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Contribution of Carbohydrate Metabolism Disorders to the Development of Target Organ Damage in Hypertensive Patients with Metabolic Syndrome

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Abstract

Objective: The relationship between glucose abnormality and cardiovascular and renal functions in hypertensive patients with metabolic syndrome (MetS) was examined in this study. **Methods:** The population included 85 hypertensive patients with MetS. MetS is defined according to IDF, 2005 criteria. Metabolic measures included lipids, plasma insulin, glucose tolerance test, and insulin sensitivity by the homeostasis model assessment. M- and B-mode ultrasounds were used to determine left ventricular (LV) hypertrophy, endothelium-dependent vasodilation and intima media thickness. **Results:** Hypertensive patients who have had either impaired glucose tolerance (IGT) and hyperinsulinemia or a combination of both have expressed a higher degree of LV hypertrophy, LV diastolic dysfunction, endothelium dysfunction and lipid disorders. **Conclusions:** The presence of the IGT and hyperinsulinemia changes for the worse cardiovascular remodeling processes in hypertensive patients with MetS and it is association with high risk of target organ damage. IJBM 2011; 1(3):132—138.

Key words: *hypertension, metabolic syndrome.*

Introduction

Metabolic syndrome (MetS), a cluster of cardiovascular risk factors, such as central obesity, insulin resistance, dyslipidemia and hypertension, is associated with an increased risk of developing cardiovascular disease and diabetes mellitus [16, 18]. Other important characteristics of MetS include low-grade inflammation, endothelial dysfunction, plasma hypercoagulability and atherosclerosis [32].

The prevalence of MetS varies greatly between countries and ethnic groups [1]. In the United States, based on the NCEP definition, the prevalence of MetS is estimated at about 34% among men and 35% among women [13]. In populations of European origin, the prevalence of MetS is estimated to be 20–25% [4]. In a large population-based Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, MetS prevalence varied from 25.9% to 35.9% in men, and from 19.7% to 34.1% in women [2]. Due to its high prevalence, MetS is considered a major public health problem in Europe, and particularly in USA, where obesity and overweight are the second leading cause of preventable death, accounting for 300,000 deaths annually [5].

Epidemiological studies suggest that MetS *per se* could represent an independent predictor of cardiovascular morbidity and mortality [23, 29, 45]. Patients with MetS are estimated to have twice the risk of developing cardiovascular disease compared with healthy individuals, and a five-fold increased risk of type 2 diabetes [17, 36]. The relative risk of developing CVD associated with MetS as defined by NCEP-ATP III or by other organizations has increased two- to five-fold in both men and women, and in various populations [19, 23, 41].

MetS has also been associated with early vascular alterations, such as increased intima-media thickness (IMT) and endothelial dysfunction [11, 26, 28]. The association with these vascular alterations might account, at least partly, for the cardiovascular risk in patients with MetS, because both increased IMT and endothelial dysfunction [25, 49] have been demonstrated to be independent

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predictors of cardiovascular morbidity and mortality.

The presence of Microalbuminuria (MAU) is one of the sure signs of MetS and could be considered a marker for increased risk of renal and CVD associated with insulin resistance and endothelial dysfunction [42]. MAU, an independent risk factor for the high incidence and fatality rate of CVD in diabetes mellitus (DM) [3], is one of the biomarkers for endothelial dysfunction [14]. Patients with MAU run a very high risk of vascular injury and apparently share the same objectives of a vascular risk factor control as patients with overt CVD [27].

Left ventricular (LV) hypertrophy, a major manifestation of hypertensive heart disease, is a strong and independent herald of cardiovascular morbidity and mortality [22, 46]. Echocardiographic studies conducted in hypertensive subjects or in the general population have generally concluded that participants with metabolic risk factors [6, 10] or with the MetS [8, 9, 24, 34] show elevated LV mass or increased prevalence of LV hypertrophy.

The aim of this study is to evaluate the prognostic value of carbohydrate metabolism disorders in relation to the incidence and outcome of cardiac (LVH), vascular (IMT and EDVD) and renal (microalbuminuria) damage in hypertensive patients with MetS.

Subjects and methods

Study population

Participants were consecutively enrolled from among the outpatients of the Hypertension Department of the Republic Center of Cardiology and written informed consent was obtained from all the participants involved in the study. Exclusion criteria included a history of myocardial infarction, angina pectoris, heart failure, stroke and chronic renal insufficiency. No subjects with clinically overt diabetes were included. All procedures were approved by the Ethics Committee of the Republican Center of Cardiology.

Anthropometric measurements

Systolic (SBP) and diastolic blood pressure (DBP) were measured using a mercury blood pressure device, after the subjects had rested longer than 5 min. Body mass index (BMI) was calculated by weight (kg) divided by the squared height (m) (kg/m^2). The waist circumference (WC) was measured in the standing position, at the level of umbilicus, located midway between the lower costal margin (bottom of the lower rib) and the iliac crest (top of the pelvic bone).

Biochemical analysis

Following a 12-hour period of fasting, blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) levels were obtained. The fasting serum insulin level was measured by immunoenzyme assay (Access ultrasensitive insulin, Beckman Coulter ™). Standard glucose tolerance test was performed for all patients. Insulin resistance status was calculated using the homeostatic model assessment-insulin resistance (HOMA-IR) [31]. The calculation formula employed is as follows:

$$HOMA - IR = (fasting\ insulin\ [\mu IU/mL] \times fasting\ blood\ glucose\ [mM/L])/22.5.$$

Microalbuminuria (MAU) was measured by immunoenzyme assay (RANDOX, Great Britain) and defined as an albumin urinary excretion between 20-200mg/ml.

Definitions of the MetS

According to the IDF (2005), MetS is present when the waist circumference increases (M>94 cm; F>80 cm) and at least two of the following factors are present: TG 1.7 mmol/l (150 mg/dl) or greater; low HDL-C (M<1.03 mmol/l; F<1.29 mmol/l); SBP greater than 130 mmHg or DBP greater than 85 mm Hg or treatment of previously diagnosed HT; increased fasting plasma glucose (>5.6 mmol/l) or previously diagnosed DM [1].

Echocardiographic measures

Echocardiography was performed using the ultrasound system (En VisorC®, PHILIPS, Nederland). Left ventricular dimension and wall thickness were measured from two-dimensional guided M-mode echocardiographic tracings on the parasternal long axis view. Ejection fraction was calculated applying the Teicholz formula. The left ventricular mass (LVM) was estimated by using the Penn convention. Body surface area was indexed to estimate the LVM index (LVMI). The presence of LVH was defined for LVMI≥125 g/m^2 [30]. The following parameters were measured by pulse-wave Doppler: peak velocities of early (E) and late diastolic filling (A), deceleration time (DT), isovolumic relaxation time (IVRT). The ratio of early diastolic to late diastolic mitral inflow velocities was also calculated (E/A).

Carotid Ultrasound Imaging

Carotid and brachial scans were obtained busing high-resolution B-mode ultrasound by a 7.5 MHz linear array transducer (S4-2, PHILIPS, Nederland). Left and right common carotids were examined in the antero-lateral, postero-lateral, or medio-lateral directions. Longitudinal images of the distal common carotid, in which the interfaces were very clear, were obtained. Carotid intima-medial thickness (IMT) was measured in the far wall of the common carotid artery, 1 cm proximal to the carotid bulb, in a plaque-free region.

Endothelial Functions

Endothelium-dependent response was assessed as the dilation of the brachial artery to increased blood flow (flow-mediated dilation, FMD) by Celermajer DS. [7]. Briefly, a B-mode scan of the right brachial artery was obtained in longitudinal section, between 5 cm and 10 cm above the elbow, employing a probe held by a stereotactic clamp to ensure a constant image. A cuff was placed around the forearm just below the elbow, inflated for 5 minutes at 250 mm Hg, and then deflated to induce reactive hyperemia. FMD was calculated as the maximal percent increase in diameter above the baseline (mean value of measures obtained during 1 minute before cuff inflation).

Statistical analysis

Data are expressed as mean±SD. The characteristics of the study groups are compared using Student *t*-test or nonparametric test, as appropriate. The differences were considered statistically significant when the probability

value <0.05. Statistical procedures were performed using the Statistica 6.0 statistical package.

Results

The study population consisted of 85 hypertensive patients with MetS. All of them were men. Mean age was 48.8±10.45 years. 28.5% of the patients were with 1 stage of HTN, 53.5% patients – 2 stage of HTN and 18% patients – 3 stage of HTN. While studying the carbohydrate metabolism disorders, impaired glucose tolerance (IGT) was detected in 19% patients, hyperinsulinemia – 32%, insulin resistance (HOMA-IR >2.77) – 64%. 87% patients showed LVH, and LV diastolic dysfunction – 34.5%. Then 69% patients showed impaired EDVD. The characteristics of the study population are as reported in Table 1.

Table 1
Characteristics of the studied subjects

Parameters	
BMI, kg/m^2	31.08±3.46
Waist ratio, cm	101.8±7.45
Mean SBP, mm Hg	157.8±14.2
Mean DBP, mmHg	101.4±7.8
Fasting glucose, mmol/l	4.69±0.91
Postload glucose, mmol/l	5.96±2.24
Fasting insulin, U/ml	21.78±2.24
TC, mg/dl	212.50±38.32
TG, mg/dl	180.67±100.85
HDL-C, mg/dl	39.9±7.06
LDL-C, mg/dl	132.83±37.59

To further study the importance of carbohydrate imbalance, more analysis was performed and the patients were divided into 2 groups (Table 2): patients with IGT (n=17) and patients without IGT (n=41).

Patients with IGT showed significantly higher SBP (165.3±12.8 vs 152.8±12.99 mm Hg, p=0.001) than those without IGT. Our investigation revealed statistically a significant increase in MAU (27.9±17.6 vs 10.78±5.45 mg/l, p=0.000) in patients with IGT than in those without IGT. Patients with IGT expressed a higher degree of dyslipidemia than those without IGT, but none significantly. Patients with IGT were noted to have significantly more evident endothelium dysfunction than those without IGT (ΔD 1.6±6.1 vs 5.15±4.6 mg/l, p=0.018). The number of patients with vasoconstriction (ΔD<0) also was significantly greater in the group with IGT (23.5% vs 2.4%, χ^2=4.372, df=1, p=0.037). The number of patients with safe and impaired EDVD between groups has not differed.

Thus this study has shown the contribution of hyperinsulinemia to the cardiovascular remodeling processes. To facilitate the study, two groups were created (Table 3): The first group included patients with hyperinsulinemia (n=29) while the second one included patients without hyperinsulinemia (n=50). Patients with hyperinsulinemia showed significantly higher SBP (161.3±14.7 vs 154.6±11.8 mm Hg, p=0.022), DBP (102.6±8.67 vs 99.3±6.8 mm Hg, p=0.05) and LVMI (176.4±44.2 vs 157.4±27.4 g/m2, p=0.022) than patients without hyperinsulinemia.

LV diastolic dysfunction was more significantly expressed in patients with hyperinsulinemia compared with patients without hyperinsulinemia (E/A 0.97±0.39 vs 1.14±0.37 g/m^2, p=0.047) and the number of patients with

LV diastolic dysfunction was significantly higher in the group with hyperinsulinemia (61.7% vs 36.7%, χ^2=4.094, df=1, p=0.043). Moreover, the common carotid IMT was significantly higher in patients with hyperinsulinemia than in patients without hyperinsulinemia: 1.0±0.17 vs 0.97±0.20 mm, p=0.018, respectively. Our investigation demonstrated a statistically significant increase in MAU (21.8±13.6 vs 15.9±12.1 mg/l, p=0.04) and the HOMA index (9.86±7.1 vs 3.6±4.4, p=0.000) in

Table 2
Central hemodynamic parameters and ED markers in hypertensive patients with and without IGT

Parameters	**HT with IGT (n=17)**	**P**	**HT without IGT (n=41)**
SBP, mm Hg	165.3±12.8	0.001	152.8±12.99
DBP, mm Hg	102.4±7.7	NS	99.02±7.18
Mean BP, mm Hg	123.3±8.7	0,008	116.95±7.75
HR, bp	74.2±13.6	NS	71.56±11.85
LVM, g	338.1±74.4	NS	336.0±65.3
LVMI, g/m^2	169.3±34.7	NS	162.9±33.7
E/A	1.0±0.3	NS	1.1±0.42
MAU, mg/l	27.9±17.6	0.000	10.78±5.45
IMT, mm	0.96±0.17	NS	0.91±0.21
ΔD, %	1.6±6.1	0.018	5.15±4.56
TC, mg/dl	225.4±30.5	NS	212.0±34.4
TG, mg/dl	193.9±86.6	NS	178.1±91.6
HDL-C, mg/dl	39.2±8.8	NS	39.7±5.3
LDL-C, mg/dl	145.7±33.9	NS	135.2±38.1
Fasting glucose, mmol/l	5.4±0.8	0.000	4.8±0.4
Postload glucose, mmol/l	9.7±1.52	0.000	5.2±1.3
Fasting insulin, U/ml	25.2±17.6	NS	25.4±29.0
HOMA-IR	6.3±4.9	NS	5.6±7.3

patients with hyperinsulinemia than in those without hyperinsulinemia. EDVD also was shown to be more greatly impaired in patients with hyperinsulinemia than in those without hyperinsulinemia: (2.6±5.2 vs 5.2±5.5, p=0.03). Pathological vasoconstriction has been found more among patients with hyperinsulinemia, but none significantly (17.6% vs 4.9%, χ^2=2.826, df=1, p=0.093). Patients with hyperinsulinemia have also shown to express a higher degree of dyslipidemia than those without hyperinsulinemia, but none significantly.

It is well known that a combination of several risk factors increases the damage to the target organs. Therefore, the influence of a combination of IGT and hyperinsulinemia on the intensity of hypertension and atherosclerosis processes was analyzed (Table 4). Patients with IGT and hyperinsulinemia (n=46) showed a significantly higher SBP (161.38±14.09 vs 152.76±11.19 mm Hg, p=0.003.) and DBP (101.91±8.51 vs 98.82±6.41mm Hg, p=0.06) than patients without IGT and hyperinsulinemia (n=39). The heart rate also was significantly higher in patients with IGT and hyperinsulinemia (80.02±9.62 vs 74.21±10.06 bp, p=0.008) than in patients without IGT and hyperinsulinemia. Moreover, those patients with glucose disorders definitely showed significantly higher LVMI compared with patients without IGT and hyperinsulinemia: 170.87±32.57 vs

Table 3

Central hemodynamic parameters and ED markers in hypertensive patients with and without hyperinsulinemia

Parameters	HT with hyperinsulinemia (n=34)	P	HT with normal insulin level (n=49)
SBP, mm Hg	161.32±14.74	0.029	154.59±11.81
DBP, mm Hg	102.64±8.64	NS	99.29±6.85
Mean BP, mm Hg	122.2±9.24	0.019	117.72±7.22
HR	82.45±7.74	0.000	73.88±10.84
LVM, g	356.0±70.7	0.009	317.8±58.6
LVMI, g/m^2	176.4±44.2	0.022	157.7±28.7
E/A	0.97±0.39	0.047	1.1±0.37
MAU, mg/l	21.77±13.61	NS	15.94±12.07
IMT, mm	1.0±0.17	0.027	0.90±0.20
ΔD, %	2.64±5.19	0.046	5.18±5.47
TC, mg/dl	220.6±45.7	NS	205.3±34.7
TG, mg/dl	193.4±98.0	NS	163.1±87.6
HDL-C, mg/dl	38.8±7.2	NS	40.3±6.9
LDL-C, mg/dl	145.7±33.9	NS	131.5±34.0
Fasting glucose, mmol/l	5.0±0.95	NS	4.7±0.6
Postload glucose, mmol/l	6.3±2.6	NS	6.3±2.2
Fasting insulin, U/ml	42.8±26.4	0.000	12.0±5,9
HOMA-IR	9.86±7.1	0.000	3.6±4.4

Table 4

Central hemodynamic parameters and ED markers in hypertensive patients with and without IGT and hyperinsulinemia

Parameters	HT with IGT+ hyperinsulinemia (n=47)	P	HT without IGT+ hyperinsulinemia (n=38)
SBP, mm Hg	161.38±14.09	0.003	152.76±11.19
DBP, mm Hg	101.91±8.51	0.066	98.82±6.41
Mean BP, mm Hg	121.74±9.08	0.006	116.8±6.53
HR	80.02±9.62	0.008	74.21±10.06
LVM, g	351.2±66.5	0.007	313.9±56.5
LVMI, g/m^2	172.4±32.6	0.017	155.9±29.1
E/A	0.98±0.35	0.016	1.2±0.4
MAU, mg/l	22.37±14.48	0.000	13.13±8.06
LVMI, g/m^2	170.87±32.57	0.036	156.6±28.4
IMT, mm	1.0±0.17	0.002	0.87±0.20
ΔD, %	2.55±4.91	0.003	5.82±4.91
TC, mg/dl	217.7±43.2	NS	201.6±34.7
TG, mg/dl	193.0±91.9	0.01	148.5±52.4
HDL-C, mg/dl	39.7±7.5	NS	39.8±6.5
LDL-C, mg/dl	134.1±40.6	NS	130.9±31.2
Fasting glucose, mmol/l	5.0±0.7	0.024	4.7±0.6
Postload glucose, mmol/l	7.2±2.7	0.000	5.2±0.8
Fasting insulin, U/ml	35.1±25.8	0.000	11.5±6.1
HOMA-IR	7.9±6.6	0.002	3.7±4.9

156.6±28.4 g/m^2, p=0.036. LV diastolic dysfunction was more significantly expressed in patients with IGT and hyperinsulinemia compared with patients without IGT and hyperinsulinemia (E/A 0.98±0.35 vs 1.18±0.40 g/m^2, p=0.016). This investigation showed high, statistically significant increase in triglycerides (193.06±91.99 vs 148.53±52.46 mg/dl, p=0.009.) in patients with IGT andhyperinsulinemia than in those without IGT and hyperinsulinemia. Further, common carotid IMT was significantly higher in patients with IGT and hyperinsulinemia compared with those without IGT and hyperinsulinemia: 1.0±0.17 vs 0.87±0.20 mm, p=0.002, respectively. EDVD abnormality also was more apparent in patients with IGT and hyperinsulinemia (ΔD 2.55±4.91 vs 5.82±4.91%, p=0.003) than patients without IGT and hyperinsulinemia. Significantly, patients with vasoconstriction were found only in the group with IGT and hyperinsulinemia: 17.0% vs 0% (χ^2=5.28, df=1, p=0.022). The number of patients with impaired EDVD was similar in both groups: 78.7% vs 84.2%, respectively, p=0.71. Patients with safe EDVD were evident more in the group without IGT and hyperinsulinemia: 15.8% vs 4.25%, but not significantly (p=0.15). MAU also was significantly higher in patients with IGT and hyperinsulinemia than those without IGT and hyperinsulinemia: 22.37±14.48 vs 13.13±8.06 mg/l, p=0.000.

Discussion

Some recent studies reported an increased prevalence of LVH, diastolic dysfunction, early carotid atherosclerosis, impaired aortic distensibility, hypertensive retinopathy and MAU in hypertensive patients with MetS compared with those without it [33]. The increased occurrence of these signs of subclinical target organ damage, most of which are recognized as significant independent predictors of adverse CV and renal outcomes, may partially explain the association of the MetS with a higher CV and renal risk.

In the present study, the presence of IGT and hyperinsulinemia has been shown to worsen the cardiovascular remodeling processes. Specifically, SBP and DBP were significantly higher in patients with IGT and hyperinsulinemia. Blood pressure levels are strongly associated with visceral obesity and insulin resistance, which is the main pathophysiologic feature underlying MetS. These factors induce sympathetic overactivity, vasoconstriction, increased intravascular fluid, and decreased vasodilatation, leading to the development of hypertension in those with metabolic syndrome [51].

Several studies have shown that in hypertensive subjects with MetS, LVH is a more common occurrence [8, 9, 15, 24, 37, 38, 44]. The results of this study further extend these findings. It has been demonstrated that LVH was expressed more in patients with IGT and hyperinsulinemia. Multiple mechanisms contribute to the LV dysfunction in MetS, including lipotoxicity associated with cardiac steatosis and lipoapoptosis, alterations in fatty acid metabolism, overproduction of cardioinhibitory cytokines, up-regulation of some neurohormones (particularly angiotensin II), myocardial fibrosis and chronic overload with LV dilatation and hypertrophy, and increased oxygen consumption [12, 40, 50]. Elevated insulin levels in patients with MetS stimulate myocyte growth and interstitial fibrosis. Insulin also causes sodium retention and activates the sympathetic nervous system which can affect cardiac performance [12, 50]. Also, fasting plasma insulin was found to be the strongest independent predictor of LVM [39]. The effect of the MetS on the LV diastolic function has also been demonstrated in the Strong Heart Study [8]. In this study, abnormalities of the LV diastolic function were identified in patients with IGT and hyperinsulinemia.

Insulin resistance was found to exert an important effect on endothelial function. In turn, endothelial dysfunction contributes to an increased risk of atherosclerosis, coronary artery disease and hypertension in insulin-resistant conditions [20, 35]. Extensive epidemiologic evidence has consistently indicated that alterations in endothelial function play a pivotal role in the development of atherosclerosis and predict the occurrence of atherosclerotic complications [43, 48]. In this study, IGT and hyperinsulinemia have been shown to be associated with impaired endothelium-dependent vasodilation (EDVD).

Further, our findings indicate that the presence of IGT and/or hyperinsulinemia increases the likelihood of early carotid atherosclerosis, as assessed by ultrasonography. Intima-media thickness (IMT) is a well-established surrogate marker of subclinical atherosclerosis [21]. Expansion of IMT develops in patients with IGT and hyperinsulinemia. Meanwhile, pathological vasoconstriction was identified in the same patients. The initiation and progression of atherosclerosis may have its origins in impaired endothelial function that can be detected in the earliest stages of MetS development.

Further, the MAU level has been seen to increase in patients with both IGT and hyperinsulinemia, in this study. MAU is one of the clear signs of MetS and may be a marker for increased risk of renal and CVD associated with insulin resistance and endothelial dysfunction. Much of the research in MetS has involved the pathological and physiological relationships between MAU and endothelial function [3, 42]. At present, the most likely possibility is that a common pathophysiological process, such as endothelial dysfunction, chronic low-grade inflammation or increased transvascular leakage of macromolecules, underlies the association of MAU with cardiovascular disease [47].

Conclusions

The presence of IGT has been associated with a more significant increase in SBP and endothelium dysfunction. Patients with hyperinsulinemia are characterized by a significant increase in both SBP and DBP, a rise in the HB level, and an expression of MAU, LV hypertrophy and endothelial dysfunction. The presence of the IGT and hyperinsulinemia changes the cardiovascular remodeling processes for the worse in patients with MetS, and is associated with high risk of target organ damage.

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