Increased Risk Of Cardiovascular Disease In Young Diabetics In Correlation With The Poor Glycemic Status And Dyslipidemia In A Tertiary Care Centre Of Upper Assam

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Abstract: *Diabetes Mellitus is considered to be a cardiovascular disease equivalent. The risk of CVD in DM is manifold, and the implications of the disease becomes even more grave when young diabetics die of cardiovascular diseases. The escalating number of young diabetics emphasises the need for early diagnosis and intervention when necessary to halt the progression of CVD. The present study is a novel attempt to assess the prevalence of CVD in young diabetics in upper Assam with poor glycemia and dyslipidemia with the aims and objectives to study the glycemic status and lipid profile in young diabetics and to study the CVD risk and involvement. It is a hospital based observational study carried over a period of 1 year which showed A total of 42.7% of cardiovascular outcomes, of which Left Ventricular diastolic Dysfunction + Concentric LVH was found in 53.2% cases, Left Ventricular Diastolic Dysfunction alone was found in 21.8%, Concentric LVH alone was found in 25%. HbA1c level was found to be statistically extremely significant with the Cardiovascular Disease outcomes, with Left Ventricular Diastolic Dysfunction (p value 0.0007) and with Concentric LVH (p value 0.003). This was a hospital based observational study conducted in upper Assam among the patients with diabetes diagnosed at an early age of 25 years and below, to identify the presence of cardiovascular risks in young diabetes and the relation with glycemic status.*

I. Introduction

Indians are predisposed to the early development of diabetes and its complications owing to certain genetic, clinical and biochemical abnormalities such as higher waist circumference, lower adiponectin and higher high sensitive C-reactive protein, which are part of the so called - "Asian Indian Phenotype" [1-3]

This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease.

It is a known fact that diabetic individuals are prone to cardiovascular diseases early in life, however, what is more alarming is the recent shift in the age of onset of the disease to a much younger age.

The ICMR-INDIAB study also showed that there is a shift of Type 2 DM to younger age groups and that the take off point of prevalence of diabetes occurs at ages 25–34 years in India.[4]

Type 1 DM was until recently considered the only form of diabetes in the young, however, of late, a large number of young diabetics have been found to be Type 2 DM. This is probably due to the alarming rates of obesity, the prevalence of both is so called – " Diabesity"

Indeed, the epidemic of T2DM is now spreading so rapidly, that already in some countries, like Japan; Type 2 DM is already more common than Type 1 DM, in children.[5,6]

There have been only few studies to evaluate the presence of cardiovascular involvement in young diabetics and its relation with the glycemic status in India, and as far as our knowledge goes, a methodical study to evaluate the cardiovascular risk factors in young diabetics has not been carried out in North East Assam. With consideration of the above facts, the present study is being conducted with the following Aims and Objectives :

Aims And Objectives:-
1) To study the glycemic status and lipid profile in young diabetics
2) To study the cardiovascular risk and cardiovascular involvement in young diabetics

II. Materials And Method

The present study 'Increased risk of cardiovascular disease in young diabetics in upper Assam in correlation with the poor glycemic status and dyslipidemia' is a hospital based observational study carried out on 75 patients of diabetes who were diagnosed at or below 25 years of age, who attended the Out Patient Department and / or were admitted in a Tertiary Care Hospital in Upper Assam during a period of one year from July 2014 to June 2015.

Selection of Cases:

All young Diabetes Mellitus patients diagnosed at or below 25 years of age, attending the Out Patient Department and / or were admitted in a Tertiary Care Hospital in Upper Assam were included in the study after considering the inclusion criteria and exclusion criteria. Written informed consent from the patients / guardian was taken. Ethical clearance was obtained from the Ethics Committee of the Institution prior to the onset of study.

Inclusion Criteria
1) Young diabetics diagnosed at ≤25 years of age.
2) Selection of cases of diabetes mellitus according to ADA 2015 guideline

Exclusion Criteria
- Diabetes Mellitus patients diagnosed above 25 years of age
- Diabetes Mellitus with Hypertension and/or Ischemic Heart Disease
- Patients on Lipid Lowering Therapy
- Family history of Hyperlipidemia
- Terminally Ill patients
- Pregnancy and Gestational DM
- Significant liver and renal disease
- Patients with severe anemia

Sample Size: After considering the inclusion and exclusion criteria, a total number of 75 cases were included in the present study
Study Design: Hospital based observational study
Method: A detailed clinical history, physical examination and investigations were done in all the patients and filled in a predesigned proforma
Case Definition of a case of Diabetes Mellitus was done according to the ADA 2015 guidelines - American Diabetes Association Diabetes Care 2015;38(Suppl. 1):S8–S16 [7]

The age of cut off of diagnosis at or below 25 years for young diabetic patients was chosen according to previous studies. [4,8]
HbA1c of <7% was considered good glycemic control, while a HbA1c >7% was considered as poor glycemic control. The selection of these cutoff values of HbA1c was based on earlier studies [9,10]
The atherogenic index of plasma (AIP) was calculated by the formula base 10 logarithm of the ratio of TG to HDL.
An AIP of > 0.21 was taken as high CAD risk, and <0.21 as low-intermediate CAD risk [11,12]

III. Results And Observations
The following tables illustrated the results of the present study:

Table .1: Gender Distribution Of Total Cases Of Young Diabetes

SEX	NUMBER OF CASES (N= 75)	PERCENTAGE%	RATIO MALE:FEMALE
MALE	42	56	
FEMALE	33	44	**1.27:1**
TOTAL	**75**	**100**	

FIG:1 GENDER DISTRIBUTION OF CASES
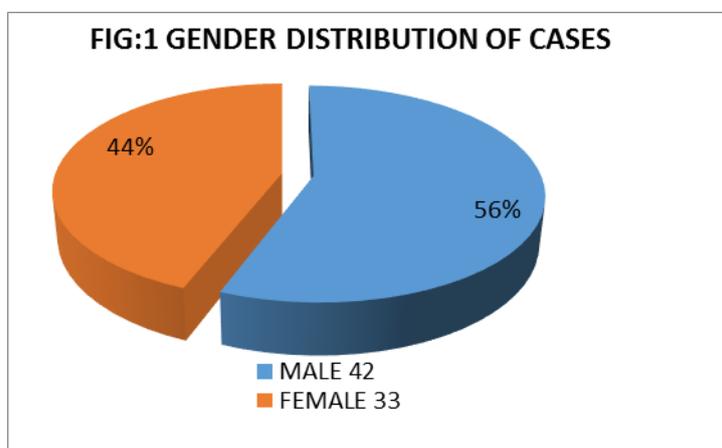
Table 2: Distribution Of Hba1c

HBAIC	NUMBER OF CASES (N=75)	PERCENTAGE %
≤ 7	17	22.7
>7	58	77.3
TOTAL	**75**	**100**

FIG: 2 DISTRIBUTION OF HBA1C

HBA1C≤ 7=22.7%
HBA1C>7=77.3%
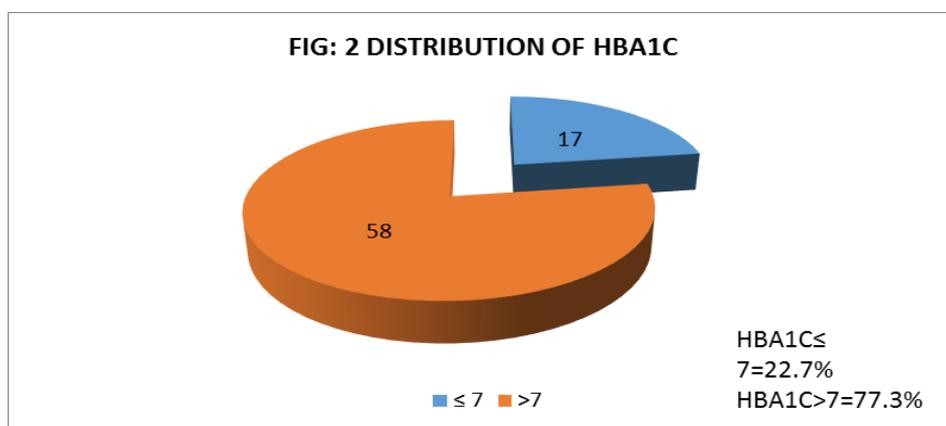
Table 3: Gender Distribution Of The Cardiovascular Outcomes

PARAMETER	MALE [N=42]	FEMALE[N=33]	p- VALUE
LV DYSFUNCTION			
PRESENT	15	9	
ABSENT	27	24	0.466
CONCENTRIC LVH			
PRESENT	19	6	**0.015**
ABSENT	23	27	**(SIGNIFICANT)**

P value significant at <0.05
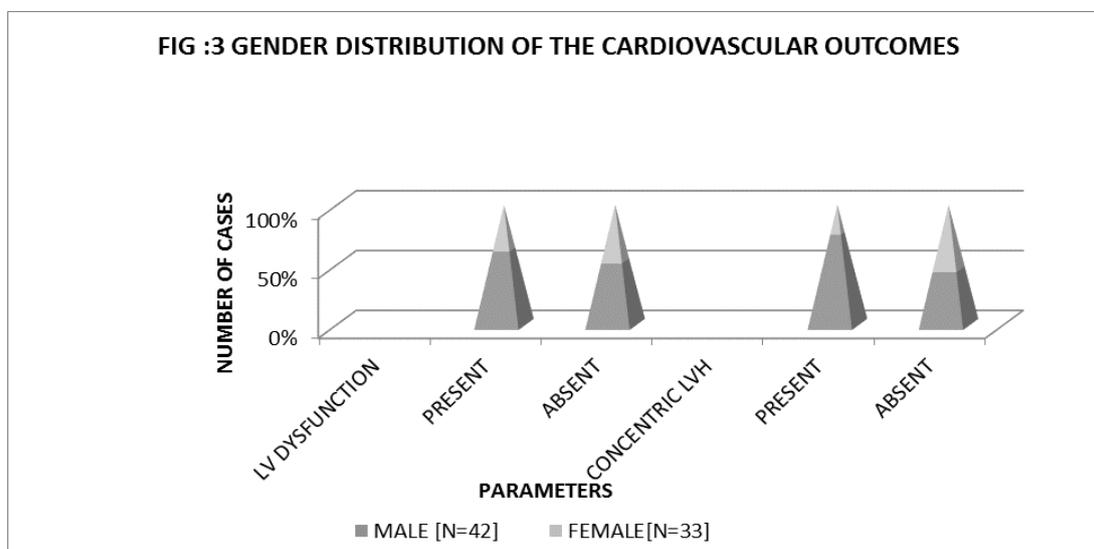
FIG :3 GENDER DISTRIBUTION OF THE CARDIOVASCULAR OUTCOMES

Table 4: Comparison Of Gender With Cvd Risk Factors And Type Of Dm And Treatment Given

PARAMETERS	MALE [N=42]	FEMALE[N=33]	p- VALUE
Age (Average± Standard Deviation)	24.49 ± 5.95	23.61± 7.15	0.56
Duration of disease			
< 1 year (no.of cases)	19	14	
>1 year(no.of cases)	23	19	0.819
BMI(Average± Standard Deviation)	19.16±4.26	19.59±4.47	0.67
HbA1c(Average± Standard Deviation)	10.54±4.09	9.23±3.31	0.139
FBS(Average± Standard Deviation)	298.57±129.87	272.13±117.43	0.364
Total Cholesterol(Average± Standard Deviation)	167.49±53.68	164.62±52.30	0.817
Triglyceride(Average± Standard Deviation)	162.78±89.28	149.44±78.50	0.500
HDL(Average± Standard Deviation)	40.82±12.13	45.68±15.91	0.137
LDL(Average± Standard Deviation)	90.36±42.85	83.42±37.27	0.464

AIP(Average± Standard Deviation)	0.57±0.33	0.53±0.35	0.613
Microalbuminuria PRESENT (no.of cases)	27	18	0.478
ABSENT(no.of cases)	15	15	
Type of DM Type 1 DM(no.of cases)	30	24	1.0
Type 2 DM(no.of cases)	12	9	
Treatment Instituted Insulin(no.of cases)	30	26	
OHA(no.of cases)	10	4	0.366
Both(no.of cases)	2	3	

Table 5: Distribution Of Hba1c With Lipid Parameters

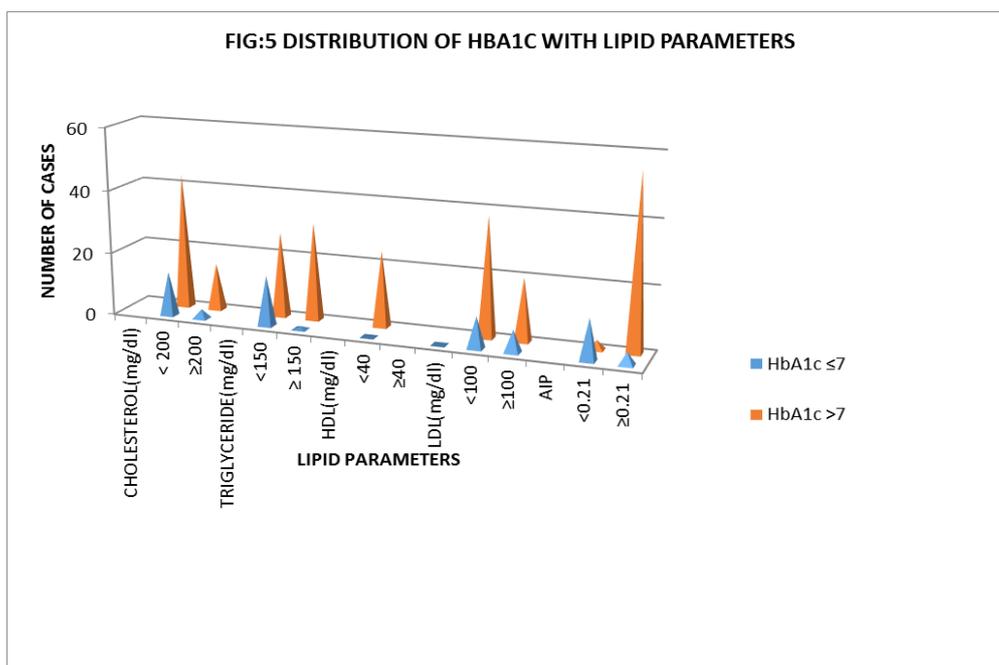| PARAMETERS	HbA1c ☐7 (no.=17)	HbA1c >7 (no.=58)
CHOLESTEROL(mg/dl) **< 200**	14	43
≥200	3	15
TRIGLYCERIDE(mg/dl) **<150**	16	27
≥ 150	1	31
HDL(mg/dl) **<40**	0	24
≥40	17	34
LDL(mg/dl) **<100**	10	38
≥100	7	20
AIP **<0.21**	13	3
≥0.21	4	55

Table 6: Distribution Of Hba1c Levels With The Cardiovascular Outcomes

PARAMETERS	HbA1c ≤7 (no.=17)	HbA1c >7 (no.=58)	P VALUE
LV DYSFUNCTION **PRESENT**(no.of cases)	**0 (0%)**	**24 (41.4%)**	**0.0007**
ABSENT(no.of cases)	**17 (100%)**	**34 (58.6%)**	**SIGNIFICANT**
CONCENTRIC LVH **PRESENT**(no.of cases)	**0 (0%)**	**25 (43.1%)**	**0.003**
ABSENT(no.of cases)	**17 (100%)**	**33 (56.9%)**	**SIGNIFICANT**

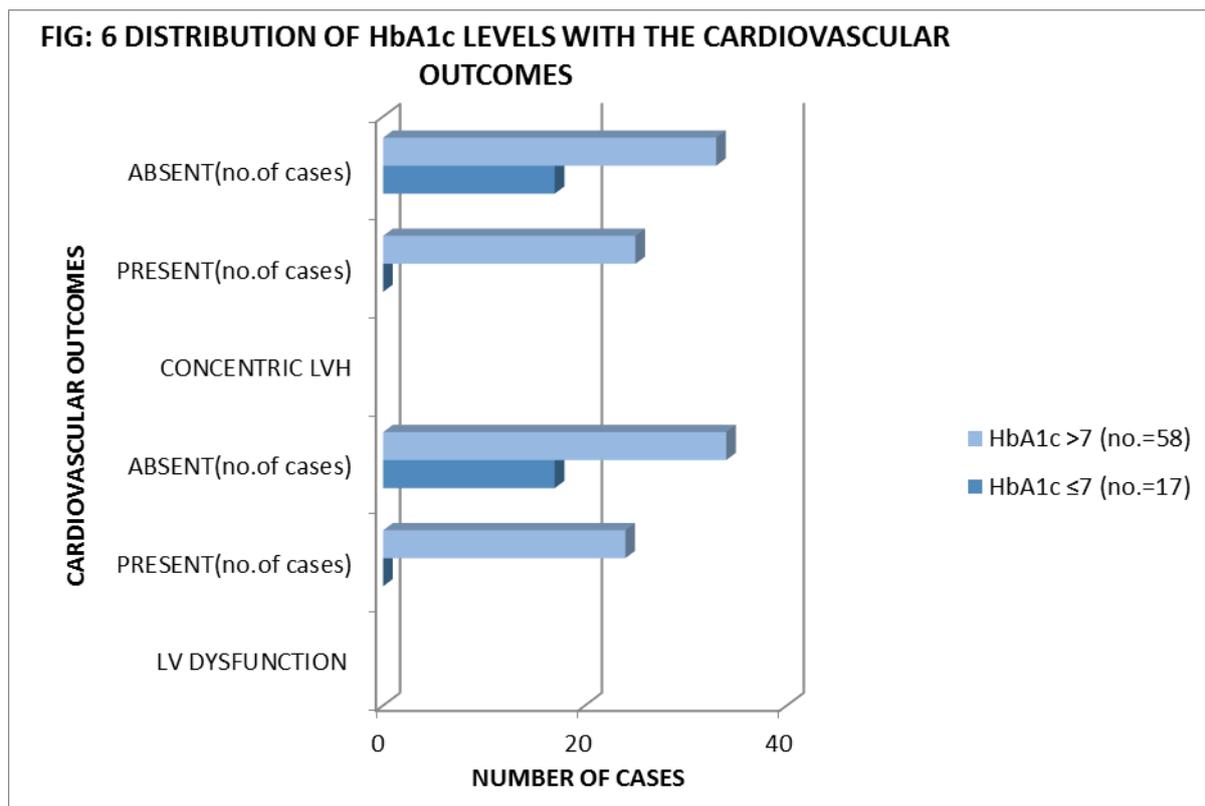FIG: 6 DISTRIBUTION OF HbA1c LEVELS WITH THE CARDIOVASCULAR OUTCOMES

TABLE 7
COMPARISON OF HbA1c LEVELS WITH CVD RISK FACTORS AND TYPE OF DM

PARAMETERS	HbA1c ≤7 (no.=17)	HbA1c >7 (no.=58)	P-value
Age (Mean± Standard Deviation)	22.97 ± 6.45	24.43 ± 6.50	0.417
Duration of disease < 1 year (no.of cases)	7	26	
>1 year(no.of cases)	10	32	0.79
BMI(Mean± Standard Deviation)	19.03 ±2.96	19.44 ± 4.67	0.734
FBS(Mean± Standard Deviation)	213.71 ± 94.4	308.4 ± 124.62	0.005
PPBS(Mean± Standard Deviation)	277.44 ± 150.22	405.51 ± 131.85	0.001
Total Cholesterol(Mean± Standard Deviation)	157.29 ± 44.82	168.84 ± 54.92	0.431
Triglyceride(Mean± Standard Deviation)	92.18 ± 34.79	175.88 ± 85.41	0.0002
HDL(Mean± Standard Deviation)	56.82 ± 10.46	38.89 ± 12.28	0.0001
LDL(Mean± Standard Deviation)	90.52 ± 42.62	86.36 ± 40.03	0.711
AIP(Mean± Standard Deviation)	0.19 ± 0.14	0.66 ± 0.31	0.0001
Microalbuminuria PRESENT (no.of cases)	2	43	<0.00001
ABSENT(no.of cases)	15	15	
Type of DM Type 1 DM(no.of cases)	11	43	

Type 2 DM(no.of cases)	6	15	0.54
Treatment Instituted Insulin(no.of cases)	13	43	
OHA(no.of cases)	4	10	
Both(no.of cases)	0	5	1.756

Significant p value at <0.05

TABLE 8
COMPARISON OF THE TREATMENT INSTITUTED WITH THE CVD OUTCOMES

PARAMETERS	INSULIN [N=56]	OHA [N=14]	BOTH [N=5]	P VALUE
LV DYSFUNCTION				
PRESENT	16	5	3	0.33
ABSENT	40	9	2	
CONCENTRIC LVH				
PRESENT	16	6	3	0.253
ABSENT	40	8	2	
Microalbuminuria				
PRESENT	31	9	5	0.139
ABSENT	25	5	0	
AIP				
<0.21	13	2	1	0.764
⩾0.21	43	12	4	

Significant value of p at < 0.05

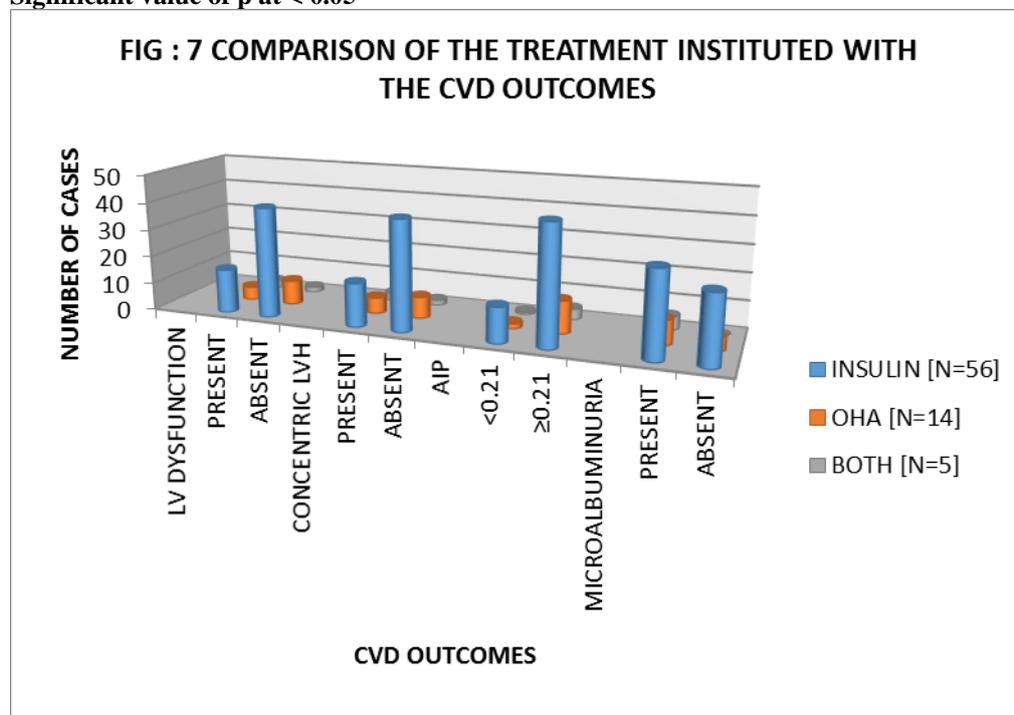FIG : 7 COMPARISON OF THE TREATMENT INSTITUTED WITH THE CVD OUTCOMES

TABLE 9
DISTRIBUTION OF THE LIPID PARAMETERS WITH VARYING HbA1c LEVELS TO SHOW CORRELATION

LIPID PARAMETERS(mg/dl)	HbA1C≤7 [N=17]	HbA1C 7.1-8 [N=16]	HbA1C 8.1-9.5 [N=11]	HbA1C ≥9.5	P VALUE

				[N=31]	
TOTAL CHOLESTEROL					
<200	14	11	8	24	0.817
≥200	3	5	3	7	
TRIGLYCERIDE					
<150	16	8	5	14	**0.0065**
≥150	1	8	6	17	
HDL					
<40	0	4	5	15	**0.0044**
≥40	17	12	6	16	
LDL					
<100	10	8	8	22	0.462
≥100	7	8	3	9	

FIG 8: DISTRIBUTION OF LIPID PARAMETERS WITH VARYING HBA1C
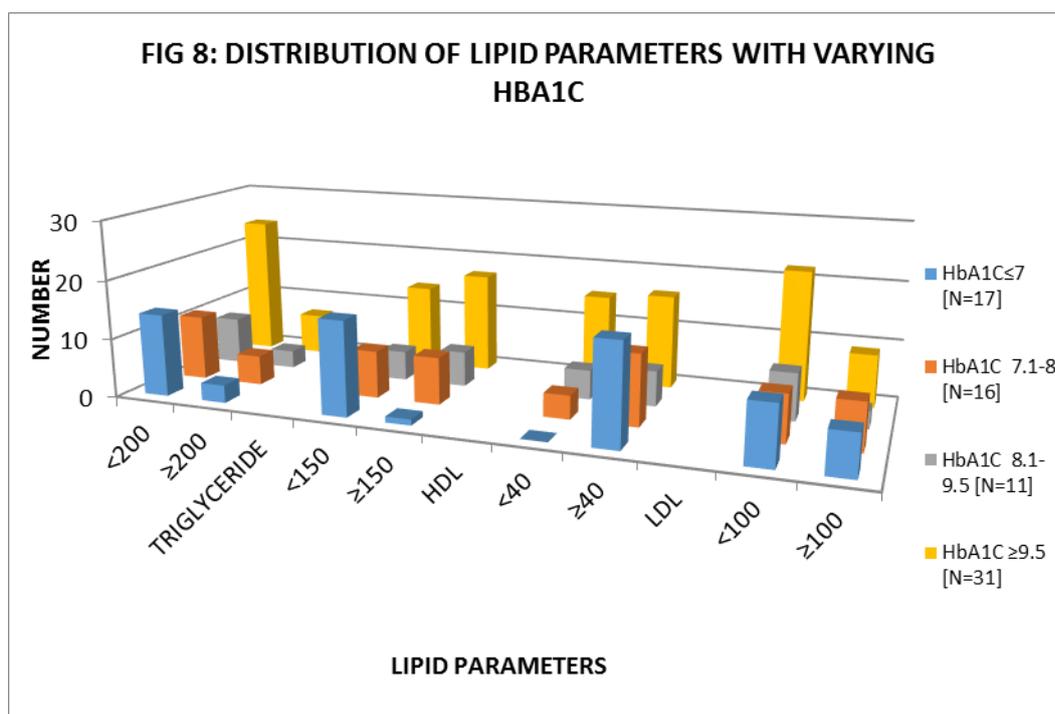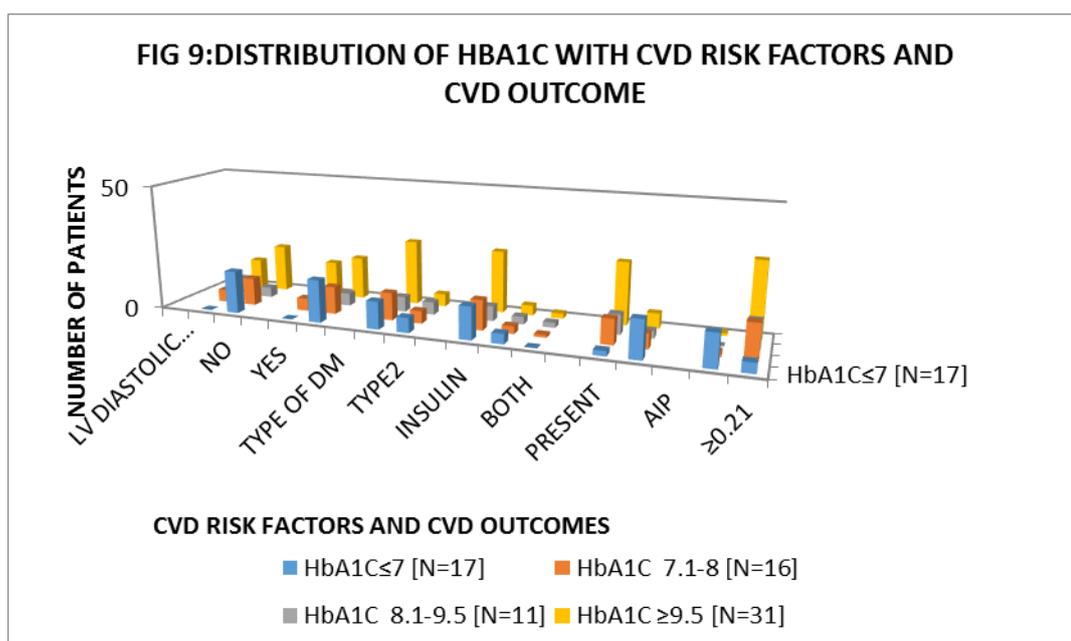
TABLE 10
DISTRIBUTION OF HbA1C LEVELS WITH CVD RISK FACTORS AND CVD OUTCOMES

CVD PARAMETERS	HbA1C ≤7 [N=17]	HbA1C 7.1-8 [N=16]	HbA1C 8.1-9.5 [N=11]	HbA1C ≥9.5 [N=31]	P VALUE
AIP					

<0.21	13	2	0	1	**< 0.00001**
≥0.21	4	14	11	30	
TYPE OF DM					
TYPE1	11	11	6	26	0.224
TYPE2	6	5	5	5	
MICROALBUMINURIA					
PRESENT	2	10	8	25	**<0.000045**
ABSENT	15	6	3	6	
LV DIASTOLIC DYSFUNCTION					
PRESENT	0	5	7	12	**0.00334**
ABSENT	17	11	4	19	
CONC LVH					
PRESENT	0	5	6	14	**0.0053**
ABSENT	17	11	5	17	
TREATMENT GIVEN					
INSULIN	13	12	6	25	0.507
OHA	4	3	3	4	
BOTH	0	1	2	2	

FIG 9:DISTRIBUTION OF HBA1C WITH CVD RISK FACTORS AND CVD OUTCOME

DISCUSSION

The present study included 75 patients, ranging from the age of 13 to 40 years, who were diagnosed at or below 25 years of age. The mean age of diagnosis was 24.11 ± 6.45 years. The majority of the patients were male (42 patients) with 56 %, while females(33) were 44% .The male to female ratio in the study was found to be 1.27:1. These data were comparable to other studies conducted by SEARCH, to study the 'Glucose Control Predicts 2-Year Change in Lipid Profile in Youth with Type 1 Diabetes' and by SEARCH, to study the 'Serum Lipids and Glucose Control'. The data were also comparable to a study conducted by Soedamah-Muthu et al, 2006, to determine the the absolute and relative risk of cardiovascular disease (CVD) in patients with type 1 diabetes in the U.K.

In the study the distribution of HbA1c was >7 was 77.3% and ≤ 7 was 22.7%. Among the males with poor control of diabetes with HbA1c >7 was 58.6%, while females were 41.4%. The average and standard deviation found in males was 10.54±4.09 and among the females was 9.23±3.31, which was not found to be statistically significant with p value of 0.139.

The distribution of the lipid parameters and glycemic status among the HbA1c < 7 and ≥ 7 were found to be statistically significant for the FBS, PPBS, Triglycerides, HDL and AIP with p value of < 0.005. However it was not found to be significant with LDL , Total cholesterol and BMI.

On comparison of the glycemic control it was seen that HbA1c was found to be statistically significantly related with certain CVD risk factors such as Triglyceride (risk at ≥ 150mg/dl), HDL (risk at < 40mg/dl) , AIP, microalbumiuria.[11,13-15]

This is supported by study conducted by Maahs et al, SEARCH to study the 'Glucose Control Predicts 2-Year Change in Lipid Profile in Youth with Type 1 Diabetes' [16] where they found that change in A1c over time was significantly associated with changes in Total Cholesterol, HDL-c, LDL-c, TG, and non-HDL-c over the range of A1c values.

In a study conducted by SEARCH, to study the 'Serum Lipids and Glucose Control'[180] they found that lipid levels increase with increasing values of HbA1c, a very high percentage of youth are classified as having "high" Total Cholesterol , LDL-C, and triglyceride concentrations in the category "poor glycemic control" for both type 1 and type 2 diabetes.

Among the cardiovascular outcomes, a total of 32 / 75 (42.7%) outcomes were found, of which Left Ventricular Dysfunction was found along with Concentric LVH in 17 / 32 (53.2%) cases, Left Ventricular Dysfunction alone was found in 7 / 32 (21.8%), and Concentric LVH was found alone in 8 / 32 (25%) cases.

Poor glycemic control with HbA1c > 7 was found to be statistically extremely significant with the CVD outcomes.

CVD outcomes were found to be statistically significantly related to microalbuminuria, however it was not significantly related to the treatment options instituted

In a study conducted by SEARCH, to study the 'Prevalence of Cardiovascular Disease Risk Factors in U.S. Children and Adolescents With Diabetes' [17], The prevalence of having at least two CVD risk factors was 21%. The prevalence was 7% among children aged 3–9 years and 25% in youth aged 10–19 years (*P*<0.0001), 23% among girls and 19% in boys (*P* =0.04), At least two CVD risk factors were present in 92% of youth with type 2 and 14% of those with type 1 diabetes (*P* < 0.0001).

The Pittsburgh Epidemiology of Diabetes Complications (EDC) study demonstrated that the incidence of major coronary artery disease (CAD) events in young adults (aged 28–38 years) with T1DM was 0.98% per year and surpassed 3% per year after age 55 years, which makes it the leading cause of death in that population.[18,19]

An increased risk of CVD has been reported in other studies, with the age-adjusted relative risk (RR) for CVD in T1DM being ≈10 times that of the general population.[13,20]

One of the most robust analyses of CVD risk in this disease derives from the large UK General Practice Research Database (GPRD), comprising data from >7400 patients with T1DM with a mean±SD age of 33±14.5 years and a mean DM duration of 15±12 years.8 CVD events in the UK GPRD study occurred on average 10 to 15 years earlier than in matched non diabetic control subjects.[21] The findings of the study were hence comparable with the rest of the studies.

There have been very few studies to assess the cardiovascular involvement in young diabetics, and echocardiographic assessment studies in young diabetics are rare. We see in the present study that 42.7 % of the patients had echocardiographic evidence of cardiovascular involvement, however we did not find evidence of ischemia or myocardial infarction. The present study was an observational study with echocardiographic findings which were subclinical as compared to the other prospective cohort studies.

This finding was probably due to the duration of study being restricted to one year period as compared to other studies conducted over several years and over a larger population

The echocardiographic findings of the present study is novel, in upper Assam, as far as our knowledge goes.

A study conducted by J.N.khan et al, [22] also supports our finding. They had assessed the presence of

subclinical diastolic dysfunction in young diabetics below 40 years of age using cardiovascular contrast enhanced magnetic resonance and found that In the Type 2 DM cohort, mean aortic distensibility correlated with peak early diastolic strain rate (PEDSR), (r =0.564, P =0.023)

CONCLUSION

Diabetes mellitus in young is a major concern owing to the increased mortality and morbidity associated with the disease. The increased mortality in the young diabetics is majorly due to the cardiovascular disease. In the present study we see that a large number of patients were diagnosed to have diabetes at a younger age (diagnosed at and below 25 years of age) in North East India, especially upper Assam.

Majority of the young diabetic patients had very poor glycemic control and dyslipidemia, both of which, along with genetic and other environmental factors create an atherogenic milieu that probably contributes to the increased cardiovascular risk.

In the present study we found that the level of HbA1c correlated with the various atherogenic lipid parameters and the increase in the level of HbA1c was associated with increased cardiovascular risk factors such as increased level of Triglyceride $\geq$ 150 mg/dl, decreased level of HDL <40mg/dl, Atherogenic Index Of Plasma (AIP) $\geq$ 0.21and microalbuminuria. The levels of HbA1c also corresponded positively with the cardiovascular outcomes such as Left Ventricular Diastolic Dysfunction and Concentric Left Ventricular Hypertrophy.

It is therefore extremely important to have a strong clinical suspicion in order to look for the presence of cardiovascular risk factors in young patients with diabetes with uncontrolled glycemic status as it predisposes the patients to early development of cardiovascular disease.

This was a hospital based observational study conducted in upper Assam among the patients with diabetes diagnosed at an early age of 25 years and below, to identify the presence of cardiovascular risks in young diabetes and the relation with glycemic status. As far as our knowledge goes, the present study is a pioneer study conducted in upper Assam, in young patients with diabetes. The study emphasizes on the need for early diagnosis of cardiovascular risks and thereby early intervention to reduce the morbidity and mortality associated with the disease in the young patients.

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