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Acute Phase Reactant Correlates and Erythrocyte Sedimentation Rate Among Type 2 Diabetes Mellitus Patients in Yenagoa, Nigeria

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Abstract :*The South-South Region of Nigeria had the highest pooled prevalence of 8.5% of type 2 diabetes mellitus (T2DM) in Nigeria between 1985 and 2016. This signals the need for the use of additional markers, as tools for the diagnosis of the disease in order to monitor and manage therapy. This study was aimed at evaluating the acute phase reactant correlates among T2DM patients in Yenagoa, a city in the region. 123 subjects (80 T2DM and 43 control) were enrolled in the study based on a cross-sectional design. Venous blood samples were collected from all subjects and tested for fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1c}), C-reactive protein (CRP), albumin, and erythrocyte sedimentation rate (ESR). Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20, and was grouped into ESR, CRP, Albumin, FPG and HbA_{1c}, for each of T2DM and nondiabetic control subjects. Difference in measured parameters between test and control were compared using the independent T-test. Pearson correlation coefficient was determined for associations between groups. All regression graphs were made using GraphPad Prism 5. An error probability (p)-value ≤ .05 was considered significant. Results showed significant difference in all studied parameters between T2DM patients and control ($t > 2.00$, $p < .01$). Strong significant correlation was observed between CRP and ESR ($r = 0.96$, $p = .01$) expressed by the regression line: $ESR = 10.72 + 1.83 \times CRP$ ($R^2 = 0.92$) of T2DM subjects. Strong significant correlation was also observed between HbA1c and FPG with linearity as $HbA1c = 3.47 + 0.37 \times FPG$ ($R^2 = 0.87$, $r = 0.93$, and $p = .01$), and albumin showed a direct relationship with FPG among these patients. We had demonstrated significant difference in levels CRP, ESR, and albumin concentration between T2DM patients and apparently healthy control subjects, we further conclude that the ESR can be used as a surrogate of CRP in conjunction with the FPG and 2h-PG in diagnosis of T2DM in our resource limiting setting*

Keywords: *–type 2 diabetes mellitus, acute phase reactants, C-reactive protein, albumin, erythrocyte sedimentation rate, HbA_{1c}*

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I. Introduction

The inflammatory response process involves a variety of chemical mediators that play inexpedient role. Some of these mediators are released by damaged cells in response to tissue damage or injury. They can also be derived from several plasma enzymes systems, generated from invading microorganisms, and produced from activated white blood cells such as neutrophils, monocytes and macrophages that take part in the inflammatory response [1]. The acute phase response is a dynamic process of homeostasis that involves all the major systems of the body in addition to the immune, cardiovascular, and central nervous system [2]. It is a molecular response to noxious stimuli [3]. Acute phase reactants (APR) are nonspecific, and have a wide range of activities that play key roles in the host defense mechanism: neutralization of inflammatory agents, reduction of the extent of local tissue damage, and take part in tissue repair and regeneration [2]. In this process, acute phase proteins (APP) are released by damaged tissues. They are secreted primarily by hepatocytes. The concentration of these proteins increase drastically during tissue-damaging infections [1].In the acute phase response process, the concomitant increase in certain mediators results in a simultaneous decrease in certain APPs. These are known as negative APPs. Examples of negative APPs are albumin, transferring, transthyretin, transcortin, and retinol-binding protein [4]. The positive chemical mediators of acute-phase response include D-dimer protein, mannose-binding protein, α-1-antitrypsin, α-1-antichymotrypsin, α-2-macroglobulin, fibrinogen, prothrombin, factor VIII, von-Willebrand factor, plasminogen, complement factors, ferritin, ceruloplasmin (Cp), haptoglobulin (Hp), serum amyloid P (SAP) complement, serum amyloid A (SAA), IL-6, and C-reactive protein (CRP) [4,5]; the last threebeing the main mediators of the acute phase response [5].CRP is one of the APPs that

is strongly associated with inflammatory response [2]. It was named for its ability to precipitate the somatic C-polysaccharide of *Streptococcus pneumonia*, and is also the first APP to be described [6]. Following liver damage, CRP binds to C polysaccharide cell wall component of bacteria and fungi; resulting in clearance of pathogen through complement-mediated lysis or complement mediated phagocytosis [1]. According to Chandrashekara (2014), CRP is increased by 1000-fold or even more in concentration during injury, inflammation or tissue death.Albumin is the most predominant serum protein [7]. It accounts for 11 – 15% of the total proteins synthesized by the liver. Its synthesis is influenced by factors such as nutrition, thyroxin, insulin, glucagon, cortisol, and systemic inflammatory cytokines [8]; that results in a decrease in its synthesis [9]. With a plasma half-life of 15 – 19 days, albumin has the primary function of maintaining colloidal osmotic pressure (COP) in the vascular and extravascular spaces. In addition, it is involved with the transportation of compounds such as free fatty acids (FFAs), phospholipids, metallic ions, amino acids, drugs, hormones, and bilirubin [9]. Another test that is often estimated in the evaluation of the acute phase response is the measurement of the erythrocyte sedimentation rate (ESR) [10]. The ESR, a nonspecific test used in monitoring disease activity and diagnosing inflammatory disorder, is the rate of sedimentation of red blood cells (RBCs) [11], in diluted whole blood after allowing to stand for 1 hour in an open-ended glass tube of 30 cm in length [10]. The rate of sedimentation of the RBCs occurs in 3 known phases: aggregation, precipitation, and finally packing. RBC aggregation which is also known as rouleaux formation is a vital factor for the sedimentation. This process is influenced by certain plasma proteins and APPs such as fibrinogen, IgM, and α-2-macroglobulin [11]. There is low level of inflammation and release of cytokines such as tumor necrosis factor-α (TNF-α) and resistin in type 2 diabetes mellitus (T2DM) [12].T2DM makes up about 90% of all cases of diabetes. It is characterized by minimal symptoms, reduced tendency for ketosis, and independence on insulin for the prevention of ketonuria[13].According to Adeloye *et al*. (2017), the South-South region of Nigeria had the highest pooled prevalence of T2DM at 8.5% between 1985 and 2016. Specifically, the highest prevalence rates of T2DM was recorded among oil company workers in Port Harcourt in 2001 and Uyo in 2010, 23.6% and 10.5% respectively [14]. The World Health Organization (WHO) and American Diabetes Association (ADA) recommended that a glycated hemoglobin A_{1c} (HbA_{1c}) concentration of 6.5% or more can be used for the diagnosis of diabetes [15]. Owing to the need for more efficient diagnosis of the disease using other serum markers like APRs, several studies have been carried out on APRs in T2DM [2,16–19]; but these have been done in other settings. It is therefore expedient that this study be carried out in Yenagoa, South-South Nigeria as well, owing to differences that may be observed in cut-off values for hyperglycemia, due to changes in the trends and attitudes of different populations [20]

II. Materials and Methods

2.1 Subjects, design, and Setting

A total of 123 subjects who were residents of Yenagoa were enrolled in this study; based on a cross-sectional design. Subjects comprised 80 T2DM subjects and 43 nondiabetic control subjects; all aged between 16 and 77 years. Written consent was obtained from all subjects. The study was conducted in the Laboratory Services Department of the Federal Medical Centre (FMC), Yenagoa, South-South of Nigeria; which also gave ethical approval. LaboratoryBlood Sample Collection. At least 6 ml of venous blood was collected from each subject; 2 ml was dispensed aseptically into EDTA bottles, 2 ml into fluoride-oxalate bottles, while the remaining 2 ml was dispensed into plain sterile evacuated tubes for obtaining serum [21]. The samples collected into EDTA and fluoride-oxalate bottles were carefully mixed, using a standardized mechanical mixer. Blood samples in fluoride-oxalate bottles were centrifuged at 1200 × g for 10 minutes to obtain plasma. The sample in the plain tubes were allowed to clot undisturbed for 1 hour at room temperature. Serum was obtained, after centrifuging at 1200 × g for 10 minutes. The supernatant was dispensed to another tube and centrifuged again at 1200 × g for10 minutes, obtaining pure serum, which was then stored at -20 ^{o}C prior to analysis.Laboratory Analysis: Fasting Plasma Glucose (FPG) concentration was determined using the glucose oxidase-peroxidase method [22]. In this method, glucose oxidase (GOD) catalyzes the oxidation of glucose to hydrogen peroxide (H_2O_2) and gluconic acid. The enzyme peroxidase (POD), then catalyzes the breakdown of H_2O_2 to release oxygen, which reacts with 4-aminophenazone (4-aminoantipyrine) and phenol to form a pink color. The absorbance of the color produced is measured spectrophotometrically at 515nm.Glycated Hemoglobin (GHb) was determined by the Direct Enzymatic HbA_{1c} Assay ^{TM}[23]. This works on the principle that oxidizing agents in a lysis buffer eliminates low molecular weight and high molecular weight signal interfering substances in the whole blood sample. After lysis, the whole blood sample is subjected to detailed digestion by proteolytic enzymes. In this process, amino acids such as glycated valines from the hemoglobin β chains are released. These Direct Enzymatic HbA_{1c} Assay glycated valines serve as substrates for a specific recombinant fructosyl valine oxidase (FVO) enzyme. This recombinant FVO cleaves N-terminal valines specifically, and produces hydrogen peroxide in the presence of certain agents. The concentration of hydrogen peroxide is measured with a

horseradish peroxidase (HRP) catalyzed reaction in the presence of a suitable chromogen. The absorbance change produced in the reaction is used to directly report the % HbA_{1c} of the sample using a suitable linear calibration curve expressed in % HbA_{1c}[24].Serum C-reactive Protein (CRP) was estimated by the Invitrogen Human C-Reactive Protein Enzyme-Linked Immunosorbent Assay (ELISA) [25]. It works on the principle that human CRP contained in the samples and standards bind to the anti-human-CRP antibodies absorbed to the plate. These are incubated and washed to remove any unbound particles and an HRP-conjugated antibody targeted at a unique epitope of human CRP is added to the micro well plate. The incubation and washing process is repeated, followed by the addition of a peroxidase substrate. A blue color is formed, which is proportional to the amount of soluble CRP present in the sample. The reaction is stopped with the addition of an acid solution that turns the liquid from blue to yellow. The color intensity of the solution is measured by reading the absorbance at 450 nm on a spectrophotometer. A dilution series of known standards are used to plot a calibration curve for the quantification of human CRP present in the samples. Serum Albumin was determined using Albumin (BCG) Assay Kit (by Colorimetry) [26]. Bromocresol green (BCG) is an indicator that is yellow in color at pH 3.5 – 4.2. When it binds to albumin in the sample, the color of the indicator changes from yellow to blue-green [22]. The absorbance of the color produced is measured in a spectrophotometer at 620nm wavelength. The signal produced is directly proportional to the concentration of albumin present in the serum. BCG does not cross react with other abundant plasma proteins like IgG. The assay has a sensitivity of 5µg (0.01 g/dl) of albumin in serum samples [26].Erythrocyte Sedimentation Rate was determined by the Westergren technique [27]. When citrated whole blood is allowed to stand in a vertically positioned Westergren pipette, red blood cells (RBCs) aggregate, form rouleaux by stacking together, and sediment through the plasma. The ESR is the rate of sedimentation of RBCs in 1 hour as indicated by the length of the column of clear plasma above the RBCs, measured in mm [27]. The rate of sedimentation of the RBCs is influenced by factors such as variations in specific gravity between RBCs and plasma, and largely by the extent of rouleaux formation [10].Statistical Analysis: We used SPSS version 20 [28] to determine the normality of the data by means of the Kolmogorov-Smirnov one sample test. This was preceded by grouping of the data into ESR, CRP, Albumin, FPG and HbA_{1c}, for each of T2DM and nondiabetic control subjects. Difference in measured parameters between test and control were compared using the independent T-test. Pearson correlation coefficient was determined for relationship between groups. All regression graphs were made using GraphPad Prism 5 [29]. An error probability (p)-value $\leq .05$ was considered significant.

III. Results

A total of 123 subjects were enrolled in this study. These subjects were aged between 16 and 77 years; and were all residents of Yenagoa, Bayelsa State, Nigeria. 55 (44.70%) males participated in the study, while females were 68 (55.30%). Other details are listed in *Table 1*.*Table 2* compares the studied parameters between T2DM patients and control, showing significant difference for all the parameters $p< .01$. *Table 3*shows the correlation between the APRs (CRP and Albumin), ESR, HbA_{1c}, and FPG among T2DM subjects. Significant correlation was observed for most of the pairs ($p< .05$). Figure 1 shows the relationship between FPG and HbA_{1c}among the T2DM patients studied, which is strongly significant at $p< .01$, and $R^2 = 0.87$. Similarly, the relationship between CRP and ESR among T2DM patients was linear and strongly significant at $p< .01$ and $R^2 = 0.92$ (*see Figure 2 below*). In addition, Figure 3 shows a linear relationship between FPG and albumin among the T2DM patients ($p< .05$).

Table 1: Demographic Details of Subjects

Parameter	Statistic	Percentage (%)
Total number	123	100.00
Gender		
• Males	55	44.70
• Females	68	55.30
Diabetic Status		
• T2DM	80	65.04
• Control	43	34.96
Occupation		
• Farming	5	4.07
• Civil Servant	66	53.66
• Business	20	16.26
• Others	32	26.02
Age Range (Y)	16 – 77	

Table 2: Comparison of Studied Parameters between T2DM Patients and Control

Parameter	$Mean \pm SD$		*t* statistic	*p* value
	T2DM (n = 80)	Control (n = 43)		
FPG (mmol/l)	14.21 ±3.68	4.07 ±0.98	23.18	.00**
HbA_{1c} (%)	8.78 ± 1.48	4.93 ± 0.85	18.33	.00**
CRP ($\times 10^{-3} g/l$)	14.90 ± 4.62	5.99 ± 1.76	15.33	.00**
Albumin (g/l)	37.41 ± 4.68	31.05 ±7.57	5.03	.00**
ESR (mm/h)	37.97 ±8.78	28.65 ±16.37	3.47	.00**

***Note*:** FPG = fasting plasma glucose, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, T2DM = type 2 diabetes mellitus, SD = Standard deviation. **Significant difference observed between T2DM and control, $p < .01$.

Table 3: Correlation between APRs, ESR, HbA1c, and FPG in T2DM Patients

		FPG	HbA1c	CRP	Albumin	ESR
FPG	r	1.00	0.93**	0.18	0.26*	0.20
	p		0.00	0.11	0.02	0.08
	n	80.00	80.00	80.00	80.00	80.00
HbA1c	r	0.93**	1.00	0.18	0.28*	0.23*
	p	0.00		0.10	0.01	0.04
	n	80.00	80.00	80.00	80.00	80.00
CRP	r	0.18	0.18	1.00	0.16	0.96**
	p	0.11	0.10		0.16	0.00
	n	80.00	80.00	80.00	80.00	80.00
Albumin	r	0.26*	0.28*	0.16	1.00	0.21
	p	0.02	0.01	0.16		0.07
	n	80.00	80.00	80.00	80.00	80.00
ESR	r	0.20	0.23*	0.96**	0.21	1.00
	p	0.08	0.04	0.00	0.07	
	n	80.00	80.00	80.00	80.00	80.00

***Note*:**FPG= fasting plasma glucose, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, r = Pearson correlation coefficient, *p* = error probability, and n = total number of subjects. **. Correlation is significant at the .01 level (2-tailed).*. Correlation is significant at the .05 level (2-tailed).

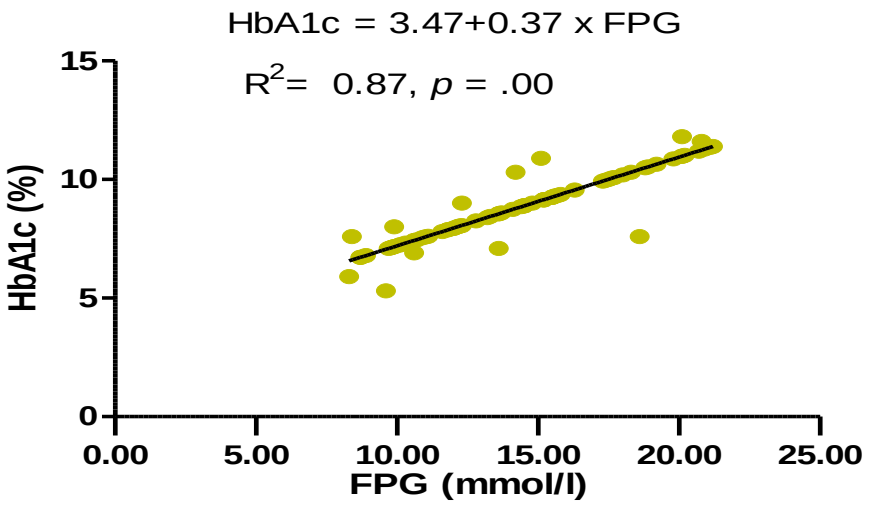

Figure 1: Relationship between FPG and HbA1c among T2DM Patients in Yenagoa.
FPG = fasting plasma glucose, HbA1c = hemoglobin A1c, and R2 = squared regression coefficient. Significant regression observed, $p < .01$.

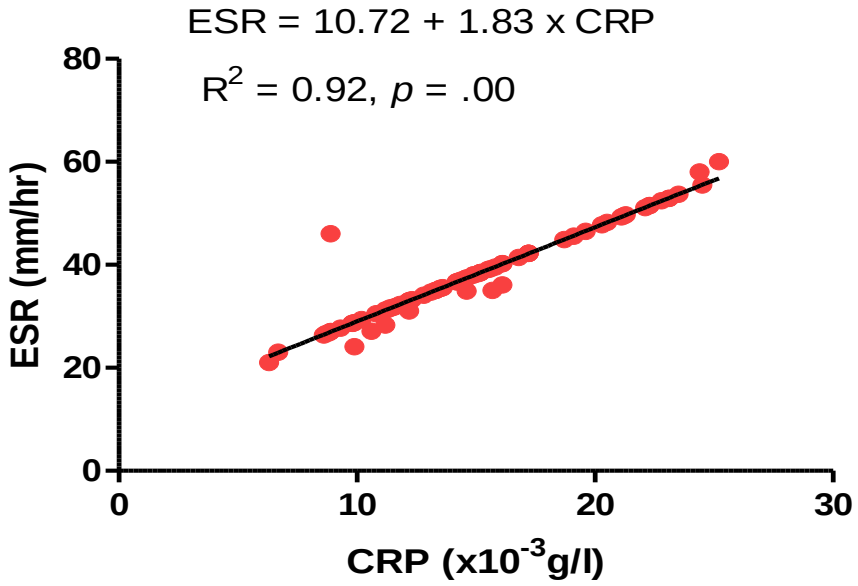

Figure 2: Relationship between CRP and ESR among T2DM Patients in Yenagoa
ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, and R2 = squared regression coefficient. Significant regression observed, p < .01

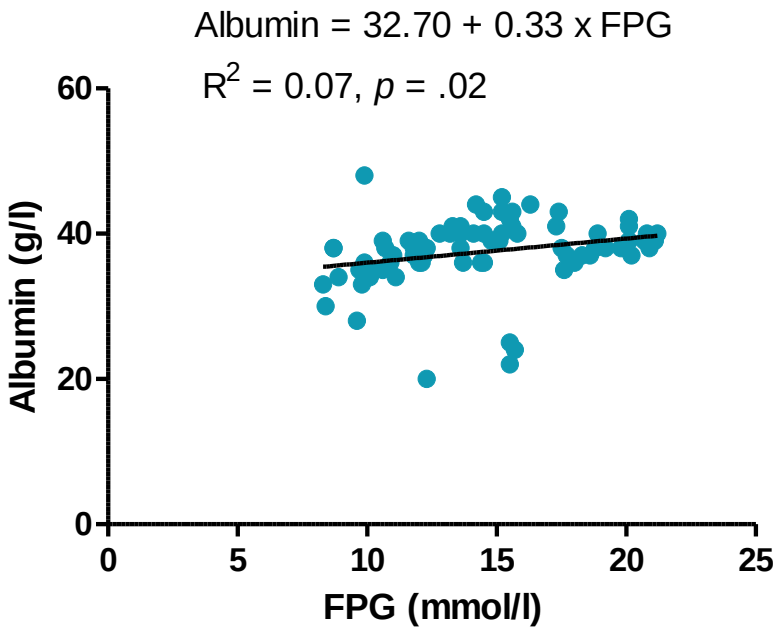

Figure 3: Relationship between FPG and Albumin among T2DM Patients inYenagoa
FPG = fasting plasma glucose, R2 = squared regression coefficient. Significant regression observed, p < .05.

IV. Discussion

Of the various types of DM, T2DM is the most predominant, accounting for 90 – 95% of all case of DM [30]. In the South-South region of Nigeria, the highest prevalence rates of T2DM were found in Port Harcourt in 2001 (26.3%), and in Uyo in 2010 (10.5%) among oil company workers [14]. This calls for the need for additional markers for the disease especially in Yenagoa, a State in this region of Nigeria. Thus, 123 subjects (80 T2DM patients and 43 apparently healthy control participants) were enrolled in this study aimed at determining the APR correlates among T2DM patients in Yenagoa. Of these subjects, 55 (44.40%) were males while 68 (55.3%) were females; all aged between 16 and 77 years. The major occupation among the subjects

was civil service (53.66%). The percentage of participants who were farmers and business persons were 4.07% and 16.26%, respectively (See *Table 1*above). The category of occupation known as 'others' included students, artisans, and the unemployed. The majority of T2DM patients were civil servants whose age were well above 40 years, with some being retired. Studies have shown that a sedentary lifestyle, physical inactivity, smoking, and alcoholism may be the predisposing factor among this group [31–34].Results from *Table 2* showed strongly significant differences (p<.01) in the mean $\pm$ SD of all parameters studied between T2DM patients and apparently healthy control subjects in Yenagoa. This level of significance is suggestive of an effect of T2DM on the CRP concentration, albumin concentration, and ESR. The effect of T2DM on the CRP as shown in this study is well in agreement with that of several studies in other setting [18,35–39].In this study, the albumin concentration in T2DM patients (37.41 $\pm$ 4.68 g/l) was significantly higher (p = .00) than that of the control subjects (31.05 $\pm$7.57 g/l) (*Table 2*). This is contrary to the result obtained by Venkataramana and associates[40], who showed a significant reduction in the serum albumin concentration in T2DM subjects relative to control in India. Moreover, this result also disagrees with the result from the study by Cheng and colleagues[41], who showed that serum albumin concentration was inversely associated with risk of ketosis among T2DM subjects in Taiwan.Similar to albumin, the ESR was also significantly higher (p =.00) in T2DM patients (37.97 $\pm$8.78 mm/h) in comparison to that of apparently healthy control subjects (28.65 $\pm$16.37 mm/h), as shown in *Table 2*. This result is in agreement with that of other studies [42–44], including a study by Odusan and associates[45] in OlabisiOnabanju University Teaching Hospital (OOUTH), Ogun State, Nigeria. This significant elevation in the ESR may be due to the activities of APRs like CRP, Hp, and Cp[10].The significant elevation of the ESR among T2DM patients in this study, strongly correlates with the CRP as shown in*Table 3* (r = 0.96, p = .00). Significant correlation between ESR and CRP has been shown in patients with rheumatoid disease, in other setting [46]. The relationship between the ESR and CRP among T2DM patients in our setting can be expressed by the regression line $ESR = 10.72 + 1.83 \times CRP$(Figure 2), with the CRP being a good predictor of the ESR (R^2 = 0.92, p = .00).There was also significant correlation (r = 0.26, p = .02) between the FPG and albumin concentration as shown in *Table 3*. The moderate effect size of this relationship is seen in the small regression coefficient (R^2 = 0.07, p = 0.02) expressed in the linear equation: $Albumin = 32.70 + 0.33 \times FPG$ (Figure 3). This is similar to the result obtained in the study by Yoon and colleagues [47]. The direct positive correlation between albumin and each of FPG (r = 0.26, p= .02) and HbA_{1c} (r = 0.28, p= .01) is in contrast with that of Dasan & Suthakara[48], who showed a negative correlation between HbA_{1c} and albumin among T2DM patients in Tamilnadu, India.We also demonstrated a strong positive correlation (r = 0.93, p = .00) between FPG and HbA_{1c} concentration among T2DM patients in Yenagoa (*Table 3*). This relationship is significantly linear (R^2 = 0.87, p = .00), and is expressed by the equation: $HbA1c = 3.47 + 0.37 \times FPG$ as shown in Figure 1. This agrees with that of several studies [49,50], with the same regression coefficient (R^2 = 0.87) [51] and has been reviewed extensively in other setting [52]. The linearity between HbA_{1c} and FPG can be affected by a number of hemoglobin variants such as HbS, HbF, and HbE. Moreover, conditions that disambiguates the red cell turnover can result in false HbA_{1c} concentration, and hence disrupt this relationship. These conditions include hemolytic anemia, chronic plasmodiasis, significant blood loss, and blood transfusion [53]. Individuals with these conditions were excluded from this study.This study has had its share of limitations. We could not monitor the APR, ESR, and HbA_{1c} concentration of the T2DM subjects in a prospective cohort. Moreover, we did not determine the red cell membrane features and zeta potential (ZP) which may influence the sedimentation process. This we hope to do in a subsequent study.

V. Conclusion

We had demonstrated significant difference in levels CRP, ESR, and albumin concentration between T2DM patients and apparently healthy control subjects, we further conclude that the ESR can be used as a surrogate of CRP in conjunction with the FPG and 2h-PG in diagnosis of T2DMresource limiting setting.

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