Original Research Paper Diabetology

STUDY TO ASSESS THE IMPACT OF METABOLIC SYNDROME ON THE OCCURRENCE OF DIABETIC RETINOPATHY AMONGST PEOPLE WITH TYPES 2 DIABETES MELLITUS IN INDIA.

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ABSTRACT

Background: People with Type 2DM have high prevalence of metabolic syndrome (MetS). Diabetic retinopathy (DR) is an important cause of morbidity, but its association with MetS is not evaluated in Indian population.

Objectives: We aim to assess the prevalence of DR and MetS and also to evaluate the impact of MetS on the occurrence of DR in T2DM.

Methods: Data of 1037 subjects with T2DM on demographics, anthropometry, blood pressure, lipids, CVD and DR was obtained. MetS was defined by NCEPATPIII guidelines.Association of DR was evaluated with other variables including MetS and it's components. Statistical analysis was done.

Results: MetS prevalence was 86.98 % (female-91.3%, male-84.5%), DR was 8.2 % and CVD was 13.5%. Waist circumference contributed the most to MetS(91.69%) followed by HDL-C(71.73%) and TG(63.08%).Age and duration of diabetes showed positive association with DR. OR for people with MetS to develop DR was high in univariate and multivariate analysis, though statistically insignificant. T2DM with High Triglyceride are at higher risk of DR with OR 2.0943 [1.2044,3.6415] (p-0.0088).

Conclusion: Prevalence of MetS in Indian T2DM people is high. MetS increases, though insignificantly, while high Triglycerides increase the risk of DR significantly.

KEYWORDS : Type 2 Diabetes Mellitus, Metabolic Syndrome, and DiabeticRetinopathy.

Introduction:

Globally, the prevalence of diabetes mellitus is on rise with recent estimate from IDF[1] predicting 424.9 million people to have diabetes worldwide, which is expected to increase to 628.6 million in 2045. IDF Atlasstates that the maximum increase will be in South East Asia. China (114.4 millions) has maintained its top position in the list of countries with maximum number of diabetics and India ranks at second position with 72.9 million diabetics (Age 20-79 years).Appx 57.9% of people in India are still undiagnosed.[2]It has been projected that by 2045, India will surpass all other countries including China and will besheltering highest number (134.3 millions) of people with diabetes globally[2]. The metabolic syndrome (MetS) is a cluster of the risk factors, which include glucose intolerance, abdominal obesity, high triglyceride, low HDL-C and high blood pressure.[3-6] Subject with three or more than three risk factors is diagnosed with MetS. It is estimated that around 20-25 percent of the World's adult population have the MetS. People with MetS have a fivefold greater risk of developing type 2 diabetes.[7] Each year, 3.2 million people around the world die from complications associated with diabetes. The more components of the MetS that are evident, the higher is the cardiovascular mortality rate.[8] The cardiovascular complications of diabetes, which is also a leading cause of blindness, amputation and kidney failure, account for much of the social and financial burden of the disease. In addition to resulting in macrovascular complications, correlations between MetS and microvascular complications, including diabetic retinopathy (DR), have been shown in American and European subjects [9, 10]. There are very few data on the relationship between MetS and DR in East Asian countries, and they are controversial. Terauchi et al.[11] found that neither the presence of MetS, nor an increased waist circumference (WC) increased the risk of DR in Japanese patients with T2DM. In contrast, Shimajiriet al.[12] suggested that MetS was associated with DR in Japanese type 2 diabetic patients. Moreover, the risk of DR increased with the number of MetS components, rather than MetS per se, in a Chinese study [13]. However, none of these studies were population- based studies with large numbers of subjects. It is not yet known whether type 2 diabetes individuals with metabolic syndrome are at a high risk for ocular changes when compared with T2DM individuals without MetS. Hence, a tertiary care center-based study was undertaken to evaluate the association of Diabetic retinopathy in metabolic syndrome[14]. Thus, in the present population-based study, we assessed the association of MetS and its individual components with DR.

Material and Methods

This is a cross sectional observational study conducted in randomly selected 1037 people with known T2DM, of 30-70 years age, not addicted to alcohol, not on any statins therapy, without history of familial dyslipidemia attending a tertiary care center from central India during Jan 2015 to Dec 2015. Study had institutional ethics committee clearance and was performed in accordance to the tenets of the Helsinki declaration.Retina evaluation was done by Zeiss fundus camera[15].Exclusion criteria included cases having media haze (corneal, lenticular, and vitreous), which was hampering complete retina evaluation. Patients who had undergone laser or surgery for glaucoma, retinopathy or retinal detachment were excluded. Patients already on treatment for dry eye or glaucoma or with pre-existent ocular illness like Stevens Johnson syndrome and other retinal vascular disorders were also excluded. Patients who were not willing or with poor general condition were not enrolled. The duration of illness was defined as the duration from the time of the diagnosis of diabetes mellitus given by the participant until the time of the examination. Current age was defined as the age at the time of the examination. The data on demographic, anthropometry, blood pressure, lipid profile, CVD (based on ECG and past history of CVD) was obtained. Anthropometric measurements, glycosylated

hemoglobin A1c and lipids tests were carried out. Generalized obesity (BMI>23kg/M^2) and abdominal obesity (WC>90cm in men and >80 cm in women) were defined using WHO Asia Pacific guidelines.[16] Metabolic Syndrome was defined as per the National Cholesterol Education Program Adult Treatment Panel III (NCEPATP-III) guidelines.[17]The association of DR was evaluated with other variables including metabolic syndrome in terms of unadjusted OR. The ORs were adjusted by considering covariates like age, gender, duration of DM and HbA1c in the logistic regression model.

Statistical methods

The data on demographic, anthropometric and metabolic parameters were obtained and summarized in terms of frequencies and percentages. The parameters on continuous scale were expressed in terms of mean and standard deviation. The risk of diabetic retinopathy associated with different factors was obtained in terms of crude odds ratio. The adjusted odds ratios were obtained using multivariate logistic regression analysis. All the analyses were performed using SPSS version 20.0 (IBM Corp., Armonk USA) and statistical significance was evaluated at 5%.

Results

Out of 1037 subjects included in the study, 657 (63.36%) were males and 380 (36.64%) were females as shown in **Table 1**. Their mean age was 50.46 ± 9.901 years and the mean duration of diabetes was 5.69 ± 5.68 years. 78.8% of studied population had generalized obesity with BMI > 23kg/m^2. Overall, patients were obese as indicated by mean BMI of 26.56 ± 4.43 kg/m^2. Majority, i.e. 1001 (96.53%) cases had abnormal (high) WHR; while 83.67% had high waist circumference. 837 (80.71%) cases had HbA1c more than 7.0. and 973 (93.83%) cases had dyslipidemia. Metabolic syndrome (MetS) was found in 902 (86.98%) subjects. The prevalence of MetS in female (91.3%) was higher than in male subjects (84.5%). The prevalence of DR in studied group was 8.2 % and of CVD was 13.5%.The association between diabetic retinopathy (DR) with the levels of different risk factors were evaluated by using unadjusted (univariate analysis) and adjusted (multivariate analysis) odds ratio and shown in **Table 2**. DR was treated as dependent variable and age, gender, duration of DM, BMI, diet, and family history of DM, waist hip ratio, HbA1C, hemoglobin, hypothyroidism and metabolic syndrome as independent variables,univariate logistic regression analysis was performed. Independent variable age showed highly significant association with the disease as indicated by p-value <**0.0009**, where the odds of having DR was 2.3762 [95% CI; 1.4224, 3.9698] times higher in group with age > 50 years, as compared to those with <= 50 years of age. As compared to patients having duration of type 2 diabetes (T2DM) <= 10 years, the odds ratio was 5.3976 [95% CI; 3.2089, 9.0791] times higher in the patients whose duration of T2DM was > 10 years. The difference was statistically significant with p-value of **< 0.0001**. Further, the odds of DR in subjects with low hemoglobin was 2.3407 [95% CI; 1.3866, 3.9512] times significantly higher as compared to patients with normal haemoglobin (p-value=**0.0015**) which is also significant.Subjects with BMI > 23kg/m2 had the crude odds ratio of 0.3588 [95% CI: 0.2153, 0.5979]; which was significantly lower (p-value < 0.0001) than those with BMI <= 23 kg/m^{2}In multivariate **l**ogistic regression model, only those independent variables (risk factors) which were found significant in univariate analysis were included in the model. The adjusted odds ratio associated with subjects having age > 50 years was 1.4389 [95% CI ; 0.8226 2.5171]; times higher as compared to subjects with <= 50 years of age; which was statistically insignificant as indicated by p-value of **0.2022**. Subjects suffering with T2DM for more than 10 years showed adjusted odds ratio of 4.1662 [95% CI ; 2.3722 , 7.3165]; times higher as compared to those having <= 10 years duration of DM (p-value**< 0.0001**) which is highly significant.Subjects with BMI > 23kg/m2 had the adjusted odds ratio of 0.3842 [0.2164, 0.6821which was significantly lower (p-value = **0.0011**) than those with BMI <= 23which is significant in MLR model.Further, the adjusted odds ratio for patient group with low hemoglobin level was 1.4903 [0.8395, 2.6457]; times higher as compared to those having normal hemoglobin level, however the effect was statistically insignificant (p-value = 0.1731). The OR for people with metabolic syndrome to develop diabetic retinopathy was high in univariate as well as multivariate analysis, though it was statistically insignificant. Meaning thereby, even though the risk factor, MetS was insignificant in univariate model i.e1.1557 [0.5577, 2.3949]; (p-value=0.6971), it was retained in the multivariate model to understand its effect on diabetic retinopathy. The effect in multivariate model was found statistically insignificant (p-value = 0.1891) with adjusted odds ratio of 1.7155 [0.7666, 3.8391]; as compared to patients without MetS. High waist circumference is the highest contributing factor to MetSwith 91.69%, followed by HDL-C with 71.73% and TG with 63.08%. (Table1,2). **Table 3** shows the unadjusted and adjusted odds ratio associated with four factors of MetS with DR as dependent variable. The crude odds ratio associated with abnormal waist circumference was 0.7233 [0.3827, 1.3669];times higher in subjects as compared to those having it in normal range (p-value =0.3185). Subjects with abnormal triglycerides levels were found at higher risk of DR, which is statistically significant 1.8733 [1.0890, 3.2225];P value = **0.0233** but lipid parameter HDL-C is not significantly associated with DR in univariate analysis 0.6478 [0.3912, 1.0728]; P value ; 0.0916..Further, hypertension has not significantly associated with DR as indicated by crude odds ratio of 1.3100 [0.7964, 2.1547];P value = 0.2876**.** In the adjusted analysis, the factors found significant in univariate analysis were included in the multivariate analysis model. The adjusted odds ratio associated with abnormal waist circumference was 0.6442 [0.3354,1.2372] times higher as compare to normal waist circumference. The effect was statistically insignificant with p-value of 0.1866. The risk of DR associated among patients having highTGwas 2.0943 [1.2044,3.6415]; P value= **0.0088** and people with low HDL-cwas0.5967 [0.3566, 0.9985];P value = **0.0493;**both variable shown statistically significant in occurrence of DR.Meaning thereby, amongst various components of Mets in person with T2DM and the risk of DR was significantly high with abnormal (high) triglycerides and the risk is low with abnormal (low) HDL-C. While, waist and hypertension did not show any such association with DR.

Discussion:-

The prevalence of obesity and metabolic syndrome amongst people with type 2 diabetes is high. High prevalence of Mets in T2DM was reported by Suranaet al[18] in urban Indian population with type 2 diabetes (77.2%) and by Foucan et al [19] in Indian immigrants in the USA with diabetes (77%). This prevalence of MS in the South Indian population with diabetes is more than two-fold higher than the reported prevalence in the general urban Indian population[20] Using a similar definition as ours (IDF), Terauchi et al[11] and Bonadonna et al[21] reported the prevalence of MS to be 58.5% and 77.6% respectively, which was comparable to that observed in our study. Our study has shown the higher prevalence of generalized obesity including overweight (78.8%), central obesity (83.7%) and metabolic syndrome (86.98%). This is because all our studied subjects have known type 2 diabetes, with mean age of 50.457 ± 9.901years and the mean duration of diabetes of 5.69 ± 5.69 years. High Waist circumference and low HDL-cholesterol were found to be the major contributors towards this high prevalence of metabolic syndrome in our population.

The prevalence of DR in this studied group was 8.2 %. Previous study by Corrêaet al.[22] found the positive association of severity of diabetic retinopathy with risk factors such as duration of disease. Our study, has also observed statistically significant positive association of DR with duration of diabetes of more than 10 years. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), when controlling other risk factors, persons in the WESDR who were underweight at baseline were more likely to develop retinopathy as those of normal weight, consistent with our results [23]. Other studies have also reported associations of lower BMI with DR [24,25]. Our study have also shown that people with high BMI of more than 23kg/m^2 are at significantly lower risk of DR versus those with normal BMI.

Hypertension is the one of the most consistent risk factors of DR in many studies, although the details differ in studies. In the prospective Wisconsin study, systolic BP predicted progression of retinopathy in patients under 30 years of age at onset [26]. The United Kingdom Prospective Diabetes Study [27] reported that the occurrence of retinopathy was associated with higher systolic BP, consistent with other studies in subjects of various ethnicities.[28] Although, we have looked in to the association of systolic or diastolic blood pressure with DR, but hypertension per se as a component of MetS did not show an association with DR in our study.

A case-controlled study, with data obtained from 2551 Chinese participants found that the trend to develop DR with metabolic syndrome was significantly higher than that without metabolic syndrome. Additively these findings supports the claim that in addition to hyperglycemia and hypertension, the hypertriglyceridemia seen in several individuals in this population may very well play a significant role in the pathogenesis of DR in this population.[29] In our study we have found the statistically significant association with hypertriglyceridemia (TG > 150) as a components of Mets in occurrence of DR. But we found an unusual finding in relation to abnormal HDL <45 with occurrence of DR where multivariate analysis is suggestive of low occurrence of DR in abnormal group which is statistically significant in this study.

Conclusion:

People with type 2 DM have high prevalence of metabolic syndrome. The association of macroangiopathy with such cohort is well established however; the risk of macroangiopathy like retinopathy in Indian population is not very well established. Our study concludes, that the prevalence of diabetic retinopathy was lower than cardiovascular disease in people with T2DM with MetS. Factors like BMI of less than 23kg/m^2, longer duration of diabetes of more than 10years, higher age of more than 50years, hypertriglyceri demia and high HDL-Cholesterol seem to be possible risk factors for developing diabetic retinopathy in Indian people with T2DM having metabolic syndrome.

Table 1: Demographic profile of patients included in study

Characteristics	Levels	No.	%
Age (years)	*<= 50*	531	51.21
	> 50	506	48.79
Gender	*Female*	380	36.64
	Male	657	63.36
Duration of DM (years)	*<= 10*	854	82.35
	> 10	183	17.65
BMI (kg/m2)	*<= 23*	220	21.22
	> 23	817	78.78
Diet	*Veg*	458	44.17
	Mixed	579	55.83
Family history of DM	*No*	369	35.58
	Yes	668	64.42
WHR	*Normal*	1001	96.53
	Abnormal	36	3.47
HbA_1C (%)	≤ 7	200	19.29
	> 7	837	80.71
HB (g/dL)	*Normal*	803	77.43
	Abnormal	234	22.57
Dyslipidemia	*No*	64	6.17
	Yes	973	93.83
Hypertension	*No*	500	48.22
	Yes	537	51.78
Thyroid	*No*	911	87.85
	Yes	126	12.15
Metabolic Syndrome	*No*	135	13.02
	Yes	902	86.98

Table 2: Contribution of various components towards metabolic syndrome

Characteristics	Levels	Metabolic Syndrome present [No. (%)]
Waist circumference	*Normal*	73 (8.09)
	Abnormal	827 (91.69)
Triglycerides (mg/dL)	*<= 150*	329 (36.47)
	> 150	569 (63.08)
HDL-C (mg/dL)	*Normal*	248 (27.49)
	Abnormal	647 (71.73)
Hypertension	*No*	376 (41.69)
	Yes	526 (58.31)

Table 3: Unadjusted and adjusted odds ratio of diabetic retinopathy (micro-angiopathy) associated with the levels of different risk factors

Characteristics	Levels	Diabetic Retinopathy patients/Total (%)	Prevalence odds ratio [95% CI]; P-value	
			Unadjusted	Adjusted
Age (years)	<= 50	25/474 (5.27)	1	1
	> 50	43/368 (11.68)	2.3762 [1.4224 , 3.9698]; 0.0009	1.4389 [0.8226 2.5171]; 0.2022
Gender	Female	18/288 (6.25)	1	
	Male	50/554 (9.03)	1.4881 [0.8512 , 2.6017]; 0.1631	
Duration of DM (years)	<= 10	37/707 (5.23)	1	1
	> 10	31/135 (22.96)	5.3976 [3.2089 , 9.0791]; <0.0001	4.1662 [2.3722 , 7.3165]; <0.0001
BMI (kg/m2)	<= 23	29/192 (15.1)	1	1
	> 23	39/650 (6.00)	0.3588 [0.2153 , 0.5979]; 0.0001	0.3842 [0.2164 , 0.6821]; 0.0011
Diet	Veg	38/473 (8.03)	1	
	Mixed	30/369 (8.13)	1.013 [0.6149 , 1.6691]; 0.9594	
Family history of DM	No	21/295 (7.12)	1	
	Yes	47/547 (8.59)	1.2265 [0.7182 , 2.0944]; 0.4546	
Waist-Hip-Ratio	Normal	1/30 (3.33)	1	
	Abnormal	67/812 (8.25)	2.6081 [0.3498 , 19.4476]; 0.3497	
HbA_1C (%)	≤ 7	8/175 (4.57)	1	
	> 7	60/667 (9.00)	2.0634 [0.9676 , 4.4004]; 0.0608	
HB (g/dL) (Male)	Normal	43/663 (6.49)	1	1
	Abnormal	25/179 (13.97)	2.3407 [1.3866 , 3.9512]; 0.0015	1.4903 [0.8395 , 2.6457]; 0.1731
Thyroid	No	60/746 (8.04)	1	
	Yes	8/96 (8.33)	1.0394 [0.4811 , 2.2457]; 0.9217	
Metabolic syndrome	No	9/125 (7.2)	1	1

	Yes	59/717 (8.23)	1.1557 [0.5577 , 2.3949]; 0.6971	1.7155 [0.7666 , 3.8391]; 0.1891

Table 4:Diabetic retinopathy and Metabolic syndrome

Characteristics	Levels	DR patients/Total (%)	Prevalence odds ratio [95% CI]; P-value	
			Unadjusted	Adjusted
Waist circumference	*Normal*	13/126 (10.32)	1.00*	1.00*
	Abnormal	55/716 (7.68)	0.7233 [0.3827, 1.3669]; 0.3185	0.6442 [0.3354,1.2372] ; 0.1866
Triglycerides (mg/dL)	*<= 150*	20/358 (5.59)	1.00*	1.00*
	> 150	47/471 (9.98)	1.8733 [1.0890, 3.2225]; **0.0233**	2.0943 [1.2044,3.6415] ; **0.0088**
HDL-C (mg/dL)	*Normal*	30/290 (10.34)	1.00*	1.00*
	Abnormal	37/532 (6.95)	0.6478 [0.3912, 1.0728]; 0.0916	0.5967 [0.3566, 0.9985]; **0.0493**
Hypertension	*No*	31/436 (7.11)	1.00*	1.00*
	Yes	37/406 (9.11)	1.3100 [0.7964, 2.1547]; 0.2876	1.3004 [0.7823, 2.1616]; 0.3110

*Reference level

Acknowledgement: Dr Dhananjay Raje, Head Data Analysis Group, MDS Bio-Analytics for statistical support.

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