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RESEARCH ARTICLE

EVALUATION OF CLINICAL AND BIOCHEMICAL PROFILE IN TYPE 2 LEAN DIABETES MELLITUS"

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Abstract

Background and objectives: Various studies in India have documented Type 2 diabetes mellitus in low body weight/lean individuals. This present study was planned to assess the clinical, biochemical profile and complications in lean patients (BMI < 18.50 Kg/m^2) with T2DM.

Methodology: This single centre hospital based descriptive study was undertaken in the Department of General Medicine, Father Muller Medical College, Mangaluru, Karnataka. A total of 28 patients diagnosed to have T2DM with BMI <18.50 Kg/m^2 were enrolled. Patients were investigated for clinical, biochemical profile and complications.

Results: Equal number of patients (50% each) were males and females with male to female ratio of 1:1. The mean age was 48.61±7.31 and 50% of the patients were aged from 41 to 50 years. The mean duration of diabetes was being 3.55±2.39 years and treatment with oral hyperglycaemic agents was noted in 50% of the patients. Majority of the patients (75%) had higher waist circumference and presented with diabetic complications that is, diabetic neuropathy and nephropathy in 75% of the patients each, diabetic retinopathy in 67.86% of the patients while lipid abnormalities that is, 82.14% had hypercholesteolaemia and 89.29% had hypertriglyceridaemia.

Conclusion and interpretation: Lean T2DM poses phenotypically a separate type of T2DM which is characterized by younger age at presentation with central obesity, overt hyperglycaemia leading to lipid abnormalities resulting early onset of microvascular complications.

Introduction:-

Diabetes Mellitus (DM) is a group of metabolic disorders characterised by deficiency in insulin secretion or insulin effect, which causes hyperglycemia, disturbances of carbohydrates, fat and protein metabolism and a constellation of chronic complications.[1] Diabetes mellitus is most common non-communicable disorder in the world. Diabetes mellitus comprises of common metabolic disorder that share the same phenotype of hyperglycemia. Depending upon

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etiology of DM, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization by body, increased glucose production.[2,3]

Two broad categories of DM are designated viz. Type 1 DM (T1DM) and Type 2 DM (T2DM). Type 2 diabetes mellitus is the most prevalent form of diabetes seen worldwide. Type 1 is immune mediated and there is absolute deficiency of insulin. Type 2 is generally associated with obesity in western population.[2,3]

Obesity has always been thought to be a risk factor for diabetes and maximum numbers of diabetics are obese; however, some studies in India have reported that most of the diabetics in India have normal range of body mass index and have reported a high prevalence of lean diabetics.[4]

Epidemiological data over the past decades have shown that the pattern and profile of type 2 diabetes mellitus are very different in India compared to the West.[5] In Europe and America majority of type 2 diabetes are obese. In 1965 Tripathy and Kar highlighted that 27% of elderly diabetics were lean.[6] Following that various studies in India have reported a prevalence of low body weight/lean T2DM. The clinical and biochemical profile of these patients are different from classic T2DM.[7-10] These patients are neither related clinically or pathophysiologically to latent autoimmune diabetes of adults (LADA). In lean diabetes, the key defect is due to impaired pancreatic insulin secretion due to reduced beta cell mass. Some studies have highlighted the role of genetic factors, intrauterine insults, which predisposes to reduced beta cell mass.[11] however in India limited number of studies have been reported on lean diabetes and no such study was undertaken in our hospital settings. Hence, the present study was planned to assess the clinical, biochemical profile and complications in lean patients (BMI < 18.50 Kg/m^2) with T2DM.

Methodology:-

This single centre hospital based descriptive study was done in the department of General Medicine, of a tertiary care teaching hospital from Mangalore city of Karnataka State, India from June 2019 till December 2019. Assuming that, prevalence of T2DM in lean individuals as 3.50% based on the study by Mohan V. et al.[7] significance level at 5% and power at 80%, standard error of 5%, the minimum sample size was calculated as 55. However as the study duration was six months, the sample size was considered as half of 55 that is, 27.5≈28. Hence a total of 28 patients of either sex and any age, diagnosed to have T2DM based on ADA guidelines[12] with BMI <18.50 Kg/m^2 were enrolled. Patients suffering from diseases that impact BMI such as kidney diseases, liver diseases, malignancy, tuberculosis were excluded from the study. Prior to the commencement, the ethical clearance was obtained from the Institutional Ethics committee. Eligible patients were briefed about the nature of the study and a written informed consent was obtained prior to the enrolment.

Patients were interviewed and demographic data like gender and age were noted. Patients were also interviewed for the detailed clinical presentation. Also Diabetic history age at onset of T2DM and duration of disease were noted. A thorough general physical examination was conducted to assess Anthropometry followed by systemic examination. The clinical parameters including height, weight, BMI, waist circumference (WC), hip circumference (HC), waist to hip ratio (WHR), blood pressure (BP), ankle jerk were evaluated.

Further Blood samples for the estimation of fasting blood sugar (FBS), post prandial blood sugar (PPBS), glycosylated hemoglobin (HbA1c) and fasting lipids that is total cholesterol, Triglycerides and urine microalbuminuria. were drawn and sent for investigations.

Based on these parameters the complications of diabetes were evaluated. The microvascular complications like nephropathy, retinopathy, neuropathy were evaluated as it is more common among lean diabetic.

Statistical Analysis

The data obtained was coded and entered into Microsoft Excel spreadsheet. Data was analysed using IBM SPSS Statistics version 20.0 for Windows. For all the continuous variables, the results were either given in Mean±SD and/or median and interquartile range (IQR). The categorical data was expressed in terms of rates, ratios and percentages. The normality of the continuous data was assessed by Shapiro Wilk test.

Results:-

In thepresent study 50% of the patients each were males and females with male to female ratio of 1:1. The age ranged from 35 to 60 years. The mean and median age was noted as 48.61±7.31 and 49 (IQR 11.75) years. 50% of the patients were aged from 41 to 50 years (Table 1 and 2). With regard to diabetic history, the duration of diabetes ranged from 1 to 12 years with mean and median duration being 3.55±2.39 and 3.00 (IQR 3.00) years while maximum patients (67.86%) reported duration of diabetes as less than five years. Majority of the patients reported family history of diabetes mellitus (71.43%). Treatment with oral hyperglycaemic agents was noted in 50% of the patients and 21.43% were on insulin while both the treatments were noted in 3.57% of the patients (Table 3). Majority of the patients (75%) had higher waist circumference (Table 4).

Majority of the patients had diabetic complications with diabetic neuropathy and nephropathy being common (75% each) diabetic retinopathy was noted in 67.86% of the patients (Graph 1). Lipid abnormalities viz. hypercholesteolaemia was present in 82.14% of the patients and hypertriglyceridaemia was noted in 89.29% of the patients (Graph 2).

Discussion:-

Type 2 diabetes mellitus accounts for the 85% of the people with diabetes worldwide. Development of the disease is summation of environmental insult to genetically predetermined metabolic disruption. Type 2 diabetes mellitus is characterized by the pathophysiological abnormalities, impaired insulin secretion, peripheral insulin resistance and excessive hepatic glucose production. Obesity visceral or central is very common in type 2 diabetes mellitus.[2,3] In the present study based on the selection criteria, the BMI of the selected patients ranged from 16.90 to 18.40 the mean and median BMI was 18.01±0.36 and 18.10 (IQR 0.40) Kg/m^2. Patients were fairly young as the mean age of the patients was (48.61±7.31 years) and based on the duration of diabetes it was evident the diagnosis of T2DM was at young age. These observations were consistent with the previous report[3] which state that, low body weight type 2 diabetes mellitus, phenotypically a separate type of T2DM which is of interest in tropical region. Characterized by its typical age presentation. The young of patients with T2DM is very important cause of concern as they are high risk of complications of diabetes mellitus at younger age clubbed with malnutrition may yield results worst outcomes leading to high morbidity and mortality. The mean BMI noted in the present study sharply corroborated with the findings reported by Barma PD et al.[13] (2011) from Imphal, Manipur India where authors reported mean BMI as 18.70±0.20 Kg/m^2 while the comparable with recent reports of Srivastav M. et al.[3] (2020) from Meerut, India who reported 17.91 Kg/m^2 as the mean BMI of type 2 DM with low BMI group.

With regard to glycaemic profile, the FBS levels ranged from 180 to 360 mg/dL. The mean and median FBS levels were 258.46 ±54.66 and 275.00 (IQR 100) mg/dL. Similarly the PPBS levels ranged from 220 to 4220 with mean and median value being 322.43±54.04 and 310.00 (IQR 97.50) mg/dL. Finally the most important measure of blood sugar levels for previous three months that is HbA1c ranged from 8.00 to 13.10 percent with mean and median values being 10.43±1.28 and 10.10 (IQR 2.43) percent suggesting poor control over the diabetes although majority of them were on treatment (75%). However, the exact reason for over hyperglycaemia in the present study may due to the poor treatment compliance but that was not considered in the present study which was an important limitation of the study. However the overt hyperglycaemia noted in the present study prompts, lean T2DM to be a phenotypically separate type of T2DM. The observations pertaining to overt hyperglycaemia in the present study contradict the observations repotrterd by Barma PD et al.[13] (2011) from Imphal, Manipur India who reported better glycaemic control in patients with lean T2DM (HbA1c 7.7 ± 2.2%).

BMI and WC are indices of general and central (visceral) obesity respectively, and are an important first step in determining the level and distribution of obesity.[14] The cutoff values of WC for overweight and obesity vary widely over different geographic regions of the world. Furthermore, for WC, 'underweight' and 'normal weight' has not been properly defined as there has been no mention in the literature of the lower limit of normal WC.[15] The second important observations of the present study was central obesity. Although, all the patients in the present study were lean they majority of them presented with central obesity (75%) with mean WC being 84.76±8.09 cms. Hence, although, oobesity has been reported to be associated with insulin resistance, dyslipidemia, and hypertension, thus increasing the risk for cardiovascular disease (CVD), regarding body fat distribution, abdominal visceral fat has been more strongly associated with cardiovascular risks than body mass index (BMI), waist circumference, and abdominal subcutaneous fat.Therefore, evaluation of visceral fat accumulation is important to reduce cardio-metabolic burdens. These observations suggest the importance of direct evaluation of visceral and subcutaneous fat

accumulation for the management of T2DM in lean individuals. Therefore it is possible that increased visceral fat with decreased subcutaneous fat accumulation is positively associated with atherosclerosis leading to early occurrence of microvascular complications.[16]

In the present study based on preliminary evaluation and investigations, majority of the patients had diabetic neuropathy (75%), nephropathy (75%) and retinopathy (67.86%). These observations were consistent with the observations reported by Barma PD et al.[13] (2011) from Imphal, Manipur India where authors noted a high prevalence of microvascular complications that is, peripheral neuropathy in 70%, retinopathy in 25% and nephropathy 13% of the patients. Mukhyaparna et al.[17] (2004) reported 35%, 6.6% and 27% prevalence of neuropathy, nephropathy and retinopathy, respectively which was low compared to the present study. Sinharoy et al.[18] (2008) reported the prevalence of neuropathy to be 32%, nephropathy 28% and retinopathy 28%. However in the present study unlike the observations from the other studies,[3,13] the frequency of microvascular complications was very high which can be explained by poor glycaemic control as well as central obesity among the patients in the present study while the latter study reported better glycemic profile of their cases for example, Barma PD et al.[13] (2011) reported better glycemic profile in their cases and narrower waist (75.1cm ± 5.1) and hip circumferences (79.5 cm ± 5.7), with waist-hip ratio (0.9 ± 0.2) in their study.

Another important finding needs to be discussed is diabetic dyslipidemia. Diabetic dyslipidemia is a complex cluster of potentially atherogenic lipid and lipoprotein abnormalities involving both quantitative and qualitative changes. Increased plasma triglycerides, low concentration of high density lipoproteins cholesterol (HDL-C), preponderance of small, dense low density lipoproteins (LDL) and excessive postprandial lipemia are its main components. As it has been recently shown, the abnormalities in lipid metabolism are not isolated but rather closely linked to each other.[19] The findings of the present study were strongly in agreement with the findings stated above as in the present study as the total cholesterol levels ranged from 160 to 320 mg/dL with mean and median values being 262.82±47.74 and 280 (IQR 80.00) mg/dL. Similarly the triglyceride levels ranged from 94 to 220 with mean and median values being 168.14±30.99 and 165 (IQR 50.00) mg/dL. Also majority of the patients had hypertriglyceridaemia (89.29%) and hypercholesterolaemia (82.14%) suggesting that almost every individual had lipid abnormalities. Despite methodological differences, the lipid abnormalities noted in in the present study were partly agreement with the several studies in the literature. For example, Sinharoy et al.[18] (2008) showed higher level of triglycerides but lower prevalence of hypercholesterolaemia and in low body weight T2 DM. Barma PD et al.[13] (2011) from Imphal, Manipur India observed that the lipid profile was not much deranged. Das et al.[20] (1995) revealed the conspicuous absence of hyperlipidemia in their patients. HDL levels were high among lean diabetic patients. High HDL has been postulated to be due excess hepatic lipase activity.[21] Earlier, Ikeda et al.[22] (1991)showed no major difference irrespective of glycemic status in lean type 2 diabetics (BMI). Again these disparities may be explained by the methodological differences, varied sample size, comparative study design and finally overt hyperglycaemic profile and central obesity of the patients in the present study.

Finally to conclude the results of this small study based on preliminary clinical and biochemical data demonstrated that, lean T2DM poses phenotypically a separate type of T2DM which is characterized by younger age at presentation with central obesity, overt hyperglycaemia leading to lipid abnormalities resulting early onset of microvascular complications. Hence these patients require timely diagnosis and close monitoring for glycaemic control with close monitoring for lipid derangements and development of microvascular complications. However, these findings require further verifications due to potential limitations of the study.

The strength of the study was that the careful selection of the patients that is patients with BMI < 18.5 Kg/m^2 after excluding kidney diseases, liver diseases, malignancy and tuberculosis were enrolled patients which makes the results of this study more reliable and valid and reflect the true clinical and biochemical profile of patients with T2DM. At the same time, this study had several limitations that is, the findings in this study were based on the data having relatively smaller sample size from a single centre and due to the smaller subset of patients subgroup analysis with respect to age and gender was not be done and finally long term outcome was not considered which was beyond the scope of this study. Although the patients were screened for the diseases which impact BMI the disease status was not confirmed through investigations. Also the complications were ascertained based on preliminary examination findings and history of other medical conditions was not taken into the consideration for example the diagnosis of nephropathy was not confirmed by estimation of serum creatinine/eGFR. Hence multicentric studies involving large sample size with age and sex analysis with detailed workup on complications, considering the long term outcomes may provide the true burden of lean T2DM.

Table 1:- Clinical profile of the patients.

Parameters	Mean (n28)		Median	IQR	Range	
	Mean	SD			Min	Max
Age (Years)	48.61	7.31	49.00	11.75	35.00	60.00
age of onset of diabetes(years)	46.07	6.71	45.50	10.00	35.00	59.00
duration of diabetes(years)/new onset	3.55	2.39	3.00	3.00	1.00	12.00
height in m2	3.01	0.46	3.06	0.80	2.25	3.72
weight in kgs	54.21	8.65	52.50	16.00	40.00	69.00
BMI(kg/m^2)	18.01	0.36	18.10	0.40	16.90	18.40
waist circumference(cm)	77.21	8.09	80.00	15.75	60.00	88.00
hip circumference(cm)	87.46	9.29	93.00	18.00	70.00	98.00
fasting blood sugar(mg/dL)	258.46	54.66	275.00	100.00	180.00	360.00
Post prandial blood sugar(mg/dL)	322.43	54.04	310.00	97.50	220.00	420.00
HbA1c(%)	10.43	1.28	10.10	2.43	8.00	13.10
total cholesterol(ng/dL)	262.82	47.74	280.00	80.00	160.00	320.00
triglycerides(mg/dL)	168.14	30.99	165.00	50.00	94.00	220.00
urine microalbumin(mg/L)	25.64	8.66	23.10	8.00	14.00	50.10

Table 2:-Distribution of patients according to the demographic data.

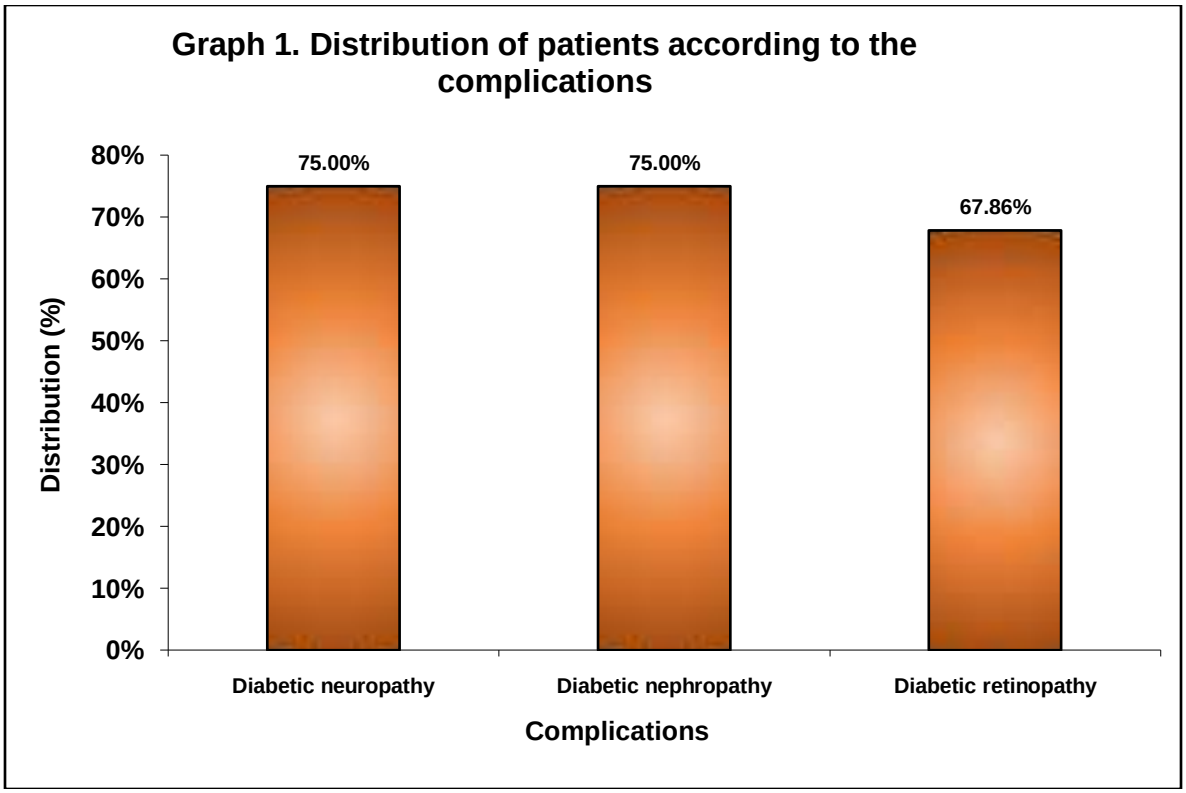
Parameters	Findings	Distribution (n=28)	
		Number	Percentage
Sex	Male	14	50.00
	Female	14	50.00
	Total	**28**	**100.00**
Age (Years)	31 to 40	5	17.86
	41 to 50	14	50.00
	51 to 60	9	32.14
	Total	**28**	**100.00**

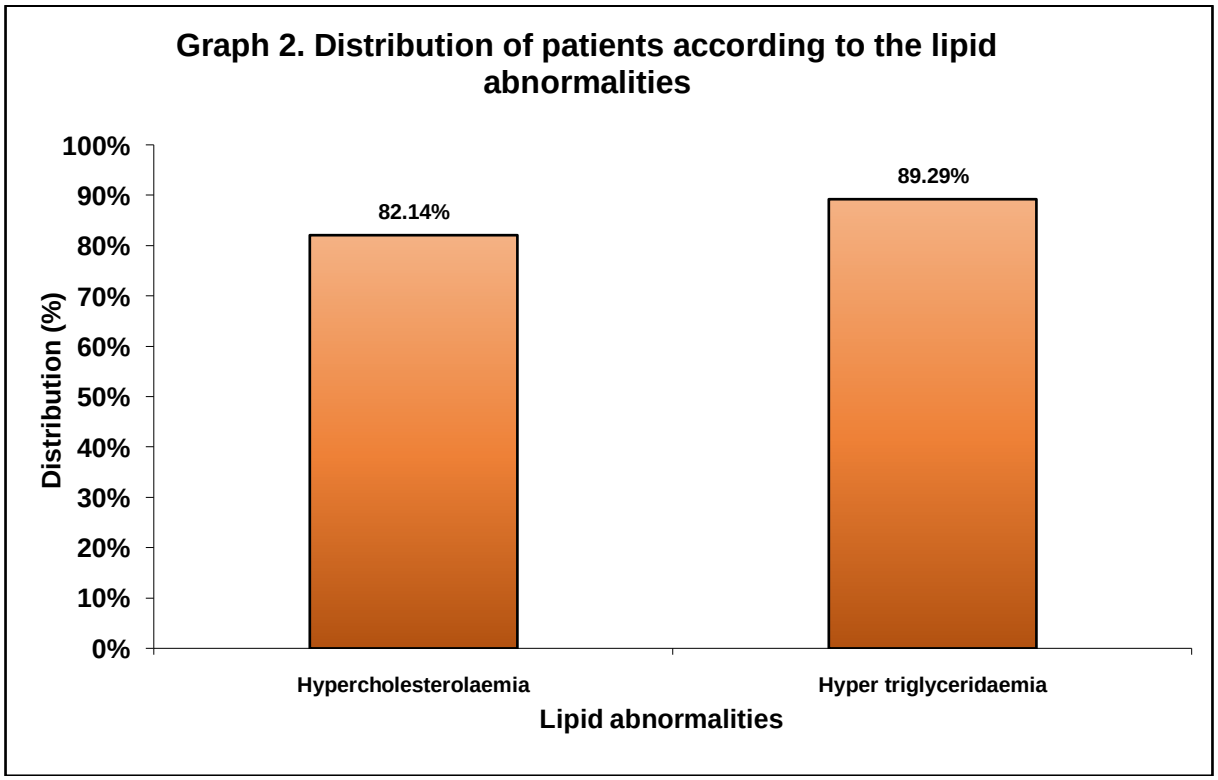
Table 3:- Distribution of patients according to the diabetic history.

		Distribution (n=28)	
		Number	Percentage
Duration of DM (Years)	Newly detected	8	28.57
	5 or less	19	67.86
	>10	1	3.57
	Total	**28**	**100.00**
Family history	Present	20	71.43
	Absent	8	28.57
	Total	**28**	**100.00**
Treatment	Insulin	6	21.43
	Insulin with OHA	1	3.57
	OHA	14	50.00
	Not on treatment	7	25.00
	Total	**28**	**100.00**

Table 4:-Distribution of patients according to the waist circumference.

Waist circumference	Distribution (n=28)	
	Number	Percentage
Raised	7	25.00
Normal	21	75.00
Total	**28**	**100.00**


Graph 1. Distribution of patients according to the complications
80%
70%
60%
50%
40%
30%
20%
10%
0%
Distribution (%)
75.00%
75.00%
67.86%
Diabetic neuropathy
Diabetic nephropathy
Diabetic retinopathy
Complications


Graph 2. Distribution of patients according to the lipid abnormalities
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Distribution (%)
82.14%
89.29%
Hypercholesterolaemia
Hyper triglyceridaemia
Lipid abnormalities

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