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MEETING CONTRIBUTION

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Epidemiology of cardiovascular complications in type 2 diabetes mellitus

Abstract Type 2 diabetes is increasing in epidemic proportions worldwide, and is strongly associated with atherosclerotic cardiovascular disease (CVD). Hyperglycaemia increases risk of CVD, but glycaemic control does not substantially reduce CVD risk. There are several potential explanations for this apparent paradox, including the roles of the metabolic syndrome and post-load hyperglycaemia in the association of type 2 diabetes and CVD.

Key words Epidemiology • Risk factors • Type 2 diabetes • Cardiovascular disease • Insulin resistance • Prevention

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Type 2 diabetes mellitus is very common, and its prevalence is rapidly accelerating worldwide, with rates expected to increase more than 165% by 2050 in the U.S. and with global prevalence rates expected to reach 5.0%–7.6% by 2025 [1, 2]. The epidemic of diabetes and its complications confers major burdens on human health and healthcare costs, particularly from atherosclerotic cardiovascular disease (CVD) [3, 4].

CVDs, including heart disease (CHD), peripheral vascular disease, and cerebrovascular disease, are the major causes of morbidity and death in type 2 diabetics [5, 6]. CVD events occur over twice as frequently as do the microvascular events specific to diabetes, and fatal CVD events may be as much as 70-times as common as fatal microvascular events [7]. Data from the FINMONICA Myocardial Infarction Register showed that during 1988–1992 the overall risk of CHD death among diabetic men relative to non-diabetic men was increased by 38%, the out-of-hospital mortality relative risk was increased by 25%, the 28-day mortality relative risk of hospitalized men was increased by 58%, and the 1-year mortality relative risk of 28-day survivors was increased by 97% (all $p \leq 0.05$). Relative risks were even higher among women with diabetes [8]. Excess risk for death after myocardial infarction has persisted over time, with about a 2-fold increased risk relative to non-diabetic subjects persisting from the "pre-coronary care unit era" through to the present "thrombolytic era" [9]. Follow-up for over 30 years among subjects of the Framingham Heart Study has shown a 2- to over 10-fold excess risk of CHD, intermittent claudication, stroke, heart failure, and CVD death among subjects with diabetes compared with non-diabetic subjects [10]. Women with diabetes have had consistently higher excess risk for CVD than men in the Framingham Heart Study.

Other longitudinal data have shown that subjects with diabetes but without clinical CVD have experienced the same increased risk of CHD mortality (as much as 2.5% per 100 person-years) as non-diabetic subjects with a prior his-

tory of CHD (about 2.5% per 100 person-years) [11, 12]. This observation has raised diabetes to the status of a CHD risk equivalent (that is, raised the recommendation that *all* patients with diabetes should be managed as if they have clinical CVD) [13] and focuses on CVD risk reduction as a primary target in type 2 diabetes management. Medical management in type 2 diabetes has traditionally focussed primarily on glycaemic control, where hyperglycaemia has a graded, positive association with risk of CHD and stroke that extends even into the high-normal range of HbA_{1C} [14]. However, intensive glycemic control in the large UK Prospective Diabetes Study (UKPDS), a randomized, controlled trial of intensive versus conventional glucose-lowering strategies, did not result in a significant reduction in CVD events or death [15]. These data pose a paradox: if hyperglycaemia is so strongly associated with CVD – then why doesn't glycaemic control reduce CVD events?

There are several potential explanations for this paradox, of which two are reviewed here. The first is the hypothesis of "common soil": that type 2 diabetes and CVD arise together from a common antecedent pathophysiology, such that medical control of diabetes cannot be expected to reduce risk of CVD [16, 17]. This common soil is thought to be the "insulin resistance syndrome" or the "metabolic syndrome" [18]. The second explanation is that post-calorie load hyperglycemia is a stronger CVD risk factor than fasting or average hyperglycemia [19].

One of the first epidemiological analyses supporting the concept of the metabolic syndrome came from the San Antonio Heart Study, where elevated levels of several CVD risk factors –body mass index, blood pressure, glucose, and insulin, and low levels of HDL cholesterol – preceded the incident development of type 2 diabetes over 8 years of follow-up of initially non-diabetic Mexican Americans [20]. More recently, investigators in the Nurses' Health Study demonstrated that risk of CHD itself increased in a graded fashion comparing non-diabetic women prior to a diagnosis of type 2 diabetes, women with new, incident diabetes, and women with diagnosed diabetes at baseline. Risk of CHD events was increased even 15 years prior to the eventual diagnosis of type 2 diabetes [21].

It is now well accepted that most CHD risk factors are also type 2 diabetes risk factors, and that the ten or so measurable CVD risk factors comprise 3 or 4 clinically recognizable phenotypes that together define the metabolic syndrome [22]. Specific diagnostic thresholds for the co-occurrence of obesity (especially central obesity), hyperglycaemia (and insulin resistance, if measured), low levels of HDL cholesterol and elevated levels of triglycerides, and hypertension have been proposed for the metabolic syndrome by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) and the World Health Organization [13, 23]. The metabolic syndrome has recently been shown in Finnish men to double the risk of CHD and all-cause death relative to men without the syndrome [24]. However, in American Indians in the Strong Heart Study, the metabolic syndrome doubled the risk of incident diabetes, but after adjustment for CVD risk factors did not increase the risk of incident CHD, relative to participants without the metabolic syndrome [25]. Similarly, in preliminary analyses of Framingham Offspring Study participants, the metabolic syndrome was associated with a >10-fold increased relative risk of incident type 2 diabetes, but only a 2-fold increased relative risk of incident CHD or CVD. Whether the metabolic syndrome, or associated insulin resistance, proves to be a true independent CVD risk factor remains to be definitively determined. However, from the perspective of CVD in type 2 diabetes, it is clear that traditional CVD risk factors are the major contributor to CVD risk. A meta-analysis of diabetic groups in 18 CVD prevention trials published as of 2000 showed a significant ~40% relative risk reduction in CVD events associated with intensive cholesterol and blood pressure control, but no significant effect of intensive glucose control [26].

Another explanation for the paradox of glycaemic control in type 2 diabetes is that all glucose-lowering trials to date have focussed on control of fasting or average glycaemia (as assessed by HbA_{1C}). However, it is increasingly recognized that post-load hyperglycaemia is an important CVD risk factor, perhaps stronger than either fasting or average hyperglycaemia [19]. Recent data from longitudinal oral glucose tolerance testing in the Baltimore Longitudinal Study of Aging (BLSA) have shown that among 488 subjects with normal glucose tolerance at baseline (over half of whom were followed for at least 10 years), at 10 years of follow-up, only 14% had progressed to a fasting plasma glucose level ≥6.1 mmol/l but 48% had progressed to 2-h post-challenge glucose level ≥7.9 mol/l. Overall, 10 times as many subjects progressed to an abnormal 2-h post-challenge glucose level than to an abnormal fasting plasma glucose level [27]. These data support the hypothesis that the pathophysiology underlying post-load hyperglycaemia has a natural history distinct from the pathophysiology determining fasting hyperglycaemia. In a preliminary BLSA analysis dividing "progressors" to abnormal glucose tolerance into four categories: non-progressors, progressors by fasting plasma glucose only, progressors by 2-h post-challenge glucose only, or progressors by both fasting and 2-h glucose, subjects progressing by 2-h glucose (alone or also by fasting glucose) had a greater mean number of metabolic syndrome traits [2] and a higher CHD cumulative incidence rate (15%–17%) compared with non-progressors or fasting glucose-only progressors (1 metabolic syndrome trait and 8% CHD incidence rate, both $p<0.002$) [28]. In an analysis of 118 Framingham Offspring Study CVD events occurring over 12 242 person-years of follow-up, 2-h post-challenge hyperglycaemia increased risk for CVD events independently of both fasting and average hyperglycemia. For each unit increase of 2.1 mmol/l in the 2-h post-challenge glucose level, the risk for CVD was 1.14 (95% CI, 1.17–1.72), but with fasting glucose considered in the same model, a 0.7

mmol/l increase in the fasting glucose level did not increase risk for CVD (RR=0.87; 95% CI, 0.7–1.0). Similar results were obtained when the 2-h post-challenge glucose was modeled together with levels of HbA_{1C} [29]. These findings suggest that if glycaemic control in type 2 diabetes is associated with risk of CVD, then interventions that focus on control of post-load hyperglycaemia may be required to show the effect. A proviso is that the epidemiological data has examined post-oral glucose load hyperglycaemia, while in practice the exposure to be modified is post-meal hyperglycemia and hypertriglyceridaemia. Whether the epidemiological data will translate into a true beneficial treatment effect can only be answered by clinical trials.

In summary, current evidence supports the contention that CVD is the major complication to be prevented in type 2 diabetes. Although epidemiologically associated with CVD, control of fasting or average hyperglycaemia has had, at best, modest effects on CVD risk reduction. This is due, in part, to the fact that type 2 diabetes and CVD appear to arise together over time from a common antecedent, such that by the time type 2 diabetes is clinically apparent, CVD may also already be present. In this case, glucose lowering alone cannot be expected to substantially prevent clinical CVD. However, the standard CVD risk factors so highly correlated with type 2 diabetes in the form of the metabolic syndrome, especially hypertension and hyperlipidaemia, are targets for CVD prevention interventions. Abundant clinical data support the value of an aggressive focus on standard CVD risk factor control in type 2 diabetes. If aggressive glycaemic control in type 2 diabetes can reduce risk of CVD, then the strategy may need to focus on control of post-load hyperglycaemia. Clinical trials are needed to adequately address this issue. Because the widening global epidemic of type 2 diabetes, continued development of strategies to control and prevent diabetes-associated CVD is an important clinical and public health priority.

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