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Influence of Vitamin D status on hematological markers of inflammation in prediabetes

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ABSTRACT

Objectives: Inflammation is the integral pathophysiological component of prediabetes. Hemogram is a routinely performed lab test, cheap and convenient to reproduce; hence hematological indices are useful to monitor the disease process. Vitamin D modulates inflammatory mediators and hence can impact the progression of prediabetes to type 2 diabetes mellitus. The study intends to find the association of hematological indices with glycemic control and vitamin D status in prediabetic subjects. *Methods:* Retrospective study was done on 270 prediabetic patients based on HbA1c (5.7 - 6.4%) and 299 normoglycemic subjects. Chi square analysis and t test were used to compare hematological indices in two groups. ANOVA used for comparison of variables under three Vitamin D categories, sufficient (≥75 nmol/L), insufficient (50-74.9 nmol/L), deficient (<50 nmol). Regression analysis was done to find odds ratio for prediabetes. *Results:* Vitamin D was lower in prediabetic subjects (57.91±20.83; p value <0.05). Neutrophil lymphocyte ratio (2.10 ± 0.85; p value <0.05), platelet lymphocyte ratio (137.70 ± 43.70; p value <0.05), mean platelet volume (8.55 ± 3.00; p value <0.001), red cell distribution width (12.65 ± 1.31; p value 0.05) were higher in prediabetes group. Neutrophil lymphocyte ratio, platelet lymphocyte ratio and red cell distribution width showed statistically significant rising trend with declining vitamin D level in prediabetic subjects. Mean platelet volume was significant predictor of prediabetes. *Conclusions:* Neutrophil lymphocyte ratio, platelet lymphocyte ratio and red cell distribution width and mean platelet volume are novel inflammatory markers to monitor prediabetic patients but should be considered along with Vitamin D status.

Keywords: Neutrophil Lymphocyte ratio, Platelet lymphocyte ratio, Mean Platelet volume, Red cell distribution Width

1. INTRODUCTION

Prediabetes is now recognized as a global health concern with an estimated prevalence of 7.3 % of adult population in 2017 and is predicted to further rise to 8.3% by 2045 (Hostalek et al., 2019). Individuals with prediabetes have high propensity to progress to overt diabetes as well as associated underlying pathological changes irrespective of apparent manifestation (Tabak et al., 2012). A meta-analysis evinced that prediabetic patients have higher

probability of cardiovascular disease (CVD), stroke and associated mortality when compared to those with normoglycemia (Donath et al., 2011). Hence, to halt the progression it is essential to detect and treat prediabetes in early stages which could probably help to mitigate the global spread of diabetes epidemic.

Chronic low grade inflammation and endothelial dysfunction as a result of hyperglycemia are the primary underlying pathophysiological mechanisms in diabetes (Huang et al., 2016). A study concluded that chronic inflammation mirrors the mortality risk in diabetic patients (Donath et al., 2016). The hematological markers such as neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), red cell distribution width (RDW), mean platelet volume (MPV) have gained much recognition in recent years as reliable predictors of inflammation and endothelial dysfunction. NLR is an effective monitoring tool in diabetes to track glycemic control status (Duman et al., 2019). RDW which is indicative of variably sized erythrocytes in circulation, also called anisocytosis, reflects increased oxidative stress and inflammation (Malandrino et al., 2012). Higher RDW has been associated with metabolic syndrome, higher odds of developing macrovascular complications, CVD in diabetic population (Sherif et al., 2013).

PLR is also considered an important marker of inflammation and a simple inexpensive measure of progression of diabetes (Atak et al., 2019). Both NLR and PLR have been highlighted as significant markers of inflammation in prediabetes in a study (Mertoglu et al., 2017). MPV is regarded as an essential index of platelet function and when raised, it indicates increasingly active platelets producing more prothrombotic factor, thromboxane A2 which leads to thrombosis (Vizioli et al., 2009). It has been firmly linked with pathogenesis of diabetes and its vascular complications (Inoue et al., 2020).

Vitamin D (VD) is a cardinal micro nutrient not just for maintenance of musculoskeletal health but also for immune system (Di Rosa et al., 2011). It modulates innate and adaptive immunity at the cellular level through cytokines and cell signaling pathways (Zhang et al., 2012). Both B and T cells express VD receptors hence their proliferation, inhibition and differentiation is modulated by VD (Korf et al., 2012). Although research shows that VD deficiency is associated with higher odds to develop type 2 diabetes mellitus, the definitive evidence is still limited. VD possibly contributes to pathogenesis of diabetes by its association with inflammation since inflammatory processes are the essential hallmark of metabolic dysregulation, development and progression of diabetes (Garbossa et al., 2017).

The present study intends to compare the hematological indices in normoglycemic and prediabetic subjects. These novel markers can be cheap and convenient tools to monitor the extent of inflammation which is the pathophysiologic basis of progression to diabetes. Furthermore, it aims to assess if VD modulates inflammation by influencing the hematological indices under study.

2. METHODS

Study Duration and Design

A retrospective case control study was done in the tertiary care hospital on first time diagnosed prediabetic patients in age group of 18-65 years. The study was performed on patients who visited hospital in two years duration from 1 st January 2019 to 31st December 2020. Equal numbers of control cases in age group 18-65 years, with no history of Prediabetes were selected in the same duration.

Target Population

All prediabetic patients diagnosed first time based on glycosylated hemoglobin (HbA1C) level of 5.7 - 6.4% (Pippitt et al., 2016).

Sample calculation and collection

All first time diagnosed prediabetic patients based on HbA1c, during the study period were included and those who had subsequent lab tests done for hemogram and Vitamin D based on clinical history. In case of multiple visits, the first results were recorded for study purpose. The sample population studied included 569 out of which 299 were normoglycemic and 270 were prediabetic.

Exclusion criteria

Previous history of diabetes, malignancies, other acute or chronic illnesses; those with history of Vitamin D supplementation and those with incomplete data were also eliminated.

Anthropometric and Laboratory parameters

Age, gender of all subjects recorded on a Microsoft excel sheet along with other information with proper coding for confidentiality. Height, weight measurements were taken to deduce body mass index (BMI) = Weight (kg)/ Height $(m)^2$, systolic, diastolic blood pressures were noted.

The lab parameters included were fasting blood sugar (FBS), HbA1c, Vitamin D and hematological indices namely, total lymphocyte count (TLC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), total platelet count (TPC), mean platelet volume (MPV), red cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR). NLR and PLR were calculated ratios while others were derived from the hemogram. VD status was assessed by serum 25(OH) vitamin D since it is more stable form and unaffected by diet and physical activity (Aksoy et al., 2000). The hemogram was obtained from Cell Dyn- Ruby Hematology Analyzer, Abbott while 25(OH) D was analyzed on Alinity i Abbott. The laboratory is accredited by College of American Pathologists. For study purpose the VD levels were categorized as sufficient (≥75nmol/L), insufficient (50-74.9 nmol/L) and deficient (<50nmol/L) (Holick et al., 2007) and variables were studied under these categories for prediabetic and normoglycemic subjects. No human or animal experiments were conducted in the study. All procedures were in accordance with standards of the institutional ethics committee.

Data Analysis

Statistical analysis was done using SPSS 20.0 version. Descriptive statistics were presented as frequency, percentage for qualitative variables and mean with standard deviation for numerical variables. For inferential statistics, categorical variables were compared by chi square analysis and continuous variables by t test. Stratified analysis for prediabetic and normoglycemic subjects was done under VD categories by ANOVA. Correlation analysis was done between indices and HBA1c and regression analysis was performed to calculate odds ratio of prediabetes with model adjustments done for age, gender and BMI. Statistical significance was defined as p value < 0.05.

3. RESULTS

Table 1 compares the variables in the two groups of subjects with total of 569 out of which 299 were normoglycemic and 270 were prediabetic.

Table 1 Clinical and Biochemical parameters of all subjects

	Normoglycemic (n=299)	Pre diabetic (n=270)	P value
Gender (Female/Male)	157/142	136/134	0.61
BMI	22.79±1.92	25.53±2.89	<0.001*
HbA1C (%)	4.89±0.29	5.93±0.19	<0.001*
FBS (mmol/L)	6.50±27.88	5.41±0.59	0.52
TLC($x10^3$/uL)	6.46±1.49	6.79±1.86	0.01*
ANC($x10^3$/uL)	3.80±1.11	4.12±1.47	0.003*
ALC($x10^3$/uL)	2.15±0.66	2.08±0.68	0.22
NLR	1.89±0.70	2.10±0.85	0.001*
TPC($x10^3$/uL)	251.93±22.56	262.15±34.99	<0.001*
MPV(fl)	7.61±0.39	8.55±3.00	<0.001*
PLR	127.30±43.57	137.70±43.70	0.005*
RDW (%)	12.47±0.80	12.65±1.31	0.05
Vitamin D (nmol/L)	63.27±23.78	57.91±20.83	0.005*
Deficient VD (%)	81(43.1%)	107(56.9%)	0.003*
Insufficien VDt (%)	146(59.6%)	99(40.4%)	
Sufficient VD (%)	72(52.9%)	64(47.1%)	

Continuos data presented as Mean +-standard deviation and catgorical data as frequency (%)/proportion (*)
p value significant; FBS- fasting blood sugar,TLC- total leucocyte count,ANC- absolute neutrophil count, ALC- absolute Lymphocyte count, NLR-neutrophil lymphocyte ratio, TPC-total platelet count, MPV-mean platelet volume, PLR-platelet lymphocyte ratio, RDW- Red cell distribution width, VD- Vitamin D

There was statistically significant difference in the mean age; 44.98 ± 9.4 years in prediabetics and 35.72 ± 8.43 years in other. BMI, systolic blood pressures were significantly higher in prediabetic patients. Mean HbA1c in prediabetic subjects was 5.9 ±0.19 (%). Vitamin D was significantly lower in prediabetic subjects with mean level of 57.9 ± 20.8 nmol/L. As for the indices, TLC, TPC, MPV, RDW, NLR, PLR were significantly higher in prediabetic patients.

Table 2 and 3 compare variables under Vitamin D categories in prediabetic and normoglycemic groups respectively. In prediabetes group BMI was higher in Vitamin D deficient class compared to other two and there was a dropping trend with rise in Vitamin D level. A similar trend was seen for HbA1c which steadily rose from sufficient to deficient category with statistical significance. Mean FBS was highest among VD deficient prediabetic subjects although no trend was observed. RDW, NLR, PLR showed a clear rising shift from sufficient towards deficient categories. On other hand for normoglycemic subjects, there was no discernible increasing trend in the indices with declining VD level except for MPV.

Table 2 Clinical and Biochemical parameters of Prediabetic subjects under Vitamin D Categories.

Pre diabetes n= 270	Deficient VD (<50 nmol/L)	Insufficient VD (50-74.9 nmol/L)	Sufficient VD (>=75 nmol/L)	P value
Age	43.71±9.45	44.73± 8.86	47.51± 9.77	0.03*
Gender(Female/Male)	61 / 46	50 / 49	23 / 41	0.02*
BMI	26.69 ±3.04	25.07±2.78	24.31±2.02	<0.001*
HbA1C (%)	6.00± 0.21	5.90 ±0.17	5.86 ±0.14	<0.001*
FBS (mmol/L)	5.50±0.5657	5.36 ±0.57	5.34±0.64	0.09
TLC(x10^3/uL)	7.90±1.91	6.31±1.59	5.67 ±0.97	<0.001*
ANC(x10^3/uL)	5.01±1.54	3.68 ±1.25	3.32±0.78	<0.001*
ALC(x10^3/uL)	2.26±0.76	2.02±0.61	1.86± 0.52	<0.001*
NLR	2.39±0.95	1.91±0.74	1.90±0.67	<0.001*
TPC(x10^3/uL)	287.71±22.05	253.07±28.3	233.46±32.98	<0.001*
MPV(fl)	8.93±4.66	8.29±0.74	8.31±0.83	0.24
PLR	141.67±48.51	135.38±39.50	134.65 ±41.50	0.48
RDW (%)	13.56 ±1.10	12.31±1.18	11.65±0.79	<0.001*
Median Vitamin D level	38.65±7.194	59.49±6.87405	87.65±12.691	<0.001*

Continuos data presented as Mean +-standard deviation and catgorical data as frequency (%)/ proportion. P value calculated by one way ANOVA (*) p value significant. FBS- fasting blood sugar, TLC- total leucocyte count, ANC- absolute neutrophil count, ALC- absolute Lymphocyte count, NLR-neutrophil lymphocyte ratio, TPC-total platelet count, MPV-mean platelet Volume, PLR-platelet lymphocyte ratio, RDW Red cell distribution width, VD Vitamin D

Table 3 Clinical and Biochemical parameters of Normoglycemic subjects under Vitamin D Categories.

Normoglycemic n= 299	Deficient VD (<50 nmol/L)	Insufficient (50-74.9 nmol/L)	Sufficient (>=75 nmol/L)	P value
Age	43.71±9.45	44.73±8.86	47.51±9.77	0.03*
Gender(Female/Male)	61 / 46	50 / 49	23 / 41	0.02*
BMI	26.69±3.04	25.07±2.78	24.31 ± 2.02	<0.001*
HbA1C (%)	4.91±0.29	4.88±0.30	4.88±0.25	0.47
FBS (mmol/L)	4.85±0.40	4.85±0.40	4.9±0.40	0.14
TLC (x10^3/uL)	6.56 ±1.57	6.35±1.38	6.56 ±1.62	0.48
ANC (x10^3/uL)	3.87 ± 1.23	3.76±1.04	3.79 ±1.12	0.77
ALC (x10^3/uL)	2.15 ±0.61	2.10±0.65	2.24 ±0.75	0.37
NLR	1.90±0.73	1.91±0.71	1.82±0.67	0.66
TPC (x10^3/uL)	248.37±20.4	252.90 ±22.60	253.97 ±24.56	0.23
MPV (fl)	7.71± 0.43	7.59 ±0.39	7.53±0.31	0.02*

PLR	124.11±42.42	130.72±43.12	123.92±45.78	0.41
RDW (%)	12.41± 0.81	12.40±0.80	12.67 ±0.77	0.06
Median Vitamin D	38.65 ±7.19	59.49±6.87	87.65±12.69	<0.001*

Continuos data presented as Mean +-standard devia±tion and catgorical data as frequency (%)/ proportion. P value calculated by one way ANOVA (*) p value significant; FBS- fasting blood sugar, TLC- total leucocyte count, ANC- absolute neutrophil count, ALC- absolute lymphocyte count, NLR- neutrophil lymphocyte ratio, TPC-total platelet count, MPV-mean platelet volume, PLR-platelet lymphocyte ratio, RDW- Red cell distribution width, VD Vitamin D

Table 4 and Figure 1 show positive correlation between HbA1c and hematological indices among prediabetic subjects.whereas it was negatively correlated with VD. TLC, MPV were significant predictors of prediabetes even after adjusting for age BMI according to Table 5.

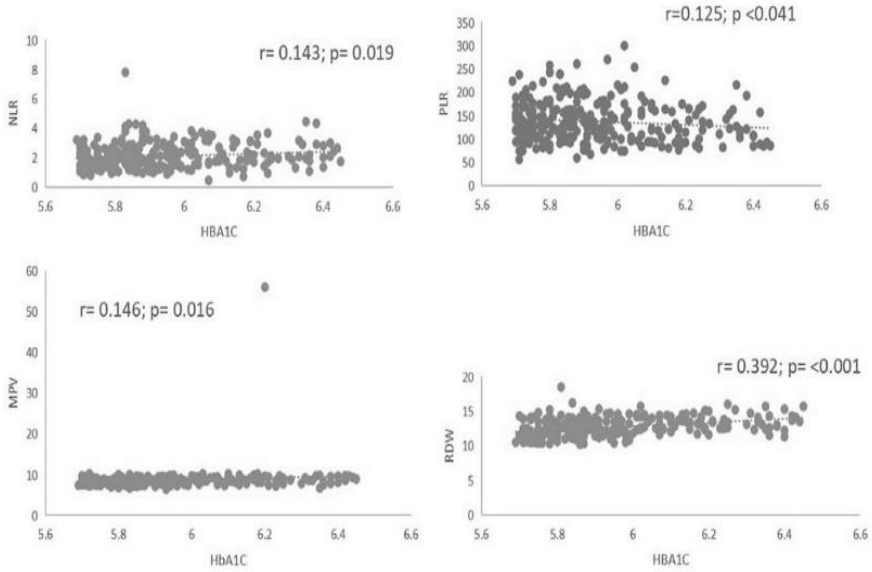

Figure 1 Scatter plot showing correlation of HbA1C with hematological indices

r = Pearson's correlation coefficient

NLR-neutrophil lymphocyte ratio; MPV-mean platelet volume; PLR-platelet Lymphocyte ratio, RDW- Red cell distribution width,

Table 4 Correlation between HbA1c and hematological Parameter in prediabetic subjects

Variable		Hba1c (%)
TLC(x10³/uL)	r	0.502
	p value	<0.001*
ANC(x10³/uL)	r	0.451
	p value	<0.001*
ALC(x10³/uL)	r	0.313
	p value	<0.001*
NLR	r	0.143
	p value	0.019*
TPC(x10³/uL)	r	0.430
	p value	<0.001*
MPV(fl)	r	0.146
	p value	0.016*
PLR	r	-0.125
	p value	0.041*

RDW (%)	r	0.392
	p value	<0.001

r = pearson's correlation coefficien (*) significant; TLC- total leucocyte count, ANC- absolute neutrophil Count, ALC- absolute lymphocyte count, NLR-neutrophil lymphocyte ratio, TPC-total platelet count; MPV-mean platelet volume, PLR-platelet Lymphocyte ratio, RDW- Red cell distribution width

Table 5 Hematological parameters and risk of prediabetes by Regression analysis

Variable	UnAdjusted		Adjusted	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P Value
TLC(x10³/uL)	1.32 (0.73-2.36)	0.349	1.07 (0.55- 2.07)	0.84
ANC(x10³/uL)	1.22 (0.54- 2.74)	0.63	1.49 (0.55- 4.05)	0.42
ALC(x10³/uL)	0.28 (0.09- 0.83)	0.02*	0.26 (0.06- 1.04)	0.05*
NLR	0.44 (0.14 -1.39)	0.16	0.36 (0.08- 1.61)	0.18
TPC(x10³/uL)	1.14 (1.07 -1.22)	<0.001*	0.99 (1.01- 1.21)	0.02*
MPV(fl)	9.16 (6.03- 13.93)	<0.001*	13.6 (7.67- 24.11)	<0.001*
PLR	1.00 (0.98 -1.01)	0.89	0.99 (0.97- 1.01)	0.81
RDW (%)	0.07 (0.02- 0.27)	<0.001*	0.10 (0.02- 0.62)	0.01*

Model adjusted for age, gender, BMI (*) p value significant

TLC- total leucocyte count, ANC- absolute neutrophil count, ALC- absolute lymphocyte count, NLR-neutrophil lymphocyte ratio, TPC-total platelet count MPV-mean platelet volume, PLR-platelet Lymphocyte ratio, RDW-Red cell distribution width, CI-Confidence interval

4. DISCUSSION

Research so far has shown that hematological indices are altered in Type 2 Diabetes mellitus (Alam et al., 2015). Persistent hyperglycemia is the temporal cause of increased oxidative stress triggering inflammation through cytokines and formation of advanced glycation end products due to glycosylation of hemoglobin, prothrombin, fibrinogen and other proteins involved in clotting mechanism (Sahajpal et al., 2019). Chronic inflammation further impairs glycemic control and worsens insulin resistance (Xia et al., 2017) making a vicious cycle. VD has been shown to have beneficial effects by reducing inflammation and slowing down the pathogenic processes in diabetes (Karonova et al., 2020).

Results of our study showed that VD is lower in prediabetic patients compared to normoglycemic subjects which are consistent with a previous study (Shankar et al., 2011). TLC, ANC and NLR were found to be higher in prediabetic subjects who are in accordance with other studies. NLR is considered a better prognostic marker over TLC for vascular complications, diabetic nephropathy, retinopathy as per one study (Shiny et al., 2014) TPC, MPV and PLR were also elevated in prediabetic subjects with statistical significance. Previous studies have reported similar findings in diabetic and prediabetic patients (Aktas et al., 2018; Zuberi et al., 2008).

The explanation is based on the effect of oxidative stress and inflammation due to hyperglycemia, which lead to platelet hyperactivity as well as increased turnover. Corroborating with previous findings current study also showed higher RDW in prediabetic group (Yin et al., 2018). MPV was statistically significant predictor of prediabetes (odds ratio: 9.1, p value: <0.05). NLR, PLR and RDW did not show similar significant association in regression analysis probably due to smaller sample size. Besides, HbA1c showed a rising trend from sufficient to deficient VD categories with statistical significance, which corroborates with previous studies concluding negative correlation between VD and HbA1c (Aldossari et al., 2017). Also, stratified analysis of hematological parameters in prediabetes and control groups showed that NLR, PLR and RDW showed an increasing trend from sufficient to deficient VD classes in prediabetes group. MPV did not show a similar trend yet mean MPV was highest in VD deficient category (8.93±4.66). Means of NLR (2.39 ±0.95), PLR (141.67±48.51) and RDW (13.56 ±1.10) were also highest among VD deficient prediabetic patients. None of these except MPV ascended with declining VD level among normoglycemic subjects.

Our study, though retrospective, had some key findings. Firstly, prediabetic patients have lower VD level. Secondly, the effect of VD status on hematological indices is more pronounced among prediabetic subjects as compared to those with normoglycemia

which points to the significance of assessing VD level among prediabetic patients. Moreover, this justifies the important role of VD in the inflammatory process underlying prediabetes.

Limitations

The study however bears certain limitations. Being a retrospective study there is possibility of selection bias. It is a single centered, small scale study hence cannot be extended to other population groups to consider ethnic and environmental differences. Longitudinal prospective studies could show the cause effect relation which lacks in this cross sectional study. Nevertheless, it is unique because very few studies have evaluated the association of Vitamin D status and hematological indices in prediabetic patients.

5. CONCLUSIONS

To summarize, Vitamin D is lower in prediabetic and is inversely related with HbA1c. Novel hematological indices, NLR, PLR, RDW and MPV are higher in prediabetes out of which MPV is a significant predictor of prediabetes. Additionally, NLR, PLR and RDW increase parallel to declining VD levels. Hence, even though the hematological indices may be cheap, conveniently reproducible inflammatory markers for monitoring prediabetes, their interpretation must carefully consider Vitamin D status as well which might modulate them and the disease status. Yet, large scale studies might further vindicate the importance of these novel hematological markers as surveillance tools in prediabetes.

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Author contributions

VB: Conception and design of the study, acquisition, analysis and interpretation of data, drafting and revising the article and final approval of the version to be published.
SK: Acquisition, interpretation of data, revising and final approval of the version to be published.
RQ: Acquisition, interpretation of data, revising and final approval of the version to be published.

Ethical approval

The study was approved by the Institutional Review Board of the Dr. Sulaiman Al Habib Medical Group (Study no. RC 21.10.27)

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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