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RESEARCH ARTICLE
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STUDY OF THE RED BLOOD CELL INDICES AND COAGULATION PROFILE IN RELATION WITH GLYCATED HEMOGLOBIN (HbA1c) IN TYPE 2 DIABETES MELLITUS INDIVIDUALS AT A TERTIARY CARE HOSPITAL.

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is characterized by hyperglycemia[(1)]. The effect of hyperglycemia in altering the aggregation and deformability of RBCs and the reduction in the lifespan of RBCs, is hypothesized to bring changes in these RBC indices. The aim of this study is to assess the red blood cell indices and coagulation impairment in type 2 diabetes mellitus (T2DM) patient, thereby preventing thromboembolic complications.

MATERIAL AND METHODS: This is a hospital-based, cross-sectional study which was conducted at SSIMS and RC hospital, Davanagere from January 2024 to May 2024. 110 cases of T2DM aged above 30 years with HbA1C ≥ 7 were included in this study. RBC count, Hb, HCT, MCV, MCH, MCHC, RDW, HbA1c, PT, INR, aPTT were measured.

RESULT: In this study, males comprised 68.1% of the participants. 45% of participants were in the age group of 51-60 years. Patients with poor glycemic control exhibited low MCH values. The study showed that, the patient with HbA1c >9 showed reduced prothrombin time.

CONCLUSION: This study shows that T2DM patients with HbA1C ≥ 9 have procoagulant state suggesting increased risk of stroke or Myocardial infarction and lower MCH levels in the context of poor glycemic control can serve as an indicator of the risk of developing DM-related vascular complications.

Keywords: Type 2 Diabetes mellitus, Red blood cell indices, MCH, HbA1c, coagulation profile, Glycemic control, thrombotic complications.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia secondary to Insulin resistance or Impaired insulin secretion[(2)]. Underlying persistent hyperglycemia is linked to harm to several of our body's target organs in individuals with Diabetes mellitus[(1)]. Hypercoagulability is a prominent feature in diabetic patients, contributing to thrombotic complications[(3)]. Hence diabetic individuals face a 2 to 4 fold higher likelihood of developing coronary artery disease[(3,4)]. In that

essence, management of diabetes fundamentally constitutes good glycemic control[1]. The burden of DM among adults has rapidly increased from 108 million in 1980 to 537 million cases and 6.7 million deaths in 2021[5]. Evidence from randomized trials has shown that intensive glycemic control can clearly reduce the microvascular complications of DM[1]. The evidence towards reducing macrovascular complications, although less compelling, supports an early and better glycemic control in T2DM[1,6].

2021 Study indicates that the incidence of diabetes in the world, Southeast Asia and India was 10.5%, 8.8% and 9.6%, respectively[7]. The effect of hyperglycemia in altering the aggregation and deformability of RBCs and the reduction in the lifespan of RBCs, is hypothesized to bring changes in these RBC indices[1,3]. Hyperglycaemia contributing to hyperfibrinogenaemia, platelet hyperreactivity, increased thrombin formation and reduced fibrinolysis[3]. PT and APTT the marker for activation of extrinsic and intrinsic pathway respectively. The hypercoagulability state demonstrated by shortened PT and APTT in diabetes mellitus may cause occlusive thrombus within coronary artery[3].

Since Glycated hemoglobin (HbA1c) gives the average blood glucose level over the preceding two to three months, it is regarded as the gold standard for assessing long-term glycemic management. However, the high expense and restricted availability of HbA1c testing pose serious obstacles to its widespread adoption in many underdeveloped nations. These drawbacks underscore the pressing need for accessible and reasonably priced substitute techniques for glycemic status monitoring.

Hence, the aim of this study is to assess the potential of red blood cell indices and impaired coagulation profile in predicting glycemic control among people living with T2DM patient, thereby helping in preventing thromboembolic complications.

AIM OF THE STUDY

OBJECTIVES

1. To assess the potential of red blood cell indices in predicting glycemic control in individuals with type 2 diabetes mellitus.
2. To assess correlation of coagulation profile with glycemic control (HbA1c).

METHOD AND MATERIALS

Study Area and Period

This is a hospital-based study which was conducted at SSIMS and RC hospital, Davanagere from January 2024 to May 2024 with sample size of 110.

Study Design

A hospital-based, cross-sectional study was conducted at a tertiary care hospital.

Study population

The study population consisted of all T2DM patients who attended the outpatient or inpatient departments of the SSIMS and RC hospital, Davanagere during the study period.

Inclusion Criteria

1. All patients with type 2 Diabetes Mellitus with HbA1c ≥7,
2. Age ≥ 30years, who who provide informed consent.

Exclusion Criteria

1. Pregnant (second or third trimester) or lactating mothers during data collection,
2. Critically ill patients,
3. Use of immunosuppressive therapy in the past 3 months,
4. Blood loss/transfusion in the past 3 months,
5. Those who are known to have hematologic disorders or Iron deficiency anemia,

6. Liver disease or renal failure,
7. Presence of acute or chronic infections and malignancy,
8. Patients on anticoagulant therapy and receiving erythropoietin.

METHODOLOGY

T2DM was diagnosed in the study population using the American Diabetic Association (ADA) criteria. A Structured data collection tool was used to collect the data from medical records, direct patient interviews and laboratory results.

- Two groups were made,

1. Individuals with HbA1c 7-9,
2. Individuals with HbA1c >9.

Sampling Method

- A consecutive sampling technique will be used to recruit eligible participants who meet the inclusion criteria.

Sampling Technique and Sampling Procedure

- Eligible patients with T2DM who attended for follow-up starting from the data collecting period were added in a consecutive manner. Study participants were recruited until the calculated sample size was reached.
- Informed Consent will be obtained from all participants.
- A brief clinical history and demographic data (age, sex, duration of diabetes, treatment) will be recorded.
- Venous fasting blood will be extracted from each patient who has given their consent. Venous blood samples will be collected under aseptic precautions:

3 mL in EDTA tube: For Complete Blood Count (CBC) and HbA1c.
3 mL in sodium citrate tube: For coagulation profile (PT, aPTT, INR).

- Samples will be processed in the hospital's central laboratory using standard procedures.
- Laboratory Parameters Assessed are Hemoglobin (Hb), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Cell Distribution Width (RDW) are Analyzed using an automated hematology analyzer such as Sysmex XN-1000.
- HbA1c measured by High-Performance Liquid Chromatography (HPLC) or Immunoturbidimetric method.
- Coagulation Profile: PT, aPTT, INR are analyzed using automated coagulation analyzer .

STATISTICAL ANALYSIS

Data was entered in Microsoft Excel and analyzed using SPSS version 10.
This software calculated mean, standard deviation and p-value with the student ‘t-test’. Descriptive statistics: Mean, Standard Deviation (SD) and proportions will be used for quantitative and qualitative variables.
SAMPLE SIZE
$N = (Z_\alpha^2 \text{ X } p \text{ X } q) / d^2$
Where,
Z_α^2 = Standardized Normal Deviate (Z value) for $\alpha = 0.05 = 1.96$, p = Prevalence of type 2 diabetes mellitus = 11.4%
q = 100-11.4 = 88.6% , d = Absolute precision = 6%, $n = (1.96^2 \text{ x } 11.4 \text{ x } 88.6)/ 6^2$
n = 108 rounded up to 110
Pearson’s correlation test will assess the relationship between HbA1c with respect to Red blood cell indices and coagulation parameters.
A p-value of <0.05 will be considered statistically significant.

ETHICAL CONSIDERATIONS

Written informed consent will be obtained from all participants.
Confidentiality of participant's data will be maintained.

RESULTS

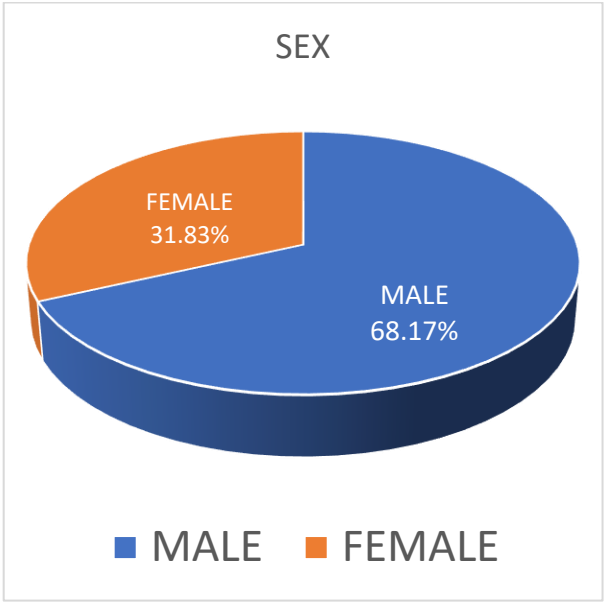


Figure 1: Sex distribution of patients with T2DM in SSIMS and RC Hospital, Davanagere (n=110), 2024. Out of 110 , 35(31.83%) were female, 75(68.17%) were male.

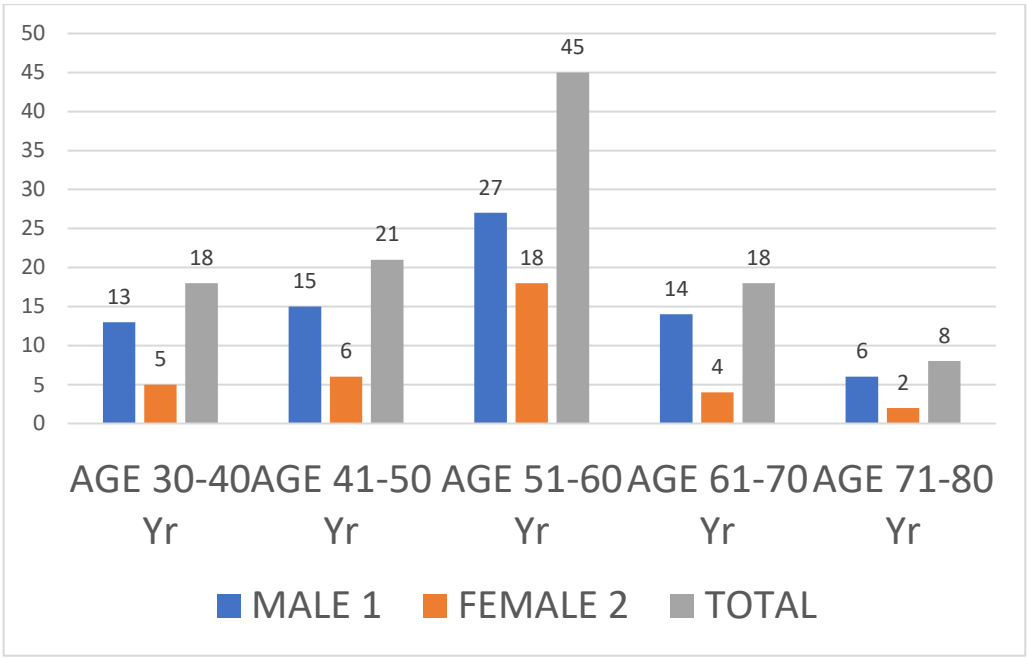


Figure 2: Age distribution of patients with T2DM in SSIMS and RC Hospital, Davanagere (n=110), 2024.

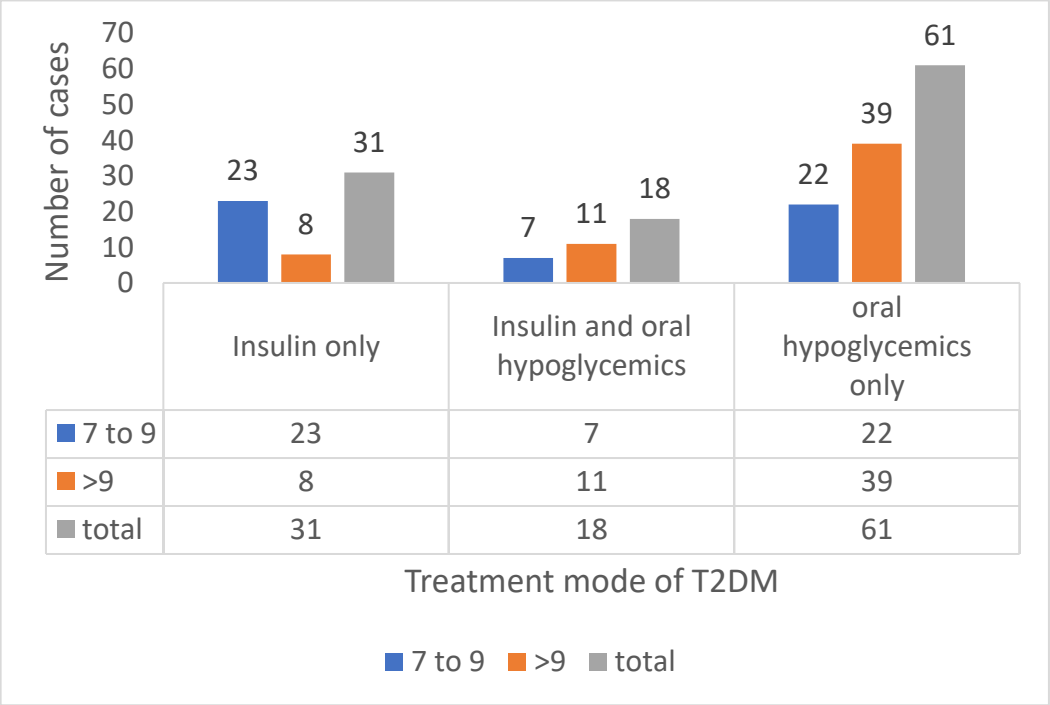


Figure 3: Clinical and Anthropometric Characteristics of Patients with T2DM.

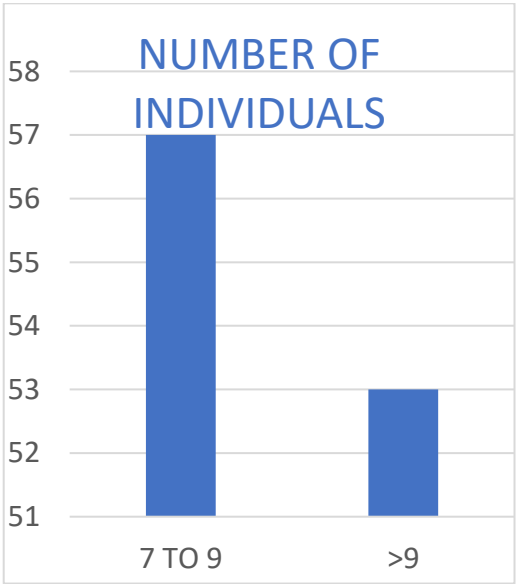


Figure 4: Distribution of T2DM individuals in two groups with respect to HbA1c values.

Y axis: number of cases
x axis: HbA1c groups

HbA1c	NUMBER OF PARTICIPANTS	PERCENTAGE (%)
7-9	57	51.8
>9	53	48.18

TABLE 1: Out of 110 T2DM cases, 57 had HbA1c 7-9 and 53 had HbA1c >9.

Table 2: Summary of RBC indices and Coagulation profile for patients with T2DM.

	Mean	Median (IQR)	Maximum	Minimum	Reference Interval
AGE	53	55 (46-60)	78	30	>30
RBC (*10^6)	4.35	4.25 (3.825 - 4.9)	6.5	3.20	4.5-6.0
Haemoglobin (g/dL)	12.35	12 (11-13.4)	16.9	10	13-18
Hematocrit (%)	37	36 (33-40.2)	50.3	29.1	40-54
MCV (fL)	84.25	85 (80.6-88.7)	120	60.5	76-97
MCH (pg)	27	28.4 (26.5-29.9)	42.5	20.1	26-32
MCHC (g/dL)	33	33.2 (32.2-34)	39	27	32-36
RDW (%)	14.42	14.1 (13.6-15)	18	11	11-15
HbA1c (%)	9.12	8.8 (7.8-10)	13	7	>6.5
PT	11.45	11.6 (10.1-12.6)	15.1	9.6	10.3-14.3
INR	0.97	0.9 (0.9-1)	1.27	0.8	0.9-1.3
aPTT	28.27	28 (24.5-31.1)	40.2	16.5	25.1-34.7

The participants had a median hemoglobin level of 12 g/dL, with an interquartile range from 10 g/dL to 16.9 g/dL, indicating that half of the participants had hemoglobin levels within this range.
The median was found to be 85fL, 28.4 pg, 33.2 g/dL and 14.1%, 11.6, 0.9, 28 for MCV, MCH, MCHC and RDW, PT, INR, aPTT respectively among the participants.

Table 3: Correlation between HbA1C level and the RBC indices and coagulation profile among patients with T2DM at SSIMS AND RC, Davanagere. (n=110), 2024

Variables	HbA1c	N	Mean	Std. Deviation	t-value	p-value
PT	7-9	57	12.609	4.0418	4.443	0.0001(sig)
	>9	53	10.208	0.5388		
INR	7-9	57	1.0685	0.34253	4.443	0.0001 (sig)
	>9	53	0.8650	0.04566		
APTT	7-9	57	28.900	4.3363	1.520	0.131 (NS)
	>9	53	27.609	4.5663		
HB	7-9	57	12.070	1.7071	-1.913	0.058 (NS)
	>9	53	12.660	1.5138		
HCT	7-9	57	36.4930	5.54230	-1.084	0.281 (NS)
	>9	53	37.5585	4.69658		
RBC	7-9	57	4.263	0.6397	-1.505	0.135 (NS)
	>9	53	4.445	0.6287		
MCV	7-9	57	84.525	9.1942	0.315	0.753 (NS)
	>9	53	83.970	9.2713		
MCH	7-9	57	27.937	3.6416	2.315	0.023 (Sig)
	>9	53	26.179	4.3141		
MCHC	7-9	57	33.067	1.3962	-0.128	0.899 (NS)
	>9	53	33.108	1.9345		

RDW	7-9	57	14.575	1.5625	1.151	0.252 (NS)
	>9	53	14.270	1.2100		
AGE	7-9	57	53.91	11.616	0.569	0.571 (NS)
	>9	53	52.72	10.330		

- Independent t-test is applied to the above table. Sig means significant and NS means not significant at 5% level of significance.
- Out of 110 cases, 57 with HbA1c and 53 with HbA1c, p value was significant for PT-INR and MCH.

DISCUSSION

DM is a global health issue and the number of diagnosed cases is dramatically increasing worldwide[8]. Thus, the management and follow-up of this disease is of worldwide importance. Our aim in the present study was to evaluate an association between some CBC parameters and the HbA1c levels.
Our study showed PT-INR were found to be significantly higher in those individuals who had HbA1c was 7-9 as compared to those whose HbA1c was >9. Out of 110 cases, between two groups the statistical difference in the P value was 0.001 which was found to be significant for PT-INR. This suggests that the more the poor glycemic control, more is the risk of hypercoagulable state. Hence it is important to stress the efficient management of glycemic status since it causes changes in the coagulation profile.

Ahmad S *et al.* conducted a study which also concluded that mean PT and APTT are shorter and mean platelet count is higher in T2DM patients than controls and that is the indication of hypercoagulability and higher tendency of thrombus formation in T2DM patients. Decrease in PT, APTT and increase in platelet count are also associated with glycemic control status of the T2DM patients[9].

It has been suggested that natural anticoagulant antithrombin III keeps the natural procoagulant inhibited. In addition protein C inactivates factors Va and VIIIa. Hyperglycemia causes non enzymatic glycation of this antithrombin III and depress it's biological activity and also directly decreases the concentration of protein C. Therefore impaired function of natural anticoagulants activate clotting factors and contribute to the onset of hypercoagulability in T2DM[3,6].
The mean Hb was 12.35 and median Hb was 12, which is not significant as per statistics in our study. Bhutto AR *et al.* study highlighted that RDW has a significant correlation with HbA1c and is an inexpensive and freely available test so it may be used as a marker of glycemic status[10]. However, unlike studies from Pakistan and Bangladesh, this study did not find a significant association between RDW and HbA1C levels.
In this study, a reverse relationship also was found between HbA1c levels and MCH. This correlation between MCH and HbA1c levels was also reported in a study conducted in Jimma, Ethiopia. High blood glucose levels alter hemoglobin's structure, increasing β-sheet content, which could affect MCH[1,11]. Meshesha et al study revealed a significant difference in MCH levels between the groups with good and poor glycemic control, with higher MCH levels seen in the group with good glycemic control (HbA1c <7%)[1].

CONCLUSION

The proportion of PT-INR and the MCH was able to separate the both glycemic control groups reliably. Our study showed that, among the diabetic Individuals, those with HbA1c >9 revealed marked variations in coagulation profile. Hence T2DM may be related to increased risk of thrombosis indicated by reduced PT and APTT. Also this study suggest lower MCH levels in the context of poor glycemic control can serve as an indicator of the risk of developing DM-related vascular complications.
This study did not find a significant association between Hb and RDW with increasing HbA1C levels.

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