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Partial normalization of components of metabolic syndrome does not influence prevalent echocardiographic abnormalities: the HyperGEN Study

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Abstract

Background and Aims—Metabolic syndrome (MetS) is a complex condition characterized by different phenotypes, according to combinations of risk factors and is associated with cardiovascular abnormalities. Whether control of MetS components by treatment produces improvement in the associated cardiovascular abnormalities is unknown. We investigated whether partial control of components of MetS was associated with less echocardiographic abnormalities than the complete presentation of MetS based on measured components.

Methods and Results—We evaluated markers of echocardiographic preclinical cardiovascular disease in MetS (ATPIII) defined by measured components or by history of treatment, in 1,421 African- American and 1,195 Caucasian non-diabetic HyperGEN participants, without prevalent cardiovascular disease or serum creatinine >2 mg/dL. Of 2,616 subjects, 512 subjects had MetS by measured components and 328 by history. Hypertension was found in 16% of participants without MetS, 6% of those with MetS by history and 42% of those with MetS by measured components. Obesity and central fat distribution had similar prevalence in both MetS groups (both $p < 0.0001$ vs No-MetS). Blood pressure was similar in MetS by history and No-MetS, and lower than in MetS by measured components ($p < 0.0001$). LV mass and midwall shortening, left atrial (LA) dimension and LA systolic force were similarly abnormal in both MetS groups (all $p < 0.0001$ vs. No-MetS) without difference between them.

Conclusions—There is little impact of control by treatment of single components of MetS (namely hypertension) on echocardiographic abnormalities. Lower blood pressure in participants with MetS by history was not associated with substantially reduced alterations in cardiac geometry and function.

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INTRODUCTION

The metabolic syndrome (MetS) is a complex condition that can be characterized by different phenotypes, according to different clustering of risk factors characterizing the syndrome. MetS may increase CV risk beyond what might be predicted by the additive effect of single components (1). Part of the MetS-related high CV risk is due to the frequent coexistence of what is called “preclinical CV disease” (2), an effect especially evident in the absence of diabetes. In epidemiological studies, MetS may be detected by documented abnormality of metabolic and/or hemodynamic components or by ongoing treatment for them. For instance, therapy for arterial hypertension means that high blood pressure is considered present for diagnosis of MetS, independently of the level of blood pressure (BP) at the time of evaluation. This approach, however, blunts understanding of whether control of components of MetS by treatment is associated with less preclinical CV disease in individuals who meet criteria for the MetS. Thus, it is unknown whether therapy-modified single components of the MetS have the same impact on the CV system as the presentation of the full spectrum of MetS components.

Accordingly, this cross-sectional study was designed to understand whether partial correction of some components of the MetS is associated with reduced echocardiographic abnormalities, compared to the full presentation requiring the presence of all altered components. To achieve this goal, we analyzed the distribution of components of the MetS based on either history of MetS components or direct evidence of abnormalities, to assess whether, and to what extent, therapeutic control of one or more components contributing to MetS diagnosis is associated with less abnormal CV phenotype, assessed with echocardiography (3).

METHODS

Study sample

The HyperGEN Study is part of the NHLBI Family Blood Pressure Program, designed to assess the genetic basis of hypertension in population-based samples (4). The HyperGEN study is a cross-sectional survey based on a sib-pair design that recruited persons with onset of hypertension before age 60, and at least one additional hypertensive sibling who could be enrolled in the study. Unmedicated adult offspring of hypertensive siblings and a random sample of age-matched subjects from the same source population were also recruited, including normotensive controls. Further details about recruitments and characteristics have been previously reported (4).

For the purpose of this study, we excluded participants with diabetes or prevalent CV disease (including coronary heart disease, history of stroke and heart failure) or more than mild renal failure, all conditions that could primarily alter cardiac morphology and function (5). Therefore this analysis included 1,421 African-American (886 women) and 1,195 Caucasian (623 women) non-diabetic (i.e. fasting blood glucose <126 mg/dl and no anti-diabetic therapy) HyperGEN participants, without prevalent CV disease or moderate-to-severe renal failure (i.e. serum creatinine >2 mg/dL). 6. IRB approval was obtained and written informed consent collected from all participants.

Definitions

MetS was defined according to the ATP III criteria (6), using direct measurements of the MetS components at the time of survey, without considering whether or not participants were taking medications. This criterion was labeled as “Direct Diagnosis” (DD). Participant who met criteria for diagnosis of MetS by DD were compared with a second group of participants who had the three components allowing the diagnosis of MetS, but in whom at

least one of these MetS components was normalized by the therapy; these participants, therefore, could not be included in the DD group because one or more treated components of the MetS were normal at the time of the survey. This criterion was labeled as “Historical Diagnosis” (HD). Participants without either DD or HD MetS were labeled as “No-MetS”.

Obesity and central fat distribution (by waist girth) were categorized according to the NIH guidelines (7): measured waist girth >88 cm in women or >102 cm in men constituted the obesity criterion of MetS for both DD and HD groups (table 1), without reference to historical information. Similarly, because diabetic participants were excluded, and no therapy was given for impaired fasting glucose, this variable was similarly included in the definition of MetS in both DD and HD groups. The other components of MetS could differ in the two groups (table 1). Thus two components of the syndrome could be modified by management: high blood pressure and dyslipidemia.

HOMA index was also calculated as an estimate of insulin resistance (HOMA_I), using fasting glucose and insulin levels (8).

Echocardiographic Methods

Imaging and Doppler echocardiograms were obtained using standardized acquisition methods employed in multiple studies and evaluated in the Echocardiography Reading Center at Weill-Cornell Medical Center (9,10), and measured according to the recommendations of the American Society of Echocardiography (11,12).

According to wide clinical and epidemiological evidence, we used three anatomical and three functional indicators of echocardiographic preclinical CV disease (3):

1. LV mass by an anatomically validated formula [$r=0.90$ vs. necropsy LV mass (13)], and normalized for height in $\text{m}^{2.7}$, which has been shown to maximize population risk attributable to LV hypertrophy in populations with high prevalence of obesity (14). Values of $> 49.2 \text{ g/m}^{2.7}$ for men and $> 46.7 \text{ g/m}^{2.7}$ for women were used to identify LV hypertrophy. LV hypertrophy is the most potent predictor of CV events after age (15). LV diastolic diameter was normalized for the linear measure of height.
2. Relative wall thickness, calculated as posterior wall thickness/LV internal radius, as a measure of LV geometry. LV concentric geometry was identified when relative wall thickness was ≥ 0.43 . LV concentric geometry has been shown to predict CV risk independently of LV mass index (16).
3. Left atrial (LA) systolic dimension, measured from the parasternal long-axis view and normalized for the linear measure of height. Left atrial dimension is another powerful and independent marker of adverse outcome (17,18).
4. Ejection fraction, measured from Doppler-assessed transaortic stroke volume (19) normalized to LV end-diastolic volume, calculated from linear measurements according to a validated method (20). Ejection fraction is the most commonly used measure of LV systolic function at the chamber level.
5. Midwall shortening, measured from linear measures at the midwall level, as previously reported (21). Midwall shortening is a measure of LV myocardial function, independent of LV geometry and less sensitive to modification of myocardial afterload than ejection fraction (21). Midwall shortening is more associated with CV events than measures of LV chamber function in patients with initially uncomplicated hypertension (22).

6. LA systolic force, a measure of LA function, assessed at the mitral annulus level, as previously reported (23). LA systolic force has been shown to be associated with CV events, independently of LV hypertrophy (24).

Statistical Analysis

Data were analyzed using SPSS 12.0 software (SPSS, Chicago, IL). Mean $\pm$ one standard deviation are shown for continuous variables. The Kolmogorov-Smirnov statistic, with a Lilliefors significance level were used to test for normal distribution. Continuous variables with non-normal distribution were log transformed for parametric statistics. Differences among the three groups of participants were assessed using ANOVA and the REGW F post-hoc test. To assess dependence among categories a χ^2 distribution test was used. Spearman correlation was used to explore trends among the groups defined by MetS and the control group without MetS.

Anatomic and functional measures were compared among the three groups, using ANCOVA, adjusting for age, sex and ethnicity. Specific differences between the HD group and the other groups were also examined after Sidak's adjustment for multiple comparisons.

The null hypothesis was rejected at two-tailed $p = 0.05$.

RESULTS

Characteristics of the study population

A total of 1 776 participants (978 women or 55%) were free of MetS (No-MetS). MetS was identified in 512 subjects (295 women or 58%) by the DD criterion, and in 328 additional individuals (235 women or 72%) by the HD criterion ($p < 0.0001$ for sex distribution vs. the other groups).

In the HD group, MetS prevalence was 13% in Caucasians, 12% in African Americans, and 25% and 15% respectively in the DD group. Anti-hypertensive therapy was given to 636 of 1 776 No-MetS (or 36%), 344 DD (67%) and 277 HD participants (or 84%; $p < 0.0001$). Lipid-lowering therapy was used in 2% of No-MetS, 10% of DD and in 27% of HD ($p < 0.0001$), paralleling the same distribution as anti-hypertensive treatment.

Table 2 shows the frequency of single components of MetS in the three groups of participants. The frequency of both high BP values (by ATP III definition) and high triglycerides levels in the DD group was nearly twice and the prevalence of high fasting glucose more than 3-fold greater than in the HD group (table 2, all $p < 0.0001$).

At the HyperGEN clinic exam, BP was in the hypertensive range (i.e. ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) in 34% of the No-MetS group, 51% of the DD group ($p < 0.0001$ vs No-MetS) and 7% of the HD group ($p < 0.0001$ vs. other groups, Figure 1).

Distribution of classes of anti-hypertensive meds among hypertensive participants (diuretics, ACE-inhibitors, AT1 receptor blockers, Ca^{++} channel blockers, β -blockers, others), was similar in the three groups, except for β -blockers that were more often prescribed in hypertensive HD ($p < 0.0001$).

In contrast to BP distribution and hypertension prevalence, central fat distribution exhibited similar higher prevalence in both MetS groups than in the No-MetS group. Obesity by BMI classification, was also more prevalent in DD (71%) and in HD (65%, $p < 0.05$ vs. DD) than in No-MetS (33%, both $p < 0.0001$).

Table 3 shows that BMI and waist circumferences were similarly greater in both the MetS groups than in the No-Mets, whereas blood pressure was higher only in the DD group, with the HD group exhibiting values very similar to the No-MetS group. Reported duration of hypertension and antihypertensive treatment was significantly longer in DD than in both HD and No-Mets (table 3, both $p < 0.0001$). Plasma glucose, insulin, HOMA_r, total cholesterol and triglycerides were also higher and HDL-cholesterol lower in both MetS groups, but DD exhibited more severe alterations than the HD group. LDL-cholesterol and heart rate were similarly higher in both MetS groups than in the No-Mets, without differences between them. Of note, whereas the natural log of circulating insulin was 25% higher in HD than in NoMetS, the difference between HD and DD was only 9%. Similar results were obtained with HOMA_r.

Echocardiographic markers of preclinical CV disease

After controlling for age, sex and race, LV dimension and mass, relative wall thickness and LA dimension were similarly greater in both HD and DD than in No-Mets. There was no difference in these values between the two MetS groups (Table 4). The prevalence of LV hypertrophy was also similarly higher in the two MetS group than in the No-MetS.

Ejection fraction was similar in the three groups. Midwall shortening was similarly slightly lower and LA systolic force more than 30% greater in both MetS groups than in no-MetS, without appreciable difference between HD and DD.

These results did not change when duration of antihypertensive therapy was added as a covariate to the ANCOVA model.

Standardized residuals of the ANCOVA of LV mass index were linearly correlated with the natural log of both fasting insulin and HOMA_r (both $r = 0.11$, $p < 0.0001$).

DISCUSSION

This cross-sectional study suggests that MetS may not be a dynamic condition, subjected to improvement of CV condition if individual components (high blood pressure and dyslipidemia) are controlled by treatment without intervention on the other components (central obesity / impaired fasting glucose-insulin resistance). Whether or not MetS was diagnosed on the basis of measured abnormalities or also using clinical history in individuals on treatment for hypertension or dyslipidemia, the association of MetS with the echocardiographic markers of CV risk used in this study did not change substantially.

The only significant difference found between DD and HD was in the level of BP, which was substantially lower when diagnosis was made on the basis of clinical history, reflecting the widespread use of antihypertensive treatment and the relatively better control of this risk factor compared to the other components of MetS. These findings indicates that inclusion by history of treatment rather than, or in addition to, abnormal lab values is justified in trials recruiting patients with MetS.

Based on the differences found between the two different diagnostic criteria for MetS, our data indicate that even partial recovery of the syndrome, with control of some of the risk factors, may not be effective in reducing target organ damage and, as a possible consequence, CV risk. This finding is even more impressive, considering that, among the components of MetS, BP was relatively controlled in the HD group. Despite this relatively good control, HD participants exhibited higher LV mass and LA dimension, more pronounced concentric LV geometry and significant abnormality of LV and LA function, similar to the alterations found in DD group in which high BP was substantially more

prevalent. This deviation from normality of markers of preclinical CV disease in HD could not be, therefore, attributable to uncontrolled hypertension.

Alternative candidates to explain the persistently abnormal values of these markers despite relative BP control, are central obesity and/or insulin resistance. We have previously shown in the Strong Heart Study that the prevalence of LV hypertrophy in participants with normal BP but MetS by ATP III criteria is similar to prevalence in participants with hypertension but without MetS (25). In the HyperGEN study (5), the probability of clear-cut LV hypertrophy in obese normotensive participants with abnormal lipid profile and diabetes was similar to the probability of LV hypertrophy in hypertensive subjects without metabolic abnormalities, but this could be due to the impact of diabetes on LV geometry (26). This is not the case in the present analysis because diabetic participants were excluded. Prevalence of the abnormal cardiovascular phenotype in MetS participants despite partial correction of the syndrome could not be attributed to abnormal BP, diabetes or less anti-hypertensive or lipid-lowering therapy, which were, in contrast, given more frequently. BMI and central fat distribution were the only components of MetS that had near-identical value in both MetS groups. Insulin resistance and hyperinsulinemia could also play a role in the association between abdominal adiposity and markers of preclinical cardiovascular disease, as previously reported (27), and suggested by the correlation between standardized residuals from ANCOVA and both circulating insulin and HOMA index. It is also relevant that, whereas circulating insulin and insulin resistance were substantially higher in HD than in NoMetS, the differences between HD and DD were negligible, indicating that insulin resistance was a characteristics also in HD.

Because this is a cross-sectional observational study, it is possible that participants in the HD group had been exposed to the clusters of risk factors for longer time, or initially had more severe abnormality, a potential stimulus to starting treatment more frequently than in those in the DD group. If this bias was encountered, it is also possible that their target organ damage was more severe than in the group less aggressively treated. In this case, a cross-sectional analysis would not be able to detect improvement in markers of preclinical CV disease that were even more abnormal prior to therapy. Other potential confounders could be elements of life style that were not considered in this analysis, such as diet (salt, vegetable and fat intake) and physical activity. However, persistence of abnormal values of these markers despite good control of BP is consistent with recent longitudinal data from the LIFE study (28), demonstrating that, for comparable effects on BP, therapy-induced regression of both ECG and echocardiographic LV hypertrophy is blunted in participants with MetS.

There is still debate on whether MetS increases CV risk beyond what might be predicted by single components. The evidence is increasing that MetS is a condition that requires medical attention (1,2,29–35) and should yield prompt and appropriate therapy to reduce risk burden (32,35). Similar to arterial hypertension, MetS is also associated with target organ damage (2,31,33,36–38) in hypertensive and non-hypertensive subjects (25,39). And, similar to arterial hypertension, a substantial part of risk attributable to MetS in the absence of diabetes can be explained by coexisting LV hypertrophy (2). If the complete control of the syndrome, including therefore control of central obesity, is the key issue for reducing target organ damage in the context of MetS, as it appears in this study, more effort should be devoted in controlling and preventing all components, namely central obesity and insulin resistance. Consistent with indications from the Diabetes Prevention Program (40–42), our study suggests that greater efforts should be devoted in the attempt to control these risk factors in addition to blood pressure and lipid profile.

As stated above, this study is a cross-sectional survey and cannot assess temporal evolution. However, our study also suggests that appropriate longitudinal investigations are needed to

evaluate the impact of control of components of MetS on reduction or regression of preclinical CV disease.

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Figure 1.

Frequency of prescriptions of anti-hypertensive medications (dark grey columns) and prevalence of uncontrolled blood pressure (BP) among treated participants without MetS (No-MetS), in those classified on the basis of direct measurements of components (DD) and in those classified on the basis of history of exposure (HD).

Table 1

Definition of metabolic syndrome according NCEP-ATPIII (7), by direct assessment of abnormality or ongoing therapy.

Factor	<i>ATPIII components in DD</i>	<i>ATPIII components in HD</i>
Abdominal obesity	>102/88 cm waist (M/W)	>102/88 cm waist (M/W)
Triglycerides	150 mg/dL	150 mg/dL or lipid lowering therapy
HDL-cholesterol	<40/50 mg/dL (M/W)	<40/50 mg/dL (M/W) or lipid lowering therapy
Blood pressure	130/ 85 mmHg	130/>85 mmHg or antihypertensive therapy
Fasting glucose	110 mg/dL	110 mg/dL

DD=diagnosis of MetS based on direct measurements of the components.

HD=diagnosis of MetS based on historical exposition, with one or more treated components of the MetS normal at the time of survey.

Table 2

Single components of ATPIII MetS on the basis of diagnostic criteria

	No- MetS	DD	HD	p<	
				MetS vs No-MetS	DD vs HD
High BP	27%	61%	34%	0.0001	0.0001
Central fat	42%	89%	88%	0.0001	ns
High glucose	1%	36%	10%	0.0001	0.001
High tryglycerides	9%	75%	34%	0.0001	0.0001
Low HDL-cholesterol	24%	81%	75%	0.0001	0.05

DD=diagnosis of MetS based on direct measurements of the components.

HD=diagnosis of MetS based on historical exposition, with one or more treated components of the MetS normal at the time of survey.

Table 3

General characteristics of the study population

	No-MetS (n=1775)	HD (n=328)	DD (n=512)
Age (yrs)	42.7±13.5	51.6±11.2 [*]	50.6±12.3 [*]
BMI (kg/m ²)	28.6±6.4	33.1±6.7 [*]	33.9±6.9 [*]
Waist (cm)	95±16	108±14 [*]	110±14 [*]
Diastolic BP (mmHg)	71.7±11.2	70.7±8.9 [†]	75.8±11.4 [*]
Systolic BP (mmHg)	121.0±19.4	122.4±14.4 [†]	135.6±20.8 [*]
<i>Duration of hypertension (yrs)</i>	<i>13.7±10.1</i>	<i>13.0±9.8[†]</i>	<i>16.0±11.2[*]</i>
<i>Duration of antihypertensive therapy (yrs)</i>	<i>12.5±9.6</i>	<i>11.4±8.8[†]</i>	<i>14.5±10.1[*]</i>
Heart rate (bpm)	66.0±10.6	68.7±11.8 [*]	69.9±11.4 [*]
Creatinine (mg/dL)	0.96±0.20	0.97±0.21	0.97±0.20
Cholesterol (mg/dL)	187.6±37.9	199.5±40.8 [*] [†]	207.0±38.5 [*]
HDL-cholesterol (mg/dL)	54.9±15.2	48.2±12.0 [*] [†]	41.7±10.9 [*]
LDL-cholesterol (mg/dL)	113.7±34.3	123.7±34.0 [*]	126.5±35.2 [*]
Triglycerides (mg/dL)	94.8±51.6	139.3±66.9 [*] [†]	203.3±102.9 [*]
Fasting glucose (mg/dL)	90.7±9.2	96.5±12.9 [*] [†]	108.0±11.8 [*]
<i>Fasting insulin (μUI/L)</i>	<i>7.1±5.4</i>	<i>10.8±9.1[*][†]</i>	<i>13.0±11.8[*]</i>
<i>HOMA₁ index</i>	<i>1.6±1.3</i>	<i>2.6±2.4[*][†]</i>	<i>3.6±4.0[*]</i>

* p<0.05 vs. No MetS;

[†] p<0.05 vs DD.

DD=diagnosis of MetS based on direct measurements of the components.

HD=diagnosis of MetS based on historical exposition, with one or more treated components of the MetS normal at the time of survey.

Table 4

Markers of preclinical cardiovascular disease in different diagnosis of MetS. Comparison is adjusted for age, sex, and race.

	No-MetS (n=1775)	HD (n=328)	DD (n=512)
LV mass index (g/m ^{2.7})	36.8±10.6	41.3±9.8 *	41.9±10.5 *
Prevalence of LVH (%)	13%	22% *	24% *
Relative wall thickness	0.32±0.05	0.34±0.05 *	0.34±0.06 *
LV dimension index (cm/m)	3.01±0.25	3.06±0.26 *	3.07±0.27 *
LA dimension index (cm/m)	1.96±0.29	2.08±0.29 *	2.10±0.27 *
Ejection fraction (%)	64.3±11.2	65.2±12.7	65.3±11.3
Midwall shortening (%)	18.0±2.0	17.6±2.0 *	17.6±2.0 *
LA systolic force (kdynes)	9.2±4.4	12.4±4.6 *	13.1±5.9 *

* p<0.05 vs. No MetS;

† p<0.05 vs. DD.

DD=diagnosis of MetS based on direct measurements of the components.

HD=diagnosis of MetS based on historical exposition, with one or more treated components of the MetS normal at the time of survey.

APPENDIX

List of HyperGEN Participating Institutions and Principal Staff

<u>Network Center/Univ. of Utah Field Center:</u>	Steven C. Hunt, Roger R. Williams (deceased), Hilary Coon, Paul N. Hopkins, Janet Hood, Lily Wu, Jan Skuppin
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<u>Boston University/Framingham Field Center:</u>	R. Curtis Ellison, Richard H. Myers, Yuqing Zhang, Luc Djoussé, Jemma B. Wilk, Greta Lee Splansky
<u>University of Minnesota Field Center:</u>	Donna Arnett, Aaron R. Folsom, Mike Miller, Jim Pankow, Gregory Feitl, Barb Lux
<u>University of North Carolina Field Center:</u>	Gerardo Heiss, Barry I. Freedman, Kari North, Kathryn Rose, Amy Haire
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<u>Molecular Genetics Laboratory, Univ. of Utah:</u>	Mark Leppert, Steven C. Hunt, Jean-Marc Lalouel, Robert Weiss
<u>National Heart, Lung, & Blood Institute:</u>	Susan E. Old, Millicent Higgins (retired), Cashell Jaquish, Martha Lundberg, Mariana Gerschenson.