

SUMMARY

THE RELATIONSHIP BETWEEN SERUM LEVEL OF BETA-2 MICROGLOBULIN AND DIASTOLIC DYSFUNCTION/ ENDOTHELIAL DYSFUNCTION AMONG PATIENTS WITH DIABETES MELLITUS

Introduction:

The prevalence of diabetes mellitus has been increasing dramatically during the last two decades. Genetic, environmental and life style factors have been shown to participate in the etiopathogenesis of this disease. It is characterized with hyperglycemia and may lead to microvascular and macrovascular complications. Cardiovascular diseases, neuropathy, retinopathy and diabetic nephropathy are among the most important complications.

Atherosclerosis and related diseases are the second and first cause of death among the population with less and more than 45 years of age worldwide, respectively. It is the most important cause of morbidity among all ages of population and its incidence is increasing dramatically. Therefore, many authors attempt to develop new methods in order to diagnose atherosclerosis before development of organ involvement and determine the prevalence of atherosclerotic disease.

The most important changes observed during the early subclinical period of atherosclerosis include endothelial dysfunction throughout all arterial bed and increase in intimal-medial thickness. Endothelial dysfunction and increase of intimal-medial thickness may be determined by using simple, inexpensive and non-invasive methods. So, therapeutic modalities can be performed before atherosclerosis becomes more diffuse. Endothelial dysfunction precedes the atherosclerotic involvement on the coronary vascular bed. It also plays an important role in the atherosclerosis of epicardial coronary arteries. However, making the diagnosis of endothelial dysfunction is both difficult and requires invasive methods. Since the endothelial dysfunction may lead to systemic symptoms, non-invasive methods imaging peripheral arteries may provide accurate information about endothelial dysfunction. Brachial artery is ideal for evaluation of endothelial dysfunction since it is easily found on the antecubital region. This advantage leads us to diagnose possible endothelial dysfunction throughout coronary vascular bed by using indirect methods.

Measurement of mitral diastolic flow and pulmonary venous flow via conventional Doppler echocardiography in order to evaluate diastolic left ventricular functions provides

important data. However, since many factors (heart rate, pre-load, after-load, valvular failure, position of sample volume) may change the haemodynamics of mitral flow echocardiographic methods have recently been utilized for evaluation of diastolic dysfunction. Tissue Doppler Imaging (TDI) has recently been increasingly used for determination of left ventricular diastolic functions and regional systolic-diastolic functions of myocardium can be evaluated by using TDI. The rate of early diastolic wave (E_m or E') on the myocardium next to mitral annulus observed via tissue doppler imaging has been demonstrated to be a useful parameter for evaluation of LV diastolic functions.

The molecular weight of beta 2 microglobulin is 11.8 kDa. It is a light chain HLA class I complex and found as free monomers in the plasma after separating from the heavy chain. It is filtrated from the glomerules and reabsorbated and degraded from the renal tubules. Its serum concentration is not dependent to the muscle mass and age of the patient. Beta 2 microglobulin is easily filtrated from glomerules. Approximately 99% of its concentration is reabsorbated from he proximal tubules via pynocytosis. Increased serum levels refer to increased cellular turnover. This increase may be observed in myelo- and lympho-proliferative disease such as AIDS and multiple myeloma. Increased urinary excretion are observed if its level exceeds the renal threshold value. Increased urinary excretion without any increase in the synthesis may be due to impairment in the reabsorption ability of proximal tubules.

In this study we planned to investigate the relationship between serum beta 2 microglobulin levels, and endothelial and diastolic dysfunction among the Type 2 diabetic patients who had normal serum albumin levels in the lack of microalbuminuria and coronary artery disease.

Materials and Methods:

Forty patients and 10 control subjects who admitted to the outpatient clinics of Adnan Menderes University Medical Faculty Department of Cardiology between January and June 2008 and had the diagnosis of type 2 diabetes mellitus have been included in our study. All the patients and controls have signed an informed consent form. The included patients had the diagnosis of type 2 diabetes mellitus with history, physical examination and laboratory results; were taking antidiabetic medical therapy; more than 30 years of age; not taking systemic glucocorticoid therapy; had no hepatic failure, malignancy or pregnancy. Patients

who had previously undergone coronary revascularization, carotis surgery or experienced cerebrovascular disease have been excluded.

10 cc venous blood was obtained from each patient after 12 hours of fasting for determination of fasting plasma glucose level, beta 2 microglobulin level, lipid parameters, blood urea nitrogen and creatinin levels. Microalbumin level in the 24 hours of urine has also been measured.

Transthorasic echocardiography was performed at all patients for evaluation of cardiac functions. Flow-induced vasodilatation test was performed in order to evaluate the endothelial dysfunction via doppler ultrasoundography from brachial artery.

Results:

This study was performed among 50 subjects (age range: 36 and 77 years) who presented to outpatient clinics of Cardiology Department of Adnan Menderes University Medical Faculty between January and June 2008. The mean age of the patients was $52,48 \pm 8,77$ years (mean \pm SD). 32 females (64%) and 18 males (36%) were included.

Diastolic dysfunction was observed at 23 (46%) patients. Endothelial dysfunction was present at 13 (26%) patients. Beta-2 microglobulin levels were significantly higher at the patients compared with control subjects ($p < 0,01$).

Beta-2 microglobulin levels were significantly higher among patients with endothelial dysfunction ($p < 0,01$).

Beta-2 microglobulin levels of the patients with both diastolic and endothelial dysfunction were significantly higher than the other patients ($p < 0,05$).

The ROC analysis performed to determine the cut-off value of beta 2 microglobulin levels according to endothelial dysfunction among study population revealed 2.74 as the cutoff point, although not ideal at all. The sensitivity, specificity, positive and negative predictive value at this point were 91,67%, 89,29%, 62,40% and 78,13%, respectively. The area under the ROC curve was found to be 0,801.

Comment:

Evaluation of diastolic dysfunction by using echocardiography and endothelial dysfunction by using flow-induced vasodilatation test from brachial artery are both early findings of coronary artery disease and atherosclerosis among type 2 diabetic patients. Significantly higher serum levels of beta-2 microglobulin among patients with endothelial dysfunction suggest that beta-2 microglobulin may serve as a predictive marker, as well as hsCRP, for future development of coronary artery disease and this study -to our knowledge- is the first trial investigating the relationship between endothelial dysfunction and serum beta-2 microglobulin levels.

Key words: Type 2 Diabetes, Endothelial dysfunction, Diastolic Dysfunction, Beta 2 Microglobulin