



## TO STUDY THE PREVALENCE OF METABOLIC SYNDROME IN THE ADULT POPULATION OF KASHMIR

### Endocrinology

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### ABSTRACT

Metabolic syndrome is an important health concern for clinicians & researchers worldwide especially due to the constellation of risk factors and their association with CVD & T2DM. Owing to the distinct lifestyle and dietary habits of Kashmiri people, this study was designed to evaluate the risk factors associated with MetS by applying the modified NCEP ATP-III criteria and IDF. In this cross-sectional study, 960 patients underwent an anthropometric assessment that included measurement of weight, height, BMI, waist circumference and blood pressure. Biochemical investigations included Blood Sugar, TGs and HDL-Cholesterol. The gender distribution was 72.9% females and 27% males. Prevalence of MetS was 76.9%. Higher prevalence was found in females (80.2%) as compared to males (68%). Further, MetS increased significantly from the fourth to the sixth decade of life. Overall, increased WC (97% in females and 90.4% in males) was the common abnormality observed followed by elevated TG (82.5% in females and 73.4% in males). 53% males and 44% females were found to be having a history of diabetes. Also, 63.1% females and 51.5% males were hypertensive. Low HDL level (33.8%) was the least common abnormality among males. The high prevalence of MetS highlights the need for awareness and identification of the individual risk factors leading to CVD and T2DM and their appropriate clinical intervention. Increased morbidity and mortality of CVD & T2DM among Asian Indians calls for the adoption of a healthy lifestyle right from childhood.

### KEYWORDS

Metabolic syndrome; diabetes mellitus; cardiovascular disease; Kashmir.

One of the important public health concern as well as a challenge for the clinicians and researchers worldwide is the prevalence of Metabolic Syndrome (MetS) especially in the wake of urbanisation, sedentary lifestyle, increased obesity, physical inactivity etc. (Deedwania & Gupta, 2006). Defined as a cluster of biochemical/metabolic/physiologic/clinical abnormalities, MetS is characterised by dyslipidemia, hypertension, hyperinsulinemia and central obesity and has been found to be associated with the development of cardiovascular diseases and Type 2 Diabetes (Moller DE & Kaufman KD, 2005). Although MetS has various definitions but for the clinical diagnosis, Adult Treatment Panel III (ATP III) remains the practical method. Based on the clinical and biochemical measurements such as waist-hip ratio, Body Mass Index (BMI), blood pressure, lipid profile, blood sugar etc., the National Cholesterol Education Program: Adult Treatment Panel III (NCEP: ATP III) published a new set of criteria, the modified ATP-III criteria as proposed by the International Diabetes Federation (IDF) for the characterisation of MetS ("Using NCEP-ATP III third report" JAMA 2001; Alberti, Zimmet & Shaw 2006). There were suggestions that for the identification of risks of Type 2 Diabetes Mellitus (DM) or Cardiovascular Disease (CVD) the ATP-III definition of MetS is not optimal and specific for the Asian Population who have not reached the overweight definition BMI (> 25 kg/m<sup>2</sup>). As a consequence, the modified ATP-III criterion of defining MetS has been proposed which is being used in recent Asian and Indian studies. This modification incorporates the waist circumference (WC) of 90cm in men and 80 cm in women. Studies have shown that such levels were associated with higher Odds Ratios (OR) for the presence of cardiovascular risk factors (Misra et al., 2006; Ramachandran, Snehalatha, Satyavani, Sivasankari & Vijay, 2003). Risk factors that increase the chances of developing the disease include high triglyceride level (or on medicine to treat high triglycerides), low HDL cholesterol level (or on medicine to treat low HDL cholesterol), high blood pressure (or on medicine to treat high blood pressure) and high fasting blood sugar (or on medicine to treat high blood sugar). A person can have any one of these risk factors by itself, but they tend to occur together. According to the new IDF definition, for a person to be identified as having metabolic syndrome they must have Central Obesity and any two of the above risk factors. Coincidence of metabolic factors in different individuals and coexistence of these factors has been shown to be more harmful than the presence of any one of them (Sadrbafooghi et al., 2006). About 50% of Diabetic patients suffer from MetS and have more chances for stroke, retinopathy, neuropathy and micro albuminuria (Rahim et al., 2017). More than half of the people with Acute Coronary Syndrome have been shown to

have three or more components of the MetS (Zaliunas et al., 2008) and studies have reported that patients with Peripheral Arterial Disease have high prevalence (95%) of MetS (Qadan, Ahmed, Safar, Al-Bader & Ali, 2008). Prevalence of Metabolic syndrome is increasing in different regions like Asia (Pan, Yeh & Weng, 2008) and developing countries (Lameira, Lejeune & Mourad, 2008). About 12.8% to 41.1% prevalence has been reported in different parts of the world (Ramachandran et al., 2003). In DECODE (Diabetes epidemiology; collaborative analysis of diagnostic criteria in Europe) study that was conducted in 9 European countries, MetS was detected in 32% of men and 28.55% of women (Qiao, DECODE study group, 2006). The prevalence in Asia has increased rapidly in the recent years due to rapid socioeconomic transitions to increasing affluence, urbanization, mechanization, auto-mobilization, and urban migration (Eapen, Kalra, Merchant, Arora & Khan, 2009). However, the ethnic, cultural, environmental and economic differences contribute to varied prevalence across Asian countries (Lao et al., 2012). Some racial and ethnic groups in the United States are at higher risk for metabolic syndrome than others. Mexican Americans have the highest rate of metabolic syndrome, followed by whites and blacks. Other groups at increased risk for metabolic syndrome include people who have a personal history of diabetes, sibling or parent with diabetes, women compared to men, women with personal history of polycystic ovarian syndrome (a tendency to develop cysts on the ovaries) and an inactive lifestyle. Metabolic syndrome is becoming more common due to a rise in obesity rates among adults. In the future, metabolic syndrome may overtake smoking as the leading risk factor for heart disease. It is possible to prevent or delay metabolic syndrome, mainly with lifestyle changes. A healthy lifestyle is a lifelong commitment. Successfully controlling metabolic syndrome requires long-term effort and teamwork with health care providers.

### Material and Methods

#### Subjects and Sampling

This was a cross-sectional study conducted on the patients attending the OPD (Department of Medicine) SMHS hospital Srinagar J&K over a period of one year from August 2016 to August 2017 after getting approval from the Departmental Ethical Committee, GMC Srinagar. A total of 960 patients above the age of 18 years participated in the study. A self-designed questionnaire including age, gender, marital status, ethnicity, education level, family as well as personal history of DM/HTN/obesity/smoking was filled for each person. Informed consent was obtained from all the patients and complete record maintained.

**Anthropometric Measurement**

Anthropometric assessment included measurement of weight, height, BMI [weight (kg)/height (m<sup>2</sup>)], WC and blood pressure. Weight was measured without shoes using digital scales in an upright position and recorded to the nearest of 0.1kg. Height was measured again without shoes in standing position using stadiometer to the nearest 0.1cm. WC was measured at the midsection between the rib cage and the top of the lateral border of the iliac crest during relaxed respiration. Circumferences were measured to within 1mm using a soft measuring tape in the standing position. Blood pressure was recorded twice at 5 min intervals by a standard sphygmomanometer after 5-10 minutes rest in sitting position. The average of the two measurements was used for data analysis.

**Biochemical Analysis**

Venous blood samples were drawn by trained phlebotomist from the participants after an overnight fast of at least 8-9 hrs. Before taking the blood samples fasting time was verified. Samples were centrifuged and analysis was done within 1-2 hrs after collection. All the samples were processed and analysed on Architect-C-4000 fully automated analyser (ABBOTT) in the Diagnostic Laboratory of Biochemistry, GMC Srinagar by a trained technician. Biochemical examinations included Blood Sugar (Fasting)/Lipid profile [Triglycerides and HDL].

**Defining the MetS Components**

MetS was defined in the participants as per the modified ATP-III criteria according to which at least three of the following five components were considered necessary for the characterisation of MetS ("Using NCEP-ATP III third report" JAMA 2001; Alberti et al.,2006). Abdominal obesity was defined as WC values of ≥ 90 cm in men and ≥ 80 cm in women. Hypertriglyceridemia was defined as TG levels of 150 mg/dl or greater. High fasting glucose 110 mg/dl or T2DM or treatment. HDL cholesterol levels of <40 mg/dl in men and < 50 mg/dl in women. Hypertension was defined as an average blood pressure (BP) ≥ 135/ 80 mmHg.

MetS defined by ATP III was also compared with IDF criteria. MetS by IDF may be defined as Central obesity {defined as waist circumference ≥ 90 cm (male), ≥80 cm (female)} and any two of the following:

- TG > 150 mg/dl (1.7mmol/L)
- HDL-C < 40 mg/dl (male), < 50 mg/dl (female)
- Blood pressure ≥ 130/85 mmHg
- Fasting plasma glucose > 100 mg/dl (5.6mmol/L).

**Statistical Analysis**

The data was analysed using Pearson's Chi square test and a p-value of <0.05 was considered statistically significant. The analysis was done using R-software version 3.4.3.

**Results**

Out of the 960 subjects who participated in the study, the highest number was of females (700) with a maximum number of 280 in the age group of 40-50 years followed by 220 in the age group of 50-60 years. Least number of females (8) was in the age group of above 70 years. Among the total of 260 males in the study, highest number of 130 was observed in the age group of 40-50 years followed by 54 in the age group of 50-60 years with the least number (8) in the age group ≥70 years.

**Demographic Characteristics**

The gender distribution was 72.9% females and 27.0% males in the study subjects of ≥18 years taken in the ethnic population of Kashmir. Of these the highest number was found in the age group of 40-50 years with 50% males and 40 % females, followed by 31.4% females and 20.7% males in the age group of 50-60 years, in <30 year age group 1.5% were males and 6.5% females; in 30-40 year age group 11.5% were males and 6.5% were females; in the 60-70 year age group 13.0% were males and 8.5% were females. In ≥70 age group, males were 3.0% and females were 1.1% (Table 1).

**Table 1. General Characteristics of the study population**

Characteristics: Age (years)	Total	Males n(%)	Females n(%)	p-value
<30	50 (5.2)	4 (1.5)	46 (6.5)	χ <sup>2</sup> = 29.47 p-value = ≤0.0001* *significant
30-40	116 (12.0)	30 (11.5)	86 (12.2)	
40-50	410 (42.7)	130 (50)	280 (40)	

50-60	274 (28.5)	54 (20.7)	220 (31.4)
60-70	94 (9.7)	34 (13.0)	60 (8.5)
≥70	16 (1.6)	8 (3.0)	8 (1.1)
<b>TOTAL</b>	<b>960</b>	<b>260 (27.0)</b>	<b>700 (72.9)</b>

In the study subjects 60% were hypertensive and 40% were normotensive. History of hypertension was more in females (63.1%) as compared to males (51.5%). Prevalence of hypertension in females was more in the age group of 50-60 years (38.4%) whereas in males prevalence was higher in the age group of 40-50 years with 47.7% (Table 2).

**Table 2. Prevalence of Hypertension in the subjects studied**

Age (years)	>130/85 mmHg n(576)		<130/85 mmHg n(384)	
	M (%)	F (%)	M (%)	F (%)
<30	1(0.7)	6(1.3)	3(2.3)	40(15.5)
30-40	4(2.9)	34(7.6)	26(20.6)	52(20.1)
40-50	64(47.7)	164(37.1)	66(52.3)	116(44.9)
50-60	42(31.8)	170(38.4)	12(9.5)	50(19.3)
60-70	16(11.9)	59(13.3)	18(14.2)	1(0.3)
≥70	7(5.2)	7(1.5)	1(0.8)	1(0.3)
<b>TOTAL</b>	<b>134(51.5%)</b>	<b>442(63.1)</b>	<b>126(48.4)</b>	<b>258(36.8)</b>
χ <sup>2</sup>	13.86		52.55	
<b>p-value</b>	0.017*		<0.0001*	

\*Significant

In the study group 53.5% were normal and 46.4% were diabetic. History of diabetes was more prevalent in males (53.0%) than in females (44%). History of Diabetes was highest at 46.3% in males and 41.5% in females in the age group of 40-50 years (Table 3).

**Table 3. Prevalence of Diabetes in the subjects studied**

Age (years)	>100 mg/dl n(446)		<100 mg/dl n(514)	
	M (%)	F (%)	M (%)	F (%)
<30	2(1.4)	14(4.5)	2(1.6)	32(8.1)
30-40	16(11.5)	38(12.3)	14(11.4)	48(12.2)
40-50	64(46.3)	128(41.5)	66(54.1)	152(38.7)
50-60	22(15.9)	96(31.1)	32(26.2)	124(31.6)
60-70	30(21.7)	30(9.7)	4(3.2)	30(7.6)
≥70	4(2.9)	2(0.6)	4(3.2)	6(1.5)
<b>TOTAL</b>	<b>138(53.0)</b>	<b>308(44)</b>	<b>122(46.9)</b>	<b>392(56)</b>
χ <sup>2</sup>	25.23		16.23	
<b>p-value</b>	<0.0001*		0.006*	

\*Significant

The prevalence of low HDL levels was found in 528 (55%) of the study population and 432 (45%) were having normal HDL levels. Incidence of low HDL levels was more prevalent in females (62.8%) than in males (33.8%). Low HDL levels were more prevalent in the age group of 40-50 years in both males (36.3%) and females (37.2%) (Table 4).

**Table 4. HDL levels in the studied group**

Age (years)	>40 mg/dl n(172)	<40 mg/dl n(88)	>50 mg/dl n(260)	<50 mg/dl n(440)
	M (%)	M (%)	F (%)	F (%)
<30	3(1.7)	1(1.1)	10(3.8)	36(8.1)
30-40	12(6.9)	18(20.4)	20(7.6)	66(15)
40-50	99(57)	32(36.3)	116(44.6)	164(37.2)
50-60	26(15.1)	27(31)	78(30)	142(32.2)
60-70	26(15.1)	8(9.0)	30(11.5)	30(6.8)
≥70	6(3.4)	2(2.2)	6(2.3)	2(0.4)
χ <sup>2</sup>	23.81		23.40	
<b>p-value</b>	<0.0001*		<0.0001*	

\*Significant

In the group studied, prevalence of high TG levels was found in 769(80%) of the total subjects with females more predominantly

having higher TG levels (82.5%). Among male group 73.4% were having higher TG levels. Higher incidence of increased TG levels was observed in the 40-50 year age group in both males and females (Table 5).

**Table 5. TG levels in the studied population**

Age (years)	>150 mg/dl n(769)		<150 mg/dl n(191)	
	M (%)	F (%)	M (%)	F (%)
<30	3(1.5)	34(5.8)	1(1.4)	12(9.8)
30-40	24(12.5)	72(12.4)	6(8.8)	14(11.4)
40-50	104(54.1)	226(39.1)	26(38.2)	54(44.2)
50-60	36(18.7)	194(33.5)	18(26.4)	26(21.3)
60-70	20(10.4)	46(7.9)	14(20.5)	14(11.4)
≥70	4(2.0)	6(1.0)	4(5.8)	2(1.6)
$\chi^2$	26.11		10.53	
p-value	<0.0001*		0.061	

\*Significant

Prevalence of increased WC was found in 913 (95.4%) of the study population and 47 (4.6%) were having normal WC. Among females of the study group 96.8% were found to be having WC of more than 80cm whereas in the male group studied 90.4% were found to be having WC of more than 90cm. Increased WC of 50% in females and 40.3% in males was both in the age group of 40-50 years (Table 6).

**Table 6. WC of the studied population**

Age (years)	>90cm n(235)	<90cm n(25)	>80cm n(678)	<80cm n(22)
	M(%)	M(%)	F(%)	F(%)
<30	3(1.2)	1(4.1)	40(5.8)	6(28.5)
30-40	28(11.8)	2(8.3)	80(11.7)	6(28.5)
40-50	118(50)	12(50)	274(40.3)	6(28.5)
50-60	50(21.1)	4(16.6)	218(32.1)	2(9.5)
60-70	32(13.5)	2(8.3)	59(8.6)	1(4.7)
≥70	4(1.6)	4(16.6)	7(1.0)	1(4.7)
$\chi^2$	17.27		26.22	
p-value	0.004*		<0.0001*	

\*Significant

BMI (kg/m<sup>2</sup>) was calculated as per the NIH (National Heart Lung & Blood Institute) criteria. In the population studied nobody was found underweight (BMI<18.5). 56 (5.8%) were having normal weight, 685 (71.3%) were overweight and 219 (22.8%) were found to be obese. Prevalence of obesity was more in females 167 (23.8%) in comparison to males 52(20%) in the study subjects (Table 7).

**Table 7. BMI (kg/m<sup>2</sup>) of the study population as per NIH (National Heart Lung & Blood Institute) reference range**

Age (years)	Normal 18.5 – 24.9		Overweight 25 -29.9		Obese 30 or >	
	M (%)	F (%)	M (%)	F (%)	M (%)	F (%)
<30	0	6	4	24	0	16
30-40	6	2	10	58	14	26
40-50	8	16	102	190	20	74
50-60	4	6	48	181	2	33
60-70	4	0	16	42	14	18
≥70	4	0	2	8	2	0
TOTAL	26(10)	30(4.2)	182(70)	503(71.8)	52(20)	167(23.8)

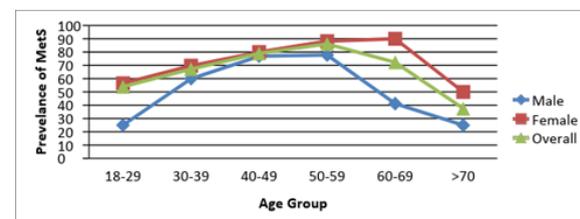
The prevalence of MetS in the group of study subjects taken was found in (739, 76.9%). Higher prevalence was found in females (562, 80.2%) as compared to males (177, 68.0%). Further it was observed that MetS increased significantly with the advancing age especially from fourth to sixth decade of life (Table 8 and Fig. 1).

**Table 8: Prevalence of MetS in the studied group**

Age (years)	Total Study Subjects			MetS Subjects		No. of MetS
	M n=260	F n=700	Total n=960	M (%) n=177	F (%) n=562	Total n=739

<30	4	46	50	1(25)	26(56.5)	27(54)
30-40	30	86	116	18(60)	60(69.7)	78(67.2)
40-50	130	280	410	100(76.9)	224(80)	324(79.0)
50-60	54	220	274	42(77.7)	194(88.1)	236(86.1)
60-70	34	60	94	14(41.1)	54(90)	68(72.3)
≥70	8	8	16	2(25)	4(50)	6(37.5)
$\chi^2$						20.23
p-value						0.001*

\*Significant



**Fig 1. Prevalence of MetS in the studied group**

Overall in our study increased WC, 97% in females and 90.4% in males was the common abnormality observed followed by elevated TG; 82.5% in females and 73.4% in males. Elevated Blood sugar was another abnormality found, 53% males and 44% females were found to be having the history of diabetes. Also in the study 63.1% females and 51.5% males were hypertensive. Low HDL levels 33.8% was the least common abnormality among males of the study group (Table 9).

**Table 9: Overall clinical characteristics of the study population**

Characteristics	Males n(%) 260(27.08)	Females n(%) 700(72.91)	Total 960	$\chi^2$	p-value
<b>BMI(kg/m<sup>2</sup>)</b>					
Normal	26(10)	30(4.2)	56(5.8)	11.94	0.003*
Overweight	182(70)	503(71.8)	685(71.3)		
Obese	52(20)	167(23.8)	219(22.8)		
<b>HTN</b>					
Normal	126 (48.4)	258 (36.8)	384 (40)	10.63	0.001*
H/O HTN	134 (51.53)	442 (63.1)	576 (60)		
<b>Blood Sugar</b>					
Normal	122 (46.9)	392 (56)	514 (53.5)	6.27	0.012*
H/O Diabetes	138(53.0)	308(44)	446 (46.4)		
<b>HDL Levels</b>					
Normal	172(66.1)	260(37.1)	432(45)	64.46	<0.0001*
Lower HDL levels	88(33.8)	440(62.8)	528(55)		
<b>WC</b>					
Normal	25(9.2)	22(3)	47(4.6)	16.47	<0.0001*
Increased WC	235(90.4)	678(97)	913(95.1)		
<b>TG</b>					
Normal	69(26.5)	122(17.4)	191(19.8)	9.09	0.003*
Increased TG	191(73.5)	578(82.5)	769(80.1)		

\*significant

**Discussion**

The presence of a constellation of abnormalities that are finally associated with the increased risk for the development of Type 2 Diabetes and Cardiovascular disease have been defined by various terms like Metabolic Syndrome; Insulin Resistance Syndrome; American Syndrome; Syndrome X. The fact that a version of the said syndrome has its own ICD-9 code (277.7) suggests that MetS is well thought and has taken hold in the medical literature (Wilson & Grundy, 2003; Grundy et al.,2004). An overall change in the disease pattern from infectious to chronic non-communicable disease (like diabetes, CVDs) has been observed globally. This transition wherein the impact of infectious diseases is decreasing whereas that of NCDs is increasing is a cause of concern both for the epidemiologists in India as well as the

international agencies such as the World Health Organization (WHO), who have been sounding the alarm on the rising burden of CVD for the past 15 years. It has been estimated that the largest cause of morbidity and mortality in India by 2020 will be CVDs with an estimated 2.6 million Indians predicted to die due to these NCDs (Borch-Johnson, 2007; Goenka, Prabhakaran, Ajay & Reddy, 2009; Reddy et al., 2006). MetS being a cluster of metabolic factors is associated with a 2-fold risk of CVD and a 5-fold risk of Diabetes. It has been reported that individuals with MetS have a 30%-40% probability of developing diabetes and or CVD within 20 years, depending on the number of components present (Enas et al., 2007).

The present study was conducted in SMHS Srinagar, Kashmir, one of the tertiary care hospitals, that caters to both the urban as well as the rural population of the state owing to its state of the art infrastructure and ideal central location. J&K being a favourite tourist destination, the hospital also attends to the needs of the tourists visiting the hospital for various ailments. But the study was specifically designed for the ethnic population of Kashmir, who have unique culture, distinct lifestyle and dietary habits which include high caloric diets like Wazwan. Substantially high frequency of MetS (76.9%) was found in the study population selected using the modified ATP-III criteria as proposed by the IDF for the characterisation of MetS. Higher frequency of MetS (80.2%) in females was found in our study subjects, as has been found by various other studies published (Wani & Bhat 2014; Prasad, Kabir, Dash & Das, 2012). Gradual increase of MetS, with age up to 60 years, was observed in our study - especially in women. Also in the age group of <30 years there was the prevalence of MetS in 25% males and 56.5% females which is a cause of concern, as such group will be more prolonged to the atherosclerotic risk factors and T2DM that are associated with the MetS. The clinical characteristics need to be recognised very early in life, for the effective prevention of CVD and DM. In the present study 22.8% were found to be obese. 23.8% females and 20% males was the prevalence of obesity in the study group. But the incidence of overweight individuals was higher with 71.8% overweight females and 70% overweight males. As the prevalence of obesity and MetS is rapidly increasing in India and other South Asian countries, leading to increased mortality and morbidity due to CVD and T2DM (Prasad et al., 2012), rapid nutritional changes and physical activity are important lifestyle modifications that warrant immediate attention. Analysis also revealed the increased WC in 95% of the study subjects. Increased WC was found to be more prevalent among females of the group studied. 97% females and 90.7% males were having increased WC using the modified ATP-III /IDF criteria that incorporate Asian-specific WC criteria (90cm in men & 80cm in women) as one of the factors of identifying MetS. Using the modified ATP-III /IDF criteria for WC will categorise more people as having MetS as compared to the ATP-III criteria alone. In the study population high levels of TG (80%) was also the predominant feature with 82% females and 73.4% males having high levels of TGs. Low HDL levels were observed in 55% of the population studied, in which 62.8% females and 33.8% males were found to have low levels of HDL-cholesterol. Elevated blood sugar, the least common abnormality in the study, was found in 46.4% of the study subjects. 53.0% males and 44% females in the study population were found to have elevated blood sugar levels. Other factors contributing to the prevalence of MetS in the study population was the history of hypertension found in 60% of the study subjects. Among them 63.1% females and 51.1 % males were reported to be hypertensive as per the stated criteria. The high rate of prevalence of MetS in the selected study population of ethnic Kashmir warrants for the large population based study, especially to identify the individual risk factors at an early age. Early identification of these risk factors and early intervention would delay the onset of advance forms of MetS, especially CVD & T2DM.

### Limitations

Though the present study was carried out in the adult population of Kashmir attending the tertiary care hospital of Srinagar (SMHS) a comparatively lesser number of subjects were present in the age group of 18-30 years. The prevalence of MetS in 54% subjects in this age group suggests the need for broader based studies especially for adolescents and early adulthood. This study should be properly funded as inclusion of these groups requires a lot of resources which were not available to us.

### Conclusion

The high prevalence of MetS in the present study conducted on the ethnic population of Kashmir J&K India highlights the need for larger studies especially in adolescents as well as young adults and awareness of the risk factors leading to CVD and T2DM. Increased morbidity and mortality of CVD & DM among Asian Indians calls for the adoption of healthy life style right from childhood. Besides this, proper identification of individual risk factors leading to metabolic abnormalities, as well as their appropriate clinical intervention is of greater importance.

**Conflict of Interest:** None

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