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ORIGINAL RESEARCH

Correlation of HBA1c and neutrophil lymphocyte ratio in type 2 diabetes mellitus as a marker of blood sugar control – A case control study

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Abstract

Introduction-Synergistic effect of diabetes and inflammation exists in promoting atherothrombosis and its complications, as well as potential avenues for diagnostic, preventive, and therapeutic benefits in the modulation of inflammatory mechanisms in diabetic atherothrombotic disease. Recent findings suggest that elevated leukocyte count within the normal range, but especially neutrophil and monocyte counts, may be a harbinger of increased systemic inflammation and subclinical disease. NLR values have been used as an assessment tool of level of glycemic control in type 2 diabetic patients.[13] Its high value is a predictor of poor diabetic control. Hence this study was conducted to find correlation of hba1c and neutrophil lymphocyte ratio in type 2 diabetes mellitus as a marker of blood sugar control.

Methodology- This case control study was conducted on 220 patient of type 2 DM and 220 age sex matched controls. Out of 220 type 2 diabetic cases, 77(35%) were newly diagnosed type 2 diabetes and 143 (65%) were previously diagnosed case of type 2 DM from September 2019 till sample size achieved.

Results: HbA1C value was found to be significantly high in newly diagnosed type 2 DM (9.93%) as compared to previously diagnosed type 2 DM (7.98%).This difference was found to be statistically significant.$p<0.001$.ESR was found to be elevated in type 2 diabetic cases resulting average to be 60.67 mm/hr which is significantly raised as compared to control group average 10.85 with p value <0.001.Mean NLR was higher in newly diagnosed type 2 DM 3.89 as compared to previously diagnosed 2.89 .NLR was found to be raised in diabetics with value highest in newly diagnosed type 2 diabetic patients.A positive correlation between HbA1c and NLR ($p<0.001$) was established. i.e. as HbA1c increased, NLR increased significantly. There was no significant correlation between NLR and ESR with $p>0.05$.

Keywords- Diabetes, HB1AC, NLR,ESR. Correlation

Introduction

The "Diabesity" epidemic (obesity and type 2 diabetes) is likely to be the biggest epidemic in human history. Diabetes has been seriously underrated as a global public health issue and the world can no longer ignore "the rise and rise" of diabetes.[1]The global diabetes prevalence in

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2019 is estimated to be 9.3% (463 million people) which denotes such a significant burden it causes on the health.[2]

It is a multiorgan disease. Macrovascular complications due to chronic hyperglycemia in diabetes are mainly represented by atherosclerotic disease and its sequelae.[3]Diabetes-related microvascular disease such as retinopathy and nephropathy are major causes of blindness and renal insufficiency.[4] Both type 1 and type 2 diabetes are powerful and independent risk factors for coronary artery disease (CAD), stroke, and peripheral arterialdisease..[5]

The emerging role of inflammation in diabetespathophysiology and associated metabolic disorders, has generated increasing interest in targeting inflammation to improve prevention and control of the disease.[6,7]

Synergistic effectof diabetes and inflammation exists in promoting atherothrombosis and its complications, as well as potential avenues for diagnostic, preventive, and therapeutic benefits in the modulation of inflammatory mechanisms in diabetic atherothrombotic disease.[8,9,10]

Total leukocyte count increases significantly in response to infection,inflammation, and certain diseases. [11] Recent findings suggest that elevated leukocyte count within the normal range, but especially neutrophil and monocyte counts, may be a harbinger of increased systemic inflammation and subclinical disease.[12] Remarkably, leukocyte count correlates positively with genuine markers of systemic inflammation like C-reactive protein and interleukin 6.[11,12].

NLR values have been used as an assessment tool of level of glycemic control in type 2 diabetic patients.[13] Its high value is a predictor of poor diabetic control.[13]When compared with other inflammatory biomarkers e.g., ESR and CRP,IL6,Serum Ferritin the Neutrophil–lymphocyte ratio (NLR) is obtained from routine complete blood count (CBC) test.When correlated with diabetic glycemic control itserveas a cost-effectiveand easyaccessible indicator

Material and method

Methodology

Permissions

Necessary permission will be taken from

1. The Ethical Committee
2. Research Review Board

Place of study

Internal medicine wards and Opd, Endocrinology wards and Opd of **American International Institute of Medical Sciences, Bedwas, Udaipur, Rajasthan**.

StudyType

Hospital based observational study.

StudyDesign

Cross sectional study

Sample method

Consecutive patients

Sample size

This study was conducted on 220 patient of type 2 DM and 220 age sex matched controls.Out of 220 type 2 diabetic cases, 77(35%) were newly diagnosed type 2 diabetes and 143 (65%)

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were previously diagnosed case of type 2 DM.

Study Period
Started from September 2019 till sample size achieved.

Inclusion criteria
Cases
- Age > 18 years
- Patients with newly or previously diagnosed type 2 Diabetes Mellitus
- Diagnosis of Diabetes
- Symptoms of diabetes plus randomblood glucose concentration ≥200 mg/dl
- Fasting plasma glucose>126 mg/dl
- 2-hr plasma glucose ≥200 mg/dl after oral glucose challenge
- HbA1c ≥ 6.5 %
- Controls
- normoglycemic patients
- Fasting plasma glucose <100 mg/dl
- 2-hr plasma glucose <140 mg/dl after oral glucoseChallenge
- HbA1c<5.6 %

Exclusion Criteria
- Severely ill patients unable to give consent
- Established source of infection / Sepsis
- Allergic reactions
- Malignancy
- On chronic drug therapy such as corticosteroids, lithium, heparin, antiepileptic drugs
- MI
- Pregnancy

This present cross sectional study was conducted on total 440 subjects,out of which 220 type 2 diabetic patient as cases and 220 healthy controls who attended internal medicine wards and Opd, Endocrinology wards and Opd of RNT medical college and associated groups of hospitals,Udaipur from September 2019 till sample size achieved.

Sampling Method
Consecutive patients

Inclusion Criteria
- **Cases**
- Age > 18 years
- Patients with newly or previously diagnosed type 2 Diabetes Mellitus
- Diagnosis of Diabetes
- Symptoms of diabetes plus randomblood glucoseconcentration ≥200 mg/dl
- Fasting plasma glucose>126 mg/dl
- 2-hr plasma glucose ≥200 mg/dl after oral glucosechallenge
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- HbA1c<5.6 %

Exclusion Criteria

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- Allergic reactions
- Malignancy
- On chronic drug therapy such as corticosteroids , lithium , heparin , antiepileptic drugs
- MI
- Pregnancy

Sample collection

Venous blood collected in vial with EDTA as anticoagulant.

Statistical Analysis

Nominal / categorical variables were summarized as frequency and percentage and were analyzed using Chi square test / Fischer's Exact test as applicable.

Continuous variables were summarized as mean and standard deviation and were analyzed using student t test (for 2 group comparison) and ANOVA test for more than two group comparison.

Correlation between two variables was analyzed using Pearson correlation coefficient. A p value < 0.05 was taken as statistically significant.

All statistical analyses was done using Epi info version 7.2.1.0.

Investigations profile

1. Complete Blood Count
2. ESR
3. FBS,RBS,PP BS
4. HbA1c
5. Lipid Profile(Cholesterol,LDL,HDL)
6. Urine Protein
7. Urine Albumin to creatinine ratio
8. ECG
9. CXR PA view

Observation and results

Table 1: Gender distribution among cases and controls

	Cases(n=220)		**Controls(n=220)**	
Sex	**No.**	**%**	**No.**	**%**
Females	109	49.54%	106	48.18%
Males	111	50.45%	114	51.81%
Total	**220**	**100.00%**	**220**	**100.00%**

p>0.05 (NS)

Graph 1-

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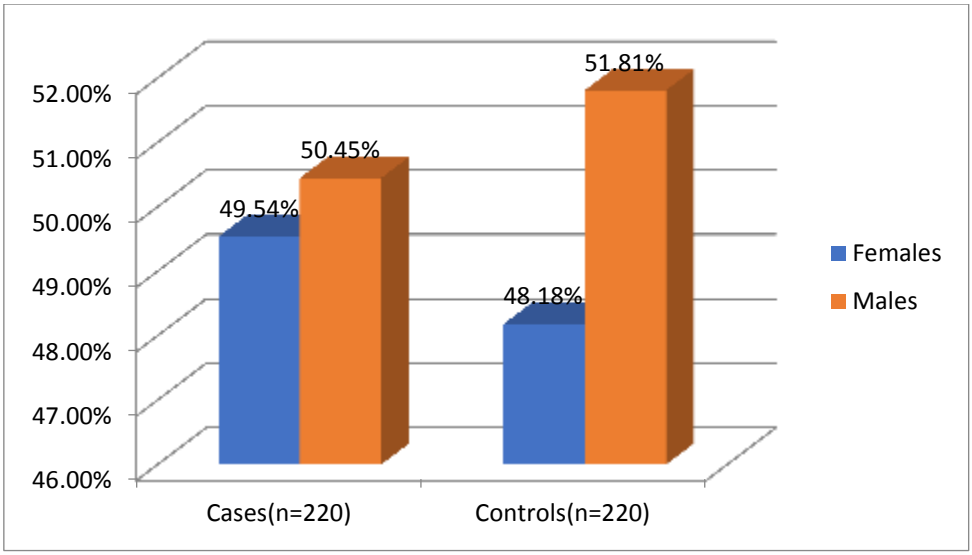


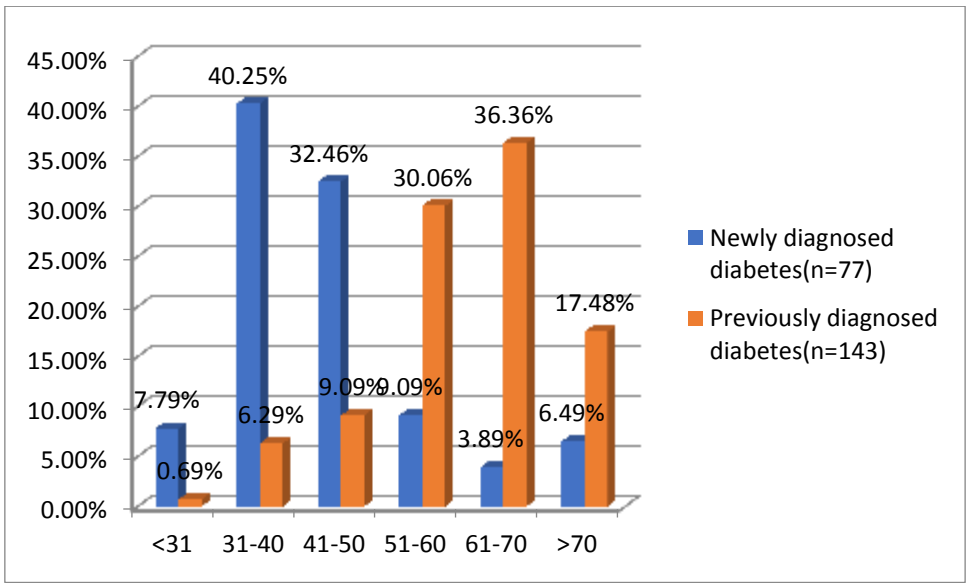
Above table shows that diabetic cases consist of 109 females(49.54%) and 111 males (50.45%) males while in the control group there were 106 female (48.18%) and 114 males (51.81%) . Difference was statistically non significant p >0.05

Table 2: Age distribution among case study groups (newly and previously diagnosed diabetes)

	Newly diagnosed diabetes(n=77)		Previously diagnosed diabetes(n=143)	
Age Group (yrs)	**No(n)**	**%**	**No(n)**	**%**
<31	6	7.79%	1	0.69%
31-40	31	40.25%	9	6.29%
41-50	25	32.46%	13	9.09%
51-60	7	9.09%	43	30.06%
61-70	3	3.89%	52	36.36%
>70	5	6.49%	25	17.48 %
Total	77	100%	143	100%

P=<0.001 (HS)

Graph no 2



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Most of the cases in newly diagnosed type 2 diabeteswere in 31-40 year age group 31 (40.25%). Among previously diagnosed type 2 diabetes maximum cases were in the age group of 61 – 70 years of age 52 (36.36%) and the difference was statistically significant p <0.05

Table 3: Mean Values of HbA1c Among the Cases and Controls

	Cases(n=220)		Controls(n=220)		
	Mean	**SD**	**Mean**	**SD**	**P value**
HbA1c	8.41	2.45	4.07	0.60	<0.001 (HS)

Above table shows a comparison of glycosylated haemoglobin among cases and control. The mean HbA1C was 4.07 in control and 8.41 in cases and the difference was statistically significant p <0.05.

Table 4:Mean Values of HbA1c Among Cases (Newly Diagnosed and Previously Diagnosed type 2 diabetes)

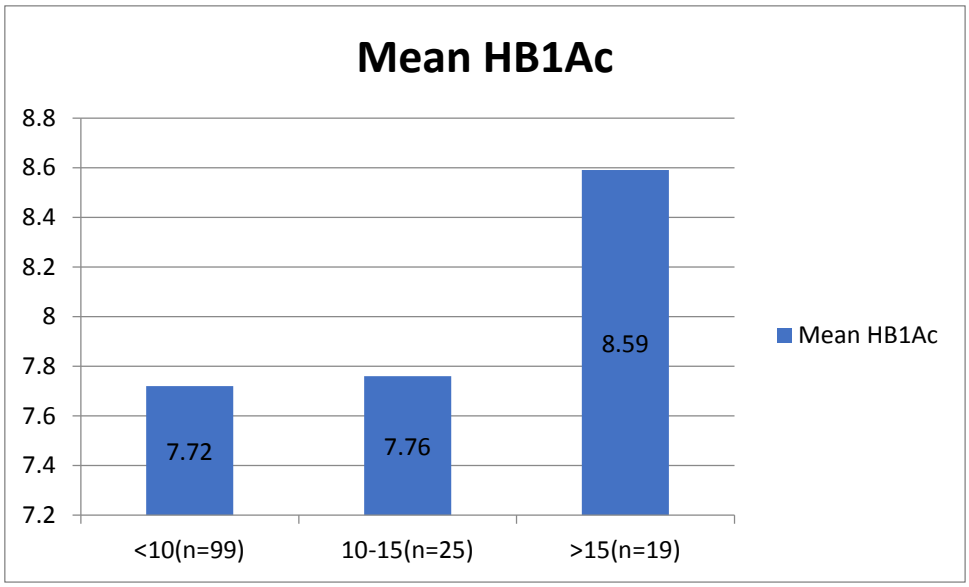
	Newly diagnosed type 2 diabetes(n=77)		Previously diagnosed type 2 diabetes(n=143)		ANOVA
	Mean	**SD**	**Mean**	**SD**	**P value**
HbA1c	9.93	2.56	7.98	2.15	<0.001(HS)

HbA1C value was found to be high in newly diagnosed type 2 DM (9.93%) as compared to previously diagnosed type 2 DM (7.98%) .Comparison was statistically significant p <0.05

Table 5: Mean Values of HbA1c Among with Duration of Diabetes in Previously Diagnosed cases (n=143)

	HbA1c	
Duration of Diabetes (yrs) in previously diagnosed cases(n=143)	**Mean**	**±SD**
<10(n=99)	7.72	1.72
10-15(n=25)	7.76	1.13
>15(n=19)	8.59	1.22
P=<0.05(S)		

Graph no 3-



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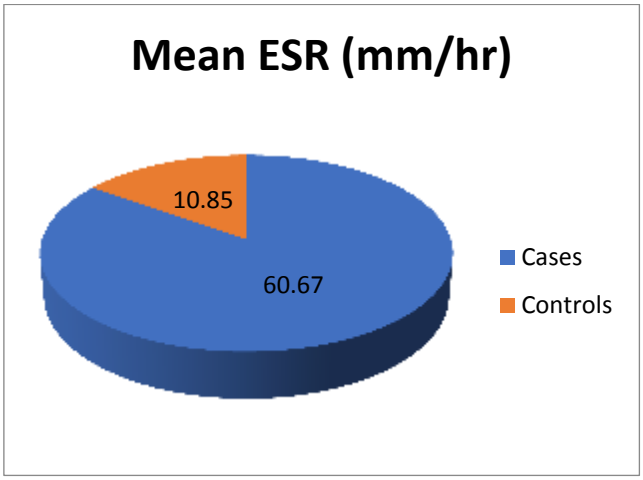
The mean HbA1C of previously diagnosed diabetics with respect to duration of diabetesshowed, mean HbA1c in patient with T2DM <10 yr was 7.72,10-15 yr T2DM 7.76 and >15 year of T2DM the mean HbA1c was 8.59.The results were statistically significant with p value <0.05.
Mean value of newly diagnosed cases was 9.93 as depicted in table number 4

Table 6: Mean Values of ESR Between Cases and controls

	ESR	
	Mean (mm/hr)	**±SD**
Cases	60.67	38.19
Controls	10.85	4.34
P value	<0.001 (HS)	

Graph no 4

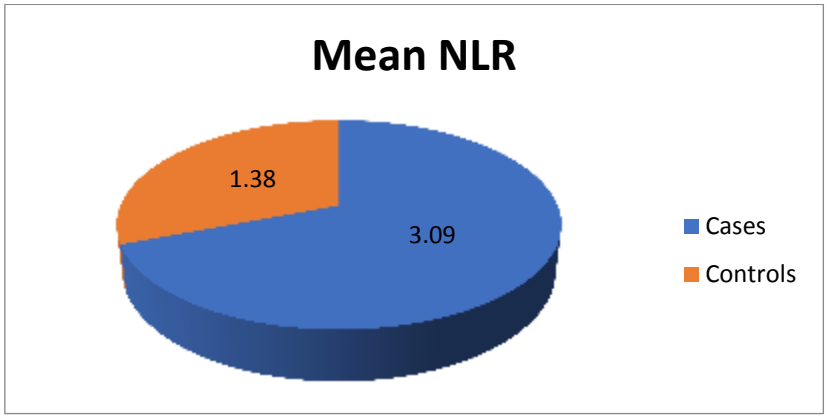


The above table shows that the mean ESR among study population. ESR, marker of inflammation was found to be raised in cases with a mean value of 60.67 mm/hr when compared to control's 10.85 mm/hr and the difference was statistically significant p <0.05

Table 7: Mean Values of NLR Between Cases and controls

	NLR	
	Mean	**±SD**
Cases	3.09	2.55
Controls	1.38	0.54
P value	**<0.001 (HS)**	

Graph no 5



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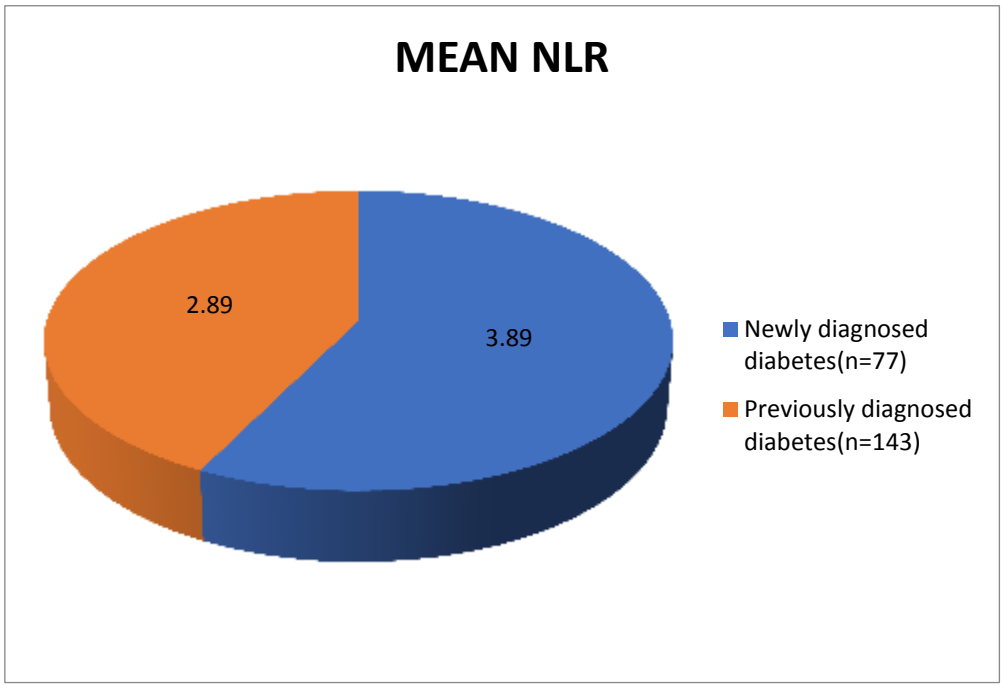
Above table shows that the mean NLR among diabetic cases was 3.09, while that in controls was lower 1.38. Difference was statistically significant p <0.05.
NLR was obtained on dividing absolute neutrophil count by absolute lymphocyte count.

$$NLR = \frac{\text{Absolute Neutrophil Count}}{\text{Absolute lymphocyte count}}$$

Table 8: Mean Values of NLR Among Cases (Newly diagnosed type 2 DM and Previously diagnosed type 2 DM)

	Newly Diagnosed		Previously Diagnosed		ANOVA
	Mean	**SD**	**Mean**	**SD**	**P value**
NLR	3.89	3.86	2.89	0.72	<0.001

Graph no 6-



Present table shows that the Mean NLR was higher in newly diagnosed DM 3.89 as compared to previously diagnosed 2.89 and the difference was statistically different with p value <0.05.

Table 9: Mean Values of HbA1c and NLR between case study groups according to glycemic control as predicted by HbA1c level variations

	NLR	
HbA1c	**Mean**	**±SD**
<7 (n=68)	1.99	0.92
7-9 (n=85)	2.60	0.98
>9 (n=67)	4.83	3.85
Total (n=220)		
ANOVA p value	<0.001 (HS)	

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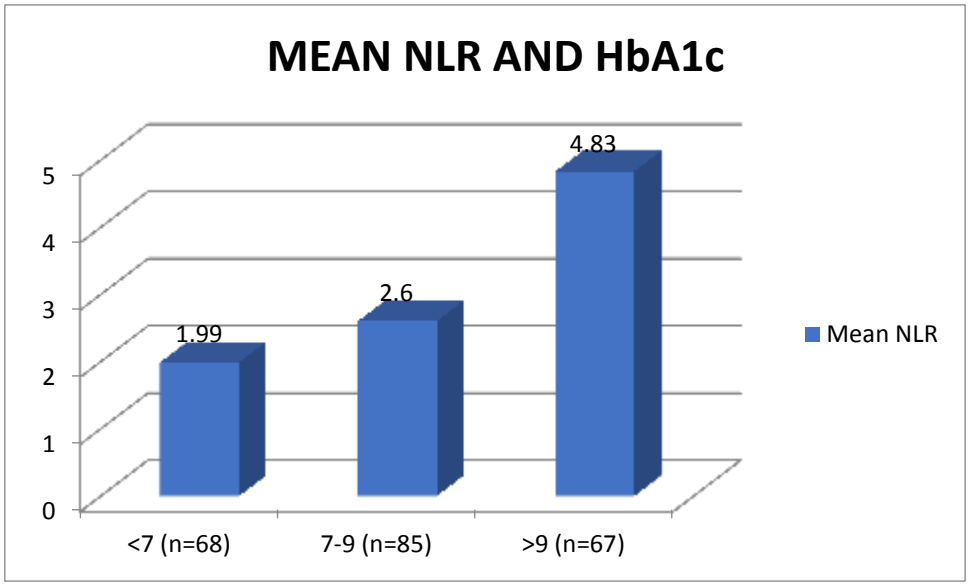
Graph no 7

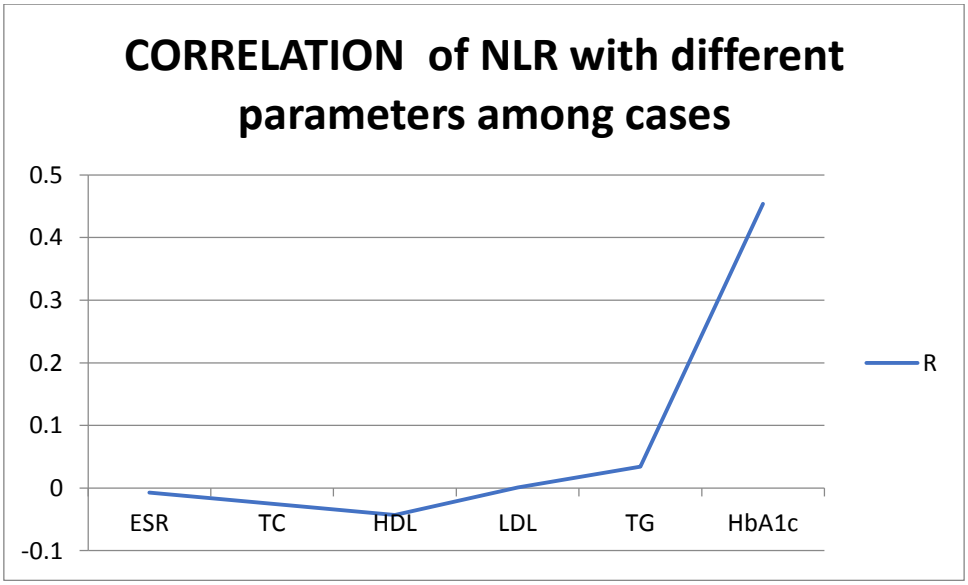


The above table shows mean NLR among the various HbA1c study groups it was (1.99) in HbA1c <7, 2.60 in HbA1c 7-9, 4.83 in HbA1c >9. Difference was statistically significant p <0.05.

Table No. 10:Correlation of NLR with different parameters among cases

	R	P value
ESR	-0.007	>0.05 (NS)
TC	-0.025	>0.05 (NS)
HDL	-0.043	>0.05 (NS)
LDL	0.001	>0.05 (NS)
TG	0.0344	>0.05(NS)
HbA1c	0.454	<0.001 (HS)

Graph no 8



This table shows that there was strong positive correlation between HbA1c and NLR of diabetic patients. with a Pearson's coefficient of correlation 0.454 and p <0.05. There no significant correlation with ESR,TC,HDL,LDL,TG with NLR p >0.05.

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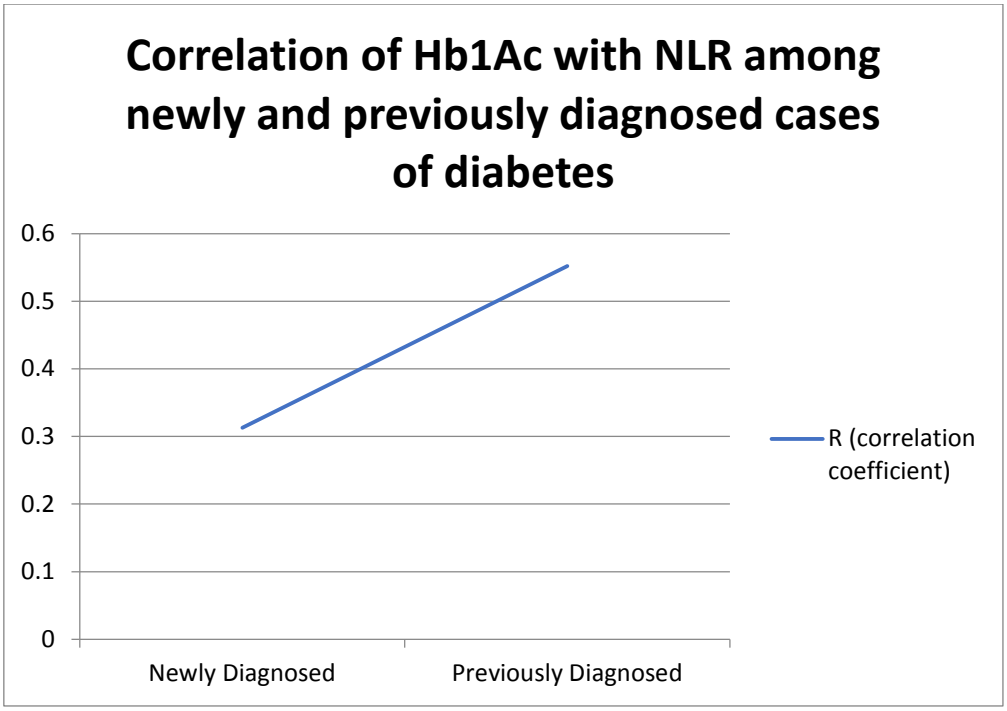
Table No. 11:Correlation of Hb1Ac with NLR among newly and previously diagnosed cases of diabetes

	R (correlation coefficient)	P value
Newly Diagnosed	0.313	<0.001 (HS)
Previously Diagnosed	0.552	<0.001 (HS)

Graph no 9



This table shows that there was moderate positive correlation between HbA1c and NLR in newly and previously diagnosed diabetic patients with p value < 0.001.

Discussion

The present study was undertaken for establishing neutrophil lymphocyte ratio as predictive co marker of dysregulation of blood sugar in type 2 diabetes mellitus.Also to find correlation of HbA1c and NLR ratio to utilise as alternative marker for disease monitoring tool. A total of 440 patients with 220 as cases and 220 as control group were assessed.Out of total 220 cases of type 2 diabetes mellitus newly diagnosed diabetic consisted of 77 (35%) and previously diagnosed diabetes 143(65%).

Out of the total 220 patients with type 2 diabetes, 111 (51%) were males and 109 (49%) were females ,showing equal prevalence among both sexes.The difference in sex distribution was statistically insignificant with p value >0.05.

Out of 220 cases maximum number of newly diagnosed diabetics 31 (40.25%) out of 77 belonged to 31-40 year age group. Where as maximally 52 (36.36%) previously diagnosed diabetic patients belonged to the age group of 61-70 yr. The difference in the age groups of newly diagnosed and previously diagnosed cases of type II diabetics was statistically significant with p value < 0.05.

A national survey of diabetes and impaired glucose tolerance (IGT) conducted in 2000 AD in six major cities of India by C Snehalatha et al [14]Subjects under 40 years of age had a higher prevalence of impaired glucose tolerance than diabetes (12.8% vs 4.6%, p < 0.0001).Diabetes showed a positive association with age,Similar results were obtained in our study as maximum cases of previously diagnosed diabetes 52(36.36%) were above 61-70 year age group.

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Hemoglobin A1c (glycated hemoglobin) assay is useful for diagnosing Diabetes and evaluating long term control of blood glucose concentrations in diabetic patients. It reflects the mean glucose concentration over the previous period of 8 to 12 weeks and is a better indicator of long term glycemic control as compared with blood glucose levels due to lesser day to day variation.

In our study, the mean HbA1c was found to be within normal limit 4.07% in controls and was significantly higher in cases with a mean value of 8.41%. The difference between cases and control was statistically significant with p value < 0.001.

Glycosylated hemoglobin value was found to be high in newly diagnosed DM 9.93% as compared to previously diagnosed DM 7.98%.This difference was found to be statistically significant on application of ANOVA test (p<0.001).

This difference was probably due to previously diagnosed type 2 diabetics being on antidiabetic medication while newly diagnosed type 2 diabetics had higher HbA1c due to persistently raised blood glucose levels without any anti diabetic treatment.

The landmark Diabetes Control and Complications Trial (DCCT)[15] completed in 1993, showed that the risk for development and progression of the chronic complications of diabetes is closely related to the degree of glycemic control, as assessed by glycohemoglobin [(GHB); specifically hemoglobin A_{1c} (HbA_{1c})] determinations.[16]

Our study showed increasing HbA1c trend with duration of diabetes among previously diagnosed cases 143. With diabetes <10 yr having mean HbA1c 7.72,while with duration 10 - 15 yr mean HbA1c was 7.76 and for diabetes >15 yr mean HbA1c 8.59 with statistically significant p value <0.05.In a study conducted by Junyi Jiang et al[17]showed among diabetic patients, the average levels of FPG, HbA1c increased and BMI decreased with increasing duration of the disease after adjusting for age, sex, oral hypoglycemic drug use and insulin use (P for trend,0.05) which was consistent with our studies.

ESR was found to be elevated in patients with type 2 Diabetes mellitus cases resulting in mean ESR 60.67 mm/hr as compared to controls with ESR 10.85 mm/hr which is significantly raised with p value < 0.001

Study conducted by Mubin Mustafa Kiyaniet al[18] showed that the relationship between erythrocyte sedimentation rate (ESR) in diabetic (DM) and non-diabetic patients of cardiovascular diseases (CVD) .Pearson correlation between ESR of CVD without DM and ESR of CVD with DM, and they determined that there is a weak relationship between these two variables. Value of Pearson ‘r' between these two variables is 0.160.

Mean NLR among diabetic cases was 3.09, while that in controls was lower 1.38. This difference was found to be statistically significant (p<0.001). Normal mean NLR value is 1.65 within the range 0.78 – 3.53. Mean NLR was higher in newly diagnosed DM 3.89 as compared to previously diagnosed 2.89 this difference was found to be statistically significant on application of ANOVA test (p< 0.001).In a study conducted by Hussain M et al[19] concluded that increased NLR level is associated with elevated HbA1c and poor glycemic control in patients of type 2 diabetes mellitus. The value of NLR was also significantly higher in worst control as compared to poor control and excellent control (4.3±2.8, 2.7±1.0 and 2.0±0.5 respectively p<0.001).In another study done byShiny et al[20]Subjects with DM showed a significantly higher NLR (2.2±1.12) compared with IGT subjects (1.82±0.63), who in turn had a higher ratio than NGT subjects (1.5±0.41) (*P*<0.01). Pearson correlation analysis showed a significant positive correlation of NLR with glycated hemoglobin (*r*=0.411), fasting plasma glucose (*r*=0.378), and HOMA-IR (*r*=0.233) (*P*<0.001).

Pearson correlation coefficient for HbA1C with NLR was 0.454. There was a positive correlation between HbA1c and NLR (p<0.001). i.e. as HbA1c increased, NLR increased significantly.Also mean NLR among the various HbA1c study groups was 1.99 in HbA1c

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<7, 2.60 in HbA1c 7-9, 4.83 in HbA1c >9. The difference was statistically significant p <0.05

Devamsh G. N et al[19] studied the relationship between NLR and glycemic control in type 2 diabetes patients. NLR had a positive correlation with HbA1c and was found to be an independent predictor of poor glycemic control in patients with type 2 diabetes mellitus.

Akin et al [20] studied A total of 278 Type 2 diabetic patients. The patients were divided into two groups: the good glycaemic control group (HbA1c ≤7.5%) and the poor glycaemic control group (HbA1c >7.5%). NLR was compared between the diabetic groups. In addition, NLR was compared with diabetic patients and control group. The NLR was statistically and significantly higher in the poor glycaemic control group compared to the good glycaemic control group .In addition, NLR was significantly higher in the patients than in the control group.

There was no significant correlation between NLR and ESR of diabetic patients with the pearson correlation coefficient being -0.007 and p value being >0.05. ESR is a nonspecific marker of inflammation and NLR is emerging marker of inflammation. Both are independent marker of inflammation.AbdulhalimSenyigit[144] studied the role of neutrophil-to lymphocyte ratio (NLR) in T2DM patients comparing with the other well-known inflammatory markers as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen.They concluded NLR is independently associated with other well-known inflammatory markers as CRP, ESR and fibrinogen, NLR level of the groups showed no correlation with any parameters including CRP, ESR,WBC, and fibrinogen. In our study also both the variables were independent and had no correlation with each other.

Summary and conclusion

This study was conducted on 220 cases and 220 control subjects, in RNT Medical College and associated group of Hospitals,Udaipur.HbA1C value was found to be signifiacntly high in newly diagnosed type 2 DM (9.93%) as compared to previously diagnosed type 2 DM (7.98%).This difference was found to be statistically significant.p<0.001.ESR was found to be elevated in type 2 diabetic cases resulting average to be 60.67 mm/hr which is significantly raised as compared to control group average 10.85 with p value <0.001.Mean NLR was higher in newly diagnosed type 2 DM 3.89 as compared to previously diagnosed 2.89 .NLR was found to be raised in diabetics with value highest in newly diagnosed type 2 diabetic patients.A positive correlation between HbA1c and NLR (p<0.001) was established. i.e. as HbA1c increased, NLR increased significantly.There was no significant correlation between NLR and ESRwith p>0.05.

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