

Clinical Perspective

Diabetes mellitus and congestive heart failure

Further knowledge needed

Introduction

Diabetes mellitus, and in particular the type 2^[1], has progressively become more common. Factors increasing the prevalence include an ageing population, an increasing body mass and decreased demands of physical activity^[2]. In type 2 diabetes manifestations of atherosclerosis are frequently present at the time of diagnosis. Approximately 20% of patients admitted to Swedish coronary care units for myocardial infarction have diabetes. In a recent health survey, 22% of diabetic patients reported that they needed to see a cardiologist during the previous 12 months and up to 50% had cardiovascular disease^[3]. As type 2 diabetes, including the pre-diabetic period, is an important risk factor for atherosclerosis the increasing prevalence suggests that there will be a considerable increase in diabetes-related cardiovascular disease in the near future^[2].

Ischaemic heart disease is still the leading cause of congestive heart failure despite advances in its prevention and treatment. Heart failure has increased in prevalence while there has been a decrease in the age-adjusted morbidity and mortality of coronary artery disease. An ageing population and increased survival of patients with myocardial infarction are likely explanations^[4]. Thus, diabetes mellitus is closely linked to congestive heart failure. Proper treatment, including meticulous metabolic control of the diabetes, may considerably improve the prognosis for diabetic patients with myocardial infarction^[5] and also possibly prevent its occurrence^[6]. Nevertheless, even with the best preventive strategies and expert treatment of established cardiovascular disease, a considerable proportion of heart failure patients will have diabetes. Further research is needed for the proper handling of these subjects. This may contribute not only to patient relief but also to a decrease of future demands on health care resources.

The objective of this review is to summarize epidemiological, prognostic and therapeutic knowledge related to congestive heart failure and diabetes.

Epidemiology

The Framingham study was the first epidemiological study to demonstrate an increased risk of congestive heart failure in patients with diabetes mellitus. Compared with non-diabetic males and females, the estimated increase in the incidences of heart failure for young diabetic males and females were fourfold and eightfold, respectively^[7].

In a retrospective survey of patients in need of hospitalization for congestive heart failure in western Sweden 10% had diabetes mellitus. Since individuals above the age of 65 years were excluded, and only patients on insulin were classified as having diabetes, this number is an underestimate of the true proportion^[8]. The large ACE inhibitor clinical heart failure trials offer somewhat less age-restricted information. The proportion of subjects with diabetes was 23% in **CONSENSUS** (Cooperative North Scandinavian Enalapril Survival Study)^[9], 25% in **SOLVD** (Studies of Left Ventricular Dysfunction)^[10], 20% in **V-HeFT II** (Vasodilator Heart Failure Trial II)^[11] and 20% in **ATLAS** (Assessment of Treatment with Lisinopril and Survival)^[12]. As studies are always carried out on selected populations these figures also need to be interpreted with caution. Ten percent of the patients in **NETWORK**, a trial planned to be representative of a complete heart failure population, had diabetes^[13]. In the **RESOLVD** (Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot trial) study^[14] the prevalence of diabetes was 27% at the time of randomization. In **RESOLVD** blood glucose was measured at baseline. Application of the most recent diagnostic criteria for diabetes^[1] resulted in a prevalence of 35%. The observed variability between different studies is due to several factors of which age, aetiology, severity of heart failure and the definition of diabetes mellitus are the most important.

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Congestive heart failure is a frequent reason for hospital admission^[15]. Reis *et al.*^[16], evaluated specialty-related differences in the care and outcome of patients admitted to hospital for heart failure. They noted that as many as 38% of all patients had diabetes mellitus requiring pharmacological treatment. Recent Italian cross-sectional data show a 30% prevalence of diabetes in an elderly heart failure population. The association with diabetes was independent of age, sex, blood pressure, body mass index or waist/hip ratio and also of a family history of diabetes. The incidence of diabetes was 29% during 3 years of follow-up among heart failure patients initially free from this disease compared with 18% in a group of matched controls. On a basis of multivariate statistics, congestive heart failure independently predicted subsequent type 2 diabetes. A possible explanation is that an increased adrenergic drive, caused by heart failure, increases free fatty acid oxidation and insulin resistance thereby decreasing glucose oxidation and precipitating type 2 diabetes^[17].

In a recent, population-based study of elderly patients it was concluded that diabetes mellitus is an independent risk factor for heart failure and that the risk increases with disease severity. Furthermore, after multivariate adjustment, a 1% increase in the baseline level of HbA1c increased the risk of developing heart failure by 15% in patients with and without known diabetes. This indicates that the independent risk for developing heart failure in diabetic patients may to some extent be mediated by poor metabolic control^[18].

In summary, there is consistent epidemiological evidence that diabetes mellitus is common in a heart failure population. Furthermore, diabetes and heart failure may be interrelated.

Prognosis

Diabetes is an independent risk factor for the development of congestive heart failure and heart failure patients with diabetes have a worse prognosis than those without diabetes. In the SOLVD study diabetes was an independent predictor of morbidity and mortality both in symptomatic and asymptomatic heart failure^[19]. This relationship was confirmed by the RESOLVD trial^[14]. Diabetic patients also experience a higher incidence of heart failure and increased mortality after acute myocardial infarction than non-diabetic patients^[20–23]. In the DIGAMI (Diabetes mellitus Insulin-Glucose infusion in Acute Myocardial Infarction) study, cohort heart failure was the most common reason for morbidity and mortality accounting for 66% of the total mortality during the first year of follow-up^[24].

Heart failure mechanisms in diabetics

Diabetic cardiomyopathy

Following the original proposal by the Danish internist Lundbäck^[25] the increased susceptibility of diabetic patients to heart failure has often been attributed to a diabetes-specific myocardial disease referred to as 'diabetic cardiomyopathy'. Although the most common cause of death in diabetic patients is not cardiomyopathy but coronary artery disease, heart failure is more frequent in diabetic than in non-diabetic patients with myocardial ischaemic injury. This does not seem to be due to more extensive myocardial damage because many reports on the subject show that infarct size is no larger in diabetic than non-diabetic patients^[20].

Morphology

Numerous investigations have been devoted to morphological alterations in the diabetic heart, as recently discussed by Hardin in an extensive review^[26]. It may be concluded that the most consistent findings are myocyte hypertrophy, interstitial fibrosis, increased PAS-positive material and intramyocardial microangiopathy. There are no lesions characteristic for diabetes only, indicating that the reason for a diabetic cardiomyopathy may be found at a functional or biochemical level. There appears to be a synergism with structural changes usually attributed to hypertension. This may have important treatment implications in the light of the favourable effect of antihypertensive therapy in diabetic patients noted in the HOT^[27] and UKPDS^[28] trials.

Diastolic dysfunction

The common response in a non-infarcted myocardial area subjected to acute ischaemia is a compensatory hyperkinesia that may almost normalize the ejection fraction^[29,30]. In GUSTO 1 (Global Utilization of Streptokinase and t-PA for Occluded coronary arteries-1), with more than 300 diabetic subjects, coronary angiograms performed 90 min after thrombolysis did not reveal any difference in the global ejection fraction between diabetic and non-diabetic patients. The normal compensatory hyperkinetic response in the non-infarcted area was, however, blunted among diabetic patients^[31]. A decreased regional ejection fraction in non-infarcted myocardial areas of diabetic patients has been reported^[32,33]. During follow-up in the GUSTO trial, congestive heart failure was almost twice as common in the diabetic as in the non-diabetic cohort^[31]. This is congruent with a report by Stone *et al.*^[20], who noted

a higher incidence of heart failure among diabetic patients despite smaller infarct sizes and ejection fractions which were similar to those in subjects without diabetes. These findings probably reflect impaired diastolic function, a finding that seems to be the most characteristic feature of diabetes-associated myocardial disease^[34–36].

Several studies verify that coronary artery disease, even in its asymptomatic form, is more common and widespread among diabetics than non-diabetics. This may explain the lack of a compensatory hyperkinetic response to ischaemia and the diastolic impairment. Diastolic dysfunction is an early sign of myocardial ischaemia^[37]. Most studies that suggested a diabetic cardiomyopathy did not angiographically exclude co-existent coronary artery disease. This differentiation is a requirement in future studies.

Myocardial blood flow

Another reason for a compromised myocardial blood flow, or an inability to increase this flow when demanded, relates to impaired endothelial dependent vasodilatation. The mechanisms behind endothelial dysfunction in the diabetic patient are not fully understood. This dysfunction has been verified both in type 1^[38,39] and type 2 diabetes^[40,41]. Diabetic patients have a reduced myocardial flow reserve compared with matched controls even in the absence of obvious heart disease. Acute hyperglycaemia may impair endothelial-derived vasodilatation in healthy humans^[42]. The inability to increase myocardial blood flow is independently related to long-term control of blood glucose, however, and not to age, blood pressure or blood lipids^[43]. Accordingly it may be assumed that elevated blood glucose by itself is of considerable importance for the impaired vascular response. This may contribute to the lack of hyperkinetic response and the diastolic dysfunction seen in diabetes mellitus. It may serve as a rationale for treatment aimed at strict glucose control to reduce cardiovascular events in a diabetic population.

Metabolic aspects

Metabolic factors may be of fundamental importance in the development of myocardial dysfunction unrelated to macrovascular disease in patients with diabetes, as has been excellently reviewed by *Rodrigues et al.*^[44–46]. In addition to incidence of hyperglycaemia, diabetes is characterized by an increased turnover of free fatty acids. The increased free fatty acids provoke increased use of myocardial oxygen and enhance intracellular accumulation of intermediates leading to several untoward effects. These effects include promotion of intracardiac conduction disturbances and arrhythmias, interference

with adenosine triphosphate dependent ion pumps, and an increased alpha-1-response causing mobilization of intracellular calcium creating calcium overload and contractile dysfunction. In addition to the effects of insulin deficiency, the increased free fatty acids inhibit both glucose transport and metabolism. Increased levels of citrate, produced by free fatty acid oxidation, inhibit phosphofructokinase. This leads to decreased glycolysis and promotes glycogen synthesis. Impaired glucose oxidation also leads to lactic acid accumulation which further promotes the degradation of free fatty acids.

In summary, a diabetes-related myocardial dysfunction — a diabetic cardiomyopathy — exists and is of clinical significance. It is characterized by a lack of compensatory response to myocardial ischaemia or injury and includes early impairment of the diastolic function. The pathophysiological mechanisms, although not fully understood, are multifactorial and include metabolic and vascular components. This suggests that interventions against hyperglycaemia and increased free fatty acid oxidation, e.g. strict use of insulin, may be beneficial. Moreover, there seems to be a synergism between diabetes and hypertension in the development of structural myocardial changes. This may explain why vigorous treatment of hypertension is of particular value in the diabetic patient.

Autonomic dysfunction

Cardiac autonomic imbalance is a common consequence of diabetes. One effect is a decreased or even an eliminated perception of ischaemic pain. Silent ischaemia may cause myocardial injury without clinical signs promoting future heart failure^[47,48]. Even more important may be the effects of a decreased vagal tone. Diabetic patients with disturbed autonomic function have a higher heart rate than non-diabetic patients. This relates to predominant parasympathetic dysfunction preceding the involvement of the sympathetic system^[49]. Tachycardia increases myocardial oxygen demand concomitantly with a decrease in the time for myocardial blood flow due to the shortened diastole. Decreased heart rate variability due to impaired vagal tone is another factor of prognostic importance. When present it is linked to an increased risk for sudden cardiac death^[50].

Treatment of heart failure in diabetics

Treatment of symptomatic heart failure in the diabetic patient follows principles extensively outlined in

the European Society of Cardiology guidelines on the treatment of congestive heart failure^[51]. Few, if any, studies have addressed in any detail the therapeutic efficacy of conventional treatment in a diabetic population.

Diuretics

Diuretics are mandatory for symptomatic treatment of heart failure. Whether the use of diuretics will improve or worsen the prognosis of diabetic patients is not known. In the absence of studies in diabetic subjects with heart failure the only available information is derived from antihypertensive trials. Warram *et al.*^[52] claimed that diuretic-based antihypertensive treatment of diabetic patients was associated with excess mortality; the treatment only related to years of treatment, however, not to the severity of concomitant nephropathy. The type of diuretic was not specified. In contrast, the SHEP (Systolic Hypertension in the Elderly Program) study reported that low-dose diuretic (saluretics) based antihypertensive therapy effectively prevented major cardiovascular events, including mortality, in patients with type 2 diabetes^[53]. Although no studies have specifically looked into the outcome of the use of diuretics in a heart failure population, loop diuretics are recommended rather than diuretics that may further impair the gluco-metabolic state.

ACE inhibitors

The use of ACE inhibitors is a cornerstone in the treatment of congestive heart failure since the landmark CONSENSUS study^[9]. As already emphasized, diabetic patients represent a fairly large subgroup in the patient cohorts in long-term trials of several ACE inhibitors, from 10% in NETWORK^[13] to 25% in SOLVD^[10]. Subgroup analysis of diabetic mortality data from those studies reveal that mortality, as could be expected, is higher within the diabetic cohort than among non-diabetic patients.

In the SOLVD prevention trial^[54], placebo or enalapril (2.5–20 mg; mean 12.7 mg) was given to patients with compromised left ventricular function (EF \leq 35%) but without signs of heart failure during an average of 37.4 months. The SOLVD treatment study recruited patients with a left ventricular ejection fraction \leq 35% and signs of heart failure. They were either given placebo or enalapril (2.5–20 mg; mean 11.8 mg) over an average follow-up period of 41 months. The efficacy of the ACE inhibitor was somewhat more marked for diabetic than non-diabetic patients in SOLVD prevention and of approximately similar efficacy in the treatment arm of SOLVD^[10].

The ATLAS trial^[12] compared high (32.5–35 mg) and low (2.5–5.0 mg) doses of the ACE inhibitor lisinopril over a median period of 45 months in heart failure patients of NYHA classes II–IV. The total patient cohort was 3164 patients of whom 611 were diabetics. The ATLAS trial therefore reports on the largest diabetic heart failure subgroup presently available. Mortality was considerably higher within the diabetic subgroup than in the non-diabetics. The mortality risk reduction in studying the efficacy of the high and low ACE inhibitor dose strategy was 6% for non-diabetics compared with 14% for the diabetic subgroup and emphasizes the need for appropriate doses of ACE inhibitors when treating diabetic as well as non-diabetic patients.

Post-myocardial infarction patients with compromised left ventricular function, defined as left ventricular ejection fraction \leq 40%, were studied in SAVE (Survival and Ventricular Enlargement)^[55,56]. According to a subgroup analysis the diabetic cohort had a higher morbidity and total mortality than the non-diabetic group. Treatment with the ACE inhibitor captopril improved this unfavourable outcome to an extent similar to that among non-diabetic patients. GISSI 3 (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardio^[57]) reported on the effect of an ACE inhibitor administered as soon as possible after onset of symptoms indicating myocardial infarction. The patients were randomized to treatment with oral lisinopril or to serve as open controls. After 6 weeks the mortality in the high-risk diabetic population was 9% in the lisinopril group compared with 12% in the control group. Non-diabetic subjects were at lower overall risk and did not further benefit from lisinopril (mortality 6% in both groups). The beneficial effect of lisinopril remained at the 6 months follow-up. The reason for the discrepancy in outcome in this trial compared with other ACE inhibitor heart failure trials, in showing a greater similarity in outcome among non diabetic and diabetic patients, is not clear.

Hypoglycaemic events have been reported to increase following the institution of ACE inhibitors in diabetic patients. As some ACE inhibitors have been shown to decrease insulin resistance, it is recommended that blood glucose is carefully monitored in the early phase following the institution of an ACE inhibitor in patients on antihyperglycaemic drugs^[58,59].

In conclusion, ACE inhibitors are of value in the treatment of diabetic patients with congestive heart failure. Perhaps the relative efficacy is more apparent in this subgroup than among non-diabetic patients, fitting into the general knowledge that patients at high risk benefit the most. There are data supporting

the use of a high-dose ACE inhibitor strategy. Precise knowledge is still lacking on the effect of ACE inhibitors in diabetic patients. Data presented are derived from subgroup analyses of clinical trials in which the diabetic population and their anti-diabetic therapy were poorly defined. The latter may very well influence the effect of other therapeutic measures.

Beta-blockers

It has been speculated that the particularly beneficial effect of early administration of beta-blockers following myocardial infarction relates to a reduced accumulation of free fatty acids and improved myocardial glucose utilization^[60]. This would be of particular value for the diabetic patient in whom glucose oxidation is already impaired. Another possible beneficial effect of beta-blockade is a reduction of the increased heart rate that is caused by a disturbed autonomic tone. Both these mechanisms would offer relief not only in the post-myocardial infarction phase but in subjects with heart failure. Evidence supporting this hypothesis has been presented as subgroup analysis of the effect of the beta-blocker carvedilol in diabetics with congestive heart failure^[61].

There are no studies that specifically address the subject of beta-blockade in diabetic subjects with heart failure. Such a use is currently advocated. Prospective stratification of diabetic patients in large clinical trials and documentation of their anti-diabetic treatment would yield important insight into the value of beta-blockade in this group of heart failure patients.

Metabolic control

There are several reasons to assume that the prognosis of patients with the combination of heart failure and diabetes mellitus would improve with a meticulous metabolic control. For example, the proposed harmful effect of an increased free fatty acid oxidation rate and decreased glucose utilization could both be attenuated by intense insulin treatment. Bersin *et al.*^[62] applied a metabolic concept in non-diabetic patients with severe heart failure in using the drug dichloroacetate. This compound stimulates pyruvate dehydrogenase activity thereby facilitating glucose oxidation and, in parallel, inhibiting free fatty acid metabolism. Myocardial extraction of lactate increased during dichloroacetate infusion. At the same time there was an improved forward stroke volume and the left ventricular minute work increased, although myocardial oxygen consumption

decreased. In the DIGAMI study, an insulin-glucose infusion followed by multidose subcutaneous insulin treatment considerably improved the long-term prognosis of diabetics with myocardial infarction^[5,24]. Since a similar concept has not yet been tested in heart failure patients, it is not known whether improved metabolic care would favourably influence the efficacy of conventional therapy in diabetics with heart failure or whether it would be of preventative value against the development of heart failure in diabetics with cardiac disease. Studies of the impact of strict metabolic care in patients with congestive heart failure are urgently needed.

Future perspectives

This review is an attempt to summarize the available information on heart failure in the diabetic subject and to identify areas in need of further studies. Many overviews have been published regarding cardiovascular disease in diabetics. Few if any have addressed heart failure despite the fact that diabetic patients are at a particularly high risk of congestive heart failure, and that the prognosis is worse than the already unfavourable outlook for non-diabetic heart failure patients. Identified reasons for this dismal prognosis include the poor outcome of myocardial infarction, the possible existence of a specific diabetic cardiomyopathy, the severity and distribution of coronary artery disease and disturbed autonomic function. To date a comprehensive approach has been lacking. It is therefore difficult to know whether there are any strategies that may prevent or at least postpone the development of heart failure among diabetic patients. It seems that such a strategy should comprise a multitude of activities including aggressive normalization of blood glucose with insulin, beta-blockade and ACE inhibition. Since there is an apparent lack of information on quality of life in the diabetic patient with congestive heart failure, future trials should include such aspects. Revascularization strategies and studies of ways to improve the outcome after coronary interventions in diabetic patients are also needed. The diabetic subject in need of coronary angioplasty or a bypass procedure has a worse prognosis than non-diabetic patients. This includes a higher risk for restenosis after coronary angioplasty and of myocardial injury after any of these interventions^[63,64].

Finally, it is clear that compromised left ventricular function may precede the development of congestive heart failure by a considerable period of time. The implication is that more aggressive metabolic care at an early stage of the disease may delay restructuring

of the myocardium and atheromatosis. Improved metabolic care may also decrease the thrombogenicity that characterizes diabetes. Currently, therapeutic efforts are frequently initiated at a late stage of the disease, a stage during which only a modest symptomatic improvement and prolongation of longevity may be obtained. The patient should be identified at an earlier stage of the disease. Combined efforts of cardiologists and diabetologists are needed in the screening of risk patients and in preventative measures. Improved knowledge among diabetologists regarding treatment and prevention of cardiovascular complications and among cardiologists regarding diabetology is a prerequisite for progress. Considering the large and rapidly increasing number of patients at risk it is certainly urgent to get started. The high costs associated with the management of diabetic patients with heart failure suggest that improved therapy is likely to be cost effective as was demonstrated, for example, in the use of aggressive metabolic care for diabetic patients with myocardial infarction^[65].

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