

# Myths, Realities and Practicalities in the Initiation and Intensification of Insulin Therapy in Type 2 Diabetes

a report by

**Andreas Liebl**

Medical Director, Centre for Diabetes and Metabolism, Wallbergklinik and Fachklinik, Bad Heilbrunn

DOI:10.17925/EE.2008.04.02.27

Although type 2 diabetes is sometimes regarded by patients as the 'milder form' of diabetes, it is a serious disease with the potential to cause severe morbidity and mortality. Pancreatic  $\beta$ -cell mass and function diminish over time and ultimately leave patients with a minimal capacity for insulin secretion. By the time type 2 diabetes is first diagnosed, there is likely to have been a substantial loss of  $\beta$ -cell function (averaging 50%), with further decline continuing over subsequent years despite treatment.<sup>1-4</sup>

While some newly developed antidiabetes therapies such as the glucagon-like peptide-1 (GLP-1) receptor agonists have the potential to limit the rate of disease progression,<sup>4</sup> it nevertheless follows that exogenous insulin therapy is likely to become necessary for most patients. However, insulin is often regarded as the treatment 'of last resort' in type 2 diabetes, and it is often perceived as avoidable.<sup>5</sup> Thus, the prospect of progression from oral antidiabetic drugs (OADs) to insulin can present a number of psychological issues for the patient. These include a sense of personal failure in disease management and anxiety about an increasing seriousness of the disease and how insulin will affect lifestyle.<sup>6,7</sup> Patients also worry that injections will cause discomfort and treatment complexity, as well as the prospect of hypoglycaemic episodes and weight gain. Healthcare providers can share these concerns and may also doubt the ability of patients to manage the perceived complexity of insulin therapy. The inevitable result is that insulin therapy is usually delayed for far too long, leaving patients exposed to unnecessarily high blood glucose (BG) levels that increase the risk of complications. This is shown in audits of the glycated haemoglobin (HbA<sub>1c</sub>) values of patients on insulin initiation, and by the high baseline values for HbA<sub>1c</sub> in the many published clinical trials of patients beginning insulin therapy.<sup>8</sup> However, the reality is that insulin therapy for type 2 diabetes can be far less complicated and better tolerated than popularly believed, with patients often experiencing an increased sense of wellbeing and empowerment following insulin initiation.<sup>6</sup> Indeed, one study showed that when insulin is given as initial therapy when type 2 diabetes is diagnosed, there are few patient acceptance issues and therapeutic success is excellent.<sup>9</sup>

## Introducing Insulin – Insulin Deficiency and Choice of Regimen

Patients with type 2 diabetes usually have some endogenous insulin secretion, so insulin injections are given (at least initially) as supplementary rather than replacement therapy. However, as a result of the insulin resistance typical of type 2 diabetes, high doses are often required compared with those usually given in type 1 diabetes.

In order to apply insulin therapy effectively, it is important to understand the insulin secretory deficiencies of type 2 diabetes. A

hallmark of this disease is a progressive loss of the prandial insulin response.<sup>10</sup> In health, carbohydrate consumption acts as a stimulus to the pancreas, which rapidly increases insulin while suppressing glucagon secretion. This response in turn signals the liver to reduce endogenous glucose output.<sup>11</sup> As a consequence of this, BG does not rise to damaging levels with the subsequent digestion and absorption of ingested carbohydrates. However, in type 2 diabetes pancreatic  $\beta$  cells can be regarded as chronically stressed due to the continual stimulus of prevailing hyperglycaemia and the confounding influences of insulin resistance and glucose toxicity.<sup>12</sup> Early in the disease process, the background rate of insulin secretion may be elevated as a response to chronic hyperglycaemia, but there may consequently be insufficient insulin reserves to quickly raise plasma concentrations further in response to prandial stimuli, and this deficit is compounded by glucotoxic/lipotoxic loss of  $\beta$ -cell function with  $\beta$ -cell apoptosis.<sup>12</sup> Therefore, prandial insulin responses become progressively delayed and blunted, fail to suppress endogenous glucose output and lead to high BG concentrations after meals.<sup>11</sup> Fasting BG subsequently becomes elevated due to the failure to return glucose levels to physiological norms between meals and during the night. There are a number of options available for initiating insulin therapy in type 2 diabetes, each with advantages and disadvantages. These are summarised below.

## Basal-only Insulin Regimens

Basal insulin is given once daily (usually in the evening) and usually as a simple addition to existing OAD therapies (basal plus OAD therapy [BOT]). Options include neutral protamine Hagedorn (NPH) insulin and the analogue insulins detemir and glargine. It may seem that BOT would not address the progressive loss of the prandial insulin response in type 2 diabetes, but if introduced early it is believed that BOT can afford prolonged periods of  $\beta$ -cell rest, and hence enable some recovery of the endogenous prandial insulin response. It is a relatively safe and simple way to begin insulin therapy and carries a low risk of

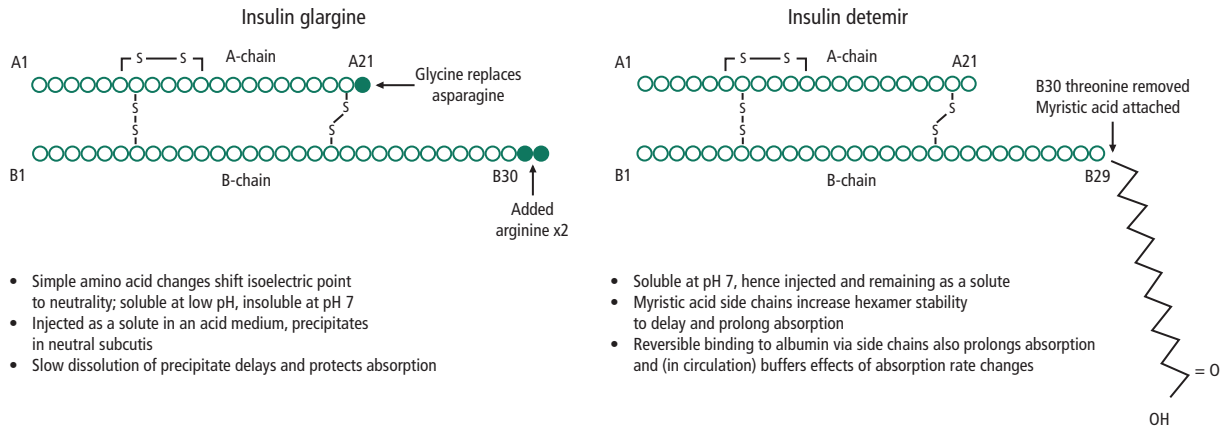


Andreas Liebl is Medical Director of the Centre for Diabetes and Metabolism at the Wallbergklinik and the Fachklinik in Bad Heilbrunn. He is Vice President of the German Diabetes Association's Working Group 'Diabetes Technology – Insulin Pumps and Blood Glucose Sensors' and is on the Scientific Board of the Artificial Insulin Delivery, Pancreas and Islet Transplantation (AIDPIT) study group of the European Association for the Study of Diabetes (EASD). Dr Liebl has prepared numerous

international and national publications and presentations at scientific meetings on the topics of insulin therapy, oral antidiabetic drugs, pharmaco-economics, diabetic foot syndrome and intraperitoneal insulin therapy.

E: dr.liabl@t-online.de

**Figure 1: Structure and Protraction Mechanism of the Basal Insulin Analogues Glargine and Detemir**



hypoglycaemia. Furthermore, the regimen can be intensified easily by the addition of short-acting mealtime insulins if needed at a later date.

### Fast-acting Mealtime (Prandial) Insulin Regimens

These regimens are also known as ‘supplementary insulin therapy’ (SIT). Rapid-acting insulins are quickly absorbed into the circulation to mimic the natural prandial insulin response. Therefore, in type 2 diabetes they supplement insulin when the physiological deficit tends to be greatest. Options include regular human insulin and the analogue insulins aspart, lispro and glulisine. Given the secretory deficits of type 2 diabetes, SIT seems a logical approach, and in some countries it is popular. However, rapid-acting insulins carry the greatest hazard for hypoglycaemia, and previously insulin-naïve patients may be intimidated by the prospect of having to inject with every meal. For these reasons, and due to the clinical successes that are achievable with simpler regimens, they are not the preferred ‘starting regimen’. SIT can be intensified by adding a basal insulin.

### ‘Pre-mixed’ or ‘Bi-phasic’ Insulin Regimens

Some products contain two insulin components in the formulation: one that is rapidly absorbed and one that has more prolonged absorption. Therefore, the regimen supplements both basal and prandial insulin secretion and is often regarded as a good compromise, but with less flexibility than other regimens.

Patients with type 2 diabetes usually have some endogenous insulin secretion, so insulin injections are given (at least initially) as supplementary rather than replacement therapy.

### Basal plus Bolus Regimen

Basal and prandial insulins can be given together in a multiple injection regimen that mimics the normal pattern of insulin secretion. This is the treatment of choice where full insulin replacement therapy is needed (type 1 and late-stage type 2 diabetes), but the regimen is generally considered unnecessarily complicated as an initiation regimen in type 2 diabetes. Nevertheless, many patients will eventually require this regimen as diabetes progresses.

### The New Paradigm – Basal Insulin plus Oral Antidiabetic Drug Therapy

BOT has become a popular therapy in recent years with the extensive clinical study of the long-acting analogue insulins glargine and detemir. These achieve their prolonged absorption and glucose-lowering action through two entirely different mechanisms (see Figure 1). However, despite these pharmacological differences most comparative pharmacodynamic studies suggest they have remarkably similar time-action profiles extending to 24 hours in patients with type 2 diabetes and enabling once-daily dosing.<sup>13–15</sup>

The analogues represent an improvement on NPH insulin by having longer and less peaked time-action profiles.<sup>16</sup> Detemir is also characterised by reduced within-subject variability of the BG-lowering effect from injection to injection compared with both NPH insulin<sup>16</sup> and glargine.<sup>14,16</sup> A reduced peak effect and reduced variability both contribute to a lower risk of hypoglycaemia, and this has indeed been a consistent finding in trials comparing the basal analogues with NPH (see Figure 2).<sup>17</sup> Hypoglycaemia is already relatively uncommon in NPH-treated type 2 diabetes, and it can be regarded as an extremely rare event with the basal analogues. In a 52-week trial comparing glargine and detemir in previously insulin-naïve patients,<sup>18</sup> hypoglycaemia occurred with similar frequencies with each insulin, with just six events per patient-year overall and just 1.3 events per patient-year being nocturnal. Most events were minor, with only 17 major events reported among 582 patients over one year. Although relatively uncommon in type 2 diabetes, hypoglycaemia is nevertheless an important issue. Severe hypoglycaemic events occur rarely, but can cause serious morbidity and undermine the patient’s confidence in his or her insulin treatment. There has also been some concern raised recently that the small excess of CVD events associated with aggressive insulin titration in some recent outcome trials, such as the ACCORD study, might relate to a relatively increased incidence of hypoglycaemia.<sup>19,20</sup>

While most trials comparing glargine with NPH have shown equal amounts of weight gain,<sup>21–25</sup> an intriguing finding with detemir that has been reported in every clinical trial in type 2 diabetes is that it causes less weight gain than the comparator.<sup>18,26–30</sup> This finding is also consistent in studies of type 1 diabetes.<sup>31</sup> Furthermore, this relative weight-sparing property increases with baseline body mass index (BMI).<sup>29,32,33</sup> The mechanism(s) responsible is currently under investigation, but appears to be independent of the reduced risk of hypoglycaemia.<sup>34,35</sup>

A low incidence of hypoglycaemia and limited weight gain are important advantages since these potential side effects represent key barriers to patient acceptance of insulin therapy. The simple once-daily injection schedule and the presentation of modern insulins in patient-friendly injection devices with fine-gauge needles also helps overcome concerns about injection discomfort. Therefore, BOT is an attractive insulin initiation option for its tolerability, but its widespread adoption is also partly due to impressive glycaemic improvements achieved in the so-called ‘treat-to-target’ studies, in which insulin dose is continually titrated against fasting glucose targets. Using this approach, reductions in HbA<sub>1c</sub> of 1.4–1.7% Hb are typically achieved – even with once-daily NPH. The basal insulin analogues generally achieve this with reduced hypoglycaemia,<sup>17</sup> offering an improved balance between glycaemic control and treatment tolerability.

The improvements seen in the intensive setting of a clinical trial are not easy to transfer to real-life clinical practice, but the observational PREDICTIVE™ study of insulin detemir has nevertheless shown a mean reduction in HbA<sub>1c</sub> of 1.3% Hb in previously insulin-naïve patients.<sup>33</sup> In summary, BOT offers a simple and well-tolerated insulin initiation option that can bring about clinically important improvements in glycaemic control without undue hypoglycaemia and weight gain. It can help build patient confidence in insulin use and safety.

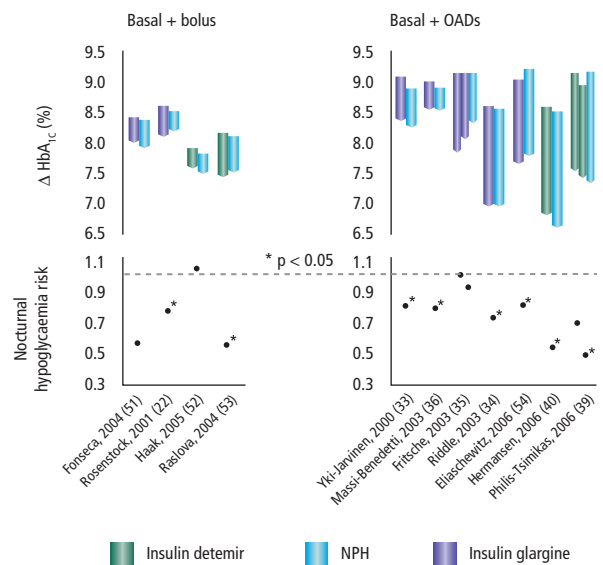
**Intensification – Why Basal Insulin Is a Part of the Journey and Not the Destination in Insulin Therapy**

The HbA<sub>1c</sub> that is ultimately achievable with BOT is largely determined by the patient’s ability to mount an endogenous prandial insulin response. When HbA<sub>1c</sub> is high or begins to rise despite optimal OAD therapy, this can indicate major loss of β-cell function, and hence the likelihood that prandial supplementation will also be needed. For a patient established on BOT therapy, there are fewer barriers to overcome when the regimen needs intensifying, but intensification is still often delayed and resisted. One reason may be perceived complexity with ‘intensive insulin therapy’ derived from the situation in type 1 diabetes where frequent BG sampling is required, food calories are counted and insulin is carefully dosed accordingly. In fact, the intensification of BOT in type 2 diabetes can be achieved relatively simply.

The HbA<sub>1c</sub> that is ultimately achievable with basal plus oral antidiabetic drug therapy is largely determined by the patient’s ability to mount an endogenous prandial insulin response.

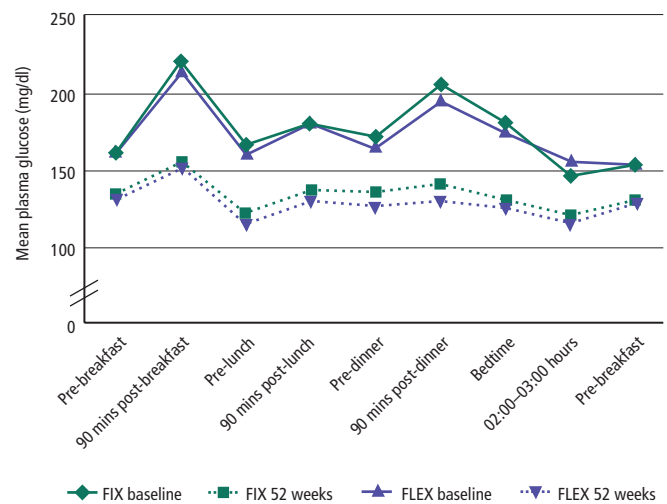
There are a number of ways in which once-daily insulin used in BOT could be intensified. One obvious possibility might be to give an additional dose of basal insulin. However, a review of clinical studies (including split-dose studies) concluded that there is a limit to the glycaemic achievement that is possible using basal insulin alone and that this is not increased with additional injections.<sup>17</sup> A second basal injection tends only to raise the insulin dose without corresponding improvement in glycaemic control. The pathophysiology of type 2 diabetes and clinical

**Figure 2: Reductions in Glycated Haemoglobin and Relative Risk of Hypoglycaemia in Trials of Basal Insulin Analogues**



\*Fritsche 2003 and Philis-Tsimikas 2006 show two bars for analogue insulin, denoting results for either once-daily morning or once-daily evening administration. Reproduced with permission from John Wiley & Sons Ltd, 2007: DeVries et al.<sup>17</sup>

**Figure 3: Mean Blood Glucose Profiles in a Study Comparing Intensive Blood Glucose Monitoring and Carbohydrate-based Insulin Dosing with a Simpler Fixed-dose Regimen in Type 2 Diabetes<sup>36</sup>**



trial evidence show that as the disease progresses it becomes necessary to directly supplement the prandial insulin response. This can be achieved by switching to a pre-mixed insulin regimen or by adding mealtime injections of rapid-acting insulin. At this point, OADs (with the exception of metformin) are usually redundant and are discontinued.

The prospect of basal-bolus therapy may imply a need for diligent calorie counting, BG monitoring and insulin dosing. However, a recent 52-week study suggests that such concerns are largely unfounded in type 2 diabetes.<sup>36</sup> In this trial, all patients received mealtime aspart, most with once-daily detemir with or without metformin. Patients were randomised to a ‘flexible-dose’ regimen involving carbohydrate-dependent prandial insulin dosing based on daily BG profiles (with three to eight measurements) or to a fixed-dose regimen involving only one or

two BG profiles per week and fixed prandial insulin doses, given in the recommended ratio of 1:1:1 breakfast:lunch:dinner.<sup>37</sup> HbA<sub>1c</sub> decreased from a baseline of ~8.2 to 6.6% with the flexible regimen and to 6.8%

It is important to recognise that type 2 diabetes is progressive and its pathophysiology means that prandial insulin therapy will probably also be needed at some point.

with the fixed-dose regimen ( $p=0.019$ ).<sup>36</sup> Although this difference was statistically significant, the outcome with the far less demanding fixed dosing was excellent and arguably not clinically different from that achieved with flexible dosing. This is supported by the mean BG profiles at 52 weeks, where it is noteworthy that both regimens greatly reduced post-prandial glucose excursions (see Figure 3). Certainly, it might be expected that the simpler fixed-dose approach would better avoid future non-adherence by the patients.

## Conclusions

Despite common misgivings, initiation and intensification of insulin therapy in type 2 diabetes can be achieved with relative ease. With the modern basal insulin analogues, initiation can be made with a once-daily injection regimen that carries a low risk of hypoglycaemia and, in the case of detemir, minimal weight gain. Such a regimen can help patients overcome concerns about insulin therapy while significantly lowering HbA<sub>1c</sub>. It is important to recognise that type 2 diabetes is progressive and its pathophysiology means that prandial insulin therapy will probably also be needed at some point. The addition of a rapid-acting mealtime insulin poses few problems in type 2 diabetes and can be given in simple fixed-dosed regimens to recover glycaemic control. In short, insulin is a potent tool for re-establishing glycaemic control as type 2 diabetes advances, and fears about tolerability and complexity are largely unfounded. Therefore, it should be embraced and used as soon as indicated – with confidence. ■

## Acknowledgements

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

- Turner RC, The U.K. Prospective Diabetes Study. A review, *Diabetes Care*, 1998;21(Suppl. 3):C35–8.
- Lebovitz HE, Insulin secretagogues old and new, *Diabetes Reviews*, 1999;7(3):139–53.
- LeRoith D, Beta-cell dysfunction and insulin resistance in type 2 diabetes: role of metabolic and genetic abnormalities, *Am J Med*, 2002;113(Suppl. 6A):3–11S.
- Horton ES, Can newer therapies delay the progression of type 2 diabetes mellitus?, *Endocr Pract*, 2008;14(5):625–38.
- Peyrot M, Rubin RR, Lauritzen T, et al., The International DAWN Advisory Panel, Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study, *Diabetes Care*, 2005;28(11):2673–9.
- Larkin ME, Capasso VA, Chen CL, et al., Measuring psychological insulin resistance: barriers to insulin use, *Diabetes Educ*, 2008;34(3):511–17.
- Phillips P, Type 2 Diabetes – failure, blame and guilt in the adoption of insulin therapy, *Rev Diabet Stud*, 2005;2(1):35–9.
- Davies M, The reality of glycaemic control in insulin treated diabetes: defining the clinical challenges, *Int J Obes Relat Metab Disord*, 2004;28(Suppl. 2):S14–22.
- Lingvay I, Kaloyanova PF, Adams-Huet B, et al., Insulin as initial therapy in type 2 diabetes: effective, safe, and well accepted, *J Invest Med*, 2007;55(2):62–8.
- Owens DR, Cozma LS, Luzio SD, Early-phase prandial insulin secretion: its role in the pathogenesis of type 2 diabetes mellitus and its modulation by repaglinide, *Diabetes Nutr Metab*, 2002;15(6 Suppl.):19–27.
- Mitrakou A, Kelley D, Veneman T, et al., Contribution of abnormal muscle and liver glucose metabolism to postprandial hyperglycemia in NIDDM, *Diabetes*, 1990;39(11):1381–90.
- Robertson RP, Harmon JS, Diabetes, glucose toxicity, and oxidative stress: A case of double jeopardy for the pancreatic islet beta cell, *Free Radic Biol Med*, 2006;41(2):177–84.
- Heise T, Pieber TR, Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies, *Diabetes Obes Metab*, 2007;9(5):648–59.
- Klein O, Lyngé J, Endahl L, et al., Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes, *Diabetes Obes Metab*, 2007;9(3):290–99.
- King A, Daily blood glucose profiles in subjects with type 2 diabetes in a randomised, crossover, double-blind comparison of insulin detemir and insulin glargine, *Diabetologia*, 2008;51(Suppl. 1):S401.
- Heise T, Nosek L, Rønn BB, et al., Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes, *Diabetes*, 2004;53(6):1614–20.
- DeVries JH, Nattrass M, Pieber TR, Refining basal insulin therapy: what have we learned in the age of analogues?, *Diabetes Metab Res Rev*, 2007;23(6):441–54.
- 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-naïve people with type 2 diabetes, *Diabetologia*, 2008;51(3):408–16.
- Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group, Effects of Intensive Glucose Lowering in Type 2 Diabetes, *N Engl J Med*, 2008;358:2545–59.
- Ismail-Beigi F, Moghissi ES, Glycemia management and cardiovascular risk in type 2 diabetes: an evolving perspective, *Endocr Pract*, 2008;14(5):639–43.
- Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators, The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients, *Diabetes Care*, 2003;26(11):3080–86.
- Fritsche A, Schweitzer MA, Häring HU; 4001 Study Group, Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial, *Ann Intern Med*, 2003;138(12):952–9.
- Massi Benedetti M, Humburg E, Dressler A, Ziemann M, A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes, *Horm Metab Res*, 2003;35(3):189–96.
- Yki-Järvinen H, Dressler A, Ziemann M, HOE 901/300s 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(8):1130–36.
- 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.
- 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(1):56–64.
- Raslová K, Bogoev M, Raz I, et al., Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes, *Diabetes Res Clin Pract*, 2004;66(2):193–201.
- Phillis-Tsimikas A, Charpentier G, Clauson P, et al., Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes, *Clin Ther*, 2006;28(10):1569–81.
- Hermansen K, Davies M, Derezinski T, et al., A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes, *Diabetes Care*, 2006;29(6):1269–74.
- Fajardo Montañana C, Hernández Herrero C, Rivas Fernández M, Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients: the PREDICTIVE BMI clinical trial, *Diabet Med*, 2008;25(8):916–23.
- Morales J, Defining the role of insulin detemir in basal insulin therapy, *Drugs*, 2007;67(17):2557–84.
- Raslová K, Tamer SC, Clauson P, Karl D, Insulin detemir results in less weight gain than NPH insulin when used in basal-bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index, *Clin Drug Investig*, 2007;27(4):279–85.
- Dornhorst A, Lüddecke 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.
- Russell-Jones D, Khan R, Insulin-associated weight gain in diabetes – causes, effects and coping strategies, *Diabetes Obes Metab*, 2007;9(6):799–812.
- Davies MJ, Derezinski T, Pedersen CB, Clauson P, Reduced weight gain with insulin detemir compared to NPH insulin is not explained by a reduction in hypoglycaemia, *Diabetes Technol Ther*, 2008;10(4):273–7.
- Milek K, Wizemann E, Martin S, et al., Near normoglycaemic control under supplementary insulin therapy in type 2 diabetes with insulin aspart and insulin detemir – is a fixed dose regimen as effective as a flexible therapy regimen?, *Diabetologia*, 2007;50(Suppl. 1):S412.
- Liebl A, Prager R, Binz K, et al., PREFER Study Group, Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER Study: a randomized controlled trial, *Diabetes Obes Metab*, 2009;11(1):45–52.