Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/15559
DOI URL: http://dx.doi.org/10.21474/IJAR01/15559

RESEARCH ARTICLE

RELATIONSHIP BETWEEN HBA1C AND COMPLETE BLOOD COUNT PARAMETERS IN ADULT PATIENTS WITH TYPE 2 DIABETES IN SAUDI ARABIA

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Manuscript Info

Manuscript History
Received: 28 August 2022
Final Accepted: 30 September 2022
Published: October 2022

Key words:-
Complete Blood Count, Glycated Hemoglobin, Diabetes Mellitus, Diabetic Complications

Abstract

Background: Hemoglobin A1c (HbA1c) measures blood glucose over a period of 2–3 months, and its level is closely related to the risk of complications. Several factors affecting HbA1c levels have not been studied. This study mainly focused on the relationship between HbA1c levels and complete blood count (CBC) parameters.

Objectives: This study aimed to analyze the relationship between HbA1c levels and CBC parameters in patients with type 2 diabetes mellitus (T2DM) and to evaluate the association of CBC parameters with abnormal HbA1c levels and diabetic complications.

Methods: This was a retrospective study of 385 Saudi patients with T2DM aged ≥18 years attending King Khalid University Hospital (KKUH) primary care clinics. Patients with type 1 diabetes mellitus, hematological diseases, infections, or allergies were excluded. AnElectronic System for Integrated Health Information (e-SiHi)was used to collect data, which were analyzed using SPSS 22 using t-test and analysis of variance, with P <0.05 considered significant.

Results: This study showed that the mean patient age was 59±13 years, with no significant difference between the sexes. In addition, the mean duration of disease was 10 years, and the mean HbA1c level was 8.5±1.9 %. CBC values were averaged according to their mean values, except for the erythrocyte sedimentation rate (ESR) (36±27 mm/hr) which was higher than the normal value (1.0–25 mm/hr).

Conclusion: This study showed an association between HbA1c levels and duration of T2DM and hemoglobin. The progression of diabetic complications was related to CBC changes; a high ESR was associated with the incidence of diabetic nephropathy and increased white blood cell count with neuropathy, vasculopathy, and nephropathy. Among all complications, vasculopathy occurred more frequently with each increase in HbA1c values.

Introduction:-

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by elevated blood glucose levels, insulin resistance, and inadequate insulin secretion. Long-term hyperglycemia is associated with organ damage that affects the heart, blood vessels, eyes, kidneys, and nerves.[1]

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Glycated hemoglobin (HbA1c) is formed through irreversible non-enzymatic glycation;[2] its blood concentration depends on two factors: the lifespan of red blood cells (RBCs) and blood glucose levels. Many factors besides hyperglycemia affect HbA1c levels, including anemia, blood loss, hemolysis, hemoglobinopathies, blood cell disorders, and myelodysplastic disease.[3]

Several other factors affecting HbA1c levels are yet to be studied, and our study aimed to evaluate the relationship between HbA1c and complete blood count (CBC) parameters. Our results could aid the future management of T2DM.

Materials and Methods:-

This was a retrospective study of 385 Saudi patients aged ≥18 years who had T2DM and attended primary care clinics at King Khalid University Hospital. Ethical approval was obtained from the respective institutional review board.Data were collected through an electronic integrated health information system (E-SIHI) from October 2019 to February 2020. Patients with type 1 diabetes mellitus, allergy, infection, pregnancy, hemoglobinopathies, or hematologic diseases (hemolytic anemia, neoplastic metastases to the bone marrow, severe arthritis, hypothyroidism, liver cirrhosis, post-hemorrhagic anemia, anemia due to renal diseases, inflammatory bowel diseases, and severe infection) in the past month that may have affected their CBC were excluded.

All case report forms containing the following information were completed: age in year, sex (male or female), duration of diabetes and the presence of risk factors including smoking. The study also included sex; anthropometric measurements; HbA1c levels; main blood groups—A, B, AB and O; Rhesus blood group; and parameters of CBC—white blood cell (WBC) and RBC count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution (RDW), platelet (PLT), and erythrocyte sedimentation rate (ESR). A history of chronic diabetic complications was reported for each eligible participant using the following definitions:

1. Diabetic retinopathy: defined as the presence of blindness, macular edema, glaucoma, cataracts, non-proliferative retinopathy, or proliferative retinopathy.
2. Diabetic nephropathy: defined as the presence of microalbuminuria, macroalbuminuria, or end stage renal disease.
3. Diabetic neuropathy: defined as the presence of sensory polyneuropathy, amyotrophy, motor neuropathy, mononeuropathy, or autonomic neuropathy.
4. Diabetic vasculopathy: defined as the presence of cardiovascular (angina or myocardial infarction), cerebrovascular (transient ischemic attack (TIA) or stroke) or peripheral vascular (intermittent claudication or limb ischemia) disease.

Vital signs, including blood pressure (BP), height, weight, body mass index, and weight/heightratio, were measured. Laboratory results of fasting and 2-hour postprandial glucose, HbA1c, total cholesterol, low- and high-density lipoprotein, triglyceride, urea, creatinine, ACR, CBC, and differential WBC counts were recorded.

The sample size was 385 and was calculated using this formula:

$$n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

$$n = \frac{1.96^2 \times 0.5(1-0.5)}{0.05^2} = 384.16$$

The collected data were encoded, entered into an Excel spreadsheet, and analyzed using SPSS version 22. Data are presented as mean and standard deviation for continuous variables (such as age and CBC parameters) and as frequency and percentages for categorical variables (such as sex and presence of complications). Moreover, the analysis of variance test was used to assess the association of CBC parameters with abnormal HbA1c levels and diabetic complications. Statistical significance was set at $P < 0.05$.

Results:-

Table 1 shows the participants' characteristics, including the clinical, metabolic, and CBC parameters. The mean age of the participants was 59±13 (range: 21–99) years. The sex discrepancy was unremarkable, with 48.10% and 51.90% men and women, respectively. The participants' average height was 161.33± 9.84 cm, and the average

weight was 81.86 ± 18.77 Kg. Data on ESR were missing in 371 patients, while CBC indices were only missing in 11. A total of 74.10% of the sample had T2DM for a duration of 6 to 10 years, with a mean duration of 10 years (range: 1–45 years). The mean systolic and diastolic blood pressures were 134±18 mmHg and 74.9±10.6 mmHg, respectively. The mean HbA1c was 8.5±1.9 %, with a median of 7.9%. WBC, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, and MPV were normal according to their mean values, except for ESR (36±27 mm/hr), which was higher than the normal value (1.0–25 mm/hr).

Tables 2 and 3 show the effects of varying HbA1c levels on clinical risk factors and CBC parameters. Statistically significant relationships were found between HbA1c levels and the duration of T2DM and HGB levels ($p = 0.006$ and 0.046, respectively). In contrast to RBCs, HCT values were not affected. The association between ESR and diabetic nephropathy was statistically significant ($p = 0.045$). The highest WBC count was observed in patients with neuropathy and vasculopathy (diabetic foot) followed by those with nephropathy. RBC indices—MCV, MCH, and MCHC—showed no dramatic changes in values with the different complications. Among the complications, vasculopathy showed a positive correlation with HbA1c, as each increase in HbA1c values corresponded to an increase in the proportion of patients with vasculopathy, whereas other complications had different values with no specific pattern.

Discussion:-

This study showed several significant relationships between HbA1c levels and the duration of T2DM as well as HGB levels. The highest WBC count was observed in patients with neuropathy and vasculopathy (diabetic foot), followed by those with nephropathy, and an association between ESR and diabetic nephropathy was noted. Among the complications, vasculopathy showed a positive correlation with HbA1c, as each increase in HbA1c levels corresponded to an increase in the proportion of patients with vasculopathy.

The results of the present study showed that the duration of T2DM was significantly correlated with HbA1c levels, which is similar to the findings of another study conducted in Jazan, Saudi Arabia.[12] Solan et al. included 288 patients with T2DM and studied the association between HbA1c levels and various factors. The results of their study showed that higher levels of HbA1c were significantly correlated with a longer duration of T2DM.[4] Another study conducted in southern California with the aim of identifying the predictors of glycemic control among patients with T2DM concluded that longer durations of the disease contributed to higher HbA1c levels and poorer glycemic control.[5] The two abovementioned studies showed results corresponding to those of the current study.

WBC count represents the sum of the following cells: neutrophils, eosinophils, lymphocytes, and monocytes. It is well established that leukocytosis is an acute-phase response signaling underlying inflammation. Numerous studies have described the inflammatory nature of glucose intolerance and its role in the pathogenesis of both type 1 and type 2 diabetes.[6] The pathogenesis of diabetic complications also reportedly relies mostly on inflammation and oxidative stress. [7]

In this study, we found that a higher leukocyte count corresponded to the presence of neuropathy and vasculopathy, followed by nephropathy. RBC indices—MCV, MCH, and MCHC—showed no dramatic changes in values with the different complications, suggesting the possibility of using the leukocyte count as an indicator of the development of diabetic complications.

We also found a significant association between ESR and diabetic nephropathy, similar to a previous study conducted on 265 patients with diabetic nephropathy, which found that ESR was independently associated with the severity of diabetic nephropathy. [8]

Vasculopathy, a common complication of diabetes, is considered the leading cause of diabetes-related mortality and disability worldwide.[9] Macrovasculopathy, a disease of the larger conduit arteries, is a complex inflammatory process that leads to myocardial infarction, stroke, and peripheral artery disease. The most prominent pathological process associated with macrovascular disease is atherosclerosis, which is greatly accelerated in diabetes. [10] Dyslipidemia, hyperglycemia, advanced glycation end-product formation, increased oxidative stress, and inflammation are the most common pathological mechanisms that closely link diabetes and vasculopathy. [10]

Further, we found that vasculopathy was positively correlated with HbA1c and that each increase in HbA1c levels corresponded to an increase in the proportion of patients who had vasculopathy. This finding reinforces that

protection against hyperglycemia remains the most protective measure against vasculopathy and also suggests the possibility of using HbA1c as a predictor of developing vasculopathy and as an early screening method for vascular injury development.

This study has some limitations. Data were obtained from an electronic medical records system with numerous missing clinical data, such as smoking status and duration of diabetes in some patients.

Tables and Graphs:

Table 1:- Characteristics and complete blood count parameters of the study participants.

	Mean (± SD)	**Median**	**Range**
Age	13±59	59	78
Duration of DM	6±10	9	44
SBP (mmHg**)**	134 ± 18	133	160
DBP (mmHg**)**	74.9 ± 10.6	75	60
BMI (Kg/m2**)**	6.32±31.45	30.66	42.92
HbA1c (%**)**	1.9±8.5	7.9	11.2
WBC	2.65±7.58	7.4	34.97
RBC (1012/L**)**	8.6±5.2	4.8	178.1
HGB (g/dL**)**	17.3±134	135	139
HCT (%**)**	5.2±40.3	40.3	63.9
MCV (fL**)**	7.1±84.2	85.5	67
MCH (pg**)**	20.1±29.5	28.7	320.4
MCHC (g/dL**)**	19.2±332.5	334	352.5
RDW (%**)**	12±15.1	13.9	245.1
PLT	80.8±270.1	263	576.1
ESR (mm/h**)**	27±36	30	117

DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HbA1c, glycated hemoglobin; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution; PLT, platelet; ESR, erythrocyte sedimentation rate

Table 2:- Correlation of HbA1c levels with clinical risk factors.

		HbA1C				
		6.5-7.00	7.00 - 8.5	8.6 - 10:00	> 10	**P-value**
Age	**<40**	25 **%**	44.40%	19.40%	11.10%	0.395
	40-60	24.20%	34.20%	15.30%	26.30%	
	> 60	24.60%	39.90%	16.90%	18.60%	
Gender	**Male**	22.60%	40.50%	19.50%	17.40%	0.092
	Female	26.20%	35.00%	13.60%	25.20%	
DM duration (years)	**<5**	45.50%	42.40%	6.10%	6.10%	0.006
	6-10	24.40%	37.30%	15.50%	22.80%	
	>10	15.10%	37.00%	24.70%	23.30%	
Smoking	**Non-Smoker**	18.60%	40.70%	15.30%	25.40%	0.273
	Ex-Smoker	50%	33.30%	16.7%	0%	
	Smoker	26.90%	42.30%	19.20%	11.50%	
BMI	**< 25**	19.60%	47.80%	21.70%	10.90%	0.242
	25 - 30	23%	36.30%	20.40%	20.40%	
	≥ 30	26.80%	38.90%	12.60%	21.7%	
SBP	**< 130**	24.40%	39.40%	17.50%	18.80%	0.636
	≥130	25.10%	37.20%	14.30%	23.40%	
DBP	**< 80**	24.40%	38.70%	15.00%	21.80%	0.953
	≥ 80	25.60%	36.80%	16.80%	20.80%	

Table 3:- Correlation of HbA1c levels and mean (±SD) of CBC parameters.

	HbA1C				
	6.5 - 7.00	**7.00 - 8.5**	**8.6 - 10:00**	**> 10**	**P-Value**
WBC	7.6±3.9	7.49±2.06	7.52±2.06	7.63±2.22	0.978
RBC	4.7±0.5	5.9±14.2	4.8±0.7	4.8±0.5	0.655
HGB	130.3±18.4	134.3±17.5	137.6±17.3	135.2±13.9	0.046
HCT	39.3±4.9	40.6±6.1	41.2±4.6	40.5±4	0.095
MCV	83.8±7.7	84.2±7.5	84.7±6.3	83.9±6.2	0.859
MCH	27.8±3.3	32.1±33	28.2±2.7	28.1±2.4	0.283
MCHC	331.1±12.3	332.9±27.5	333.6±11.3	332.3±13.4	0.852
RDW	15±2.2	16±19.8	14.2±1.5	14.2±1.4	0.649
PLT	274.7±88.7	268.9±88.6	285.7±69.5	261.3±65.4	0.307
MPV	8.4±0.9	8.5±1	8.6±1.1	8.7±1	0.344
ESR	40±31	32±25	32±24	49±34	0.437

Table 4:- Mean ± SD of the different CBC parameters and presence of chronic complications.

		WBC	**RBC**	**HGB**	**HCT**	**RDW**	**PLT**	**MPV**	**ESR**
Neuropathy	Absent	7.6 ±2.68	5.2 ± 8.7	134.1 ± 17.3	40.3 ± 5.2	15.1 ± 12.3	270.9 ± 80.4	8.5 ± 1	35 ± 27
	Present	7.52 ± 2.05	0.7±4.8	132.6± 16.5	39.9 ± 4.8	14.4 ± 1.4	230.5 ± 29.6	8.8 ± 0.6	
	P-Value	0.935	0.895	0.817	0.826	0.875	0.157	0.511	
Retinopathy	Absent	7.6 ± 2.7	5.3 ± 9.2	134.1 ± 17.2	40.4 ± 5.2	15.1 ± 12.9	271.2 ± 81	8.6 ± 1	35 ± 29
	Present	7.53 ± 2.42	4.8 ± 0.7	133.2 ± 18.3	39.9 ± 5.2	14.8 ± 2.7	261.2 ± 70.8	8.3 ± 0.9	39 ± 13
	P-Value	0.861	0.737	0.747	0.566	0.854	0.429	0.106	0.732
Vasculopathy	Absent	7.52 ± 2.15	5.3 ± 9.2	134.4 ± 17.4	40.5 ± 5.3	15.2 ± 13	268.8 ± 80.5	8.6 ± 1	32 ± 25
	Present	8.15 ± 5.03	4.7 ± 0.6	131.4 ± 16.9	39.3 ± 4.7	14.5 ± 1.7	279.9 ± 75.4	8.5 ± 1.1	46 ± 35
	P-Value	0.39	0.647	0.251	0.126	0.705	0.358	0.638	0.228
Nephropathy	Absent	7.59±2.67	5.2± 8.7	134.1 ± 17.3	40.4 ± 5.2	15.1 ± 12.2	270 ± 79.9	8.5 ± 1	34 ± 27
	Present	7.54 ± 1.82	4.7 ± 0.6	132.1 ± 17.1	39.9 ± 4.3	14.5 ± 1.2	267.5 ± 107.4	8.8 ± 1.6	74 ± 30
	P-Value	0.944	0.832	0.674	0.739	0.867	0.915	0.549	0.045
Neuropathy and vasculopathy	Absent	7.58 ± 2.68	5.2 ± 8.7	134.1 ± 17.4	40.3 ± 5.3	15.1 ± 12.2	269.5 ± 79.6	8.5 ± 1	34 ± 27
	Present	8.2 ± 1.55	4.7 ± 0.2	130.5 ± 13.3	39.4 ± 3.3	15.2 ± 1.9	311.1 ± 97.1	8.5 ± 0.5	60 ± 53
	P-Value	0.574	0.894	0.617	0.673	0.992	0.207	0.935	0.208

Table 5:- Association between different HbA1C values and presence of diabetic complications.

		Diabetic Complications		**Diabetic Neuropathy**		**Diabetic Retinopathy**		**Diabetic Vasculopathy**		**Diabetic Nephropathy**		**Neuropathy and Vasculopathy**	
		Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
HbA1C	6.5 - 7.00	25.1%	22.3%	23.9%	28.6%	23.7 %	26.2 %	24.6 %	19.1 %	24.0 %	41.7 %	24.4 %	0.0%
	7.00 - 8.5	38.4%	35.1%	37.7 %	42.9%	38.3 %	33.3 %	38.2 %	34.0 %	38.1 %	16.7 %	37.3 %	66.7%
	8.6-10:00	16.8%	14.9%	16.3%	14.3%	16.5 %	14.3 %	16.1 %	17.0 %	15.9 %	33.3 %	16.2 %	16.7%

	> 10	19.7%	27.7%	22.1%	14.3%	21.5 %	26.2 %	21.0 %	29.8 %	22.0 %	8.3 %	22.1 %	16.7%
	P-Value	0.434		0.952		0.844		0.531		0.111		0.252	

	Range	Neuropathy	Retinopathy	Vasculopathy	Nephropathy	Neuropathyandvasculopathy
HbA1C	6.5 - 7.00	Absent: 97.90% Present: 2.10%	Absent: 88.50% Present: 11.50%	Absent: 90.60% Present: 9.40%	Absent:95.00% Present:5.00%	Absent: 100.00% Present:0.00%
	7.00 - 8.5	Absent: 98.00% Present: 2.00%	Absent: 90.70% Present: 9.30%	Absent: 89.40% Present:10.60%	Absent: 98.70% Present:1.30%	Absent: 97.40% Present:2.60%
	8.6- 10:00	Absent: 98.50% Present: 1.50%	Absent: 90.80% Present: 9.20%	Absent: 87.70% Present:12.30%	Absent: 94.00% Present:6.00%	Absent: 98.50% Present:1.50%
	> 10	Absent: 98.90% Present: 1.10%	Absent: 87.50% Present:12.50%	Absent: 84.10% Present:15.90%	Absent: 98.90% Present:1.10%	Absent: 98.90% Present:1.10%
	P-Value	0.952	0.844	0.531	0.111	0.252

(N%) = Sample Size Percentage.

Conclusion / Recommendations:-

In conclusion, this study showed an association of HbA1c levels with duration of T2DM and HGB levels. The progression of diabetic complications was related to CBC changes; a high ESR was associated with the incidence of diabetic nephropathy and raised WBC count with the occurrence of neuropathy, vasculopathy (diabetic foot), and nephropathy. Among the complications, vasculopathy occurred more frequently with each increase in HbA1c values.

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