Blood Glucose and Bodyweight in Type 2 Diabetes – Are These Compatible Treatment Targets?

a report by

David Russell-Jones

Professor of Medicine, Department of Diabetes and Endocrinology, Royal Surrey County Hospital

DOI:10.17925/EE.2008.04.02.31

The Importance of Weight Control in Type 2 Diabetes

The increase in incidence of type 2 diabetes in the developed world is closely associated with the increasing prevalence of obesity.[1] Weight gain is a major risk factor in the development of the disease,[2,3] with a 9% relative increase in prevalence being reported for every 1kg gain in bodyweight.[4] As many as 80–90% of patients with type 2 diabetes are overweight, and this negatively influences the existing physiological and metabolic disorders associated with the disease. In particular, hyperglycaemia, hyperlipidaemia and hypertension[2,5] can greatly increase the risk of early death.[6] The development of obesity promotes insulin resistance and impaired glucose tolerance (IGT), which are major factors in the pathophysiology of type 2 diabetes. A decrease in the uptake of glucose by tissue cells in response to insulin secretion can combine with a declining prandial insulin response and the failure to suppress hepatic glucose output to cause post-prandial hyperglycaemia. Although there are defects in prandial insulin secretion by pancreatic β cells in the early stages of type 2 diabetes, an increased rate of basal insulin secretion can initially compensate for insulin resistance to restore fasting normoglycaemia.[7] However, once diabetes has become established, the gradual subsequent decline of β-cell function accounts for progressive deterioration of glycaemic control, resulting in prolonged and uncontrolled hyperglycaemia.[8]

Individuals who are unable to maintain glycaemic control face a number of debilitating microvascular and macrovascular complications, including retinopathy, nephropathy, neuropathy, heart disease and stroke. Coronary heart disease is the main contributor to excess mortality in this patient group,[9] with every 1% increase in glycated haemoglobin (HbA_{1c}) associated with a 20% increase in the relative risk of cardiovascular disease.[10]

In a study examining the influence of obesity on mortality in patients with type 2 diabetes, risk by body mass index (BMI) produced a U-shaped curve reflected in all ages and in both sexes[6] (see *Figure 1*). The data showed a 43% greater risk of death among patients with a BMI of 35–54kg/m^2 than seen in those with a 'normal' BMI (20–24kg/m^2). The increased risk among those with a BMI of 30–34kg/m^2 was also significantly raised, while those who were overweight but not obese had no increase in the risk of mortality. This underlines the importance of prevention of further weight gain in patients who are already overweight, and of advocating weight loss in those with a BMI ≥30kg/m^2.

Studies have shown that interventions to reduce weight in the early stages of type 2 diabetes can reverse the progression of the disease, thereby indicating that weight is linked to the disease process itself. A study investigating the effects of surgically induced weight loss in obese patients with type 2 diabetes (less than two years) on glycaemic control compared conventional diabetes therapy (with lifestyle change-induced weight loss) with laparoscopic adjustable gastric banding as an addition to conventional diabetes care.[11] Remission of type 2 diabetes was reported in 73% of the surgical group and 13% in the conventional-therapy group. Surgical and conventional therapy groups lost a mean of 20.7 and 1.7% of bodyweight, respectively, at two years ($p<0.001$). Remission of type 2 diabetes was related to weight loss ($R^2=0.46$; $p<0.001$) and lower baseline HbA_{1c} levels (combined $R^2=0.52$; $p<0.001$). The study concluded that patients randomised to surgical therapy were more likely to achieve remission of type 2 diabetes through greater weight loss.

In overweight patients with diabetes, active weight loss has been shown to improve insulin sensitivity and glycaemic control,[3] reduce mortality[12] and improve lipid profile and blood pressure.[2] A further important consideration of weight control in patients with diabetes is the impact that weight gain can have on psychological wellbeing. The Diabetes Attitudes, Wishes and Needs (DAWN) study found that anxiety and stress are very common in patients with diabetes.[13] Patients listed worry about worsening of their disease, weight gain, hypoglycaemia and the effect of the disease on their family life and financial commitments as their most common major concerns. All of these concerns can contribute to a reluctance to comply with antidiabetic therapy regimens. In summary, there are several compelling arguments for weight control as an important aspect of disease management in type 2 diabetes.

Therapy in Type 2 Diabetes

The involvement of excess bodyweight in type 2 diabetes has long been recognised, hence treatment historically begins with attempts to control weight through diet and exercise. However, in practice adherence to lifestyle advice tends to be poor and these interventions are seldom enough to achieve the blood glucose levels below which health complications can arise without further intervention.[14]

David Russell-Jones is a Professor of Medicine in the Department of Diabetes and Endocrinology at the Royal Surrey County Hospital and University of Surrey. His principal areas of research are diabetes and endocrinology, and his research programme uses stable isotope techniques to understand metabolism and the defects caused by disease processes such as diabetes. He has a particular interest in insulin and insulin-like growth factor 1 (IGF-1), and uses stable isotopes to investigate their action. Professor Russell-Jones has lectured on the topics of his research worldwide, has published more than 150 papers, review articles and abstracts in journals and is a member of several scientific associations. He graduated in medicine from the University of London in 1985 and was awarded a doctorate in 1994.

E: drj@royalsurrey.nhs.uk

Figure 1: Mortality Hazard Ratio in Patients with Type 2 Diabetes in the UK

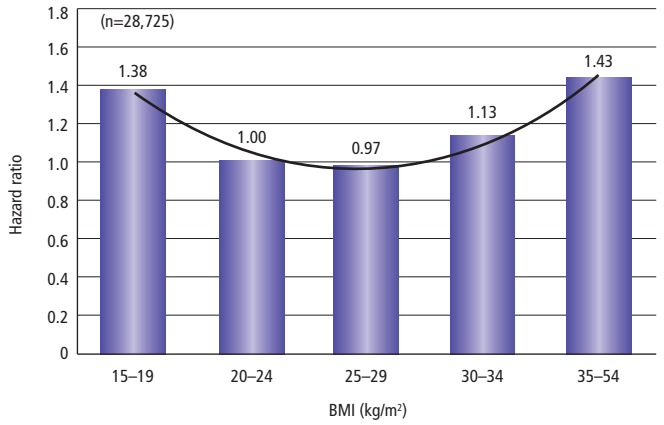
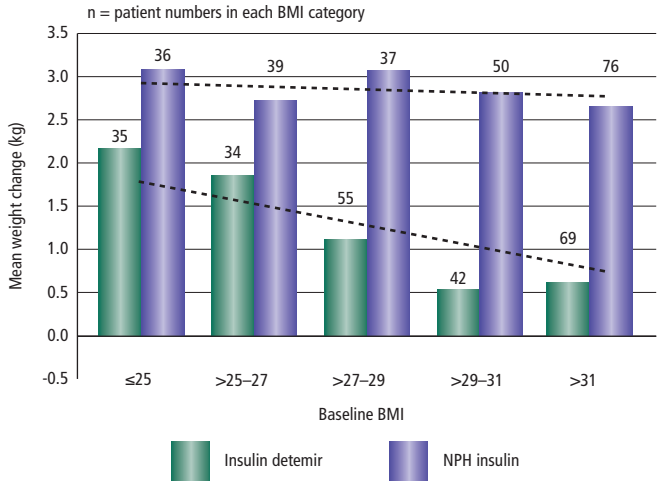


Figure 2: The Body Mass Index Effect of Insulin Detemir



Change in weight by baseline body mass index (BMI) insulin detemir versus neutral protamine Hagedorn (NPH) insulin.
Copyright © 2005 American Diabetes Association. From Diabetes®, *2005;54(Suppl. 1):A67. Modified with permission from The American Diabetes Association.*[30]

Consequently, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) now recommend that the antidiabetic drug metformin is also initiated at diagnosis.[15] One of the reasons for recommending this drug above others is that it is not associated with weight gain, so will not compromise the achievements that patients can make through lifestyle changes. In addition, studies have demonstrated that metformin can also reduce cardiovascular risk. In the UK Prospective Diabetes Study (UKPDS), metformin use was associated with a 39% reduction in myocardial infarction (MI) rates compared with patients not taking metformin and receiving conventional treatment. In the same study, diabetes-related deaths and all-cause mortality were also lowered in the metformin group (42 and 36%, respectively).[16]

As β-cell failure progresses, oral antidiabetic drug (OAD) monotherapy is superceded by multiple OAD therapy and, finally, by OADs plus exogenous insulin as endogenous insulin secretion becomes increasingly compromised. The clinical reality of the treatment of type 2 diabetes is often that large numbers of patients fail to achieve glycaemic targets despite using these successive interventions. Results from the UKPDS, showed that the majority of patients on sulfonylureas (SUs) failed to maintain targets in the six years after diagnosis,[17] and most required exogenous insulin six to 10 years after diagnosis.[18] This treatment pardigim is far from optimal as the majority of the drugs used to control blood glucose, such as sulphonylureas, thiazolidinediones and insulin, tend to increase weight gain rather than address it as a significant factor. Thus, by the time insulin therapy is needed, many doctors abandon weight control as a disease management goal for their patients.

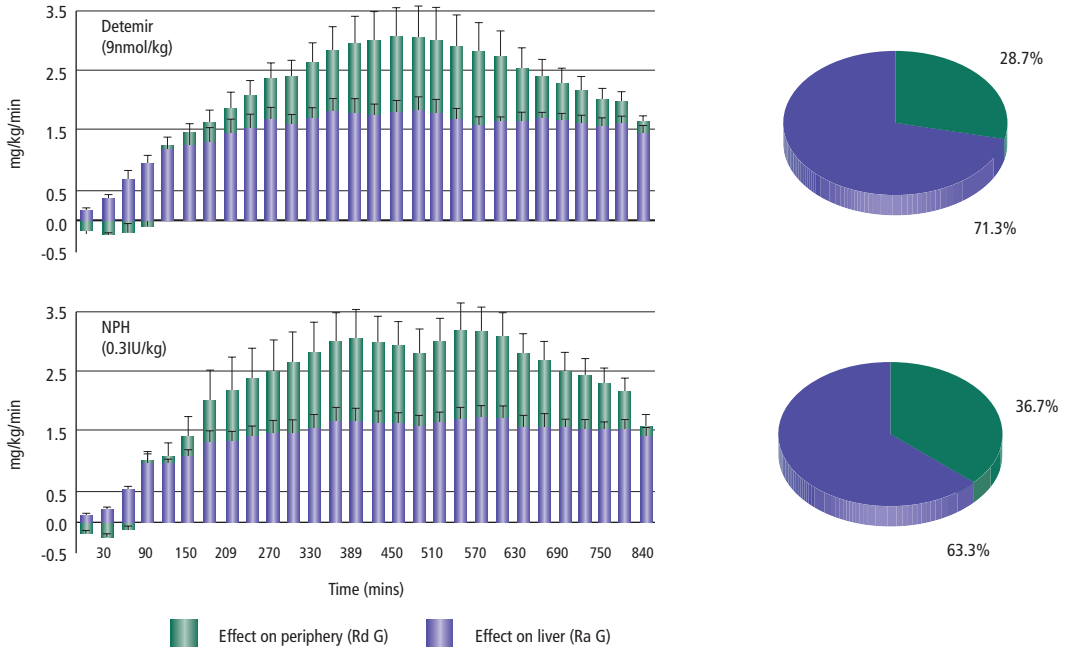
Addressing the Balance – Therapy without Weight Gain

Any therapeutic regimes that can limit weight gain, or even reduce weight, while simultaneously controlling blood glucose levels will be welcomed by patients and care providers alike. Such interventions are likely to enhance patient compliance and maximise prognostic benefits. New treatments that target the incretin system such as the glucagon-like peptide 1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors (which slow the enzymatic breakdown of endogenous GLP-1) can offer further options to patients who do not achieve glycaemic control with OAD mono- or combination therapy, but who still preserve some β-cell function. GLP-1 is a potent insulinotropic gut hormone that is secreted by the small intestine in response to stimuli such as food intake and physical exercise.[19] GLP-1 stimulates the secretion of insulin and inhibits the secretion of glucagon, thereby limiting the release of glucose by the liver.[19] GLP-1 also plays a role in reducing gastric emptying, appetite and food intake via the central nervous system, so it has beneficial implications for diabetic weight control.[19] Native GLP-1 has limited treatment value as it is rapidly degraded following systemic administration.[20] However, GLP-1 mimetics and analogues have been developed to overcome this issue. The once-daily long-acting human GLP-1 analogue liraglutide and the twice-daily GLP-1 mimetic exenatide have been shown in clinical studies to improve glycaemic control while simultaneously promoting weight loss.[21] The DPP-4 inhibitors do not cause weight loss, but they can improve glycaemic control (especially when added to metformin) without weight gain.

As diabetes progresses, the initiation of insulin becomes inevitable to regain glycaemic control and with it the perception of inevitable weight gain. Weight gain with exogenous insulin is a well-recognised problem that arises from a variety of mechanisms.[22] The best known cause of insulin-associated weight gain in type 2 diabetes is the retention of glucose (which was previously renally excreted) as a result of improved insulin-mediated tissue uptake of glucose that is not compensated by reduced food consumption. Other causes of insulin-associated weight gain include more efficient metabolic processing of glucose,[23] increased food consumption to protect against hypoglycaemia,[24] a possible impairment of satiety due to central nervous system (CNS) insulin

Any therapeutic regimes that can limit weight gain, or even reduce weight, while simultaneously controlling blood glucose levels will be welcomed by patients and care providers alike.

Figure 3: Relative Peripheral and Hepatic Effects of Insulin Detemir and Neutral Protamine Hagedorn Insulin



Copyright: adapted with kind permission of Springer Science and Business Media; Hordern et al.[38]

resistance,[25] reduced basal energy expenditure[26] and the relative over-insulinisation of peripheral tissues that arises when subcutaneously administered insulin is absorbed into the systemic circulation (contrasting with its physiological secretion into the portal circulation).[27]

New insulin analogues are being developed in order to re-create a more physiological insulin profile and one in particular, insulin detemir, has shown that glycaemic control can be achieved without the degree of weight gain associated with other basal insulins. In randomised controlled clinical trials, significantly lower weight gain has been a consistent finding when insulin detemir has been compared with neutral protamine Hagedorn (NPH) insulin. In a basal–bolus treatment regimen, patients administering insulin detemir gained an average of 0.4kg in weight over a six-month period compared with those administering NPH insulin, who gained 1.3kg (p=0.017).[28] Similarly, when used as a basal add-on therapy with OADs, insulin detemir was associated with an average weight gain of 1.2kg over six months compared with 2.8kg with NPH insulin (p<0.001).[29] Furthermore, analysis of these data revealed an interesting relationship between the BMI of patients and weight gain with insulin detemir. The higher the patients' baseline BMI, the less weight they gained during treatment with insulin detemir, in contrast to the constant level of weight gain seen with NPH insulin (see *Figure 2*).[30] This observation is further supported by a similar trial, where once-daily detemir added to OADs in previously insulin-naïve patients improved glycaemic control with less weight gain, particularly in overweight or obese patients, compared with NPH.[31]

Insulin detemir was also found to have a weight advantage over another insulin analogue, glargine. In a study of insulin initiation in patients on OADs, insulin detemir treatment was associated with a 3kg mean weight gain after one year compared with a 3.9kg gain with glargine (p=0.01).[32] This difference was more marked for patients who completed the study on once-daily detemir (2.3kg gain). In a further study, as part of a basal–bolus regimen in patients with type 2 diabetes who had previously received treatment with another insulin and/or OADs, subsequent treatment with detemir was associated with significantly less weight gain than treatment with glargine (p<0.05).[33] Meta-analyses comparing both of these insulin analogues with NPH demonstrated that at comparable levels of HbA_{1c}, only insulin detemir resulted in less weight gain than human insulin.[34,35]

The effects of insulin detemir treatment have also been evaluated in a large prospective observational study. The Predictable Results and Experience in Diabetes Through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE™) trial aims to report on the safety and efficacy of insulin detemir in 'real-life' healthcare outside the controlled environment of clinical trials. An analysis of patients with type 2 diabetes who were enrolled in this study after transferring from treatment with either NPH or insulin glargine plus OADs to insulin detemir plus OADs showed modest but significant weight loss at 12 weeks (NPH -0.7kg; p<0.01, insulin glargine -0.5kg; p<0.05) and significant improvements in glycaemic control (HbA_{1c} reductions of -0.2%; p<0.05 and -0.6%, p<0.0001, respectively).[36] Moreover, previously insulin-naïve patients with type 2 diabetes who were enrolled in the PREDICTIVE™ study improved their glycaemic control (mean HbA_{1c} reduction: -1.3%; p<0.0001) with a mean weight loss of -0.7kg (p<0.0001).[37]

The mechanisms behind the weight advantage of insulin detemir treatment has yet to be defined, but one of the current hypotheses is that the unique structure of detemir with a lipophylic fatty acid side chain and its albumin-binding properties may help partially restore the normal hepatic/peripheral insulin gradient seen with endogenous insulin (see *Figure 3*).[38] This kinetic profile would limit the distribution of detemir to peripheral tissues relative to hepatocytes compared with exogenously administered human insulin or insulin glargine, and thereby cause a relatively greater suppression of hepatic glucose output.[38] A relative reduction in the exposure of peripheral adipocytes

to insulin detemir might result in reduced weight gain due to reduced insulin-mediated lipid storage and lipogenesis.

Another theory regarding the unique weight-regulating properties of detemir currently being investigated is based on evidence that insulin is an anorexic hormone with hypothalamic actions that plays a role in the CNS-mediated regulation of bodyweight and adiposity.[39–42] Experimental studies in mice have shown that the time course and extent of activation of the insulin-signalling cascade in the liver and muscle were comparable between insulin detemir and human insulin, whereas in the brain the action of insulin detemir was enhanced.[43] Therefore, it is possible that the structure of insulin detemir might favour a relatively increased uptake into the cerebrospinal fluid to regulate appetite control.

Conclusion

Weight gain is considered to be inevitable in the natural progression of type 2 diabetes. A large percentage of patients are overweight and this negatively influences the existing physiological and metabolic disorders associated with the disease. Obesity alone can accelerate the progression of insulin resistance towards hyperglycaemia, increasing the chance of cardiovascular risk. Conversely, weight loss can lead to remission if achieved early enough, and can improve cardiovascular prognosis. Antidiabetic therapies that can control blood glucose levels but promote weight gain may have a negative effect on patient perception and adversely effect adherence. Ideally, weight control and hyperglycaemia need to be treated in parallel to limit the pace of disease progression and achieve the best clinical outcomes. The development of promising new therapies such as GLP-1 and insulin analogues with weight-sparing properties means that weight control can now be considered to be an achievable treatment target that is compatible with the maintenance of glycaemic control throughout the disease course of type 2 diabetes. In making treatment choices, the impact on weight can and should be considered at all points of the type 2 diabetes treatment pathway. ■

Acknowledgements

The author would like to thank Helen Coulson (Watermeadow Medical, Witney, UK) for writing and editorial assistance. This article was supported by an educational grant from Novo Nordisk A/S, Denmark.

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL, Prevalence and trends in obesity among US adults, 1999–2000, *JAMA*, 2002;288:1723–7.
2. Maggio CA, Pi-Sunyer FX, The prevention and treatment of obesity: application to type 2 diabetes, *Diabetes Care*, 1997;20: 1744–66.
3. Pi-Sunyer FX, Medical hazards of obesity, *Ann Intern Med*, 1993;119:655–60.
4. Mokdad AH, Ford ES, Bowman BA, et al. Diabetes trends in the US: 1990-1998, *Diabetes Care*, 2000;23:1278–83.
5. Wing RR, Weight loss in the management of type 2 diabetes. In: Gerstein HC, Haynes RB (eds), *Evidence-Based Diabetes Care*, Hamilton, Ontario: BC Decker Inc., 2000:252–76.
6. Mulnier HE, Seaman HE, Raleigh VS, et al., Mortality in people with Type 2 diabetes in the UK, *Diabetic Medicine*, 2006;23(5): 516–21.
7. Festa A, Williams K, D'Agostino R Jr, et al., The natural course of beta-cell function in nondiabetic and diabetic individuals: the Insulin Resistance Atherosclerosis Study, *Diabetes*, 2006;55: 1114–20.
8. Weyer C, Bogardus C, Mott DM, Pratley RE, The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus, *J Clin Invest*, 1999;104:787–94.
9. Ochi JW, Melton LJ III, Palumbo PJ, Chu CP, A population-based study of diabetes mortality, *Diabetes Care*, 1985;8:224–9.
10. Selvin E, Marinopoulos S, Berkenblit G, et al., Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus, *Ann Intern Med*, 2004;141(6):421–31.
11. Dixon JB, O'Brien PE, Playfair J, et al., Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial, *JAMA*, 2008;299(3):316–23.
12. Williamson DF, Thompson TJ, Thun M, et al., Intentional weight loss and mortality among overweight individuals with diabetes, *Diabetes Care*, 2000;23:1499–1504.
13. Rubin R, Peyrot M, Siminerio L, on behalf of the international DAWN advisory panel, Health Care and Patient-Reported Outcomes. Results of the cross-national Diabetes Attitudes, Wishes and Needs (DAWN) study, *Diabetes Care*, 2006;29: 1249–55.
14. 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), *Lancet*, 1998;352:837–53.
15. American Diabetes Association. Standards of medical care in diabetes 2008, *Diabetes Care*, 2008;31(Suppl. 1):S12–54.
16. UK Prospective Diabetes Study (UKPDS) Group, Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34), *Lancet*, 1998;352:854–65.
17. Wright A, Burden AC, Paisey RB, et al., UK Prospective Diabetes Study (UKPDS) Group, Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57), *Diabetes Care*, 2002;25:330–36.
18. UK Prospective Diabetes Study Group (UKPDS 16), Overview of 6 years' therapy of type 2 diabetes: A progressive disease, *Diabetes*, 1995;44:1249–58.
19. Geelhoed-Duijvestijn PH, Incretins: a new treatment option for type 2 diabetes?, *Neth J Med*, 2007;65:60–64.
20. Ahren B, Schmitz O, GLP-1 receptor agonists and DPP-4 inhibitors in the treatment of type 2 diabetes, *Horm Metab Res*, 2004;36:867–76.
21. Pi-Sunyer FX, The effects of pharmacologic agents for type 2 diabetes mellitus on body weight, *Postgrad Med*, 2008;120(2): 5–17.
22. Russell-Jones D, Khan R, Insulin-associated weight gain in diabetes – causes, effects and coping strategies, *Diabetes Obes Metab*, 2007;9(6):799–812.
23. Carlson MG, Campbell PJ, Intensive insulin therapy and weight gain in IDDM, *Diabetes*, 1993;42:1700–1707.
24. Snoek FJ, Barriers to good glycaemic control: the patient's perspective, *Int J Obes Relat Metab Disord*, 2000;24(Suppl. 3):S12–20.
25. Schwartz MW, Porte D Jr, Diabetes, obesity, and the brain, *Science*, 2005;307(5708):375–9.
26. Purnell JQ, Weyer C, Weight effect of current and experimental drugs for diabetes mellitus: from promotion to alleviation of obesity, *Treat Endocrinol*, 2003;2:33–47.
27. Torbay N, Bracco EF, Geliebter A, et al., Insulin increases body fat despite control of food intake and physical activity, *Am J Physiol*, 1985;248:R120–24.
28. 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.
29. Hermansen K, Derezinski T, Kim H, Gall MA, Treatment with insulin detemir in combination with oral agents is associated with less risk of hypoglycaemia and less weight gain than NPH insulin at comparable levels of glycaemic improvement in people with Type 2 diabetes, *Diabetologia*, 2004;47 (Suppl. 1):A273.
30. Hermansen K, Tamer S, The advantage of less weight gain increases with baseline obesity when insulin detemir rather than NPH Insulin is added to oral agents in type 2 diabetes, *Diabetes*, 2005;54(Suppl. 1):A67.
31. Philis-Tsimikas A, Koenen C, Pedersen C B, Thorsteinsson B, Less Weight Gain with Insulin Detemir Once-Daily Compared to NPH Insulin Particularly for Obese Subjects with Type 2 Diabetes, *Diabetes*, 2007;56(Suppl.1):A130.
32. Rosenstock J, Davies M, Home PD, et al., A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes, *Diabetologia*, 2008;51:408–16.
33. Hollander P, Cooper J, Bregnhøj J, Pederson CB, A 52 week, multinational, open-label, parallel-group, non-inferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with meal-time insulin aspart in patients with type 2 diabetes, *Clinical Therapeutics*, 2008;30(11): 1976–87.
34. Monami M, Marchionni N, Mannucci E, Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: A meta-analysis, *Diabetes Res Clin Pract*, 2008;81(2):184–9.
35. Bazzano LA, Lee, LJ, Shi L, et al., Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials, *Diabetic Medicine*, 2008;25:924–32.
36. Dornhorst A, Lüddeke HJ, Koenen C, et al., PREDICTIVE Study Group, Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE, *Diabetes Obes Metab*, 2008;10:75–81.
37. Dornhorst A, Lüddeke HJ, Sreenan S, et al., PREDICTIVE Study Group, Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study, *Int J Clin Pract*, 2008;62(4):659–65.
38. Hordern SV, Wright JE, Umpleby AM, et al., Comparison of the effects on glucose and lipid metabolism of equipotent doses of insulin detemir and NPH insulin with a 16-h euglycaemic clamp, *Diabetologia*, 2005;48:420–6.
39. Plank J, Bodenlenz M, Sinner F, et al., A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir, *Diabetes Care*, 2005;28: 1107–12.
40. Patel BK, Koenig JI, Kaplan LM, Hooi SC, Increase in plasma leptin and Lep mRNA concentrations by food intake is dependent on insulin, *Metabolism*, 1998;47:603–37.
41. McGowan MK, Andrews KM, Kelly J, Grossman SP, Effects of chronic intra-hypothalamic infusion of insulin on food intake and diurnal meal patterning in the rat, *Behav Neurosci*, 1990;104(2):373–85.
42. Benedict C, Hallschmid M, Hatke A, et al., Intranasal insulin improves memory in humans, *Psychoneuroendocrinology*, 2004;29:1326-34.
43. Hennige AM, Sartorius T, Tschritter O, et al., Tissue selectivity of insulin detemir action *in vivo*, *Diabetologia*, 2006;49: 1274–82.