ORIGINAL ARTICLE

Frequency and risk of metabolic syndrome in prediabetics versus normal glucose tolerant subjects — a comparative study

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Abstract

Objective: To compare the frequency and risk of metabolic syndrome in pre-diabetics against normal glucose-tolerant subjects attending diabetes screening camps in an urban centre.

Methods: The cross-sectional study was carried out at the Jinnah Postgraduate Medical Centre, Karachi, from January to August, 2008, and comprised subjects recruited through diabetes screening camps. They were ≥30 years of age, without prior history of diabetes and were screened through fasting plasma glucose and 2-hour oral glucose tolerance test. Demographic, anthropometric, clinical and biochemical measurements were done. Frequency of different components and their constellation as metabolic syndrome were determined according to the Adult Treatment Panel-III criteria. Relative risk was estimated to find the risk of metabolic syndrome in pre-diabetics versus normal glucose-tolerant subjects.

Results: The study sample comprised 80 subjects; 40(50%) normal glucose-tolerant in Group A and 40(50%) pre-diabetics in Group B. In Group A, there were 25(62.5%) men and 15(37.5%) women, while Group B had 22(55%) men and 18(45%) women. The mean age in Group A was 38.08±5.35 years, while in Group B it was 39.09±6.12 years. The frequency of various cardiovascular risk factors was higher in pre-diabetics ($p<0.05$). Central obesity was the most prevalent risk factor (85%, CI: 75.74-96.06), followed by low levels of high density lipoprotein (82.5%, CI: 72.64-94.27), raised triglycerides (67.5%, CI: 55.35-82.01), hypertension (57.5%, CI: 44.68-72.82), and fasting plasma glucose >100mg/dl (42.5%, CI: 29.68-57.82). Metabolic syndrome was found in 23(57.5%) in Group B compared to 9(22.5%) Group B, according to Adult Treatment Panel-III criteria. Calculated relative risk indicated that Group B was 1.9 times more prone to be suffering from metabolic syndrome compared to Group A.

Conclusions: Pre-diabetics were more prone to developing cardiovascular disorders than normal glucose-tolerant subjects.

Keywords: Metabolic syndrome, Risk factors, Pre-diabetes. (JPMA 65: 496; 2015)

Introduction

Over the last two decades, there has been a tremendous increase in the number of people with metabolic syndrome (MeS).[1] Even in the United States its prevalence has risen promptly from 22% in 1988-1994 to 34.5% in 1999-2002.[2] A similar trend was observed in other parts of the world in general and in Asia in particular where prevalence of MeS has been reported consistently to range from 10% to 40%.[3-5] Pakistan is also confronting a growing epidemic of MeS with reported prevalence of 34.8% and 40% in urban and rural areas respectively.[6,7] The high prevalence of MeS has important health implications and is considered to be a driver of the modern day epidemics of diabetes and cardiovascular diseases (CVDs).[8]

The term 'prediabetes' is cumulative for two intermediate conditions - impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).[9] Glucose intolerance in MeS could be IFG, IGT or diabetes. Presence of any one of these glucose abnormalities, though not obligatory, along with other factors is suffice to make the diagnosis of MeS.[8,10] Therefore, in some individuals, MeS co-exists with glucose dys-regulation.[11] While in others MeS is present without glucose dysregulation.[12,13] Whether or not MeS has component of glucose dysregulation, it has equal prognostic value for cardiovascular outcomes. However, propensity to have CVD is increased when glucose dysregulation is present as a component of MeS.[14] This predisposition rises further when diabetes is present as a component of MeS.[11] Due to increased predilection for CVDs, MeS and pre-diabetes both become leading health concerns. The study was planned to determine the distribution of various cardiovascular risk factors and to

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compare the frequency and risk of MeS between normal glucose-tolerant (NGT) and pre-diabetic subjects.

Subjects and Methods

The observational cross-sectional study was carried out at the Department of Biochemistry, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi, from January to August 2008, and comprised subjects recruited through various diabetes screening camps. Of all those screened, the subjects were selected on the basis of systematic random technique. Methodology of the present study was described in detail elsewhere.[15]

A detailed information leaflet was provided to all consenting participants to whom study objectives, procedures and the risks and benefits involved were explained and they were assured about the confidentiality of data. An informed consent was signed by each participant. After an overnight fast of at least 10-12 hours, blood was collected to estimate fasting plasma glucose (FPG), serum cholesterol, serum triglyceride (TG) and high density lipoprotein (HDL) cholesterol level. Low density lipoprotein (LDL) cholesterol was calculated by using the Friedewald's equation.[16] A solution of 75g of glucose dissolved in water was administered and 3ml of blood was drawn 2 hours later for estimation of glucose. Demographic, anthropometric and clinical parameters of each subject were collected on an interviewer-administered questionnaire. Anthropometric measurements, including weight, height and waist measurements, were obtained using standardised techniques on the screening day.[17] Folding screens were used to isolate the subjects. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg with a mercury sphygmomanometer.

Due to unknown local population of pre-diabetics, the priori sample size was not calculated. However, screening for pre-diabetics continued along the study period until the power of the study was statistically attained. Power based on normal approximation with continuity correction was calculated to be 85.74% with 95% confidence interval (CI) by Open Epi.[18]

Based on FPG results and two-hour oral glucose tolerance test (OGTT), subjects were categorized according to American Diabetes Association (ADA) and World Health Organisation (WHO)[19] classification of diabetes into NGT, IFG, IFG with IGT, IGT and diabetic groups. Individuals having IFG (≥110-≤125mg/dl) and/or IGT (≥140-≤200 mg/dl) were grouped together as pre-diabetics. Different International bodies have defined the term MeS. Among all of them, the National Cholesterol Educational Programme-Adult Treatment Panel-III (NCEP-ATP III) is the most widely used definition due to its simple approach for diagnosing MeS.[20-22]

Frequency of individual risk factors and their constellation as MeS was determined according to ATP-III guidelines between NGT and pre-diabetic subjects and expressed in simple frequencies and percentages with 95% CI. Relative risk (RR) was estimated to find the risk of MeS in pre-diabetics compared to NGT subjects.

Results

Of the 608 subjects screened, 83(13.6%) were found to have pre-diabetes. The final study sample comprised 80 subjects; 40(50%) NGT and 40(50%) pre-diabetics. Among

Table-1: Comparison of demographic, anthropometric, clinical and biochemical characteristics of normal glucose tolerant and prediabetic (n=80).

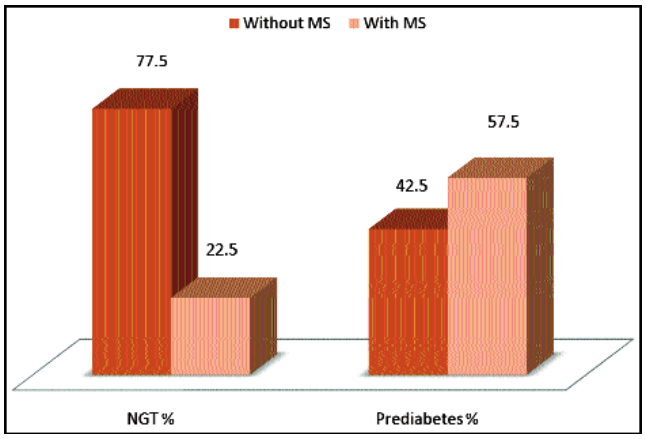
Biophysical parameters	Normal Glucose Tolerant (Control)	Prediabetes	p-value
N	40	40	
Males	25(62.5%)	22(55%)	0.496
Females	15(37.5%)	18 (45%)	
Age (years)	38.08±5.35	39.09±6.12	0.474
BMI (kg/m^2)	26.66±3.12	29.62±3.19	0.000
Waist (cm)	86.30±8.13	93.95±8.09	0.000
Systolic BP (mmHg)	116.38±11.20	124.0±18.98	0.032
Diastolic BP (mmHg)	80.25±7.67	86.00±11.16	0.009
Fasting Plasma Glucose (mg/dl)	89.98±10.36	99.30±12.41	0.000
2 hour Plasma Glucose (mg/dl)	112.25±9.17	175.80±18.91	0.000
Cholesterol (mg/dl)	169.03±36.34	201.18±44.21	0.001
Triglyceride (mg/dl)	138.70±62.22	185.05±78.18	0.004
High density lipoprotein (mg/dl)	42.10±7.46	37.55±6.64	0.005
Low density lipoprotein (mg/dl)	102.93±34.55	125.19±43.19	0.013

Data presented as n (%) or mean ±standard deviation (SD). Chi-square or t- test where applicable was used as a test of significance. A p-value of >0.05 was considered as statistically significant.
BMI: Body mass index.

Table-2: Comparison of components of metabolic syndrome in normal glucose tolerant and prediabetic subjects.

Cardiovascular risk factors	NGT n=40	Prediabetic n=40	p-value
Central obesity (waist ≥ 80 90 cm)	20 (50%) (37.03-65.49)	34 (85%) (75.74-96.06)	0.001
HDL (≤ 40 / 50mg/dl)	22 (55%) (42.09-70.41)	33 (82.5%) (72.64-94.27)	0.008
TG (≥150 mg/dl)	13(32.5%) (20.35-47.01)	27 (67.5%) (55.35-82.01)	0.002
HTN (≥130/85 mmHg)	13 (32.5%) (20.35-47.01)	23 (57.5%) (44.68-72.82)	0.025
FPG (≥100 mg/dl)	6 (15%) (5.74-26.06)	17 (42.7%) (29.68-57.82)	0.007

Data was presented as n(%) with 95% confidence interval (CI).
HDL: High density lipoprotein
HTN: Hypertension
FPG: Fasting plasma glucose.



NGT: Normal glucose-toelrant. ATP-III:Adult Treatment Panel-III.
MS: Metabolic syndrome

Figure: Comparison of metabolic syndrome frequency in NGT and prediabetic subjects according to ATP III criteria.

Table-3: Contingency table for calculating risk of metabolic syndrome in prdiabetics.

Glucose Tolerance	Metabolic Syndrome		Total
	Present	Absent	
Prediabetes	17	23	40
NGT	9	31	40
Total	26	54	80

Relative Risk (RR) = (a/r1)/(c/r2) =1.9 (95% CI; 0.91-4.13)[49]
NGT: Normal glucose-tolerant.

the NGTs, there were 25(62.5%) men and 15(37.5%) women, while there were 22(55%) men and 18(45%) women pre-diabetics. The mean age was 38.08±5.35 years, and 39.09±6.12 years respectively (Table-1).

The frequency of various cardiovascular risk factors was higher in pre-diabetics ($p<0.05$). Central obesity was the most prevalent risk factor (85%, CI: 75.74-96.06), followed by low HDL (82.5%, CI: 72.64-94.27), raised TG(67.5%, CI: 55.35-82.01), hypertension (57.5%, CI: 44.68-72.82), and FPG?100mg/dl (42.5%, CI: 29.68-57.82) (Table-2)

MeS was found in 23(57.5%) pre-diabetics compared to 9(22.5%) NGTs, according to ATP-III criterion (Figure). Calculated RR indicated that pre-diabetics were 1.9 times more prone to be suffering from MeS compared to NGTs (Table-3).

Discussion

MeS encompasses a myriad of seemingly unrelated disorders such as hypertension (HTN), hyperlipidaemia, atherosclerosis and inflammation.[20] The current consensus definition of MeS includes increased blood glucose level as one of its components. Others are abdominal obesity, elevated blood pressure (BP), elevated TG, and reduced HDL cholesterol (HDL-c). Any three of these five components or any two along with central obesity confer a diagnosis of the syndrome.[21] Pre-diabetes, being one of the components of MeS, shares the same underlying metabolic soil of insulin resistance, therefore, considerable overlap exists between the two conditions.[22]

In the present study a higher frequency of cardiovascular risk factors were found in pre-diabetics compared to NGT subjects. Increased waist circumference, which is a measure of central obesity, and low HDL-c were the more frequent risk factors, 68% and 69% respectively. Increased waist circumference indicates intra-abdominal accumulation of adipose tissues. These tissues release excess fatty acids and a variety of adipokines that seemingly elicit metabolic risk factors that predispose to CVD. Altered adipokines secretions are claimed to be the missing link that connects obesity with glucose dysregulation.[23,24] Increased frequency of waist circumference among pre-diabetics in the present study is in accordance with the growing epidemic of obesity in the country. The epidemiological survey of Urban Karachi, Pakistan, also revealed that 68% and 46% of women and men $\geq$25 years of age respectively were obese, according to Asian cut-off for waist circumference.

Beside central obesity, low level of HDL-c is a common feature encountered in MeS. Studies revealed that not only subjects with MeS but nearly 10-15% of healthy subjects also had HDL-c levels less than the 15th percentile for age and gender. According to different studies, nearly 65-83% patients with MeS had low HDL-c(25-28). A study from Pakistan also reported low HDL-clevels among all females with MeS.[29] In the present study, 86.7% females with pre-diabetes had low HDL-c level. A low level of HDL-c is not only a component trait of MeS, but it is also an independent risk factor for coronary artery disease (CAD).[30] In various prospective epidemiological studies, the relationship between low HDL-c and CAD has been found.[31-34] According to a study, 68.5% people in the community and 81% patients with type 2 diabetes had low HDL-c levels.[35] Our observation for low HDL-c in pre-diabetics is consistent with the aforementioned study even though we searched low HDL-c retrospectively in pre-diabetics as component of MeS.

Increased TG is another characteristic lipid disturbance seen in MeS. An increasing number of subjects in the present study, including those with pre-diabetes, had higher TG levels. In the present study, 50% participants had hypertriglyceridemia, and among them 34% had pre-diabetes. This is nearly in between the reported frequency

of hypertriglyceridaemia in a community-based and in a hospital-based study on type 2 diabetics where observed frequencies were 27.2% and 54% respectively.[35,36] Hypertriglyceridaemia not only has strong association with CVD, but it may also predict subsequent development of type 2 diabetes in subjects with IFG.[37,38] It is therefore suggested that subjects with hypertriglyceridaemia should be kept under surveillance to rule out type 2 diabetes. Hypertriglyceridaemia in pre-diabetes is due to insulin resistance, which leads to increased hepatic very low density lipoprotein (VLDL) production and defective removal of chylomicrons and chylomicron remnants that often reflects poor glycaemic control.[39]

More than half of people with pre-diabetes in the present study suffered from HTN (57.5%). This may be due to association of BP with obesity and insulin resistance. Though the exact mechanism of HTN in pre-diabetes is not understood, plausibly it may be caused by mechanisms that connect insulin resistance with HTN in MeS. Accumulating data indicated that insulin stimulates renal sodium re-absorption.[40-42] This anti-natriuretic effect is preserved, and may be increased in individuals with insulin resistance and this effect may play an important role in the development of HTN in MeS. Another proposed mechanism by which HTN is linked with central obesity and, thus, by pre-diabetes is over-activation of sympathetic nervous system and renin-angiotensin aldosterone system (RAAS) that consequently cause sodium retention and volume expansion, endothelial dysfunction and alteration in renal function.[43-45]

Based on the prevalence of individual components of MeS it is argued that fasting hyperglycaemia is the last component that developed in the natural course of this syndrome.[46] The present study contradicts this hypothesis. We explored the presence of MeS in some rather than in all pre-diabetic subjects. This suggests that the expression of various components of this syndrome do not follow any defined sequence.

Our study showed higher frequency of MeS in pre-diabetics according to ATP-III guidelines. This increased frequency of MeS in pre-diabetics was consistent with other studies originating from the region.[47,48] Possible reason for the higher rate of MeS in pre-diabetics may be the common metabolic thread of insulin resistance in both conditions.

Our study explored an increased rate of various cardiovascular risk factors among study population. It also discovered an increased frequency of MeS in pre-diabetic subjects by ATP-III criteria. The study thus underscores the importance of keeping an eye on various risk factors of MeS in pre-diabetics to avoid impending cardiovascular events.

Though the present study did attain statistical power, due to small sample size, a multi-centre prospective study on a larger population is needed to ascertain its external validity.

Conclusion

Pre-diabetes is generally regarded as a condition of glucose dysregulation leading to diabetes and not much importance is given to its other consequences. This observational study showed a high frequency and risk of MeS in pre-diabetics compared to NGT subjects. Thus pre-diabetes may not only be considered a condition of impending diabetes, but measures should also be taken to lessen the awaiting cardiovascular events.

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