Cardiovascular complications in type 1 diabetes mellitus

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Abstract

Although the issue of cardiovascular complications in type 2 diabetic patients is widely discussed, and recommendations for such screening are available, it is less common to do so for type-1 diabetes. Yet, independent of age, the mortality rate due to ischaemic cardiac disease is higher among type 1 diabetic patients (both male and female) than in the general population. Type 1 diabetic patients have certain specific characteristics related not only to atherosclerotic plaque and cardiovascular risk factors, but also to their capacity for physical activity and to the prevention of cardiovascular complications induced by hypoglycaemia.

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1. Introduction

Although the issue of cardiovascular complications in type 2 diabetes is widely discussed, it is less common to do so in cases of type 1 diabetes. However, according to recent 2009 data provided by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies, concerning long-term complications (30 years) in type 1 diabetes, the cumulative incidence of cardiovascular disease was 14% in the conventional-treatment group and 9% in the intensive-treatment group [1]. The results observed in the conventional-treatment group are the same as those observed in the Epidemiology of Diabetes Complications (EDC) study [2]. Thus, cardiovascular disease is an important issue in type 1 diabetes.

2. Background

Results from the Diabetes UK cohort, a study that included more than 23,000 patients aged < 30 years old and receiving insulin therapy, followed for a mean of 17 years, showed that ischaemic cardiac disease is responsible for 8% of deaths before the age of 40 years and for 47% of deaths in men over that age, and 11% and 40% of deaths, respectively, in women [3]. When type 1 diabetic patients are compared with the general population, their rate of mortality is higher. Also, the rate of mortality in type 1 diabetic women is not only higher than in non-diabetic women, but is also dramatically higher than in non-diabetic men. Concerning the mortality rate due to cardiac
ischaemia in this population of type 1 diabetic patients, there is no difference between men and women aged <40 years. However, in those aged >40 years, the rate is higher in men than in women, although the difference is less marked than that seen in the general population. Between 20 and 29 years of age, a woman with type 1 diabetes has a 45-times greater risk of dying from ischaemic heart disease than does a non-diabetic woman of the same age and, between 30 and 39 years of age, the risk is 40 times higher.

3. Particularities of type 1 diabetic patients

In the Oslo study by Larsen et al. [4], 39 asymptomatic type 1 diabetic patients (60% male; mean age: 43 years; mean duration of diabetes: 30 years) underwent a stress test. Impaired stress tests were found in 15% of patients, even though none of these patients reported chest pain during the test. Coronarography was performed in 29 patients and revealed that 34% had a significant coronary lesion, with stenosis of >50% in one or more coronary arteries. In addition, intravascular ultrasound (IVUS) in these 29 patients showed that all had significant atherosclerotic lesions. Yet, in this study, none of the classical parameters—such as gender, hypertension, body mass index (BMI), tobacco use, microalbuminuria, triglycerides and high-density lipoprotein (HDL)—correlated significantly with the mean degree of stenosis observed in the IVUS. However, HbA1c levels did correlate significantly with the mean degree of stenosis after adjusting for age and total cholesterol. Thus, this study highlights three essential points:

1. there is a high prevalence of silent coronary atheromatosis in type 1 diabetic patients;
2. long-term glycaemic control is a significant predictor of coronary atherosclerosis;
3. sensitivity of the stress test in the detection of silent ischaemia is poor.

Indeed, in a third of these patients, coronarography showed vascular stenosis of >50%, whereas only 15% of patients had a pathological stress test. Evaluation of carotid intima–media thickness is a less invasive way to evaluate coronary atherosclerosis in diabetic patients. Nowadays, it is well known that the carotid intima–media thickness is linked to coronary atherosclerosis and is a predictive factor of coronary events [5]. Carotid intima–media thickness was increased in the type 1 diabetic patients in the Oslo study, and corresponded to that observed in non-diabetic subjects who were 20–30 years older [6]. Also, the same Oslo study by Larsen et al. [6] of 39 type 1 diabetic patients, HbA1c and age correlated significantly with carotid intima–media thickness in type 1 diabetic women, but not in men. In these women, an increase of 1% in HbA1c values during the 18-year follow-up corresponded to an increase in carotid intima–media thickness. These results highlight the importance of long-term hyperglycaemia in the development of atherosclerosis, especially in type 1 diabetic women. Furthermore, in type 1 diabetic children with a mean age of 11 years and a mean duration of diabetes of 4 years, both the carotid and aortic intima–media thicknesses were significantly higher compared with those of healthy children of the same age [7].

4. Differences between type 1 and type 2 diabetes

Although atheromatosis is frequently seen in both type 1 and type 2 diabetic patients, there are some differences between these two populations in terms of atheromatous mass, as visualized by multislice computed tomography (CT), a technique that is used to determine arterial calcium score and arterial integrity. This device has been used in asymptomatic type 1 and type 2 diabetic patients to compare the extent, degree and morphology of coronary atherosclerosis in these two patient populations [8]. The two patient groups were matched for age, gender, tobacco use, familial history, lipid status, hypertension and renal function. There were significant differences in BMI (23.8 kg/m² vs. 28.2 kg/m², respectively; $P < 0.001$), duration of diabetes (23 years vs. 7.5 years, respectively; $P < 0.001$) and level of HbA1c (7.6% vs. 8.3%, respectively; $P = 0.04$). However, the prevalence of atherosclerosis and the mean arterial calcium scores were similar in both groups, although multivessel injuries and obstructive stenosis (stenosis $\geq 50\%$) were less frequent in the type 1 vs. type 2 diabetic patients ($P = 0.001$ vs. $P = 0.02$, respectively). Phenotype analyses of the plaques revealed a greater degree of calcification in plaques from type 1 diabetic patients ($P < 0.001$; Fig. 1). As it is known that calcified plaques are more stable than non-calcified plaques, this suggests that the risk of acute coronary events is higher with the latter.

5. Known cardiovascular risk factors in type 1 diabetics

The known cardiovascular risk factors in young type 1 diabetic patients [9] include a family history of type 2 diabetes and/or hypertension, which are the most important risk factors for cardiovascular disease. Also, uncontrolled glycaemia may play a role, although there is some controversy as to the
precise role of glycaemia in the development of atherosclerosis. In the Oslo study, the increase in carotid intima–media thickness correlated with HbA1c levels over the 18 years that preceded the examination [6]. In the Stockholm study, strict control of glycaemia over a period of 10 years had positive effects on endothelial function and carotid stiffness, two indirect markers of atherosclerosis [10]. However, in the DCCT, although the number of cardiovascular events was lower in the intensive-treatment group, the difference was not significant. Several reasons have been suggested to explain this—in particular, the fact that the patients in the study were relatively young and the follow-up period lasted only 6 years [11]. In contrast, in the DCCT/EDIC studies, after a follow-up period of 17 years, the risk of developing a first cardiovascular event decreased by 42% in the intensive-treatment group compared with those receiving conventional treatment \( (P = 0.02) \), and the risk of suffering a first non-fatal myocardial infarction, stroke or cardiovascular death decreased by 57% \( (P = 0.02) \) [12].

Another cardiovascular risk factor is urinary proteins. In type 1 diabetic patients with diabetic nephropathy, the risk of cardiovascular death is 100 times greater than in the general population [13], although the majority of type 1 diabetic patients who develop cardiovascular disease do not have nephropathy. Hypertension is another factor. Blood pressure below the 90th percentile according to age, gender and height should be the goal in young type 1 diabetic patients [14]. In cases of pre-hypertension (90–95th percentile), nutritional advice, weight loss and physical activity should be prescribed. If this fails after 3–6 months, then pharmacological treatment should be given. In cases of actual hypertension (> 95th percentile), pharmacological treatment should be implemented immediately.

Dyslipidaemia is another risk factor in type 1 diabetic patients, and quantitative abnormalities have been reversed by tight control of HbA1c. Qualitative atherogenic abnormalities have been observed, too (Table 1), but these do not respond to tight control of glycaemia [15]. Also, although statins are effective in controlling levels of low-density lipoprotein (LDL) cholesterol, their effects on qualitative abnormalities have not been proven.

Impaired platelet function, coagulation and fibrinolysis are further risk factors for cardiovascular disease and, although aspirin has shown benefits in adults, it is not recommended for patients aged < 21 years because of the high risk of Reye’s syndrome. In addition, high levels of fibrinogen have been associated with a more rapid progression of coronary calcification in type 1 diabetic patients, and was independent of the other usual cardiovascular risk factors after adjusting for renal function [16]. Finally, sedentary lifestyle, obesity and tobacco use are cardiovascular risk factors that constitute further challenges for young type 1 diabetic patients.

In 2009 [17], the risk factors for fatal ischaemic cardiac disease were evaluated in type 1 diabetic patients who had a long history of the disease (mean duration of diabetes: 30 years). Altogether, 389 type 1 diabetic patients were followed for 13 years. By the end of this follow-up period, 30% had died. After adjusting for age, gender and duration of diabetes, HbA1c was significantly associated with all-cause mortality, cardiovascular mortality and ischaemic heart disease, whereas HDL was negatively associated with these parameters. Renal failure was associated with a higher incidence of cardiac mortality and morbidity, and macroalbuminuria—but not microalbuminuria—was also associated with all-cause and cardiac mortality. However, there was no relationship between ischaemic heart disease and either micro- or macroalbuminuria.

### Table 1

<table>
<thead>
<tr>
<th>Quantitative abnormalities</th>
<th>Qualitative abnormalities</th>
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<tr>
<td>High HbA1c (lack of insulin)</td>
<td>Lipoproteins rich in triglycerides</td>
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<tr>
<td>Hypertriglyceridaemia</td>
<td>Increase in LDL cholesterol (LDL-C)</td>
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<td></td>
<td>Decrease in HDL cholesterol (HDL-C)</td>
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<tr>
<td>Optimal control of diabetes</td>
<td>Levels of triglycerides normal or slightly decreased</td>
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<td></td>
<td>Levels of LDL-C normal or slightly decreased</td>
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<tr>
<td></td>
<td>Levels of HDL-C normal or slightly increased</td>
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<td></td>
<td>Quality abnormalities</td>
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<tr>
<td>Very low-density lipoprotein (VLDL)</td>
<td>VLDL is enriched by esterified cholesterol</td>
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<td>Increase in free cholesterol/lecithin ratio in VLDL peripheral membrane, which induces a decrease in fluidity and stability of the lipoprotein</td>
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<td>Low-density lipoprotein (LDL)</td>
<td>LDL is enriched by triglycerides</td>
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<td>Increase in the number of small dense LDL, which is preferentially picked up by macrophages</td>
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<td></td>
<td>Small dense LDL infiltrates the arterial wall and is more susceptible to oxidation</td>
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<tr>
<td>High-density lipoprotein (HDL)</td>
<td>HDL is enriched by triglycerides</td>
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<td></td>
<td>Increase in sphingomyelin/lecithin ratio, which leads to rigidity of HDL</td>
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<td></td>
<td>Significant decrease in paraoxonase activity</td>
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</tbody>
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Adapted from Vergès [15].

Lipids (triglycerides, LDL) were positively associated with all-cause mortality, cardiovascular mortality and ischaemic heart disease, whereas HDL was negatively associated with these parameters. Renal failure was associated with a higher incidence of cardiac mortality and morbidity, and macroalbuminuria—but not microalbuminuria—was also associated with all-cause and cardiac mortality. However, there was no relationship between ischaemic heart disease and either micro- or macroalbuminuria.

### 6. Type 1 diabetics and physical activity: the cardiovascular risk

In young patients about to embark on a moderate-intensity \( (\text{VO}_2\text{max}: 40–59\% ; \text{maximum heart rate}: 55–69\% ) \) to high-intensity \( (\text{VO}_2\text{max}: > 60\% ; \text{maximum heart rate}: > 70\% ) \) physical activity programme, it is essential to evaluate their underlying cardiovascular risk, based on the following criteria: age > 35 years; age > 25 years and type 1 diabetes of > 15 years’ duration; presence of any additional risk factors for coronary disease; and presence of microvascular disease, peripheral vascular disease...
or autonomic neuropathy [18]. However, as it is clear that the stress test alone is insufficient for detecting coronary disease in type 1 diabetic patients [4], coronaryography and IVUS may also have to be carried out in type 1 diabetic patients. For patients planning to participate in low-intensity physical activities such as walking, physicians need to use their clinical judgment to decide whether or not to recommend an exercise stress test or other examinations [18].


Hypoglycaemia in type 1 diabetic patients (both induced and spontaneous) is associated with a prolongation of the QT interval on electrocardiography (ECG) known to trigger ventricular tachyarrhythmia. Hypoglycaemia is also associated with raised plasma catecholamine levels and low serum potassium, which can augment the arrhythmogenic effect of QT prolongation. The ‘hypoglycaemia–arrhythmia’ theory is an attractive explanation for the so-called ‘dead-in-bed syndrome’, and was observed in 25 type 1 diabetic patients, aged 20–50 years with a diabetes duration of 5–20 years, who were free of significant retinopathy, nephropathy, established macrovascular disease and drugs likely to affect cardiac function or rhythm. These patients underwent two separate 24-h monitoring sessions, during which they were attached to a 24-h ECG monitor that gave a continuous QTc (QT interval corrected for heart rate) measurement. The patients were also linked to a continuous glucose monitoring system (CGMS). The abnormalities in cardiac rate or rhythm observed during nocturnal hypoglycaemic episodes were ventricular ectopic beats, sinus bradycardia (<40 beats/min), atrial ectopic beats and P-wave abnormalities. This offers support for an arrhythmia basis for the ‘dead-in-bed syndrome’.

8. Conclusion

Cardiovascular complications in type 1 diabetic patients are frequent and severe, and arise early in the disease and, therefore, are often underestimated and undertreated. Given this observation, it is imperative to consider cardiac disease as early as possible to obtain good control of any known cardiovascular risk factors and to offer early cardiac follow-up in the affected patients. As for its detection and follow-up, the stress test is insufficiently sensitive; coronaryography is an invasive procedure, which raises the question of how frequently it may be used; and multislice CT is expensive and requires teams that are trained in its use. Finally, there is a serious lack of information concerning cardiovascular disease in type 1 diabetes.

Conflict of interest statement

The authors do not have any conflicts of interest to declare.

References