Coronary Heart Disease in Diabetes : Role of Hyperglycaemia and Hyperinsulinaemia

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The ability to control glycaemia in patients with diabetes has resulted in a significant increase in their longevity. The major causes of morbidity and mortality in diabetics in the present era are vascular complications. While recent studies, including the Diabetes Control and Complications Trial (DCCT), have greatly enhanced understanding of the pathogenesis, prevention and treatment of microvascular disease, our understanding of the relative roles of different pathogenetic factors for macrovascular disease is still quite limited. This is not surprising, considering the complex interplay of interdependent factors that are involved in the process.

It has been suggested that atherosclerosis is initiated at a younger age and has a more rapid progression in diabetic patients. Coronary heart disease (CHD), cerebrovascular accidents and peripheral vascular disease are the results of the atherosclerotic process. It remains unclear as to whether these macrovascular disorders are truly complications of diabetes or are more in the nature of associations. In other words, is the onset of these complications before the onset of hyperglycaemia itself?

Data from the Joslin's clinic have provided us with much valuable information about the natural history of CHD in diabetes. The risk of CHD was estimated in a cohort of patients whose IDDM was diagnosed between birth and age 20 and who were followed for 20 to 40 years after diagnosis [1]. When mortality in this cohort was compared with data from the Framingham population, it was found that the CHD deaths first occurred early in the first decade in both the populations. However, when followed for 25 years, one-third of the IDDM patients died, whereas among the non-diabetics in the Framingham study, only 8% men and 4% women died of CHD [2]. A similar analysis of NIDDM patients (onset of diabetes between ages of 35-64 years) revealed increased mortality at the end of 4 years of follow-up as compared to age and sex-matched non-diabetics. The difference in mortality became progressively greater with increasing duration of follow-up [3].

Interestingly, in Pima Indians, who have a 1ow prevalence of CHD, high prevalence of diabetes does not increase the risk for CAD. This observation, coupled with the observation that age at onset of IDDM did not significantly influence the mortality pattern, suggests that the diabetic state cannot initiate atherosclerosis but can only accelerate the process [4]. This is quite compatible with our understanding of the atherosclerotic process which is initiated very early in life i.e. during infancy.

Role of Hyperglycaemia

While substantial data is now available on the role of hyperglycaemia in the pathogenesis of microvascular complications, data on its relationship with macrovascular complications remains largely confusing and conflicting. Recent studies from Finland have shed some light on this relationship. Two hundred and twentynine Finnish NIDDM patients, 65-74 years of age were followed for a period of 3.5 years. Baseline glycaemic control as measured by HbA_{1c} was the most important predictor of CHD mortality and morbidity. Long duration of diabetes without concomitant high HbA_{1c} increased CHD event rate considerably less than did high HbA_{1c} with a short duration of diabetes [5]. In another study, 133 newly diagnosed Finnish Type 2 diabetics were followed for a period of 10 years (1981-1991) and the impact of various risk factors was examined with univariate analyses. Fasting blood glucose at base line and fasting blood glucose and glycated HbA_1 at 5-year follow-up were higher in diabetic subjects who died of CHD during the study period [6].

Hyperglycaemia could aggravate CHD by several mechanisms. Hyperglycaemia alters vascular reactivity, platelet aggregation, clot formation and lysis and foam cell formation. All these factors enhance atherosclerosis. Hyperglycaemia predisposes to formation of advanced glycation end products (AGE). Increased uptake of AGE in vascular wall has shown to increase vascular permeability and decrease its vasodilatory response to nitroglycerin and acetylcholine [7]. AGE products also activate leucocytes or vessel wall cells to enhance production of oxygen metabolites that can promote lipoprotein oxidation. Glycation of matrix proteins afso increases their stability, thus promoting their accumulation, which is characteristic of hyperplastic diseases [8].

Normal endothelium synthesises substances that contribute to maintenance of vascular tone such as PGI_2 and endothelium derived relaxation factor (now identified as Nitric Oxide – NO). PGI_2 also inhibits

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platelet aggregation. Synthesis of NO is decreased and its removal increased by advanced glycation end products. Its inactivation by oxygen free radicals is also enhanced and this leads to increased vascular resistance and platelet adhesion to endothelium [8]. Decreased synthesis of PGI_2 also adds to vasoconstriction and vessel wall reactivity. Enhanced activity of protein kinase C in endothelial cells might contribute to synthesis of vasoconstrictor prostanoids [8].

Impaired endothelium mediated vasodilatation could result in hypertension and shear induced platelet aggregation. Reactivity of platelets and adhesion to vessel wall is enhanced by interaction with glycated LDL and increased levels of von Willebrand factor [9]. Altered metabolism due to decreased platelet polyphosphoinositide content causes enhanced release of thromboxane B_2 which leads to increased platelet aggregation. Hyperglycaemia leads to glucose auto-oxidation and release of free radicals. Free radicals activate platelets and moreover, oxidative stress decreases the activity of antithrombin III. Decreased synthesis of heparin sulphate also results in antithrombin III underactivity [10]. This, coupled with increased fibrinogen levels results in enhanced fibrin clot formation. Lipoprotein(a) is known to inhibit acitivity of plasminogen. Decreased fibrinolytic activity further increases the stability of the clot formed. Lipoprotein(a) levels are also increased in diabetics [10].

The macrophage is the precursor of the cholesterol engorged foam cell, characteristic of atherosclerotic lesions. LDL and VLDL isolated from diabetic patients are taken up by the macrophages and they induce cholesterol ester synthesis and accumulation giving rise to foam cells [11]. Hyperglycaemia and oxidative stress can increase monocyte binding to endothelial cells and thus result in accelerated atherosclerosis [12].

Role of Hyperinsulinaemia

Insulin resistance and hyperinsulinaemia are characteristic features of NIDDM. A state of hyperinsulinaemia is also often present in patients being administered insulin. The suggestion that hyperinsulinaemia per se could be an important factor in macrovascular disease has important implications for diabetics. Resistance to insulin mediated glucose uptake is associated with hyperinsulinaemia, hypertension, abnormal glucose tolerance, increased triglyceride levels and low circulating HDL-cholesterol. Also present are upper body obesity, hyperuricaemia and physical inactivity. This cluster of abnormalities (Syndrome-X plus) has been shown to predispose to CHD [13]. While most workers would agree that this cluster of abnormalities is in fact associated with an increased risk of CHD, several studies that have tried to use insulin levels per se as a predictor of CHD, have come up with highly variable results. In the Helsinki study, 1059 non-diabetic policemen aged 35-59 were followed for 14 years. Incidence of all CHD events were significantly increased in individuals with high post-glucose insulin levels [14]. Similarly, in the Paris Prospective study, 6903 non-diabetic policemen were followed for 15 years. At 11 years, CAD mortality was correlated to basal fasting and 2-hour post-glucose load insulin levels. At 15 years, only fasting insulin levels were associated with CHD mortality [15]. The Busselton study also showed a similar trend [16]. However, several studies reported recently do not confirm these observations. In the Gothenburg study, 644 men aged 67 years were followed for 8 years. The end-point was fatal or non-fatal CHD event or death due to some other cause. After exclusion of diabetic patients, no significant association was found in relation to basal fasting or post-load insulin levels with CHD mortality [17]. The Edinburgh and Pima Indian studies also failed to find any correlation between insulin levels and CHD morbidity or mortality [18, 19].

Similarly, in diabetics there are opposing views on insulin being an important independent determinant of CAD. The Veterans Administration (VA) co-operative study demonstrated that patients on intensive insulin therapy had more cardiac events in a 2-year follow-up [20]. On the other hand, the Bedford study (n=241, follow-up 10 years) and Pima Indian study (n=436, cross-sectional) concluded that there was no association between hyperinsulinaemia and risk of CAD in diabetics [19, 21].

There is plenty of experimental evidence implicating insulin in atherogenesis. The earliest comes from a study in which alloxan induced diabetic rabbits failed to develop arterial lesions but when these animals were treated with insulin, they developed cholesterol deposition in the arteries. Smooth muscle cells have been, shown to be playing a major role in atherogenesis as they are capable of accumulating lipids and laying down collagen matrix. Insulin and IGF-1 interact with IGF-1 receptors on vascular smooth muscle cell and enhance proliferation. Insulin probably serves as a comitogen in this process. Increased expression of platelet derived growth factor as a result of insulin action is also known to enhance IGF-1 expression [22].

Insulin resistance and hyperinsulinaemia correlate strongly with VLDL-TG secretion rate and plasma TG concentration. Once the pool of VLDL-TG increases, HDL levels are decreased. The strong

association of low HDL with CAD risk has been shown in many studies. Whether hypertriglyceridaemia is an independent risk factor for CAD is still controversial. The risk for CAD is further accentuated with increase in small dense LDL levels, which in turn is associated with insulin resistance. Another associated finding is that of post-prandial lipaemia [23]. Insulin stimulates the activity of 3-methylglutaryl-CoA reductase, a major enzyme in cholesterol synthesis. Binding of LDL to bovine smooth muscle cells is also enhanced by insulin. Hyperinsulinaemia inhibits the binding of HDL to its specific binding sites on human skin fibroblasts and thus retards the transfer of intracellular sterol to cell membrane and its transfer to HDL [24]. These actions may contribute to cholesterol accumulation and formation of foam cells. Plasminogen activator inhibitor-1 (PAI-1) levels vary directly with insulin resistance and are associated with recurrent myocardial infarction in younger men [10]. Hyperinsulinaemia and insulin resistance are associated with enhanced thrombus formation in response to endothelium injury: This coupled with low fibrinolytic activity accentuates the athero-thrombotic process.

Hypertension is known to accelerate atherosclerosis via endothelial injury and platelet aggregation. The role of hyperinsulinaemia in the pathogenesis of hypertension is plausible as several reports have indicated that patients with high blood pressure are relatively glucose intolerant, insulin resistant and have higher circulating levels of insulin. It is still not clear whether this association or relationship is a casual one. Available evidence points towards the fact that insulin is known to act on tubular cells resulting in sodium and fluid reabsorption. However, it remains to be proved whether this mechanism is active in the long-term. Increased CNS sympathetic activity and alteration in membrane ion transport systems has also been suggested [25]. Patients with insulinoma do not have raised blood pressure or lipid abnormalities [26]. This suggests that presence of insulin resistance is also essential if hypertension or dyslipidaemia is to result. Insulin increases the expression of the powerful vasoconstrictors and endothelins from the vascular endothelium of diabetic patients, resulting in increased peripheral resistance and blood pressure [27].

Conclusion

Why, one might ask, is there such discrepancy in the results of various studies on the role of insulin in the pathogenesis of macrovascular disease in diabetes? Many of these differences are related to the selection of subjects, while another major factor is the variability in study design. In addition, statistical analysis and interpretation of these studies is fraught with difficulties, since there are numerous risk factors, many of which are interdependent. The ultimate answer as to whether hyperinsulinaemia is involved in the pathogenesis of macrovascular disease remains unanswered - the final word on this subject has not yet been said. While Reaven and associates feel that insulin resistance and compensatory hyperinsulinaemia is important [23], critics of this hypothesis like Jarett have recently stated that "It is stressing the obvious to state that the risk factor status of insulinaemia in terms of subsequent CHD is at best weak and at worst non-existent" [28]. Perhaps it would be best to quote Fontbonne, whose Paris study was the first to really put insulin on the map - "having put insulin on trial has served double purpose; it has found no evidence of guilt and it has revealed that insulin can nevertheless indicate a situation of greater cardiovascular risk" [29]. In other words, while insulin is an important component of the Syndrome X, it may not be the primary or initiating event and may be just an indicator of increased risk.

What bearing do these findings have on practical management?

In 1995, the management guidelines in our opinion, should be as follows:

(1) Aim for normoglycaemia: use insulin if required. Since the evidence of the deleterious effects of hyperglycaemia on microvascular complications is irrefutable, there is likely to be at least some adverse effects on macrovascular disease too, specially in the light of recent Finnish studies. Thus, normoglycaemia is definitely desirable even at the expense of hyperinsulinaemia.

(2) Weight reduction (in obese diabetics) and exercise will reduce insulin resistance and also help in acheiving euglycaemia.

(3) One could conceivably argue against the use of diuretics and beta blockers in diabetics, since these drugs could enhance insulin resistance and use ACE-inhibitors instead [30], which might actually decrease insulin resistance.

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