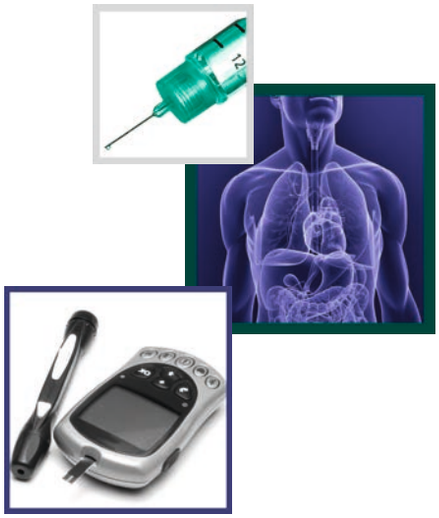
EDITORIAL



Do the benefits of analog insulins justify their costs?

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"Since their launch, insulin analogs have had an increasing impact on the amount of money the NHS spends on diabetes."

Diabetes mellitus is a chronic condition that affects 346 million people worldwide and more than 80% of people with diabetes live in low-to-middle income countries [101]. The aim of treatment is to reduce the symptoms of diabetes and reduce blood glucose levels as uncontrolled hyperglycemia is associated with an increased risk of macrovascular and microvascular complications. Patients with Type 1 diabetes always require treatment with exogenous insulin. For Type 2 diabetes, treatment options begin with diet modification and lifestyle interventions but often oral hypoglycaemic agents or insulin or both are required as the disease progresses.

Currently, there are three different types of insulin by molecular origin on the market. From oldest to newest, these are animal insulin, human insulin and analog insulin. Human insulin was introduced in the 1980s and was thought to be less immunogenic than animal insulin, thus, leading to lower antibody titers. However, no clinically relevant differences, in terms of adverse effects or glycemic control between animal (particularly purified porcine insulin) and human insulin, could be detected [1]. Despite this, human insulin was used routinely and the use of animal insulin declined rapidly [1,2]. By 2000, the National Health Service (NHS) in the UK was spending £102.1 million per year on human insulin but just £7.4 million on animal insulin at 2010 prices [3]. In developing countries there was concern that human insulin would be unaffordable and that the major insulin manufacturers would stop producing animal insulin, thus, leading to a shortage [1].

Insulin analogs were developed through structural modification of human-sequence insulin to better mimic the pharmacokinetic profile of endogenous insulin. Since their launch, insulin analogs have had an increasing impact on the amount of money the NHS spends on diabetes [3]. In the UK, the overall NHS spend on insulin doubled between 2000 and 2010. In 2000, human insulin accounted for 85% of the total cost of insulin, whereas insulin analogs accounted for just 12%. By 2010, this situation had reversed, and sales of analog insulin dominated the market [3].

The popularity of insulin analogs could be due in part to successful marketing. In

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addition, as insulin manufacturers focus on newer, patentable insulin analog products, they have withdrawn some of their older human insulin products. Most recently, Mixtard® 30 was withdrawn in the UK in December 2010, necessitating a change to an alternative product for an estimated 90,000 users [4]. This is not to say that insulin analogs are devoid of clinical benefit. The pharmacokinetic profiles of insulin analogs do appear to improve glycemic control and reduce incidence of hypoglycemia, compared with human equivalents [5,6]. Long-acting insulin analogs have a longer duration of action and, in the case of insulin glargine, no peak plasma concentrations in comparison to neutral protamine Hagedorn (NPH) insulin [7,8]. Shorter-acting insulin analogs have a lower tendency for self-association, faster absorption and higher peak plasma concentrations that are achieved more quickly than with soluble human insulin [9]. Insulin analogs are available in new injection devices that may be more appealing to patients compared with those used for human insulin products [10]. Additionally, insulin detemir has been associated with less weight gain than other long-acting insulin formulations [2].

Despite this evidence, most commentators agree that analog insulins provide only modest benefits for the patient despite their significantly higher cost. A Cochrane systematic review compared short-acting insulin analogs with regular human insulin and found a small, statistically significant improvement in glycemic control for people with Type 1 diabetes using short-acting insulin analogs but no benefit in Type 2 diabetes patients. Both analog and human insulin were associated with similar levels of hypoglycemia [5]. The Cochrane review comparing long-acting insulin analogs with NPH insulin in Type 2 diabetes patients concluded that there was no evidence of a beneficial effect in terms of glycemic control and only a minor benefit in terms of symptomatic nocturnal hypoglycemic events [6]. The longest trial comparing insulin glargine and NPH found that, over 5 years' observation, there was a similar progression to retinopathy but less improvement in the glycated hemoglobin level for insulin glargine as the mean HbA1c change from baseline was -0.55% with insulin glargine and -0.76% with NPH insulin (the LS mean difference was 0.21 higher with NPH insulin, 95% CI: 0.06–0.35; p = 0.0053) [11]. Epidemiological data from the UK indicates that, between 1997 and 2007, despite general improvements in provision of diabetes care and introduction of insulin analogs, there was no observable improvement in glycated haemoglobin levels for patients with Type 2 diabetes using exogenous insulin [12].

How do healthcare reimbursement agencies view the analog insulins? In the UK, the NICE has recommended insulin glargine and rapid-acting insulin analogs as an option for patients with Type 1 diabetes but has stated that long-acting insulin analogs should only be used in Type 2 diabetes patients in specific circumstances [102,103]. The Canadian Agency for Drugs and Technologies in Health recommends that NPH should be used as a first-line therapy in both Type 1 and 2 diabetes and that long-acting insulin analogs should only be used if significant episodes of hypoglycemia occur. If bolus insulin therapy is required, the Canadian Agency for Drugs and Technologies in Health again recommends human insulin as first line therapy in Type 2 diabetes patients but rapid-acting analog insulin can be used first-line in Type 1 diabetes sufferers [104]. The German Institute for Quality and Efficiency in Health Care has stated that there are insufficient studies investigating the long-term effects of using insulin analogs and that rapid-acting and long-acting insulin analogs have no proven superiority over short-acting human insulin for Type 1 and 2 diabetes [105–108]. In New Zealand, insulin glargine and insulin detemir were only recommended with special authority criteria, although, there is now agreement to widen access to insulin glargine [109,110]. The WHO has found that some countries spend a significant amount of their drug budget on insulin analogs and there are problems with a lack of availability of human insulin. They have advised that insulin analogs offer no clinical advantage over human insulin and raise the concern that insulin analogs may not be cost effective in low- and middle-income countries [111].

Despite the wholesale shift to analog insulin in high-income countries, there is a lack of literature on the long-term efficacy and safety of insulin analogs. The methodological rigor of previous randomized controlled trials comparing human and analog insulin has been criticized, especially the over reliance on proxy measures of outcome as the primary end points [5,6,111]. Longer-duration randomized controlled trials are required to demonstrate whether insulin analogs are superior to human insulin for long-term patient-important outcomes, such as mortality, morbidity and quality of life. Until such evidence is available, adherence to prescribing guidelines would reduce the cost of prescribing insulin in diabetes.

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