

INTRODUCTION

Diabetes is considered as a growing epidemic and a major public health problem. Left untreated, diabetes can lead to serious medical complications including heart disease, amputation, stroke, renal failure and blindness. Number of cases of diabetes expected to increase in developing countries by 170%, and in developed countries by 42% from 1995 to 2025 (*King et al., 1998*).

Prevalence of diabetes by age 65 years or older is 18.4 % of all people in this age group have diabetes in US 2002 (*National Diabetes Statistics fact sheet, 2003*).

Diabetic patients always show increased risk for microvascular complications e.g. diabetic retinopathy, neuropathy and nephropathy. These complications are directly related to hyperglycemia, and macrovascular complications as coronary heart disease, stroke and peripheral vascular disease those may be aggravated by the presence of the metabolic syndrome (*Bate and Jerums, 2003*).

Diabetic cardiomyopathy is considered a serious complication to diabetes mellitus, many factors may play a role in the pathogenesis of diabetic cardiomyopathy as alterations in intramyocardial coronary arteries, endothelial proliferation (*Ledet, 1968*).

Capillary basement membrane thickening and capillary microaneurysms (**Factor et al., 1980**). Small vessel disease which is present in 72% of diabetic patients while it was present only in 12% of non diabetic subjects (**Zoneraich et al., 1980**), interstitial accumulation of advanced glycation end products (collagen, elastin, other connective tissue proteins) may play a role (**Van Hoeven and Factor, 1990**).

Metabolic disturbances occur in diabetic patients play a role in development of diabetic cardiomyopathy (**Fang et al., 2004**).

Hyperglycemia causes generation of advanced glycation end products (AGEs) which deactivate (NO) (**Tang and Young, 2001**). Advanced glycation of SERCA protein lead to decreased its activity and prolonged cardiac relaxation (**Hayat et al., 2004**).

The dependence of diabetic myocardium on fatty acid oxidation also decreases glucose and pyruvate utilization by inhibiting pyruvate dehydrogenase, with the collective effect of increasing myocardial oxygen consumption. Uncoupling of mitochondrial oxidative phosphorylation may therefore be a primary mechanism by which diabetes alters myocardial bioenergetics and contraction/relaxation coupling (**Rodrigues et al., 1998**).

Some epidemiological and clinical arguments suggested that diastolic abnormalities may contribute to the high

morbidity and mortality among diabetic patients, in the community setting, data from the Framingham Heart Study have shown an increased incidence of congestive heart failure in diabetic subjects irrespective of coronary heart disease and hypertension (*Kannel et al., 1974*).

It has also been demonstrated that a reduced mitral E/A ratio is independently associated with increased all-cause mortality as well as cardiovascular mortality in a population-based sample of middle-aged and elderly adults (*Bella et al., 2002*).

Diastolic abnormalities present in diabetic patients without diabetic complications or cardiovascular disease has been suggested as an earliest functional effect of a specific diabetic cardiomyopathy (*Ruddy et al., 1988*).

It was also observed that impaired diastolic function in patients with newly diagnosed diabetes or with a short duration of the disease and with no microangiopathic complications suggesting that this alteration may occur early in the history of type II diabetes and would not be related to microvascular complications (*Di Bonito et al., 1996*).

There is only scanty information on left ventricular (LV) diastolic function in patients with minor abnormalities of glucose homeostasis available. It was observed that early signs of diastolic dysfunction (assessed by E/A mitral flow ratio), not only in patients with diabetes but also in those with impaired

glucose tolerance, independent of the confounding role of ischemia, body weight, and blood pressure (*Celentano et al., 1995*).

Diastolic dysfunction was studied in relation to diabetic retinopathy (*Uusitupa et al., 1988*), diabetic nephropathy (*Watschinger et al., 1993*), and autonomic neuropathy (*Airaksinen et al., 1989*) and incidence of diastolic dysfunction increased in patients with complicated diabetes in all previous studies.

Although, many clinical studies have been performed to correlate diabetes mellitus and diastolic dysfunction, but there is a defect in this research aspect in the elderly despite the higher prevalence of both diabetes mellitus and diastolic dysfunction in the elderly.

AIM OF THE WORK

The aim of this work is to study the relationship between diabetes mellitus and diastolic dysfunction in the elderly.

DIASTOLIC DYSFUNCTION IN ELDERLY

Heart failure is common in the elderly population. Approximately 6 to 10 percent of the population 65 years or older have heart failure. Heart failure is the most common reason for hospitalization in elderly patients. Heart failure with preserved systolic function is common in the elderly because aging has a greater impact on diastolic function than systolic function (*Yamasaki et al., 2003*).

33% of patients with obvious heart failure have normal ejection fraction (EF) suggesting that they are suffering from diastolic heart failure (*Zile and Simsic, 2000*).

A study performed by Zile and Simsic found that the risk of diastolic heart failure increases with age. It occurs in 15% in patients under 60 years, 35% in patients 60 to 70 years and 50% in patients over 70 years old (*Zile and Simsic, 2000*).

Moreover, the same study revealed that the prognosis of diastolic heart failure is better than systolic heart failure. Annual mortality in those suffering from diastolic heart failure is about 5 to 8%, while it is about 10 to 15% in patients suffering from systolic heart failure. While the annual mortality in healthy people of the same age is about 1%. In diastolic heart failure patients, prognosis is also affected by the cause. When coronary artery disease is not the cause, annual mortality is much better, at about 2% to 3%. Age also affects risk of death.

The 5-years mortality rate in diastolic heart failure patients is about 25% in patients under 60 years old ,35% in patients 60 to 70 years and 50% in patients over70 years (**Zile and Simsic, 2000**).

Additionally, in the study of Redfield et al., who conducted a cross-sectional survey among randomly selected residents of Olmsted County, Minnesota, aged 45 years or older. They reported that the prevalence of validated congestive heart failure was 2.2% with 44% having an EF higher than 50%. Overall, 20.8% of the population had mild diastolic dysfunction, 6.6% had moderate diastolic dysfunction, and 0.7% had severe diastolic dysfunction with 5.6% of the population having moderate or severe diastolic dysfunction with normal EF. The prevalence of any systolic dysfunction (EF $\leq$ 50%) was 6.0% with moderate or severe systolic dysfunction (EF $\leq$ 40%) being present in 2.0% . Congestive heart failure was much more common among those with systolic or diastolic dysfunction than in those with normal ventricular function. However, even among those with moderate or severe diastolic or systolic dysfunction, less than half had recognized congestive heart failure (**Redfield et al., 2003**).

The prevalence of mild diastolic dysfunction without clinical symptoms and moderate diastolic heart failure with exercise induced symptoms isn't known (**Zile, 1999**).

Several studies were conducted to detect the determining factors of diastolic function, and it was found that there are several factors interact to determine diastolic function:

Left ventricular relaxation: as normal ventricle relaxes forcefully, rapidly decreasing its cavity pressure during early diastole and suctioning blood from the left atrium across the mitral valve, allowing the ventricle to fill with blood in the presence of normal or low left atrial pressure. Slow or incomplete relaxation decreases this gradient in early diastole (**Garcia, 2000**).

Other studies found that relaxation is energy dependent and requires adenosine triphosphate for the reuptake of calcium by the sarcoplasmic reticulum, thus allowing the release of the actin and myosin bridges. Since left ventricular relaxation is energy-dependent, ischemia rapidly affects it (**Courtois and Ludbrook, 1994**).

Decreased levels or activity of the sarcoplasmic reticulum calcium ATP-ase pump (SERCA) can slow the removal of calcium from the cytosol. Increased levels or activity of phospholamban (the naturally occurring SERCA-inhibitory protein) can also impair relaxation. Increased cAMP, resulting from adrenergic stimulation or inhibition of cardiac phosphodiesterase, phosphorylates phospholamban to remove its inhibitory effect on SERCA (**Brad and Grossman, 2003**).

Interestingly, levels of SERCA decrease with age, coincident with impaired diastolic function (*Cain et al., 1998*).

Pathological left ventricular (LV) hypertrophy secondary to hypertension or aortic stenosis results in decreased SERCA and increased phospholamban. Similar changes are seen in the myocardium of patients with hypertrophic or dilated cardiomyopathy (*Brad and Grossman, 2003*).

Left ventricular diastolic stiffness also play a role in diastolic function. Once the left ventricle pressure falls below the left atrial pressure, blood enters the left ventricle, rapidly increasing its volume. This increase in the cavity volume causes the myocardial fibers to stretch. The muscle fibers resist stretching in a nonlinear fashion. Thus, the pressure required to stretch a muscle fiber increases geometrically. The curvilinear relationship between filling pressure and volume is a measure of left ventricular diastolic stiffness. It is influenced by myocardial fiber distensibility, elasticity of the connective tissue, cavity diameter, wall thickness, and the constraining effect of the pericardium. In a normal left ventricle, stiffness is low during diastole, and relatively large increases in volume cause relatively small increases in pressure (*Factor et al., 1988*).

Increased ventricular stiffness occurs in conditions such as systemic hypertension, hypertrophic cardiomyopathy, and aortic stenosis. Increased myocardial stiffness also occurs with increased deposition of collagen (left ventricular hypertrophy

and chronic myocardial ischemia) or protein (amyloidosis) (*Spencer and Lang, 1997*).

Additionally, left atrial function is an important determinant of LV diastolic function. The left atrium acts as a reservoir of blood, as a conduit, and as an active pump at the end of diastole. According to the Frank-Starling mechanism, the left atrial volume and pressure determine the force of contraction. In young, healthy patients, the left atrial contribution in ventricular filling is minimal (<20%); however, in patients with early diastolic dysfunction and impaired LV relaxation, the left atrium compensates, increasing its contractility and contributing up to 50% of the filling volume (*Garcia, 2000*).

Patients with diastolic dysfunction are particularly susceptible to the loss of atrial contraction during atrial fibrillation, which can lead to significant underfilling of the left ventricle and a sudden decrease in stroke volume (*Garcia, 2000*).

Diastolic dysfunction occurs when the LV is unable to fill adequately at normal diastolic pressures (*Grossman, 1991*).

Diastolic dysfunction was linked to variable causes such as ischemia, tachycardia, atrial fibrillation, ventricular load and chronic hypertension which is the most common cause of diastolic dysfunction and failure. It leads to left ventricular hypertrophy and increased connective tissue content, both of

which decrease cardiac compliance (**Lorell and Carabello, 2000**).

The effect of ischemia on diastolic dysfunction was explained by **Nayler et al. (1979)** who reported that relaxation of the ventricles involves the active transport of calcium ions into the sarcoplasmic reticulum, which allows the dissociation of myosin-actin crossbridges. Hypoxia inhibits the dissociation process by altering the balance of the adenosine triphosphate-to-adenosine diphosphate ratio, which may contribute to diastolic dysfunction

The heart rate determines the time that is available for diastolic filling, coronary perfusion, and ventricular relaxation. Tachycardia adversely affects diastolic function by several mechanisms, it decreases left ventricular filling and coronary perfusion times, increases myocardial oxygen consumption, and causes incomplete relaxation because the stiff heart cannot increase its velocity of relaxation as heart rate increases. Patients with diastolic dysfunction do not tolerate tachycardia or exercise well (**Gutierrez and Blanchard, 2004**).

It was also found that patients with heart failure are at increased risk for atrial fibrillation (**Benjamin et al., 1994**). When the ventricle stiffens and develops higher end-diastolic pressures, the atria are distended and stressed; this situation often results in atrial fibrillation. The loss of atrial contraction worsens the symptoms of heart failure, because patients with diastolic dysfunction often are dependent on atrial filling of the

left ventricle (atrial kick). Atrial fibrillation also can worsen symptoms if the ventricular rate is uncontrolled (**Benjamin et al., 1994**).

At the end of normal systole, a small residual volume of blood remains in the left ventricle. If this residual volume increases, it interferes with the normal elastic recoil of the heart, the relaxation of the heart, and the development of a negative pressure gradient between the ventricle and atria. As a result, rapid early diastolic filling is impaired (**Guiterrez and Blanchard, 2004**).

Diastolic dysfunction is more common in elderly persons, partly because of increased collagen cross-linking, increased smooth muscle content, and loss of elastic fibers. These changes tend to decrease ventricular compliance, making patients with diastolic dysfunction more susceptible to the adverse effects of hypertension, tachycardia, and atrial fibrillation (**Wei , 1992 & Gaasch, 1994**).

The weight of the heart increases between 1 g and 1.5g per year between the third and the ninth decade of life (**Kitzman et al., 1988**).

The myocyte hypertrophy and the increase in connective tissue matrix, particularly in collagen type II, result in reduced relaxation and increased stiffness (**Klein et al., 1989**).

Yet despite these age-related abnormalities, most older people do not have symptoms of heart failure under normal circumstances. However, they often develop symptoms of heart failure if atrial fibrillation occurs (*Garcia, 2000*).

Diastolic dysfunction is common in patients with restrictive cardiomyopathies, disorders characterized by small left ventricular cavity size, abnormal relaxation, and increased stiffness (*Keren and Popp, 1992*).

In restrictive cardiomyopathy the wall thickness is increased due to infiltration or fibrosis and not to myocyte hypertrophy. Therefore, the electrocardiographic QRS voltage is normal or low. Systolic function may also be impaired in patients with advanced disease. However, the ejection fraction is usually normal in patients with diastolic dysfunction. Common causes of restrictive cardiomyopathy include primary and secondary amyloidosis, radiation treatment, glycogen storage disorders, and some types of muscular dystrophy (*Guiterrez and Blanchard, 2004*).

Hypertrophic cardiomyopathy causes diastolic dysfunction via myocardial fiber disarray and a global or segmental increase in left ventricular wall thickness (*Wigle, 1994*).

In hypertrophic cardiomyopathy LV chamber stiffness is increased and relaxation is impaired by the asynchronous

deactivation of muscle fibers caused by abnormal electrical conduction (*Brutsaert et al., 1993*).

Constrictive pericarditis can cause diastolic dysfunction via increased LV stiffness related to the constraining effects of the thickened and rigid pericardium. LV relaxation is normal in these patients, and symptoms of right heart failure predominate (*Oh et al., 1994*).

Also alterations in LV diastolic function are detected in most patients with dilated cardiomyopathy. LV filling abnormalities have been shown to have important independent prognostic implications in these patients (*Oh et al., 1994*).

Diagnosis of diastolic dysfunction:

Patients with diastolic heart failure may present with dyspnea, cough, edema, exercise intolerance, or fatigue. Reduced left ventricular filling leads to decreased stroke volume and symptoms of low cardiac output. On the other hand, diastolic dysfunction may occur with appropriately increased diastolic volume but marked elevation in left atrial pressure, leading to dyspnea. Thus, isolated diastolic dysfunction may mimic classic systolic heart failure (*Spencer and Lang, 1997*).

Patients with diastolic dysfunction usually cannot tolerate exercise for several reasons. The stiff left ventricle may prevent the increase in end-diastolic volume needed to increase stroke

volume with exercise. Patients with abnormal relaxation are also more sensitive to shortening of the diastolic filling period that occurs with increasing heart rate (*Spencer and Lang, 1997*).

It is difficult to differentiate between systolic and diastolic dysfunction but to some extent the history, physical examination, ECG and chest radiographs provide some clues that can be helpful in differentiating systolic and diastolic dysfunction. For example, predominantly systolic dysfunction is suggested by a history of myocardial infarction and younger patient age, a displaced point of maximal impulse and S₃ gallop on the physical examination, the presence of Q waves on the ECG and the finding of cardiomegaly on the chest radiograph. In contrast, diastolic dysfunction is suggested by a history of hypertension and older patient age, a sustained point of maximal impulse and S₄ gallop on the physical examination, left ventricular hypertrophy on the ECG and a normal-sized heart on the chest radiograph. However, the findings can overlap considerably, and echocardiography of the heart is usually necessary (*Shamsham and Mitchell, 2000*).

The concepts of diastolic dysfunction and failure are still not well understood by many clinicians. This is another reason why the diagnosis and clinical prevalence continue to cause major controversies. One reason for confusion is use of the terms ‘diastolic dysfunction’ and ‘diastolic failure’ interchangeably. Diastolic dysfunction should be viewed as a