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ORIGINAL ARTICLE

Association between hematological parameters, serum retinol, and glycemic indices in diabetes mellitus: a preliminary case–control study

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ABSTRACT

Background: The global prevalence of type 2 diabetes mellitus (T2DM) is on the rise. Hyperglycemia, free radical damage, and inflammation are commonly implicated as the etiopathological factors of diabetes mellitus. This preliminary study aims to investigate the association of the disease with serum retinol and hematological parameters and compare these parameters with non-diabetic controls.
Methods: The biophysical profiles of 85 subjects with diabetes and the same number of healthy controls were recorded using standard techniques. Biochemical and hematological investigations were carried out. The data are expressed as median with interquartile range (IQR) values. Mann–Whitney *U*-test was conducted to assess the difference between the two groups.
Results: There were a significant increase in median values of glycated hemoglobin (HbA1c), fasting blood glucose (FPG), and white blood cells (WBC) and a significant decrease in median values of monocytes in subjects with T2DM as compared to controls. There was a significant negative correlation between eosinophils and FPG in subjects with T2DM. In healthy controls, there was a significant positive correlation between serum retinol, certain hematological parameters, and HbA1c; and there was a significant negative correlation between WBC and FPG. The T2DM group had a significant negative correlation between eosinophil count and FBG.
Conclusion: Our study shows that serum retinol levels are not reflective of oxidative stress, but a routine WBC and differential count can shed light on the chronic inflammatory status. These results help with the formulation of targeted treatment to delay progression of the disease and prevent its complications.
Relevance for Patients: Vitamin A plays a pivotal role safeguarding the immunity and eye health for diabetic patients, but serum retinol estimation is not reflective of inflammatory or glycemic control status in diabetic patients. They would benefit from a hematocrit test.

1. Introduction

The current global prevalence of type 2 diabetes mellitus (T2DM) is 8.5%, almost double from 4.7% in 1980 [1]. In India, there has been a rapid increase in the prevalence of T2DM, from 26 million (5.5%) in 1990 to 65 million (7.7%) in 2016 [2].

Insulin resistance, impaired insulin secretion, abnormal fat metabolism, and excessive hepatic glucose production are the major contributors of hyperglycemia in subjects with T2DM [3]. Hyperglycemia leads to increased production of superoxide radicals, resulting in increased generation of free radicals and impairment in antioxidant defence mechanisms [4]. Oxidative stress due to hyperglycemia also further worsens insulin resistance [5]. The increase in reactive oxygen species (ROS) plays a significant role in the onset, progression, and pathogenesis of diabetic complications [6]. Further, the interaction between advanced

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glycation end-products (AGE) and their receptors (RAGE) results in the transduction of various signaling pathways, leading to the generation of ROS, pro-inflammatory cytokines, and chemokines that would trigger cellular dysfunction [7].

In the development of diabetic complications, unfavorable hyperglycemia induces biochemical as well as hematological changes. Due to altered biochemical and blood tissue products, their interactions lead to alteration in erythrocyte functional properties, leukocyte indices, and platelet indices in diabetes mellitus [8]. A large cohort study in Israel found that a rise in white blood cell (WBC) count serves as an independent risk factor for T2DM development in normoglycemic subjects not being affected by other risk factors such as obesity, family history, or dyslipidemia [9]. Total count, differential number of WBC, and neutrophil/lymphocyte ratio (NLR) are known markers of inflammation. High NLR is associated with insulin resistance and acts as a prognostic marker in T2DM along with glycated hemoglobin (HbA1c) [10].

Vitamin A, an antioxidant [8], can be obtained as provitamin A carotenoids like β-carotene from edible plants or as retinyl esters from animal sources [11]. The data regarding serum vitamin A levels in T2DM patients are ambiguous. Despite the controversy surrounding the vitamin A status changes in T2DM patients, new evidence lends credibility to decreased vitamin A levels in individuals suffering from T2DM [4,12].

As there is a paucity of reports on the association of serum retinol and hematological parameters with T2DM, the preliminary study was designed to determine the association of the above parameters in subjects with T2DM and healthy controls. The objectives of this study were to estimate the serum retinol, hematological parameters, and indicators of glycemic control in T2DM and healthy controls; compare them between the two groups; and investigate the correlation of fasting blood glucose and HbA1c with serum retinol and hematological parameters in the two groups.

2. Methods

The patients who attended our non-communicable disease (NCD) prevention clinic in AIIMS, Bhubaneswar, India, from August 2018 to August 2019, were recruited to this cross-sectional, observational study after giving consent to participate. Ethics approval was granted to this study (IEC approval number: IEC/AIIMS BBSR/PG Thesis/2018-19/10 dated – 13th July 2018). Convenient sampling was conducted to recruit cases and age-matched healthy controls. The procedures used in this study adhered to the tenets of the Declaration of Helsinki. Study participants were given clear explanations regarding this study in languages they understand, and informed written consent was obtained from each of them. Participants were coded with numbers to ensure anonymity.

The inclusion criteria of cases and controls are as follows:

a. Adults who consented to participate in the study
b. T2DM adults with HbA1c levels ≥6.5% (as cases)
c. Non-diabetic adults with HbA1c <5.7% (as control)
d. Adults aged 18–65 years
e. Treatment-naïve patients

Individuals with the following features were excluded from the study:

a. Pre-diabetic adults with HbA1c between 5.7% and 6.4%
b. Individuals using oral hypoglycemic agents or insulin for the management of diabetes
c. Individuals using vitamin A or multivitamin supplemented with vitamin A for any non-related conditions
d. Subjects addicted to smoking/alcohol/drug abuse
e. Pregnant or lactating women
f. Individuals with acute or chronic liver disease
g. Subjects who had received blood transfusions in the previous 3 months
h. Individuals with symptomatic thyroid dysfunction
i. Patients on lipid-lowering drugs
j. Patients on hormone replacement therapy, including oral contraceptive drugs
k. Patients with acute infections
l. Patients who were too ill to participate or had emergency health conditions
m. Patients on antiepileptic drugs

The demographic data and relevant history were obtained using a questionnaire. The biophysical profiles of subjects, encompassing height, weight, waist circumference (WC), and hip circumference (HC) were recorded using standard techniques. Single-trained personnel recorded weight using the same digital weighing scale with a minimum graduation of 10 grams. The height of each individual (standing straight with arms at the side and knees kept together) was measured using the same stadiometer with a minimum graduation of 1 mm. The WC and HC were measured using a measuring tape; the WC was measured at the narrowest portion of the waist above the umbilicus when the individual was standing upright and the HC was measured at the broadest part of the hips. The body mass index (BMI) and waist–hip ratio (WHR) were calculated.

Fasting venous blood was collected for all biochemical and hematological investigations. HbA1c and fasting plasma glucose (FPG) were estimated using Beckman Coulter AU 5800 fully automated chemistry analyzer coupled with reagent kits from Beckman Coulter (Ireland), after quality checks using QC material from Bio-Rad. Serum retinol was estimated by reverse-phase high-pressure liquid chromatography (HPLC) in HPLC Agilent LC Infinity 1200. Measurements of WBC count, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT) count, red cell distribution width–coefficient of variation (RDW-CV), platelet distribution width (PDW), mean platelet volume (MPV), platelet larger cell ratio (P-LCR), plateletcrit (PCT), neutrophil, lymphocyte, monocyte, and eosinophil parameters of complete hemogram were performed in fully automated analyzer SYSMEX XN 1000 (Sysmex America, Inc.,

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IL, USA). Neutrophil–lymphocyte ratio (NLR) was calculated by dividing the number of neutrophils by lymphocytes.

Considering a 15% difference in serum retinol levels between cases and controls, the sample size calculated was 85 in each arm with an alpha error of 0.05 and 90% power of the study [13].

The data were analyzed using SPSS version 25.0. All data were tested for normality using the Kolmogorov–Smirnov test. Most of the data were not normally distributed, so the data are expressed as median with interquartile range (IQR) values. The difference between the two groups was assessed with Mann–Whitney *U*-test (2-tailed). A *P*-value of less than 0.05 was considered statistically significant.

3. Results

The participants were selected after screening 335 patients. They were selected on the basis of their glycated hemoglobin levels; 85 treatment-naive T2DM and 85 normal healthy individuals were recruited in the study (Figure 1). A total of 165 subjects were excluded due to one or more exclusion criteria. The demographic and general clinical characteristics of T2DM and control are expressed as median with IQR values in Table 1. There was no significant difference in median values of BMI, WC, WHR, systolic and diastolic blood pressure (SBP and DBP), serum retinol, RBC, Hb, HCT, MCV, MCH, MCHC, PLT, RDW-CV, PDW, MPV, P-LCR, PCT, neutrophils, lymphocytes, eosinophils, and NLR between T2DM and control subjects. However, there were a significant increase in median values of HbA1c, FPG, and WBC and a significant decrease in median values of monocytes in subjects with T2DM as compared to controls (Table 1).

In T2DM patients, the eosinophil count was significantly negatively correlated with FPG (Table 2). In controls (non-diabetic subjects), there was a significant positive correlation between serum retinol, RBC, Hb, HCT, MCV, MCH, MCHC, and HbA1c (Table 2). A significant negative correlation between RDW-CV and HbA1c was also observed in controls (Table 2). Further, in subjects with non-diabetes, WBC count was negatively correlated with FPG (Table 2). The T2DM group had a significant negative correlation between eosinophil count and FBG. In both groups, there was a significant positive correlation between FPG and HbA1c (not shown in the Table 2).

Table 1. Demographic, anthropometry, biochemical and hematological parameters in diabetic and non-diabetic subjects

Parameters (unit)	Type 2 diabetic subjects	Non-diabetic subjects	*P*
Age (years)	43 (37, 59)	43 (36, 59)	0.959
T2DM duration (years)	3 (2, 5)	-	-
BMI (kg/m²)	25.4 (22.8, 27.9)	25.3 (22.2, 26.7)	0.285
Waist circumference (cm)			
Male (N=48,49)	90.5 (87.0, 95.0)	86.0 (83.0, 94.0)	0.088
Female (N=37,36)	82.0 (78.0, 88.5)	83.0 (73.0, 92.0)	0.808
Waist-hip ratio			
Male	0.96 (0.92, 0.99)	0.94 (0.91, 0.98)	0.358
Female	0.89 (0.85, 0.90)	0.90 (0.83, 0.93)	0.526
Systolic BP (mm/Hg)	120 (114, 130)	120 (110, 130)	0.111
Diastolic BP (mm/Hg)	80 (70, 83)	80 (70, 81)	0.252
HbA1c (%)	8.1 (7.15,9.65)	5.1 (4.8, 5.4)	<0.001
FPG (mg/dL)	165.0 (138.5, 221.0)	96.0 (90.0, 101.5)	<0.001
Serum retinol (µg/dL)	31.4 (27.8, 41.5)	32.53 (26.0, 40.5)	0.863
WBC (10^3/µL)	8.3 (7.0, 9.7)	7.4 (6.8, 8.7)	0.014
RBC (10^6/µL)			
Male	5.3 (4.8, 5.6)	5.2 (4.8, 5.5)	0.613
Female	4.7 (4.4, 5.1)	4.5 (4.2, 4.8)	0.066
Hb (g/dL)			
Male	14.1 (12.7, 15.1)	13.5 (13.1, 15.1)	0.920
Female	12.4 (10.9, 13.2)	11.9 (10.9, 12.7)	0.357
HCT (%)			
Male	44.8 (41.0, 47.3)	44.2 (41.6, 46.8)	0.843
Female	40.3 (36.1, 41.8)	38.7 (35.8, 41.7)	0.508
MCV (fL)	85.1 (80, 89.4)	87.2 (81.5, 90.2)	0.315
MCH (pg)	27.0 (24.4, 28.4)	27.2 (25.1, 28.5)	0.448
MCHC (g/dL)	31.1 (30.3, 32)	31.1 (30.2, 32.0)	0.745
Platelet count (10≥/µL)	277.0 (229.5, 326.5)	280.0 (235.0, 327.5)	0.959
RDW-CV (%)	14.0 (13.2, 15.1)	14.3 (13.5, 15.1)	0.277
PDW (fL)	13.35 (11.3, 16.5)	13.85 (10.93, 17.45)	0.735
MPV (fL)	11.0 (9.8, 12.3)	11.25 (10.15, 12.50)	0.267
P-LCR (%)	33.9 (23.8, 43.1)	35.4 (25.4, 45.2)	0.256
PCT (%)	0.31 (0.25, 0.37)	0.32 (0.27, 0.36)	0.548
Neutrophils (%)	62.6 (56.5, 69.5)	62.5 (56.8, 66.4)	0.252
Lymphocytes (%)	28.9 (23.0, 36.1)	29.9 (26.6, 35.2)	0.255
Monocytes (%)	2.2 (1.3, 3.0)	2.6 (1.6, 3.5)	0.034
Eosinophils (%)	3.5 (1.6, 6.3)	2.9 (2.1, 5.2)	0.888
Basophils (%)	0.3 (0.2, 0.5)	0.4 (0.3, 0.5)	0.079
NLR ratio	2.2 (1.6, 2.9)	2.1 (1.6, 2.5)	0.193

Data are given as median and IQR (Interquartile range).
Abbreviations: BMI: Body mass index; FPG: Fasting blood glucose; Hb: Hemoglobin; HbA1c: Glycated hemoglobin; HCT: Hematocrit; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR, Neutrophil/lymphocyte ratio; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet larger cell ratio; RBC: Red blood cell; RDW-CV: Red cell distribution width–coefficient of variation; T2DM: Type 2 diabetes mellitus; WBC: White blood cell

4. Discussion

In this case–control study, we found no statistically significant difference in serum retinol levels between T2DM and non-diabetic individuals, and the serum retinol levels of both groups remained within normal limits. This finding was consistent with other studies where normal serum retinol level was observed in T2DM patients [13-15]. Despite the report of lower serum retinol levels in diabetic individuals than in healthy controls [16], the liver retinol levels were found to be higher in diabetic animal model, suggesting that the liver inhibits retinol mobilization in people with diabetes. There is no difference in serum retinol levels between subjects with T2DM and non-diabetes, probably because serum retinol levels are typically maintained within a narrow range in individuals with adequate liver vitamin A stores [17]. In this study, however, there was a significant positive correlation between serum retinol level and HbA1c in healthy controls,

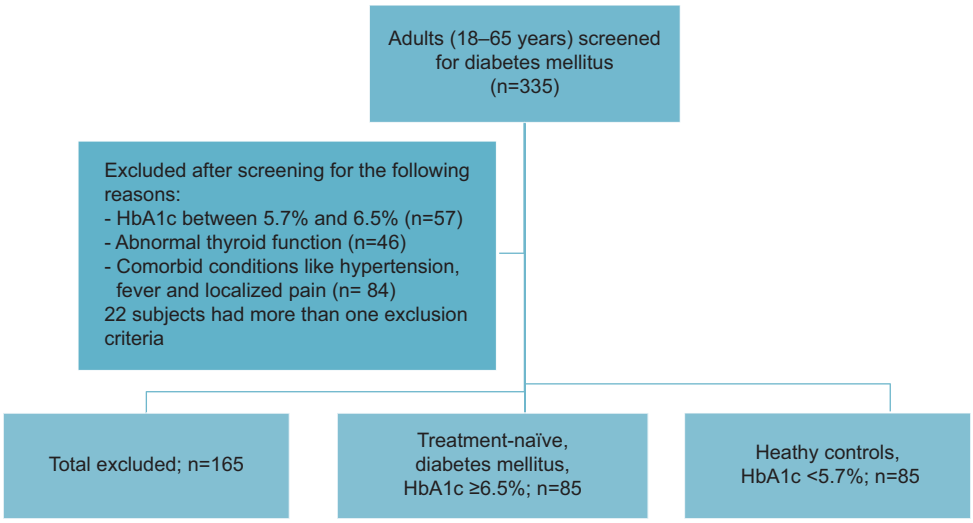

Figure 1. CONSORT flow diagram for patient enrolment.

Table 2. Correlation of glycemic indices with retinol and hematological parameters in diabetic and non-diabetic subjects

Parameters	Type 2 diabetic subjects (cases)				Non-diabetic subjects (controls)			
	HbA1C		FPG		HbA1C		FPG	
	R[a]	*P*[b]	*R*[a]	*P*[b]	*R*[a]	*P*[b]	*R*[a]	*P*[b]
Serum retinol	0.078	0.479	0.123	0.260	0.234	0.031	0.164	0.134
WBC	0.034	0.759	0.056	0.613	0.05	0.651	−0.3	0.005
RBC	0.038	0.731	−0.004	0.971	0.064	0.563	−0.002	0.989
Hb	−0.035	0.750	−0.06	0.588	0.251	0.021	−0.01	0.926
HCT	−0.008	0.939	−0.096	0.384	0.222	0.041	−0.056	0.610
MCV	−0.026	0.812	0.013	0.906	0.227	0.037	0.025	0.821
MCH	−0.009	0.937	0.042	0.700	0.256	0.018	0.101	0.356
MCHC	−0.073	0.504	0.007	0.952	0.256	0.018	0.173	0.113
Platelet count	−0.034	0.758	0.106	0.334	−0.095	0.387	0.016	0.884
RDW-CV	−0.087	0.427	−0.111	0.311	−0.342	0.001	−0.048	0.666
PDW	0.205	0.089	0.008	0.946	−0.105	0.395	−0.02	0.871
MPV	0.138	0.257	−0.021	0.867	−0.103	0.404	−0.09	0.464
P-LCR	0.145	0.231	0.002	0.989	−0.107	0.385	−0.088	0.475
PCT	−0.011	0.931	0.082	0.502	−0.233	0.056	−0.059	0.634
Neutrophils	0.004	0.968	0.135	0.218	0.017	0.876	−0.063	0.568
Lymphocytes	−0.08	0.464	−0.186	0.088	0.044	0.692	0.137	0.212
Monocytes	0.038	0.728	−0.018	0.871	0.106	0.333	0.032	0.770
Eosinophils	−0.164	0.135	−0.262	0.015	−0.028	0.801	−0.118	0.281
Basophils	0.145	0.186	0.033	0.766	0.102	0.353	−0.057	0.603
NLR ratio	0.059	0.589	0.17	0.119	−0.016	0.884	−0.108	0.326

[a]Spearman's correlation. [b]$P<0.05$.
Abbreviations: FPG: Fasting blood glucose; Hb: Hemoglobin; HbA1c: Glycated hemoglobin; HCT: Hematocrit; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet larger cell ratio; RBC: Red blood cell; RDW-CV: Red cell distribution width–coefficient of variation; WBC: White blood cell

possibly due to the mobilization of liver retinol stores to meet the demands of increased oxidative stress as a result of increased blood glucose levels [18]. The retinol-binding protein-4 (RBP4) is an inflammatory adipokine that is associated with insulin resistance and implicated in the pathogenesis of diabetes [19]. In this preliminary study, despite a decrease in retinol levels in the diabetic patients and a positive correlation with inflammation as seen in the NLR of the same group, our results were not statistically significant. This is in agreement with other studies showing that free RBP4 plays a role in the pathogenesis of atherosclerosis and diabetes mellitus [20]. Hence, either the low serum retinol levels or an increased synthesis of RBP4 from adipocytes needs to be investigated for the purpose of guiding treatment planning in future.

In the present study, there was a significant difference in WBC between subjects with T2DM and controls. Significant negative correlation between WBC and FPG was only observed in non-diabetic subjects. The increased WBC count is caused by chronic inflammation in T2DM resulting from insulin resistance and glucotoxicity [21,22]. Several other studies have also shown that WBC count might be associated with T2DM and its complications [23-27]. The chemical substances produced in leukocytes affect various tissues, such as vascular endothelial cells and pancreatic β cells, suppressing insulin secretion and its action and accelerating progression of T2DM [28]. It was also observed that there is an increase in baseline white cell counts in individuals who developed diabetes compared to those who had not developed diabetes at follow-up [29]. An increased circulating WBC count independently associated with worsening glucose metabolism even when the WBC level was within the normal range has been reported in a large Chinese population consisting of middle-aged and elderly subjects [30]. It was also reported that total leukocyte count is significantly increased in diabetic patients [30,31].

This study also showed that the difference in monocyte count between T2DM subjects and non-diabetic controls was significant. Decreased monocyte count may be attributed to monocyte adhesion to the endothelium, a critical factor in initiating early atherosclerotic lesions. The cause for increased monocyte

adhesion to the endothelium in diabetes may be secondary to advanced protein glycosylation of the endothelium [32]. There was no difference in the NLR between the two groups in this study, probably because of the convenient sampling used and that it was a hospital-based, instead of a community-based, study.

Among the non-diabetic, healthy controls in this study, there was a significant positive correlation between serum retinol, RBC, Hb, HCT, MCV, MCH, and MCHC with HbA1c, which was not seen in the T2DM cases. Such findings were congruent with a report by Bhutto *et al.* with a focus on T2DM [33]. A significant negative correlation between RDW-CV and HbA1c in controls indicates the role of these parameters in modulating cardiovascular risk [33,34].

5. Conclusion

Our study showed that serum retinol levels do not reflect oxidative stress, but a routine WBC and differential count can illuminate the chronic inflammatory status. These results may assist with the formulation of targeted treatment for delaying disease progression and preventing complications. A holistic approach to improving patient's well-being encompasses raising awareness for lifestyle changes, consuming healthy antioxidant-enriched diet and doing exercises (yoga, aerobics, meditation, *etc.*). Future studies should focus on investigating the efficacy of monitoring chronic inflammation in the normoglycemic population by means of hematological parameter measurements in disease prevention.

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Conflict of interest

None of the authors have any competing interests to report in this study. This was a non-funded study.

Ethics approval and consent to participate

Ethics approval was granted to this study (IEC approval number: IEC/AIIMS BBSR/PG Thesis/2018-19/10 dated – 13th July 2018). Written consent was obtained from the study participants before their participation.

Consent for publication

Written consent was obtained from study participants for using their data without disclosing their identity.

Availability of data

Data are available from the corresponding author upon reasonable request.

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