# SUMMARY (VII)

## THE RELATIONSHIP BETWEEN SERUM LEVEL OF CYSTATİN C AND DIASTOLIC DYSFUNCTION/ ENDOTHELIAL DYSFUNCTION AMONG PATIENTS WITH DIABETES MELLITUS

**Introduction:**

The prevalance of diabetes mellitus has been increasing dramatically during the last two decades. Genetic, enviromental and life style factors have been shown to participitate in the etiopathogenesis of this disease. It is characterized with hyperglisemia 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 aterosclerosis before development of organ involvement and determine the prevalance of aterosclerotic disease.

The most important changes observed during the early subclinical period of aterosclerosis include endotelial 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 preceedes 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 dysfunciton. 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 convantional 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 (Em 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.

Cystatin C is a molecule composed of 122 aminoacides and has a molecular weight of 13 kDa. It is a cystein protease inhibitor and involves a non-glycolized polypeptide. It is synthesized by all cells with nuclei. It is produced in a constant rate which is not affected by other factors such as immunological and inflammatory processes or body muscular mass. It is easily filtrated from glomerules due to the low molecular weight and non-acidic pH and its serum levels are stable. Cystatin C is a member of the cystatin superfamily in which all components are cystein protease inhibitors.

In this study we planned to investigate the relationship between serum Cystatin C 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 expreinced 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, Cystatin C 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 dysfunciton via doppler ultrasoundography from bracihal 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±8,77 years (mean±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. Cystatin C levels were significantly higher at the patients compared with control subjects ($p < 0,001$).

Cystatin C levels were significantly higher among patients with endothelial dysfunction ($p < 0,002$).

Cystatin C levels of the patients with both diastolic and endothelial dysfunction were significantly higher than the other patients ($p < 0,004$).

The ROC analysis performed to determine the cut-off value of Cystatin C levels according to endothelial dysfunction among study population revealed 1834 as the cutoff point, although not ideal at all. The sensitivity, specificity, positive and negative predictive value at this point were 91,67%, 78,57%, 64,71% and 95,65%, respectively. The area under the ROC curve was found to be 0,893.

**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 diasease and atherosclerosis amnog type 2 diabetic patients. Significantly higher serum levels of Cystatin C among patients with endothelial dysfunction suggest that Cystatin C 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 Cystatin C levels.

**Key words:** Type 2 Diabetes, Endothelial dysfunction, Diastolic Dysfunction, Cystatin C