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THE NATURAL HISTORY OF PATIENTS WITH ISOLATED METABOLIC SYNDROME

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Abstract

Objectives—To define the natural history of patients with Isolated metabolic syndrome.

Patients & Methods—Metabolic syndrome (MS) is associated with increased risk of cardiovascular mortality. Isolated MS patients are a subset of MS patients who don't meet the diagnostic criteria of hypertension (HTN) and diabetes mellitus (DM). Data was collected prospectively on a population-based random sample of 1042 Olmsted County, Minnesota, residents aged 45 years or older who underwent clinical evaluation, medical record abstraction, and echocardiography (Visit 1 January 1, 1997–December 31, 2000). The cohort was subdivided into healthy controls, isolated MS and MS with HTN and/or DM groups. After four years, patients returned for Visit 2 (September 1, 2001–December 30, 2004). After Visit 2, we have a median of 8.3 years of follow-up.

Results—There was a higher incidence of hypertension, diabetes and obesity in the isolated MS group at Visit 2 ($P < .001$) than healthy controls. Patients with isolated MS did not have significantly higher rates of cardiovascular mortality (HR=0.85 95% CI 0.23–3.13, $P=0.80$) or development of heart failure (HR 1.29 95% CI 0.58–2.73, $P=0.53$) than healthy controls over eight years of follow-up after Visit 2. However, patients with MS with HTN and/or DM had higher rates of cardiovascular mortality (HR=2.40 95% CI 1.00–5.83, $P=.02$) and heart failure (HR 2.24 95% CI 1.16–4.32, $P=.02$) than healthy controls over eight years of follow-up after Visit 2.

Conclusion—Isolated MS was associated with increased risk for the development of hypertension, diabetes and obesity, but not increased mortality or heart failure over an eight year period compared to healthy controls. Future studies should determine if aggressive management of risk factors in Isolated MS will prevent progression to MS.

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INTRODUCTION

Metabolic syndrome (MS) is associated with significant cardiovascular morbidity and mortality¹. It is defined per current ATP-NCEP-III (Adult Treatment Panel-National Cholesterol Education Program III) criteria as the presence of more than three of the following five characteristics: 1) abdominal obesity, defined as a waist circumference in men 102 cm (40 in) and in women 88 cm (35 in); 2) Serum triglycerides 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides; 3) Serum HDL cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C; 4) blood pressure 130/85 mmHg or drug treatment for elevated blood pressure; 5) fasting plasma glucose (FPG) 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose².

Isolated MS is defined as a subset of MS patients who do not meet the diagnostic criteria for hypertension or diabetes and are not on drug treatment for them either³. Previously, a cross sectional study in the same cohort as our study found that the prevalence of Isolated MS was 21.7% in men and 16.7% in women. Left ventricular (LV) mass index was higher and LV diastolic dysfunction was more prevalent in women with Isolated MS than in women without MS³. No such difference was found in men. However, that study did not delineate long term mortality and cardiovascular outcomes in patients with Isolated MS.

Our aim for this study is to delineate the natural history, the long-term mortality and cardiovascular outcomes of patients with Isolated MS in the same cohort.

METHODS

This study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center prior to data collection. In 1997, a random sample of Olmsted County residents aged 45 years or older (predominantly Caucasian) was identified by applying a sampling fraction of 7% within each sex and age specific (5 years) stratum. Of the 4203 residents invited, 2042 residents participated at Visit 1 which made up the cohort for this study⁴. These patients underwent clinical evaluation, medical record abstraction, and echocardiography during Visit 1 (January 1, 1997-September 30, 2000). After 4 years, 1402 patients returned for Visit 2. Our study cohort included 1042 of the patients (after excluding those who did not have MS and did not meet the criteria for health controls) who returned for visit 2 (September 1, 2001-December 30, 2004).

Subgroup classification

The study patients were classified into one of three categories at Visit 1: a) 576 healthy controls; b) 225 patients with Isolated MS; and c) 241 patients with MS with HTN and/or DM. Metabolic syndrome was defined per current ATP-NCEP III (Adult Treatment Panel-National Cholesterol Education Program III) criteria by the presence of any three of the following five characteristics: 1) abdominal obesity, defined as a waist circumference in men 102 cm (40 in) and in women 88 cm (35 in); 2) Serum triglycerides 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides; 3) Serum HDL cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-

C; 4) blood pressure $\geq 130/85$ mmHg or drug treatment for elevated blood pressure 5) fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose². Since we were interested in studying MS patients with HTN and/or DM, we only included those MS patients in this group who had BP $\geq 130/85$ and with HTN diagnosis (Dx) or on antihypertensives for blood pressure criterion and FBG ≥ 100 and with DM Dx for elevated fasting blood glucose criterion.

Isolated metabolic syndrome was defined as a subset of MS patients with same criteria as MS for central obesity, elevated triglycerides and low HDL and BP $\geq 130/85$ but no HTN Dx nor on antihypertensives for blood pressure criterion and FBG ≥ 100 and no DM Dx for elevated fasting glucose criterion. Healthy controls were patients who 1) did not meet criteria for metabolic syndrome 2) didn't have any cardiovascular disease and 3) were not on any cardiovascular medications.

Echocardiography

2-dimensional, M-mode, and tissue Doppler echocardiography was performed for all patients [4]. All echocardiograms were interpreted by a single echocardiologist. M-mode echocardiography, quantitative 2-dimensional (biplane Simpson) method, and semiquantitative 2-dimensional visual estimate method were used to quantitate ejection fraction [4]. Since there was a high correlation between these 3 methods, visual estimate ejection fraction was used in final interpretation [4]. To quantitate the LV (Left Ventricular) mass, standard formulas based on M-mode measurement of diastolic dimension and wall thickness were utilized. Pulsed-wave Doppler examination of mitral flow (before and during Valsalva maneuver) and pulmonary venous inflow, as well as by Doppler tissue imaging of the mitral annulus were used to measure diastolic dysfunction as previously described⁵. A four-point ordinal scale was created to grade diastolic dysfunction as following: 1) normal; 2) mild diastolic dysfunction, defined as abnormal relaxation without increased LV end-diastolic filling pressure (peak early (E) to peak late [atrial] [A] diastolic filling velocity ratio < 0.75); 3) moderate or "pseudonormal" diastolic dysfunction, defined as abnormal relaxation with increased LV end-diastolic filling pressure (E/A ratio of 0.75 to 1.5, deceleration time > 140 ms, and two other Doppler indices of elevated LV end-diastolic filling pressure); and 4) severe diastolic dysfunction, defined as advanced reduction in compliance with restrictive filling (E/A ratio > 1.5 , deceleration time < 140 ms, and Doppler indices of elevated LV end-diastolic filling pressure).

Outcomes

All cause-mortality, cardiovascular mortality and development of congestive heart failure (CHF) were primary outcomes. These outcomes were defined from Visit 2 (i.e. outcomes occurred after Visit 2) since every patient was required to have a second visit and were electronically collected from the medical record using appropriate ICD-9 codes. Secondary outcomes included development of hypertension (HTN), diabetes mellitus (DM), dyslipidemia, obesity, coronary artery disease (CAD), myocardial infarction (MI), stroke, atrial fibrillation/flutter, and renal insufficiency (eGFR < 60 mL/min/1.73m²) and worsening of diastolic dysfunction. Joint National Committee VI criteria were used for diagnosis of hypertension⁶. The diagnosis of diabetes mellitus was based on documentation by a staff

physician in medical records. Framingham criteria was used to diagnose incident heart failure between Visit 1 and Visit 2. Cardiac structure parameters such as systolic dysfunction (EF<50%), diastolic dysfunction and LV mass index and neurohormonal activation markers like aldosterone, galectin-3, NT-pro-BNP were also recorded.

Follow-up

All patients returned for Visit 2 after an average of 4 years from Visit 1 (range 2.1-5.7 years). After Visit 2, we have a median (IQR) of 8.3 (7.3, 9.2) years of follow-up.

Statistical analysis

Categorical data were reported as frequency (%) and compared between groups using a Chi square test or a Fisher's exact test. Continuous variables were reported as mean + SD or median (IQR), and compared between groups using a two-sample t-test or a Wilcoxon rank sum test. For prevalence of echocardiographic abnormalities among patients with isolated metabolic syndrome, logistic regression analysis stratified by sex was performed to compare with healthy controls and those with metabolic syndrome.

Patients who already had diagnosis of certain conditions like HTN and T2DM at Visit 1 were excluded in reporting prevalence of such conditions during Visit 2. Time to event outcomes which occurred after Visit 2 were analyzed using Kaplan-Meier methods (with Visit 2 used as time 0) and survival was compared between groups using the log-rank test. Cox proportional hazards regression was used to test for differences in outcomes between groups after adjustment for gender and age at Visit 2. Results of these analyses are summarized as Hazard Ratio (HR) and 95% CI. Patients in these analyses without events were censored at the last known follow-up and those with prevalent CHF at Visit 2 were excluded from evaluation of CHF outcomes and likewise for other outcomes. Statistical significance was defined as $P<.05$. SAS version 9.3 (SAS Institute, Cary, NC) was used to perform analysis.

RESULTS

Baseline characteristics

The baseline characteristics of the overall cohort at Visit 1 are reported in Table 1 and baseline characteristics of men and women are reported in Table 2. Distribution of metabolic syndrome criteria amongst the three groups was as follows (data not shown): elevated TG (17%), low HDL (34%), elevated blood pressure (27%) and elevated fasting glucose (10%) for healthy controls; elevated TG (74%), low HDL (90%), elevated blood pressure (80%) and elevated fasting glucose (41%) for Isolated MS group; elevated TG (68%), low HDL (85%), elevated blood pressure (95%) and elevated fasting glucose (67%) for MS group. As expected, the prevalence of elevated BP and hyperglycemia was lower in Isolated MS group compared with MS group.

Isolated MS vs Healthy Controls—At baseline, patients with Isolated MS were older than healthy controls. A subgroup analysis showed that this was true for women (63 ± 9 years vs 58 ± 9 years, $P<.001$) but not for men (Table 2). Furthermore, Isolated MS group had fewer

women than healthy controls group (42% vs 57%, $P<.001$). Due to the inclusion criteria, patients with Isolated MS had higher prevalence of metabolic syndrome components such as obesity, larger waist circumference, dyslipidemia, elevated blood pressure and hyperglycemia as compared to healthy controls. The glomerular filtration rate (eGFR) was lower in the Isolated MS group as compared to the healthy controls. (82 ± 16 vs 85 ± 15 ml/min/1.73m², $P=.05$). Patients with Isolated MS had higher prevalence of diastolic dysfunction as compared to the healthy controls. A subgroup analysis showed that this was true for women but not men (Table 2). Patients with Isolated MS had higher neurohormonal activation as they had higher aldosterone level (5.1 nag/dL vs 3.8 nag/dL, $P<.001$) and galectin-3 level (12.8 nag/dL vs 12.1 nag/dL, $P<.001$). Interestingly, NT-proBNP levels were similar between the two groups.

Isolated MS vs MS with HTN and/or DM—Patients with MS with HTN and/or DM were older (64 ± 9 years vs 60 ± 9 years, $P<.001$) than patients with Isolated MS. A subgroup analysis showed this was true for men (64 ± 9 years vs 58 ± 9 years, $P<.001$) but not women (Table 2). Patients with MS with HTN and/or DM had a higher prevalence of CAD (19% vs 4%, $P<.001$), CHF (3% vs 0%, $P=.006$) and renal insufficiency (eGFR<60) (22% vs 12%, $P=.02$) than those with Isolated MS.

Patients with MS with HTN and/or DM had higher LV mass index (102.8 ± 24.5 g/m² vs 94.4 ± 19.0 g/m², $P<.001$) and higher prevalence of diastolic dysfunction ($P<.001$) as compared with patients with Isolated MS. A subgroup analysis showed that only men with MS had a higher prevalence of diastolic dysfunction (moderate/severe) compared with men with Isolated MS (13% vs 4%, $P=.003$). Patients with MS with HTN and/or DM had higher neurohormonal activation as they had higher aldosterone level (6.4 nag/dL vs 5.1 ng/dL, $P<.001$), galectin-3 level (13.7 ng/dL vs 12.8 ng/dL, $P=.001$) and NT-proBNP level (62.0 pg/mL vs 34.1 pg/mL $P<.001$).

Incidence of comorbidities and progression of diastolic dysfunction at Visit 2

Isolated MS vs Healthy Controls—At Visit 2 (after ~4 years), there was a higher incidence of HTN (34% vs 14%, $P<.001$), DM (12% vs 1%, $P<.001$) and obesity (21% vs 8%, $P<.001$) in Isolated MS group as compared with healthy controls (Table 3). There was no difference in diastolic dysfunction at baseline between women with Isolated MS and men with Isolated MS (data not shown). However, the progression of diastolic dysfunction grade was more prevalent in women with Isolated MS compared with men with Isolated MS at Visit 2 (40% vs 22% $P=.005$). Blood pressure at baseline was similar between women with Isolated MS and men with Isolated MS (data not shown).

Isolated MS vs MS with HTN and/or DM—At Visit 2, there was no difference in incidence of HTN and DM between MS with HTN and/or DM group and Isolated MS group. Patients with MS with HTN and/or DM (overall) had higher incidence of CAD (10% vs 5%, $p=.03$ and MI (4% vs 0%, $p=.02$) compared with patients with Isolated MS. A subgroup analysis by gender showed that men with MS with HTN and/or DM had higher incidence of MI (6% vs 1%, $p=.03$) compared with men with Isolated MS. There was a trend towards significance for higher incidence of CHF (3% vs 0%, $P=.05$) and worsening of

diastolic dysfunction (34% vs 22%, $P=.05$) in men with MS compared with men with Isolated MS. There was no difference in worsening of diastolic dysfunction in overall population between MS with HTN and/or DM group and Isolated MS group.

Clinical Outcomes after Visit 2

The Kaplan-Meier curves for all-cause mortality, cardiovascular mortality and CHF after Visit 2 are displayed in Figure 1. There were significant differences in all-cause mortality ($p<.001$), cardiovascular mortality ($p<.001$), and CHF ($p=.002$), risk between the three groups. However, there was no difference in age- and gender-adjusted hazard ratios for all-cause mortality (HR 0.5195% CI: 0.23-1.15, $P=.10$), cardiovascular mortality (HR=0.85 (0.23-3.13), $P=0.80$) or CHF risk (HR 1.29 (0.58-2.73), $P=0.53$) between Isolated MS and healthy controls. Patients with MS with HTN and/or DM had higher risk of all-cause mortality (HR 3.59 (1.58-8.15), $P=.002$) but not cardiovascular mortality (HR=2.84 (0.79-10.16), $P=.11$) nor CHF development (HR 1.74 (0.77-3.91), $P=.18$) compared with patients with Isolated MS. Patients with MS with HTN and/or DM had higher risk of all-cause mortality (HR 1.83 (1.12-2.98), $P=.02$), cardiovascular mortality (HR=2.40 (1.00-5.83), $P=.02$) and CHF (HR 2.24 (1.16-4.32), $P=.02$) compared with healthy controls.

Biomarker Data Analysis

NT-pro BNP level was associated with increased risk for all-cause mortality (HR 1.53, 95% CI 1.21 -1.93 , $p=0.0003$), cardiovascular mortality (HR 2.01, 95% CI 1.33-3.02 , $p=0.0009$) and CHF (HR 1.66, 95% CI 1.21 -2.28 , $p=0.0002$) long term. Gal-3 level from Visit 1 was associated with increased risk for all-cause mortality (HR4.32, 95% CI 1.55 -12.05 , $p=0.005$) and cardiovascular mortality (HR 6.00, 95% CI 1.01 -35.81 , $p=0.05$) but not CHF long term. Aldosterone level from Visit 1 was not associated with increased risk for all-cause mortality, cardiovascular mortality, or CHF long term. A higher aldosterone level at Visit 1 (overall in healthy, Isolated MS and MS groups) was associated with development of HTN (5.1 ng/dL vs 4.3 ng/dL, $p=.003$) and T2DM (6.3 vs 4.9, $p=.02$). Similarly, a higher Gal-3 level was associated with development of obesity (13.0 ng/dL vs 12.1 ng/dL, $p=0.009$).

Discussion

The current study is the first to define the natural history of patients with Isolated Metabolic Syndrome who are a subset of MS patients. There were three major findings in our study. First, Isolated MS is associated with a higher risk for developing HTN, DM and obesity vs. healthy controls.. Second, the progression of diastolic dysfunction was higher in women with Isolated MS compared with men with Isolated MS after ~4 years. Third, although patients with MS with HTN and/or DM had higher risk for cardiovascular mortality and CHF development compared with healthy controls over the eight year period after Visit 2, patients with Isolated MS did not have this higher risk compared with healthy controls.

An important finding in our study was that Isolated MS increases risk for development of HTN,DM and obesity vs. healthy controls. Majority of patients with Isolated MS had prehypertension (systolic BP 120-139 and diastolic BP 80-89 mm Hg) or prediabetes

(fasting glucose between 100 to 125 mg/dL) in our study. Patients with prehypertension have increased risk for developing HTN, CAD, CHF and stroke ⁷⁻⁹. Interventions such as weight loss, reduced sodium intake and angiotensin receptor blocker therapy have been shown to prevent progression to hypertension ^{7,10}. However, it is not clear if antihypertensive therapy is required for longer sustained time periods to reduce the incidence of other cardiovascular outcomes. Similar to prehypertension, patients with prediabetes are at increased risk for developing diabetes and cardiovascular disease ¹¹. Weight loss and Metformin have been shown to prevent progression of prediabetes to diabetes although weight loss is more effective than Metformin. ^{12,13}. Pharmacologic therapy like Acarbose has been shown to prevent progression to diabetes, hypertension and myocardial infarction ^{14,15}. Rosiglitazone has been shown to prevent progression to diabetes but at increased risk for heart failure ¹⁶. Aggressively treating Isolated MS patients (a substantial proportion of which have prehypertension and prediabetes) may prevent progression to HTN and DM, both of which are associated with substantial cardiovascular morbidity and mortality. However, this remains to be studied.

Previously, in the same patient cohort, Aijaz et al described the baseline patient characteristics and echo parameters³. They demonstrated that the prevalence of LV diastolic dysfunction was higher in women with Isolated MS than men with Isolated MS (28.2% vs. 14.9%; $p < 0.001$)³. We expanded upon this work and defined the natural history of Isolated MS with a repeat visit at approximately 4 years and follow up over eight years after Visit 2. Our study demonstrated that over ~4 years, women with Isolated MS had worsening of diastolic dysfunction compared with men with Isolated MS. This is consistent with previous studies which have shown that women without coronary artery disease may have higher prevalence of diastolic dysfunction than men ¹⁸. Furthermore, women with diabetes ¹⁹ and metabolic syndrome may have higher risk of developing cardiovascular disease including CAD, stroke and heart failure with preserved ejection fraction (HFpEF) compared with men²⁰⁻²². Indeed, the difference in progression of diastolic dysfunction between men and women may suggest that underlying pathophysiology of diastolic dysfunction between the genders is different. This may explain the challenges of identifying specific patients in HFpEF trials who likely benefit from trial drugs. Therefore, a treatment strategy to address risk factors in Isolated MS may need to account for the disproportionate cardiovascular risk in women compared to men.

The current study established that the long term outcomes of patients with Isolated MS were similar to the healthy controls. However, metabolic syndrome is associated with significant cardiovascular morbidity and mortality¹. Consistent with previous findings, our study showed that patients with MS with HTN and/or DM had higher risk of cardiovascular mortality and CHF development compared with healthy controls over an eight year period after Visit 2. However, patients with Isolated MS did not have a higher risk of cardiovascular mortality or CHF development compared with healthy controls. Per AHA/ACC classification for heart failure, stage A is asymptomatic at risk patients without structural heart disease while stage B is asymptomatic at risk patients with structural heart disease ²³. Our findings suggest that Isolated MS may be a very early stage of heart failure like AHA/ACC stage A or B heart failure since majority of Isolated MS patients had normal to asymptomatic structural heart disease. Furthermore, Isolated MS may represent an early

stage in the continuum of MS before developing into full blown MS with HTN and/or DM. Indeed, the ten year ASCVD risk calculator which estimates the ten year risk of hard cardiovascular events has some variables such as HDL, systolic BP and diastolic BP that are part of Isolated MS²⁴. Studies have shown that components of Isolated MS like systolic BP and diastolic BP predict development of hard cardiovascular events²⁵. Aggressively treating Isolated MS early on through lifestyle changes and pharmacologic therapy may prevent progression to MS and CHF development. Studies have shown that lifestyle changes such as weight loss, Mediterranean diet and physical activity prevent development of metabolic syndrome.^{26,27,28,29,30,31} The HOPE study was a prospective randomized trial which showed that angiotensin converting enzyme (ACE) inhibitor therapy reduced rates of cardiovascular mortality, myocardial infarction and stroke in high risk patients with cardiovascular disease or diabetes plus one other cardiovascular risk factor³². The STOP-HF study was a prospective randomized trial in an at risk population which showed that aggressive treatment of cardiac risk factors in the intervention group (those with BNP >50 pg/mL) compared with control group led to reduction in hospitalization for major cardiac events and asymptomatic left ventricular dysfunction³³. The PONTIAC study was a prospective randomized trial which showed that optimizing the dosage of renin-angiotensin-system antagonists and beta blockers in asymptomatic diabetic patients without cardiac disease led to a reduction in mortality and hospitalization due to cardiac disease³⁴. These studies showed that intervening early in asymptomatic high risk patients led to better cardiovascular outcomes. Similarly, aggressively treating Isolated MS early on may prevent progression to full blown metabolic syndrome and cardiovascular disease, including heart failure, and possibly improve survival, although this remains to be studied.

There was a difference in some variables like LDL, BMI, Diastolic BP, Calculated GFR MDRD, Renal Insufficiency, CAD, CHF, stroke, ACE Inhibitor use, ARB use, Nitrate use, Antiarrhythmic use, EF, Aldosterone level, Galectin-3 level, and NT-proBNP level between men and women at baseline is certainly interesting. These findings are certainly interesting and further studies are needed to elucidate the underlying mechanisms for these differences. It is known that women have higher neurohormonal activation than men which may explain their higher BNP level at baseline compared with men³⁵. For variables like LDL and BMI, the metabolic syndrome may manifest differently in each gender. Variables such as CKD, CAD, CHF, and stroke are known to have higher prevalence in one gender over the other due to biological or other unclear reasons.

Limitations

Since our patient population was predominantly Caucasian, these findings need to be confirmed in other ethnic groups. Other limitations include a relatively small power, some patients lost to follow up and a follow up of only eight years. A longer follow up may have shown different outcomes in Isolated MS group. There may have been some participation bias at Visit 2. As mentioned in the methods section, 1402 patients of 2042 patients from Visit 1 returned for Visit 2. At Visit 1, those who did not return for Visit 2 were older and had higher co-morbidities like HTN, DM, MI, CHF and diastolic dysfunction compared with participating patients. Mortality was also higher in these nonreturning participants over 5 years⁴.

Conclusions

Isolated MS is associated with a higher risk for developing HTN, DM and obesity vs. healthy controls. Patients with Isolated MS don't have a higher risk of cardiovascular mortality or CHF development compared with healthy controls over an eight year period. These findings suggest that aggressively treating Isolated MS early may prevent progression to cardiovascular disease and perhaps mortality. Furthermore, clinical management of Isolated MS may need to account for the disproportionate cardiovascular risk in women compared to men.

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Dr. Pratik Patel (Department of Internal Medicine, Mayo Clinic), Dr. Horng Chen (Division of Cardiovascular Diseases, Mayo Clinic) and Dr. Richard Rodeheffer (Division of Cardiovascular Diseases, Mayo Clinic) are responsible for conception and design of the study, data analysis and interpretation, and drafting of manuscript. Mr. Christopher Scott (Division of Biomedical Statistics and Informatics, Mayo Clinic) also contributed to data analysis and drafting of the manuscript.

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Abbreviations List

CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
DM	Diabetes Mellitus
Dx	Diagnosis
HTN	Hypertension
MS	Metabolic Syndrome
MI	Myocardial Infarction

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No MS	100.0(650)	99.7 (616)	98.9 (598)	96.7 (557)	95.0 (383)	92.7 (50)
Isol MS	100.0(202)	99.5 (185)	98.9 (179)	97.2 (170)	96.0 (120)	96.0 (23)
MS	100.0(190)	96.7 (176)	95.6 (171)	92.2 (158)	84.8 (100)	79.5 (23)

No MS	100.0(648)	99.7 (614)	99.5 (597)	99.0 (556)	98.8 (383)	98.0 (50)
Isol MS	100.0(202)	100.0(185)	100.0(179)	99.4 (170)	98.2 (120)	98.2 (23)
MS	100.0(189)	97.8 (175)	97.8 (170)	96.6 (157)	93.2 (99)	91.6 (22)

Figure 1.

Survival to death after Visit 2 (time 0) due to all-cause mortality, cardiac mortality and CHF in healthy controls (No MS), Isolated MS and MS groups. Numbers given below the curves are Kaplan-Meier estimate (number at risk).

CHF: Congestive Heart Failure, Isolated MS : Isolated Metabolic Syndrome, MS: Metabolic Syndrome

Table 1

Baseline Characteristics for Overall cohort

Variable	Healthy controls (N=576)	Isolated MS (N=225)	MS with HTN and/or DM (N=241)	p-value ^a	p-value ^b
Age at Exam (years)	58± 9	60± 9	64± 9	0.003	<0.001
Women, n (%)	327 (57%)	94 (42%)	118 (49%)	<0.001	0.12
Current Smoker, n (%)	43 (7%)	18 (8%)	19 (8%)	0.79	0.97
HDL<=50M, <=40F, n (%)	198 (34%)	202 (90%)	204 (85%)	0.004 ^c	0.10
Trig>200, n (%)	42 (7%)	84 (37%)	87 (36%)	<0.001 ^c	0.78
LDL>160 ^d , n (%)	83 (14%)	46 (21%)	30 (12%)	0.04 ^c	0.02
LDL>190, n (%)	16 (3%)	12 (5%)	6 (2%)	0.04 ^c	0.11
Serum Glucose (mg/dL)	91± 7	100± 15	112± 33	<0.001	<0.001
Waist Circumference(cm)	84± 12	101± 12	100± 13	<0.001	0.86
BMI (kg/m ²)	26± 4	31± 5	32± 5	<0.001	0.16
Systolic BP (mm Hg)	122± 17	140± 16	139± 19	<0.001	0.46
Diastolic BP (mm Hg)	71± 9	78± 9	75± 11	<0.001	0.02
Hypertension	0 (0%)	0 (0%)	212 (88%)	N/A	N/A
Diabetes	0 (0%)	0 (0%)	70 (29%)	N/A	N/A
Calculated GFR (MDRD)mL/min/1.73m ²	85± 15	82± 16	77± 20	0.05	<0.001
Renal Insufficiency (eGFR<60)	35 (6%)	26 (12%)	49 (20%)	0.009	0.01
CAD (%)	0 (0%)	8 (4%)	46 (19%)	N/A	<0.001
CHF (n%)	0 (0%)	0 (0%)	8 (3%)	N/A	0.006
MI n _i (%)	0 (0%)	2 (1%)	12 (5%)	N/A	0.01
Atrial Fib/Flutter n _i (%)	0 (0%)	7 (3%)	13 (5%)	N/A	0.22
Stroke n _i (%)	0 (0%)	0 (0%)	5 (2%)	N/A	0.03
Aspirin n _i (%)	134 (27%)	62 (31%)	100 (42%)	0.31	0.01
Antilipemic n _i (%)	0 (0%)	25 (12%)	80 (34%)	N/A	<0.001
Beta Blocker n _i (%)	0 (0%)	0 (0%)	79 (33%)	N/A	N/A
Calcium Channel Blocker n _i (%)	0 (0%)	0 (0%)	39 (16%)	N/A	N/A
ACE Inhibitor n _i (%)	0 (0%)	0 (0%)	57 (24%)	N/A	N/A
ARB n _i (%)	0 (0%)	0 (0%)	18 (8%)	N/A	N/A

Variable	Healthy controls (N=576)	Isolated MS (N=225)	MS with HTN and/or DM (N=241)	^a p-value	^b p-value
Diuretic n,(%)	0 (0%)	0 (0%)	111 (47%)	N/A	N/A
Anticoagulant n,(%)	0 (0%)	0 (0%)	5 (2%)	N/A	0.04
Nitrate n,(%)	0 (0%)	1 (0%)	11 (5%)	N/A	0.008
Antiarrhythmic n,(%)	0 (0%)	3 (1%)	4 (2%)	N/A	0.87
Ejection Fraction (%)	64± 5	64± 6	64± 7	0.91	0.99
Average LV Mass Index (g/m ²)	90.7± 15.8	94.4± 19.0	102.8± 24.5	0.02	<0.001
Diastolic Dysfunction, n (%)				0.004	<0.001
Normal	480 (87%)	162 (77%)	130 (59%)		
Mild	52 (9%)	36 (17%)	62 (29%)		
Moderate/Severe	21 (4%)	12 (6%)	27 (12%)		
Aldosterone, median (Q1, Q3) ng/dL	3.8 (2.5, 6.1)	5.1 (3.0, 8.0)	6.4 (3.6, 12.2)	<0.001	<0.001
Galectin-3, median (Q1, Q3) ng/dL	12.1 (10.6, 13.7)	12.8 (11.2, 14.8)	13.7 (11.6, 16.2)	<0.001	0.001
NT-proBNP, median (Q1, Q3) pg/mL	52.2 (23.8, 97.2)	34.1 (17.4, 78.9)	62.0 (27.7, 154.7)	0.30 ^c	<0.001

ARB: Angiotensin Receptor Blocker; CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, MI: Myocardial Infarction N/A: No comparison made based on criteria used to define groups.

^a p-value for Healthy Controls vs Isolated MS

^b p-value for Isolated MS vs MS with HTN and/or DM

^c gender adjusted p-value

^d patients with LDL>160 included LDL>190 as well as those with LDL between 160-190

Table 2

Baseline characteristics of Women and Men

Variable	Women				Men					
	Healthy Women (N=327)	Isolated MS (N=94)	MS with HTN and/or DM (N=118)	p-value ^a	p-value ^b	Healthy Men (N=249)	Isolated MS (N=131)	MS with HTN and/or DM (N=123)	p-value ^a	p-value ^b
Age at Exam (years)	58± 9	63± 9	64± 10	<0.001	0.52	58± 9	58± 9	64± 9	0.60	<0.001
Current Smoker, n (%)	17 (5%)	5 (5%)	9 (8%)	0.95	0.50	26 (10%)	13 (10%)	10 (8%)	0.86	0.63
HDL<=50M,<=40F, n (%) mg/dL	97 (30%)	82 (87%)	94 (80%)	<0.001	0.14	101 (41%)	120 (92%)	110 (89%)	<0.001	0.55
Trig>200 mg/dL n (%)	24 (7%)	32 (34%)	43 (36%)	<0.001	0.72	18 (7%)	52 (40%)	44 (36%)	<0.001	0.52
LDL>160 mg/dL n (%)	45 (14%)	21 (22%)	17 (14%)	0.05	0.13	38 (15%)	25 (19%)	13 (11%)	0.32	0.05
LDL>190 mg/dL n (%)	10 (3%)	9 (10%)	5 (4%)	0.007	0.12	6 (2%)	3 (2%)	1 (1%)	0.95	0.34
Serum Glucose (mg/dL)	90± 7	97± 11	108± 29	<0.001	<0.001	92± 7	101± 17	116± 36	<0.001	<0.001
Waist Circumference(cm)	77.1± 8.8	94.5± 11.5	95.6± 11.0	<0.001	0.47	94.0± 8.4	105.0± 10.6	105.0± 12.4	<0.001	0.99
BMI (kg/m ²)	25± 4	31± 5	32± 5	<0.001	0.15	27± 3	31± 4	32± 5	<0.001	0.66
Systolic BP (mm Hg)	120± 18	141± 16	139± 21	<0.001	0.42	124± 16	139± 17	138± 18	<0.001	0.74
Diastolic BP (mm Hg)	68± 9	75± 9	71± 10	<0.001	0.02	74± 8	80± 8	79± 9	<0.001	0.65
Calculated GFR MDRD (mL/min/1.73m ²)	85± 15	82± 16	77± 19	0.18	0.02	85± 14	83± 16	76± 22	0.14	0.01
Renal Insufficiency (eGFR<60)	17 (5%)	5 (5%)	21 (18%)	0.96	0.006	18 (7%)	21 (16%)	28 (23%)	0.007	0.17
CAD n,(%)	0 (0%)	2 (2%)	10 (8%)	N/A	0.05	0 (0%)	6 (5%)	36 (29%)	N/A	0.001
CHF n,(%)	0 (0%)	0 (0%)	2 (2%)	N/A	0.20	0 (0%)	0 (0%)	6 (5%)	N/A	0.01
MI n,(%)	0 (0%)	0 (0%)	3 (3%)	N/A	0.12	0 (0%)	2 (2%)	9 (7%)	N/A	0.02
Atrial Fib/Flutter n,(%)	0 (0%)	2 (2%)	3 (3%)	N/A	0.84	0 (0%)	5 (4%)	10 (8%)	N/A	0.15
Stroke n,(%)	0 (0%)	0 (0%)	2 (2%)	N/A	0.20	0 (0%)	0 (0%)	3 (2%)	N/A	0.07
Aspirin n,(%)	65 (22%)	20 (22%)	39 (33%)	0.96	0.07	69 (35%)	42 (38%)	61 (51%)	0.60	0.05
Antilipemic n,(%)	0 (0%)	9 (10%)	33 (28%)	N/A	0.001	0 (0%)	16 (15%)	47 (39%)	N/A	<0.001
Beta Blocker n,(%)	0 (0%)	0 (0%)	39 (33%)	N/A	N/A	0 (0%)	0 (0%)	40 (33%)	N/A	N/A
Calcium Channel Blocker n,(%)	0 (0%)	0 (0%)	18 (15%)	N/A	N/A	0 (0%)	0 (0%)	21 (18%)	N/A	N/A
ACE Inhibitor n,(%)	0 (0%)	0 (0%)	19 (16%)	N/A	N/A	0 (0%)	0 (0%)	38 (32%)	N/A	N/A
ARB n,(%)	0 (0%)	0 (0%)	13 (11%)	N/A	N/A	0 (0%)	0 (0%)	5 (4%)	N/A	N/A
Diuretic n,(%)	0 (0%)	0 (0%)	68 (58%)	N/A	N/A	0 (0%)	0 (0%)	43 (36%)	N/A	N/A

Variable	Women					Men				
	Healthy Women (N=327)	Isolated MS (N=94)	MS with HTN and/or DM (N=118)	p-value ^a	p-value ^b	Healthy Men (N=249)	Isolated MS (N=131)	MS with HTN and/or DM (N=123)	p-value ^a	p-value ^b
Anticoagulant n,(%)	0 (0%)	0 (0%)	2 (2%)	N/A	0.21	0 (0%)	0 (0%)	3 (3%)	N/A	0.10
Nitrate n,(%)	0 (0%)	0 (0%)	3 (3%)	N/A	0.12	0 (0%)	1 (1%)	8 (7%)	N/A	0.02
Antiarrhythmic n,(%)	0 (0%)	2 (2%)	3 (3%)	N/A	0.86	0 (0%)	1 (1%)	1 (1%)	N/A	0.95
Ejection Fraction (%)	65± 4	66± 5	65± 6	0.02	0.55	62± 5	62± 5	62± 7	0.73	0.91
LV Mass Index (g/m ²)	86.4± 14.6	89.8± 17.5	98.5± 21.5	0.08	0.004	96.9± 15.5	98.6± 19.6	107.5± 26.7	0.44	0.01
Diastolic Dysfunction, n (%)				<0.001	0.28				0.47	<0.001
Normal	279 (88%)	62 (71%)	67 (60%)			201 (86%)	100 (81%)	63 (58%)		
Mild	28 (9%)	18 (21%)	31 (28%)			24 (10%)	18 (15%)	31 (29%)		
Moderate/Severe	11 (3%)	7 (8%)	13 (12%)			10 (4%)	5 (4%)	14 (13%)		
Aldosterone, median (Q1, Q3) ng/dL	3.4 (2.5, 5.8)	4.2 (2.5, 6.9)	6.9 (3.1, 12.9)	0.06	0.001	4.5 (2.5, 6.5)	5.6 (3.7, 8.4)	6.2 (4.0, 11.7)	0.001	0.13
Galectin-3, median (Q1, Q3) ng/dL	12.5 (10.7, 13.9)	13.8 (12.1, 15.8)	15.1 (12.3, 17.5)	<0.001	0.02	12.0 (10.6, 13.2)	12.2 (10.6, 13.6)	12.7 (11.2, 15.2)	0.16	0.05
NT-proBNP, median (Q1, Q3) pg/mL	75.4 (42.3, 115.7)	68.1 (34.1, 118.0)	88.5 (39.5, 197.0)	0.47	0.04	26.1 (11.8, 52.4)	23.1 (11.2, 45.7)	47.2 (13.5, 113.4)	0.42	<0.001

ARB: Angiotensin Receptor Blocker, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, MI: Myocardial Infarction, N/A: No comparison made based on criteria used to define groups.

^a p-value for Healthy Controls vs Isolated MS

^b p-value for Isolated MS vs MS with HTN and/or DM

Table 3

Incidence of co-morbidities and progression of diastolic dysfunction at Visit 2

Variable	Overall					Women					Men				
	Healthy controls (N=576)	Isolated MS (N=225)	MS with HTN and/or DM (N=241)	p-value ^a	p-value ^b	Healthy controls (N=353)	Isolated MS (N=99)	MS with HTN and/or DM (N=94)	p-value ^a	p-value ^b	Healthy controls (N=249)	Isolated MS (N=131)	MS with HTN and/or DM (N=123)	p-value ^a	p-value ^b
New HTN	14%	34%	45%	<0.001	0.24	13%	38%	60%	<0.001	0.38	14%	31%	42%	<0.001	0.28
New DM DX	1%	12%	11%	<0.001	0.75	0%	7%	9%	<0.001	0.79	1%	15%	13%	<0.001	0.68
New CAD DX	3%	5%	10%	0.15	0.03	0%	1%	6%	0.39	0.07	6%	7%	15%	0.55	0.07
New CHF DX	0%	0%	3%	0.28	0.07	0%	1%	3%	0.22	0.63	0%	0%	3%	-	0.05
New MI DX	1%	0%	4%	0.99	0.02	0%	0%	2%	0.99	0.50	1%	1%	6%	0.98	0.03
New Obesity DX	8%	21%	26%	<0.001	0.49	8%	23%	30%	0.03	0.75	9%	21%	25%	0.02	0.66
New Stroke DX	1%	1%	3%	0.69	0.22	1%	0%	4%	0.58	0.07	0%	2%	3%	0.12	0.99
New AF/Aflutter DX	1%	3%	4%	0.14	0.68	1%	4%	3%	0.07	0.70	3%	6%	14%	0.69	0.31
New Renal Insufficiency (eGFR<60) DX	5%	9%	16%	0.07	0.05	7%	12%	18%	0.11	0.32	3%	6%	14%	0.15	0.08
Worsening of Diastolic Dysfunction	30%	30%	35%	0.85	0.23	30%	40%	36%	0.06	0.57	31%	22%	34%	0.08	0.05

ARB: Angiotensin Receptor Blocker, CAD: Coronary Artery Disease, CHF: Congestive Heart Failure, DM: Diabetes Mellitus, DX: Diagnosis, HTN: Hypertension, MI: Myocardial Infarction

-: Unable to calculate p-value due to no subjects in either group with new DX.

^a p-value for Healthy Controls vs Isolated MS

^b p-value for Isolated MS vs MS with HTN and/or DM

^c p-value for Women with Isolated MS vs Men with Isolated MS