Editorial

Are Diabetic Patients at Increased Risk of Arrhythmias?

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Diabetes and cardiovascular disease often appear to be two sides of the same coin. Diabetes mellitus has been said to be equivalent to coronary heart disease, while conversely many patients with established coronary heart disease suffer from diabetes or its prestates. Of patients with an acute coronary syndrome 20-30% have diabetes and as many as 40% have impaired glucose tolerance.[1] There is evidence that both in-hospital and long-term mortality rates after an acute myocardial infarction are twice as high for patients with diabetes as for those without.[1] Hyperglycaemia, insulin resistance and the consequent cellular shift to increased oxidative stress carry a high risk for the development of comorbidities and cardiovascular risk factors, mainly hypertension, lipid disorders, pro-inflammatory state, and activation of coagulation and thrombosis.[2] As a consequence, the mortality and the incidence of all forms of cardiovascular disease are two- to eightfold higher in persons with diabetes, and coronary artery disease accounts for 75% of all deaths in such individuals.[2]

There is evidence that, apart from coronary artery disease, diabetic patients are also at increased risk of arrhythmias. The underlying risk factors for an arrhythmogenic substrate in patients with diabetes mellitus include imbalance in autonomic tone, silent ischaemia, slowed conduction, heterogeneities in atrial and ventricular repolarisation, and the extent of myocardial damage and scar formation.

Cardiac autonomic neuropathy and silent myocardial ischaemia

The risk for cardiovascular autonomic neuropathy depends on the duration of the diabetes and the degree of glycaemic control. It is caused by injury to the autonomic nerve fibres that innervate the heart and blood vessels.[3] It has been estimated that about 20% of asymptomatic diabetic patients have abnormal cardiovascular autonomic function.[3]

Heart rate variability and baroreflex testing[4] may help in the detection of diabetic autonomic neuropathy. Nerve conduction abnormalities may not be the only component of autonomic dysfunction in diabetes. Relationships between vascular stiffness and dysfunction of the baroreflex response have also been noted.[4,5] Furthermore, some studies have suggested that the primary dysfunction may be the defective activation of central parasympathetic pathways.[5]

Data concerning the actual prevalence of cardiovascular autonomic neuropathy and its related mortality rates are conflicting. However, various studies and meta-analyses reveal that mortality rates among diabetic subjects with cardiovascular autonomic neuropathy are many times higher than among those without.[6,7] Subjects

with diabetes and depressed indexes of autonomic function (baroreflex sensitivity, heart rate variability, and classical Ewing tests) had an approximately two-fold risk of mortality in the Hoorn Study.[6] Moreover, there is evidence that abnormalities of the autonomic nervous system, reflected by increased heart rate and reduced heart rate variability, are associated with cardiovascular mortality and morbidity, and they have been proven to be strong predictors of focal coronary atherosclerosis.[7] A recent study has shown that patients with impaired glucose tolerance have an increased heart rate and elevated levels of pro-inflammatory cytokines (interleukin-6 and tumour necrosis factor-α) in comparison to healthy controls.[8] In the same study, heart rate and heart rate variability parameters were positively associated with serum inflammation markers in diabetic patients; these changes may constitute an index of the primary atherosclerotic process.[8]

The main underlying mechanisms responsible for the strong association between cardiac autonomic neuropathy and cardiovascular mortality are shown in Table 1.

Global myocardial blood flow and coronary flow reserve, studied by positron emission tomography, were subnormal in diabetics with cardiovascular autonomic neuropathy. Cardiovascular autonomic neuropathy may provoke ischaemic episodes by upsetting the balance between myocardial supply and demand.[4-6] Moreover, there is evidence that a prolonged QT interval (a risk factor for ventricular arrhythmias and sudden cardiac death) in patients with diabetes mellitus is associated with the extent of cardiovascular autonomic neuropathy.[9]

Table 1. Factors that are associated with cardiovascular autonomic neuropathy in patients with diabetes mellitus and can lead to increased cardiovascular morbidity and mortality.

Dysfunctional heart rate control
Abnormal vascular dynamics and cardiac denervation
Exercise intolerance
Silent myocardial ischaemia
Diabetic cardiomyopathy
Orthostatic hypotension
Increased prevalence of other cardiovascular risk factors:
Microvascular events
Diabetic nephropathy
Hypertension and dyslipidaemia

Diabetes and atrial fibrillation

In an animal model of diabetes, the occurrence of atrial fibrillation was enhanced by adrenergic activation in the diabetic heart, in which the sympathetic innervation was evident.[10,11] Moreover, the intra-atrial conduction delay and fibrotic deposition in the atria were found to play a major role in producing atrial tachyarrhythmias.[10,11] A heterogeneous increase in sympathetic innervation was proved to be associated with the promotion of atrial fibrillation in several studies.[10,11]

Apart from experimental data, several studies have shown that diabetes favours the occurrence of atrial fibrillation, although the underlying mechanisms remain to be elucidated. In the Framingham Heart Study, diabetes was shown to favour new-onset atrial fibrillation in a large cohort of men and women followed up for 38 years (odds ratio, OR 1.4 for men and 1.6 for women).[12] The Manitoba Follow-up Study estimated the age-specific incidence of atrial fibrillation in 3983 males in order to identify risk factors for the development of this arrhythmia. Diabetes was significantly associated with atrial fibrillation, with a relative risk of 1.82 in the univariate analysis.[13] However, in the multivariate model the association with diabetes was not significant, suggesting that the increased risk of atrial fibrillation in diabetic men may depend on the presence of ischaemic heart disease, hypertension, or heart failure.[13]

In a sub-study of the Framingham Heart Study diabetes was not recognized as a risk factor for atrial fibrillation (hazard ratio, HR 1.10, 95% confidence interval, CI 0.57–1.38, $p=0.43$).[14] However, age, sex, significant murmur, heart failure, systolic blood pressure, hypertension treatment, body mass index, and electrocardiographic PR interval were associated with incident atrial fibrillation (clinical model C statistic 0.78, 95% CI 0.76–0.80; $p<0.05$).[14]

Nichols et al showed that the prevalence of atrial fibrillation was significantly greater among patients with diabetes than in non-diabetic patients (3.6% vs. 2.5%, $p=0.0001$).[15] After full adjustment for other risk factors, diabetes was associated with a 26% increased risk of atrial fibrillation among women (HR 1.26, 95% CI 1.08–1.46), but diabetes was not a statistically significant factor among men (HR 1.09, 95% CI 0.96–1.24).[15] In a retrospective analysis of the prospective VALUE trial, patients with new-onset diabetes had a significantly higher event rate of new-onset atrial fibrillation (HR 1.49, 95% CI 1.14–1.94, $p=0.0031$) compared with patients without diabetes, and there was a trend towards more atrial fibrillation in patients who had diabetes at baseline.[16] More-

over, patients with new-onset diabetes and atrial fibrillation were at greater risk of heart failure compared to patients who had new-onset diabetes without atrial fibrillation (HR 3.56, 95% CI 2.86–4.44, p<0.0001).[16] In the ADVANCE study, after multiple adjustments, atrial fibrillation was associated with a 61% (p=0.0001) greater risk of all-cause mortality and comparable higher risks of cardiovascular death, stroke, and heart failure (all p=0.001).[17] The same study concluded that atrial fibrillation in diabetic patients should be regarded as a marker of particularly adverse outcomes and recommended prompt aggressive management of all risk factors.[17]

The risk stratification of patients with atrial fibrillation for thromboembolic events and stroke is based on the scoring systems $CHADS_2$ and CHA_2DS_2-VASc.[18] In both systems one point is assigned for diabetes mellitus.[18] The update to the current atrial fibrillation guidelines of the European Society of Cardiology recommends that in diabetic patients (one clinically relevant non-major risk factor, CHA_2DS_2-VASc:1) oral anticoagulation therapy with an adjusted-dose vitamin K antagonist (INR 2–3), or a direct thrombin inhibitor (dabigatran), or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban), should be considered, based upon an assessment of the risk of bleeding complications and the patient's preferences (Class IIa, Level of Evidence A).[18]

Undoubtedly, diabetes and atrial fibrillation share common antecedents, such as hypertension, atherosclerosis, and obesity. Diabetes has long been recognised as a risk factor for atrial fibrillation, and this was subsequently reconfirmed in several studies. However, the potential independent contribution of diabetes to the prevalence and incidence of atrial fibrillation has not been evaluated and the confluence of these two conditions clearly warrants additional studies.

Diabetes and sudden cardiac death

The risk factors for the development of an arrhythmogenic substrate in diabetes mellitus are heterogeneities in atrial and ventricular repolarisation, and the extent of myocardial damage and scar formation. There is evidence that the incidence of cardiac arrhythmias, including ventricular fibrillation and sudden death, is greater in diabetic patients.[19-28]

Diabetes is associated with an increased risk of sudden cardiac death that is due, at least in part, to the greater presence and extent of coronary atherosclerosis (macrovascular disease). Diabetes is also associated with microvascular disease and autonomic neuropathy, and these non-coronary atherosclerotic pathophysiological processes have the potential to increase the risk of sudden cardiac death.[29] The arrhythmological substrate in ischaemic heart disease includes myocardial re-entry due to scar formation, compensatory hypertrophy in non-infarcted myocardium, and progressive ventricular remodelling and neurohormonal abnormalities.[29] In addition, changes in autonomic nervous system activity, metabolic disturbances, electrolyte abnormalities, acute volume and/or pressure overload, and ion channel abnormalities may all contribute to creating the substrate for ventricular arrhythmogenesis and sudden cardiac death.[29] Moreover, as mentioned above, prolongation of the QT interval is known to be associated with an increased risk of sudden cardiac death in patients with diabetes.[9] Recent evidence favours the concept that the risk is related to the glucose level and is already present at the stage of impaired glucose tolerance.[28]

Interestingly, a positive association (2- to 4-fold increase in the risk of sudden cardiac death) was found in studies with a long-term follow up (typically >20 years).[24-28] In the Paris Prospective Study I, a study of middle-aged men free of clinical heart disease working for the city of Paris, the risk of sudden cardiac death, but not of fatal myocardial infarction, was greater in diabetes patients than in normal subjects.[30]

However, in two other prospective studies of middle-aged men from Finland and England (British Heart Regional Study), diabetes and glucose level were not associated with sudden cardiac death.[31,32] Several reasons may explain these apparent discrepancies. In the Finnish study, the prevalence of diabetes was low, only 1.5% of study participants. Finally, these two studies had a relatively short duration of follow up, 8 and 11 years, respectively.[31,32]

In another study, higher glucose levels were also associated with the risk of sudden cardiac death, both in the absence and in the presence of microvascular disease.[28] When compared with patients without diabetes, a progressively higher risk of sudden cardiac death was found to be associated with borderline diabetes (OR 1.24, 95% CI 0.98–1.57), diabetes without microvascular disease (OR 1.73, 95% CI 1.28 – 2.34), and diabetes with microvascular disease (OR 2.66, 95% CI 1.84 – 3.85), after adjustment for potential confounders (p=0.001).[28] Another study evaluat-

ed the incidence of sudden cardiac death in 3276 patients with acute myocardial infarction between 1996 and 2005.[33] Among diabetic patients, the incidence of sudden cardiac death was higher (5.9%) than in non-diabetic patients (1.7%) (HR 3.8, 95% CI 2.4–3.8, $p<0.001$, and HR 2.3, 95% CI 1.4–3.8, $p<0.01$, after adjustment for other cardiovascular risk factors.[33] The incidence of sudden cardiac death in post-myocardial infarction type 2 diabetic patients with a left ventricular ejection fraction >35% was equal to that of non-diabetic patients with a left ventricular ejection fraction <35% (4.1% versus 4.9%, $p=0.48$).[33]

The Rochester Diabetic Neuropathy Study was designed to define the risk factors for sudden cardiac death and the role of diabetic autonomic neuropathy in a population of 462 diabetic patients followed for 15 years.[34] Interestingly, necropsy findings demonstrated that all victims of sudden cardiac death had signs of coronary artery or myocardial disease.[34] Kidney dysfunction and atherosclerotic heart disease are the most important determinants of the risk of sudden cardiac death, while neither autonomic neuropathy nor QT interval corrected to heart rate (QTc) are independent predictors.[35] Moreover, in another study, QT dispersion (QTd) values did not differ between individuals with and without diabetes ($p=0.15$) and cardiac autonomic neuropathy did not affect QTd in diabetics ($p=0.07$).[36]

The identification of independent predictors of sudden cardiac death in diabetic patients has not yet progressed to a stage where it is possible to devise a risk stratification scheme for the prevention of sudden deaths. However, microvascular disease and nephropathy may be indicators of an increased risk.[28,29]

It is unclear whether diabetes alters the incidence of sudden cardiac death via mechanisms that include autonomic dysfunction arrhythmias, perhaps triggered by hypoglycaemia, altered cardiac repolarisation, or cardiomyopathy, which may be distinct from the contributions of coronary disease. Current guidelines for managing sudden cardiac death risk in diabetics acknowledge their increased risk, but fall short of specific recommendations because of the lack of data. Based on available evidence, it seems that glucose intolerance, even at a pre-diabetic stage, is associated with progressive development of a variety of abnormalities that adversely affect survival and predispose to sudden cardiac death.[33] Moreover, control of glycaemia, even in the pre-diabetic stage, is important to prevent the development of the alterations that predispose to sudden cardiac death (Class I, Level of Evidence C).[35] Microvascular disease and nephropathy are indicators of an increased risk of sudden cardiac death in diabetic patients (Class IIa, Level of Evidence B).[35]

In conclusion, arrhythmias are a major cause of cardiovascular complications and mortality among patients with diabetes. The causal pathophysiological and electrophysiological mechanisms need to be verified in further studies. Since there are evidence-based risk factors for arrhythmias that may be specifically related to diabetes, such as microvascular disease and autonomic neuropathy, for now, the focus of interventions should be on the primary prevention of diabetes, atherosclerosis, coronary heart disease and the secondary prevention of the cardiovascular consequences of these common conditions. However, continued investigation into specific therapies and strategies targeting the unique diabetes-linked risks for arrhythmias and cardiovascular complications remains a critical global health imperative.

References

1. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339: 229-234.
2. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. Circulation. 2000; 102: 1014-1019.
3. Valensi P, Huard JP, Giroux C, Attali JR. Factors involved in cardiac autonomic neuropathy in diabetic patients. J Diabetes Complications. 1997; 11: 180-187.
4. Skrapari I, Tentolouris N, Katsilambros N. Baroreflex function: determinants in healthy subjects and disturbances in diabetes, obesity and metabolic syndrome. Curr Diabetes Rev. 2006; 2: 329-338.
5. Nesto RW, Libby P. Diabetes mellitus and the cardiovascular system. In Braunwald E, Zipes DP, Libby P (eds): Heart Disease. A textbook of cardiovascular Medicine. 6th ed. Philadelphia: WB Saunders; 2001. p 2133.
6. Gerritsen J, Dekker JM, TenVoorde BJ, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease: the Hoorn Study. Diabetes Care. 2001; 24: 1793-1798.
7. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. Eur Heart J. 2003; 24: 13-15.
8. Diakakis GF, Parthenakis FI, Mavrakis HE, et al. Association of impaired glucose tolerance with increased heart rate and subclinical inflammation. Hellenic J Cardiol. 2005; 46: 394-401.
9. Cardoso CR, Salles GF, Deccache W. Prognostic value of QT interval parameters in type 2 diabetes mellitus: results of a

long-term follow-up prospective study. J Diabetes Complications. 2003; 17: 169-178.
10. Schmid H, Forman LA, Cao X, Sherman PS, Stevens MJ. Heterogeneous cardiac sympathetic denervation and decreased myocardial nerve growth factor in streptozotocin-induced diabetic rats: implications for cardiac sympathetic dysinnervation complicating diabetes. Diabetes. 1999; 48: 603-608.
11. Olgin JE, Sih HJ, Hanish S, et al. Heterogeneous atrial denervation creates substrate for sustained atrial fibrillation. Circulation. 1998; 98: 2608-2614.
12. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA. 1994; 271: 840-844.
13. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995; 98: 476-484.
14. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet. 2009; 373: 739-745.
15. Nichols GA, Reinier K, Chugh SS. Independent contribution of diabetes to increased prevalence and incidence of atrial fibrillation. Diabetes Care. 2009; 32: 1851-1856.
16. Aksnes TA, Schmieder RE, Kjeldsen SE, Ghani S, Hua TA, Julius S. Impact of new-onset diabetes mellitus on development of atrial fibrillation and heart failure in high-risk hypertension (from the VALUE Trial). Am J Cardiol. 2008; 101: 634-638.
17. Du X, Ninomiya T, de Galan B, et al. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. Eur Heart J. 2009; 30: 1128-1135.
18. Camm AJ, Lip GY, De Caterina R, et al. Focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012; Aug 24 (Epub ahead of print).
19. Fox CS, Coady S, Sorlie PD, et al. Trends in cardiovascular complications of diabetes. JAMA. 2004; 292: 2495-2499.
20. Lee CD, Folsom AR, Pankow JS, Brancati FL. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation. 2004; 109: 855-860.
21. Hu FB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med. 2001; 161: 1717-1723.
22. Lotufo PA, Gaziano JM, Chae CU, et al. Diabetes and all-cause and coronary heart disease mortality among US male physicians. Arch Intern Med. 2001; 161: 242-247.
23. Cho E, Rimm EB, Stampfer MJ, Willett WC, Hu FB. The impact of diabetes mellitus and prior myocardial infarction on mortality from all causes and from coronary heart disease in men. J Am Coll Cardiol. 2002; 40: 954-960.
24. Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J. 1998; 136: 205-212.
25. Albert CM, Chae CU, Grodstein F, et al. Prospective study of sudden cardiac death among women in the United States. Circulation. 2003; 107: 2096-2101.
26. Curb JD, Rodriguez BL, Burchfiel CM, Abbott RD, Chiu D, Yano K. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. Circulation. 1995; 91: 2591-2595.
27. Balkau B, Jouven X, Ducimetière P, Eschwège E. Diabetes as a risk factor for sudden death. Lancet. 1999; 354: 1968-1969.
28. Jouven X, Lemaître RN, Rea TD, Sotoodehnia N, Empana JP, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. Eur Heart J. 2005; 26: 2142-2147.
29. Siscovick DS, Sotoodehnia N, Rea TD, Raghunathan TE, Jouven X, Lemaitre RN. Type 2 diabetes mellitus and the risk of sudden cardiac arrest in the community. Rev Endocr Metab Disord. 2010; 11: 53-59.
30. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation. 1999; 99: 1978-1983.
31. Suhonen O, Reunanen A, Knekt P, Aromaa A. Risk factors for sudden and non-sudden coronary death. Acta Med Scand. 1988; 223: 19-25.
32. Wannamethee G, Shaper AG, Macfarlane PW, Walker M. Risk factors for sudden cardiac death in middle-aged British men. Circulation. 1995; 91: 1749-1756.
33. Junttila MJ, Barthel P, Myerburg RJ, et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. Heart Rhythm. 2010; 7: 1396-1403.
34. Suarez GA, Clark VM, Norell JE, et al. Sudden cardiac death in diabetes mellitus: risk factors in the Rochester diabetic neuropathy study. J Neurol Neurosurg Psychiatry. 2005; 76: 240-245.
35. Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007; 28: 88-136.
36. Psallas M, Tentolouris N, Cokkinos A, Papadogiannis D, Cokkinos DV, Katsilambros N. QT dispersion: comparison between diabetic and non-diabetic individuals and correlation with cardiac autonomic neuropathy. Hellenic J Cardiol. 2006; 47: 255-262.