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Consequences of Weight Gain Associated With Insulin Therapy in Adolescents

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Abstract: Intensive insulin therapy is associated with the delayed onset and reduced risk of the development of microvascular complications in type 1 diabetes and is therefore recommended for most patients, including children and adolescents. Intensification of insulin therapy can be accompanied by increased weight gain, and fear of weight gain can represent a major barrier to adherence to intensive regimens. This is particularly true for adolescent girls who may have poor self-esteem and body image issues, and adopt behaviors such as insulin omission and disordered eating to prevent weight gain. Strategies to reduce insulin-associated weight gain include lifestyle interventions to improve nutritional intake and increase physical activity. The use of pharmacologic agents that minimize weight gain such as the inclusion of insulin detemir, agents that alter satiety and insulin sensitizers should also be considered and investigated further. In addition to understanding treatment strategies to limit insulin-related weight gain, the diabetes healthcare team should be aware of the early warning signs of disordered eating and insulin omission in the adolescent so that appropriate referral for psychologic intervention can occur.

Key Words: weight gain, diabetes, intensive insulin therapy, disordered eating, diabetes

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Learning Objectives

- Compare the effects on body weight and body mass index of conventional and intensified insulin treatment in adolescents with type 1 diabetes mellitus.
- Point out the adverse consequences that may take place when adolescent diabetics omit insulin doses, and list warning signs indicating that such behavior may be taking place.
- Identify and evaluate the strategies adopted for limiting insulin-associated weight gain.

One of the many barriers to achieving optimal glycemic control in type 1 diabetes is the fear of weight gain. The Diabetes Control and Complications Trial (DCCT) showed that excess weight gain was associated with intensive diabetes management.[1] The reasons for weight gain in patients with improved glycemic control include the need to treat the resultant excess of hypoglycemia with oral glucose, the resolution of glycosuria, and the metabolic effects of intensive insulinization. As patients realize that weight gain is a side effect of intensive management, they may lose the motivation to strive for optimal control. In extreme cases, some patients, particularly adolescent girls, may develop a variant eating disorder that involves binge eating and withholding insulin treatment to promote weight loss.[2,3]

The purpose of this review is to evaluate the evidence concerning weight gain with insulin therapy in children and adolescents with diabetes. By analyzing what is known about the pathophysiology of weight gain resulting from insulin therapy and understanding the psychologic issues in youth associated with insulin-mediated weight gain, it is hoped that strategies can be developed to intensify insulin therapy and mitigate this unwanted side effect.

EVIDENCE FOR WEIGHT GAIN WITH INSULIN THERAPY IN TYPE 1 DIABETES

Since the DCCT, it has been recommended that most adolescents with type 1 diabetes receive intensive insulin therapy aimed at achieving glycemic control as close to

normal as possible to minimize the risk of long-term diabetes complications.[4] However, there is convincing evidence that the intensification of insulin treatment can lead to significant weight gain.[1,5,6] In the DCCT, weight gain in adults exceeded ideal values, because intensively treated patients gained on average significantly more weight than those who received conventional insulin therapy (3.3 vs 1.2 kg, $P < 0.0001$) during the first year of treatment.[6] The mean increase in body mass index (BMI) was also significantly higher in the intensive treatment group (1.2 vs 0.4 kg/m^2, $P < 0.0001$) during this time. During the next 8 years, body weight continued to increase to a greater extent in the intensively treated group with an approximate gain of 5 kg more than in the conventionally treated group. In some individuals, this weight gain was considerable, with BMI increasing by more than 5 kg/m^2 ($P \leq 0.01$). This effect was particularly pronounced in women, affecting approximately 35% of women in the intensive group compared with 14% in the conventional group. The respective data for men were approximately 28% in the intensive group and <5% in the conventional group.

Further studies corroborate these findings in adults. Weight gain was examined in a population-based sample of patients with type 1 diabetes participating in the Wisconsin Epidemiologic Study of Diabetic Retinopathy.[7] The mean body weight of 405 patients followed during a 4-year period increased significantly (mean weight gain 1.8 ± 5.9 kg) and correlated with increasing number of insulin injections and changing the treatment regimen from a single insulin injection formulation to basal–bolus therapy. Weight gain was also correlated with improvements in glycosylated hemoglobin (HbA_{1c}), in which the quartile of patients with the greatest improvements in glycemic control gained 3.4 kg and the quartile of patients with the smallest improvements in glycemic control lost 0.6 kg. These results suggest that weight gain in type 1 diabetes can be an adverse consequence of improved glycemic control.

EVIDENCE FOR INSULIN-ASSOCIATED WEIGHT GAIN IN ADOLESCENTS

Like with adults, the DCCT examined whether weight gain was associated with intensive insulin treatment in adolescents (n = 125, aged 13–17 years).[8] After 5 years of treatment, intensively treated male patients gained a mean of 4.04 kg and females 3.25 kg more than their conventionally treated counterparts (Fig. 1). This weight gain was accompanied by a significantly greater increase in BMI in males (approximately 2 kg/m^2, $P < 0.001$) and females (approximately 1.5 kg/m^2, $P = 0.019$) compared with the conventional treatment group. The risk of becoming overweight as defined by BMI was almost 2-fold greater in the intensive treatment group than in the conventional treatment group.

A study investigating the contributions of age, gender, and insulin administration in type 1 diabetes showed weight gain in diabetes to be a more significant problem during puberty than during childhood. BMI and standard deviation score for BMI, based on the Zurich longitudinal growth study, were evaluated in 427 patients.[9] The data showed standardized BMI to be higher in both male and female

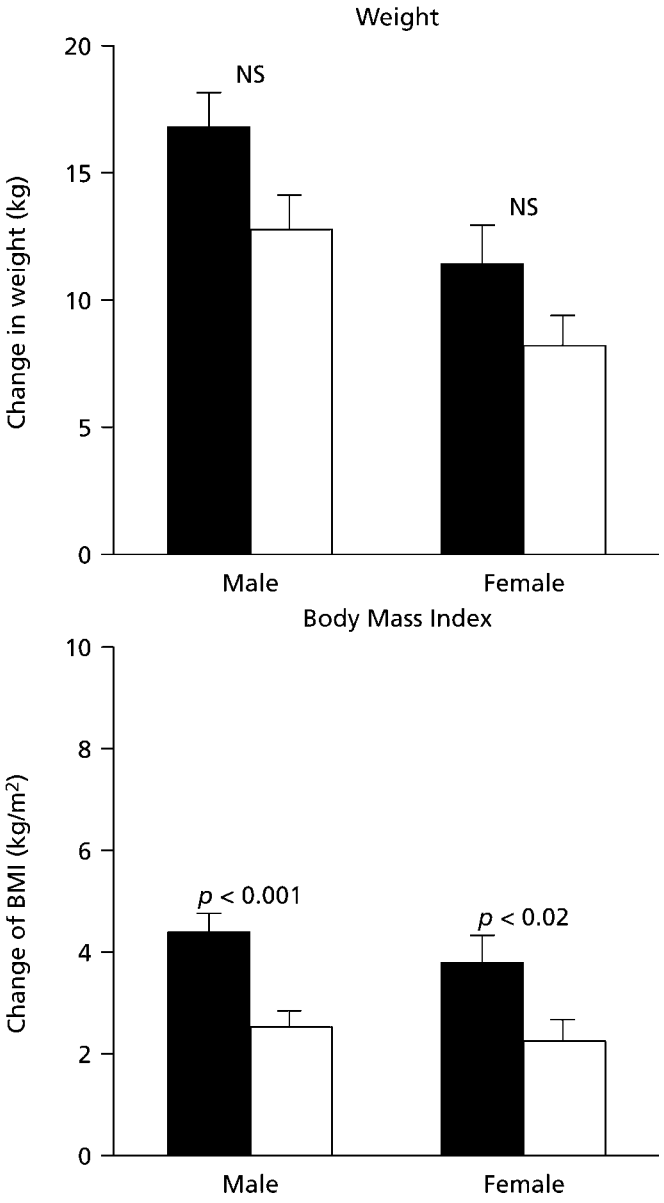

FIGURE 1. Change in weight (top) and body mass index (bottom) in the intensively treated (black bars) and conventionally treated (white bars) groups during the DCCT.[8]

pubertal children (1.07 ± 0.06 kg/m^2) compared with prepubertal children (0.68 ± 0.07 kg/m^2, $P < 0.002$) and was found to be significantly higher in pubertal children on intensified insulin regimens (3 or 4 daily injections, approximately 1.5 kg/m^2) compared with pubertal patients receiving 2 injections (approximately 0.75 kg/m^2, $P < 0.05$).

Adolescent girls with type 1 diabetes appear to be at particular risk for obesity compared with their peers without diabetes. A cross-sectional study of a representative sample of 76 adolescents aged 11 to 18 years found that girls with type 1 diabetes were significantly heavier compared with girls without diabetes.[10] This was in concordance with a second study assessing BMI, relative weight, and body fat in 48 girls

aged 10 to 19 years, which found that girls with type 1 diabetes were more overweight than their peers without diabetes according to all measures of obesity (including BMI, relative weight, body fat from skinfold thickness).[11]

HYPOTHESES FOR WEIGHT GAIN

Insulin-associated weight gain is recognized as a common problem related to diabetes treatment, yet the underlying mechanisms are not fully understood. There are a number of potential mechanisms such as counteracting hypoglycemic events and an alteration of regulators of adiposity, which may explain how insulin treatment causes weight gain.

For people with diabetes, particularly children and their parents, the fear of hypoglycemia, especially nocturnal hypoglycemia, can lead to excessive caloric intake by the child as a means of hypoglycemia prevention. The American Diabetes Association (ADA) recommends that target blood glucose levels for children must vary by age as a means of preventing nocturnal hypoglycemia. If a child does not achieve that target and mild hypoglycemia is experienced, it is recommended that additional calories be consumed before to going to sleep.[12] This may lead to excess snacking by the child to mitigate hypoglycemia, further altering energy balance.

A proven cause of weight gain in diabetes is the conservation of calories in previously poorly controlled patients. Conservation of ingested calories occurs as improved glycemic control returns patients' blood glucose levels to below the renal threshold. This effect was demonstrated in 6 adult patients with type 1 diabetes who received conventional insulin therapy for 6 months and then subsequently switched to an intensified insulin regimen while maintaining a constant calorie intake for 2 months.[13] Glycemic control improved in the intensive group after 2 months. Significant decreases were observed in mean daily blood glucose concentration (from 14.8 to 7.7 mmol, $P < 0.01$), glycosuria (from 428 to 39 mmol/d, $P < 0.05$), and total HbA_{1c} (from 12.9 to 9.6%, $P < 0.01$). This was accompanied by an increase in body weight of 2.6 kg ($P < 0.05$), of which 70% was accounted for by improved conservation of ingested calories, with the remaining 30% by a decrease in energy expenditure. Another potential mechanism involves the anabolic effect of insulin, which leads to increased skeletal muscle mass[14] thought to be mediated by the increased occurrence of intracellular glucose, increased transport of amino acids into muscle,[15] or by a direct effect on protein synthesis[16] or breakdown.[17]

Leptin resistance has also been proposed to be of significance in weight gain in diabetes, particularly when there is excessive weight gain for height in youth with type 1 diabetes. Increased leptin levels have been observed in children and adolescents with type 1 diabetes receiving intensive insulin therapy, and it has been hypothesized that these high levels may lead to resistance to leptin through hypothalamic feedback. Evidence to support this hypothesis originates from a study in which continuous administration of insulin resulted in increased leptin levels in excess of those predicted by gain in fat mass.[18] This finding suggests that insulin has a long-term effect on the indirect production of leptin, probably through the trophic effect of insulin on adipocytes.

A recent longitudinal study showed BMI to be consistently higher in both boys and girls with diabetes compared with healthy control subjects. For girls, this finding was largely reflected by a greater proportion of body fat, whereas for boys, the observation was accompanied by a reduction in the proportion of body fat. Hyperinsulinemia and raised leptin levels were associated with gain in fat mass throughout puberty in girls, but not boys, suggesting that some sexual dimorphism exists in the regulation of leptin levels and gain in fat mass.[19]

CONSEQUENCES OF WEIGHT GAIN

In people with type 1 diabetes, weight gain has been associated with hypertension and increased lipid levels. In the DCCT, the patients with the largest weight gain (Fig. 2A) and an average BMI of 31 kg/m^2 also had the largest increases in blood pressure, total cholesterol, and low-density lipoprotein (LDL) cholesterol, despite equivalent glycemic control across all patients in the trial (Fig. 2B).[1] The weight gain-associated increase in blood pressure and cholesterol might predispose the patients to cardiovascular disease over time. The presence of cardiovascular risk factors in these patients may lead to the development of metabolic syndrome.[20] The prevalence of metabolic syndrome was found to be more frequent in patients with type 1 diabetes compared with patients without diabetes and correlated with worsening glycemic control.[21] There is no evidence at present to support that metabolic syndrome is associated with weight gain in type 1 diabetes, although there is a strong link with obesity in type 2 diabetes.

INSULIN OMISSION AND DISORDERED EATING

The prospect of weight gain associated with insulin therapy and the discipline required to stop weight gain with lifestyle modifications can often lead to negativity on the part of the patient.[3] This effect is likely to be further enhanced in adolescents who live with a strong societal influence to be thin. In adults with type 2 diabetes, the perception that weight gain will occur is now widely recognized as a psychologic barrier to the initiation of insulin therapy.[22,23] This can result in a delay in insulin initiation by both patients and physicians. Although "time of insulin initiation" is not an issue that applies in young patients with type 1 diabetes, adherence to prescribed regimens may be adversely affected by a desire to avoid weight gain. The realization of weight gain may lead to the "diabetes burnout" phenomenon, a psychologic condition commonly seen in young adults characterized by chronic frustration and feelings of failure, resulting in insulin avoidance or neglect of self-management.[24]

Strategies such as deliberate insulin omission or dose manipulation can offer a unique and potentially dangerous form of controlling weight in those with diabetes. Furthermore, insulin misuse as a form of weight control can be closely linked to disordered eating. The omission of insulin can be used to induce glycosuria, allowing excess caloric intake while avoiding weight gain. Insulin omission is more common in females with type 1 diabetes, and reported incidences increase in frequency as children reach adolescence

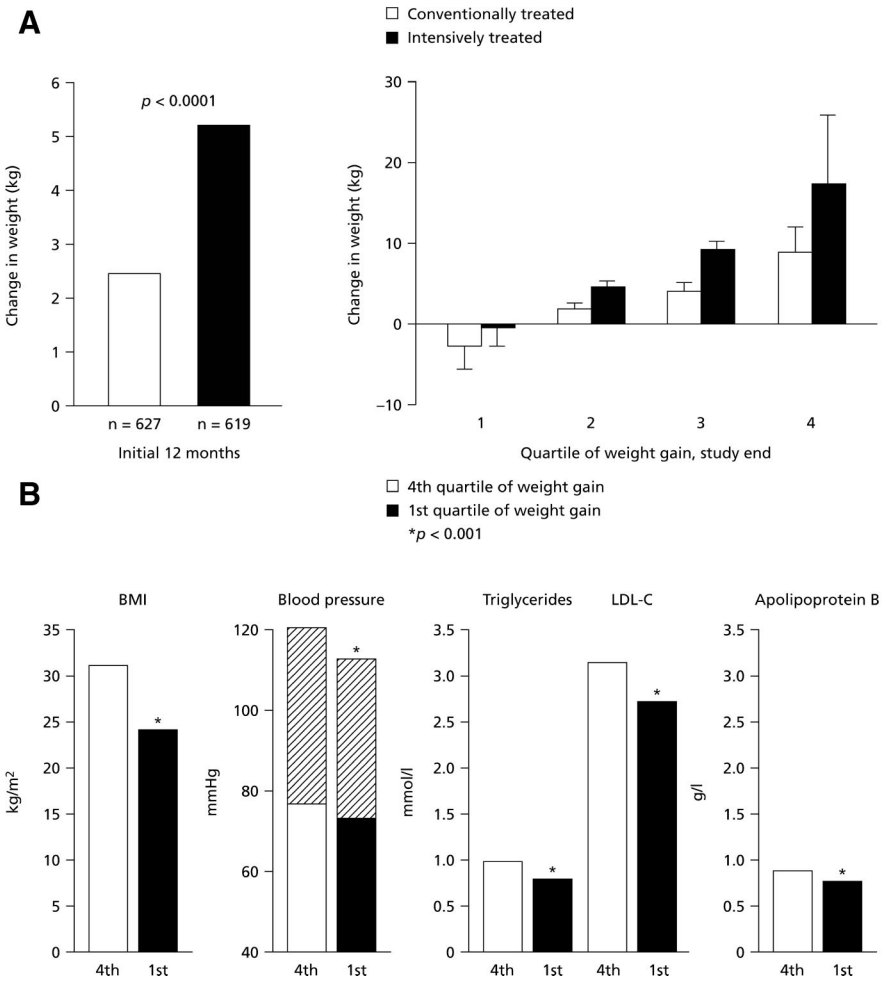

FIGURE 2. A. Increase in weight in patients on insulin therapy. Most weight gain is seen in patients treated with intensive insulin regimens. Data from references 1 and 5. B, Weight gain is associated with increases in parameters of cardiovascular risk such as body mass index (BMI), blood pressure (stripped bars represent systolic pressure; solid bars represent diastolic pressure), triglycerides, low-density lipoprotein cholesterol, and apolipoprotein B. Data from reference 1.

and young adulthood.[25] A cross-sectional study conducted in 76 adolescents aged 11 to 18 years with type 1 diabetes found that adolescent girls were heavier compared with healthy female individuals and were dieting more intensively to control their shape and weight.[10] Although in this study, clinical eating disorders were no more common among adolescent girls with diabetes than among those without the disease, 15% of girls with diabetes had omitted or reduced their insulin dose to influence their shape and weight. Eating habits, insulin misuse, and weight change were followed up in these patients 10 years later, and 30% of adolescent or young adult females surveyed admitted to omitting insulin to reduce weight gain.[3] Furthermore, although 38% of the women had developed microvascular complications overall, 46% of those with complications had deliberately misused insulin to prevent weight gain. Despite the reported occurrences of insulin misuse, mean weight and BMI increased over the 10-year study. Women were overweight both as adolescents and adults, whereas men tended to become overweight during young adulthood.

Insulin omission is not limited to younger women. In a study of 341 women with type 1 diabetes aged 13 to 60 years, approximately 31%, representing all ages, reported intentional insulin omission and almost 9% reported frequent insulin omission.[26] Approximately 50% of insulin-omitters were doing so for weight management purposes. The women who omitted insulin reported more disordered eating attitudes and behaviors than nonomitters. They also had poorer glycemic control, more diabetes-related hospitalizations, greater psychologic distress, and fear of hypoglycemia as well as higher rates of retinopathy and neuropathy than women who were insulin-adherent and those not preoccupied with weight gain (Table 1). These data support previous findings indicating that women with type 1 diabetes and eating disorders, many of whom are also likely to be omitting insulin, are at increased risk of developing long-term diabetes complications.[27,28]

The coexistence of type 1 diabetes and eating disorders such as anorexia nervosa and bulimia nervosa is estimated to be as high as 16%.[29] Disordered eating behaviors among youth with diabetes have been associated with poor metabolic control, weight gain, a tendency to omit prescribed insulin, and an increased prevalence of microvascular complications.[30] Jones et al found the prevalence of eating disorders in female adolescents with type 1 diabetes (10%) to be twice as high as that found in their peers without diabetes (4%).[2]

Disordered eating behaviors can also develop over time in patients with type 1 diabetes. Rydall et al found that of the 71% of women with normal eating behavior at baseline, 15%

TABLE 1. Differences in Medical Factors Between Nonomitters, Weight-Related Omitters, and Nonweight-Related Omitters

	Omitters			
	Weight-Related	**Nonweight-Related**	**Nonomitters**	***P***
n	45	51	237	
Mean HbA_{1c} (%)	12.3 ± 2.6	11.1 ± 2.0	10.3 ± 1.8	<0.0005*
Recent hospitalizations	1.0 ± 2.4	0.3 ± 0.8	0.2 ± 0.7	<0.0005†
Recent emergency room visits	0.9 ± 2.3	0.3 ± 0.6	0.3 ± 1.2	<0.005†
Neuropathy (%)	46.5	18.2	16.6	<0.0005†
Retinopathy (%)	72.1	54.6	49.8	<0.05†
Hypoglycemic events in past month	8.1 ± 9.6	7.6 ± 9.9	6.5 ± 6.1	NS

Data are means ± standard deviation.

*For HbA_{1c}, recent hospitalizations, recent emergency room visits, hypoglycemic events, and differences were examined by one-way analysis of variance. For neuropathy and retinopathy, differences were examined with χ^2 (for weight-related omitters, n = 43; for nonweight-related omitters, n = 44; for nonomitters, n = 193). Pairwise comparisons were investigated by Tukey's test. For pairwise comparisons, weight-related omitters are significantly different from nonweight-related omitters and nonomitters, and nonweight-related omitters are significantly different from nonomitters.

†Weight-related omitters are significantly different from nonweight-related omitters and nonomitters.

Reprinted from Polonsky WH, Anderson BJ, Lohrer PA, et al. Insulin omission in women with IDDM. *Diabetes Care.* 1994;17:1178–1185.

NS indicates $P > 0.05$.

had disordered eating at follow up 4 to 5 years later (Fig. 3).[30] The severity of disordered eating behavior was closely associated with glycemic control; HbA_{1c} was highest in the group with highly disordered eating and lowest in the group with nondisordered eating. When disordered eating was severe at baseline, 86% developed retinopathy 4 years later at follow up compared with 24% of those with nondisordered eating behavior.

Studies examining the prevalence of disordered eating behaviors and insulin misuse found both practices to be positively associated with high levels of weight dissatisfaction and negatively associated with family cohesion.[31,32] This led the authors to conclude that special attention needs to be focused on young people with weight concerns and those from less cohesive families to assist with healthy diabetes management practices.

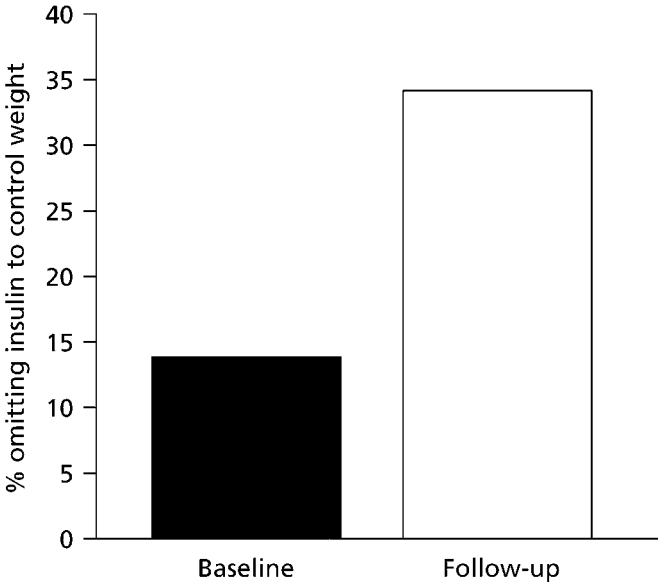

FIGURE 3. Young women (n = 91) with type 1 diabetes were followed for 4 to 5 years. At baseline, 14% reported omitting or underdosing insulin to lose weight. At follow up, 4 to 5 years later, 34% reported insulin omission ($P = 0.003$). Adapted from reference 30.

SPOTTING THE WARNING SIGNS

It is clear that insulin omission in young women with type 1 diabetes is becoming increasingly common and, for that reason, practitioners should be aware of the early warning signs. It is also important that parents are familiar with these signs as well. Symptoms of disordered eating behaviors, including insulin omission, may include: frequent diabetic ketoacidosis, erratic blood glucose levels and suboptimal control, significant weight loss without illness, anxiety about or avoidance of being weighed, binging with food or alcohol, frequent and severe hypoglycemia, nonadherence to the treatment regimen as reported by family members, or delay in puberty or failure to grow.[33] In addition, it is important that healthcare providers routinely ask women with type 1 diabetes about eating behavior and insulin omission in a nonthreatening and nonjudgmental manner. It can be helpful not to use the negative word "diet" and instead place the emphasis on healthy eating and meal planning.[34] It can be supportive for the patient, when possible, to have frequent family meals.

A multidisciplinary team, including a registered dietitian/nutrition therapist, preferably with a background in eating disorders, can identify unhealthy eating behaviors by conducting a nutrition assessment to examine current eating habits.[35]

Patients should be aware that if they experience unwanted weight gain there are options available to help with weight control such as altering their meal plan, changing their exercise program, or altering insulin therapy. If insulin omission or disordered eating is suspected, referral to a social

worker or psychologist, preferably experienced with diabetes, can identify any concerns about weight, body image, and/or self-esteem as well as common comorbid mental health issues. Diabetes management may not improve until the patient is given the appropriate treatment of the concurrent eating disorder.[35]

LIMITING INSULIN-ASSOCIATED WEIGHT GAIN

Approaches to help control weight include lifestyle education as well as determining ways to deliver insulin that are better matched to physiological requirements. Lifestyle education may have a positive effect on improvement of glucose control and maintenance of healthy weight. Nutritional advice and exercise have been shown to have positive effects on glycemic control in patients with type 1 diabetes,[36,37] but further studies need to be implemented to ascertain their individual and combined effect on weight in adolescence.

USE OF INSULIN ANALOGS TO MITIGATE WEIGHT GAIN

The rapid-acting insulin analogs (insulin aspart, insulin lispro, and glulisine) appear to better control glycemia after meals and have been shown to reduce the risk of hypoglycemia.[38] They can be injected directly before or after (rather than in advance of, like with conventional insulins) food intake. This increases flexibility and means that the insulin dose can be more closely tailored to the meal content.

Insulin glargine, a long-acting basal insulin analog, has been shown to improve the balance between glycemic control and hypoglycemic risk compared with intermediate-acting insulin preparations.[38] Insulin analogs can theoretically be used to more accurately match plasma insulin concentration to physiological need. This, plus the reduced risk of hypoglycemia, should enable weight gain to be minimized, but there is little clinical evidence to date to support this.

INSULIN DETEMIR

Insulin detemir, another recently introduced basal insulin analog, has been shown to be associated with a reduced tendency for weight gain in comparative studies. Insulin detemir is a novel long-acting insulin–fatty acid hybrid that is an acylated analog of human insulin. Pharmacologic[39,40] and clinical[41–44] trials with insulin detemir have demonstrated a more reproducible and prolonged action profile compared with NPH insulin. This is presumed to contribute to the improved ratios between glycemic control and hypoglycemic risk found in clinical trials.

In phase 3 trials, insulin detemir showed a relative reduction in weight gain in comparison with NPH insulin. In studies of patients of all ages, including adolescents and children with type 1 diabetes, insulin detemir did not appear to cause excessive weight gain. In adults with type 1 diabetes, insulin detemir was associated with weight neutrality or even small nonsignificant reductions in weight over periods of up to 12 months. This finding is in contrast to NPH insulin, which was associated with weight gain of 0.7 to 0.8 kg over 6 months[41–45] and 1.2 to 1.4 kg over 12 months.[46,47] A multinational study in children and adolescents with type 1 diabetes (n = 347) receiving insulin detemir or NPH insulin once or twice daily found that baseline-adjusted BMI was lower with insulin detemir (19.3 vs 19.8 kg/m^2, $P < 0.001$) after 26 weeks and closer to mean Z-score (normative) values.[48] There was also a risk reduction for nocturnal hypoglycemia of some 50% with insulin detemir in this study. It is possible that the reduced risk of weight gain with insulin detemir might relate to the risk reduction for hypoglycemia, but other mechanisms, including a reduced ratio of peripheral:hepatic action[49] and a central effect on appetite,[50] have been suggested.

ADJUNCT THERAPY WITH APPETITE-SATIATING HORMONE ANALOGS TO REGULATE WEIGHT

Amylin, a peptide hormone, is cosecreted along with insulin from beta cells in the pancreas and inhibits glucagon secretion, alters gastrointestinal nutrient delivery, and acts as a satiety signal. Pramlintide is a synthetic analog of amylin, which shows promise in improving metabolic control when used for amylin replacement as an adjunct to insulin therapy in people with type 1 diabetes.[51] Pramlintide administration has been shown to control weight gain as well as control hyperglycemia in type 1 diabetes. Addition of pramlintide (4 times daily) to insulin in the treatment of adults with type 1 diabetes led to significant reductions in body weight (0.4-kg reduction from baseline, $P < 0.05$). In contrast, patients gained weight in the placebo group (0.8-kg increase from baseline over 52 weeks). Furthermore, HbA_{1c} was significantly reduced (0.34% reduction from baseline, $P < 0.001$) compared with the placebo group (0.04% reduction from baseline) over the 52-week period.[52] This reduction in HbA_{1c} with pramlintide was obtained without an increase in concomitant insulin use. In adolescents (aged 12–18 years) with type 1 diabetes, pramlintide has been documented to be effective in the suppression of glucagon and control of glycemic excursions; however, weight change in this study was not assessed.[53]

METFORMIN AS A POTENTIAL INSULIN-SPARING AGENT

The biguanide, metformin, has been found to be beneficial when used in addition to insulin therapy in the treatment of a subset of poorly controlled adolescents with type 1 diabetes.[54] In a randomized, controlled trial of 27 poorly controlled adolescent patients with type 1 diabetes, HbA_{1c} was 0.6% lower in the metformin group than in the placebo group after 3 months of treatment ($P < 0.05$). This was achieved at lower insulin doses (−0.14 U/kg/d vs 0.02 U/kg/d for placebo, $P = 0.01$) with no significant change in BMI. Although the use of metformin in conjunction with insulin therapy has been studied less frequently in type 1 compared with type 2 diabetes, it may provide a valuable adjunct therapy to enable reduction in insulin dose while maintaining good glycemic control in overweight or obese patients with type 1 diabetes. Long-term studies are required to quantify the potential benefits of adding potential insulin-sparing therapy in adolescents with type 1 diabetes.

CONCLUSION

Excessive weight gain is often the consequence of intensive diabetes management and may be a particular problem for adolescent girls with type 1 diabetes. Weight gain itself and the fear of gaining weight can lead to poor diabetes outcome by causing an element of insulin resistance and by leading to insulin misuse and eating disorders. Present strategies to limit weight gain associated with insulin treatment may involve a combination of diet and exercise measures, including attention to eating patterns under the guidance of qualified advisors as well as the use of insulin-sensitizing drugs such as metformin or novel insulin analogs such as insulin detemir. Most importantly, diabetes healthcare providers need to remain alert to the warning signs that patients are becoming concerned about weight gain and hence may be susceptible to insulin misuse and deterioration of diabetes control.

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