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Sudden cardiac death and diabetes mellitus

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ABSTRACT

Sudden cardiac death (SCD) affects a significant percentage of diabetic patients. SCD in these patients can be due to several factors, such as diastolic dysfunction, heart failure, altered platelet function, inflammation, sympathetic nervous stimulation and other factors. In the present review, we discuss the association between diabetes mellitus and SCD.

1. Introduction

Diabetes mellitus (DM) is a major health and socioeconomic problem with many complications, such as coronary heart disease (CHD), heart failure (HF) and stroke (Mandavia, Aroor, Demarco, & Sowers, 2013). For example, a recent study (Vasiliadis et al., 2014) reported that 37.6% of HF patients (i.e. 73/194) had DM; 27.3% type 2 DM (T2DM) and 10% Type 1 DM (T1DM). A recent review reported that cardiovascular (CV) disease is associated with T2DM resulting in morbidity and mortality (particularly due to CHD, HF and stroke) (Schlienger, 2013). Furthermore, the risk of CV death appears to be similar between patients with previous myocardial infarction (MI) but no DM and those with DM but no MI (Schramm et al., 2008). DM also is a risk factor for atrial fibrillation (AF), which in turn increases the risk of HF (Mischke, Knackstedt, Marx, & Vollmann, 2013).

Sudden cardiac death (SCD) is more common in the elderly and possibly in those with DM (Tung & Albert, 2013). SCD is responsible for 5.6–15% of annual mortality in the USA (Chugh et al., 2004) and represents the major cause of mortality in HF and CHD. There is evidence of an association between DM and SCD (Li-na et al., 2012).

In this review we will discuss the association between DM and SCD as well as the need to develop preventive measures (Al-Khatib et al., 2013).

2. Definition of SCD

The most widely accepted definition of SCD is death from unexpected circulatory arrest due to cardiac causes, heralded by abrupt loss of consciousness within 1 h of the onset of acute symptoms, in an individual with or without known pre-existing heart disease, but in whom the time and mode of death are sudden (Gaziano, 2001; Zheng et al., 2001). This definition has limitations. For example, a significant proportion of SCDs are not witnessed and it follows that clinical information is incomplete. Secondly, determining the unexpectedness of death is problematic in end-stage HF or renal disease where there is a high burden of comorbidities.

2.1. Epidemiology of SCD

Every year in the USA a significant percentage of people experience SCD (Adabag, Luepker, Roger, & Gersh, 2010; Lombardi, 2013; Siscovick et al., 2010), More than 300,000 cases of SCD occur annually in the USA alone (Adabag et al., 2010). Furthermore, SCD underlies 50% of cardiovascular mortality and 20% of total mortality in the Western world. Men are 2–3 times more likely to experience SCD

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than women (George, 2013). Similar rates have been reported in other countries (Adabag et al., 2010).

2.2. Etiology of SCD

The main etiology of SCD is a terminal arrhythmia, which is most often due to ischemic myocardium, ruptured arterial plaque, focal myocardial scar, reduced left ventricular ejection fraction (LVEF) and/or genetic mutations (Huikuri, Castellanos, & Myerburg, 2001). The most common terminal arrhythmia observed in the general population who experience SCD is ventricular tachyarrhythmia.

Abnormalities in genes that encode a variety of ion channels cause rare inherited disorders such as long QT syndrome that may present with SCD. Also, mutations of other genes (such as NOS1AP) are linked with the risk of SCD (Spooner, 2009).

Cigarette smoking might induce cardiac arrhythmias. This effect in the presence of DM may increase the risk of SCD (D'Alessandro, Boeckelmann, Hammwhöner, & Goette, 2012). Other factors may influence the risk of SCD. For example, Stang et al. suggested that midday naps in non-Mediterranean populations increase the risk of SCD (Stang et al., 2012). It is of interest that midday naps may reflect poor sleep quality during the night. In turn, this may be related to the presence of Obstructive Sleep Apnea Syndrome which is associated with obesity and risk of DM (Mannarino, Di Filippo, & Pirro, 2012). Furthermore, increased arterial stiffness has been shown to be associated with age and DM (Benetos et al., 2002). Arterial stiffness seems to be a vascular risk factor itself, as it was independently related to the risk of stroke, MI and CV death (including SCD) (Dijk et al., 2005).

3. DM

The role of DM in increasing the risk of SCD has been evaluated in a small number of studies. All have consistently identified DM as a strong predictor of SCD.

An analysis was performed in approximately 6000 middle-aged, healthy male civil servants who participated in the Paris Prospective Study (Jouven, Desnos, Guerot, & Ducimetiere, 1999). After 23 years of follow up there were 120 SCDs. In a multivariate analysis, DM independently conferred a significant risk for SCD (relative risk (RR) 2.21; 95% confidence interval (95%CI) 1.10 - 4.44) after controlling for several variables (age, body mass index, tobacco use, history, heart rate, systolic blood pressure, cholesterol and triglyceride levels) (Balkau, Jouven, Ducimetiere, & Eschwege, 1999). Similar findings were reported by the US Nurses Study (Albert et al., 2003) Physicians Health Study (Albert et al.,2000) and a retrospective clinical database analysis from a health cooperative in Seattle (Jouven et al., 2005).

DM may contribute to the pathogenesis of SCD by several mechanisms which include: i) Silent cardiac ischemia, ii) Imbalance in autonomic tone, iii) Slowed conduction, iv) Heterogeneity in atrial and ventricular repolarization and high prevalence of abnormal prolongation of the corrected QT (QTc) interval (Cardoso, Salles, & Deccache, 2003; Veglio, Borra, Stevens, Fuller, & Perin, 1999), and, v) Myocardial damage and scar formation (Feola et al., 2008; Junttila et al., 2010). Also, hyperinsulinemia increases hepatic very-low-density triglyceride synthesis, plasminogen activator inhibitor-1 synthesis, thromboxane-dependent platelet activation, sympathetic nervous system activity and promotes sodium reabsorption. These factors are discussed below.

3.1. Epidemiology of DM

The prevalence of SCD may have decreased due to better management of MI and CV risk factors (Haffner, Lehto, Rönnemaa, Pyörälä, & Laakso, 1998). However, an opposite trend is observed in the prevalence of DM and metabolic syndrome raising the possibility that the incidence of SCD may eventually rise (Haffner et al., 1998). In this context, there is evidence that both in-hospital and long-term mortality rates after an acute MI are twice as high for patients with DM as for those without (Feola et al., 2008). From patients with an acute coronary syndrome, 20–30% have DM and as many as 40% have impaired glucose tolerance (Haffner et al., 1998).

3.2. Cardiac pathophysiology of DM

The increased risk SCD in DM may exist but specific management recommendations are not available due to lack of evidence. It is unclear if DM increases the incidence of SCD (Haffner et al., 1998) independently from the contribution of CHD (Haffner et al., 1998) due to factors such as autonomic dysfunction, altered cardiac repolarization or cardiomyopathy. Furthermore, whether diabetic patients have a higher incidence of SCD than matched non-diabetic patients is also not clear. These discrepancies may relate to the distribution of populations being studied. These may differ in several characteristics (e.g. extent of CHD, glycemic control, medication and length of follow-up) (Haffner et al., 1998).

Junttila et al. compared 3276 post-MI patients for 10 years. In those with DM, the incidence of SCD was higher (5.9%) than in non-DM patients (1.7%); adjusted HR = 2.3 (95% CI 1.4–3.8; $P < 0.01$). In DM patients with LVEF >35%, the incidence of SCD was nearly identical to that of non-DM patients with LVEF ≤35% (4.1 vs 4.9%; $P = 0.48$) (Junttila et al., 2010).

DM is associated with microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (atherosclerotic) complications (Forbes & Cooper, 2013). Pathologic changes in the myocardium of diabetic patients may account for any observed functional impairment. These changes include fibrosis, and alterations in the myocardial capillary basement membrane, including the formation of microaneurysms (Balofsky, 2010; Law, Fowlkes, Goldsmith, Carver, & Goldsmith, 2012), These changes may occur in the absence of established vascular risk factors. Myocardial fibrosis, advanced glycation end product deposition and cardiomyocyte resting tension were compared in diabetic and non-diabetic HF patients without CHD with normal LVEF (28 patients, 16 diabetic) or reduced LVEF (36 patients, 10 diabetic) (Sun, Su, Li, & Wang, 2013). Diabetic HF patients had greater diastolic LV stiffness irrespective of LVEF. Significantly increased myocardial collagen volume fraction was observed only among diabetic patients with reduced LVEF; on the other hand, increased cardiomyocyte resting tension was observed only in diabetic patients with normal LVEF (van Heerebeek et al., 2008).

3.3. Kidney function

DM is associated with impaired kidney function (Sun et al., 2013). The risk for SCD is increased 20- to 30-fold in hemodialysis patients compared with populations without significant chronic kidney disease (CKD). CV deaths account for about 40% of all deaths of patients with CKD, particularly those on dialysis; SCD might be responsible for as many as 60% of deaths in patients undergoing dialysis (Bonato, Lemos, Cassiolato, & Canziani, 2013; Franczyk-Skóra et al., 2012), Renal dysfunction can lead to electrolyte disturbances promoting arrhythmogenesis (Shamseddin & Parfrey, 2011). Furthermore, end stage CKD with dialysis is associated with an increased risk arrhythmogenesis (Athyros et al., 2004; Ho, Waters, Kean, & Wilson, 2012; Tekin, Tekin, Sezgin, & Müderrisoğlu, 2008). These factors contribute to the high incidence of SCD in these patients.

Impaired kidney function often accompanies HF and is associated with a worse prognosis (Valente et al., 2014). Improvement in renal function, in patients with CKD treated with high dose atorvastatin, was associated with a reduction in hospitalizations and decreased HF morbidity (Athyros, Karagiannis, Katsiki, & Mikhailidis, 2012). The benefit of cholesterol-lowering medications in terms of vascular