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Should we Fear Insulin Therapy in the Treatment of Type 2 Diabetes?

David Haslam*

Bariatric Physician, Luton and Dunstable University Hospital NHS Foundation Trust, UK

Abstract: Obesity is the primary risk factor for the development of type 2 diabetes (T2DM) and, as the prevalence of obesity continues to increase, so does the incidence of type 2 diabetes. For most patients with T2DM, the disease will progress beyond the control of lifestyle measures, diet and oral glucose-lowering drugs. In these patients, insulin therapy is ultimately required to lower blood glucose concentrations to acceptable levels. 'Psychological insulin resistance' is a major barrier to the initiation of insulin therapy for patients with T2DM and for clinicians treating them. This may have a negative impact on patients' health and weight, and also the healthcare system due to increased incidence of diabetes-related complications if HbA_{1c} remains poorly controlled. Ensuring timely and appropriate initiation of insulin therapy requires physicians to recognize patients' fears and to reassure them. This review explores the concerns behind psychological insulin resistance and how they can potentially be addressed in light of recent developments in the treatment of diabetes.

Keywords: Clinical inertia, hypoglycemia, insulin therapy, psychological insulin resistance, psychosocial, type 2 diabetes.

SHOULD WE FEAR INSULIN? TREATING TYPE 2 DIABETES

Obesity is the primary risk factor for the development of type 2 diabetes (T2DM) [1, 2], and the increasing prevalence of obesity has foreshadowed a rise in T2DM diagnoses [3]. The prognosis for diabetes patients has improved significantly over the past century. Since the first successful clinical use of insulin in 1922, it has remained an essential aspect of diabetes treatment. As our understanding of the pathophysiology of diabetes and the influence of insulin has improved, so has the technology to address many of the therapeutic and safety issues that patients and clinicians face. The focus has shifted from simply prolonging life to improving quality of life and minimizing the adverse effects of diabetes and its treatment, presenting a challenge to be met by health practitioners and the pharmaceutical industry.

Type 2 diabetes mellitus is a progressive disease and, whilst oral glucose-lowering agents and injectable incretin-based therapies may successfully control blood glucose over a number of years, many patients ultimately require supplementary insulin to achieve glycemic targets and protect against complications. Despite the benefits – and sometimes the clinical necessity – of insulin, some physicians are reluctant to initiate therapy despite HbA_{1c} levels remaining well above guideline values [4, 5]. Surveys indicate that this problem is widespread, aggravated by the fact that up to a third of patients are unwilling to take insulin as prescribed [6, 7]: a situation termed 'psychological insulin resistance' (PIR) [5]. Delayed or suboptimal insulin therapy means that glycemic control deteriorates, with serious implications for prognosis by increasing risk of fractures, frailty, depression, cognitive decline, cardiovascular (CV) disease, blindness, kidney failure, amputations and premature death [8]. Added to this is the economic impact upon society through increased treatment costs and reduced productivity [9, 10].

Fear of hypoglycemia is a major reason behind reluctance to initiate insulin therapy, but there are other issues for *some* patients such as concerns over weight gain, fear of injections, inflexible injection schedules, the perception that the disease must be worsening or that they are failing to control their blood glucose, and social stigma [5]. Psychological insulin resistance also affects patients already receiving insulin and can result in poor adherence with treatment regimens; a large proportion of patients report skipping or reducing insulin doses following a hypoglycemic episode [11]. Whilst missing a dose may seem inconsequential, this is not the case. The impact of missed insulin doses on glycemic control was calculated using data on the relationship between blood glucose profiles and HbA_{1c}. Regularly skipping two bolus doses per week was shown to elevate HbA_{1c} concentrations by 0.3–0.4% points [12].

Recent advances in insulin therapy and other diabetes treatment technologies, however, provide an opportunity to revisit the concerns behind PIR and assess ways in which the barriers to initiating insulin might be overcome.

BENEFITS OF INSULIN

The primary benefit of insulin therapy is reduction of the risk of diabetes-related complications arising from high

*Address correspondence to this author at the Watton Place Clinic, 60 High Street, Watton-at-Stone, Hertfordshire SG14 3SY, UK;
Tel: +44 (0)1920 830784; Fax: +44 (0)1438 830005;
E-mail: dwhaslam@aol.com

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blood glucose concentrations. Insulin therapy is one of the most effective methods of achieving this goal. It is also possible to 'fine-tune' an insulin regimen to meet an individual's requirements, making it suitable for a wide range of patients.

Evidence that insulin yields improvements in microvascular outcomes in patients with T2DM came from the UK Prospective Diabetes Study (UKPDS), which evaluated the role of treating to intensive versus conventional glucose targets in recently diagnosed patients. UKPDS established that incidences of retinopathy, nephropathy and, to some extent, neuropathy are reduced by lowering blood glucose levels to a strict, aspirational target, which frequently required adding insulin to existing therapies. Patients treated intensively achieved a median HbA_{1c} of 7.0% (53 mmol/mol) compared with a median HbA_{1c} of 7.9% (63 mmol/mol) with conventional therapy. The overall rate of microvascular complications was decreased by 25%. The 10-year post-trial follow-up of the UKPDS study showed patients were still benefiting from their original intensive treatment despite a subsequent convergence of HbA_{1c} levels between the groups. Improvements in microvascular risk were sustained, with additional reductions in risk of myocardial infarction (MI) and all-cause mortality observed in those patients originally randomized to intensive treatment [13]. The conclusions from UKPDS have since been backed up by similar findings in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, in which insulin use was 41% in the intensive group compared with 24% in the standard group. Intensive glucose control, targeting HbA_{1c} of 6.5% (48 mmol/mol), was reported to decrease the incidence of microvascular events, primarily due to a 21% reduction in nephropathy, and was not significantly different in terms of major macrovascular outcomes or death compared with the conventional glucose control group [14].

While the microvascular benefits of tight glycemic control are unquestionable, evidence regarding the macrovascular benefits is conflicting. The ACCORD study shed doubt by inadvertently highlighting the potential risks of intensive treatment in patients with high CV risk profile, 77% of whom used insulin during the study compared with 55% in the conventional treatment group. During the trial, 28% of ACCORD subjects gained >10 kg of body weight. Not only did intensive glucose-lowering fail to reduce the risk of CV events compared with a less aggressive conventional treatment approach, it was actually associated with a 22% increase in relative risk of death ($p = 0.04$) [15]. Simultaneously, the Veteran Affairs Diabetes Trial (VADT) provided the first evidence of increased risk of death (hazard ratio [HR] 3.72; 95% confidence interval [CI], 1.34; 10.4; $p < 0.01$) and all-cause mortality (HR 6.37 [95% CI, 2.57; 15.8]; $p = 0.0001$) within 90 days following a severe hypoglycemic event. As with ACCORD, VADT failed to show improvement in CV risk for intensively treated patients, 86% of whom used insulin, compared with 73% in the conventional treatment group; however, it should be noted that participants had a relatively long duration of diabetes (11 years) before enrollment, alongside additional risk factors. Consequently, CV disease may have been too established for any benefit to be observed. Continuing follow-up did show a signal for reduced CV events in patients who had received intensive therapy. Therefore, whilst *treatment* had risks, there appeared to be possible long-term benefit from the *effects* of treatment [16, 17]. This theory appears to be validated by the recently published *post hoc* analysis of data from the Sibutramine Cardiovascular OUTcomes (SCOUT) trial. Surrounded by considerable debate about optimal HbA_{1c} for obese patients with T2DM at high CV risk, the SCOUT trial suggests that higher HbA_{1c} levels are associated with an increased risk of CV events and all-cause mortality, with the respective HRs increasing by 1.17 (95% CI 1.11; 1.23) and 1.16 (1.09; 1.23) per percentage-point increase in HbA_{1c} [18]. Thus, better blood glucose control was shown to result in improved CV outcomes, in an analysis that included patients using insulin [18].

The different populations under investigation in each of these trials might explain the discrepancy between results. The clinical practice implication is that striving for challenging blood glucose targets in newly diagnosed patients, as in the UKPDS study, has lasting prognostic benefits and is recommended. However, in patients with a longer duration of diabetes and a high CV risk profile, such as those purposefully selected for trials such as ACCORD, ADVANCE and VADT, strict glycemic targets may not be beneficial. In attempting to establish optimal HbA_{1c} targets in diabetes, one study observed that survival of patients on insulin is a function of HbA_{1c} presenting as a U-shaped curve, with lowest HR at 7.5% [19]. To mitigate the risks outlined by ACCORD and VADT, health professionals should individualize treatment goals based on their patient's risk profile, with higher HbA_{1c} targets recommended for patients with CV comorbidities [20, 21].

MAJOR CONCERNS AROUND INSULIN

Hypoglycemia

Hypoglycemia is one of the most feared side effects of insulin therapy and is a barrier to initiation. Hypoglycemia symptoms result from the physiological changes that occur to protect the brain when blood glucose falls below 3.8 mmol/L. They are unpleasant, but this provokes recognition and self-management, minimizing the severity of the event [22]. If the event is left unmanaged, neuroglycopenic symptoms occur, eventually leading to cognitive dysfunction [23]. For more than two decades physicians have been aware of the magnitude of patients' fear of hypoglycemia; a survey of 411 patients reported that their worries about severe hypoglycemia were ranked equivalent to serious chronic sequelae including blindness and renal failure [24]. Chronic anxiety about hypoglycemia may itself affect sleep, work, and social and home life [25]. Self-imposed limits on social functioning caused by the perennial fear of hypoglycemia are compounded by recommendations about consistency in mealtimes, physical activity, blood glucose monitoring, injection timings, and also legislative restrictions on driving [26]. Barriers to insulin initiation and intensification may not

only be patient originated, as 72% of primary care physicians and 79% of diabetes specialists have reported that they would treat patients more intensively if hypoglycemia was not a concern [27]. Given the concomitant effects of hypoglycemia, the lifestyle restrictions that hypoglycemia avoidance may require, and health professionals' dearth of clinical evidence with which to reassure patients, it is not surprising that some patients may resist insulin treatment.

On rare occasions, hypoglycemia can lead to serious complications, even death, although the challenges in identifying events that are directly linked to hypoglycemia in clinical practice make quantification difficult. While glucose supply to the central nervous system can be maintained during a short, mild hypoglycemic event, further or prolonged reductions in cerebral glucose supply can cause oxidative stress, disappearance of the brain's electrical activity and eventually neuronal necrosis [28]. This cerebral pathophysiology, as well as various other mechanisms, has been implicated to link severe hypoglycemia with CV-related mortality. For example, the sympatho-adrenal response to hypoglycemia involves the release of catecholamines, causing increased cardiac output, tachycardia and potentially arrhythmia. Patients with CV disease may also be at greater risk of endothelial dysfunction, coagulation anomalies and inflammatory responses as a result of hypoglycemia [29, 30]. Each of these responses can potentially lead to myocardial ischemia. Reassuringly, the UK Hypoglycaemia Study Group explored the hypothesis that diabetes type and treatment duration influence the risk of hypoglycemia, finding that both severe and mild hypoglycemia were far less frequent in patients with T2DM than in patients with type 1 diabetes [31]. They also found that during early use (<2 years) of insulin in patients with T2DM, the risk of hypoglycemia was little different to that observed in patients treated with sulfonylureas (SUs) (0.2 and 0.1 episodes per subject-year respectively). On this basis, rejecting insulin over continued use of SUs is illogical and may worsen prognosis [31]. Treatment intensification also appears to be implicated in increasing the risk of severe hypoglycemia, as suggested by the UKPDS, ADVANCE, ACCORD and VADT studies and confirmed in a recent single-center observational study [32].

The paradox is therefore clear: patients with diabetes can reap long-term benefits from intensive blood glucose control; however, such treatment protocols can increase the risk of severe hypoglycemia.

Weight Gain

Many glucose-lowering therapies increase body weight, which is a common reason for reluctance to begin insulin therapy. Approximately 80% of patients with T2DM are already overweight and, aside from mental or social concerns, there are important clinical considerations where weight gain is exacerbated. There are several mechanisms by which insulin therapy might promote weight gain, the best known of which is the retention of glucose calories that would previously have been 'lost' in the urine when blood glucose control is improved, resulting in the concentration falling below the renal threshold for elimination. Additionally, insulin is an anabolic hormone that inhibits lipolysis as well as promoting protein synthesis. Insulin lowers blood glucose largely by inhibiting glucose release by the liver. In contrast to endogenous insulin, which is secreted into the portal vein and transported directly to the liver where the majority is extracted, exogenous insulin is absorbed into the systemic circulation, resulting in comparative over-exposure of adipose and muscle tissue to elicit a similar glucose-lowering effect. Compared with endogenous insulin, exogenous insulin might therefore provoke greater lipid storage [33]. Furthermore, insulin-treated patients may indulge in 'defensive snacking', whereby they consume carbohydrate-rich foods in an attempt to prevent hypoglycemic events or when they perceive impending hypoglycemia. This creates a clinical challenge: patients with diabetes should reduce their calorie intake to limit weight gain, yet they are fearful of doing this due to the risk of hypoglycemia.

Injections

The burden of self-injection plays a significant role in patients' failure to adhere to an insulin therapy regimen. A survey found that ~20% of patients commonly, and intentionally, skip insulin injections and that fear of self-injection is the major driver of this behavior. Patients also cited daily injection frequency, planning daily activities around insulin injections, interference with activities of daily living, and pain and embarrassment as significant factors in omission of insulin injections. For some patients, the difficulty of adhering to rigid injection schedules is a concern. Not only are there practical issues with injecting at the same time every day (e.g. shift working or traveling), the social stigma of injecting in public is also a factor [34].

OVERCOMING FEAR OF INSULIN

Overcoming barriers to insulin treatment requires partnership working to strengthen the therapeutic relationship between the patient and healthcare professional, thereby fostering mutual trust to alleviate some of the concerns that surround the initiation of insulin treatment. Self-blame can be diminished by appropriately managing patients' expectations when T2DM is diagnosed, informing them that insulin treatment is likely to be required due to the progressive nature of the disease and the importance of not delaying treatment.

A significant proportion of primary care physicians in the US (68%) reported patient fear or resistance to insulin injections to be a major barrier to the decision to recommend initiation of insulin [35]. This highlights the need for health professionals to enquire about, and fully address, patient concerns at the outset and for the duration of treatment. Negotiation of treatment regimens directly with individual patients can increase adherence [36]. To achieve good glycemic control and address patients' fear of hypoglycemia, it is important to involve them in setting HbA_{1c} targets and creating individualized treatment regimens. This should include identifying and including the patient's personal goals. Lifestyle measures and oral glucose-lowering agents

remain first-line options for newly diagnosed patients; however, where insulin is required, patients can be reassured that new formulations may help in overcoming their fears.

Selecting the most appropriate insulin treatment can overcome many potential barriers. For many years, neutral protamine Hagedorn (NPH) insulin was the only basal insulin option. However, frequent hypoglycemic events drove the development of basal analogs designed to produce pharmacokinetic and pharmacodynamic profiles that more closely met physiological need. Both insulin glargine (Lantus®) and insulin detemir (Levemir®) resulted in far fewer hypoglycemic episodes than NPH, and in the case of insulin detemir, less weight gain [37, 38]. The recent approval of insulin degludec (Tresiba®) in the EU offers further convenience and reassurance for patients, especially those who fear hypoglycemia and the impact of insulin treatment on their daily lives. Insulin degludec is a basal insulin with a long duration of action that is derived from its unique mechanism of protraction. Insulin degludec's extended duration of action (>42 hours [39]) offers the potential for flexible dosing so patients can adjust timing of an insulin dose, occasionally, when it is inconvenient to administer insulin [40, 41]. In a clamp study, insulin degludec was shown to have four-times lower within-subject pharmacodynamic variability than insulin glargine [42]. This reduction in blood glucose variation and the flat time–action profile, with a terminal half-life of 25 hours [42], may be responsible for insulin degludec's association with a lower risk of hypoglycemia, particularly nocturnally, when compared with insulin glargine [43]. Concerns about a basal insulin with a duration of action exceeding 24 hours are unfounded, as steady state will be reached after 2–3 days, meaning that the number of units injected and eliminated daily are equal [44].

Concerns about weight gain may be alleviated by early referral to a dietitian to consider strategies to avoid this. Where appropriate, combining insulin with glucagon-like peptide-1 (GLP-1) receptor agonists, for example, enables the insulin dose to be minimized while providing greater glycemic control, a low risk of hypoglycemia and limited weight gain (and in some cases, weight reduction) [45–47]. With this in mind, there are a number of combination products in development, such as insulin glargine/lixisenatide and insulin degludec/liraglutide.

Insulin treatment initiation should include structured education and support from an experienced healthcare professional [19]. Diabetes educational programs have been shown to be associated with better psychological outcomes and higher levels of empowerment [48]. Structured education and ongoing support for people with diabetes, family members, healthcare professionals and society at large should focus on raising awareness of hypoglycemia. Patients and those who care for them can be empowered through knowledge about the causes and risk factors for hypoglycemia and how to prevent, recognize and treat them. Through greater support, knowledge and self-actualization, patients and healthcare providers alike may be released from the fear of insulin.

CONCLUSION

For the foreseeable future, insulin remains an essential therapy for diabetes. In accordance with the pathophysiology of the disease, lifestyle measures and first- and second-line treatment options should be exhausted before starting insulin; however, T2DM is a progressive disease and, over time, most patients will require supplementary insulin. Therefore, overcoming PIR is an important aspiration in improving patient care and reducing the economic burden imposed by the growing diabetes population. Although there are risks associated with insulin, the unsurpassed glycemic control it offers brings broad-ranging benefits. Ongoing advances in the development of glucose-lowering medications and medical devices, coupled with patient education, coaching and support, may be able to help address the challenges that patients face as a result of their busy modern lifestyles. Research into the clinical and lifestyle benefits of new insulin formulations and clinicians' growing experience of how they assist their patients may provide significant reassurance to those who are fearful of initiating insulin. This allows a new chapter on the treatment of T2DM to be opened, improving glycemic control and reducing the fear of insulin.

CONFLICT OF INTEREST

DH acts as advisor to Novo Nordisk, Sanofi, Boehringer Ingelheim, Bristol-Myers Squibb/AstraZeneca and Merck Sharp & Dohme.

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ABBREVIATIONS

CI	=	confidence interval
CV	=	cardiovascular
GLP-1	=	glucagon-like peptide-1
HR	=	hazard ratio
MI	=	myocardial infarction
NPH	=	neutral protamine Hagedorn

PIR = psychological insulin resistance

SU = sulfonylurea

T2DM = type 2 diabetes mellitus

VADT = Veteran Affairs Diabetes Trial

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