Initiating Insulin in Type 2 Diabetes Mellitus: the Earlier the Better

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Diabetes mellitus is an insulin-insufficient state. Since insulin deficiency is the hallmark of type 1 diabetes, replacement therapy is the accepted and practiced primary treatment modality for this type of diabetes. In type 2 diabetes the deficiency is relative at onset, and evolves eventually toward absolute deficiency [1,2].

Treatment of type 2 diabetes is directed at the underlying pathogenic processes of insulin resistance and insulin deficiency and is dependent on the disease stage. To overcome insulin resistance several drugs were developed that directly increase post-receptor activity (metformin, PPAR-γ agonists), or indirectly by decreasing free fatty acids (metformin, PPAR-γ agonists), resistin (PPAR-γ agonists), or increasing adiponectin (PPAR-γ agonists). It is also possible to overcome the target tissue resistance to insulin by attaining high serum insulin levels either by using insulin secretagogues (sulfonyl urea, meglatindes, alanine, glucogon-like peptide 1, exendinn 4) or high doses of exogenous insulin. The deterioration of beta-cell function is paralleled by a failure of insulin secretagogue treatment, and initiating insulin therapy is necessary. Since insulin replacement seems to be an appropriate therapy for type 2 diabetes, the pertinent question is how early should insulin therapy be initiated in type 2 diabetes?

Three issues will be addressed in favor of early insulin treatment: a) which treatment modality better accomplishes the therapeutic goals of euglycemia – both pre- and post-prandial? b) which treatment modality has a more favorable effect on cardiovascular risk factors? c) safety issues regarding long-term use and cardiotoxicity of the treatment modalities.

Is insulin treatment the best modality to achieve euglycemia?

Early insulin treatment has the long-term advantage of preserving endogenous insulin secretion in patients with type 2 diabetes [3,4]. The preservation of beta-cell function is manifested by an increase in C-peptide levels and is associated with better control and fewer diabetes-associated complications. In addition, continuing C-peptide (insulin) secretion is important to avoid hypoglycemia [5]. Although the United Kingdom Prospective Diabetes Study (UKPDS) reported that not all treatment arms sustained the initial insulin (and thereby C-peptide) secretion, as assessed by the homeostatic model assessment (HOMA B), the endogenous insulin secretion (i.e., meal or glucagon test) in the insulin-treated patients was not assessed [5]. The progressive nature of type 2 diabetes is mainly due to the decrease in beta-cell function. Therefore, it is not surprising that therapeutic modalities based on beta-cell stimulation eventually fail. For example, in a UKPDS sub-study the rate of sulfonylurea failure in newly diagnosed type 2 diabetic patients was 53% within 6 years [6]. Early insulin treatment makes it possible to obtain and maintain the therapeutic glycemic goals in the long term [7,8]. The UKPDS [9] observed the same increase in glycosylated hemoglobin with insulin as with sulfonylurea treatment, and this finding is used to counterclaim the superiority of insulin therapy. However, the lack of better glucose control with insulin was mainly due to the strategy of insulin treatment; namely, aiming at reducing fasting glucose levels while not meticulously correcting the post-prandial glucose levels. With the new insulin analogues, achieving euglycemia is brought forward with less hypoglycemia and weight gain. Thus, the use of insulin early in the course of the disease can prevent the gradual deterioration of glycemic control, which necessitates a step-up approach to treatment, i.e., changing therapeutic modalities once a previous step fails [10].

Contrary to popular belief, insulin therapy was not found to impinge on the patients' well-being [3].

Is insulin atherogenic?

Unequivocally, diabetes-related microangiopathic complications are reduced by better glucose control regardless of treatment modality [1]. The association of macroangiopathy or atherosclerosis with hyperglycemia is more complex, as evidenced by observational studies showing that hyperglycemia was related to macrovascular disease, but the evidence is less compelling for the preventive role of glucose control in intervention trials [1,11,12]. A concern raised in the past regarding the direct atherogenicitiy of insulin [13–16] was based on *in vitro* studies and on cross-sectional data [17]; however, mounting recent evidence suggests that it is not the insulin per se that is atherogenic but the insulin-resistant state (marked by hyperinsulinemia) that increases the risk of coronary heart disease through other factors [18].

Type 2 diabetes, obesity and atherosclerosis were all recently shown to be associated with a pro-inflammatory state resulting

from an increase in inflammatory markers and cytokines [19,20]. Consistent data from Dandona and co-workers [20,21] point to the fact that insulin has an anti-inflammatory and potential anti-atherogenic effect. Mechanisms are related to the inhibition of cytokines such as tumor necrosis factor-alpha, C-reactive protein, and macrophage inhibitory factor, suppression of the expression of intercellular adhesion molecule-1 and monocyte chemoattractant protein-1, and the suppression of the intranuclear binding activity of nuclear factor-kappa (κB) and an increase in κB expression. Insulin also has a suppressive effect on regulatory factors of the matrix metalloproteinases. The latter are central in the initiation and rupture of the atherosclerotic plaque. It is postulated that the insulin-resistant state of the vascular cell attenuates the above insulin-induced anti-inflammatory and antithrombotic action similar to the reduction of adhesion molecule expression [22]. These data suggest that: a) early insulin treatment can overcome the tissue resistance to its anti-inflammatory and antithrombotic action, and b) given the effects of insulin on several cytokines in addition to its effect on free fatty acids and glucose, it seems that insulin itself has therapeutic advantages regarding atherosclerosis beyond tight blood glucose control.

Are sulphonylureas cardiotoxic?

Recently, the DIGAMI trial (Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction) found a 30% reduction in mortality when intensive insulin treatment was initiated during the acute phase of myocardial infarction, and the reduced mortality was maintained even after a mean follow-up of 3.4 years [23]. Speculation on whether the benefits were secondary to the use of insulin versus the withdrawal of sulphonylureas brought back into focus the debate regarding the cardiovascular safety of the sulphonylureas [24,25].

One of the potential underlying mechanisms for the cardiovascular risk associated with sulfonylureas has been the process of myocardial ischemic preconditioning, by which the myocardium protects itself from impending ischemic injury. This process depends on opening K channels, the same channels that are blocked by glyburide. Lee and Chou [26] recently demonstrated that the cardiotoxic effect of glyburide in patients with type 2 diabetes is caused by impairment of the myocardial ischemic preconditioning [26]. Although there are no compelling long-term studies and no clear-cut recommendations or contraindications for using sulphonylureas in diabetic patients with cardiovascular disease, it seems that insulin may be safer for use in diabetic patients.

Conclusions

With the increasing requirement for an early aggressive approach in order to obtain strict glucose and metabolic control for preventing microvascular and macrovascular complications, more and more patients with type 2 diabetes are potential candidates for intensive insulin therapy. Fortunately, the introduction of insulin analogs has created the potential for safer and more physiologic insulin therapy. The logical background is set for "the earlier the better approach" to insulin therapy.

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