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Sedentary life style, Obesity, Hyperlipidemia and Diabetes Mellitus.

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ABSTRACT

Diabetes mellitus (DM) and obesity are interrelated disorder that is often associated with cardiovascular events due to hyperlipidemia. The incidence of obesity and DM are in alarming upward trend in Indian population and 80% Diabetics are overweight and obese. This report seeks to determine the co-morbid association of obesity and Diabetes mellitus on lipid parameters. Sedentary Non-obese and obese diabetic patients based on their BMI were evaluated for lipid abnormalities. The study subjects had statistically significant lipid abnormalities as compared to controls. Elevated T-CHOL(96%), TG(100%), LDL-C(96%), VLDL-C(72%) and reduced HDL-C (92%) were noted in the obese diabetics as compared to T-CHOL(42%), TG(98%), LDL-C(44%), VLDL-C(48%), and reduced HDL-C (30%) in the Non obese diabetes and controls. The study strongly indicates the co-morbid effect of obesity and sedentary life style on lipid parameters in Diabetic patients. "Diabetes lipidus" This morbid association has to be treated together

Keywords: BMI, β cells, Diabetes-Lipidus, Lipid Triad, Obesity.

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INTRODUCTION

The world is witnessing Obesity pandemic, the burning Global problem. It is a complex preventable nutritional disorder of 21 st century [1] raising concern because of its potential impact on health. WHO has recognized obesity as the global epidemic. Globally one billion people are overweight and over 30 million of them are obese with BMI > 30 [2]. An average increase in BMI by 5 kg/m² is associated with overall mortality by 30% [3]. India is facing obesity epidemic [4] morbid obesity affecting more than 5% of our population [5] which is an alarming signal. Obesity, measured in terms of BMI, reflects multigenic predisposition, endocrine imbalance implicated by derangement of energy homeostasis due to imbalance between energy intake and energy output. Obesity is known to induce insulin resistance [6-8] and strongly associated with dyslipidemia [9,10]. Insulin resistance is associated with diabetes mellitus and decreased levels of lipoprotein lipase resulting in hypertriglyceridemia, increased levels of VLDL-C and LDL-C levels leading to Lipid Triad a strong predictor of endothelial dysfunction and intima-media thickness [11] and cardiovascular diseases a leading cause of morbidity and mortality worldwide. Lipid Triad is increase in Triglycerides, Total Cholesterol and decrease in High Density Lipoprotein levels. Various studies in diverse and ethnic groups have shown strong association between obesity and Lipid Triad. There are strong links between Obesity, Diabetes, Thrombosis, Vascular changes and Atherosclerosis [10-18].

DM is the metabolic disorder characterized by hyperglycemia and dyslipidemia due to defect in insulin secretion/action/resistance affecting carbohydrate, protein and lipid metabolism. As per the WHO report there are 285 million people with DM and has predicted the prevalence to increase by 438 million by 2030, out of which 51 millions live in Asia. Out of 51 millions in Asia, 60% live in India [19]. India is leading the world with the largest DM patients, earning the dubious distinction of being termed as Diabetic capital of the world, projected to increase 80 million by 2030 [20]. India is facing both obesity and diabetic epidemic. DM, rare before 20th century [1] is no longer the disease of rich as once known [21] as it is dramatically spreading in all over the world from the last 50 years. It is directly associated to globalization and urbanization [22] with increase in BMI [23] due to change in life style patterns and dietary habits. Prevalence of Diabetes mellitus was 3 times higher in obese individuals with light physical activity [24]. The incidence of obesity and DM are in alarming upward trend ranging from 55-85% [5] with 3-4 fold increase in many regions of India [25] and 80% Diabetics are overweight and obese [5, 13, 18]. Studies have shown that Indians are inherently more insulin resistant with genetic predisposition [26] as compared to other world population and develop Diabetes at a younger age [27], Obesity and Diabetes mellitus, the co-morbid association is the most prevalent and preventable disorder with interrelated nutritional, hormonal, vascular and neuropathic components. Prevention and management of obesity is like preserving β cell mass and its functional integrity as obesity leads to proliferation of β cells to meet the extra demand [28] Obesity leads to Insulin resistance [6-8], insulin resistance leads to hyperglycemia. Chronic hyperglycemia affects the carbohydrate and lipid metabolism at large, leading to Gluco toxicity and dyslipidemia (Lipotoxicity), so the appropriate term is "Diabetes lipidus" and they have to be treated together [29].

Chronic Glucotoxicity and lipotoxicity are toxic to pancreas [30] which further affects the insulin resistance a vicious cycle as shown in the figure(fig 1)

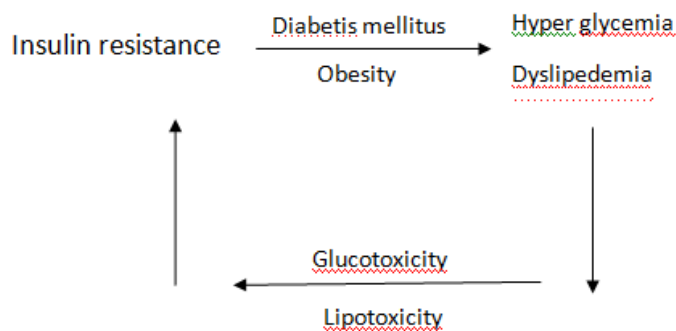


Fig 1: Diabetes Lipidus

Metabolic syndrome and cardio metabolic risk factors have been clearly shown to be closely related to Diabetes and obesity [7, 9, and 31] eventually the potential risk factors for the incidence of CVD and CHD [9, 13-17]. Several studies have identified links between obesity and Diabetes mellitus involving proinflammatory cytokine release from adiposites, which affects β cell function [32, 33] pro-atherogenic risk profile in obese women [34]. Visceral fat being more metabolically active, rich in β adrenergic supply results in excess release of free fatty acids. Free fatty acids not only result in impaired insulin action on target tissues including muscle but also on pancreas by impairing insulin secretion by β cells. Increased insulin resistance progressively affects the β cell function resulting in inexorable β cell exhaustion [35]. Increased influx of fatty acids with increase β oxidation results in increased levels of triglycerides and cholesterol. Hyper triglyceridemia predisposes to acute pancreatitis [36]. Insufficiency of Insulin decreases lipoprotein lipase in adipose tissue and muscle resulting in decreased VLDL-C breakdown, which further adds on to the increased levels of triglycerides, VLDL-C and LDL-C [37]. Elevated Hepatic lipase catabolise HDL-C resulting in decreased levels of HDL-C, a predisposer to atherosclerosis.

Increased VLDL-C and LDL-C levels leads to unregulated LDL-C uptake by the scavenging receptors leading to plaque formation [38] more vulnerable to rupture among diabetic patients, the root cause for micro vascular and macro vascular complications. Assessment of Plasma cholesterol, TG and HDL-C levels in patients are clinically important as they are the major treatable risk factors for CVD.

Total cholesterol appears to be low in Indian population due to low HDL-C values [39]. Ratio of atherogenic to atherogenic protective factors, T.CHOL/HDL-C, TG/HDL-C, and LD-C/HDL-C are better indices and predictors of CVD [12, 39, and 40]. The optimum ratio for TC/HDL-C is 3, If the ratio is more than 5 it is a predictor of CVD, which increases the risk of MI by 49%.

If LDL-C/HDL-C ratio is more than 2.5 it is deleterious with 75% increased risk of MI [43]. Increased ratios were observed in 25% of industrial and 32% of urban female population of India [39].

The Present study intends to find the effect of co-morbid association of Diabetes and obesity on atherogenic factors.

MATERIALS AND METHODS

The study was carried out in the Department of clinical Biochemistry, Bangalore Medical College. Controls were chosen from the subjects attending the outpatient department of Victoria hospital for their routine checkup diabetic patients were selected from OPD and diabetic clinics of Victoria hospital and Lady Curzon hospitals attached to Bangalore Medical College. They were categorized as Obese and Non obese Diabetic patients depending on their BMI.

Protocol of the study was to study and compare the linear relationship of obesity and dyslipidemia in Diabetic Obese persons to Diabetic Non obese persons. The protocol was based on inclusion and exclusion criteria and was approved by local ethical committee. Written consents were obtained from both cases and controls.

Inclusion criteria

Controls:

N=25 age and sex matched healthy individuals with normal weight (BMI 20-25) without clinical evidence of any disease were involved in the study with their consent.

Cases

- Diabetic patients with duration of 1-5 years under medication were divided into two groups based on their BMI.
- 50 Non obese diabetic persons with BMI 20-25.
- 50 Obese diabetic persons with BMI >30.

Exclusion criteria

Diabetic patients with

- Hypertension, thyroid and liver disorders.
 - Infection and inflammation.
 - Overt complications of diabetic neuropathy, nephropathy and retinopathy
 - On drugs like diuretics and lipid lowering medications.
 - On anti obesity and on oral contraceptives (women).
- Were excluded from the study.

Both cases and controls were Non alcoholics and Non smokers.

Weight and height were recorded for all subjects. BMI was calculated by using the formula:

$$\text{BMI} = \frac{\text{Weight in Kgs}}{\text{Height in meter}^2}$$

Diabetic Patients with BMI between 20-25 were grouped under Non obese group.

Diabetic Patients with BMI >30 were grouped under obese group.

Controls were age and sex matched with BMI 20-25, without any disease.

Written consent was taken from both cases and controls. Detailed history of all subjects regarding their socio economic status, dietary habits, family history for metabolic disorders, their physical activity were taken. Patients were on sedentary life style with overeating tendencies.

Venous blood was collected on overnight fasting at morning 9AM. Blood samples were allowed to clot and serum was separated by centrifugation and used for estimation of fasting blood sugar and lipid parameters. Blood for postprandial sugar levels were collected after two hours as per WHO protocol giving 75 gms of glucose.

Baseline evaluation included determination of urea, bilirubin and creatinine levels to rule out metabolic disease and organ dysfunction. Fasting and postprandial Blood sugar, Triglycerides, cholesterol, HDL-C, LDL-C and VLDL-C levels were assayed in both cases and controls on the same day of blood collection in auto analyzer-ERBA 600 by using standard kits from Boehringer Mannheim.

Analysis of variance (ANOVA) has been used to find the significance of study parameters

RESULTS

A case control study comprising of 25 normal weight ,Non-diabetic controls (BMI 20-25) without any etiology of disease, 50 Non obese diabetic patients(BMI 20-25) and 50 Obese Diabetic patients (BMI>30) were undertaken to study the effect of obesity and Diabetes mellitus on Lipid parameters.

The mean age of controls was 43.88±14.46 as compared to 51.34±7.19 and 48.26±6.25 in non obese diabetics and obese diabetics respectively.(Table 1)

Samples are gender matched with 64% was males and 36% were female under the control group. The study groups comprised of 70% males and 30% females in Non obese patients and 76% males and 24% females under obese diabetics(Table2).

The blood sugar levels in controls were within normal levels to support the Nondiabetic population as compared to increased blood sugar levels in both obese and non obese diabetic patients. Fasting blood sugar and Post prandial blood sugar levels in Non obese Diabetics was 160.70 ± 32.14 and 221.46 ± 39.33 as compared to 169.80 ± 20.82 and 246.38 ± 27.81 in obese diabetics with statistical significance of $p < 0.001$.(Table3)

Table 1: Age distribution of patients and controls studied

Age in years	Normal		Non obese DM		Obese DM	
	No	%	No	%	No	%
<40	12	60.0	4	4.0	5	14.0
41-50	4	16.0	24	48.0	25	50.0
51-60	6	24.0	18	36.0	18	36.0
>60	3	6.0	3	0.0	3	0.0
Total	25	100.0	50	100.0	50	100.0
Mean \pm SD	43.88 \pm 14.46		51.34 \pm 7.19		48.26 \pm 6.25	

$P < 0.001^{**}$

Table 2: Gender distribution of patients and controls studied

Gender	Normal		Non obese DM		Obese DM	
	No	%	No	%	No	%
Male	16	64.0	35	70.0	38	76.0
Female	9	36.0	15	30.0	12	24.0
Total	25	100.0	50	100.0	50	100.0

Samples are gender matched with $P = 0.506$

Table 3: Comparison of sugar parameters in two groups of patients and controls studied

	Normal	Non obese DM	Obese DM	P value
FBS (mg/dl)	90.40 \pm 16.81 (71-140)	160.70 \pm 32.14 (102-225)	169.80 \pm 20.82 (129-214)	<0.001**
PPBS mg/dl	117.56 \pm 8.62	221.46 \pm 39.33 (168-300)	246.38 \pm 27.81 (198-310)	<0.001**

Statistical significance of $p < 0.001$

Table 4, shows the BMI of case and controls. Mean value of BMI in Obese diabetic Patients was 31.76 ± 1.09 as compared to 21.83 ± 2.04 and 22.8 ± 2.61 in Non obese diabetic patients and controls.

Table 4: Comparison of BMI(kg/m²) in two groups of patients and controls studied

	Normal	Non obese DM	Obese DM	P value
BMI (kg/m ²)	22.8 \pm 2.61	21.83 \pm 2.04	31.76 \pm 1.09	<0.001**

Statistical significance of $p < 0.001$

Table 5 shows the mean values of lipid parameters and the atherogenic indices. The Total cholesterol level was 184.12 ± 45.21 in controls and in Non obese diabetics and obese Diabetics the levels were 226.24 ± 32.88 and 276.78 ± 30.06 respectively. The cholesterol levels were significantly increased ($P < 0.001$) in both Non obese and obese diabetics with large effect size. ($d = 2.56$).

Table 5: Comparison of lipid parameters in two groups of patients and controls studied

Lipid parameters	Normal	Non obese DM	Obese DM	P value	Effect size	
					Normal vs. Non-Obese DM	Normal vs. Obese DM
Cholesterol mg/dl	184.12±45.21	226.24±32.88	276.78±30.06	<0.001**	1.11(L)	2.56(VL)
Triglyceride mg/dl	144.91±47.86	198.08±26.18	235.10±53.67	<0.001**	1.51(VL)	1.72(VL)
HDL mg/dl	41.72±9.54	36.06±3.74	30.70±4.29	<0.001**	0.89(L)	1.68(VL)
LDL mg/dl	108.48±34.44	150.26±33.28	199.44±29.55	<0.001**	3.38(VL)	2.82(VL)
VLDL mg/dl	21.91±3.59	39.54±5.21	46.87±10.84	<0.001**	4.64(VL)	7.23(VL)
Chol/HDL	4.62±1.72	6.33±1.04	9.22±1.73	<0.001**	1.30(VL)	2.64(VL)
TGL/HDL	5.30±6.26	5.56±1.04	7.80±2.08	<0.001**	0.06(N)	0.53(M)
LDL/HDL	2.69±1.04	4.21±0.99	6.67±1.52	<0.001**	1.49(VL)	3.03(VL)

Statistical significance of $p < 0.001$

Triglycerides in controls were 144.91 ± 47.8 and the mean values in Non obese diabetics and in obese Diabetics were 198.08 ± 26.18 and 235.10 ± 53.67 respectively. Triglyceride levels were clinically and significantly elevated in obese diabetics with large effect $d = 1.72$ with significance of $P < 0.001$.

HDL-C levels were significantly decreased in both Non obese (36.06 ± 3.74) and obese diabetics (30.70 ± 4.29) as compared with the controls (41.72 ± 9.54).with a large effect of 1.68. showing significance of $P < 0.001$. VLDL-C levels in controls were 21.91 ± 3.59 . VLDL-C in Non obese diabetics was 39.54 ± 5.21 and in obese diabetics 46.87 ± 10.84 . VLDL-C levels were statistically elevated in Non obese diabetic and obese diabetics with significance of $P < 0.001$ as compared to controls.

LDL-C levels were elevated in obese diabetics with very large effect of 2.82 with significance of $P < 0.001$. LDL-C in controls was 108.4 ± 34.44 as compared to 150.26 ± 33.28 and 199.44 ± 29.55 in Non obese diabetics and in obese diabetics respectively.

Ratio of Atherogenic to Non Atherogenic factors shows an increased trend in atherogenic indices in obese diabetics as compared to Non obese diabetics and normals.

T .CHOL/ HDL-C ratio was 4.62 ± 1.72 in normals as compared to 6.33 ± 1.04 and 9.22 ± 1.73 in nonobese and obese diabetics respectively with effect size of 2.64 in obese diabetics as compared to normals.

Ratio of TG/HDL-C in normals was 5.30 ± 6.26 as compared to 5.56 ± 1.04 and 7.80 ± 2.08 in Non obese and obese diabetics respectively with an effect size of 0.53 in obese diabetics as compared with normals.

Ratio of LDL-C/HDL-C in normals was 2.69 ± 1.04 , and the ratio in Non obese and obese diabetics was 4.21 ± 0.99 and 6.67 ± 1.52 respectively with very large effect size of 3.03 in obese diabetics as compared with normals.

Table 6, shows the comparison of percentage and OR values in the parameters of lipid profile. About 42% of Non obese Diabetic patients had elevated cholesterol as compared to 96% in obese Diabetic patients indicates that the patient with obesity are more likely to have elevated total cholesterol as compared to Non obese Diabetics and controls.

Diabetic patients with obesity (100%) had elevated triglyceride levels as compared to Non obese diabetics(98 %) with OR of 62.36.

Patients in obese diabetics had 92% decreases in HDL-C as compared to 30% in Non obese diabetics. Obese diabetics had 96% elevated LDL(>150 mgs/dl) when compared to 44 % in Non Obese diabetics and 12% in controls. Patients with obesity are more likely to have elevated VLDL(72%) as compared to non obese diabetics(48%).

Table 6: Comparison of percentage and OR in lipid parameters in two groups of patients and controls studied.

Lipid parameters	Normal (n=25)	Non obese DM (n=50)	Obese DM (n=50)	P value	OR(95%CI)	
					Normal vs. Non-Obese DM	Normal vs. Obese DM
1.Cholesterol >230mg/dl	2(8.0%)	21(42.0%)	48(96.0%)	<0.001**	8.32 (1.77-39.24)	276.0 (36.96-2084)
2.Triglyceride >150 mg/dl	11(44.0%)	49(98.0%)	50(100.0%)	<0.001**	62.363 (7.39-525.59)	62.36 (7.39-525.59)
3.HDL <35 mg/dl	7(28.0%)	15(30.0%)	41(92.0%)	<0.001**	1.10 (0.38-3.18)	11.74 (3.77-36.35)
4.LDL >150 mg/dl	3(12.0%)	22(44.0%)	48(96.0%)	<0.001**	6.76 (1.79-25.53)	176.0 (27.42-1129.0)
5.VLDL >40 mg/dl	5(20.0%)	24(48.0%)	36(72.0%)	<0.001**	96.0 (17.17-536.54)	10.28 (3.23-32.75)

statistical significance of $p < 0.001$

DISCUSSION

Cardiovascular disease is the major cause of morbidity and mortality in obesity and Diabetes mellitus. Among the established risk factors, the lipid triad (elevated TG, elevated T.CHOL and decreased HDL-C) is a powerful risk factor for CVD and CHD. [7-17] The study shows the co- morbid association of obesity and diabetes mellitus on the atherogenic risk factors. Raised levels of cholesterol, triglycerides, LDL-C, VLDL-C levels with decreased levels of HDL-C is seen in cases as compared to controls. Similar findings have been reported by many studies [17, 31-33, 39,40] supporting the fact that obesity causes Insulin resistance, the cause of diabetes mellitus leading to Glucotoxicity. Impairment of glucose metabolism affects the normal metabolism of lipids leading to Lipo toxicity. Gluco toxicity and Lipo toxicity further affects the Insulin resistance, a vicious cycle resulting in Metabolic Syndrome. Unregulated LDL-C uptake by scavenger receptors leads to plaque formation [41], a predictable risk factor for micro and vascular macro complications [7-17, 31-33, 40, 41]. Patients with elevated LDL-C have greater risk of MI as LDL-C is the major carrier of cholesterol for metabolic functions including synthesis of cholesterol.

High incidence of CHD and CVD occurs when such lipid profiles coexist with overweight and obesity among diabetic patients. Treatment of dyslipidemia has shown to benefit diabetic patients to decrease CHD risk.

Ratios of Atherogenic to Atherogenic protective factors clearly indicates dyslipidemia associated with Glucotoxicity and Lipotoxicity. T.CHOL/HDL-C ratio was 9.22 ± 1.73 in obese diabetics as compared to 6.33 ± 1.04 in nonobese diabetics indicating the impact of obesity on diabetes. The ratios of TG/HDL-C was 7.80 ± 2.08 in obese diabetics as compared to 5.56 ± 1.04 in non obese diabetics. Ratio of LDL-C/HDL-C was 6.67 ± 1.52 and 4.21 ± 0.99 in obese and non obese diabetics respectively. The ratios suggest the impairment in agreement with other studies [39, 40]. Altered ratios suggests metabolic interaction of atherogenic factors in increasing the risk of micro and macrovascular diseases. There is inverse relationship between LDL-C clearance and HDL-C levels. Several epidemiological studies demonstrated that proportion T.CHOL/HDL-C and LDL-C/HDL-C ratios could be better predictors of atherosclerosis than any single lipid parameter [40, 41]. Increased levels of Lipoprotein Lipase due to insulin resistance in adipose tissues and muscles results in decreased breakdown of VLDL-C accounting for increase in Triglycerides, VLDL-C and LDL-C levels in diabetes mellitus [41] with unregulated uptake of LDL-C uptake by scavenger receptors leading to plaque formation.

Increase in hepatic Lipase which catabolises HDL-C results in decreased HDL-C. Low HDL-C levels are commonly seen in Indian population and Asian Indians [42].

An inverse relationship was seen between TGL and HDL-C levels. Combination of low HDL-C and High TG is related to increase CHD [11, 43] HDL-C is known for its antioxidant, anti thrombotic anti inflammatory action [44]. These antioxidant and anti-inflammatory properties of HDL-C may be as important as its cholesterol efflux function, in terms of protecting against the development of atherosclerosis.

Poor physical activity with increased calorie intake leads to proinflammatory state which are the precipitating factors for CVD and CHD [24, 45].

CONCLUSION

Dramatic increase in obesity and diabetes Mellitus from 21st century once known as “Disease of Rich” is no more a fact as its prevalence is increasing in middle and low income group. Increased prevalence of this co-morbid disease clearly indicates excess of food and energy intake, lack of exercises, sedentary life style due to urbanization and advent of mechanization.

Cardiovascular disease is the major cause of morbidity and mortality in diabetes and obesity. Among the established risk factors, Lipid Triad is a powerful risk factor for atherosclerosis. There is enough evidence in literature to support the beneficial effect of life style pattern and exercises in lowering serum lipids which helps in retarding/preventing microvascular and macrovascular complications.

We hope our data will help to sensitize clinicians in screening obesity and diabetes in people for early detection and timely intervention. Dietary intervention to control obesity, physical exercises, and awareness about the morbid effects are the main strategies in the management.

Research to understand the molecular mechanisms underlying Neuronal regulation on energy intake, energy storage(adipogenesis, lipogenesis),lipolysis, thermogenesis is imperative to prevent obesity. Study of insulin action at different sites like muscle, liver and adipose tissue, and insight into the cellular mechanisms that regulate energy expenditure is necessary in understanding and in combating the co-morbid double trouble of obesity and Diabetes Mellitus.

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