

Weight Gain and Management Concerns in Patients on Insulin Therapy

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ABSTRACT

Background: The benefits of tight glycemic control in preventing the onset and progression of microvascular complications in patients with type 2 diabetes mellitus (DM) are unarguable. The majority of patients with type 2 DM will eventually require insulin to achieve adequate glycemic control. Using insulin earlier rather than later in the course of type 2 DM may diminish the deleterious effects of hyperglycemia on β -cell function and therefore help prolong good glycemic control and prevent the occurrence of microvascular complications. However, weight gain is a potential adverse effect of insulin therapy.

Objective: The goal of this article was to describe the benefit of insulin therapy early in the course of type 2 DM, review the association of weight gain with insulin therapy, and examine potential detrimental effects that insulin-associated weight gain could have in patients with type 2 DM.

Methods: Materials used for this article were identified through a search of MEDLINE (1966–2006). English-language articles were chosen using the search terms *diabetes mellitus type 2*, *insulin*, and *obesity*.

Results: Intensive insulin therapy is often associated with weight gain. Although there is concern that weight gain in patients with type 2 DM may have adverse effects on risk factors for cardiovascular disease, unfavorable changes in blood pressure and lipid levels have not been consistently observed in clinical trials. Furthermore, clinical evidence, including data from the United Kingdom Prospective Diabetes Study, supports the view that intensive insulin therapy does not increase the risk for cardiovascular disease.

Conclusions: Early insulin therapy in patients with type 2 DM may be a strategy that will help patients achieve and maintain good glycemic control, thereby reducing the risk of developing microvascular complications. Although weight gain is commonly associated with insulin therapy, it does not appear to put these patients at greater risk for cardiovascular disease. (*Insulin*. 2007;2:31–36) Copyright © 2007 Excerpta Medica, Inc.

Key words: type 2 diabetes mellitus, insulin, weight gain, cardiovascular disease.

INTRODUCTION

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive treatment leading to tight control of glucose delays the onset and progression of microvascular complications in patients with type 2 diabetes mellitus (DM).¹ Based on such evidence, the current clinical practice recommendations of the American Diabetes Association state that the glycosylated hemoglobin (A1C) goal for patients in general is <7.0%, and the A1C goal for the individual patient is a value as close to normal (<6.0%) as possible without significant hypoglycemia.²

The goal of this article was to describe the benefit of insulin therapy early in the course of type 2 DM, review the association of weight gain with insulin therapy, and examine potential detrimental effects that insulin-associated weight gain could have in patients with type 2 DM.

MATERIALS AND METHODS

Materials used for this article were identified through a search of MEDLINE (1966–2006). English-language articles were chosen using the search terms *diabetes mellitus type 2*, *insulin*, and *obesity*.

THE POTENTIAL VALUE OF INSULIN THERAPY IN OBESE PATIENTS WITH TYPE 2 DIABETES MELLITUS

The UKPDS reported that glucose control deteriorated over the course of study, even in the intensively treated patients.³ Measurement of β -cell function in this group of newly diagnosed type 2 DM patients showed that a loss of ~50% of β -cell function had already occurred by the time of diagnosis and that there was a steady decline of β -cell function thereafter.³ Thus, the waning of control over the course of the study was attributed to the decline in insulin secretion by

the β -cells. This progressive nature of β -cell impairment suggests that most patients with type 2 DM will ultimately need insulin to maintain acceptable glycemic control.

Insulin has often been regarded as the treatment of last resort in patients with type 2 DM.⁴ However, there is evidence that earlier and more intensive therapy with insulin may preserve β -cell function and therefore maintain the ability of the β -cell to secrete insulin as it should.⁵⁻¹⁰ In addition, one study found that early insulin therapy in newly diagnosed type 2 DM patients (N = 39), in contrast to treatment with a sulfonylurea, had the effect of prolonging endogenous insulin secretion.¹¹ The treatment with insulin also promoted better glycemic control.

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Early insulin therapy may ameliorate or even reverse the toxic effect of glucose and free fatty acids on β -cell structure and function. Any preservation or improvement of the β -cells should, in turn, help sustain glycemic control. Thus, early use of insulin in patients with type 2 DM may prove to be an important tactic for providing good long-term control. All of these studies showing the benefit of using early intensive insulin therapy in patients with type 2 DM included overweight and/or obese patients^{5-9,11}; one study¹⁰ involved nonobese patients. Thus, a strategy of early intensive insulin use could offer advantages to typical type 2 DM patients.

WEIGHT GAIN WITH INTENSIVE INSULIN THERAPY

Unfortunately, the benefits of good control with insulin therapy also come with the potential adverse effect of weight gain. The UKPDS and other studies in patients with type 2 DM have demonstrated that improvement of glycemic control with insulin is often accompanied by weight gain.^{1,12-15} Weight gain on the order of ~3% to 9% over pretreatment body weight, depending on the study duration and intensity of control, may be seen after the initiation of insulin therapy.¹⁶ In the UKPDS, patients in all treatment groups gained weight. Weight gain was significantly greater in the intensively treated group than in the conventionally treated group ($P < 0.001$).¹ Among those in the intensively treated group, patients treated with insulin had a greater mean weight gain (4 kg) than those treated with chlorpropamide (2.6 kg) or glibenclamide (1.7 kg).¹

Several factors influence how much weight patients with type 2 DM will gain with insulin therapy. Weight gain is directly correlated with both the mean daylong serum insulin level and the total exogenous insulin dose.¹² Thus, the higher the dose—and consequently the higher the serum insulin level—the greater the weight gain may be. In addition,

it has been estimated that weight gain in type 2 DM patients during the first year of insulin therapy is ~2 kg for every 1-point reduction in A1C.¹⁷ This would suggest that the magnitude of improvement in glucose control is also a predictor of the amount of weight gained.

Long-term studies of insulin therapy in patients with type 2 DM suggest that most of the weight gain occurs during the first 3 years of insulin therapy.^{1,14,18} After this, the weight gain tends to level off.

MECHANISMS OF WEIGHT GAIN ASSOCIATED WITH INSULIN THERAPY

Various mechanisms are involved in the weight gain associated with insulin therapy. Insulin has anabolic effects on muscle (causing muscle protein synthesis) and fat (causing lipogenesis).^{19,20}

A potentially major contributor to weight gain is the reduction of glycosuria. Improved glycemic control results in retention of calories previously lost as glucose in the urine.¹³ If insulin therapy is started after glycosuria has developed, weight gain will occur with improved control unless the caloric intake is reduced by an amount commensurate with the reduction of glycosuria.

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Obviously, patients will gain weight with insulin therapy if they increase the number of calories consumed. There is some evidence that hyperinsulinemia, at least when it is induced by IV glucose and insulin infusion, may result in increased appetite.²¹ Increased caloric intake may occur if extra calories are eaten in response to—or out of fear of—hypoglycemia.²²

Improved glycemia may promote weight gain by reducing the basal metabolic rate (BMR).¹³ It has been reported that the BMR decreases by 5% when fasting glucose is reduced by 5.9 mmol/L (106 mg/dL).¹³ Thus, the degree of glycemic control may be a determinant of BMR.

Part of the weight gain seen during insulin therapy may simply be due to patients regaining weight they had previously lost. Weight loss often precedes the diagnosis of type 2 DM.^{18,23} A longitudinal study of Pima Indians (N = 816) found that patients steadily gained weight before the diagnosis of type 2 DM.²³ After the diagnosis, weight loss was generally seen before any therapy was initiated. A retrospective study of patients with type 2 DM (N = 58) whose disease was poorly controlled (mean A1C, 10.9%) on oral agents also showed that weight loss had started at the time of diagnosis.¹⁸ The mean weight at diagnosis was 80 kg, whereas the

previous mean maximum weight was 86 kg. Mean weight at the start of insulin therapy was 73.8 kg. Although these patients gained a large amount of weight after beginning insulin treatment (ie, 7.6 kg during the first 2 years of therapy), they were still 4.6 kg less than their maximum prediagnosis weight. The weight these patients reached after starting on insulin was highly correlated with their maximum pretreatment weight.¹⁸

Often patients are started on insulin after they have had a period of poor control of their disease using oral agents. Thus, some of the weight gain they experience with better control may be a reflection of their "re-equilibrating" back to their pre-DM weight.

CONSEQUENCES OF INCREASED WEIGHT WITH INSULIN THERAPY

Most patients with type 2 DM are overweight or obese at the time of diagnosis. Weight gain, especially in these patients, would appear to be an unwanted adverse effect of therapy. Obesity is a risk factor for hypertension and dyslipidemia as well as cardiovascular disease (CVD), which is the major cause of death in patients with type 2 DM.^{24,25} Thus, weight gain is not only a cosmetic problem for these patients but also raises legitimate health concerns.

One argument for avoiding insulin therapy in patients with type 2 DM is that it leads to weight gain, which would then exacerbate the insulin resistance that characterizes patients with type 2 DM, especially those who are overweight or obese.²⁶ However, there is evidence that intensive insulin therapy does not worsen insulin resistance and that it actually can reduce it.²⁷⁻²⁹ These studies used the glucose-insulin clamp technique, a method that measures peripheral insulin sensitivity. Patients who were treated for 2 to 4 weeks with intensive insulin therapy were found to have improvement in their insulin sensitivity. Thus, the insulin therapy reduced their insulin resistance. The benefit of intensive glycemic control on peripheral insulin resistance has also been reported in patients who gained weight in association with intensive insulin therapy.¹² Whether this improvement in insulin sensitivity with insulin therapy persists over time is not known.

Abdominal obesity is a major component of the metabolic syndrome, a clustering of conditions that is associated with increased cardiovascular risk even in those without DM.³⁰ Thus, the distribution of any weight that is gained with insulin therapy may be relevant to the patient's risk for CVD. It has been estimated that about one half to two thirds of the weight gain is adipose tissue and about one third to one half is lean body mass.^{31,32} It appears that the increase in adipose tissue is proportionately divided between the abdominal and peripheral areas.³² Thus, the weight gained does not appear to have a particular propensity for the intra-abdominal region.

The Finnish Multicenter Insulin Therapy Study (FINMIS) of insulin-treated patients with type 2 DM (N = 100) reported a significant ($P < 0.001$) 8-point increase in systolic blood

pressure at 12 months.¹⁵ This was weakly positively correlated with the weight gained during the 12 months of the study ($r = 0.22$; $P < 0.02$). Diastolic blood pressure did not change significantly. A smaller study (N = 21) reported no significant increase in blood pressure in patients with type 2 DM despite a mean weight gain of 8.6 kg after 27 months of insulin therapy.¹⁴ The Kumamoto Study (N = 102) reported no significant difference in blood pressure levels between patients with type 2 DM treated intensively or conventionally with insulin for 6 years; however, it was not noted if blood pressure changes occurred from baseline to the study's end.³³

Triglycerides have been reported to decrease significantly ($P < 0.05$) with insulin therapy.^{14,15} In the FINMIS study, low-density lipoprotein levels did not increase significantly after 1 year in the obese patients with type 2 DM, although they did in the nonobese group.¹⁵ Levels of triglycerides, cholesterol, and high-density lipoprotein did not change significantly in the Kumamoto Study.³³

Thus, despite the weight gain seen in many of these studies, the data derived from them do not consistently show an adverse effect on CVD risk factors or components of the metabolic syndrome. However, more important than looking at specific risk factors for the metabolic syndrome and CVD is to examine the clinical end point: the development of CVD. The UKPDS demonstrated that long-term treatment of patients with type 2 DM using intensive insulin therapy does not have any adverse effect on cardiovascular outcomes, despite the fact that it did cause weight gain.¹ Those randomized to intensive insulin therapy had a nonstatistically significant ($P = 0.052$) 16% reduction in risk for myocardial infarction. The difference in A1C values between the intensively treated and the conventionally treated groups was 0.9%. Although the risk reduction was not statistically significant, it did correlate with an epidemiologic study that determined a 14% relative risk reduction of myocardial infarction for every 1% decrease in A1C.³⁴

In the Kumamoto Study, no increased risk of cardiovascular events was found in the intensively treated group after 6 years of follow-up.³³ Instead, the conventionally treated group had an ~2-fold increased risk for major cardiovascular, cerebrovascular, and peripheral vascular events that was not statistically significant.

The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (N = 620) and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study (N = 1394) are other clinical trials which provide evidence that intensive insulin therapy is not associated with increased cardiovascular risk.^{35,36} The DIGAMI study showed that patients with type 2 DM who received an insulin-glucose infusion at the time of an acute myocardial infarction and were managed with intensive insulin therapy afterwards had a reduced risk of mortality that persisted through 5 years of follow-up.³⁵ The DCCT/EDIC study, a long-term observational study of the DCCT cohort, found after a mean

follow-up of 17 years that prior intensive glycemic control was associated with a significant ($P = 0.02$) 57% relative risk reduction of nonfatal myocardial infarction, stroke, or death from cardiovascular causes in these patients with type 1 DM.³⁶

Altogether, this group of studies supports the view that intensive insulin therapy does not increase the risk of CVD or have an adverse effect on CVD outcomes, despite causing weight gain. Although it might appear that weight gain associated with insulin therapy would worsen risk factors for CVD and therefore increase its risk, this has not been observed in clinical trials. It is also important to keep in mind that microvascular complications are associated with hyperglycemia, regardless of the size of the patient. Tight glycemic control with insulin prevents patients from developing microvascular complications, and this is true even if they gain weight because of the therapy.¹

POSSIBLE STRATEGIES TO AMELIORATE WEIGHT GAIN WITH INSULIN THERAPY

First, it is important to recognize that although weight gain with insulin therapy occurs commonly in studies, it is not a universal observation.^{28,33} In the Kumamoto Study, weight gain with insulin therapy was not statistically significant.³³ The authors did not comment on whether specific measures were taken to prevent weight gain in their patients. The study was conducted in Japan, and the patients as a group were not overweight, so the results may represent a different group of patients from what is typically seen in the United States. Another study using intensive insulin therapy in 13 patients with type 2 DM was able to accomplish substantial improvement in glycemic control without any weight gain despite using large amounts of insulin (mean dose, 198 U/d).²⁸ After starting insulin therapy, the daily caloric intake was reduced a mean of 270 kcal/d. Before starting insulin, the patients were losing ~280 kcal/d of glucose in their urine. The patients remained in the hospital's metabolic ward throughout the 1-month study, so it was possible for the researchers to be sure that the diet was strictly followed. Thus, this study proved that it is possible for patients with type 2 DM to be controlled with insulin without gaining any weight. However, achieving this requires adequate reduction in caloric intake and/or increase in calories expended. If the patient could start and maintain compliance with a weight-reducing diet and a program to increase physical activity, weight gain should be limited with insulin therapy.

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Insulin analogues are newer forms of insulin that are available. Short-acting (aspart, lispro, glulisine) and long-

acting (detemir, glargine) insulin analogues provide a more physiologic insulin profile than older formulations (lente, regular, neutral protamine Hagedorn [NPH], ultralente). Trials in patients with type 2 DM have shown that the degree of control achieved with rapid- and long-acting analogues is similar to that seen with regular and NPH insulin, but the incidence of hypoglycemia appears to be reduced.³⁷⁻⁴⁰ Some studies in patients with type 2 DM have found that the long-acting analogues are associated with less weight gain than NPH insulin,^{39,40} while others have not.³⁸ Although the differences in weight gain were not large (ie, ~0.8–1.0 kg over the 26–28 weeks of study), they were statistically significant ($P < 0.007$ and $P = 0.017$, respectively).^{39,40}

Weight gain with insulin may be limited by combining insulin with metformin.^{13,41} One study randomized patients whose DM was poorly controlled with treatment using a sulfonylurea to treatment with a bedtime intermediate-acting insulin plus glyburide, metformin, glyburide plus metformin, or a second injection of intermediate-acting insulin in the morning.⁴¹ At 1 year, the mean weight gain in patients receiving bedtime insulin plus metformin was 0.9 kg but increased by 3.9, 3.6, and 4.6 kg in patients receiving bedtime insulin plus glyburide, bedtime insulin plus glyburide and metformin, and bedtime insulin plus morning insulin, respectively ($P < 0.001$ for the metformin group vs all other groups). In addition, the greatest decrease in the A1C value was observed in the bedtime insulin plus metformin group ($P < 0.05$ vs all other groups). Combinations of other oral agents with insulin are not as successful with respect to their effect on weight.¹⁷

Two new classes of glucose-lowering agents may improve glucose control in conjunction with weight reduction. Exenatide is a long-acting analogue of the gut hormone glucagon-like peptide-1. It has several effects that contribute to its ability to lower glucose, including glucose-dependent stimulation of insulin secretion, suppression of glucagon secretion, and delay of gastric emptying.⁴² There is also evidence that it has an anorectic effect with an accompanying weight loss.⁴² Currently, exenatide is approved for use in patients with type 2 DM who are also being treated with a sulfonylurea and/or metformin. Pramlintide is an analogue of the β -cell hormone amylin. Pramlintide may exert its glucose-lowering effect by suppressing postprandial glucagon secretion and delaying gastric emptying.⁴² Studies in patients with type 2 DM have shown that pramlintide is able to improve glycemic control while inducing weight loss.⁴² Pramlintide is approved for patients with type 2 DM being treated with insulin.⁴² Both exenatide and pramlintide are taken subcutaneously before meals.

The weight loss agents sibutramine and orlistat have been shown in clinical studies to enhance weight loss in patients on pharmacologic therapy for type 2 DM,⁴³⁻⁴⁵ including patients taking insulin.⁴⁴ These studies have also shown improvement in glycemic control that was associated with the weight loss. Diet drugs may be an appropriate option for some patients; however, weight is commonly regained after the medication is discontinued.

CONCLUSIONS

Introducing insulin therapy early in the course of treatment of type 2 DM may, because of its potential benefit on β -cell function, provide a therapeutic advantage beyond an acute improvement of glycemic control. Commonly, however, insulin treatment is associated with weight gain. Because these patients are often overweight or obese when insulin therapy is started, further weight gain is a valid concern. Obesity is a risk factor for hypertension, dyslipidemia, and CVD. However, the available evidence does not suggest that intensive therapy—even with associated weight gain—places these patients at greater risk for CVD. Furthermore, although weight gain is an undesirable effect of insulin

therapy, these patients will obtain the benefits of tight control that prevents microvascular complications from occurring regardless of any increase in weight.

Although weight gain may lead to cosmetic concerns, good glycemic control will have a positive impact on the patient's overall health and promote a reduced risk of morbidity and mortality from DM.

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REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837–853.
2. Members of the Professional Practice Committee. Summary of revisions for the 2006 Clinical Practice Recommendations. *Diabetes Care*. 2006;29(Suppl 1):S3.
3. Matthews DR, Cull CA, Stratton IM, et al, for the UK Prospective Diabetes Study (UKPDS) Group. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. *Diabet Med*. 1998;15:297–303.
4. Nathan DM. Clinical practice. Initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med*. 2002;347:1342–1349.
5. Glaser B, Leibovich G, Neshler R, et al. Improved beta-cell function after intensive insulin treatment in severe non-insulin-dependent diabetes. *Acta Endocrinol (Copenh)*. 1988;118:365–373.
6. Karvestedt L, Andersson G, Efendic S, Grill V. A rapid increase in beta-cell function by multiple insulin injections in type 2 diabetic patients is not further enhanced by prolonging treatment. *J Intern Med*. 2002;251:307–316.
7. Ilkova H, Glaser B, Tunckale A, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care*. 1997;20:1353–1356.
8. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care*. 2004;27:1028–1032.
9. Li Y, Xu W, Liao Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care*. 2004;27:2597–2602.
10. Kayashima T, Yamaguchi K, Konno Y, et al. Effects of early introduction of intensive insulin therapy on the clinical course in non-obese NIDDM patients. *Diabet Res Clin Pract*. 1995;28:119–125.
11. Alvarsson M, Sundkvist G, Lager I, et al. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes Care*. 2003;26:2231–2237.
12. Henry RR, Gumbiner B, Ditzler T, et al. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-month outpatient trial. *Diabetes Care*. 1993;16:21–31.
13. Makimattila S, Nikkila K, Yki-Jarvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with type II diabetes mellitus. *Diabetologia*. 1999;42:406–412.
14. Lindstrom T, Eriksson P, Olsson AG, Arnqvist HJ. Long-term improvement of glycemic control by insulin treatment in NIDDM patients with secondary failure. *Diabetes Care*. 1994;17:719–721.
15. Yki-Jarvinen H, Ryysy L, Kauppila M, et al. Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*. 1997;82:4037–4043.
16. Mudaliar S, Edelman SV. Insulin therapy in type 2 diabetes. *Endocrinol Metab Clin North Am*. 2001;30:935–982.
17. Yki-Jarvinen H. Combination therapies with insulin in type 2 diabetes. *Diabetes Care*. 2001;24:758–767.
18. Larger E, Rufat P, DuBois-Laforgue D, Ledoux S. Insulin therapy does not itself induce weight gain in patients with type 2 diabetes. *Diabetes Care*. 2001;24:1849–1850.
19. Wolfe RR. Effects of insulin on muscle tissue. *Curr Opin Clin Nutr Metab Care*. 2000;3:67–71.
20. Kersten S. Mechanisms of nutritional and hormonal regulation of lipogenesis. *EMBO Rep*. 2001;2:282–286.
21. Rodin J, Wack J, Ferrannini E, DeFronzo RA. Effect of insulin and glucose on feeding behavior. *Metabolism*. 1985;34:826–831.
22. Heller S. Weight gain during insulin therapy in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2004;65(Suppl 1):S23–S27.
23. Looker HC, Knowler WC, Hanson RL. Changes in BMI and weight before and after the development of type 2 diabetes. *Diabetes Care*. 2001;24:1917–1922.
24. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: The Framingham study. *Circulation*. 1979;59:8–13.
25. Pi-Sunyer FX. Medical hazards of obesity. *Ann Intern Med*. 1993;119:655–660.
26. Genuth S. Insulin use in NIDDM. *Diabetes Care*. 1990;13:1240–1264.
27. Scarlett JA, Gray RS, Griffin J, et al. Insulin treatment reverses the insulin resistance of type II diabetes mellitus. *Diabetes Care*. 1982;5:353–363.
28. Andrews WJ, Vasquez B, Nagulesparan M, et al. Insulin therapy in obese, non-insulin-dependent diabetes induces improvements in insulin action and secretion that are maintained for two weeks after insulin withdrawal. *Diabetes*. 1984;33:634–642.

29. Garvey WT, Olefsky JM, Griffin J, et al. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. *Diabetes*. 1985;34:222-234.
30. Nambi V, Hoogwerf RJ, Sprecher DL. A truly deadly quartet: Obesity, hypertension, hypertriglyceridemia, and hyperinsulinemia. *Cleve Clin J Med*. 2002;69:985-989.
31. Groop L, Widen E, Franssila-Kallunki A, et al. Different effects of insulin and oral antidiabetic agents on glucose and energy metabolism in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1989;32:599-605.
32. Bagg W, Plank LD, Gamble G, et al. The effects of intensive glycaemic control on body composition in patients with type 2 diabetes. *Diabetes Obes Metab*. 2001;3:410-416.
33. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117.
34. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ*. 2000;321:405-412.
35. Malmberg K, for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ*. 1997;314:1512-1515.
36. Nathan DM, Cleary PA, Backlund JY, et al, for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.
37. Anderson JH Jr, Brunelle RL, Keohane P, et al, for the Multicenter Insulin Lispro Study Group. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. *Arch Intern Med*. 1997;157:1249-1255.
38. Yki-Jarvinen H, Dressler A, Ziemer M, for the HOE 901/3002 Study Group. 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. *Diabetes Care*. 2000;23:1130-1136.
39. 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;24:631-636.
40. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2005;7:56-64.
41. Yki-Jarvinen H, Ryysy L, Nikkila K, et al. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130:389-396.
42. Hoogwerf RJ. Exenatide and pramlintide: New glucose-lowering agents for treating diabetes mellitus. *Cleve Clin J Med*. 2006;73:477-484.
43. Gokcel A, Karakose H, Ertorer EM, et al. Effects of sibutramine in obese female subjects with type 2 diabetes and poor blood glucose control. *Diabetes Care*. 2001;24:1957-1960.
44. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial [published correction appears in *Diabetes Care*. 2003;26:971]. *Diabetes Care*. 2002;25:1033-1041.
45. Derosa G, Cicero AF, Murdolo G, et al. Comparison of metabolic effects of orlistat and sibutramine treatment in type 2 diabetic obese patients. *Diabetes Nutr Metab*. 2004;17:222-229.

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