ISSN: 1850-1044

HIGHLIGHTS

Artículos destacados en insuficiencia cardíaca y diabetes

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Heart disease in diabetic patients
Semin Nephrol 2005 Nov;25(6):372-8.
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Cardiac artery disease and heart failure are major causes for morbidity and mortality in diabetes in general and in those with chronic kidney disease (CKD) in particular. Hypertension and dyslipidemia are more common in diabetes and the prevalence of coronary artery disease in diabetics is two-fold to four-fold higher than in nondiabetics. In those with CKD the incidence of cardiovascular complications is nearly two-fold higher than those without CKD. Recent studies suggest that the pathophysiology of cardiac disease is complex process involving both microvascular and macrovascular disease. In addition, myocardial lipotoxicity may be a novel contributing factor particularly in type 2 diabetics. Compelling evidence from cardiovascular outcomes trials indicates that treatment with drugs that block the renin-angiotensin system are cardioprotective in diabetics with microalbuminuria and early stages of kidney disease. Multiple risk factor intervention aimed at optimal blood pressure control (BP <130/<80 mmHG), lowering LDL cholesterol below 100 mg/dl, lowering triglyceride level to 150 mg/dl, A1C <6.5%, treatment with an ACE inhibitor or an angiotensin II receptor blocker, administration of once daily low-dose aspirin and smoking cessation together reduce cardiovascular morbidity and mortality in type 2 diabetics. Novel studies including diabetics with nephropathy aimed at improving outcomes in diabetics by treatment of anemia and optimal control of dyslipidemia are now underway. These and other clinical trials should provide important new insights into improving the quality of life in diabetics and ultimately preventing cardiac disease.

The association between glucose abnormalities and heart failure in the population-based Reykjavik study
Diabetes Care. 2005 Mar;28(3):612-6.
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OBJECTIVE: Diabetes is an independent risk factor for heart failure, whereas the relation between heart failure and abnormal glucose regulation (AGR) needs further evaluation. We studied this combination in the Reykjavik Study. RESEARCH DESIGN AND METHODS: The Reykjavik Study, a population-based cohort study during 1967-1997, recruited 19,381 participants aged 33-84 years who were followed until 2002. Oral glucose tolerance tests and chest X-rays were obtained from all participants. Cases were defined in accordance with World Health Organization criteria for type 2 diabetes or AGR (impaired glucose tolerance or impaired fasting glucose) and European Society of Cardiology guidelines for heart failure. RESULTS: The overall prevalence of type 2 diabetes and heart failure was 0.5% in men and 0.4% in women, while AGR and heart failure were found in 0.7% of men and 0.6% of women. Among participants with normal glucose regulation, heart failure was diagnosed in 3.2% compared with 6.0 and 11.8% among those with AGR and type 2 diabetes, respectively. The prevalence of type 2 diabetes in the age-group 45-65 years increased in both sexes during the period (P for trend = 0.007). The odds ratio was 2.8 (95% CI 2.2-3.6) for the association between type 2 diabetes and heart failure and 1.7 (1.4-2.1) between AGR and heart failure. CONCLUSIONS: There is a strong association between any form of glucometabolic perturbation and heart failure. Future studies in this field should focus on all types of glucose abnormalities rather than previously diagnosed diabetes only.

Dobutamine stress echocardiography in patients with diabetes mellitus: enhanced prognostic prediction using a simple risk score
J Am Coll Cardiol. 2006 Mar 7;47(5):1029-36.
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OBJECTIVES: We sought to determine the prognostic value of dobutamine stress echocardiography (DSE) for predicting long-term outcomes in a large cohort with diabetes mellitus and to develop a simple risk score using clinical and echocardiographic data. BACKGROUND: Neither risk scores nor long-term prognostic value of DSE has been described in a large diabetic population. METHODS: We studied 2,349 patients with diabetes mellitus (1,338 men, 67 +/- 11 years of age) during a

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Trabajo recibido: 03/04/06
Trabajo aprobado: 10/04/06

follow-up of 5.4 +/- 2.2 years. RESULTS: Mortality and morbidity (myocardial infarction and late coronary revascularization) occurred in 1,044 (44%) and 309 (13%) patients, respectively. Addition of stress echocardiographic variables to the clinical and rest echocardiographic model provided incremental prognostic information for predicting mortality (chi-square = 243 to 270, p < 0.0001) and morbidity (chi-square = 38 to 78, p < 0.0001). For each end point, a simple risk score was derived according to the estimated values of beta coefficients of multivariate predictors (insulin therapy, smoking, failure to achieve target heart rate, percentage of ischemic segments, and impaired left ventricular systolic function) and resulted in an assessment of risk among all age groups. The C-statistic values were 0.60 to 0.64, indicating modest discrimination. The estimated five-year event-free survivals of patients in three risk categories were 94%, 86%, and 80% for morbidity (p < 0.00001) and 69%, 60%, and 47% for mortality (p < 0.0001). CONCLUSIONS: In patients with diabetes mellitus, a simple and practical risk score using clinical variables and results of DSE stratified patients into three risk groups for mortality and cardiovascular morbidity.

Diastolic dysfunction is associated with anaemia in patients with Type II diabetes

Clin Sci (Lond). 2006 Jan;110(1):109-16.

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Anaemia is common in patients with diabetes and associated with an increased risk of diabetic complications. Although the role of anaemia in heart failure is established, we hypothesize that anaemia also contributes to an increased risk of cardiac dysfunction in patients with Type II diabetes. In the present study, 228 consecutive adults with diabetes were investigated using transthoracic echocardiography. Echocardiographic parameters were correlated with the Hb (haemoglobin) level and adjusted for other risk factors for cardiac dysfunction using multivariate analysis. More than one in five patients (23%) had anaemia, which was an independent risk factor for cardiac dysfunction on echocardiography. Over one-third of all patients with evidence of abnormal cardiac function (diastolic and/or systolic dysfunction) on echocardiography had anaemia compared with <5% of patients with normal echocardiographic findings. Most patients with anaemia had cardiac dysfunction (94%), with the major abnormality being diastolic dysfunction associated with an increased left ventricular mass and impaired relaxation indices. A continuous association between diastolic function and Hb was also observed in patients without anaemia. In patients with a history of cardiovascular disease, systolic dysfunction was twice as common in patients with anaemia. Anaemia was also correlated with plasma markers of cardiac risk, including BNP (brain natriuretic peptide), CRP (C-reactive protein) and AVP (arginine vasopressin). Notably, the predictive utility of these markers was eliminated after adjusting for Hb. Consequently, the inexpensive measurement of Hb may be a useful tool to identify diabetic patients at increased risk of cardiac dysfunction.

Heart failure in diabetes mellitus: causal and treatment considerations.

Minerva Cardioangiol. 2004 Dec;52(6):491-503.

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The metabolic abnormalities associated with diabetes mellitus result in macrovascular and microvascular complications in multiple organ systems; it is the cardiovascular impact that accounts for the greatest morbidity and mortality associated with this disease. Heart failure, both with reduced and preserved systolic function, is a major complication, arising from the frequent associations with coronary atherosclerosis, hypertension, and a specific heart muscle dysfunction (cardiomyopathy) that occurs independently of coronary artery disease. Hyperglycemia, insulin resistance, and hypertension, together with activation of both circulating and tissue renin-angiotensin-aldosterone systems, contribute to structural fibrosis and autonomic neuropathy. Thus it becomes imperative to identify cardiac abnormalities early in the course of both type 1 and type 2 diabetes in order to allow early and aggressive intervention to control glucose and blood pressure and to normalize blood lipid profiles. Patients with diabetes should be treated to secondary prevention targets, including blood pressure less than 130/80 mm Hg and LDL less than 100 mg/dL. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, certain calcium channel blockers, statins, and aspirin have all been demonstrated to significantly reduce cardiovascular morbidity and mortality in patients with diabetes.

Antidiabetic therapy and the risk of heart failure in type 2 diabetic patients: an independent effect or confounding by indication

Pharmacoepidemiol Drug Saf. 2005 Oct;14(10):697-703.

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PURPOSE: This study assesses the effect of the type of antidiabetic treatment on the risk of developing congestive heart failure (CHF) in type 2 diabetes. METHODS: The study was derived from the U.K.-based General Practice Research Database (GPRD) comprised of 3.5 million subjects followed between 1987 and 2001. A total of 21 888 type 2 diabetic patients were identified. A 6:1 matched nested case-control design was employed. Conditional logistic regression was used to derive adjusted odds ratios (ORs) for the association of drug treatment with CHF controlling for diabetes duration and for diseases known to affect the risk of CHF. Antidiabetic drug exposure was defined as the receipt of at least one prescription for an antidiabetic medication within the 3 months prior to the date of CHF diagnosis. RESULTS: There were 1301 incident cases of CHF in the cohort, matched to 7788 controls. After risk factor adjustment, there was a 1.2-fold increase in the risk of CHF for sulphonylureas (SUs) (OR = 1.17; 95%CI = 1.00-1.37) and metformin monotherapies (OR = 1.22; 95%CI = 0.97-1.52), a 1.6-fold increase with combinations of metfor-

min and SUs (OR = 1.62; 95%CI = 1.30-2.02), a 2.2-fold increase with oral tricombinations (OR = 2.16; 95%CI = 0.96-4.86) and a 1.5-fold increase for insulin compared to no exposure (OR = 1.52; 95%CI = 1.06-2.17). Compared to SUs, bicombinations of metformin and SUs showed a statistically significant 1.4-fold increase in the odds of CHF (OR = 1.38; 95%CI = 1.13-1.69). CONCLUSIONS: All antidiabetic medications were associated with an increased likelihood of CHF compared to no antidiabetic exposure. The risk of CHF increased with the complexity of the antidiabetic regimen suggesting that it is the diabetes severity, which imparts risk and not necessarily the antidiabetic regimen itself.

Insulin-treated diabetes is associated with a marked increase in mortality in patients with advanced heart failure
Am Heart J. 2005 Jan;149(1):168-74.
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OBJECTIVES: This study aimed to investigate the effect of diabetes and insulin use on survival in a large cohort of patients with advanced heart failure (HF) of multiple etiologies. BACKGROUND: Although diabetes is a well-known risk factor for both systolic and diastolic dysfunction, the impact of diabetes and insulin treatment on prognosis of patients with HF has not been well studied. METHODS: History of diabetes and insulin treatment was assessed in 554 consecutive patients with advanced systolic HF who presented to a single center for HF management and/or transplant evaluation (mean age 52.0 +/- 13.1 years, ejection fraction 24.6 +/- 7.4). Patients were stratified into 3 groups based on presence or absence of diabetes and insulin use. Differences in patient characteristics and survival were evaluated. RESULTS: There were 132 patients (23.8%) with diabetes; 43 patients (7.8%) were insulin treated and 89 patients (16.1%) were non-insulin-treated patients with diabetes. The groups were similar in sex, smoking history, medication profile, ejection fraction, body mass index, and serum sodium. Survival at 1 year was 89.7% for nondiabetic patients, 85.8% for non-insulin-treated diabetic patients, and 62.1% for insulin-treated diabetic patients (P < .000 01). After Cox multivariate analysis, insulin-treated diabetes was found to be an independent predictor of mortality (hazard ratio 4.30, 95% CI 1.69-10.94) whereas non-insulin-treated diabetes was not (hazard ratio 0.95, 95% CI 0.31-2.93). Similar findings were seen in clinically relevant subgroups. CONCLUSIONS: Insulin-treated diabetes is associated with a significantly worse prognosis in patients with advanced HF. Further investigations into mechanisms for the association of insulin treatment and mortality in patients with HF are warranted.

Comentario sobre epidemiología y fisiopatología

La enfermedad arterial coronaria y cerebrovascular son causantes del 30% del total de muertes cada año, siendo la enfermedad cardiovascular la más prevalente de la diabetes mellitus[1]. Esto va de la mano con el aumento de incidencia de la diabetes tipo 2 que ya se detecta en etapas más tempranas de la vida, entre los 40 y 65 años, producto de la obesidad, dietas ricas en carbohidratos y grasas, inactividad física, sin olvidarse de la predisposición genética[2]. Estos pacientes tienen también mayor prevalencia de otros factores de riesgo, avance acelerado de la aterosclerosis y por lo tanto mayor morbimortalidad.
Del *Framingham Heart Study*, se extrae que la incidencia de insuficiencia cardíaca (IC) en hombres y mujeres con diabetes comparados con aquellos sin diabetes es de 2 a 5 veces mayor, aún controlando los factores de riesgo adicionales[3]. Tienen mayor riesgo de morbimortalidad con corazones estructuralmente "sanos" y aún después de la corrección quirúrgica o hemodinámica de la enfermedad arterial coronaria.

¿Se podría hablar entonces de cardiomiopatía diabética?

Esto ha sido ampliamente debatido que el solo trastorno metabólico provoque anormalidades estructurales y funcionales del miocardio debido a la coexistencia de hipertensión arterial (HTA) y enfermedad arterial coronaria. Hay evidencias que sostienen la existencia de cambios morfológicos en el corazon diabético que pueden incrementar la susceptibilidad de estos pacientes a la IC. Trabajos con ecocardiografía que demostraron la presencia de aumento de la masa ventricular y del grosor parietal corregidos con el índide masa corporal (IMC) y presion arterial[4] y de aumento de la ecogenicidad de las paredes del miocardio[5] que se correlaciona con hallazgos histopatológicos de hipertrofia miocítica con fibrosis intersticial y perivascular e incremento del deposito de colágeno[6]. Esto trae como consecuencia serias alteraciones de la relajación y *compliance* ventricular diastólica, aun previas al comienzo de la HTA, enfermedad renal, vasculopatía o hiperglucemia en ayunas[7]. Hay otros que demostraron que la función sistólica se vería afectada en etapas tempranas de la enfermedad, detectados por sensibles índices de *performance* contráctil[8].
La prevalencia de HTA en diabéticos es el doble comparada con controles no diabéticos, quizás como consecuencia de la hiperinsulinemia, injuria renal y disfunción endotelial[9], con mayor fibrosis y depósito de colágeno intersticial cuando coexisten ambas enfermedades, que en cada entidad en forma aislada[10]. Por otra parte el efecto sinérgico de la actividad neurohormonal y *stress* oxidativo, promueve a la apoptosis miocítica e inicia la transición desde un estado de hipertrofia e IC compensada a una cardiomiopatía dilatada e IC descompensada[11]. La sensibilidad disminuida a la insulina y la resultante hiperglucemia y alteración

del metabolismo graso es un nuevo factor contribuyente de disfunción vascular y miocárdica.
El tratamiento de estos pacientes consiste en mantener bajo estricto control los niveles de glucemia al igual que los factores de riesgo que acompañen a esta alteración metabólica. La HTA deberá ser tratada con IECA y con beta bloqueantes, siendo efectivos en la prevención primaria de eventos cardiovasculares y reduciendo la incidencia de nuevos eventos en pacientes con infarto agudo de miocardio (IAM) previo. Deben prescribirse estatinas independientemente de los valores de LDL y AAS desde 75 mg/día. El *UK Prospective Diabetes Study (UKPDS)* demostró una falta de beneficio, si se realiza un intensivo control glucémico con insulina y sulfonilureas para mejorar el riesgo de desarrollar enfermedad macrovascular o IC, pero sus resultados son controvertidos. El tratamiento actual consiste en prescribir estas drogas al igual que la metformina, ya que el mayor riesgo de IC podría deberse a la severidad del trastorno metabólico y sus consecuencias, que a la farmacoterapia en sí.
Como vemos, es un proceso complejo que provoca enfermedad macrovascular, microvascular y daño miocárdico por sí misma. Los nuevos lineamientos del *American College of Cardiology* y la *American Heart Association*, reconocen que, debido al rol que juega la diabetes en el desarrollo y progresión de la IC, clasifica a los pacientes diabéticos en estadío I de la IC, aun en ausencia de aparente daño estructural, ya que tienen alto riesgo en desarrollarla[12].

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