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Early use of insulin in type 2 diabetes

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Abstract

Type 2 diabetes is a disease characterised by peripheral insulin resistance, as well as by pancreatic beta cell dysfunction. This process is in part due to elevated blood glucose and free fatty acids – termed glucolipotoxicity. The traditional pathway of treating type 2 diabetes in a stepwise manner, beginning with life style modifications and continuing with oral hypoglycaemic agents leads to a protracted period of unnecessary hyperglycaemia. A new approach, targeted at alleviating the deleterious effects of hyperglycaemia and elevated free fatty acids by acutely lowering both with intensive insulin therapy, has yielded prolonged remissions in therapy in which only diet was necessary to maintain normoglycaemia. This new approach, its rationale, benefits and misgivings are discussed in this review.

Keywords: Early insulin treatment; Diabetes mellitus type 2; Glucotoxicity; Hypoglycemia

Insulin has been used since the 1920's for the management of diabetes mellitus. It is a life-saving therapy for patients with type 1 diabetes and plays an important role in achieving glycaemia control and decreasing the risk of chronic complications in patients with type 2 diabetes (T2DM). Most patients with T2DM eventually require insulin therapy because of the progressive nature of their disease and subsequent pancreatic beta cell dysfunction [1]. Unlike type 1 diabetes there is uncertainty regarding the optimal position of insulin among a wide range of different treatment options such as increased physical activity, dietary intervention and oral hypoglycaemics [2]. No longer considered as a purely salvage treatment, insulin use is increasingly being considered earlier in the disease process. Still in many instances, the time to initiate insulin therapy can be a contentious decision.

The traditional pathway for management of T2DM involves a stepwise approach, starting with lifestyle changes (with an emphasis on physical activity and dietary management) [3]. Failure to achieve normoglycaemia would lead to the commencement of an oral glucose lowering drug. Further on, and as shown in the United Kingdom Prospective Diabetes Study (UKPDS) blood glucose control continues to deteriorate, and in 2 years a second, and eventually a third oral hypoglycaemic agent would be needed [2]. To these one should

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add other treatment modalities such as lipid-lowering agents and antihypertensive drugs that are often required. Only when all else fails insulin would be added. When examined in a prospective, population-based study of over 7000 diabetic patients, this traditional stepwise approach revealed very low efficacy in maintaining normoglycaemia. By the time insulin therapy was begun, the average patient would accumulate 5 years with $HbA1_c$ of >8% and 10 years of $HbA1_c > 7\%$ [4].

Early insulin use would therefore imply a more intensive approach to maintaining normoglycaemia, perhaps starting with insulin as the first drug to be administered after lifestyle changes, or when management with the first oral agent fails. Further on, combination regimens of insulin and oral hypoglycaemics, may have a synergistic effect in establishing adequate blood glucose control. The optimal strategy for insulin add-on therapy is yet to be determined. One approach would be the use of a basal long acting insulin (Glargine or bedtime NPH) [5] to supplement oral drug therapy relatively early in the natural history of T2DM [6]. An alternative approach is to use a rapid-acting insulin analogue (Aspart-Lyspro) at mealtimes while leaving residual endogenous insulin secretion to maintain basal blood glucose control [7]. The choice of regimen might then depend on whether basal or post-prandial hyperglycaemia predominates.

1. The rationale and benefits of earlier insulin use

The pathophysiology of T2DM involves a combination of peripheral insulin insensitivity (also known as insulin resistance) and progressive beta cell dysfunction leading to a temporal decline in insulin secretion. Both these processes begin before the onset of hyperglycaemia [8], which develops only when increasing peripheral insulin demands fail to be met by the ailing beta cell.

Beta cell dysfunction is therefore a key pathophysiologic event in the development of diabetes. It is manifested in reduced conversion of proinsulin to insulin, altered patterns of insulin secretion and a quantitative defect in insulin secretion [9]. The subsequent development of hyperglycaemia further enhances these pathologic processes by beta cell glucotoxicity.

Beta cell dysfunction as a result of glucotoxictiy is a combination of several pathologic processes. The initial stage of glucotoxicity involves beta cell exhaustion (a depletion of insulin stores), and beta cell desensitization, both of which are rapidly reversed upon return to normoglycaemia [10]. Further on, elevated blood glucose levels cause an increase in the production of reactive oxygen species, causing havoc in the unusually free radical prone beta cell [10,11]. This is usually accompanied by elevated levels of plasma free fatty acids (FFA), inflicting further deleterious effects on beta cells [12–14]. The mechanism of these effects is most probably similar to free radical mitochondrial damage in the beta cell (i.e. glucotoxicity) [15]. These effects can be reversed by powerful antioxidants in in vitro conditions and in laboratory animals [16].

Oxidative stress exerts its deleterious effect in a few distinct pathologic processes. In the mitochondria, oxidative stress causes an elevation of uncoupling protein 2 (UCP2) and a subsequent reduction in glucose stimulated insulin secretion [17]. Reactive oxygen species cause post-transcriptional defects in several key genes, among them the PDX gene, causing a reduction in insulin gene expression and production [10]. These effects lead to an elevated beta cell apoptosis [18,19] and islet amyloid polypeptide (IAPP) deposition [20,21] with a subsequent reduction of up to 60% in beta cell mass [19,22]. Further hyperglycaemia-induced beta cell apoptosis can be attributed to activation of the Fas pathway and autocrine release of interleukin 1 beta (IL-1beta) [23].

Glucotoxicity is at least partially reversible. When intensive insulin treatment (up to near normoglycaemia) was administered to patients, whose treatment by maximal doses of oral hypoglycaemics failed, a significant improvement in beta cell function occurred [24–26]. Furthermore, when administered early in the disease, intensive insulin therapy for short periods (even as short as 2 weeks at a time) induced a long ''remission'' (up to 13 months) during which diet alone was sufficient to maintain euglycaemia [27–29].

Comparative evidence between insulin therapy and oral agents based on the UKPDS, suggested that microvascular disease could be reduced either by insulin or oral agents. A reduction in $HbA1_c$ was also [2] achieved. Still insulin did seem to have an advantage since oral agents often have a limited