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BRIEF REVIEW

Cardiomyopathy in diabetics: a review of current opinion on the underlying pathological mechanisms

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Abstract Diabetes is one of the few growing causes of a cardiomyopathy around the world and cardiomyopathy is a common complication of diabetes causing significant mortality and morbidity.

This cardiomyopathy is seen commonly in young people with diabetes and those without pre-existing coronary artery disease, suggestive of a specific entity linked directly to diabetes.

In recent years there has been a real upsurge in the research devoted to this growing problem as other causes of heart disease such as tobacco smoking wane. More and more animal model studies and human tissue studies have enabled researchers to begin to develop ideas of the processes causing this cardiomyopathy.

As the pathological processes causing this cardiomyopathy are beginning to be better understood, we present an overview of the various potential pathological mechanisms under investigation that may constitute a cardiomyopathy related to diabetes.

In our review we describe 6 possible processes, which may begin to explain the cardiomyopathy related to diabetes beyond the standard ischaemia-infarct model. These mechanisms which are still under investigation include, reduced metabolic function, reactive oxygen species damage, damage to the ryanodine receptor, up-regulation of ADH, a cardiac autonomic neuropathy, and changes in cardiac structure.

PALABRAS CLAVE
Expresión génica;
Insuficiencia cardíaca;
Metabolismo cardíaco;
Radicales oxígeno

Miocardiopatía en personas con diabetes: revisión de la opinión actual sobre los mecanismos anatomopatológicos subyacentes

Resumen La diabetes es una de las escasas causas crecientes de miocardiopatía en el mundo, y la miocardiopatía es una complicación común de la diabetes que provoca una importante morbilidad y mortalidad.

Tal miocardiopatía se observa habitualmente en personas jóvenes con diabetes y sin coronariopatía previa, lo que sugiere una entidad específica relacionada directamente con la diabetes.

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Los últimos años han sido testigos de una oleada de investigaciones dedicadas a este creciente problema, a medida que disminuían otras causas de cardiopatía, como el tabaquismo. Una gran cantidad de trabajos sobre modelos animales y sobre tejido humano han permitido a los investigadores iniciar el desarrollo de una idea sobre los procesos que causan esta miocardiopatía.

Dado que se comienza a conocer mejor los procesos anatomopatológicos que provocan esta miocardiopatía, presentamos una revisión de los distintos posibles mecanismos anatomopatológicos en investigación que podrían desembocar en una miocardiopatía relacionada con la diabetes.

Nuestra revisión describe 6 posibles procesos que podrían empezar a explicar la miocardiopatía relacionada con la diabetes más allá del modelo habitual de isquemia-infarto. Estos mecanismos, todavía en investigación, son la disminución de la función metabólica, la lesión por radicales oxígeno, el daño al receptor de rianodina, la regulación al alza de la ADH, una neuropatía del sistema autónomo cardíaco y alteraciones en la estructura cardíaca.

Introduction

The association between diabetes and coronary heart disease is widely recognised, but diabetes as a cause of heart failure, irrespective and independent of coronary disease, has been the subject of much research. In 1972, Rubler and co-workers first described diabetic cardiomyopathy in 4 patients with diabetes presenting with clinical heart failure in the absence of hypertension, coronary or structural heart disease.[1]

In the UK, the estimated prevalence of diabetes is 4.3% while the prevalence of diabetes in people with congestive heart failure is quoted as between 20 and 35%per cent reflecting the earlier work in Framingham.[2]

There are many other epidemiological associations between diabetes and heart failure. In the Framingham study, there was an increased incidence of congestive cardiac failure in people with diabetes, which was independent of age, hypertension, hyperlipidaemia and coronary heart disease.[3] The presence of hypertension, coronary artery disease and systolic impairment conferred a much poorer prognosis in these patients. People with diabetes are also more likely than those without, to develop heart failure following myocardial infarction even when infarct size is comparable.[4] Heart failure symptoms with a preserved ejection fraction, as can be seen in many patients with diabetes, carries a significant mortality risk.[5]

Healthy, asymptomatic patients with diabetes have been shown to demonstrate subtle differences in systolic and diastolic function. Children with type 1 diabetes have been found to have subtle changes suggestive of cardiac impairment, including impaired myocardial relaxation patterns, a phenomenon that was previously confirmed in adult diabetes studies.[6]

In this review we will look at what is the current thinking on the pathological mechanisms causing diabetic cardiomyopathy so we can understand the pathology of a process that affects so many patients with diabetes and which carries such a significant impact on their mortality and quality of life.

In this review we will focus on six potential pathological mechanisms that are currently the subject of much research both in human and animal studies. While there may be a difference between the two, animal work has often proved illustrative of the human processes.

Cardiac Energy Usage and Consumption

The heart is one of the most energy intense organs in the body and uses a between two- thirds to one-third ratio of free fatty acids to pyruvate for energy metabolism.

This careful balance is altered in people with diabetes and leads to a reduction in the heart's ability to meet its energy requirements and thus leads to heart failure.[7] Glucose utilisation is vital in maintaining efficient energy production and also in protecting against periods of ischaemia[8] and in diabetes glucose utilisation is impaired.

The key areas affected in diabetes seem to surround GLUT-4 and an excess of fatty acids for metabolism and we will review these areas now.

In all patients with heart failure, there is a reduction in the expression of the GLUT-4 receptor, the main glucose transporter in the heart, which causes reduced energy production. Down regulation of GLUT-4 expression in diabetes occurs through a reduction in the expression of myocyte enhancer factor 2C (MEF2C), which is a regulatory factor for GLUT-4 and key to ongoing production.[9] In diabetes specifically, glucose metabolism seems to be also reduced due a reduction in the translocation of GLUT-4 to where it is needed, which seems to be the main difference between people with diabetes and heart failure and those without.[8]

As alluded to above, fatty acids in excess lead to reduced glucose utilisation and therefore reduced energy production, and in animal models excess free fatty acid metabolism leads to inhibition of phosphofructokinase, a rate-limiting step in glycolysis.[10] Adipocytes that generate the offending excess free fatty acids become resistant to negative signalling in diabetes and help down regulate insulin mediated glucose uptake.[11]

Above we have looked at how glucose metabolism is inhibited and therefore the heart's energy demands cannot be met, but fatty acids do not just affect glucose usage, they are toxic in themselves. In patients with diabetes and