Diabetes mellitus and sudden cardiac death: What are the data?

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Abstract

Diabetes mellitus has long been linked to an increased risk of sudden cardiac death. However, the magnitude of this association, and the mechanism accounting for this phenomenon, have not been precisely defined. In this review, we evaluate the epidemiological data pertaining to the association between diabetes mellitus and sudden cardiac death and discuss various proposed mechanisms that may account for this relationship. Potential factors contributing to the increased risk of sudden cardiac death observed in patients with diabetes mellitus include silent myocardial ischemia, autonomic nervous system dysfunction, abnormal cardiac repolarization, hypoglycemia, a hypercoaguable state secondary to diabetes mellitus, diabetic cardiomyopathy, and impaired respiratory response to hypoxia and hypercapnea.

We conclude that diabetes mellitus does appear to be associated with an increased risk of sudden cardiac death. Although this increased risk is relatively modest, given the large number of diabetic patients worldwide, the absolute number of sudden cardiac deaths attributable to diabetes mellitus remains significant. Little evidence exists to support any specific mechanism(s) accounting for this association. Further investigation into the pathophysiology of sudden cardiac death in diabetes mellitus may yield improved risk stratification tools as well as identify novel therapeutic targets. (Cardiol J 2010; 17, 2: 117–129)

Key words: diabetes mellitus, sudden cardiac death, autonomic

Introduction

Diabetes mellitus (DM) affects an estimated 171 million people worldwide (2000 estimate), a number projected to double to 366 million by 2030 [1]. Compared to their non-diabetic counterparts, this substantial portion of the world's population appears to be at a significantly higher risk of sudden cardiac death (SCD) [2–9]. Recent longitudinal data from the Framingham cohort and their off--spring demonstrates that approximately one-fifth of sudden deaths occur in the setting of DM, a pro-portion that has doubled over the past five decades [10]. Given the recent estimate of up to 400,000 SCDs each year in the United States [11], this would suggest approximately 80,000 sudden deaths occur each year in diabetic patients in the United States alone. While this represents a large number of SCDs, it is only a very small fraction of the DM population (< 0.05%).

Despite several epidemiological findings linking DM to SCD, the physiological mechanism(s) responsible for the increased frequency of sudden death in diabetic patients has yet to be elucidated.

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This article reviews the epidemiological data regarding the association between DM and SCD, as well as exploring the proposed mechanisms behind SCD in people with DM.

The study of sudden cardiac death

It is important to briefly review some of the complicating factors that have made the study and characterization of SCD so challenging to date. Firstly, the lack of a single, accepted definition of SCD has made data comparison between studies, as well as generalizations based on available studies, quite difficult. SCD has typically been defined as unexpected death occurring within a specific period of time after the onset of initial symptoms. The time frame used to define SCD has varied significantly among studies, ranging from less than one hour after symptom onset up to 24 hours [12] (WHO definition). The impact that the time frame chosen can have on the etiology of sudden death is illustrated in an older study of 3,421 natural deaths. Twelve percent of natural deaths were sudden when 'sudden death' was defined as < 2 hours from the onset of symptoms, and 88% of these were from a cardiac etiology. In contrast, 32% of natural deaths were 'sudden', and only 75% were from a cardiac etiology, when the definition was extended to death within 24 hours of symptom onset [13].

Another factor that introduces variability into the study of SCD is the variety of methods used for confirming cases of SCD. These range from relying solely on information found on death certificates to more complex assessments, including combinations of autopsy report review, eyewitness interviews, and expert panel discussions. Chugh et al. [14] compared a prospective, comprehensive approach for the identification of SCD (including analysis of circumstances of death, medical records, and available autopsy data) to a retrospective surveillance approach using only death certificate information in a population of 660,486 people. Interestingly, the retrospective death certificate-based review had a positive predictive value of only 19% when compared to the prospective comprehensive approach, demonstrating the sizeable effect that the method used to identify cases of SCD has on study results.

Diabetes and sudden cardiac death

In the published epidemiological studies pertaining to the role of DM in SCD, patients with DM appear to be at a higher risk of SCD. Table 1 [2–9, 15, 16] lists these available studies including study type, study populations, outcomes measured, and multivariate adjusted relative risk. Of the seven studies listed, five are prospective population studies while the remaining two are of case-control design. Overall, five of the seven studies (three prospective studies and the two case-control studies) noted a positive, statistically significant relationship between DM and SCD, while the two remaining studies failed to find an association.

On closer examination, several differences can be identified that could potentially contribute to the heterogeneity of data. In examining the differences in study populations, the percentage of study subjects with DM was lowest (of those with data available) in the two negative studies. The follow-up duration was also substantially shorter in these two negative studies compared to the positive prospective studies. Following more subjects for a longer time may have increased the ability of the positive studies to detect a significant effect of DM on SCD that could not be detected in the shorter, negative studies that had fewer diabetic participants.

Another difference to consider is that incidence rates of SCD were substantially higher in the two negative studies compared to the positive studies. This was probably partly a result of differences in the inclusion and exclusion of subjects with known coronary artery disease. Two of the three prospective studies with positive results excluded patients with a history of coronary artery disease (CAD), while the two studies with negative results both included subjects with a history of CAD (25% and 32% of total study populations, respectively). It is possible that the competing risks for SCD related to CAD and other associated factors in these populations overweighed the increased risk related to DM. It is therefore critical to assess the risk for SCD in the comparator population.

Turning now to how SCD cases were defined and identified in the studies, Table 2 lists the definitions of SCD used in each study, along with the methods used to identify cases of SCD. In the Group Health Cooperative study, Jouven et al. [6] do not specifically state a cut-off for defining SCD, but all other studies use < 1 hour from symptom onset in their definition. An 'unwitnessed death' (a death in which the specific time intervals from symptom onset until death could not be determined), was excluded from the definition of SCD in all studies except for the Suhonen et al. [16] study. Interestingly, this study also had the highest incidence rate of SCD. The methods used to identify cases of SCD are also listed in Table 2 for each study and could also contribute to the differences among studies.

Table 1. Epidemiological studies of diabetes mellitus (DM) and sudden cardiac death (SCD).

Author	Type	Number of diabetic subjects/total	Subjects with known CAD at start of study (%)	Age (years)	Male (%)	Follow up time (years)	Number of SCD cases with DM/total cases of SCD	Overall SCD incidence rates (cases per 10,000 person-years)	SCD cases with identified CAD or cardiac disease at enrollment	RR (multivariate)
Jouven et al. 1999 [2] (Paris Prospective Study)	Prospective cohort DM based on self report	191/7,072 (2.7%)	0% (excluded)	43–52	100%	23	9/118 (7.6%)	7.25	Excluded	2.21 (95% CI: 1.10–4.44)
Balkau et al. 1999 [3]* (Paris Prospective Study)	DM based on screening and self report	413/6,539 (6.3%)	0% (excluded)	43–52	100%	17.5	NA	NA	Excluded	1.82 (95% CI: 1.04–3.17)
Albert et al. 2003 [4]	Prospective cohort	Person-years: 105,267/2,569,041 (4%)	NA	30–55	0%	22	58/244 (23.8%)	0.95	31%	2.93 (95% CI: 2.13–4.04)
Curb et al. 1995 [5]	Prospective cohort	NA 8,006	0% (excluded)	45–68	100%	23	< 1 h: 115 < 24 h: 244	< 1 h: 6.25 < 24 h: 13.25	Excluded	**< 1 h:** 2.24 (95% CI: 1.19–4.23) **< 24 h:** 2.76 (95% CI: 1.77–4.31)
Jouven et al. 2005 [6]	Case control Type 1 DM excluded	SCD cases: 465/2,040 (22.8%) Control cases: 418/3,800 (11%)	SCD cases: 1343/2,040 (66%) Control cases: 2150/3,800 (57%)	40–79	SCD cases: 71% Control cases: 69%	14	465/2,040 (22.8%)	NA	66%	OR: 1.73 (95% CI: 1.28–2.34) for DM without microvascular complications 2.66 (95% CI: 1.84–3.85) with microvascular complications
Sexton et al. 1997 [9]	Population based Case-control study	SCD cases: 13/102 (13%) Control cases: 3/204 (1.5%)	0% (excluded)	25–75	100%	3	13/102 (13%)	NA	Excluded	OR: 4.22 (1.39–12.81)
Wannamethee et al. 1995 [15]	Prospective population survey	120/7,735 (1.6%)	25%	40–59	100%	8	2/117 (1.7%)	18.9	**62%**	1.0 (0.2–4.0)
Suhonen et al. 1988 [16]	Prospective population survey	58/3,589 (1.6%)	32%	40–59	100%	11	5/150 (3.3%)	38.0	**61%**	1.2 (not significant)

*Used the same study population as Jouven et al. 1999 (Paris Prospective Study); NA — not available; CAD — coronary artery disease; RR — relative risk; 95% CI — 95% confidence intervals; OR — odds ratio

Table 2. Determination of sudden cardiac death (SCD) by study and accounted for covariates.

Author	Definition of SCD	Method to determine etiology of SCD	Covariates
Jouven et al. 1999 [2]	'a natural death occurring within **1 hour** of onset of acute symptoms'	**Data**: medical records, primary care physicians, death certificates **Review**: independent review board of 3 physicians	Age, BMI, tobacco use, HR, blood pressure, cholesterol level, triglyceride level, parental history of MI, parental history of sudden death
Balkau et al. 1999 [3]*	As above	As above	As above
Albert et al. 2003 [4]	'death or cardiac arrest that precipitated the terminal event occurred within **1 hour** of symptom onset'	**Data**: death certificates, medical records, next of kin interviews **Review**: cases reviewed by 2 cardiologists	Age, BMI, tobacco use, hypertension, hypercholesterolemia, parental history of MI, prior CAD, menopausal status, postmenopausal hormone use
Curb et al. 1995 [5]	Non-traumatic death occurring suddenly or unexpectedly **< 1 or < 24 hours** after the onset of the terminal episode and resulting from coronary heart disease or unknown cause	**Data**: abstracted death certificates, hospital and autopsy records, reports from family, attending physician, or medical examiner **Review**: panel of physicians	Age, BMI, tobacco use, blood pressure, cholesterol level, triglycerides, alcohol use, left ventricular hypertrophy
Jouven et al. 2005 [6]	'sudden pulseless condition in the absence of evidence of a non-cardiac condition as the causes of cardiac arrest'	**Data**: death records, medical record, pharmacy record	Age, BMI, tobacco use, HR, systolic blood pressure, cholesterol level, history of MI, antidiabetic treatment, CHF, creatinine
Sexton et al. 1997 [9]	'SCD occurring in a person without any prior overt manifestations of ischemic heart disease, where a SCD is one that occurs within **1 hour** of the onset of symptoms of myocardial ischemia'	**Data**: death records, necropsy reports, hospital records, questionnaires completed by the subjects doctor, family member interviews	Age, BMI, tobacco use, hypertension, hypercholesterolemia, family history of CAD, exercise amount, alcohol use
Wannamethee et al. 1995 [15]	'an event in which death occurred within **1 hour** after the onset of symptoms' patients found dead in bed were not classified as SCD	**Data**: inquiry forms for the doctor that certified the death	Age, HR, systolic blood pressure, cholesterol level, CHD, arrhythmia, physical activity, hematocrit, and white blood cell count
Suhonen et al. 1998 [16]	'coronary deaths ensuing within **1 hour** of the onset of symptoms **or unwitnessed** were classified as sudden'	**Data**: death certificates, hospital and necropsy records, information from witnesses	Age, BMI, tobacco use, blood pressure, cholesterol level, CHD

*Used the same study population as Jouven et al. 1999 (Paris Prospective Study); BMI — body mass index; CAD — coronary artery disease; CHF — congestive heart failure; MI — myocardial infarction; HR — heart rate; CHD — coronary heart disease

Another major factor to consider in examining each study is the validity of the covariate analysis. Given that certain traditional risk factors for SCD, such as CAD, hypercholesterolemia, and hypertension are also quite common in patients with DM, this puts a great deal of weight on proper covariate identification and analysis in determining any independent relationship between DM and SCD. Overall, major covariates related to SCD appear to be taken into account in all the studies examined (Table 2),

although the development of CAD and its identification during the studies' follow-up periods is not specifically addressed in many of the studies.

Despite these issues, the data lends overall support to the existence of a relationship between DM and SCD. However, further studies of larger, more diverse populations are needed to solidify the nature and scope of this relationship.

Mechanisms of sudden cardiac death

Although many mechanisms have been proposed to explain the increased risk of sudden death in patients with diabetes, little definitive clinical evidence exists to support any one in particular. Overall, it is important to remember that SCD is a complex, heterogeneous entity with several different pathophysiological processes manifesting in the same final outcome (SCD). It is also important to realize that chronic factors, as well as acute factors, play a role in the overall pathogenesis of SCD in most cases. For instance, chronic factors such as structural heart disease or underlying coronary heart disease may make individuals more susceptible to SCD by lowering their threshold for lethal arrhythmia; but an acute event is also usually needed such as an acute plaque rupture, an electrolyte imbalance, or a surge of sympathetic activity, in order to trigger the fatal event. It is this heterogeneity and level of complexity that has made the characterization of SCD etiologies and risk factors so difficult in the past.

Before discussing mechanisms of SCD in the diabetic population, it is important to first briefly review causes of SCD in the general population. Although difficult to study, arrhythmia has been reported as the mechanism of sudden death in approximately 90% of sudden cardiac deaths [4, 17]. Hinkle and Thaler [17] used the definition of 'an abrupt collapse with pulse ceasing prior to circulatory collapse' to define arrhythmic death in their study of 142 deaths; they found that 58 (41%) of these deaths occurred within one hour of the terminal illness. Of these 58 deaths, 53 (91%) were classified as 'arrhythmic deaths'.

Albert et al. [4] examined 570 sudden deaths in women and found that 88% were arrhythmic using this same definition. Other etiologies, such as acute heart failure from massive myocardial infarction, occur far less frequently. In another study, SCD was classified further into three categories in a sample of 106 SCDs. In this study, 47% of SCDs were arrhythmic (without evidence of ischemia), 43% were ischemic (i.e. with any evidence of

ischemia or infarction) and 8% were secondary to myocardial pump failure [18].

Coronary artery disease is thought to play a major role in SCD in the general population and is present in approximately 80% of cases of SCD in Western countries, while non-ischemic cardiomyopathies make up only 10–15% of SCD cases. Various autopsy studies have shown that between 55% and 86% of patients who experience SCD have significant (> 75%) stenosis of at least two coronary arteries [19–21]. While underlying chronic CAD appears to be common in SCD, the frequency of finding acute coronary thrombosis in cases of SCD is far less clear. In a compilation of studies reported by Farb et al. [19], acute coronary thrombi were found in 5–73% of SCD autopsy cases, depending on the cohorts studied and definition of SCD used. Thus, while chronic coronary disease appears to play a significant role in SCD, the acute inciting events that precipitate SCD are less clear. Other major risk factors that have been established for SCD include decreased left ventricular ejection fraction, intraventricular conduction delay, autonomic nervous system abnormalities, risk factors associated with the development of coronary artery disease, left ventricular hypertrophy, history of prior cardiac arrhythmia, clinical congestive heart failure, and family history of SCD.

Mechanisms of sudden death in diabetes mellitus

Within the diabetic population, several mechanisms have been proposed to account for the excess of SCD observed. These mechanisms include silent myocardial ischemia, autonomic dysfunction, QT interval prolongation, hypoglycemia, a hypercoaguable state associated with DM, diabetic cardiomyopathy, and decreased ventilatory response to hypoxia and hypercapnea.

Silent ischemia

Several authors have suggested that silent, unrecognized ischemia eventually leads to lethal arrhythmias and SCD in diabetic patients. To date, the DIAD (Detection of Ischemia in Asymptomatic Diabetics) trial is the only prospective trial to evaluate the prevalence of silent myocardial ischemia in a large group of diabetic subjects. In this trial, 522 asymptomatic type 2 diabetic subjects (average age 60.7 years) without a history of coronary artery disease underwent stress testing by single photon emission-computed tomography (SPECT) imaging, with 15.9% of subjects demonstrating abnormal

myocardial perfusion [22]. This is a significantly smaller percentage compared to two large retrospective studies of 826 [23] and 1,427 [24] subjects which found abnormal SPECT imaging in 39% [23] and 58% [24] of asymptomatic diabetic patients, respectively.

Of the available studies, the reported prevalence of 'silent' ischemia ranges from 6–59% [22––28] in subjects with diabetes. Of note, no large scale prospective study has reported the results of angiographic evaluation following positive imaging studies in these asymptomatic diabetics. In addition, many of these studies do not report rates of 'silent ischemia' in non-diabetic control subjects, although 2.5–15% [29, 30] of non-diabetic patients have been reported to have 'silent ischemia' in other studies.

Little is known regarding the prognostic implications of 'silent ischemia' in DM. In one study of 1,737 diabetic patients consecutively referred for cardiac stress testing, asymptomatic subjects with abnormal myocardial perfusion testing were found to have an annual event rate (events defined as myocardial infarction or cardiac death) of 3.4%, versus an event rate of 1.6% in asymptomatic subjects with normal myocardial perfusion scans (p = 0.009) [23].

Another non-randomized trial demonstrated that asymptomatic diabetic patients with high risk SPECT imaging had a survival benefit at five years from coronary artery bypass graft surgery (85% survival) or percutaneous coronary intervention (72%) versus medical therapy alone (67%) [31].

There are no studies that report on the attributable risk of SCD due to silent ischemia in diabetic patients. In the absence of screening for silent ischemia in SCD studies, the higher rate of unrecognized CAD in diabetic subjects would not be taken into account in multivariable analysis models. Therefore the additional risk of SCD afforded by this unrecognized CAD may instead be attributed to diabetes itself. Further studies of the impact of silent ischemia on the risk of SCD are needed. In addition, screening for silent ischemia should ideally be performed at the onset of all studies pertaining to DM and SCD to ensure that all known SCD risk factors are completely accounted for in multivariable analysis.

Autonomic dysfunction

An imbalance in autonomic tone has been linked to an increased risk of sudden death and/or susceptibility to ventricular arrhythmias in a number of different settings in diabetic and non--diabetic populations. For example, animal studies have demonstrated that sympathetic stimulation causes an increased incidence of reperfusion-induced ventricular fibrillation in dogs [32]; and conversely that parasympathetic stimulation decreases the incidence of ventricular fibrillation during ischemia in exercising dogs [33].

Changes in autonomic tone are frequently seen in diabetic patients and have been studied using a number of different methods. Diabetic cardiac autonomic neuropathy (CAN) has been assessed using a number of tests, including: measurements of heart rate and blood pressure response to specific maneuvers (standing up, sustained handgrip, and Valsalva) [34] and various measures of heart rate variability. The prevalence of CAN varies widely depending on the cohort studied and the tests and criteria used for its assessment, but ~15–20% of asymptomatic individuals with diabetes appear to have abnormal cardiovascular autonomic function [35–38]. Earlier studies on CAN supported the premise that parasympathetic dysfunction (diminished heart rate variability) precedes sympathetic dysfunction (such as orthostatic hypotension) in the natural course of the disease [39, 40]. However, some have argued that the higher sensitivities of tests that assess parasympathetic function compared to tests of sympathetic function could account for the earlier detection of parasympathetic abnormalities [41]. In fact, Schnell et al. [42] describe the detection of sympathetic denervation in subjects with type 2 DM and no evidence of CAN (assessed through five cardiac reflex tests) using I-123-metaiodobenzylguanideine (I-123-MIBG) scintigraphy.

Both patient age and duration of DM appear to be significant risk factors for the development of CAN in both type 1 and type 2 DM [43–47], although CAN has been found in both children and adults at initial diagnosis of DM. In a study of 3,250 subjects with type 1 DM followed prospectively over a ten year period, age was associated with an increased risk of developing CAN with an odds ratio of 1.3 per decade (95% CI 1.1–1.7) in a multivariate regression model [47]. In a study of 325 type 1 DM patients, duration of DM was found to be an independent predictor for the development of CAN at two year follow-up based on Cox proportional hazards modeling (Coeff/S.E. = 4.48, p = 0.0000) [43].

Within the diabetic population, the presence of autonomic nervous system dysfunction appears to impart a higher mortality risk [43, 48–61]. In a meta-analysis of 15 studies among individuals with DM, CAN was found to be consistently and significantly associated with subsequent mortality [43, 51, 54, 59–61]. The pooled relative risk for studies that

defined CAN by the presence of two or more abnormal cardiac reflex tests was 3.45 (95% CI 2.66––4.47; p < 0.001) [51]. In addition to an increase in all-cause mortality risk, diabetic patients with CAN have an increased risk of major cardiovascular events [56, 62] and post-myocardial infarction mortality [63, 64] as well.

An increased frequency of sudden cardiac death among subjects with CAN has been reported in a number of studies [49, 54, 59, 65, 66]. While early small observational studies suggested that CAN was independently associated with an increased risk of sudden cardiac death [49, 54, 59, 65], a more recent, larger prospective study [66] has questioned the strength of this association. In this recent study by Suarez et al. [66], 462 patients with DM were followed over 15 years, with 21 cases of SCD reported over this period. Subjects with CAN were found to have a hazard ratio of 1.52 (1.2–1.91) for SCD on univariate analysis, although this was not significant after multivariate analysis. Review of medical records and necropsy reports of the cases of SCD showed that all subjects had either severe coronary atherosclerosis with myocardial damage at necropsy or a clinical history of atherosclerosis with left ventricular dysfunction. This led the authors of the study to postulate that underlying coronary atherosclerosis, myocardial injury and kidney disease alone appeared to be sufficient to account for sudden cardiac death in these patients, with CAN probably playing a lesser role.

Several factors may account for the discrepancies among these studies. Firstly, the relatively small sample sizes of these studies, particularly the earlier ones, brings into question the general applicability of the data obtained from each. Another major difference is the various methods used to define CAN. Measurements and scoring for CAN in the studies differ significantly in terms of both the tests used and the overall numeric scoring systems and thresholds applied. For instance, the 'sudomotor' component that makes up approximately one third of the CASS score used by Suarez et al. [66] to assess for CAN is not present in systems used by the other studies. It should be noted that this sudomotor portion of the CASS score had the least degree of association with SCD on multivariate analysis (0.66; 95% CI 0.27–1.60), with the other two portions of the CASS score both showing adjusted hazard ratios trending towards an association with SCD (adrenergic 1.27; 95% CI 0.65–2.47) and cardiovagal 1.49 (95% CI 0.82–2.72). Overall, the data on the association between CAN and SCD is very limited and appears insufficient to make a reliable conclusion regarding the relationship between these two entities at this time.

QT interval prolongation

QT interval prolongation reflects changes in ventricular repolarization and predicts mortality in many populations. A prolonged QT interval (QTc > 440 ms) on the surface electrocardiogram (ECG) is an independent predictor of increased mortality in patients with ischemic heart disease and heart failure [67–69] as well as in apparently healthy subjects [70]. An increased incidence of SCD associated with QTc prolongation has also been described in a number of studies [67, 70]. The Rotterdam QT Project examined 6,693 consecutive patients undergoing 24 hour ECG monitoring and found that after a two year follow-up, QTc > 440 ms resulted in a RR of 2.1 (95% CI 1.4–3.1) for SCD compared to patients with a QTc < 440 ms [67].

Prolongation of the QT interval is common in DM [71–74]. In a study of 379 type 1 DM patients and 118 non-diabetic control subjects, the QTc interval was greater than 440 ms in 7.6% of control subjects, 25.6% of diabetic patients, and 30.8% of those with diabetic autonomic neuropathy [71]. Similarly, in a cohort of 1,357 patients with type 2 DM, the prevalence of QTc prolongation was found to be 25.8% [74].

The poor prognostic significance of QTc prolongation is present in DM patients as well [55, 57, 75–80]. In several recent studies, QTc interval prolongation was found to be a significant risk factor for all-cause and cardiac mortality in type 1 DM patients. Even after adjustment for other established risk factors for excess mortality in diabetic patients (e.g. age, duration of disease, blood pressure, ischemic heart disease, and smoking), QT interval prolongation remained a significant, independent and powerful predictor of mortality. For example, in a study of 316 type 1 DM patients with an overall mortality of 6.23% at five years, prolonged QTc (> 440 ms) was the only variable associated with increased mortality in multivariate analysis with an odds ratio of 24.6 (95% CI 6.51–92.85) [57].

A prospective study of 182 subjects with newly diagnosed type 2 DM without apparent complications at baseline and followed up for a mean of 10.3 years, showed a significant (p < 0.001) relationship between cardiac death and maximum QTc interval at baseline visit. Additionally, maximum QTc and QT dispersion were both highly significant and independent predictors of cardiac death at three year and six year visits [75]. In the Strong Heart Study of 994 American Indians with type 2 DM followed over a mean of 4.7 years, QTc interval > 460 ms

demonstrated a hazard ratio of 2.03 (95% CI 1.32–3.12) for all-cause mortality [81]. In another prospective study of 697 patients with type 1 DM (mean age 41 years) followed for ten years, QTc prolongation was an independent predictor of mortality. Mortality was 29% in those with prolonged QT intervals, compared to 19% in those with normal QTc (p < 0.001) [76].

Prolongation of baseline QTc interval has also been suggested as increasing the risk of SCD in the diabetic patient, although little data exist to confirm this association. A single case control study consisting of 79 cases of SCD and 214 controls with type 2 DM and no known coronary heart disease, found a 3.5 (1.6–7.6)-fold higher risk of SCD for subjects with baseline QT interval lengths in the fourth quartile (longest) compared to subjects in the first quartile of baseline QT interval length (shortest) after adjustment for age and race [80]. Obviously, more studies are needed regarding this association before generalizations can be made regarding QTc as a significant risk factor for SCD in the diabetic population.

Association between cardiac autonomic neuropathy and QT interval

Interestingly, a strong association exists between CAN and QT interval prolongation. The QT interval has even been proposed as a screening tool to identify diabetic patients with CAN. Multiple studies have found a linear relationship between the severity of CAN and the degree of QTc prolongation in diabetic patients. For instance, in one study of 100 diabetic patients, the coefficient of correlation between CAN score (0–3) and QT interval was 0.73 (p < 0.001) [82]. In a smaller study of 30 patients with type 1 DM, a similar coefficient of correlation was found between CAN score (0–5) and QTc interval both at rest (r = 0.718, p < 0.001) and with exercise (r = 0.719, p < 0.001) [83]. While a number of identified factors, such as age and coronary artery disease, have been associated with prolongation of QTc intervals, a specific autonomic contribution to QTc prolongation in patients with CAN has been suggested. One retrospective study examined QT/RR interval relationships from 24 hour ECG recordings performed initially and then repeated several years later (average three years, range 2–6 years) for three groups of patients (control subjects [n = 13], diabetic subjects without CAN [n = 13], and diabetic subjects with CAN [n = 13]) [65]. Significant changes in the QT/RR relationship (longer QT for any given RR) were found to be associated only with changes in autonomic function testing and were not significantly correlated with age or length of time between recordings. Although the exact mechanism behind increased QT interval duration in CAN has yet to be elucidated, imaging studies using radiotracers (MIBG) to evaluate myocardial sympathetic innervation have demonstrated intracardiac sympathetic imbalance in patients with CAN [84–87] suggesting that this may be a potential contributing factor to QT prolongation. This relationship offers yet another mechanism by which autonomic dysfunction in DM may contribute to SCD through the induction of abnormalities of ventricular repolarization, which in turn may lead to ventricular tachyarrhythmias.

Hypoglycemia

Experimentally induced hypoglycemia has been shown to cause changes in ventricular repolarization in a few small studies [88–90]. In one study of 15 subjects with DM (seven with type 1 DM, eight with type 2 DM), significant changes in QTc were found after controlled hypoglycemia was maintained using hyperinsulinemic glucose clamps. In patients with type 1 DM, QTc increased from 421 ms (362–436 ms) at baseline to 583 ms (421––633 ms) after 120 minutes of hypoglycemia (glucose level of approximately 55 mg/dL; p < 0.01) [88]. A similar trend was demonstrated when patients with type 2 DM underwent the same study. In a follow-up study, beta-blockade was found to nearly abolish the effects of hypoglycemia on QTc prolongation, while potassium infusion did not have a significant effect on QTc during hypoglycemia [90]. This, along with data showing increases in catecholamines associated with hypoglycemia, supports the theory that QTc prolongation is driven by sympathoexcitation during hypoglycemia.

Dead in bed syndrome, a term used to describe the phenomenon of unexpected death in young (< 50) type 1 diabetics while sleeping, was first described by Tattersall and Gill [91] in 1991 through a review of 22 cases of sudden death in otherwise healthy young type 1 diabetic patients with no significant structural heart disease found on autopsy. Subjects were often found with their beds undisturbed (no signs of struggle, seizure or sweating), leading many to hypothesize that death was secondary to sudden lethal arrhythmia. Given the fact that these deaths occurred at night, and the fact that the nadir of glucose levels typically occurs at night during sleep, many have also implicated hypoglycemia as a contributing mechanism to death in these cases.

Unfortunately, given the difficulty in identifying hypoglycemia by post-mortem examination, the

etiology behind this phenomenon remains, for the most part, theoretical. A recent study by Gill et al. [92] used continuous glucose monitoring and 24 hour ECG recordings in 25 type 1 diabetic patients (ages 20–50 years) to monitor for hypoglycemia and any related rhythm disturbances. Thirteen episodes of nocturnal hypoglycemia were identified in the study, with eight cardiac rate and rhythm disturbances noted during these periods. These electrocardiographic disturbances included sinus bradycardia with heart rate <40 bpm (3), ventricular ectopic beats (3), atrial ectopic beats (1) and P wave abnormalities (1). Notably, these abnormalities were not observed when monitoring during normoglycemia. Some have hypothesized that baseline QTc prolongation from CAN, transient QTc prolongation from hypoglycemia, and an underlying genetic predisposition all combine to induce a lethal arrhythmic event in cases of dead in bed syndrome [93]. Interestingly, in a single study of 28 type 1 diabetic subjects and eight control subjects, subjects with CAN tended to show smaller increases in QTc with hypoglycemia compared to diabetic subjects without CAN and non-diabetic controls [94].

The ACCORD trial noted increased mortality in patients with type 2 DM randomized to intensive glucose lowering compared to standard therapy [95]. This group also experienced increased hypoglycemic episodes. Although an increased incidence of fatal arrhythmias was not documented in the intensive glucose lowering group, it is possible that there is a link between hypoglycemic episodes and SCD.

Hypercoaguable state

Other authors have suggested that a hypercoaguable state exists in patients with DM and leads to a higher incidence of catastrophic coronary thrombosis after plaque rupture, thus resulting in a higher rate of sudden fatal coronary events. Indeed, expression of glycoprotein IB and IIB/IIIA have been shown to be increased in DM [96], which in theory augments the interaction of platelets with both von Willebrand factor and fibrin.

In addition, plasma coagulation factors such as factor VII, thrombin and other procoagulants such as tissue factor have been shown to be increased in DM [97–99]. Plasminogen activator inhibitor-1 (PAI-1) which inhibits fibrinolysis has also been shown to be increased in patients with type 2 DM [100, 101]. In theory, all these factors could lead to increased thrombosis following plaque rupture, although outcomes studies, correlating coagulation measures in patients with diabetes with subsequent SCD outcomes, have not been performed.

Diabetic cardiomyopathy

Diabetic cardiomyopathy is the term used to describe the effects of diabetes on cardiac structure and function in the absence of coronary artery disease or hypertension. Data from the Framingham cohort has demonstrated increased rates of heart failure in diabetic subjects even after adjustment for coronary artery disease, hypertension, hypercholesterolemia and obesity [102]. Several possible mechanisms have been identified, including interstitial fibrosis [103], glycation of collagen leading to impaired contractility [104, 105], changes in calcium homeostasis [106], and autonomic dysfunction. In addition to systolic dysfunction, diastolic dysfunction has also been found to be common in diabetic patients, with a prevalence as high as 30–60% reported in some studies [107, 108].

Given that systolic dysfunction increases the risk of SCD in the general population and that the effect of diastolic dysfunction on SCD is relatively unknown, some have proposed that diabetic cardiomyopathy may account for the increased rates of SCD in diabetic patients. While most studies examining the association between SCD and DM have excluded patients with clinical congestive heart failure, the incidence of clinically unrecognized systolic dysfunction in people with diabetes is unknown. Further studies on the characterization of diabetic cardiomyopathy as well as outcomes associated with it are needed.

Impaired respiratory response

Some authors have proposed that a decrease in ventilatory response to hypoxia and hypercapnea contributes to increased SCD in patients with diabetes, particularly those with CAN. Several small studies have demonstrated a decreased response to hypoxia [109–111] in diabetic cohorts, with this deficit being most pronounced in diabetic subjects with CAN. Other studies have failed to find a difference [112, 113]. The response to hypercapnea in subjects with diabetes has varied, with studies showing increased [114], unchanged [112] and decreased ventilatory rates [111, 114] in response to experimentally induced hypercapnea in various diabetic cohorts. Interestingly, Tantucci et al. [114] found a blunted response to hypercapnea in diabetic subjects without CAN, and in diabetic subjects with CAN and only parasympathetic dysfunction. In contrast, diabetic subjects with evidence of CAN with both parasympathetic and sympathetic dysfunction had an increased response to hypercapnea compared to controls. Unfortunately, no significant outcome data have been published to establish an
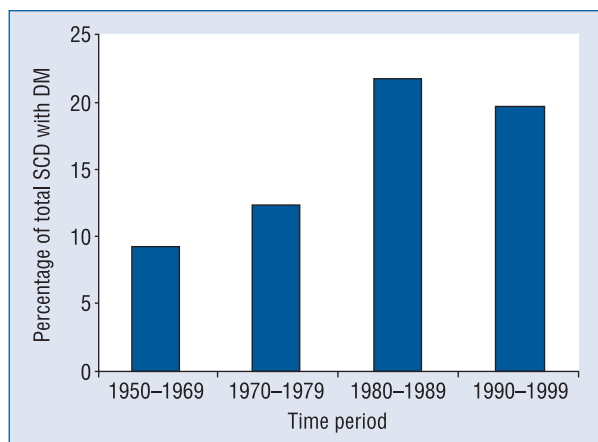
Figure 1. Percentage of sudden cardiac deaths (SCD) with a history of diabetes mellitus (DM). Based on data from Fox et al. [10].

association between ventilatory changes associated with DM and the risk of SCD.

Summary and future directions

In summary, it appears plausible that DM is associated with an increased risk of SCD. Although this increased risk appears relatively small, given the large number of diabetic patients worldwide this may in fact represent a large number of SCDs and a substantial percentage of all SCDs (Fig. 1).

Multiple pathophysiological changes associated with DM have the potential to increase the risk of SCD. However, at this time there are insufficient data to define the contributions that any of these changes have on the risk of SCD in patients with diabetes.

Future studies on SCD and DM are needed to solidify the relationship between these two entities. These studies should focus on identifying and accounting for covariates that are known risk factors for SCD but may be unrecognized in patients with DM (i.e. silent CAD or undiagnosed structural heart disease).

In order to unravel the mechanism(s) behind the increased risk of SCD in DM, further investigation is needed. Rates and degrees of acute and chronic coronary artery disease and myocardial damage have yet to be adequately defined in diabetic patients with SCD and need to be compared with cases of SCD in non-diabetic patients. Variables such as cardiac autonomic tone, ventilatory control, coagulation factor levels, diastolic ventricular function, hypoglycemia frequency/awareness, and the presence or absence of symptoms with myocardial ischemia have yet to be adequately assessed for their associations with SCD.

Defining a unique or preferentially more common mechanism behind SCD in the diabetic patient offers an exciting opportunity for new and improved SCD risk stratification methods that are specifically tailored to the diabetic patient. It may also lend further insight into the risks and benefits of commonly prescribed treatments such as beta-blockers, anticoagulants, aggressive glycemic control, and exercise programs in patients with DM.

Acknowledgments

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