Early insulin therapy and the risk of cardiovascular disease in Type 2 diabetes

`...there are favorable indications towards cardiovascular prevention and pathophysiologic benefits for initial exogenous insulin administration in Type 2 diabetic patients.'

Diabetes has reached pandemic proportions, with 171 million people currently affected worldwide [1]. This number is expected to more than double by the year 2030, to an incredulous figure of 366,212 million [1,2]. Furthermore, the prevalence of prediabetes, as well as undiagnosed diabetes, is also on the rise. A recent report from the UK indicates that more than a fifth of older white British men and women have either undiagnosed diabetes or impaired fasting glucose [3]. This global rise in the prevalence of diabetes and prediabetes is attributed to aging, obesity and sedentary lifestyle [2]. It is also associated with a rapid rise in cardiovascular disease (CVD), the major cause of morbidity and mortality in diabetes [4], with women and ethnic minorities being disproportionately affected [5]. Although the control of CVD risk factors in people with diabetes, such as hypertension and dyslipidemia, has been shown to reduce CVD risk, accumulating evidence indicate that only a minority of patients achieve optimal blood pressure, lipid and glycemic control [6,7]. Therefore, therapeutic agents that help reduce CVD burden in people with Type 2 diabetes are urgently needed. Among these agents, insulin has generated a lot of interest, as well as controversy [8-10].

Hyperinsulinemia & atherosclerosis

Based on the evidence that hyperinsulinemia is associated with atherosclerosis and increased CVD [11], and also based on early epidemiologic studies [12–14], a concern was raised as to whether insulin is actually atherogenic. For example, in the Helsinki policemen study, hyperinsulinemia predicted coronary heart disease (CHD), independent of other CVD risk factors. [14]. However, the predictive value of hyperinsulinemia decreased with lengthening follow-up time.

However, in the 1966 study of the population of Busselton, Australia, hyperinsulinemia predicted CHD in men aged between 60 and 69 years [12]. However, hyperinsulinemia did not predict CHD in men younger than the age of 60 years. In women, no association between serum insulin and CHD or cardiovascular disease could be found [12]. Furthermore, higher risk ratios were demonstrated at the higher blood sugar level of 200 mg/dl or greater. These findings indicate that hyperglycemia might explain the apparent association for hyperinsulinemia and CHD. Finally, in The Paris Prospective Study, a long-term study of CHD risk factors in a large population including 7028 men and 6093 women, major independent predictors of CHD death were:

- Blood pressure
- Smoking
- Plasma cholesterol level
- Fasting and 2 h postload plasma insulin level

In this study however, impairment of glucose tolerance, including overt diabetes, did not rank as an independent predictor for CHD [13].

While insulin resistance and compensatory hyperinsulinemia in the context of impaired glucose tolerance or Type 2 diabetes and associated insulin resistance is a predictor of CVD, neither endogenous hyperinsulinemia per se, nor exogenous insulin administration, appear to be associated with increased CVD risk [15-17]. For example, a low risk for CVD was found in a cohort of 70 patients with surgically proven insulinomas and documented hyperinsulinemia. In this study, there was no correlation between insulin levels and other components of the metabolic syndrome such as hypertension and increased triglycerides [15]. These data suggest that hyperinsulinemia does not increase CVD risk when associated low glucose levels and increased risk of CVD in the insulin resistance states might be conferred through hyperglycemia itself and or other components of the metabolic syndrome [4,11].

Exogenous insulin therapy was not associated with increased CVD risk. In the University Group Diabetes Program (UGDP) [17], there was no association between insulin therapy and

Therapy (2005) 2(5), 685-688







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CVD risk. In this study, there was actually a trend towards improved CVD risk with insulin treatment. The UGDP study consisted of three groups of Type 2 diabetes patients who were randomized to three different treatment strategies, these included diet and oral placebo, fixeddose insulin and variable insulin regimen, in which the latter was an intensive treatment. Although there was inadequate glycemic control within the study as a whole, patients defined to be in good control in the variable insulin treatment group had all-cause deaths of 17% compared with 21% in the standard insulin and 35% in the placebo group. Furthermore there was a trend towards CVD reduction in the variable insulin treatment group [17]. These data indicate that exogenous insulin administration does not increase CVD risk and that intensive glycemic control with insulin therapy might, in fact, decrease CVD risk.

In the UK Prospective Diabetes study (UKPDS) there was no increase in CHD events in the insulin arm, compared with conventional oral therapy [16]. In this study, there was also a trend towards reduced macrovascular disease with intensive glycemic control that did not reach statistical significance [16].

Benefits of insulin as initial therapy

Insulin has been shown to achieve optimal glycemic control in short-term intensive therapy in both lean and obese patients [8]. Furthermore, the use of insulin as initial therapy in the early stages of diabetes has been found to have long-term effects in achieving glycemic control up to 6 months after treatment was stopped and the patients remained on diet control [8,18,19]. In a study by our group, intensive glycemic control, including initial insulin therapy, for newly diagnosed African-Americans with Type 2 diabetes, was associated with long-term near normoglycemic remission of the disease [20]. This long-term benefit in glycemic control is probably due to the beneficial physiologic effects of insulin, such as preserving β-cell function, thereby improving insulin secretion and insulin resistance, as well as reversing glucose toxicity and lipotoxicity [8].

Insulin therapy is also beneficial in states of acute stress such as surgery, infection and acute illness [8]. Suppression of endogenous insulin secretion by counter-regulatory hormones is only likely to perpetuate hyperglycemia and glucose toxicity, an effect that cannot be reversed by insulin sensitizers or sulfonylureas [8].

Insulin therapy & CVD outcomes

The Diabetes mellitus Insulin–Glucose infusion in Acute Myocardial Infarction (DIGAMI) trial [21], lends credence to insulin improving cardiovascular outcomes. In this study, diabetic patients hospitalized for acute myocardial infarction were randomized to intensive insulin infusions versus conventional therapy (control group). The DIGAMI trial showed a 1-year allcause mortality reduction of 30% in the insulintreated group [21]. Most deaths were attributed to CVD in this study.

`...use of insulin...in the early stages of diabetes has been found to have long-term effects in achieving glycemic control'

Interestingly, those who had not had previous insulin treatment benefited the most in terms of improved 1-year mortality [21]. This study demonstrated a favorable outcome in cardiovascular mortality in those treated with insulin, and strongly suggests that exogenous insulin administration decreases CVD events in diabetic patients. However, the DIGAMI-2 trial, conducted to confirm the results of the DIGAMI trial, did not demonstrate a significant difference in total mortality and cardiovascular morbidity with insulin therapy compared with control [22]. The negative results of DIGAMI-2 might be explained by the lack of achievement of glucose targets in the intensive group. The results of the DIGAMI trial; however, were more or less reproduced in a prospective, randomized, controlled study involving adults admitted to surgical intensive care unit [23]. In this study, intensive insulin therapy to maintain blood glucose at or below 110 mg/dl reduced morbidity and mortality among critically ill patients [23].

Metabolic & cardiovascular effects of insulin therapy

The clinical beneficial effects of insulin therapy might be explained by a number of metabolic and cardiovascular effects of insulin (Box 1). These include potent acute anti-inflammatory effects such as a reduction in intranuclear nuclear factor (NF) κ B, which induces the transcription of proinflammatory cytokines, adhesion molecules and enzymes generating reactive oxygen species (ROS) in mononuclear cells [24]. In an *in vivo* study involving ten obese subjects, insulin was found to inhibit the

Box 1. Beneficial cardiovascular effects of insulin therapy.

- Decreased inflammation.
- Decreased reactive oxygen species (ROS).
- Decreased plasminogen activator inhibitor-1 (PAI-1).
- Improved platelet function.
- Decreased circulating free fatty acids (FFA).
- Decreased myocardial oxygen consumption.
- Stimulate nitric oxide formation by vascular endothelium.

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inflammatory processes of mononuclear cells by decreasing the transcription factor, NF κ B [24]. Further, insulin also stimulated the production of I κ B, an inhibitor of NF κ B and decreased p47phox subunit, a key protein of the NADPH oxidase complex. Insulin also suppressed the production of other inflammatory mediators, such as soluble intercellular adhesion molecule (sICAM)-1, monocyte chemoattractant protein (MCP)-1, and plasminogen activator inhibitor (PAI)-1. These effects point to the possibility that insulin has, in fact, an anti-atherogenic agent.

Insulin suppresses free fatty acids (FFAs) by directly inhibiting lipoprotein lipase activity [24,25]. This is particularly important in a setting of myocardial ischemia, in which there is an increased secretion of catecholamines, circulating FFAs and impaired glucose metabolism.

In ischemic conditions, oxidation of FFAs yield toxic free radicals, which may provoke arrhythmia, cell death and mechanical dysfunction [25]. Furthermore, exposure to elevated levels of FFAs has been shown to induce insulin resistance in liver and muscle cells thereby perpetuating the diabetic state [26].

Lastly, insulin stimulates nitric oxide, which promotes vasodilation, improves cell membrane stability, myocardial contractility and endothelial function [27]. Nitric oxide synthase (NOS) inhibitors (NG-methyl-L-arginine-NMMA [L-NMMA], and NG-L-argininemethyl-ester [L-NAME]) reverse the vasodilation produced by insulin *in vivo* and *in vitro*, indicating that most of the vasodilatory action of insulin is mediated by NO. Impaired NO formation by the vascular endothelium due to a

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decrease in insulin production has been implicated in the pathophysiology of diabetes thereby supporting the hypothesis that early insulin therapy can help in the prevention of the disease [27,28].

These data indicate that insulin has beneficial CVD effects that warrant consideration for initial or early insulin therapy in patients with Type 2 diabetes. Also, intensive glycemic control appears to decrease mortality, particularly cardiovascular death. However, there is no conclusive evidence as to whether insulin-mediated normoglycemia (or tight control of blood glucose) is superior to conventional therapy in terms of reduction of CVD risk reduction. Two large clinical trials are underway to help answer this question: the Action to Control CardiOvascular Risk in Diabetes study (ACCORD), which is evaluating the effects of intensive glycemic control on cardiovascular morbidity and mortality. This study; however, is not specifically designed to determine the effects of insulin administration on cardiovascular disease.

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The Outcome Reduction with Initial Glargine INtervention trial (ORIGIN), a multicenter, international, randomized study to evaluate the effects of insulin glargine versus standard of care in reducing cardiovascular morbidity and mortality in patients with impaired fasting glucose, impaired glucose intolerance, and early Type 2 diabetes mellitus will help to answer this question. Until then, there are favorable indications towards cardiovascular prevention and pathophysiologic benefits for initial exogenous insulin administration in Type 2 diabetic patients.

Acknowledgement

This work is supported by grants from the NIH, K12HD043428, BIRCWH to JN and SIM and by grant support from the American Diabetes Association, 7–05-RA89, to SIM.

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