, during which time the event rate for nonfatal myocardial infarction (MI), stroke, or death from cardiovascular disease was reduced by 57% ($p = 0.02$) among patients who received

intensive therapy during the DCCT study. This observation was made despite the mean HbA_{1c} values of the two study groups converging after completion of DCCT, as most patients elected to receive intensive therapy. A reduction in macrovascular events with improved glycemic control was also suggested for patients with type 2 diabetes in the UKPDS study, where for each 1% reduction in HbA_{1c} there was a 14% reduction in events such as MI, stroke and amputation ([5]). An increased risk in cardiovascular mortality and morbidity is also thought to be associated with high glucose levels after eating ([6]).

The complications of diabetes, such as blindness, kidney failure and MI, contribute considerably to the morbidity and mortality suffered by patients with diabetes, and severely affects their quality of life ([7]). In order to minimize the development and impact of complications, good glycemic control should be aimed for at all times. Standards of care have been published by the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and International Diabetes Federation (IDF) recommending glycemic control targets for HbA_{1c}, fasting blood glucose (FBG) and postprandial blood glucose (Table 1). To achieve these targets, the healthcare team must be knowledgeable about a wide range of tools: pharmacological intervention, nutritional and physical activity, together with appropriate education and patient support.

Figure 1

Table 1: Glycemic control targets from the ADA, ACCE, and IDF

	ADA	ACCE	IDF
HgA_{1c}	< 7.0	≤ 6.5	≤ 6.5
Fasting/preprandial	90-130 mg/dL 5.0-7.2 mmol/L	< 110 mg/L < 6.1 mmol/L	< 100 mg/dL < 5.6 mmol/L
2-hour postprandial	< 180 mg/dL < 10.0 mmol/L	< 140 mg/dL < 7.8 mmol/dl	< 135 mg/dL < 7.5 mmol/L

Insulin is the cornerstone of treatment in patients with type 1 diabetes, while medical nutritional therapy (MNT), exercise and oral antidiabetic agents are current first-line treatments for patients with type 2 diabetes. However, type 2 diabetes is a progressive disease that ultimately requires insulin treatment in the long term. The clinical trials referred to above have shown that insulin therapy, through reduction of elevated blood glucose levels, can give the best possible prognosis to patients with type 1 or type 2 diabetes. In all instances, patients with the best outcomes regarding the prevention of development or progression of diabetic complications were those in the intensively-treated insulin therapy groups.

LIMITATIONS OF INSULIN TREATMENT

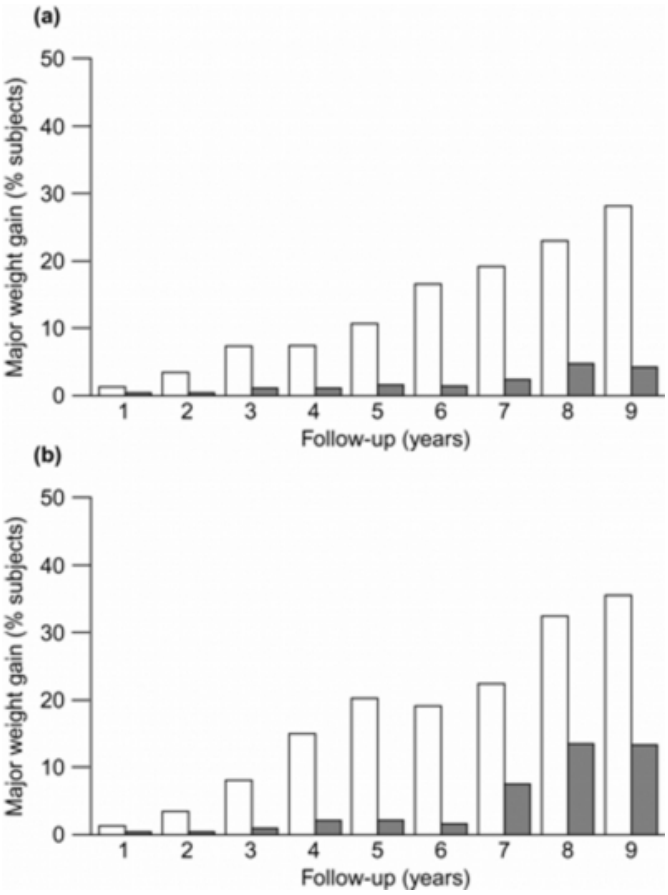
The benefits of insulin treatment in lowering blood glucose are clear; however, there may be drawbacks with insulin treatment that may influence healthcare providers and patients in their choice of treatment regimens. Two main limitations to insulin therapy exist: the risk for hypoglycemia, and weight gain. Hypoglycemia is a feared side effect of insulin therapy, which can cause symptoms such as confusion, disorientation, sweatiness, or in serious cases, coma, convulsions, or even death. Naturally, patients with diabetes wish to avoid hypoglycemia and the APN as well as the diabetes nurse educator are in a prime position to provide patient education to help them in this goal. A less widely addressed issue is the problem of weight gain with insulin treatment.

WEIGHT GAIN IS COMMON WITH INSULIN THERAPY

Improved glycemic control with insulin is known to be associated with weight gain ([3], [8], [9]). In a population-based sample of 405 patients with type 1 diabetes, weight gain was significantly associated with improvements in HbA_{1c} ($p < 0.001$); the patients with the best improvements in glycemic control gained the most weight ([9]). This finding is consistent with findings from the DCCT where those patients in the intensively treated insulin group gained more weight (by a mean of 4.75 kg) than those in the conventionally treated group ($p < 0.001$) ([10]). In this study, many patients (~30%) receiving intensive insulin therapy experienced major weight gain, with an increase in body mass index (BMI) of more than 5 kg/m^2 (Figure 1).

Figure 2

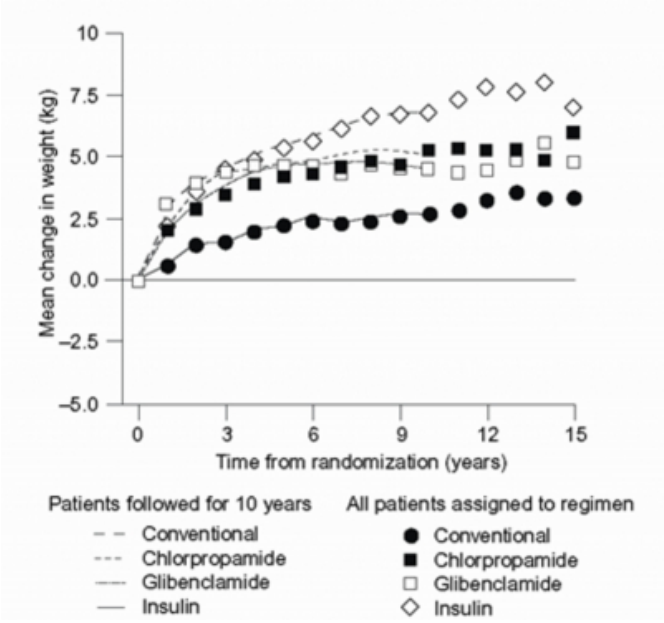
Figure 1: The percentage of adult men (a) and women (b) with major weight gain (increase in BMI of more than 5 kg/m) receiving intensive (white bars) or conventional (black bars) insulin therapy in the DCCT. The overall pattern of differences over time was significant (< 0.01) for both sexes (DCCT 2001). Â© 2001 of, and reproduced with permission from, 2001, 24: 1711Â–1721 ().



Similarly, patients with type 2 diabetes treated with insulin in the UKPDS gained a mean 6.5 kg – more than twice the weight gain of those assigned to the conventional (diet and exercise) group ($p < 0.001$) (Figure 2) ($_3$). Those in the insulin-treated group did achieve a significantly better level of metabolic control: median HbA_{1c} 7.1% vs. 7.9% in the conventional group, $p < 0.0001$.

Figure 3

Figure 2: Weight gain in patients involved in the UKPDS. © 1998 of, and reproduced with permission from 1998; 352: 837–853 ().



THE REASONS FOR WEIGHT GAIN ASSOCIATED WITH INSULIN THERAPY

At the simplest level, weight gain results from an increase in energy intake, or a decrease in energy expenditure, or both. There are several mechanisms by which insulin administration may influence the balance of energy input/output, and glycemic control itself may be one of them, as patients have a higher energy turnover when their diabetes is poorly controlled than when their glycemic control is improved. This mechanism was illustrated in a study by Carlson and Campbell looking at the effects of insulin treatment on weight, where six patients with type 2 diabetes and a mean HbA_{1c} of 12.9% were switched from conventional to intensive insulin therapy ($_{11}$). The intervention reduced the patients' HbA_{1c} to 9.6%, but their bodyweight increased by 2.6 kg and was associated with a 5% decrease in metabolic rate ($_{11}$). A certain percentage of calories are lost in the diuresis that occurs secondary to hyperglycemia. However, this diuresis means that patients with poorly controlled diabetes have a net loss of energy as glucose is actively excreted into the urine. Thus, improving metabolic control reduces this glucosuria, so energy is retained. Furthermore, the dehydration caused by hyperglycemia is reduced. The net effect is that weight can be quickly gained when glycemic control is improved due to improved fluid balance and glucose retention ($_{12}$). Thus, in

the study by Carlson and Campbell ([11]) a calculated 30% of the weight gain could be accounted for by decreased metabolic rate while the remaining 70% was due to the effects of eliminating glucosuria.

Insulin is an anabolic hormone, hence can act in the body to build muscle cells, and this effect could also contribute to the weight gain seen with insulin therapy of diabetes. But insulin also acts upon adipocytes to inhibit lipolysis, thus increases in fat mass can also be expected. Indeed, data from the DCCT suggest that the weight gain associated with intensive insulin therapy is due to increases in both fat-free mass (all portions of body tissues not containing fat) and fat mass ([10]). Similar results have been reported in type 2 diabetes. For example, a 6-month study assessed body weight and composition changes in 35 patients with type 2 diabetes during their first 6 months of insulin therapy. Glycemic control improved with insulin (HbA_{1c} decreased from 9.66% to 7.26, $p < 0.0001$), and was associated with a gain of both fat (0.85 kg) and fat-free mass (0.55 kg) ([13]).

Another effect that insulin may have upon weight is via the brain, as insulin is known to act on pathways that affect appetite. These pathways may be impaired in patients with type 2 diabetes, so potentially insulin cannot regulate food intake in the same way as in individuals without diabetes ([14], [15]).

Finally, weight gain with insulin therapy may be connected with the treatment of hypoglycemia. Low blood glucose levels can be remedied by ingestion of glucose or food. If patients fear the onset of a hypoglycemic episode they may eat to prevent experiencing the symptoms associated with an event, or if a hypoglycemic event occurs they may over-treat by consuming more carbohydrate calories than necessary. In the DCCT, patients who experienced one or more episodes of severe hypoglycemia gained more weight (6.8 kg, $p < 0.001$) than patients who did not experience any severe episodes (4.7 kg) ([8]).

THE PROBLEM WITH WEIGHT GAIN WITH INSULIN THERAPY

Despite the benefits of improved glycemic control with insulin therapy, weight gain is a serious issue, especially in patients with type 2 diabetes who may already be overweight. A well known fact is that bodyweight and cardiovascular risk are associated ([16]) and that losing weight improves the cardiovascular risk profile in patients with type 2 diabetes ([17]). Even in patients with type 1 diabetes, excessive weight gain has been associated with a worsening of cardiovascular risk markers such as blood pressure and total cholesterol ([18]). Weight gain in children diagnosed with type 1 diabetes is associated with features of type 2 diabetes, such as insulin resistance ([19], [20]). This observation has contributed to recently articulated concepts such as “double diabetes” (insulin resistance concomitant with immunogenic diabetes) and “the accelerator hypothesis” (weight gain as a causal trigger for type 1 and type 2 diabetes, according to genetic background) ([20], [21], [22], [23]).

Gaining weight with insulin not only has potential health consequences but is also unwelcome for patients from a psychological point of view. Weight gain can affect self-esteem and prove frustrating for patients who are trying to follow a nutrition plan and exercise programs. Body image is an important consideration for patients, many of whom are aware that their insulin treatment can also be misused in order to control weight. A study into the eating habits and insulin use of 76 adolescents with type 1 diabetes showed that insulin omission in order to prevent weight gain was common in girls ([24]). Consequently, weight gain with insulin use may be a barrier that can undermine the beneficial effects of improving glycemic control.

The fear of weight gain (along with hypoglycemia) is also a barrier to the initiation of insulin in patients with type 2 diabetes ([25]). Many studies have recommended that insulin treatment should be initiated early in the course of this disease to achieve the best prognosis ([26]). However, initiation of insulin is sometimes delayed by physicians, and patients with type 2 diabetes are often reluctant to commence insulin therapy due to a variety of reasons, including concern about weight gain ([25]).

OVERCOMING INSULIN-ASSOCIATED WEIGHT GAIN

An important issue is that the barrier of weight gain with insulin therapy is overcomed; the APN and diabetes nurse educator can play an instrumental role in this. By entering into discussions with the patients about eating patterns, the concept of weight management can be introduced prior to insulin initiation, and before difficulties with adherence to prescribed insulin therapy becomes an issue. This intervention in itself may help to minimize weight gain with insulin therapy. The APN and diabetes nurse educator also has to reassure the patient about the obvious benefits of insulin therapy when discussing the negative effects of weight gain. Some weight gain may be inevitable and the

patient should be encouraged to continue to follow nutritional therapy and physical activity regimens while maintaining glycemic control at levels as near as possible to optimal.

The impact of nurse follow-up with respect to adherence to diabetes regimens has, in fact, been studied in a randomized, controlled trial of 36 patients with insulin-treated diabetes ([27]). The intervention group was prescribed continuing education and reinforcement of medical nutritional therapy, physical activity recommendations, and frequent self-monitoring of blood glucose levels; this intervention was achieved through nurse telephone calls and patient self-management logs (including a nutrition and physical activity diary reviewed by a dietitian). The patients receiving frequent nurse contact demonstrated a reduction in HbA_{1c} levels from baseline (HbA_{1c} 1.2%, $p < 0.05$) compared to the control group (no intervention, routine care), which demonstrated an increase in HbA_{1c} of 0.6%, $p < 0.05$. In the intervention group, a greater increase in the adherence to nutritional recommendations than in the control group was found, demonstrating that nurse intervention can have a positive effect on motivation, disease management and metabolic control.

Furthermore, an audit of 43 prospectively referred, poorly-controlled ($HbA_{1c} > 7.5\%$) insulin-treated patients with diabetes followed for 6 months also showed that intervention by diabetes nurse educators was effective in metabolic control and bodyweight management ([28]). In those patients who improved their metabolic control (63% of patients achieved a final HbA_{1c} of <7.0% or achieved a reduction in HbA_{1c} of >1.0%), no increase in bodyweight (measured by change in BMI from baseline) occurred and no episodes of severe hypoglycemia were observed. Adherence to nutritional plans was discussed by the nurses with patients and referral to registered dietitians was recommended where necessary. Thus, skilled intervention from the APN and/or diabetes nurse educator can assist the patient minimize weight gain in patients treated with insulin.

The choice of insulin and the regimen used may have an impact on weight management in patients with diabetes. The APN should therefore have a solid understanding of available insulins and insulin regimens to be able to best advise and treat patients. Continuous subcutaneous insulin infusion (CSII) with a rapidly absorbed insulin, or basal-bolus therapy (in which patients take up to six injections each day, using both a long- and short-acting insulin formulation) are regarded as the optimal insulin regimens and are commonly used in patients with type 1 diabetes. Patients with type 2 diabetes who still preserve some capacity for endogenous insulin secretion may administer once- or twice-daily insulin in combination with oral antidiabetic agents. With advancing disease they may also need to progress to basal-bolus regimens or CSII.

In recent years, novel insulin analogs have been developed with improved pharmacological characteristics compared to human insulin formulations ([29]). For example, the basal insulin analogs, insulin glargine and insulin detemir, have more prolonged and less variable absorption profiles than NPH insulin ([30], [31]), and are associated clinically with a reduced risk of nocturnal hypoglycemia ([32], [33]). Insulin detemir has shown particular promise in clinical trials with regard to weight outcomes. When compared to NPH insulin, in trials of both type 1 and type 2 diabetes, insulin detemir has been associated with a reduction in weight gain (mean weight difference, 0.5–1.7 kg in 6–12-month studies) at similar or better levels of glycemic control ([34], [35], [36], [37], [38], [39], [40], [41]). A study of 475 patients with type 2 diabetes showed that insulin detemir or NPH insulin can be added to oral antidiabetic agents to achieve excellent mean HbA_{1c} levels (6.6% and 6.5%, respectively, NS) ([42]). However, weight gain with insulin detemir was significantly less than with NPH insulin (1.2 vs. 2.8 kg, $p < 0.001$).

The oral antidiabetic agent, metformin, is often prescribed for overweight patients with type 2 diabetes, and is commonly used in conjunction with insulin. Metformin helps in reducing insulin resistance and also reduces appetite. In combination with insulin, this agent has been associated with less weight gain than placebo, other agents and insulin monotherapy, while achieving comparable or better glycemic control ([43], [44], [45]). For example, in the study by Douek and colleagues ([43]), 183 patients with type 2 diabetes maximally controlled on oral agents were randomized to receive metformin or placebo. Insulin was initiated in both groups according to local practice. Those patients treated with metformin experienced less weight gain (difference 1.5 kg, $p = 0.02$) and a greater decrease in HbA_{1c} (difference of 0.5%, $p = 0.02$) than those receiving placebo.

Two novel antihyperglycemic agents that have recently been introduced are also showing promise in regulating weight in patients with diabetes. Exenatide is the first mimetic of the incretin hormone, GLP-I, and its therapeutic actions include glucose-dependent insulin secretion ([46]) and suppression of

inappropriate glucagon secretion in the postprandial period ([47]). Exenatide is injected subcutaneously and, when used in combination with metformin and/or sulfonylureas in patients with type 2 diabetes, has been found to significantly improve glycemic control compared with placebo ([48, 49, 50]). In these and other studies, significant weight loss of up to 1.8 kg has been seen with exenatide treatment ([48, 50, 51]). Exenatide was also associated with favorable weight loss when compared with insulin glargine in a study of 551 patients with type 2 diabetes ([52]). Both insulin glargine or exenatide added to existing oral therapy improved HbA_{1c} levels by 1.11% from baseline, but patients treated with exenatide lost 2.3 kg in weight, whereas those given insulin glargine gained 1.8 kg (difference, 4.1 kg [CI: 4.6 to 3.5 kg]). However, a significantly higher incidence of gastrointestinal adverse effects in the exenatide group occurred although these effects tend to be transient.

The second novel antihyperglycemic agent is the amylin analog, pramlintide, which is also given by subcutaneous injection. Amylin is a naturally occurring hormone that is co-secreted with insulin from pancreatic beta cells in response to meal stimuli and exerts its antidiabetic effects via suppression of postprandial glucagon secretion and delaying of gastric emptying ([53]). Endogenous amylin secretion is deficient in patients with type 1 or type 2 diabetes, so pramlintide (amylin analog) can be use to complement insulin treatment ([54]). Preprandial pramlintide, as an adjunct to insulin, has significantly reduced HbA_{1c} in comparison to placebo in patients with type 1 or type 2 diabetes in studies of up to one year ([55, 56, 57]). This improvement in glycemic control has also been accompanied by a decrease in bodyweight, of up to 2 kg ([55, 56, 57, 58]). These novel agents, as well as others in development, appear to present new treatment options for patients with diabetes, especially in those concerned about their weight.

CONCLUSION

Treatment with insulin of both type 1 and type 2 diabetes has obvious benefits. However, drawbacks to insulin treatment can exist, one being the tendency for patients to gain weight. Consequently, the issue of weight management with insulin therapy is an area that should be addressed by the both the APN and diabetes nurse educator. This important role will involve advising, encouraging and motivating patients with regard to their nutritional therapy and exercise programs. New insulins and other novel antidiabetic agents may also be able to offer fresh therapy options for preventing weight gain in patients with diabetes. Nurses providing patient education need to acquire and maintain a knowledge of these agents so they can advise patients about their use, and recognize opportunities for their introduction into patients' therapeutic and weight management regimens. While weight gain is currently a common and unwelcome aspect of insulin therapy, the problem that must be kept in perspective and that can be mitigated by appropriate interventions.

CONFLICT OF INTEREST

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