RESEARCH ARTICLE

GLYCATED HEMOGLOBIN (HBA1C) IS A PREDICTOR OF DYSLIPIDEMIA IN TYPE 2 DIABETES NEPALESE PATIENTS.

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Abstract

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Background: Type 2 diabetes mellitus (T2DM) have an increased prevalence of dyslipidemia. Dyslipidemia is characterized by high cholesterol (TC), high triglyceride (TG), high LDL cholesterol (LDL-C) and decrease HDL cholesterol (HDL-C) and is major risk factor for cardiovascular disease in T2DM. HbA1c serve as a gold standard indicator of glycaemic status over long term.

Aim: The study aimed to investigate the correlations between lipid profile parameters, as well as the glycated hemoglobin (HbA1c) values of Nepalese population with type 2 Diabetes mellitus (T2DM).

Material and Methods: This was a cross sectional, retrospective study of 140 T2DM patients (81 male and 59 female) who had visited department of Internal Medicine, Manmohan Memorial Community Hospital were included in this study. Venous blood samples were collected for fasting plasma glucose, HbA1c and serum lipid profile from all subjects in the morning after at least 8 hours fasting by using methods following standard operating procedures (SOPs). The statistical analysis was done by SPSS.

Results: There is alteration in the serum levels of FBS, total cholesterol (TC), triglycerides, LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) were noted in patients with T2DM. The HbA1c was found to be significant correlation with FBS, TC, TG, and LDL-C but there was no significant relation noticed with HDL-C. Values of HbA1c >6.5 % showed significant correlation with TC, LDL-C, TG, LDL-C/HDL-C and TC/HDL-C ratio, as compared to patients with HbA1c ≤ 6.5% (p<0.05).

Conclusion: In conclusion, our study demonstrates that in Nepalese with type 2 diabetes mellitus, dyslipidemia is more common. To reduce the burden **of** morbidity and mortality from different complications, it necessary to control diabetes and lipid levels in diabetic patients and

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emphasises the additional possible use of HbA1c as a predictor for dyslipidemia.

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Introduction:-

The diabetes mellitus is becoming more and more prevalent in every corner of the globe and a projection for the future is alarming. Type 2 Diabetes Mellitus (T2DM), a metabolic disorder characterized by the hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism due to insulin resistance or relative insulin deficiency. The chronic hyperglycemia of diabetes results in macrovascular complications including heart disease and stroke and microvascular complications including nephropathy, neuropathy and retinopathy [1]. Furthermore, abnormal serum lipids- dyslipidemia, characterized by increased triglycerides level, high low density lipoproteins and low high density lipoproteins [2] are likely contribute to the risk of coronary artery disease, cerebrovascular disease, peripheral vascular diseases and associated with greater risk of morbidity and mortality [3]. It has remained a major concern of healthcare professionals from long time due its strong association with cardiovascular diseases (CVD) [4]. Several factors are likely to be responsible for diabetic dyslipidemia: insulin effects on liver apoprotein production, regulation of lipoprotein lipase (LpL), actions of cholesteryl ester transfer protein, and peripheral actions of insulin on adipose and muscle [5, 6]. In each year, about 5% of all deaths are caused by diabetes globally [7]. This risk, however, can be reduced by good management and control of hyperglycemia as well as dyslipidemia [8].

According to American Diabetes Association (ADA), Glycated Haemoglobin (HbA1c) more than or equal to 6.5% is considered diabetes [9] and it is routinely used marker for long term diabetic control preceding 8-12 weeks of time. As HbA1c functions as an indicator for the mean blood glucose level, it is now considered as an independent risk factor in diabetic patients [10]. Several observational studies demonstrated that a higher HbA1c level was associated with increased risks of cardiovascular diseases and deaths [11, 12]. Furthermore, an elevated level of HbA1c is now considered as an independent risk factor for cardiovascular disease in any subject with or without diabetes. For each 1% increase in HbA1c level increases the risk of CVD by 18% and positive association between HbA1c and CVD has been demonstrated in non-diabetic patients even within normal range of HbA1c. At present HbA1c is the best alternate marker we have for setting goals of treatment [13].

Diabetes complications and control trial established that strict control of diabetes reduces micro vascular complications and glycated hemoglobin as gold standard investigation of diabetes control [14]. If hyperlipidemia is detected early in the course of diabetes mellitus, it will reduce the risk for cardiovascular and cerebrovascular diseases. Lifestyle changes such as diet and exercise are very important in improving diabetic dyslipidemia, but often pharmacological therapy is needed [15, 16]. Keeping in view the large number of type 2 DM patients and poor knowledge of the subject, most patients are prone to develop multiple lipid disorders. Therefore, this study was aim to find out the association between HbA1c (glycemic control) and serum lipid profile in Type 2 Diabetic patients attended at Manmohan Memorial Community Hospital, Kathmandu, Nepal.

Materials and methods:-

Patients' characteristics;

One hundred and forty Type 2 diabetes patients were enrolled in the current study. They were selected from the outpatient clinics of Internal Medicine department, Manmohan Memorial Community Hospital. Patients' consent was obtained according to the regulations of Nepalese Ministry of Health and study design was approved by the local ethics committee.

Furthermore, fasting (at least 8 hours) venous blood samples were collected from the selected patients. Then, serum was analyzed for fasting blood sugar, lipid profile panel- Total cholesterol, Triglyceride, HDL-cholesterol and LDL-cholesterol, and HbA1c.

For defining Diabetes Mellitus, American Diabetic Association (ADA) was used whereas for defining dyslipidemia, the reference levels were used as per National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guideline according to which hypercholesterolemia is defined as TC>200mg/dl, hypertriglyceridemia as TAG>150mg/dl, high LDL-C when the value exceeds 100mg/dl and low HDL-C when the value is below 40mg/dl. And presence of any one of abnormalities in serum lipid concentration it was defined as dyslipidemia. Glycated haemoglobin more than 6.5% is taken as abnormal as per ADA guideline.

The Inclusion criteria for all participants:
Type 2 Diabetic patients of age between 30-70 years were only included in the study.

The exclusion criteria:
Those patients under lipid lowering therapy and having diabetic complications and endocrinopathies such as Thyroid disorders were excluded from the study.

Statistical analysis:
The study data was analyzed by using SPSS program to compute descriptive parameters including mean and frequencies, and inferential statistics was used including student's t test to test the significance of the differences between the mean values of two continuous variables and Chi-squire test (X^2) test the difference in proportions categorical variables between two groups. The level of confidence (*P*<0.05) was considered as cutoff value for significance.

Results:-

Diabetic (study group) 140 subject (81 male and 59 female) were enrolled in this study. The mean age of the males was 53±15 years (range 10-84) and 54±15years (range 22-87) for females with no statistical significant difference, P= 0.911. Fasting Blood Glucose (FBG), Hemoglobin A1c (HbA1c), Triglycerides (TG), Total Cholesterol (TC), High Density Lipoproteins (HDL) and Low Density Lipoproteins (LDL) were studied to assess the association of diabetic condition with the lipids profile.

Table1: Comparison of studied parameters between gender types within study group.

Parameters	Male (n=81)	Female(n= 59)	P- value
Age, years			
Means ± SD	53±15	54±15	0.911
Range	10-84	22-87	
FBS			
Means ± SD	169.9±62.7	168.8±41.6	0.910
Range	90-372	90-279	
HbA1c			
Means ± SD	7.96±2.7	7.66±1.9	0.433
Range	4.7-18.0	5.1-12.5	
TG			
Means ± SD	181.1±60.1	185.1±65.8	0.714
Range	55-310	100-329	
TC			
Means ± SD	216.7±48.8	214.2±44.9	0.752
Range	110- 301	145-301	
HDL			
Means ± SD	36.6±5.7	38.7±5.6	0.014
Range	27- 48	27-53	
LDL			
Means ± SD	144.2 ± 44.1	138.4 ± 41.3	0.430
Range	39- 221	63- 216	
P value based on Student's t-test: significant at (p< 0.05)			

Table1 shows the statistics of biochemical parameters computed for males and females which point out that the results were found to be FBG (169.9±62.7and 168.8±41.6, P= 0.910), HbA1c (7.96±2.7and 7.66±1.9, p= 0.433) , TG (181.1±60.1and 185.1±65.8, P= 0.714) , TC (216.7±48.8 and 214.2±44.9, P= 0.752), HDL (36.6±5.7and 38.7±5.6, P= 0.014) , HDL (36.6±5.7and 38.7±5.6, P= 0.014) and LDL (144.2 ± 44.1and 138.4 ± 41.3, P= 0.430) respectively with statistical significance only in HDL parameter.

Table 2:- Percentage of abnormal parameters values and association with gender within study group.

Parameters	Male (n=81)		Female(n=59)		X2	P- value
	Normal	Abnormal	Normal	Abnormal		
FBS	20	61(75%)	9	50(85%)	1.85	0.173
HbA1c	16	65(80%)	8	51(86%)	0.92	0.336
TG	27	54(67%)	19	40(68%)	0.02	0.888
TC	37	44(54%)	34	25(42%)	1.94	0.162
HDL	28	53(65%)	22	37(63%)	0.11	0.740
LDL	10	71(88%)	8	51(86%)	0.04	0.832
P value based on chi squire test (p< 0.05) significant						

Table 2 shows that percentage of abnormal result within study group for male and female was found to be FBS (75% and 85%, P=0.173), HbA1c (80% and86%, P=0.336), TG (67% and 68%, P=0.888), TC (54% and42%, P=0.162), HDL (65% and63%, P=0.740), LDL (88% and86%, P=0.832) respectively, with no statistical significance difference.

Table 3:- Percentage of abnormal parameters values and association with age within study group.

Parameters	Less than 40 year		More than 40 year		X2	P- value
	Male	Female	Male	Female		
FBS	15(33%)	9(18%)	46	41	0.70	0.401
HbA1c	11(20%)	8(16%)	54	43	0.03	0.858
TG	13(32%)	9(23%)	41	31	0.03	0.858
TC	11(33%)	6(24%)	33	19	0.01	0.926
HDL	10(23%)	7(19%)	43	30	0.0	0.995
LDL	16(29%)	9(18%)	55	42	0.44	0.509
P value based on chi squire test (p< 0.05) significant						

Table 3 shows that percentage of abnormal result within study group for male and female base on the age category (< 40 year and > 40 year). For the less than 40 years the result shows that FBS (33% and 18%, P=0.401), HbA1c (20% and16%, P=0.858), TG (32% and 23%, P=0.858), TC (33% and24%, P=0.926), HDL (23% and 19%, P=0.995), LDL (29% and 18 %, P=0.509) respectively, with no statistical significance difference. The association between less and more than 40 years between gender types was depicted in (**figure 1, 2**).

Table 4: Correlation between HbA1c and studied parameters within study group.

Parameters	Person correlation (r)	P- value
FBS	0.731	< 0.001
TG	0.250	0.003
TC	0.373	< 0.001
HDL	-0.341	< 0.001
LDL	0.382	< 0.001
P value based on chi squire test (p< 0.01) significant		

Table 4 shows the correlation result between HbA1c and studied parameters within study group. All the results indicate there was positive relationship with statistical significance except a negative correlation between HbA1c and HDL. The correlation between HbA1c, HDL and LDL is depicted in (**figure 3, 4**).

Table 5:- Biochemical parameters according to patients glycemic control.

Parameters	**HbA1c**		**P- value**
	<6.5% (n=45)	≥ 6.5 % (n=95)	
FBS	134.6±25.3	186.8±57.0	0.001
TG	165.9±59.1	190.8.0±62.6	0.004
TC	199.3±40.8	223.3±48.0	0.025
HDL	38.1±5.3	36.9±6.0	0.229
LDL	128.0±38.9	148.2±43.3	0.009
TC/HDL	5.4±1.8	6.3±2.1	0.013
LDL/HDL	3.5±1.5	4.2±1.7	0.017
P value based on chi squire test (p< 0.05) significant			

Table 5 The patient's data were categorized on the basis of HbA1c ≤6.5% and ≥6.5. It was found that patients having HbA1c ≥6.5% have higher all the parameters and showed statistically significant ($p<0.05$) except HDL levels compared to patients having HbA1c ≤6.5% .
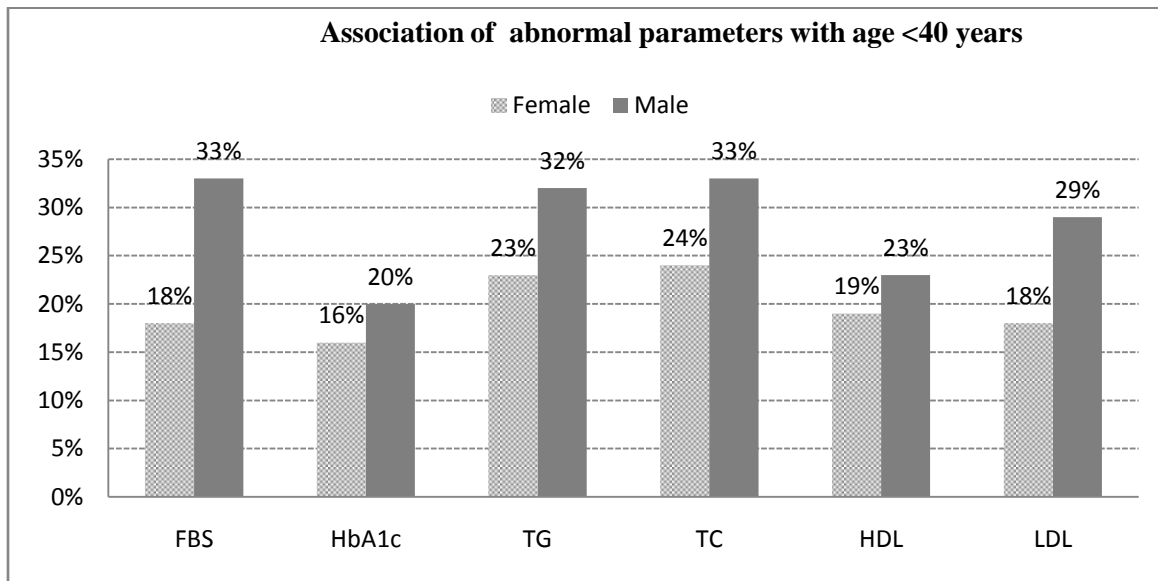

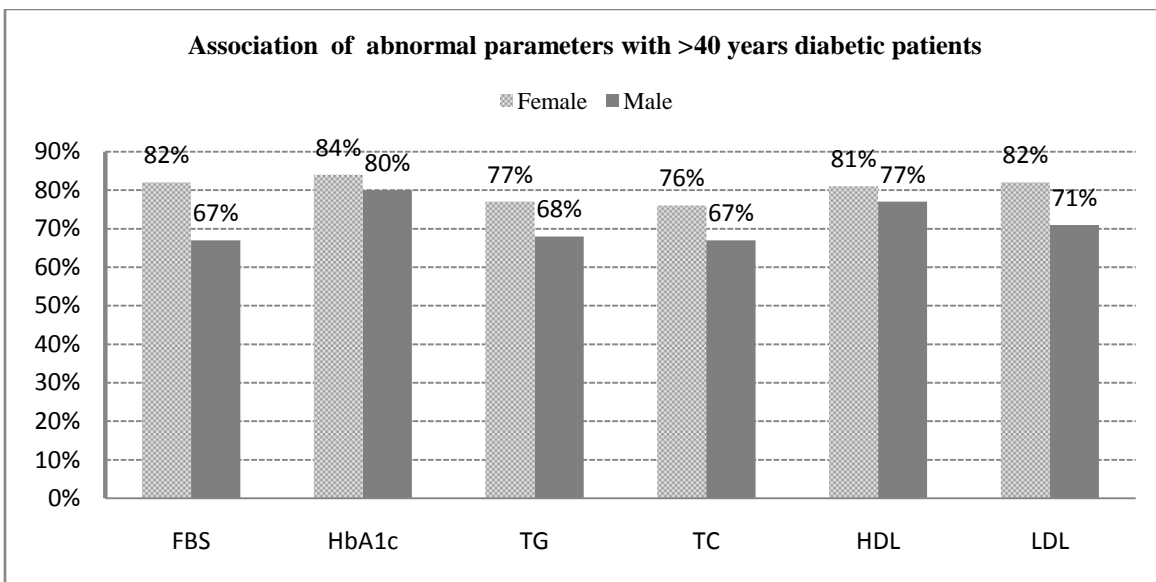**Figure 1:-** Association of abnormal result with < 40 years diabetic patients' gender

Figure 2:- Association of abnormal result with >40 years diabetic patients' according to gender
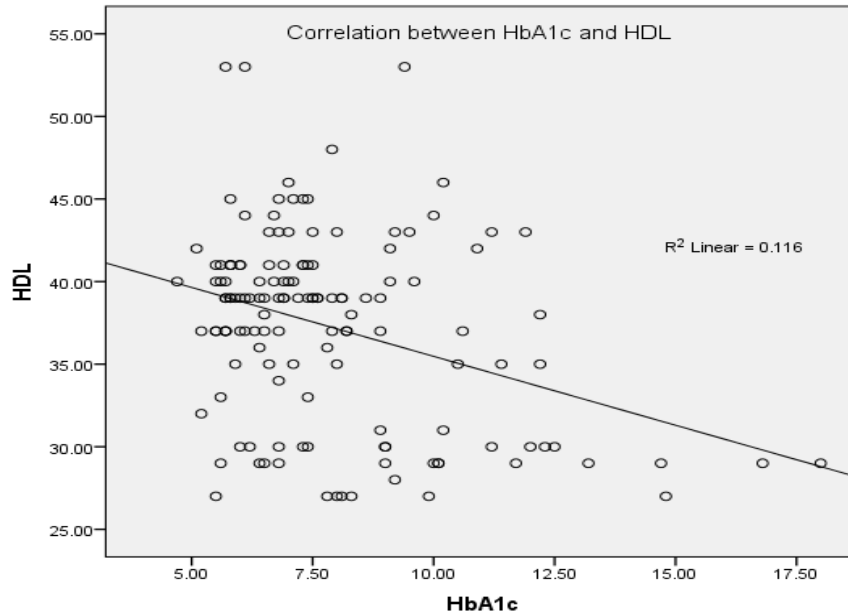
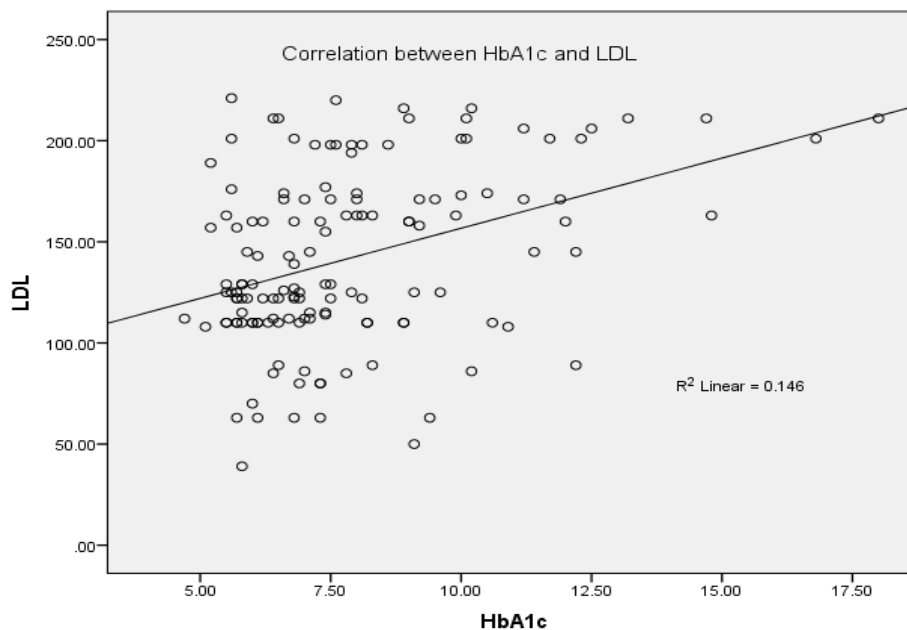**Figure 3:-** Correlation between HbA1c and HDL.

Figure 4:- Correlation between HbA1c and LDL.

Discussion:-

Type-2 diabetes mellitus (T2DM) is a well-known risk factor for the development of cardiovascular disease, cerebrovascular disease and peripheral vascular disease. Lipids play a vital role in the pathogenesis of diabetes mellitus. Alterations in lipid and lipoprotein profile contribute to atherosclerosis in T2DM [**17**]. Dyslipidemia is a metabolic abnormality that is frequently associated with diabetes mellitus and both of them play important predictors that can progress to coronary artery disease (CAD) and may even be a prerequisite for CAD, occurring before other major risk factors come into play. [**18**].

Its prevalence is variable, depending on the type and severity of diabetes, glycaemic control, nutritional status, age and other factors. Glycaemic control is directly related to lipid metabolism. Therefore, in this present study, we have

evaluated the pattern of lipid profile parameters in the patients with T2DM along with their correlation with HbA1c. The results of this study clearly showed that there is alteration in the serum levels of FBS, TC, TG, LDL-C and HDL-C were noted in patients with diabetes, which are well known risk factors for cardiovascular diseases among patients when compared to the normal values. However, the levels of HbA1c, FBG, TC, TG and were LDL-C not affected by patients gender as neither of these parameters differed significantly between male and female diabetic patients. Some of the previous studies showed that the results of lipid profile in female diabetic patients had significantly higher levels of LDL, and TC, which is in contrary with our report [19].

In addition, no such age-related differences were found in women but the frequency of normal HDL-C values in women was significantly higher than in men. Generally, the results from this study have been in accordance with one of the previous research [20]. This may reflect better adherence to diabetic management by females as well as the known higher HDL cholesterol in females due to gender effect particularly estrogen effect during reproductive age. However, our finding is contrary with the similar studies reported earlier [21, 22]. Hyperlipidemia in females may be attributed to the effects of sex hormones and body fat distribution, leading the differences in altered lipoproteins.

In addition, we have analyzed the percentage of abnormal parameters values and association with gender and age within study group. We have noticed that male group has more number of abnormal parameters than female albeit there was no any statistically significant difference between the groups. We also categorized our test results in two groups, age >40 years and <40 years and analyzed the abnormal parameters in these groups and found that more number of abnormal parameters noticed among both genders in age group >40 years. It seems that type 2 diabetic patients of > 40 years of age are slightly more vulnerable in this respect compared to the < 40 age group. However, study done by Al Lawati et al [8], reported that the younger Omani type 2 diabetics exhibited worse glycemic state compared to older patients.

Glycosylated hemoglobin (HbA1c) is the main indicator which is used for evaluation of glycemic control in diabetes mellitus. The high values of HbA1c were associated with an increased risk of complications in patients with type-2 diabetes mellitus. Apart from classical risk factors like dyslipidemia, elevated HbA1c has now been regarded as an independent risk factor for cardiovascular disease in subjects with or without diabetes [23]. A highly significant correlation between HbA1c and FBS, TG, TC, LDL-C and HDL-C were observed in this study, which is in agreement with the findings of several other investigators who also reported significant correlations between HbA1c and individual blood lipid [24, 25]. A significant correlation between HbA1c level and lipid abnormalities were also noted and suggested importance of control of diabetes and control of lipids in Chinese study [26].

In previous studies, the degree of impaired glycaemic control was defined by different HbA1c cut off values. According to American Diabetes Association (ADA), glycated haemoglobin (HbA1c) more than or equal to 6.5% is considered diabetes. So, we have analyzed our parameters on the basis of cut off value 6.5%.

Significant correlation between HbA1c and various circulating lipid parameters and significant difference of lipid parameters in two groups (<6.5% and >6.5%) of glycated hemoglobin were observed. In addition, patients with high HbA1c ($\geq$ 6.5%) exhibited significant increase in FBS, TC, TG, LDL-C, TC/HDL and LDL/HDL ratio in comparison to patients with normal HbA1c (< 6.5%), which is consistent with the findings reported by Hammed et al. [27]. Khan *et al.* reported that HbA1c screening not only reflected glycaemic control, but predicted serum lipid profiles in diabetic patients as well [28]. However, there was no significant difference noticed in HDL levels. Diabetic patients with poor glycaemic control exhibited a significant increase in TC/HDL-C and LDL-C/HDL-C ratios. The reason maybe because that the change of ratios is earlier than individual lipid, especially in patients with normal blood lipid. Improving glycaemic control can substantially reduce the risk of cardiovascular events in diabetics. It has been estimated that reducing the HbA1c level by 0.2% could lower the mortality by 10%. [7].

Conclusions:-

It was concluded from the results of this study that HbA1c can be used as a predictor of dyslipidemia in type 2 diabetes mellitus in addition to as glycemic control parameter. HbA1c measurement helps to control diabetes mellitus and helps to identify dyslipidemia and will help for the better management of diabetes in preventing cardiovascular diseases due to dyslipidemia.

HbA1c can be used as a good indicator of glycemic control as well as a predictor of lipidemic state in type 2 diabetics.

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