

Cardiovascular risk in type 1 diabetes mellitus

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ABSTRACT

Commonly cardiovascular risk (CVR) is linked to type 2 diabetes mellitus as this type is known to be part of the metabolic syndrome, which includes other cardiovascular factors such as hypertension, dyslipidemia. Inversely, CVR of type 1 diabetes mellitus (T1DM) is currently being debated apart from the occurrence of diabetic nephropathy (DN). For this, we did a review of CVR in patients with T1DM complicated or not with DN. The place of novel non-invasive techniques in screening of subclinical vascular damage is also discussed in this review.

Key words: Cardiovascular risk, diabetic nephropathy, subclinical atherosclerosis, type 1 diabetes mellitus

INTRODUCTION

Diabetes mellitus is characterized by progressive destruction of pancreatic beta cells via a cytokine-induced apoptosis.^[1] The specificity of each type of diabetes is the etiologic mechanism and the speed of this apoptosis. In type 2 diabetes mellitus (T2DM), apoptosis is progressively favored mainly by glucotoxicity and lipotoxicity; whereas in type 1 diabetes mellitus (T1DM), apoptosis is rapidly induced by irreversible autoimmune process.^[2]

Hyperglycemia is a major cause of vascular and neuropathic complications that are seen in patients with T1DM. However, during the past few years, researchers have identified a number of patients with unexpectedly few complications despite extremely long duration diabetes (≥ 50 years).^[3]

Insulin, despite improvements in its delivery systems during the last decades, still remains a potential contributor to morbidity and mortality since patients on current conventional therapies are exposed to some risks such as

hyperglycemias, ketosis, hypoglycemic episodes, ultimately resulting in the development of micro and macrovascular complications.

The published results of the diabetes control and complications trial/epidemiology of diabetes interventions and complications (EDIC) study marked a turning point for the management of T1DM patients by confirming by confirming the relationship between glycemic control and micro and macrovascular complications.^[4,5]

Cardiovascular risk (CVR) factors remain the most controversial chronic complication in T1DM patients. They have long been attributed to T2DM and T1DM complicated by nephropathy. In the absence of renal disease, there is still no consensus about of assessment of CVR in T1DM because of the multitude of specific risk factors that have been reported.

The assessment of subclinical vascular damage has recently benefited from the advent of sensitive techniques, such as measurement of carotid intima-media thickness (IMT), determination of the ankle-brachial index (ABI) and other sophisticated digital imaging techniques.

We reviewed, in this paper, different aspects of CVR in T1DM and the place of non-invasive techniques in the screening of vascular damage. We also propose a prevention strategy of CVR in T1DM.

Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/2230-8210.119489

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MORTALITY IN T1DM

Mortality is a major factor limiting the long-term studies of patients with T1DM. The analysis of the literature leads to a conclusion: T1DM is subject to a heavy premature mortality. Although the mortality rate varies from one study to another, it remains high, especially for young patients group. In a recent review in Finland, mortality in patients with T1DM is estimated at 361/100,000 person-years.^[6] Depending on the duration of diabetes, mortality dominates during the first two decades of diabetes. Beyond diabetes duration of 30 years, mortality seems to decline significantly.

Mortality was the prerogative of the old series where diabetes was seriously compromising the vital prognosis due to acute hyperglycemic crisis. Thus, in the oldest study, Diabetes Epidemiology Research International (DERI) Study, T1DM was associated with a 7-fold greater mortality rate than the age-matched non diabetic population.^[7]

Interestingly, the same study have shown a reduction of 35% in mortality rate from 1965 to 1979,^[8] however, this positive trend was noted only in males.^[9]

The literature review shows that the causes of death vary according to the duration of diabetes.

Early mortality prevails during the first decade. It is mainly due to interlinked acute conditions i.e., ketosis, severe hypoglycemia, infections, suicide and sudden death in the morning related to hypoglycemia and its subsequent cardiac arrhythmias (Dead-in-bed syndrome).^[10,11]

In the Pittsburgh study^[12] and DERI study,^[13] 64% and 73% of patients died as a result of decompensated diabetic emergencies. However, over time, mortality due to metabolic decomposition has declined markedly. This decrease was estimated at 57% of causes of death when she was only 38% for renal causes.^[12,13]

During the second decade of diabetes history, mortality is more related to chronic kidney disease and cardiovascular accidents. Although delayed, these mortality causes affect young patients.^[9]

ATHEROSCLEROSIS AND T1DM

In this part of the current review, we will assess three components of the cardiovascular damage in T1DM: Atherosclerosis risk factors, peripheral arterial disease (PAD) and diabetic cardiomyopathy.

CVR factors in patients with T1DM

As in T2DM, traditional factors such as hyperlipidemia, hypertension and smoking have been incriminated in CVR of T1DM.^[14,15] However, unlike their role in T2DM, these factors are rarely associated with the development of diabetes in children and are typically developed after several years of diabetes history. Therefore, they cannot alone explain the CVR in T1DM.

Unpublished data of a study conducted in our center showed that smoking and hypertension were found in respectively 20.3% and 36.6% of patients with T1DM. In addition, 10% of diabetics have become obese while 61.5% of women and 6.6% of men have a visceral distribution of fat. The Pittsburgh epidemiology of diabetes complications (EDC) study showed that Framingham criteria failed to predict CVR over 10 years in T1DM suggesting the existence of specific vascular factors for this type of diabetes.^[16]

Indeed, several specific risk factors have been suggested in the pathophysiology of CVR in T1DM: Nephropathy, cardiac autonomic neuropathy, hyperglycemia, hypoglycemia, low high-density lipoprotein (HDL)-cholesterol, insulin resistance and also genetic factors.^[17]

Coronary disease and cardiomyopathy in T1DM

Commonly described in T2DM, CVR have been mentioned in T1DM in the late of 70s.^[18,19] The comprehensive review of the literature reveals an increased risk of cardiovascular mortality from coronary heart disease (CHD).

- In the Tunisian National Register in 1984: The CVR of CHD was multiplied by 10^[20]
- In the Medalist Study: CVR was multiplied by 6 compared with the risk calculated using the Framingham criteria.^[21]
- In the Wisconsin Epidemiologic Study of Diabetic Retinopathy: The risk of ischemic heart disease was multiplied by 9.1 in males and 13.5 in females for patients aged less than 30 years^[22]
- In DERI Study, cardiovascular causes were a rare cause of death in the early ages^[23]
- In the Pittsburgh EDC study: After more than 10 years of evolution affect 16% of ischemic heart disease was observed^[24]
- For the older (between 20 and 30 years) in the same cohort, a 0.98% annual risk of fatal cardiovascular events with or without revascularization was noted^[25]
- In the study EURODIAB prospective complications study: After 7.3 years of evolution, the incidence of ischemic heart disease was at 7%^[26]
- In the UK cohort, controlled trial of 7479 diabetics between 1992 and 1999 study found the risk of cardiovascular events of 7.7 in women and 3.6 in men

including myocardial infarction (MI), revascularization and stroke.^[27]

Beyond 30 years of diabetes history, cardiovascular causes dominate the prognosis. The UK cohort study, showed among patients with a diabetes history over 30 years an increase in cardiovascular diseases such as hypertension, cardiomyopathy, heart failure and MI.^[28]

Thus, unlike chronic renal failure, there has not been found a decline of cardiovascular mortality over time.^[29,30]

It turns out that T1DM is characterized by a long-term cardiac damage independent of hypertension and coronary artery disease. This damage has been confirmed by ultrasound and isotopic methods and by autopsy.^[31]

In our series, we showed a decrease in systolic ejection fraction in 56.3% of cases, despite the absence of overt ischemic heart disease or hypertension (unpublished data).

Left ventricular dysfunction is explained by diabetic microangiopathy affecting small vessels of heart, a heart progressive fibrosis and cardiac autonomic neuropathy.

Diastolic dysfunction occurs early at 6 years history of diabetes, whereas systolic dysfunction is later occurring after a mean of 18 years of evolution.^[32-34]

The left ventricular dysfunction leads to impaired compliance and is more marked as diabetes is long-standing or poorly controlled.^[35]

Stroke in T1DM

In our series, proven stroke was diagnosed in 13.3% of patients with over 20 years of T1DM history predominantly in females. The stroke risk is actually increased in T1DM.^[36] The relative risk is estimated at 4 in women in the United States controlled study performed between 1976 and 2002 on 116,316 female patients aged between 30 and 35 years.^[37] This particular risk in females was confirmed in the UK cohort showing that the risk of stroke is 4.8 higher in women.^[27]

In the Australian study of Davis on 126 patients with T1DM conducted between 1993 and 1996 over a mean of 7.2 years, the occurrence of stroke was observed in 4.7% of cases, this risk is correlated with low HDL-C level.^[38]

Outside the atherosclerotic disease of carotid arteries, some authors emphasize the role of microangiopathy as one diabetes-related cause of brain injury.^[39-41]

Measurement of carotid IMT was introduced by Pignoli in Italy in 1986^[42] and has since been improved.

Increased IMT is the first sign of carotid artery disease and is present before the development of the atherosclerotic plaque. The measurement of carotid IMT is now an accepted surrogate marker of subclinical atherosclerosis. A Swedish study has recently shown that increased IMT can predict stroke even in the absence of obvious carotid plaques.^[43]

According to our experience, we have noted carotid ultrasound abnormalities in 72.7% of patient with long-surviving T1DM with a mean value of IMT of 0.72 mm.

In a cross-sectional study conducted in South Africa and involving 148 T1DM patients (duration of diabetes >18 years), a mean value of IMT of 0.62 mm was noted and atherosclerotic carotid plaque was detected in 18.9% of cases.^[44]

In a case-control study involving 40 Egyptian patients with a 3-25 years history of T1DM, the mean value of IMT was 0.6 mm.^[45]

Another Hungarian controlled study of Vastagh *et al.* conducted on 42 patients with T1DM (age 34 ± 10 years; average duration of diabetes 15 ± 10 years), the IMT was significantly more increased in diabetic patients compared with controls (0.567 vs. 0.523 mm respectively).^[46,47]

This progression of IMT seems to be early because it was found even in patients with a 9 year-history of T1DM.^[48]

An association between IMT and CVR factors has been noted in many studies, such as with age, body mass index, duration of diabetes, hypertension, smoking, glycated hemoglobin and decreased HDL-cholesterol.^[30,44,48,49]

IMT is also a valuable parameter for interventional studies. Thus, in a meta-analysis of 2004 Amarenco *et al.*^[50] found a strong correlation between the reduction of low-density lipoprotein (LDL) and IMT in the effect of statins with fewer strokes, but no direct impact on mortality. Angiotensin receptor blockers also have demonstrated efficacy in reducing CVR and IMT^[51] and for calcium channel blockers and glitazones^[52] in the evaluation of treatment of metabolic syndrome.

Data from epidemiological and clinical studies have prompted the American Heart Association to retain the use of IMT in the assessment of CVR in asymptomatic subjects aged over 45 years.^[53]

PAD

In T1DM, endothelial dysfunction develops from the first decade of evolution.^[49,54-56] Peripheral arterial lesions are independent predictors of atherosclerosis. Anatomical and biomechanical studies on thoracic aortic tissue of patients with T1DM showed a reduction in extensibility that positively correlated with duration of diabetes.^[57]

The use of index ankle-brachial systolic pressure (ABP) began in 1968 with the publication of the work of Carter.^[58] Since then, this evaluation has been technically progressed with the use of Doppler. In 1970, Yao showed that the average value of the ABP decreases with the increase of the severity of PAD.^[59]

It is measured by comparing the pressure between the arm and ankle. This is seen when the index is below 0.9 or above 1.3^[60] or 1.4^[61,62] reflecting extreme rigidity. The use of ABP allows the diagnosis of PAD in 9 times out of 10. An ABP value less than 0.90 multiplies by 2.5 the cardiovascular mortality at 10 years; while an ABP value above 1.4 multiplies by 2 the cardiovascular mortality at 10 years.

Other techniques for the screening of subclinical PAD are proposed such as the study of endothelial cells that are biomarkers of CVR. A low level of circulating CD34+ CD33+ and CD31+ and a high level of circulating CD34+ CD45- seem to be a witness of endothelial damage.^[63]

Endothelial damage seems to depend on the age of patients;^[64] female sex;^[64] retinopathy;^[64] diabetic autonomic neuropathy;^[54] smoking;^[65] hypertension;^[65] and genetic factors such as some polymorphisms of nitric oxide synthase.^[66]

CARDIOVASCULAR PREVENTION STRATEGIES IN T1DM

It is based on several measures:

1. Glycemic control: All studies agree to stress on this factor. According to the EDIC study, glycemic control can reduce by 42% cardiovascular events.^[5]
2. Prevention and management of CVR factors:
 - To stop smoking and to avoid weight gain induced by insulin and sweet food excess
 - To detect lipid abnormalities since 12 years of diabetes history and to repeat the exam every 5 years if normal.^[67] According to Pediatric and American Dental Association (ADA) recommendations on the lipids, targets are as follows: LDL <2.6 mmol/L; HDL-c >1.1 mmol/L and triglycerides <1.7 mmol/L. Medical treatment (statins or

resins prescribed from the age of 10-year-old) should be considered if the LDL >4.1 mmol/L or >3.4 mmol/L (1.3 g/L) in the case of high CVR. According to short-term trials, statins show efficacy and safety in children and adolescents. Nevertheless, the recommendations remain cautious about the use of statins in children^[68,69]

- To stratify the CVR in patients with T1DM [Table 1]: Common recommendations only consider the diabetic nephropathy in high CVR. In the absence of nephropathy, scientific societies (European society of cardiology, European association for the study of diabetes, HAS, ADA) have not yet established consensus score to stratify the cardiovascular risk in T1DM.^[70,71] For this reason, non-invasive tests, such as IMT and ABP measurements, may provide a valuable opportunity to identify patients at high CVR after a 10 year history of diabetes. Patients at high CVR: IMT >1 mm or ABI <0.9 should benefit from preventive measures based on lifestyle modifications, angiotensin-converting-enzyme inhibitors, statins [Table 2]. Other tests such as

Table 1: Comparison between CVR in T2DM and in T1DM

	T2DM	T1DM
Prevention of diabetes	Possible	Not possible
Frequency of CV events	×2-3	×6-10
Age of diagnosis	>30 ans	20-30 ans
Occurrence of CV		
Before the diagnosis of diabetes	++	Never
At the same moment	++	Never
After the diagnosis of diabetes	++	Later
Glycemic control as a CVR factor	++	++
Impact of intensification		
Metabolic memory	++	++
Harmfulness of hypoglycemia	++	Severe and repeated hypoglycemia
The role of common CVR factors (smoking, lipid anomalies, hypertension)	++	+
The role of insulin resistance (metabolic syndrome)	++	Induced by over dose of insulin
The role of nephropathy	++	++

CVR: Cardiovascular risk, CV: Cardiovascular, T2DM: Type 2 diabetes mellitus, T1DM: Type 1 diabetes mellitus

Table 2: Stratification of CVR in patients with T1DM (adapted from^[72])

	Moderate CVR	High CVR %	Very high CVR %
IMT	<1 mm or <50-75 ^{ème} percentile	≥1 mm or >75 ^{ème} percentile	≥1 mm or >75 ^{ème}
Plaque Strategy	No Life style modifications	Stenosis<50 Life style modifications	Stenosis≥50 Life style modifications
Targets	LDL-C<130 mg/dL	LDL-C<100 mg/dL	LDL-C<0,7 mg/dL+ sophisticated tests

CVR: Cardiovascular risk, IMT: Intima-media thickness, T1DM: Type 1 diabetes mellitus, LDL-C: Low-density lipoprotein cholesterol

stress testing or coronary angiography are not indicated in routine and reserved for patients with very high CVR.^[72]

CONCLUSION

Taken to account all reviewed data, we can definitely say that cardiovascular damage in T1DM is a real, serious and complex complication. Review summary of this risk with a comparison between CVR risk in T2DM and T1DM are presented in Table 1.

The dogma saying that CVR in T1DM begins only with the occurrence of nephropathy is no longer valid. Non-invasive tests should be more frequently used in order to detect subclinical damage and stratify CVR in patients with T1DM.

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Cite this article as: Slim IH. Cardiovascular risk in type 1 diabetes mellitus. *Indian J Endocr Metab* 2013;17:S7-13.

Source of Support: Nil, **Conflict of Interest:** No.