Controversies in Management of Diabetes in Patients with Coronary Heart Disease

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Type 2 diabetes • Coronary heart disease • Insulin • Sulphonylurea • Selectivity

Abstract
A global epidemic of type 2 diabetes exists and in the near future it may be closely associated with an epidemic of cardiovascular disease. Since the diabetic population is at risk of developing cardiovascular disease, diabetes management should target tight glycaemic control. Two controversial issues in the management of diabetics with coronary heart disease (CHD) are discussed in this review. Firstly, exogenous insulin administration and increased risk of cardiovascular disease, and, secondly, the effect of sulphonylurea treatment on potassium ATP channels and risk of myocardial ischaemia. The consensus of opinion is that high circulating serum insulin level is simply a marker of an insulin-resistant state and therefore does not have a direct role in the pathogenesis of atherosclerosis in diabetic patients. However, overwhelming evidence exists for the linear association between worsening glycaemic control and increased risk for coronary heart disease. The United Kingdom Prospective Diabetes Study reported intensive blood glucose control decreased the risk of myocardial infarction by 16%. The benefits of tight glycaemic control outweighs the theoretical concept of hyperinsulinaemia being atherogenic. Safety concerns about sulphonylurea date back to 1970. The mechanism of action of sulphonylureas by closure of potassium ATP channels identified in pancreatic beta cells, cardiomyocytes and vascular smooth muscle cells caused great concern about safety because of the risk of developing myocardial ischaemia. Brief episodes of cardiac ischaemia render the heart more resistant to subsequent ischaemic events, this phenomenon is called ‘ischaemic preconditioning’. Activation of potassium ATP channels completely mimicked the preconditioning phenomena; moreover, blocking these channels with some of the sulphonylurea compounds abolished this protective effect. The concept of selectivity of sulphonylurea compounds therefore emerged and the choice of drug should be based on this fact. Every compound should be studied individually for its efficacy and safety vis-à-vis the relevant end points for type 2 diabetes, i.e. cardiovascular morbidity and mortality.

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Introduction

Existence of the global epidemic of diabetes mellitus is well known since over 150 million people worldwide suffer from the disease and a conservative estimate is that this number will be doubled by the year 2025 [1]. Type 2 diabetes accounts for most of the current and the predicted figures, and its close association with cardiovascular disease seems to emerge from a common soil, insulin resistance. Hence, it is believed that in the near future this global epidemic of type 2 diabetes will be closely associated with an epidemic of cardiovascular disease. Furthermore, diabetes mellitus increases mortality risk and reduces life expectancy, the leading cause of death being cardiovascular disease [2, 3]. The 16-year follow-up of the Framingham study [4] demonstrated an equal risk of cardiovascular morbidity and mortality among diabetic men and women. Since the diabetic population is at risk of developing cardiovascular disease, the approach to diabetes management should target a tight glycaemic control because of the recent evidence for its beneficial effects [5, 6]. In this paper, two controversial issues concerning the management of diabetics with cardiovascular disease are reviewed.

Exogenous Insulin Administration and Cardiovascular Risk in Type 2 Diabetes mellitus

Early epidemiological studies [7, 8] reported insulin as an independent risk factor for cardiovascular disease. The 5-year follow-up analysis of the Helsinki Policemen Study [9] supported the hypothesis that high circulating level of insulin is related (although probably indirectly) to an increased incidence of complications of atherosclerosis such as myocardial infarction and angina pectoris. A current controversial issue is whether intensive insulin treatment of diabetes decreases the risk for cardiovascular complications by lowering glucose levels or increases the risk by postulated direct atherogenic effects of high circulat ing levels of exogenous insulin.

A growing number of investigators believe that the high circulating serum insulin level is simply a marker for an insulin-resistant state and therefore does not have a direct role in the pathogenesis of atherosclerosis. Although some in vitro experiments and animal models of atheroma formation have shown that high insulin level leads to accelerated plaque formation [10, 13], clinical evidence does not exist as yet. A substantial amount of indirect data suggests that hyperglycemia may have a causal role in atheroma formation [14, 15] and may have a prothrombotic effect on the coagulation cascade [16]. Improved glycemic control has been shown to lower low-density lipoprotein cholesterol levels [17, 18], which theoretically should lower the risk of developing CHD for patients with diabetes. Prospective epidemiologic studies [19, 20] that had analyzed the relationship between the fasting blood glucose (FBG) level or the glycosylated haemoglobin A1c (HbA1c) level and the risk of CHD showed a linear association between worsening glycaemic control and an increased risk for CHD, although Singer et al. [21] disagreed. In the most compelling study, the Wisconsin Epidemiological Study of Diabetic Retinopathy, investigators analyzed cause-specific mortality over a 10-year period and found that death due to CHD was much more common in patients with worse glycemic control (relative risk, 1.10 for each 1% increase in HbA1c; 95% confidence interval, 1.07–1.17) [22] than in others. In 3 randomized controlled trials of glycemic control in type 2 diabetes, a sufficient number of cardiovascular events were recorded to make meaningful comparisons between treatment groups. Too few events were recorded in the Kumamoto study [23] because of the exclusion of patients with hypertension, hypercholesterolemia and obesity. In the University Group Diabetes Program (UGDP) [24], no significant difference was found in the rate of myocardial infarction between the intensive and conventional treatment groups (20.6 vs. 20.2%, respectively, p = 1.00, Fisher’s exact test), despite a much higher prevalence of cardiac risk factors in the intensive treatment group. A shorter study, ‘Diabetes mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction Study Group (DIGAMI) [25]’, tested the hypothesis that intensive metabolic treatment with insulin glucose infusion followed by multidose insulin treatment in patients with diabetes mellitus and acute myocardial infarction improved the prognosis. The authors concluded that insulin treatment in diabetic patients with acute myocardial infarction improved long-term survival by nearly a third, and the effect seemed to last for at least 3.5 years. Much more importantly, the absolute reduction in mortality was 11%, implying one saved life for 9 patients treated according to the insulin glucose infusion protocol. The reduction in mortality was most apparent in patients without previous insulin treatment and at a low cardiovascular risk.

The United Kingdom Prospective Diabetes Study (UKPDS) [6] projected to have a 91% power to detect 20% treatment group difference in the first cardiovascular outcome among the type 2 diabetic population reported that an intensive blood glucose control policy
with an 11% reduction in median HbA1c over the first 10 years decreased the risk for myocardial infarction by 16% (p = 0.0052), including non-fatal and fatal myocardial infarction and sudden death. The diabetes-related mortality and all-cause mortality did not differ between the intensive and conventional groups. The study did not have sufficient power to exclude a beneficial effect on fatal outcomes. It is commonly stated that insulin is a risk factor for atherosclerosis (cardiovascular or CHD) and in the insulin resistance syndrome, hyperinsulinaemia appears to be the motor that drives the other components of the syndrome – hypertension and dyslipidaemia [26]. Jarret reported several studies including his own analysis of the Bedford Study [27] that showed no significant associations with insulin levels and CHD in diabetes compared to the control group. A possible explanation is the significant associations between insulinemia and several well-documented risk factors of CHD: elevated blood pressure and very-low-density lipoprotein-triglyceride levels, reduced high-density lipoprotein-cholesterol levels, obesity, and visceral fat [28]. Furthermore, evidence exists that associations with cardiovascular risk factors are stronger for insulin-like molecules than for insulin itself [29].

An attractive hypothesis is that of Hales and Barker [30] which suggests a fetal origin for associations seen in later life, including those between insulin-like molecules and undoubted cardiovascular risk factors.

The benefits of tight glycaemic control outweigh the theoretical concept of hyperinsulinaemia being atherogenic and management should target associated risk factors: obesity, hypertension and hyperlipidaemia.

**Does Sulphonylurea Treatment of Type 2 Diabetes mellitus Contribute to the Cardiovascular Risk?**

Historically, the concern about the safety of sulphonylurea (SU) dates back to 1970 when the UGDP [31] concluded that tolbutamide treatment caused increased cardiovascular mortality, a study which at the time led to curtailment of oral antidiabetic treatment in USA, but was received with scepticism in Europe. Later criticism of its methodology reduced the impact of the study. However, the question of the safety of SU in type 2 diabetic patients with CHD has been reopened because of new experimental data. SU has been prescribed by three generations of diabetologists. SU provided alternative therapy to insulin for type 2 diabetes. However, despite their relatively long use it is only recently that the mechanism of action of this therapeutic class of drugs at molecular level has been clearly understood. Sulphonylureas stimulate insulin secretion in type 2 diabetic patients by blocking ATP-sensitive K\textsubscript{ATP} channels in the pancreatic \(\beta\)-cell membrane by binding to the SU receptor (SUR1) subunit of the channel. K\textsubscript{ATP} channels are also present in a range of extrapancreatic tissues, but may contain alternative types of SUR subunit (SUR2A in heart and SUR2B in smooth muscle). The SU sensitivity of K\textsubscript{ATP} channels varies with the type of SUR subunit: thus, glibenclamide and tolbutamide potently block the \(\beta\)-cell (SUR1), but not the cardiac (SUR2A) or smooth muscle (SUR2B) types of K\textsubscript{ATP} channel. In contrast, glibenclamide and glimepiride block all three types of K\textsubscript{ATP} channel with similar potency. Therefore, administration of a SU compound such as glibenclamide that has a K\textsubscript{ATP}-channel-blocking effect should be expected to increase ischaemic damage and abolish the protective action of channel openers.

It is known from in vitro as well as in vivo studies that activation of K\textsubscript{ATP} channels constitutes an important cardio-protective mechanism against ischaemic damage. Since the discovery of K\textsubscript{ATP} channels in the heart [8], numerous investigators have evaluated their role in cardiac adaptation to ischaemic insults. The high levels of ATP in the normal cardiomyocyte probably keep most K\textsubscript{ATP} channels in the closed state [32], but these are opened when the level is lowered thereby leading to multiple changes in cardiac metabolism, electrical activity and mechanical function, which results from ischaemia. Soon after the onset of ischaemia, activation of outward flow of K\textsuperscript{+} currents through the K\textsubscript{ATP} channels results in earlier repolarization of the myocyte and shortening of the action potential, which leads to a reduction of calcium influx through voltage-gated calcium channels [38–41]. The resulting decrease in contractility protects the ischaemic cardiomyocyte by reducing its oxygen demand. In addition, opened arterial wall K\textsubscript{ATP} channels during ischaemia decrease the vascular resistance, thus increasing coronary blood flow [42, 43]. Another consequence of ischaemia is intracellular accumulation of adenosine derived from the breakdown of ATP, which may leak out from cells and activate plasma membrane-A1 receptors in an autocrine manner, thus leading to opening of K\textsubscript{ATP} channels [44, 45]. Adenosine has been suggested to be a major cardio-protective agent, it seems to mediate its effect through a variety of mechanisms, including direct vasodilatory and anti-arrhythmic actions, attenuation of the heart response to sympathetic stimuli, inhibition of platelet aggregation,
and reduction of free radical formation [46–48]. The latter may be specially important in the protection against post-infarct reperfusion injury, believed to be caused by the burst of free radicals on reoxygenation.

Brief episodes of ischaemia render the heart more resistant to subsequent ischaemic events, with marked reduction in infarct size and contractile dysfunction [49, 50]. This phenomenon, called ‘ischaemic preconditioning’, operates in most species including man [51, 52]. Activation of $K^+_\text{ATP}$ channels completely mimicked the preconditioning, moreover, blocking the channels with antagonists such as glibenclamide abolished the protective effect of preconditioning [53, 54]. Adenosine also seems to be important for preconditioning: short-term infusion of adenosine reduced the extent of myocardial necrosis in dogs with the same efficacy as preconditioning, the effect being mediated through a $K^+_\text{ATP}$-channel-related mechanism, blocked by glibenclamide pretreatment [55, 56]. Preconditioning is not limited to the heart, it is probably a major protective mechanism in many other tissues.

The other effects of SU on cardiovascular risk factors should be taken into consideration, namely lowering lipid levels. It has been shown that SU lowers plasma total cholesterol, total triglyceride, VLDL cholesterol, LDL cholesterol and apolipoprotein B [57]. In some [58] but not all [59] studies HDL cholesterol was lower in patients treated with insulin, despite comparable glycaemic control. Most of these investigations were conducted with gliclazide. In addition, gliclazide has been shown to inhibit thrombus formation, improve fibrinolysis and reduce platelet adherence and aggregation [60].

The UKPDS study [6] recruited 3,867 newly diagnosed type 2 diabetic patients into a multi-centre randomized controlled trial that sought to compare the effects of intensive blood glucose control (with SU or insulin) with conventional treatment (diet) on risk of microvascular or macrovascular complication in diabetes. A total of 1,138 patients and 2,729 patients were, respectively, assigned conventional and intensive treatment in 23 centres in the UK. The study end-points were: diabetes-related end points, diabetes-related death, and all-cause mortality. The results suggested that intensive blood glucose control significantly decreased the risk of microvascular, but not macrovascular disease in patients with type 2 diabetes. There was no particular adverse cardiovascular risk with SU or insulin. It would therefore appear that the potential advantage of SU in modulating hyperglycemia far outweighs any theoretical risk from a postulated increased liability to macrovascular disease.

### Conclusion

A great deal of evidence exists that an elevated glucose level alone has been shown to be a risk factor for cardiovascular complications in individuals with diabetes mellitus, most notably demonstrated in the UKPDS and that lowering glucose levels reduces this risk. Therefore, our clinical target should be tight glycaemic control either by insulin therapy or oral hypoglycaemic agents. The choice of a SU agent should be guided on the basis of its selectivity for $K^+_\text{ATP}$ receptor in particular in the diabetic patient with documented CHD. Every SU drug needs to be studied individually for its efficacy and safety vis-à-vis the relevant end points for type 2 diabetes, i.e. cardiovascular morbidity and mortality rather than study being limited to surrogate markers. Besides glycaemic control, multiple risk management policy that includes obesity, hypertension and hyperlipidaemia would be of utmost importance.

Moreover, most studies indicate that second generation SU may have positive effects on lipid metabolism, platelet function and the coagulation system, hence on the accelerated atherosclerosis of the diabetic. The relative contribution of improved metabolic control has been proven and should be targeted by clinicians. On the basis of currently available data it is difficult to delineate the exact role played by SU in diabetic subjects with CHD. Several million diabetic patients, at an age bracket where cardiovascular morbidity is a realistic expectation, are treated with SU derivatives. It is of utmost importance to determine unequivocally whether SU are beneficial or deleterious for these patients. Therefore, large-scale, well-designed prospective studies are urgently needed to determine the benefit or harmful effect of SU and to define their role in the treatment of diabetic patients with CHD.
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References


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