Leukocytosis in Association with Diabetic Nephropathy among a Diabetic Population in Kumasi, Ghana

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Abstract

Several studies have suggested that White Blood Cells (WBC) play a role in the development and progression of the complications of diabetes, and a raised WBC count, even within the normal range, has been associated with the development of chronic complications in type 2 diabetes. This study was conducted to determine the relationship, if any, between WBC count and diabetic nephropathy in a Ghanaian diabetic population. 153 diabetics were recruited by simple random sampling. 52 (33.99%) were normoalbuminuric (controls), and 101 (66.01%) had microalbuminuria or overt nephropathy (subjects). Anthropometric, haematological and biochemical data were taken. GFR was determined using the CKD-EPI formula. Participants with higher WBC counts had an elevated platelet count, ESR, total protein and globulin ($p<0.05$). There was a significantly negative correlation between total WBC count and GFR in participants with microalbuminuria ($p<0.05$) and a significant positive correlation between microalbuminuria and total WBC count ($r=0.171$; $p=0.035$) and neutrophil count ($r=0.257$; $p=0.002$). Participants with GFR below 60 ml/min 1.73 m^2 had significantly higher total WBC count and neutrophil count compared to those with GFR above 60 ml/min 1.73 m^2 ($p<0.05$). Total and differential white cell count, especially neutrophil count, provide valuable information about the development and progression of diabetic nephropathy, and should thus receive careful attention from caregivers.

Keywords: *Diabetic Nephropathy, White Blood cells, Leucocytosis, Glomerular Filtration Rate*

1.0 INTRODUCTION

Africa has a double burden of dealing with many communicable and non-communicable diseases as well as abject poverty in several parts of the continent. In Ghana, non-communicable diseases account for 43% of all deaths. (WHO, 2018). Diabetes mellitus (DM) is one of these non-communicable diseases with a rapidly increasing incidence, especially in developing countries including Ghana.

Almost half a billion people live with diabetes today, and that number is expected to rise by 25% in 2030 and 51% in 2045 if intervention measures are not put in place (Saeedi et al., 2019).

Diabetes is associated with reduced life expectancy, significant morbidity due to specific diabetes-related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of

life. Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in most countries. (Chen et al., 2020blood pressure control, and the use of renin-angiotensin system blockades, the prevalence of DKD remains high. Recent studies suggest that the spectrum of DKD has been changed and many progresses have been made to develop new treatments for DKD. Therefore, it is time to perform a systemic review on the new developments in the field of DKD. Summary: Although the classic clinical presentation of DKD is characterized by a slow progression from microalbuminuria to macroalbuminuria and by a hyperfiltration at the early stage and progressive decline of renal function at the late stage, recent epidemiological studies suggest that DKD patients have a variety of clinical presentations and progression rates to ESRD. Some DKD patients have a decline in renal function without albuminuria but display prominent vascular and interstitial fibrosis on renal histology. DKD patients are more susceptible to acute kidney injury, which might contribute to the interstitial fibrosis. A large portion of type 2 diabetic patients with albuminuria could have overlapping nondiabetic glomerular disease, and therefore, kidney biopsy is required for differential diagnosis for these patients. Only a small portion of DKD patients eventually progress to end-stage renal failure. However, we do not have sensitive and specific biomarkers to identify these high-risk patients. Genetic factors that have a strong association with DKD progression have not been identified yet. A combination of circulating tumor necrosis factor receptor (TNFR, Umanath & Lewis, 2018, Ghaderian et al, 2015, El Minshawy et al 2014)

The overall prevalence of diabetic nephropathy in Africa has been assessed by Noubiap, (2015) between 11-83.7%, whilst in Ghana, the prevalence of proteinuria in diabetics was estimated by Brenyah *et al* (2013) to be 13.8%. Several studies have suggested that White Blood Cells (WBC) play a role in the development and progression of the complications of diabetes. Elevated WBC count has been found to correlate with the incidence of coronary heart disease (Madjid & Fatemi, 2013, Kim et al., 2017))

M. et al., (2017) reported that an increase in WBC count, even if still within the reference range, was associated with the development of chronic complications in type 2 diabetes. Szydełko et al., (2018) also reported a measurement of white cells and changes in the various subpopulations as a useful tool in predicting the development of diabetic complications in type 2 diabetics.

This study was conducted to assess the relationship, if any, between WBC count and diabetic nephropathy in a Ghanaian diabetic population.

2.0 MATERIALS AND METHODS

2.1 Research Design and Method

Type 2 diabetics who are managed at the Diabetes Clinic of Komfo Anokye Teaching Hospital were randomly selected for the study. A total of 153 diabetics (35 males, 118 females) were recruited from the outpatient department of the Diabetic Clinic of the Komfo Anokye Teaching Hospital by simple random sampling. Among the participants, 52 (33.99%) were normoalbuminuric (controls), and 101 (66.01%) had microalbuminuria or overt nephropathy (subjects). Structured questionnaires were administered to the study participants to find out among other things their age, duration of disease and the type of treatment plan they were on. Anthropometric variables including height without shoes, weight to the nearest 0.1kg, arm and wrist circumference were estimated.

BMI was calculated by dividing the study participants' weight (kg) by the height squared (m^2). Blood pressure was taken using an analogue sphygmomanometer and stethoscope. Measurements were taken from the upper arm with the hand at the heart level after the patient had been sitting for more than 5 minutes.

Patients' complete blood count including differential white cell count was done. Also, patient levels of fasting blood glucose, electrolytes, serum levels of triglycerides, total cholesterol, HDL-cholesterol, and creatinine were estimated.

Complete blood count was analysed using Sysmex XT 2000i Haematology Analyzer. Biochemical tests (except fasting blood sugar) were run on Selectra ProS analyzer using ELITech Clinical Systems reagents. Electrolytes were measured using Dry ISE (Ion Selective Electrode) unit attached to the Selectra ProS analyzer. Fasting blood sugar was also measured using COBAS Integra 4OO Chemistry Analyzer. GFR was determined by using the CKD-EPI formula. Patients' data were analyzed using GraphPad Prism Version 5.

3.0 RESULTS

This study involved 118 females and 35 males with average ages of 57.36 and 56.94 respectively. Other baseline characteristics are described in Table 1. The mean BMI, FBS, total cholesterol, triglyceride, very low-density lipoprotein, GFR and urea: creatinine ratio were statistically significant and high among females compared to male participants ($p<0.05$). Meanwhile, there were significantly elevated serum creatinine levels in males compared to females ($p<0.05$).

Table 1: Clinical, anthropometric measurements, total and differential WBC and biometabolic characteristics of type 2 diabetes patients, categorized according to Gender

Parameters	Male (n=35)	Females (n=118)	p-value
Age (years)	56.94 ± 1.59	57.36 ± 0.86	0.8190
BMI(Kg/m2)	23.64 ± 0.52	26.41 ± 0.51	**0.0054**
WC (cm)	90.53 ± 1.54	94.04 ± 1.09	0.1104
WHR	0.97 ± 0.01	0.96 ± 0.01	0.3046
SBP (mmHg)	141.4 ± 4.61	142.7 ± 1.92	0.7602
DBP (mmHg)	82.00 ± 2.20	82.63 ± 0.92	0.7625
Total WBC count ($x10^9$/l)	6.24 ± 0.29	6.02 ± 0.17	0.5244
Neutrophil count ($x10^9$/l)	3.08 ± 0.17	2.75 ± 0.12	0.1900
Lymphocyte count ($x10^9$/l)	2.41 ± 0.15	2.56 ± 0.07	0.3133
Monocyte count ($x10^9$/l)	0.54 ± 0.039	0.49 ± 0.02	0.1512
Eosinophil count ($x10^9$/l)	0.15 ± 0.04	0.18 ± 0.02	0.4098
Basophil count ($x10^9$/l)	0.035 ± 0.01	0.03 ± 0.01	0.5833
Platelet count ($x10^9$/l)	241.2 ± 15.76	263.4 ± 7.87	0.1878
FBS (mmol/l)	8.57 ± 0.68	10.40 ± 0.40	**0.0280**
Total Protein (g/L)	81.71 ± 1.83	83.04 ± 1.05	0.5430

Albumin (g/L)	44.74 ± 0.71	44.86 ± 0.39	0.8773
Globulin (g/L)	37.03 ± 1.45	38.19 ± 0.89	0.5251
T cholesterol (mmol/l)	4.73 ± 0.17	5.34 ± 0.11	**0.0096**
Triglyceride (mmol/l)	1.45 ± 0.08	1.853 ± 0.08	**0.0065**
VLDL (mmol/l)	0.65 ± 0.03	0.84 ± 0.03	**0.0039**
LDL Cholesterol (mmol/l)	2.99 ± 0.14	3.35 ± 0.09	0.0609
HDL Cholesterol (mmol/l)	1.09 ± 0.05	1.14 ± 0.03	0.4083
Serum Urea (mmol/l)	4.93 ± 0.54	4.15 ± 0.16	0.0607
Serum Creatinine(umol/l)	166 (138.0 - 197.0)	120 (98.75 - 145.3)	**0.0004**
GFR (ml/min 1.73 m^2)	45.49 ± 3.34	55.89 ± 2.64	**0.0463**
Urea: Cr ratio	0.02 ± 0.01	0.04 ± 0.01	**0.0111**
Na+ (mmol/l)	148.5 ± 2.54	144.0 ± 1.29	0.1045
K+ (mmol/l)	4.50 ± 0.14	4.43 ± 0.07	0.6166
CL- (mmol/l)	110.3 ± 2.37	110.0 ± 1.28	0.8933

Table 2 summarizes the clinical and biometabolic characteristics of type 2 diabetes patients, stratified according to the quintiles of WBC count. Participants with higher WBC counts had an elevated platelet count, ESR, total protein and globulin ($p<0.05$). Interestingly, there was a significantly low GFR among participants with a higher WBC count ($p<0.05$).

Table 2: Clinical and biometabolic characteristics of type 2 diabetes patients, categorized according to WBC count quintiles

	WBC (x 10^9/l)					
	(2.5-4.6)	(4.7-6.6)	(6.7-8.6)	(8.7-10.6)	(10.7-12.6)	
Parameters	N=34	N=71	N=34	N=12	N=2	p-value
Age (year)	55.00 ± 1.55	57.46 ± 1.04	58.71 ± 1.76	57.83 ± 3.24	60.50 ± 0.50	0.7254
BMI (kg/m2)	26.14 ± 0.78	25.41 ± 0.54	25.58 ± 0.75	27.59 ± 3.11	24.78 ± 4.46	0.7254
WC (cm)	93.59 ± 1.76	92.50 ± 1.26	93.96 ± 1.99	96.33 ± 5.17	82.50 ± 5.50	0.5436
WHR	0.94 ± 0.01	0.96 ± 0.01	0.9667 ± 0.01	0.98 ± 0.02	0.87 ± 0.02	0.0920
SBP (mmHg)	141.9 ± 4.13	142.4 ± 2.35	145.9 ± 4.14	132.5 ± 7.29	150.0 ± 30.00	0.4969
DBP (mmHg)	85.94 ± 1.80	81.52 ± 1.22	82.06 ± 1.93	79.17 ± 3.13	85.00 ± 15.00	0.2487
Duration of disease (yrs)	2.029 ± 0.19	2.04 ± 0.12	2.53 ± 0.19	1.917 ± 0.36	3.00 ± 1.00	0.1285
Platelet (x 10^9/l)	215.5 ± 11.61	253.7 ± 9.11	289.9 ± 16.04	291.0 ± 25.6	418.5 ± 176.5	0.0002
ESR (mm fall/hr)	34.82 ± 5.67	36.03 ± 3.54	40.26 ± 4.91	61.75 ± 11.79	77.50 ± 37.50	0.0366
FBS (mmol/l)	8.385 ± 0.57	10.76 ± 0.58	10.34 ± 0.58	9.09 ± 1.56	8.65 ± 0.750	0.0968
Total protein (g/L)	77.06 ± 2.07	82.51 ± 1.28	86.29 ± 1.73	88.92 ± 2.73	87.50 ± 4.50	0.0025
Albumin (g/L)	43.94 ± 0.54	45.25 ± 0.52	45.50 ± 0.71	43.67 ± 1.79	40.50 ± 0.50	0.2067
Globulin (g/L)	33.32 ± 1.80	37.36 ± 0.96	41.59 ± 1.25	45.25 ± 2.72	47.00 ± 5.00	< 0.0001
Total cholesterol (mmol/l)	5.135 ± 0.19	5.07 ± 0.13	5.56 ± 0.23	5.25 ± 0.41	4.35 ± 0.45	0.3051
Triglyceride (mmol/l)	1.932 ± 0.19	1.69 ± 0.09	1.75 ± 0.09	1.78 ± 0.24	1.25 ± 0.45	0.5618
LDL Cholesterol	3.171 ± 0.15	3.158 ± 0.11	3.57 ± 0.20	3.41 ± 0.30	2.85 ± 0.35	0.2997
HDL Cholesterol	1.097 ± 0.06	1.16 ± 0.04	1.14 ± 0.06	1.05 ± 0.08	0.88 ± 0.03	0.6340
Serum urea (mmol/l)	4.235 ± 0.58	4.16 ± 0.18	4.50 ± 0.30	4.54 ± 0.59	7.40 ± 1.60	0.3024
Serum creatinine (umol/l)	111.5 (86.50-163.3)	128.0 (112-154)	139.0 (110.3-176.3)	151.0 (119.0-203.5)	245.0 (155.0-335.0)	0.4363
GFR (ml/min 1.73 m^2)	62.09 ± 5.83	54.68 ± 3.24	46.65 ± 2.86	44.17 ± 4.93	25.00 ± 11.00	0.0475

Data are means ± SD or median (interquartile range). BMI: Body mass index; WC: Waist circumference; WHR: Waist to Hip ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; GFR: Glomerulus filtration rate

The results of correlation between WBC count and anthropometric and biometabolic profile in participants with or without microalbuminuria showed a significant positive correlation between total WBC count and platelet count, total protein and globulin in both participants with microalbuminuria and normoalbuminuria ($p<0.05$). However, there was a significantly negative correlation between total WBC count and GFR in participants with microalbuminuria ($p<0.05$) **(Table 3).**

Table 3: Pearson's correlation of WBC count with anthropometric and biometabolic profile in subjects with type 2 diabetes with or without microalbuminuria

Parameters	Total WBC count			
	Microalbuminuria group (n=110)		Normoalbuminuria group (n=43)	
	r	p-value	r	p-value
Age	0.129	0.054	-0.048	0.735
Duration of DM	0.128	0.200	-0.055	0.696
BMI	0.133	0.186	-0.106	0.454
WHR	0.163	0.104	0.161	0.253
Platelet count***	0.353	**0.0001**	**0.456**	**0.001**
ESR	0.183	0.065	0.201	0.154
FBS	0.140	0.162	0.101	0.187
Total Protein***	0.400	**0.003**	0.062	**0.003**
Globulin***	0.433	**0.001**	0.225	**0.024**
T Cholesterol	0.081	0.421	-0.084	0.553
Triglyceride	-0.002	0.984	0.022	0.875
LDL Cholesterol	0.093	0.356	-0.061	0.666
VLDL	0.027	0.786	0.096	0.499
HDL Cholesterol	-0.029	0.775	0.042	0.769
Urea	0.138	0.170	0.218	0.121
Creatinine	0.172	0.085	0.234	0.094
Na+	0.005	0.959	0.069	0.628
K+	0.003	0.976	0.186	0.186
Cl-	0.069	0.490	-0.09	0.524
GFR ***	-0.198	**0.047**	-0.197	0.161
Urea:Cr ratio	0.027	0.785	-0.047	0.741

r: Correlation coefficient

Table 4 shows the correlation between microalbuminuria and both total and differential WBC count. There was a significant positive correlation between microalbuminuria and total WBC count($r=0.171$; $p=0.035$) and neutrophil count ($r=0.257$; $p=0.002$). But there is no significant correlation of microalbumin with lymphocytes, eosinophil, basophils and monocytes count ($p>0.05$)

Table 4: The Pearson's Correlation between total and differential Leukocytes count and Microalbuminuria in type 2 diabetic patients

Parameter	Microalbuminuria	
	R	p-value
Total WBC count	0.171	**0.035**
Neutrophil count	0.257	**0.002**
Lymphocyte count	0.006	0.947
Monocyte count	0.091	0.268
Eosinophil count	-0.065	0.433
Basophil count	0.049	0.555

r: Correlation coefficient

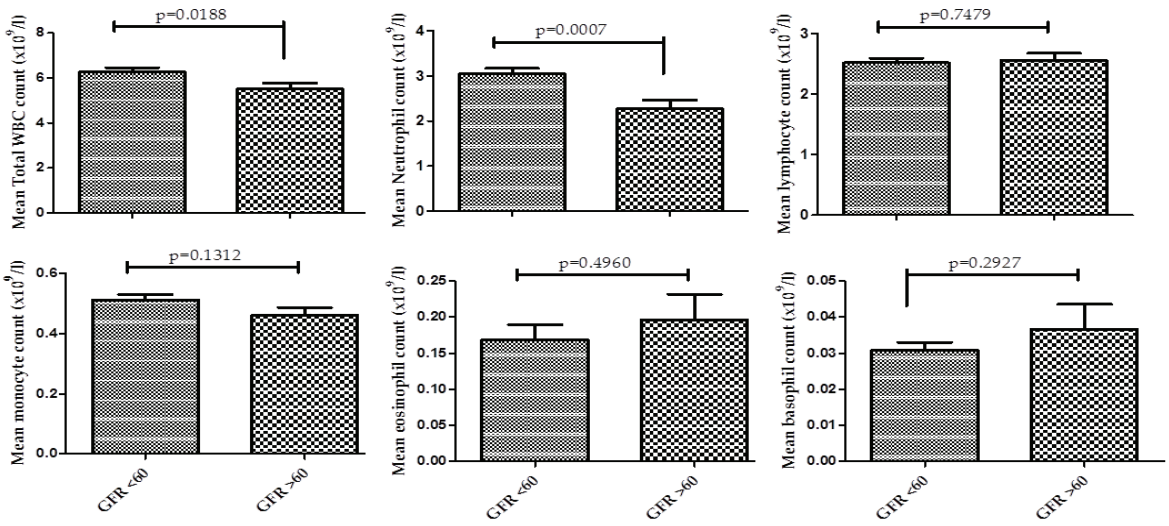

Figure 1. Mean total and differential WBC counts categorized by severity of GFR

As shown in **Figure 1**, participants with GFR below 60 ml/min 1.73 m^2 had significantly higher total WBC count and neutrophil count compared to those with GFR above 60 ml/min 1.73 m^2 ($p<0.05$). No statistically significant difference was observed between mean lymphocytes, eosinophils, basophils and monocytes count among participants with GFR below 60 ml/min 1.73 m^2 compared to those with GFR above 60 ml/min 1.73 m^2 ($p>0.05$).

4.0 DISCUSSIONS

The association between BMI and diabetes, as well as the risk of developing its complications, has been established in several studies (Chan et al., 2018, Ganz *et al* 2014, Gray *et a*l 2015). This present study also established that females who had significantly higher BMI also had

significantly higher fasting blood sugar levels, since increased BMI is associated with increased insulin resistance. This finding agrees with the findings of Amartey *et al* (2015). Increased blood glucose levels has been associated with increased lipogenesis and hence dyslipidaemia. Narindrarangkura et al., 2019 and Homma et al., 2015 reported dyslipidaemia in female diabetics especially those with poor glycaemic control. Similarly, in this study, the female population who had significantly higher blood glucose levels also showed significantly higher serum total cholesterol, triglycerides, and very low-density lipoproteins (VLDL). Excess blood glucose provides the substrates for fatty acid synthesis, while at the same time most of the participants in this study were also menopausal and hence prone to having increased lipid levels.

This study reported characteristically higher creatinine levels in males than females, as well as significantly higher urea levels in females. This finding contrasts the report by Bamanikar et al., (2016), Singh *et al* (2014) and Mafuratidze *et al* (2014) who reported no significant difference in the urea levels of male and female diabetics. This contrasting finding may probably be cosmetic resulting from the participant demographics.

Platelets (Sonmez & Sonmez, 2017emerging data indicates that platelets have considerable roles in inflammation and immune response. Platelets gather at the damaged cite and adhere to white blood cells. Subsequently, they release cytokines and chemokines which are chemotactic for neutrophils and monocytes. Therefore, platelets are necessary for targeting lymphocytes, neutrophils and monocytes to inflammation site. Those interactions enhance inflammation. Moreover, platelets serve as an immune cell by engulfing microbes. Presence of platelets affect prognosis in some bacterial or viral infection and several other diseases.","author":[{"dropping-particle":"","family":"Sonmez","given":"Ozge","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Sonmez","given":"Mehmet","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"Porto Biomedical Journal","id":"ITEM-1","issue":"6","issued":{"date-parts":[["2017","11","1"]]},"page":"311-314","publisher":"Ovid Technologies (Wolters Kluwer Health, Cognasse et al., 2019), Erythrocyte Sedimentation Rate (ESR) (Ganesan et al., 2017) and globulins (Wu et al., 2019) have all been associated with the inflammatory response. Recent studies (Wirth et al., 2018, Chmielewski & Strzelec, 2018) have asserted that chronic inflammation which can be indicated by a raised WBC count may play an important role in the development of diabetic complications. In the study, it was observed that platelets, ESR and globulin levels all increased significantly as WBC count increased.

The involvement of white blood cells in micro- and macrovascular disease has lately become the focus of many studies. Vozarova *et al* in (2002) reported that white blood cells were involved in worsening insulin insensitivity and eventual development of type 2 diabetes. Vozarova *et al* (2002) further hypothesized that long term activation of the immune system could possibly lead to overproduction of certain cytokines such as interleukin 6, which causes insulin resistance and is also a known white blood cell differentiation factor. The current study, however, did not establish a correlation between total WBC count and glucose levels. While several studies ((M. et al., 2017b, Moradi et al., 2012 and Tong *et al*, 2004) have associated WBC with macrovascular disease, this study did not report any association between WBC and macrovascular complications of diabetes.

Ravi *et al*, 2006 identified White cell count as an independent risk factor for microalbuminuria. The actual mechanism for the role of white blood cells in diabetic complications is the subject

of much speculation and hypotheses. Tong *et al*, (2004) postulated that the cumulative effect of long term subclinical inflammation could lead to vascular injury with endothelial dysfunction and increased oxidative stress with the proliferation of growth factors and cytokines, and when coexisting with other risk factors, result in the micro and macrovascular pathology seen in type 2 DM patients. While this study showed evidence of an inflammatory state in all the subjects, it also showed that WBC levels, especially neutrophil counts, increased significantly as renal function deteriorated. Several other studies have reported an association between inflammatory markers including white blood cells and the development and progression of diabetic complications. (Szydełko et al., 2018, Ravi *et al*, 2006, Chung *et al*, 2005 and Tong *et al,* 2004). Diabetic nephropathy is now recognized as having multifactorial causes including chronic inflammation mediated by blood cells such as neutrophils.

Chung *et al* (2005) reported that neutrophils, monocytes and lymphocytes are associated with the development and progression of diabetic nephropathy. They proposed leptin, which is an adipocytokine, to be a factor that accentuates the release and activation of white cells from the bone marrow.

There have been suggestions (Lee et al., 2017, Segel *et al*, 2011) that the neutrophil, though very essential for human survival, may also play a role in causing damage to renal vasculature by their release of certain proteases, reactive oxygen species and their interaction with adhesion molecules.

Diabetes mellitus is currently considered to be a prothrombotic condition with altered platelet morphology and function. Sterner *et al* (1998) reported thrombocytosis as a common finding in diabetes mellitus patients who had developed nephropathy. Magri and Calleja (2011) also reported an increased platelet count in incipient diabetic nephropathy. However, Pahim and Megalamane (2017) reported similar platelet count between diabetics with and without nephropathy. Sokunbi *et al* (1994) also reported a positive correlation between WBC and platelets in diabetics on peritoneal dialysis. This study also found platelet count to be positively correlated to white cell count which is itself an independent risk factor for microalbuminuria.

5.0 CONCLUSION

The current study has demonstrated that as has been established in other populations around the world, there is a correlation between the development and progression of diabetic nephropathy and total and differential white cell count, especially neutrophil count. Clinicians should therefore pay more attention to the white cell profile of diabetic patients.

This study is the first of its kind in a Ghanaian population as far as we are aware, and we recommend that a similar study should be conducted on a larger scale in the Ghanaian diabetic population.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflict of Interest: The authors declare no conflict of interest.

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