

## Do female patients with metabolic syndrome have masked left ventricular dysfunction?

### *Metabolik sendromlu kadınlarda gizli sol ventrikül disfonksiyonu mu var?*

Dear Editor,

In the National Cholesterol Education Program's Adult Treatment Panel III report, the metabolic syndrome (MetS) has been defined as the presence of three out of five quantitatively defined markers: abdominal obesity, high triglycerides, low high density lipoprotein (HDL) cholesterol, high blood pressure, and elevated fasting glucose (1). Insulin resistance is a key player in the pathophysiology of the MetS and has even been postulated as its underlying cause (2).

The MetS encompasses a cluster of metabolic risk factors that is associated with an increased risk for type 2 diabetes mellitus (DM) and for cardiovascular disease (3,4). Additionally, MetS has impacts on left ventricular (LV) geometry and function, which are potent bioassays of preclinical cardiovascular disease. The components of the MetS are independently associated with prevalent LV hypertrophy (LVH) and/or dysfunction, even in the absence of coronary artery disease.

Diminished insulin sensitivity with regard to glucose utilization causes a substantial increase of insulin production in an attempt to maintain normal glucose utilization, making it possible that cardiovascular trophic effects and other actions of insulin that were not blunted could, in fact, be exaggerated in the setting of high insulin levels. Hyperinsulinemia/insulin resistance has been known to cause the altered collagen/muscular ratio (5). A previous study has demonstrated that glucose intolerance exaggerates LV dysfunction (6).

The cause of altered LV function in MetS is not fully understood. The relatively high prevalence of insulin resistance and the attendant hyperinsulinemia among obese, hypertensive, and diabetic patients (7) makes it difficult to dissect their separate roles in cardiac structure and function compared with the effect of body size, blood pressure, and hyperglycemia. Furthermore, even in otherwise healthy individuals, insulin resistance/hyperinsulinemia tend to aggregate with small, subclinical changes in body mass index, blood pressure, and glucose level (7). Nevertheless, strong associations between fasting plasma insulin levels and abnormalities of LV structure, function, and systemic hemodynamics are attenuated, but not completely eliminated when the effects of overweight and other covariates are taken into account (8).

Insulin resistance, hyperinsulinemia, a decline in insulin-mediated glucose uptake and nonoxidative glucose metabolism are associated with LVH (9,10). Majority of the components of MetS affect ventricular function via generating LVH (11-13). In a recent study that assessed LV structure and function in patients with MetS, subjects with MetS showed greater LV dimension, mass and relative wall thickness, and a higher prevalence of

LVH, with lower mid-wall shortening, impaired LV chamber and wall mechanics, and abnormal early diastolic LV relaxation than those who did not have MetS (12). But, it has also been demonstrated that some of the components of MetS affect myocardium independent of hypertrophy. Concentric LV geometry is associated with impaired LV function in hypertensive and/or diabetic patients regardless of hypertrophy (13).

In hypertensive patients, the presence of LVH has been associated with a more severe degree of insulin resistance. Change of the echocardiographic patterns from normal to concentric hypertrophy is associated with a trend to impairment of insulin-mediated glucose uptake and nonoxidative glucose metabolism (14). And this alteration of the LV geometry is associated with impairment of ventricular both systolic and diastolic function (11). In another study, obesity was shown to be associated with concentric LV remodeling and decreased systolic and diastolic function in young otherwise-healthy women. Early LV dysfunction was shown by reduced mitral annular systolic and diastolic tissue Doppler velocities in the longitudinal plane in the presence of normal standard parameters of global LV function (15).

The progressive addition of metabolic risk factors including central obesity, DM and hypercholesterolemia are associated with higher LV mass normalized by height, independent of hypertension (HT) and other important biological covariates (16). There is also a relationship between LV mass and metabolic parameters, such as total cholesterol, HDL cholesterol, triglyceride and fasting blood glucose, in normotensives and hypertensives (16). Dyslipidemia and a CE fatty acid composition predict the development of LVH to a similar degree as HT and obesity. The impact of obesity, dyslipidemia, and an unfavorable fatty acid profile on LVH was independent of the other clinical variables (17). Regarding LV geometry, relative wall thickness was positively related to triglycerides and blood glucose and inversely to HDL-cholesterol (18).

Left ventricular mass exceeding the compensatory needs for workload is associated with delayed LV relaxation as well as mild LV mid-wall and chamber systolic dysfunction, independently of demographic, clinical, and hemodynamic confounders. The impairment of both systolic and diastolic LV function occurring with inappropriate LV mass suggests that the excess LV mass may not be comprised in normally functioning muscle. In particular, it can be inferred that when contractile failure also affects LV chamber function, myocardial contraction is compromised to a degree that can no longer be offset by more concentric LV geometry to maintain an efficient contraction gradient at the endocardium (19), and that a further increase in LV mass (not necessarily all functioning myocytes) negatively effects LV chamber function. This progres-

sion of myocardial disease is also associated in all studies with major metabolic abnormalities (obesity and DM), which might influence quality of myocardial growth.

It should be emphasized that a biological effect of chronic hyperinsulinemia and/or insulin resistance on cardiac muscle growth and remodeling is fully plausible and may mediate, at least in part, the effect of body size and blood pressure on LV mass. On the other hand, a number of previous studies have evaluated relations between fasting or post-challenge plasma insulin levels and measures of LV structure and function, with variably positive or negative results (8-10,14,20-24). Number and kind of patients studied (healthy, obese, hypertensive, diabetic, and combinations thereof), index measurement (fasting plasma insulin, plasma insulin at various times after a glucose load, intravenous glucose tolerance test, insulin clamp), and adjustment for confounders have been quite variable, probably contributing to the discrepant outcome.

Also, the LV geometric correlates of insulin resistance are not clear. In contrast to above mentioned studies, some ones (14,24) have found insulin resistance or impaired glucose tolerance to be more closely related to thick LV walls or increased relative wall thickness than to LVH. But, this condition is also related to impaired myocardial function. Type 2 DM is more strongly associated with increased LV relative wall thickness, a measure of concentricity of LV geometry, and a worse LV systolic chamber and myocardial function (13). In hypertensives, increased relative wall thickness is independently associated with both systolic and diastolic LV dysfunctions (13). Hypercholesterolemia in normotensive non-diabetic adults is also independently associated with a mildly concentric LV geometry (25).

The impacts of the conditions that are characterized by increased insulin resistance on LV structure and function are gender specific. Left ventricular mass and wall thickness increased with worsening glucose intolerance, an effect that was more striking in women compared with men (26). In the previous issue of *The Anatolian Journal of Cardiology*, a study by Dursunoğlu et al. also reports that women with MetS have impaired LV systolic and diastolic dysfunction (27). Although the percentage of the patients with HT or DM was not reported, it is intelligible from the given fasting blood glucose and blood pressure values that noteworthy proportion of patients have HT and DM according to known cut-off values. Diabetes mellitus and HT are associated with independent and additive increases in the prevalence and degree of abnormalities of LV structure and function. Noninvasive studies have described early modifications of LV structure and function in DM (28). Diabetic subjects have lower myocardial systolic function than nondiabetic subjects independent of covariates. The study of Dursunoğlu et al. was performed in only women (27). In the light of above mentioned gender differences, the findings of this study are not to be generalized for men. Another point is that the assessment of the impact of each component of MetS on LV structure and function could make this study more meaningful.

Dursunoğlu et al. assessed LV functions by mitral atrioventricular plane displacement (AVPD) and myocardial performance index (MPI) in addition to conventional methods (27). The former methods have some advantages compared to the latter.

Determination of AVPD by echocardiography is an uncomplicated, rapid, reliable, and highly reproducible method for the assessment of LV function (29,30). It is proposed to reflect LV

systolic function, and particularly useful since it is readily measured even in patients with poor image quality. There are, however, a number of factors, which might influence left AVPD, such as age, heart rate, LV and atrial size, and myocardial thickness. A ventricle with concentric hypertrophy might demonstrate a normal ejection fraction despite subnormal movement of the atrioventricular plane. It is also demonstrated that AVPD in addition to being an index of systolic function reflects diastolic performance (31). Although Dursunoğlu et al. used AVPD during systole in order to examine systolic function (27), this measurement is equal during systole and diastole since total AVPD was obtained. Thus, the reduction in AVPD in MetS may depend on impaired LV filling, systolic dysfunction, or both.

On the other hand, the MPI is a non-geometrical and non-invasive index of global LV function including components from both systole and diastole (32). The MPI correlates to invasive measures of both systolic and diastolic function (33). There are some advantages of MPI compared with other echocardiographic methods. Currently, there are no parameters of both systolic and diastolic cardiac function that are easily measured. Additionally, MPI does not depend on geometric assumptions. Although patients with MetS had similar LV ejection fraction and LV fractional shortening with controls, the MPI was beyond the controls' levels. The MPI has been shown to be better than LV ejection fraction in predicting the prognosis and survival (32,34). Therefore, the increased MPI with normal LV ejection fraction in patients with MetS strongly suggests the presence of LV dysfunction.

As a conclusion, MetS and/or each of its components can cause myocardial dysfunction, generally both systolic and diastolic. Impairment of LV function can be reliably and more sensitively demonstrated by some relatively new echocardiographic methods rather than conventional methods.

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## Author's reply

Dear Editor

We would like to thank the author of the Letter to the Editor for comments

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