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Identification of Population Specific Risk Phenotypes Contributing Towards Development of Metabolic Syndrome

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Authors' Contribution

GKR and SMSN designed the study. MF and FR collected samples and data from the hospital and performed laboratory based analysis. GKR, MF and FR wrote the article. All others were involved in data analysis and statistical analysis.

Key words

Dysglycemia, T2D, abdominal obesity, BMI.

ABSTRACT

Common risk factors associated with metabolic syndrome (MetS) are well known world-wide, however, clustering of population specific disease markers have also been reported. Therefore we aimed to identify MetS risk markers in a local adult Pakistani population and, based on their clustering, its prevalence. Adult subjects visiting Out-Patient Departments of local hospitals were screened for MetS based on International Diabetes Federation (IDF) criteria. Anthropometric and biochemical assay results were recorded. Data was analyzed using SPSS software (16.0). Our results showed that total MetS prevalence was 46.0% with significantly higher disease rates in obesity (82%, $p<0.0001$), old age (57.6%, $p<0.0001$), and male gender (52.1%, $p=0.016$). The frequency of all disease risk factors were significantly raised in obesity with varying rates in age and gender specific population sub-groups. It is concluded evident that obesity along with hyperglycemia and dyslipidemia are common population specific MetS risk markers.

INTRODUCTION

Metabolic syndrome (MetS) is regarded as the 21st century's health epidemic, and is amongst the fastest growing global health problems (Wen-Harn *et al.*, 2008; Scott, 2008; Julie *et al.*, 2014). It is a cluster of various acquired and/or inherited risk factors, and a primer for serious life-threatening ailments, including type 2 diabetes, cardiovascular diseases and severe liver dysfunction (Alberti *et al*., 2006, Hassan *et al.*, 2010). The disease is developed due to the combined effect of risk factors which include visceral obesity, hypertension dyslipidemia, insulin resistance etc. (Scott, 2008). However, the main causes of MetS are considered to be insulin resistance and obesity (Jaspinder, 2014; Jafar *et al.*, 2004). International Diabetes Federation has defined cut-off values for MetS risk factors with special emphasis on abdominal obesity measured by waist circumference (WC) along with T2D/hyperglycemia, dyslipidemia and hypertension (Alberti *et al.*, 2006). When at least three of these risk factors; including abdominal obesity, cluster in a person chances of developing MetS increase many folds (Lorenzo *et al*., 2007). Overweight and obesity especially upper-body obesity (abdominal) is more strongly associated with several persistent diseases including hyperinsulinemia, hypertension and dysglycemia and diabetes mellitus in comparison with lower-body obesity (Misra and Khurana, 2008). Due to an alarming increase in sedentary life style, obesity has been declared as a chronic condition and global disease burden affecting all ethnic, gender (Anthonia, 2010) and age groups (Johan *et al*., 2010). With rise in obesity especially abdominal, there has been a large increase in the MetS populations around the globe (Beltrán-Sánchez *et al*., 2013; Marcin *et al*., 2014). It is estimated that 25–29% of World's adult population experiencing MetS complications are twice as likely to die at an early age as compared to those with no MetS (Peter *et al.*, 2005). In Pakistan weight gain, hyperglycemia, hypertension along with T2D and CVDs seem to prevail at an alarming rate (Hakeem and Fawwad, 2010; Jafar *et al.*, 2004; Sultan *et al.*, 2014; Mazhar *et al.*, 2010; Jafar *et al.*, 2003) especially due to the drastic changes in dietary life-style in the past decade or so. All these health complication clearly seem to either cluster into MetS or stem from it (Ahmed *et al.*, 2012; Tariq *et al.*, 2011; Shahid *et al.*, 2010; Firdous *et al.*, 2007). However, the severity of MetS based on its clustering metabolic risk phenotypes has yet to be realized fully in Pakistan. Therefore, present study was planned to explore prevalence of MetS in adult subjects visiting hospital with general metabolic disturbances and to identify risk phenotypes that increase susceptibility towards disease.

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MATERIALS AND METHODS

Data collection and sampling

In our hospital based population study, sampling was conducted in the out patient department (OPDs) of local hospitals located in Rawalpindi and Islamabad, Pakistan using designed questionnaire. Relevant information was obtained by personal interviews and through physician's diagnosis based medical records. The study was approved by the Ethics Committees of PIMS. All study subjects gave their written informed consent for participation in study.

The diagnosis of MetS was conducted based on IDF criterion (Alberti *et al.,* 2006) where abdominal obesity, accessed through increased waist circumference (WC), is a compulsory component (>94 cm in men and >80 cm in women) with two or more of the following risk phenotypes: raised fasting blood glucose (FBG≥100 mg/dL), raised triglycerides (TG ≥150 mg/dL), reduced HDL-cholesterol (<40 mg/dL in men and <50 mg/dL in women), or raised systolic and diastolic blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg).

For anthropometric data height, body weight, WC, SBP and DBP measurements were recorded. For body weight recording (using an electronic balance), subjects removed heavy clothes and shoes. For height measurements, a wall mounted measuring tape was used while subjects in standing position and feet together (Sawant *et al.*, 2011). A non-elastic measuring tape (placed at narrowest part of torso between lowest rib and level of the iliac crests at end expiration) was used to measure WC in standing position. A ratio of body weight in Kg to the height in meter^2 (kg/m^2) was computed to estimate BMI. Blood pressure readings were taken twice using a mercury sphygmomanometer with subject in a sitting position and average values recorded.

A 4-5 ml venous blood sample was withdrawn from each subject using disposable sterile syringes and collected in evacuated gel tubes. (Gel helps in faster blood clotting) after an overnight fast of 12 to 14 h (Sawant *et al.*, 2011). For biochemical assays, serum was separated at 3500 rpm for 30 min within 2 h of sampling and aliquots stored at -20 °C until analysis. The assays for FBG, TG, TC, LDL, and HDL were conducted on automated chemistry analyzer (Roche Hitachi 912 Chemistry Analyzer, Roche Diagnostics, USA) using commercial kits (Roche Diagnostics, USA). All anthropometric measurements, blood sampling and biochemical assays were performed by experienced medical staff.

Statistical analysis

The results for continuous variables were expressed as mean ± standard deviation (SD). The MetS population group was also sub-grouped based on sex (male and female), age (<40 years of age and >40years of age) and BMI based obesity sub-groups (Non-obese, BMI <29.9Kg/m^2 vs obese BMI >29.9Kg/m^2). Comparisons of all risk factors among gender, age and BMI based MetS subgroups were also computed using student's t-test. The prevalence of MetS was estimated in total study population and on the basis of gender, age and BMI using proportions difference test. A nominal two-sided p-value of <0.05 was considered significant. All statistical tests were computed using SPSS v21 software.

RESULTS

The descriptive statistics for study subjects are presented in Table I. The mean age of subjects was 42.82±8.07 years with a range of 25-55 years. The mean values of anthropometric parameters were as follows; SBP 128.01mmHg and DBP 87.8mmHg, weight 70.67Kg, WC 86.23cm, and BMI 26.05Kg/m^2. The recorded mean ranges for biochemical variables were as follows; TG 172.35mg/dL, TC 189.95mg/dL, LDL 114.06mg/dL, HDL 40.98mg/dL and 116mg/dL.

Table I.- Descriptive statistics of study population.

Variables	Minimum	Maximum	Mean±SD
Age (Years)	25.00	55.00	42.82±8.07
SBP (mmHg)	95.00	210.00	128.04±15.62
DBP (mmHg)	60.00	130.00	87.80±11.63
Weight (Kg)	35.00	135.00	70.67±11.94
WC (cm)	73.66	116.84	86.23±9.04
BMI (Kg/m^2)	16.00	42.00	26.05±4.80
TC (mg/dl)	56.00	419.00	189.95±48.34
TG (mg/dl)	65.00	630.00	172.35±87.58
HDL (mg/dl)	10.00	98.00	40.98±10.40
LDL (mg/dl)	130.00	411.00	114.06±39.88
FBG (mg/dl)	42.00	647.00	116.00±58.95

BMI, body mass index; DBP, diastolic blood pressure; WC, waist circumference; FBG, fasting blood glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

A comparison of risk variables among MetS and non-MetS subjects is presented in Table II. The ranges of all anthropometric and biochemical risk variables were significantly raised in MetS studied population (≤0.0001) as compared to the non-MetS ones. The gender, age and BMI groups based MetS risk variables comparisons are summarized in Table III. In gender and age based comparisons, anthropometric parameters DBP, weight, and BMI were all significantly raised (p-values below 0.05) in >40 years females while SBP in <40 years

Table II.- MetS risk factors in total population and comparison in disease and health status.

Risk factors	Total	Disease status		p-value
		MetS	Non-MetS	
SBP (mmHg)	128.04±15.62	133.6±16.7	123.2±12.8	≤0.0001
DBP (mmHg)	87.80±11.63	91.2±11.5	84.7±10.2	≤0.0001
Weight (Kg)	70.67±11.94	76.0±12.6	66.6±8.5	≤0.0001
Waist (cm)	86.23±9.04	97.5±5.8	84.58±6.0	≤0.0001
BMI (Kg/m^2)	26.05±4.80	28.1±5.7	23.9±3.8	≤0.0001
TG (mg/dl)	172.35±87.58	227.5±109.9	119.3±19.5	≤0.0001
TC (mg/dl)	189.95±48.34	205.2±49.7	179.8±39.4	≤0.0001
HDL (mg/dl)	40.98±10.40	36.8±8.8	44.5±9.0	≤0.0001
LDL (mg/dl)	114.06±39.88	121.6±44.4	110.2±34.4	≤0.0001
FBG (mg/dl)	116.00±58.95	146.0±72.3	90.0±11.8	≤0.0001

Significance levels p-value ≤0.05
For abbreviations see Table I.

female group. The WC measurements in female subjects lacked any age based significant difference (p=0.956). In male subjects, SBP was significantly but mildly (0.027) increased in >40 years age group (134.77±16.3) while WC increased significantly in <40 years group (94.53±10.31, p=0.004). For biochemical risk variables, gender and age based statistically significant but low differences were observed only for TG (p=0.05) and FBG (0.012). The >40 years female and male MetS subgroups had significantly raised FBG levels (female 162.65±85.6, male 144.82±75.9) as compared to the <40 years gender groups (female 145.17±68.4, male 125.03±53.4). Only in MetS male population, TG levels were significantly raised in <40 years age group (245.55±10.37) as compared to the >40 years age (223.67±9.6). On the other hand, in BMI based obesity groups of MetS subjects, all risk variables were significantly raised in obese subjects (>29.9 Kg/m^2 BMI) while HDL significantly lowered as compared to non-obese subjects (<29.9 Kg/m^2 BMI). In obese vs non-obese subgroups, highly significant increase (<0.0001) was found in TG (244.94±105.80 vs 214.13±93.88 mg/dL) and FBG (161.34±86.00 vs 138.13±66.81 mg/dL) followed by weight (86.36±12.29 vs 69.58±8.93 Kg) and WC (93.92±11.43 vs 90.75±9.57) with a power of <0.0001.

The results computed for MetS prevalence in total study population as well as in gender, age and BMI based groups are presented in Table IV. Based on IDF definition criteria, an overall MetS prevalence in our study population was 46.0%. The 52.1% disease prevalence in male subjects was significantly high (p=0.016) as compared to 47.9% in females. The MetS prevalence in >40 years age group (55.6%) was greatly increased (<0.0001) as compared to the <40 years age (44.4%). The results for obesity related MetS prevalence rates in our study population are presented in Table IV. We found significantly high (<0.0001) disease frequency of 82% in obese population subgroup with BMI >29.9Kg/m^2 as compared to 36.7% in <29.9Kg/m^2 BMI.

DISCUSSION

Based on IDF definition criteria, a high MetS prevalence was found in our study population. The disease also showed age, gender and obesity based trends. Among MetS population subgroups, disease frequency was highest among obese, advanced aged male subjects. Though response of IDF defined risk factors among age and gender specific MetS subgroups was quite diverse, all were significantly raised in obesity. Irrespective of age and gender, raised BMI along with hyperglycemia and dyslipidemia seems to be the common significant MetS marker in our study population.

Our criterion for MetS definition was based on IDF (http://www.idf.org/) which considers abdominal obesity as one of the major health complications. In present study BMI and WC were estimated in order to explore combined effects of abdominal obesity (WC) and overall obesity (BMI). Within this group increases in TG and BSF were of strong statistical significance followed by body weight and WC. The prevalence of MetS in obese was amongst the highest in our selected population (82.0% in BMI >29.9 Kg/m^2 vs 36.7 in BMI <29.9 Kg/m^2, p<0.0001) as compared to total (46%), gender (Males 52.1% vs Female 47.9%), and age (44.4% in ≤40 years vs 55.6% in <40 years) based disease prevalence rates (Table IV). However it is worth to mention here that a large proportion of the study population cohort, approaching risk limits of WC (86.23±9.04), was within over-weight BMI range (26.05±4.80) with a minor

Table III.- Comparison of MetS risk factors based on gender, age and BMI.

Risk Factors	Females		p-value	Males		p-value	BMI		p-value
	<40 Years	>40 Years		<40 Years	>40 Years		<29.9 Kg/m^2	>29.9 Kg/m^2	
SBP (mmHg)	130.56±15.2	135.90±17.9	0.006	130.68±16.2	134.77±16.3	0.027	132.52±16.86	135.54±16.30	0.024
DBP (mmHg)	89.19±10.4	93.38±12.2	0.002	89.06±11.6	91.50±11.5	0.064	90.38±11.54	92.62±11.7	0.016
Weight (Kg)	72.67±11.0	76.29±13.1	0.012	76.49±12.5	76.43±14.0	0.968	69.58±8.93	86.36±12.29	<0.001
WC (cm)	91.41±9.4	91.49±10.4	0.956	94.53±10.31	91.05±10.66	0.004	90.75±9.57	93.92±11.43	<0.001
BMI (Kg/m^2)	27.97±4.3	29.80±5.7	0.003	28.19±5.4	27.39±4.7	0.158			
TG (mg/dl)	207.50±82.7	226.80±19.5	0.086	245.55±10.37	223.67±9.6	0.05	214.13±93.88	244.94±105.80	<0.0001
TC (mg/dl)	200.72±48.3	204.71±51.7	0.493	206.77±47.7	206.70±50.6	0.991	200.89±50.45	212.26±48.5	0.004
HDL (mg/dl)	37.40±9.9	37.19±10.9	0.844	36.24±7.5	35.49±8.5	0.42	37.14±9.6	35.3±8.9	0.015
LDL (mg/dl)	120.01±42.7	124.86±42.9	0.327	118.09±43.8	119.90±44.2	0.714	117.11±42.18	127.89±45.09	0.002
FBG (mg/dl)	145.17±68.4	162.65±85.6	0.05	125.03±53.4	144.82±75.9	0.012	138.13±66.81	161.34±86.00	<0.0001

Significance levels p-value ≤0.05
For abbreviations see Table I.

Table IV.- Total, gender, age, and BMI based prevalence of MetS.

Study groups	Prevalence (%)	p-value
Gender		
Male	52.1	0.016
Female	47.9	
Age (Years)		
≤40	44.4	≤0.0001
≥40	55.6	
BMI (Kg/m^2)		
<29.9	36.7	<0.0001
>29.9	82.0	

Significance levels p-value ≤0.05

proportion approaching extreme obesity (42.00Kg/m^2). Studies have reported Asians being genetically predisposed to accumulate more body fats at a given BMI as compared to the western world populations (Marcin *et al.*, 2014). In addition Asian females are also predisposed to high waist to hip ratio as compared to Europeans which leads to high occurrence of MetS (Raji *et al*., 2001). The clustering of MetS susceptibility risk parameters among >29.9Kg/m^2 BMI population subgroup strongly indicates obesity being the major health issue in our population. Other local studies reported MetS prevalence on the basis of T2D. Although T2D correlates with a number of advanced stage health disorders especially CVDs (Johan *et al.*, 2010 Peter *et al*., 2005), fatty liver (Elizabeth *et al.*, 2010) and kidney disorders (Khaled and Brent, 2014; Ihab and Robert, 2007), the disease itself has long been reported as an onset of obesity (Peter *et al.*, 2005). A higher incidence of weight gain along with hyperglycemia, dyslipidemia and hypertension among general Pakistani population might be responsible for an increased susceptibility towards MetS. The results from present study report 42% disease prevalence in a general population. The MetS prevalence rate of 30-40% has already been documented for South Asian populations (Basit and Shera, 2008; Misra and Khurana, 2009; Katulanda *et al.*, 2012; Masuma *et al.*, 2011) which are much higher as compared to the ≤20% in South East and East Asian countries (Huang *et al.*, 2008; Arai *et al.*, 2006; Villegas *et al.*, 2009) like Taiwan (Huang *et al.*, 2008), Japan (Arai *et al*., 2006), Korea (Im and Gyeong, 2015), and China (Villegas *et al.*, 2009). The high disease trends in South Asian populations have been associated with central/overall obesity arising from extensive urbanization, unhealthy dietary habits and sedentary life style (Deepak *et al.*, 2013). As South Asian populations are reported to be highly prone to central as

well as overall obesity (Marcin *et al.,* 2014), it could be predicted that a high MetS frequency in our study Pakistani population might be arising from lifestyle triggers of obesity in a genetically favorable environment.

Besides lifestyle, advancing age and gender have also been shown to increase predisposition towards MetS (Ford *et al.,* 2002; AlSaraj *et al.,* 2009; Im and Gyeong 2015; Guang-Rong *et al.,* 2013: Julie *et al.,* 2014). In accordance with previous studies, we also report a high MetS prevalence in >40 years of age group (55.6%) as compared to the younger population. Though there are contrasting results for gender specific disease trends (Anthonia, 2010; Mabry *et al.,* 2010), male gender is shown to be at higher MetS risk as compared to females in different ethnic world populations (Firdous *et al.,* 2007; Raji *et al.,* 2001, Sawant *et al.,* 2011; Guang-Rong *et al.,* 2013; Manopriya *et al.,* 2010). Our Pakistani male gender cohort also had significantly high disease prevalence rates as compared to females (p=0.016). It is worth to mention here that a large proportion of our female subjects were found within 40 years of age group and thus might not have provided a true prevalence rate contrast as compared to males.

Within BMI based MetS sub-groups, all IDF defined risk factors were significantly raised but with mixed trends in gender and age based sub-groups (Marcin *et al.,* 2014). Among IDF defined risk factors, DBP, BMI and FBG were all found to be important disease risk markers in >40 years old females while SBP in <40 years old. In >40 years old males SBP, WC and FBG were found significant risk markers whereas TG in <40 years males. The common MetS disease markers in gender and age specific subgroups of our study population seem to be SBP and FBG. Irrespective of BMI, our >40 years male population seems to be in pre-hypertensive and pre-hyperglycemic state with raised WC. Globally these metabolic complications are now regarded as a huge health burden leading to severe complications like T2D and CVDs (Johan *et al.,* 2010; Peter *et al.,* 2005; Masuma *et al.,* 2011). However, lifestyle modifications that reduce obesity especially abdominal obesity could improve/reverse MetS and its associate complications (Peter *et al.,* 2005; Gretchen *et al.,* 2013; Niloufer *et al.,* 2012). So raised BMI along with WC seems to be the strongest indicator of MetS in our Pakistani population especially in older males. In order to reduce MetS prevalence in Pakistan there is a strong need to create general awareness about disease with emphasis on obesity management through active life style adoption.

CONCLUSIONS

In conclusion, over-weight and abdominally obese male population cohort from local Pakistani populations with hyperglycemia, dyslipidemia and pre-hypertension, seem at higher risk of developing MetS.

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Statement of Conflict of Interest

Authors have no financial, institutional or personal conflicts of interest regarding this work.

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