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Full Length Research Paper

Sex based pharmacological treatment in patients with metabolic syndrome: Findings from the Isfahan healthy heart program

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Pharmacological therapy is a critical step in the management of individuals with the metabolic syndrome (MetS) when lifestyle modifications cannot achieve the therapeutic goals. However, it has been well-documented that there is no single best therapy other than weight loss, and that treatment should be targeted at individual components of the MetS. The objective of this study was to investigate the treatment of individual components of the MetS in a population-based sample of individuals with clustering MetS components. In a cross-sectional population-based survey, we studied a randomly collected sample of men and women who had participated in the baseline survey of a community-based program in three Central Iranian counties in 2000 to 2001. Demographic data, medical status, and drug history were obtained by questionnaire. We evaluated the association between clustering of the MetS components and pharmacological treatment of cardiovascular risk factors. The most common pharmacologic agents prescribed for individuals with the MetS were beta-blockers (72.8%), followed by lipid-lowering agents (36%) with no significant gender difference. A high level of compliance with drug treatment was noted. Further research is warranted to understand the compliance behavior of patients with the MetS.

Key words: Iran, metabolic syndrome, pharmacological treatment, compliance.

INTRODUCTION

Despite the international campaign against non-communicable diseases (NCD) over the past 20 years, cardiovascular diseases (CVD) remain the leading cause of death in most of the Western world, with a rapidly increasing trend in developing countries (Alsaraj et al., 2009). The metabolic syndrome (MetS) is associated with increased risk of developing NCD, notably diabetes and CVD (Grundy et al., 2005). It has been demonstrated that many middle-aged individuals with the MetS are at increased 10-year absolute risk of CVD (Grundy et al., 2005). Individuals with coronary heart disease, stroke or diabetes are in the high-risk category and should be treated (Deedwania and Gupta, 2006). Delavari and colleagues have reported alarming prevalence rates of the MetS and its components, as defined by different sets of criteria. The age-standardized prevalence of the MetS was about 34.7% based on the ATP III criteria, and was higher in women, in urban areas, and in the 55 to 64 year

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Abbreviation: NCD, Non-communicable disease; **CVD,** cardiovascular disease; **MetS,** metabolic syndrome; **LDL,** low density lipoprotein cholesterol; **IHHP,** Isfahan healthy heart program; **BMI,** body mass index; **WC,** Waist circumference.

age-group compared with the prevalence in men, in rural areas, and in other age groups, respectively (Delavari et al., 2009). Components of the MetS that need controlling are atherogenic dyslipidemia, hypertension, elevated fasting glucose, prothrombotic factors and proinflammatory states (5). The therapeutic approach involves intervention at a macro level, and control of multiple risk factors using lifestyle modifications (diet control and increased physical activity, pharmacotherapy (obesity control drugs) and targeted approach to individual risk factors (Delavari et al., 2009; Deedwania and Volkova, 2005; Esteghamati et al., 2006; Sarrafzadegan et al., 2009; Misra et al., 2002). Pharmacological therapy is a critical step in the management of individuals with the MetS when lifestyle modifications fail to achieve desirable therapeutic goals (Grundy, 2005).

A recent American Heart Association and National Heart Lung Blood Institute scientific statement highlights the importance of controlling individual risk factors in the MetS. However, it has been demonstrated that other than weight loss, there is no “single best” therapy, and that treatment should target individual components of the MetS (Grundy et al., 2005). The objective of this study was to investigate the prevalence of pharmacological treatment of individual components of the MetS in a population-based sample of individuals with clustering of the Mets components.

MATERIALS AND METHODS

The Isfahan healthy heart program (IHHP) was conducted in three Central Iranian counties; Isfahan and Najaf-Abad were intervention areas and Arak served as a reference area. Located at 375 km north-west of Isfahan, Arak was selected as the reference area owing to similarity of its socioeconomic, demographic and health profile to that of intervention areas, as well as good cooperation (Sarraf-Zadegan et al., 2003). Started in 2000, IHHP consisted of three phases; baseline survey and situational analysis were conducted in phase I, interventions in phase II (late 2001 to 2005), and post-intervention survey for outcome evaluation in phase III (2007) (Sarrafzadegan et al., 2006, 2009).

IHHP aimed to reduce modifiable CVD risk factors in the general population through 10 distinct interventional projects, targeting diet, physical activity and smoking. Details and methods of the study have been described elsewhere (Sarrafzadegan et al., 2006, 2009). Briefly, IHHP featured a multistage sampling design. The clusters were selected from the community based on demographic and socioeconomic characteristics. Sample units aged ≥19 years were selected randomly and stratified according to age and sex. Socio-demographic data and information on health behaviors, including nutritional habits, physical activity and smoking, as well as medical status, drug history, and laboratory data were collected. Written informed consent was obtained from all participants before they entered the study. The Research and Ethical Committee of Cardiovascular Research Center approved IHHP. This sub-study reports the findings of the baseline survey of IHHP in 2000 in Isfahan.

Exclusion criteria

Pregnant women and those with known thyroid abnormality and/or mental disease were excluded.

Physical examination

Anthropometric measurements

Weight and height were measured with calibrated instruments using standard protocols. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Waist circumference (WC) and hip circumference were measured and recorded in centimetres using standard WHO methods (Tavassoli et al., 2010).

Laboratory measurements

Fasting (>12 h) venous blood samples were collected from all participants. Standard laboratory kits (Pars Azmoun Co., Tehran, Iran) and methods were used to measure serum lipid profiles and fasting blood glucose (FBG). All blood samples were frozen at -20°C to be assayed within 72 h at the central laboratory of Isfahan Cardiovascular Research Center (ICRC) which is subject to external national, and international quality control. An Elan auto-analyzer (made in Germany) was used in the baseline survey and was validated against the Department of Epidemiology, K.U. Leuven, Belgium. A Hitachi auto-analyzer (made in Japan) was used in the 2007 survey and was validated against lab quality external assessment services, Helsinki, Finland. Both quality controls showed good correlations.

Participants

In the first phase of IHHP some parameters, such as insulin resistance were not collected so we used the updated ATP-III definition for the MetS. Participants were considered as having the MetS when they met three or more of the following criteria: WC ≥102 cm (40 in) in men and ≥88 cm (35 in) in women; HDL <1.03 mmol/L (40 mg/dl) in men and <1.30 mol/L (50 mg/dl) in women or receiving specific treatment for this lipid abnormality; triglycerides ≥1.7 mmol/L (150 mg/dl) or specific treatment for this lipid abnormality; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension; and fasting glucose ≥5.6 mmol/L (100 mg/dl) (15).

Pharmacological treatment

The pattern of medication use was defined according to the type of drugs used to control and/or treat the MetS components. Medications used for hypertension, dyslipidemia and insulin resistance were recorded in detail. Medications were later classified according to pharmacological category. Anti-hypertensive drugs were calcium channel blockers, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and thiazides. Drugs used for diabetes were thiazolidinediones, biguanides and insulin. Dyslipidemic drugs were statins, fibrates, nicotinic acid, and statin plus fibrate. Aspirin use was also recorded.

Statistical analyses

Results are reported as the mean ± standard deviation (SD). The difference between quantitative variables was assessed using the independent t-test. Chi-square test was used to evaluate the difference between qualitative variables in individuals with the MetS and those without according to sex. P values of 0.05 or less were

Table 1. Baseline characteristics of population studied by sex.

	Sex	Without metabolic syndrome Mean ±SD	With metabolic syndrome Mean ±SD	
Age(years)	Female	34.68±12.85	46.93±14.35	0.001
	Male	37.53±14.799	50.12±14.39	<0.001
	Total	36.27±14.05*	47.73±14.42*	<0.001
Waist circumference (cm)	Female	87.98±13.30	101.85±10.997	<0.001
	Male	86.59±11.01	102.53±10.71	<0.001
	Total	87.20±12.09*	102.01±10.93	<0.001
Systolic blood pressure (mmHg)	Female	108.40±15.16	128.04±22.75	<0.001
	Male	113.97±15.87	134.76±21.15	<0.001
	Total	111.51±15.81*	129.72±22.55*	<0.001
Diastolic blood pressure (mmHg)	Female	71.92±9.74	81.67±12.55	<0.001
	Male	74.54±9.59	85.35±11.71	<0.001
	Total	73.39±9.75*	82.59±12.45*	<0.001
Triglyceride (mg/dl)	Female	124.75±68.64	235.17±109.94	<0.001
	Male	167.06±112.53	265.09±137.91	<0.001
	Total	148.399±97.96*	242.66±118.26*	<0.001
Fasting blood sugar (mg/dl)	Female	78.00±12.97	94.19±38.31	<0.001
	Male	80.47±20.47	103.87±48.58	<0.001
	Total	79.38±17.60*	96.61±41.33*	<0.001
High density lipoprotein-cholesterol (mg/dl)	Female	50.00±10.43	44.71±9.31	<0.001
	Male	45.91±9.79	39.89±9.11	<0.001
	Total	47.71±10.28*	43.51±9.49*	<0.001

SD: Standard deviation.

considered as statistically significant. All statistical analyses were performed using SPSS (SPSS Inc. Chicago, IL) version 15.

RESULTS

We studied 12514 individuals, of whom 6391 (51.1%) were women (mean age: 38.79±14.57 years) and 6123 (48.9%) were men (mean age: 38.99±15.29 years). Demographic data of participants are shown in Table 1. The MetS was documented in 2832 participants (22.8%), including 2124 women (33.4%) and 780 men (11.7%). Abdominal obesity, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels were found in 86.4, 89.8 and 75.8% of the participants, respectively. Table 2 demonstrates the percentage of CVD risk factors in individuals with and without the MetS. Hypertriglyceridemia was the most prevalent risk factor among individuals with the MetS (89.8%). Systolic blood pressure was elevated in 65.2% of men and 48.4% of women with the MetS, compared to 13.9% of women and 6.7% of men without MetS. The prevalence of abdominal obesity and low HDL-C was 86.4 and 75.8%, respectively.

Table 3 shows the number of patients receiving different categories of drugs for control of various MetS components, according to sex. Beta-blockers accounted for the most commonly used single medications (54%), with no significant difference between men (58.1%) and women (52.8%).

The least frequently used drugs were thiazides. Glucose-lowering agents were the most commonly prescribed drugs for individuals with the Mets (men: 90.5%, women: 90.7%, total: 90.7%). Statins were the least frequently used medications in both men (3.4%) and women (1.7%). Aspirin was used by 7%, and the use of herbal medicine was uncommon.

Hypertension and diabetes were more frequently managed with beta-blockers (54%) and glibenclamide (90.6%), respectively. No significant difference was observed between men and women regarding the types of medications used.

Table 2. Prevalence of cardiovascular risk factors (15) in individuals with or without metabolic syndrome (IHHP).

Risk factors	Sex	With Metabolic syndrome mean ±(SD)	Without metabolic syndrome mean ±(SD)	P value
Abdominal obesity	Female	2008(94.6)	1912(45.3)	<0.001
	Male	434(61.6)	299(5.6)	<0.001
	Total	2442(86.4)*	2211(23.1)*	<0.001
Systolic hypertension	Female	1028(48.4)	284(6.7)	<0.001
	Male	461(65.2)	743(13.9)	<0.001
	Total	1489(52.6)*	1027(10.7)*	<0.001
Diastolic hypertension	Female	758(35.7)	227(5.4)	<0.001
	Male	361(51.2)	516(9.6)	<0.001
	Total	1119(39.6)*	743(7.8)*	<0.001
Hyper triglyceridemia	Female	1868(88.4)	904(21.6)	<0.001
	Male	663(93.9)	2323(43.8)	<0.001
	Total	2531(89.8) *	3227(34)*	<0.001
Fasting glucose≥110 mg/dL	Female	346(16.4)	51(1.2)	<0.001
	Male	189(26.8)	119(2.2)	<0.001
	Total	535(19)*	170(1.8)*	<0.001
Low HDL Cholestrol	Female	1671(79.5)	1993(48.4)	<0.001
	Male	454(64.9)	1397(26.6)	<0.001
	Total	2125(75.8)*	3390(36.2)*	<0.001

*indicates: p-value<0.001 from comparison between sex and risk factors.

DISCUSSION

We found a high rate of pharmacological treatment in Iranian subjects with the MetS. The prevalence of the MetS in Iranian populations has already been reported (Grundy et al., 2005). While the MetS has been more commonly reported in the elderly (Sarrafzadegan, 2008), we documented the MetS in men and women of relatively lower mean age (men: 38.796±14.57 years, women: 38.99±15.29 years). Of the participants, 86.4, 89.8 and 75.8% had abdominal obesity, hypertriglyceridemia and low HDL-C levels, respectively. Except for WC, we found significant differences in the prevalence of MetS components in men and women. In this study, increased WC in women with the MetS was more prevalent than in men. Some earlier studies have reported similar findings (Pacholczyk et al., 2008; Bjornsson, 2008). Epidemiologic data suggest low HDL and high triglyceride (TG) levels as major CVD risk factors associated with the MetS (Grundy et al., 2004). Among the risk factors evaluated in this study, hypertriglyceridemia was the most prevalent in men with MetS, whereas low HDL was the most common risk factor in non-MetS subjects. However, the most frequent risk factor reported in other studies has been hyper-triglyceridemia, with systolic and/or diastolic hypertension being less common (Israili et al., 2007). Apparently, risk factors such as hypertension and diabetes, which produce more evident complications are more frequently monitored and managed. It may be assumed that the high prevalence of the MetS is due to the high prevalence of hypertriglyceridemia which is more silent in nature and is therefore less frequently monitored and managed.

Pharmacological management is suggested next to lifestyle change in management of the MetS. Medication must address the multipronged pathological processes of the MetS and each component should be identified and properly treated. Current therapies for the MetS consist of strategies for management of obesity, insulin resistance, dyslipidemia, and hypertension (Israili et al., 2007).

The pharmacological agents most often suggested are those which decrease insulin resistance (e.g. metformin and thiazolidinediones). Among the medications used in MetS therapy are also fibrates and statins for atherogenic dyslipidemia, and antihypertensives, such as beta-blockers, ACE inhibitors and angiotensin receptor

Table 3. Pharmacological management the components of the metabolic syndrome by sex (IHHP).

	Subjects with metabolic syndrome	Female N (%)	Male N (%)	Total N (%)	P-value
Anti hypertensive treatment	Calcium channel blockers	15(3.5)	5(3.9)	20(3.6)	0.79
	Beta blockers	229(52.8)	75(58.1)	304(54)	0.28
	ACE inhibitors	44(10.1)	16(12.4)	60(10.7)	0.46
	Thiazides	2(0.5)	2(1.6)	4(0.7)	0.23
	C- Chanel blockers	41(9.4)	17(13.2)	58(10.3)	0.22
Lipid lowering treatment	Fibrates	132(50)	28(48.3)	160(49.7)	0.81
	Nicotinic acid	29(11)	4(6.9)	33(10.2	0.35
	Statins	9(3.4)	1(1.7)	10(3.1)	0.69
	Statin , fibrate combination	139(52.7)	29(50)	168(52.2)	0.71
	Metformin, Phenformin	6(3.5)	4(4.8)	10(3.9)	0.73
Anti diabetic treatment	Glibenclamide	156(90.7)	76(90.5)	232(90.6)	0.95
	Insulin-crystal-NPH	23(13.4)	7(8.3)	30(11.7)	0.24
Aspirin		125(5.9)	72(10.2)	197(7)	>0.001

blockers (ARBs) (Bianchi et al., 2007). In this study, beta-blockers were the most frequently prescribed medications for individuals with the MetS, and lipid-lowering agents were prescribed less frequently than antihypertensives (72.8 vs. 36%, respectively). This is in line with another Iranian study demonstrating that beta-blockers were the most commonly prescribed antihypertensives (Khosravi et al., 2006).

Although data on the use of aspirin for primary CVD prevention are being reviewed, 7% of individuals with the MetS in Iran take aspirin on a regular basis. The low rate of aspirin use in our study population may be due to low mean age and low prevalence of CVD risk factors. Owing to its availability and low price, aspirin is the most frequently used antiplatelet drug in Iran. We studied mainly healthy subjects with the MetS, in whom antiplatelet use might not have been indicated, especially given their mean age (men: 38.796±14.57 years, women: 38.99 ± 15.29 years). On the other hand, most patients receiving long-term aspirin therapy remain at substantial risk of thrombotic events due to insufficient inhibition of platelets; estimates suggest that between 5.5 and 60% of patients using aspirin may exhibit “aspirin resistance (Gasparyan et al., 2008). Beta-blockers, the statin-fibrate combination and glibenclamide were prescribed more frequently for individuals with the MetS in our study population, reflecting the latest guidelines (Bianchi et al., 2007).

Conclusion

Complications of the MetS were not addressed effectively by management strategies in our study, possibly explaining the increased CVD risk in individuals with the MetS despite pharmacologic treatment. At the same time, our findings suggest that hypertension (systolic and/or diastolic) can be more readily managed in individuals with the MetS.

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