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Coronary heart disease and diabetes mellitus

S. Fava*, J. Azzopardi*

ABSTRACT: Much of the excess mortality in diabetic subjects is due to cardiovascular disease. Diabetic subjects are at increased risk of developing coronary artery disease and have a higher case fatality after acute myocardial infarction and after unstable angina. Diabetes is associated with microvascular disease, accelerated atherogenesis and left ventricular dysfunction. We review the data on the epidemiology, pathogenesis and management of coronary artery disease in diabetic patients.

*Department of Medicine, St. Luke's Hospital, Gwardamangia

Correspondence: Dr S. Fava, Department of Medicine, St. Luke's Hospital, Gwardamangia, Malta

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Introduction

Diabetic patients have a 2-3 fold increased risk of cardiovascular mortality. This has been documented in the Framingham study [1] and subsequently confirmed by other investigators [2,3]. The increased atherogenesis in diabetic subjects is probably multifactorial; contributory factors include increased prevalence of dyslipidaemia [4-6], increased platelet adhesiveness and activation [7,8], decreased fibrinolysis secondary to increased plasminogen activator inhibitor [9,10], hyperfibrinogenaemia [11] and abnormal glycation of intimal proteins [12,13]. In addition to increased atherosclerosis leading to macrovascular (large vessel) disease, there is also a substantial body of evidence implicating a more specific microvascular disease in diabetic subjects [14-17]. It is thought that initially there is increased microvascular pressure and flow leading to microvascular endothelial injury and basement membrane thickening [18].

A particularly interesting aspect is that of insulin resistance in type 2 diabetes. Reaven hypothesised that insulin resistance and subsequent compensatory hyperinsulinaemia are the basic defects in the so-called syndrome X [19]. Only when the pancreas fails to secrete enough insulin to overcome peripheral resistance does clinical diabetes develop. Hyperinsulinaemia and insulin resistance are thought to predispose not only to diabetes but also to obesity, hypertension, dyslipidaemia and cardiovascular disease [20,21]. There is considerable evidence for the clustering of cardiovascular risk factors in patients with high fasting insulin levels [22,23]. Indeed there is also evidence that the increased cardiovascular risk in type 2 diabetic subjects predates the onset of diabetes [24,25]; this is consistent with the notion of hyperinsulinaemia being an independent risk factor. It is, however, not known whether hyperinsulinaemia and insulin resistance are the basic defects leading to increased risk of coronary artery disease or whether they are markers of a genetic predisposition. It should be noted that type 1 and non-obese type 2 diabetic patients are usually insulinopaenic. Hyperinsulinaemia cannot, therefore, be the sole mechanism involved.

Acute myocardial infarction

Approximately one third of all acute myocardial infarctions in Malta occur in diabetic patients. This has been documented by Zammit Maempel in 1978 [26] and more recently by Pullicino et al [27] and by our own group [28]. This proportion is much higher than that in other countries, such as the 16% reported in the Minnesota Heart Survey [29] and is consistent with a high prevalence of non-insulin dependent diabetes mellitus in Malta.

Not only do diabetic subjects have an increased prevalence of coronary artery disease but they also exhibit a higher case fatality after acute myocardial infarction (AMI). Early studies done before the advent of coronary care units showed a mortality of 40-60% in diabetic subjects [30,31]. Later studies showed that, although mortality had decreased, it was still higher than in non-diabetic patients. For example, in the Minnesota Heart Survey [29] the mortaltiy was 18.0% in diabetic males and 10.1% in non-diabetic males (there was no statistically significant difference in mortality between diabetic and non-diabetic females in this study).

As these studies were done in the pre-thrombolytic era, we investigated the effect of diabetes on mortality in the modern era in a prospective case-control study [28]. We found a three month mortality of 17.3% in diabetic patients compared to 10.2% in controls ($p<0.05$). Our data is consistent with that of the GISSI-2 trial [32] and International Tissue Plasminogen Activator/ Streptokinase Mortality Trial [33], both of which also showed a higher mortality in diabetic subjects. However, both these studies only considered patients receiving thrombolytic therapy. Those with contraindications to thrombolysis, who are more likely to have complications were excluded; this might have introduced a selection bias.

Left ventricular failure

We found that the prevalence of left ventricular failure after AMI was approximately twice as high in diabetic subjects as in controls (38.3% vs 16.8%, $p<0.001$) and the prevalence of cardiogenic shock approximately three times (9.7% vs 3.6%, $p<0.05$) [26]. This is similar to the data from the Minnesota Heart Survey [29] and that reported by Yudkin & Oswald [34]. It should be noted that left ventricular failure [35-37] and dilation [38] are strong predictors of an unfavourable outcome after AMI in the general population; this is possibly related to remodelling of the non-infarcted myocardium [39]. It is therefore probable that the excess mortality observed in diabetic patients with AMI is related to the increased prevalence of left ventricular failure; if this is so angiotensin converting enzyme inhibition might be particularly beneficial in diabetic patients.

It is interesting that the increased prevalence of heart failure in diabetic subjects occurs in spite of a similar infarct size [28,34,40]. There is evidence for the existence of non-ischaemic congestive cardiomyopathy in diabetic subjects [41-45]; this could be related to non-enzymatic glycosylation of myocardial proteins [45]. It is also probable that diabetic patients with AMI have more extensive coronary artery disease so that parts of the non-infarcted myocardium are ischaemic.

Thrombolytic data

In our study we found that only 23.5% of diabetic subjects compared to 34.2% of controls ($p<0.05$) received thrombolytic therapy [28] and that this difference was mainly due to the presence of proliferative retinopathy [46]. This aroused considerable interest. Commenting in a recent leader in the BMJ, Ward & Yudkin [47] have suggested that proliferative diabetic retinopathy should no longer be regarded as contraindication to thrombolysis (as is presently generally accepted). They point out that there have been only two case reports of ocular haemorrhage occurring after thrombolytic therapy: one in a diabetic patient [48] and the other in a non-diabetic patient [49]. This has to be set against the undoubted benefit of thrombolytic therapy in diabetic subjects [50]. However, intraocular haemorrhage following thrombolytic therapy in diabetic patients may be under-reported, especially if physicians regard it as a recognised complication. Furthermore, intraocular bleeding may be rare only because thrombolytic therapy is rarely given to those with proliferative diabetic retinopathy. In a retrospective analysis of 507 diabetic patients admitted with acute myocardial infarction, we found that of the 172 who received thrombolytic therapy, only 14 had diabetic retinopathy and none had proliferative changes. Of the 26 with proliferative retinopathy none received thrombolytic therapy [51].

Gray et al [52] and our own group [28] have shown that thrombolyzed diabetic patients are less likely than non-diabetic ones to show clinical evidence of reperfusion. The latter has been shown to correlate well with angiographic data [53]. The reasons for the less successful thrombolysis are unclear but could include a larger fixed stenosis, microvascular disease and resistance to thrombolytic agents due to abnormalities in the coagulation and/or fibrinolytic systems.

Risk stratification after AMI

An important aspect in the care of both diabetic and non-diabetic patients with AMI is that of risk stratification, namely the identification of those patients at the highest risk of further adverse events. This will help in the best utilisation of resources by selecting those patients most likely to benefit from aggressive management whilst at the same time avoiding unnecessary investigations in those who are at low risk.

As stated previously, the presence of clinical, radiological or echocardiographic evidence of left ventricular failure correlates very strongly with poor outcome [34-38]. It is important to detect these patients as they will benefit from angiotensin converting enzyme (ACE) inhibition [54-55].

Our group was the first to show the correlation of loss of heart rate variability to mortality after AMI in diabetic subjects [28]; this has also been confirmed in non-diabetic subjects and has been shown to correlate with the risk of arrhthymias [56,57]. Loss of heart rate variability can be detected with Holter monitoring. The latter technique is also useful in detecting myocardial ischaemia which is another predictor of an adverse outcome [58-59]. Holter monitoring is especially useful in the risk stratification of those who cannot undergo exercise stress testing.

In a study of 333 diabetic patients admitted with acute myocardial infarction, we found that blood glucose on admission correlates very strongly with mortality ($r = 0.92$, $p<0.05$) [60]. Interestingly, most of the excess mortality of diabetic patients with AMI occurred in those with hyperglycaemia. It is probable that hyperglycaemia after AMI is a marker of a stress hormone response but it is also possible that hyperglycaemia may itself be toxic to the myocardium. Whatever the mechanism, a high blood glucose can serve as an inexpensive, minimally invasive and readily available predictor of poor outcome in diabetic patients with AMI.

As in non-diabetic patients, exercise stress testing can also be used in risk stratification. A positive stress test is associated with poor outcome [61,62] and selects those patients requiring more intensive management.

Finally post-infarct angina is associated with an up to a 10-fold increased risk of early re-infarction and death [63,64,65]. These patients should therefore proceed to early angiography and possible revascularisation; there is usually little point in doing exercise testing in this group.

Circadian rhythm of AMI

There is currently great interest in circadian rhythms of physiological parameters in relation to occurrence of certain diseases. AMI shows a significant morning peak in non-diabetic subjects [66-68]; this is probably related to a morning increase in platelet adhesiveness [68,69], a morning decline in fibrinolytic activity [70,71] and a morning rise in arterial blood pressure [72,73] and in blood viscosity [74]. Interestingly, we have demonstrated in a prospective trial that diabetic subjects do not exhibit a significant circadian variation in the onset of AMI and we have suggested that this is due to blunting of diurnal variation in physiological parameters, such as blood pressure and blood coagulability [75].

Unstable angina

Unstable angina has been less extensively studied than AMI. In a prospective case-control study [76] we found that the three month mortality was 8.6% in diabetic patients and 2.5% in controls (p=0.14). The one year mortality was 16.7% in diabetic patients and 5.4% in controls (p=0.29). Two other studies [77, 78] have shown that diabetes is a predictor of adverse outcome after unstable angina; however both were part of a multiple subgroup analysis. In our study the frequency of AMI, coronary artery bypass grafting (CABG) and of further episodes of unstable angina were similar in the diabetic and control groups. Diabetic patients underwent coronary angiography and angioplasty less frequently than controls. This could be due to a higher frequency of ischaemia in diabetic subjects being silent. Indeed, of those who underwent coronary angiography, a higher proportion of diabetic patients needed CABG than controls. These data suggest that diabetic patients with unstable angina have more extensive coronary artery disease and that they should be more aggressively investigated. This might include Holter monitoring to detect silent ischaemia.

Conclusions

Diabetes mellitus is associated with an increased mortality and morbidity from coronary artery disease. One of the targets of the St. Vincent Declaration is to reduce death from coronary artery disease. This can be achieved by tighter glycaemic control and by modifying other risk factors for coronary artery disease. The latter includes stopping smoking, losing weight, treating hypertension and correcting dyslipidaemia by dietary manoeuvres and, if necessary, drug treatment. The landmark Diabetes Control and Complications trial [79] has shown that tight glycaemic control decreases cardiovascular mortality in type 1 diabetic subjects. There is evidence that this also applies to type 2 diabetic subjects [80-82].

Although diabetic patients may have small vessel disease, they are also at an increased risk of having large vessel disease. Diabetic patients with suspected ischaemic heart disease should therefore be investigated along the same lines as their non-diabetic counterparts. This is often rewarded by finding disease that is amenable to angioplasty or bypass grafting. It should be borne in mind, however, that the results of revascularisation procedures are worse in diabetic patients.

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