Introduction

The underlying insulin resistance and impaired insulin secretion in patients with type 2 diabetes worsen over time, necessitating the use of antidiabetic drugs, often in combination, to control glycaemic levels [1]. From the UKPD study the main explanation for the progressive history of type 2 diabetes seems to be a failure of beta-cell function over time [2], while insulin resistance may be more constant from diagnosis [2]. Therefore, it is not surprising that insulin treatment is necessary in most patients 10–15 years after diagnosis to maintain HbA1c level as close to normal as is safely possible [2]. A consensus recommendation for the treatment of type 2 diabetes has recently been published [1]. The algorithm for treatment strategy includes early and aggressive use of insulin, the most powerful antidiabetic drug, to achieve treatment goals. Many patients and health care professionals delay insulin treatment due to concerns about injection-site pain, hypoglycaemia and weight gain, despite the fact that several studies have suggested that improvement of glycaemic control by insulin treatment improves the well-being and quality of life [3,4]. The absorption rate of the fast-acting human insulin is with a peak action 2–4 h after injection and does not provide the early and quick rise in plasma insulin required to prevent exaggerated postprandial hyperglycaemia after a meal. The pharmacokinetic profile also increases the risk of hypoglycaemia 3–5 h after a meal, especially if snacks are omitted [6]. The intermediate acting NPH insulin cannot deliver insulin in a constant and reproducible low-level rate that characterises normal insulin secretion, but produces a peak in insulin concentration 4–6 h after injection, which increases the risk of nocturnal hypoglycaemia [6]. On this background the new insulin analogues were developed, making a more physiological insulin regimen realistic for many patients, since onset and duration of the action of these analogues more closely mimic human insulin secretion. At the moment we have three rapid-acting insulin analogues with similar pharmacokinetic
profiles for targeting postprandial hyperglycaemia, two long-acting insulin analogues, and several biphasic premix analogues.

The present narrative review will discuss whether the new insulin analogues have improved the treatment of type 2 diabetic patients. First the two long-acting analogues glargine and detemir will be discussed, followed by a review of the biphasic premix insulins. Comments will be given on the rapid-acting insulin analogues used in combination with NPH insulin or the long-acting insulin analogues. The use of inhaled insulin in the treatment of type 2 diabetes will also be mentioned. Combination therapy with insulin plus oral antidiabetic drugs versus treatment with insulin alone and the comparison of human insulin versus insulin analogues are also a part of the present review. Lastly, it is helpful to distinguish between basal and postprandial hyperglycaemia caused by ingestion of food, since the strategies for treatment of diabetes primarily control one or the other of these aspects of hyperglycaemia. Recommended HbA1c targets for treatment of subjects with type 2 diabetes are between 6.5% and 7.0% [1]. The majority of individuals with type 2 diabetes in both the USA and Europe do not achieve a HbA1c <7.0 [7,8].

Treatment with NPH Insulin and the Long-Acting Insulin Analogues

One treatment concept has gained popularity in recent years following its success in clinical trials: the addition of a long-acting basal insulin formulation to an existing oral antidiabetic drug (OAD) treatment, followed by aggressive titration of the insulin dose to achieve target levels of glycemia. Adding basal insulin has been shown to lower the entire 24-h blood glucose profile, and in combination with metformin the increase in weight after initiation of insulin treatment has been significantly reduced [9,10].

Both long-acting insulin analogues – insulin glargine and insulin detemir – have been implemented in the “treat to target” approach used in type 2 diabetic patients. The analogues are injectable, clear solutions, but the mechanisms by which they achieve prolonged activity differ entirely as described in detail in Chapter 8 and in [11,12].

Insulin Glargine (Lantus)

Insulin glargine (Lantus) was the first available long-acting human insulin analogue [12]. Glargine is a clear solution and there is no need to thoroughly mix it before injection. Insulin glargine (21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin) differs from native insulin in that the 21 amino acid residue asparagine on the A chain has been substituted with a glycerine residue and 2 arginine residues have been added to the C terminus of the B chain, making glargine soluble in the acidic environment at pH of 4 [12]. Glargine precipitates in the neutral pH of subcutaneous tissue, which prolongs its absorption to the blood. The addition of zinc as a hexamer-stabilising agent further prolongs the duration of action. Insulin glargine must not be mixed with other insulins [12].

Clamp studies in normal subjects and type 1 diabetic patients have confirmed that the duration of glargine is longer than NPH insulin and the action profile is flatter. Median duration of action is 23 h for glargine versus 14 h for NPH insulin, and during the first 12 h intra-individual variability of the absorption rate is lower with glargine [13]. The pharmacokinetic suggests that glargine is more suitable than NPH human insulin to mimic the normal pattern of physiological basal insulin secretion.

Insulin glargine has been compared with NPH in type 2 patients. In theory, basal insulin supplementation with glargine offers the advantage of a simple once-daily injection regimen, which is easy to add to current oral glucose-lowering drugs.

In the “treat-to-target” studies glargine was administered once daily at bedtime and NPH was given once daily at bedtime or twice daily at bedtime and in the morning in combination with sulfonylurea (glimepiride)[14–19]. The overall conclusions from the studies are that the reduction in HbA1c was similar in the glargine and NPH groups and that the number of patients reaching the target of HbA1c <7.0% was not different. The fasting blood glucose was lower in the glargine groups than in the NPH groups. Except for one of the studies, comparing either bedtime or morning glargine versus bedtime NPH insulin, significantly more patients reached an HbA1c <7.5% with morning glargine than with bedtime glargine and bedtime NPH insulin [16]. In another study there was no difference in the reduction in HbA1c between