Original

Assessment of TNF-Alpha, Interleukin-10, Glycated Hemoglobin and Red Blood Cell Indices in Type 2 Diabetes Mellitus Patients With or Without Malaria Co-Infections

[1]Friday Alfred Ehiaghe, [1]Rebacca Chinyelu Chukwuanukwu, [1]Vivian Chinasa Okafor, [2]Joy. Imuetinyan Ehiaghe, [2]Usiosefe Raphael Erhunmwunse, [3]Ogochukwu Godfrey Ezema, [4]Sylvia Ifeoma Obu, [5]Nkiruka Nwamaka Eze, [6]Progress Arhenrhen Obazelu, [7]Ndudi Mary Dibigbo-Ibeaji, [5]Patrick Onochie Manafa

[1] Department of Immunochemistry and Immunology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria
[2] Department of Medical Laboratory Science, Benson Idahosa University, Benin City, Edo State Nigeria
[3]Department of Medical Laboratory Science, David Umahi Federal University of Health Sciences, Uburu, Ebonyi State, Nigeria
[4]Molecular Laboratory, Centre for Disease Control and Research, Federal Medical Center Asaba, Delta State, Nigeria
[5]Department of Clinical Chemistry, Nnamdi Azikiwe University, Anambra State, Nigeria
[6]Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Benin City, Nigeria.
[7]College of Medicine, Novena University, Ogume, Delta State, Nigeria.

Corresponding author: ***Ehiaghe F. A,*** Department of Immunochemistry and Immunology, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria. fa.ehiaghe@unizik.edu.ng;+234063327432

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ABSTRACT

Background: Malaria and type 2 diabetes are both inflammatory conditions. Tumor necrosis factor alpha (TNF-α), interleukin 10 (IL-10), glycated hemoglobin, and red blood cell indices were measured in this case-control study in individual with co-morbid malaria and type 2 diabetes in Nnewi, Anambra State.

Methods: Using a simple random sampling technique, 200 participants were studied and split into 4 groups: Group A (50 people with T2DM and malaria; Group B (50 people with T2DM without MP); Group C (50 people with Mp only); and Group D (50 people without T2DM and MP (control group)). Enzyme immuno assay method were used to assay TNF-alpha and IL-10 levels, while ion exchange resin method was used to measure glycated hemoglobin (HbA1c). The MCV, MCH, and MCHC was determined using haematology analyzer.

Results: The mean HbA1c and serum TNF-α levels in T2DM with and without MP were considerably higher ($p<0.05$) in the MP group compared to the control group. Additionally, T2DM with MP had a mean MCHC that was considerably greater than T2DM without MP, MP group alone, and control group ($p<0.05$). TNF-α levels and MCH levels in T2DM with MP were found to be negatively correlated.

Conclusion: Malaria can worsen the severity of T2DM via changes in TNF-α, IL-10, glycated haemoglobin, MCV, MCH and MCHC levels. To properly understand the mechanisms underlying the current findings, more research is required.

Keyword: Cytokines, Red blood cell indices, Type 2 Diabetics with malaria co-morbidity

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INTRODUCTION

T2DM is a chronic metabolic disease with a primary defect of a progressive failure of insulin secretion and a secondary defect of peripheral insulin sensitivity [1, 2,3]. T2DM is one of the major preventable causes of death in the world [4, 5]. The challenge is especially serious in developing countries such as Nigeria, where the incidence of the disease is on the rise. Recent data, from systematic reviews and meta-analyses [6,7], indicate that approximately 5.77% of the population of Nigeria are estimated to be diabetic. This localized surge is emblematic of a larger crisis on the continent: In 2021, the International Diabetes Federation (IDF) reported that approximately 24 million adults were living with diabetes across Africa, highlighting the significant impact of diabetes on people's lives, families and health systems [8].

Concurrently, malaria remains a monumental global health threat. Caused by protozoan parasites of the genus Plasmodium and transmitted via the bites of infected female Anopheles mosquitoes, the disease is highly endemic to Africa, with Nigeria bearing the world's highest burden. [9, 10] Human malaria is driven by five distinct species: *Plasmodium falciparum*, *P. vivax*, *P. malariae, P. ovale,* and *P. knowlesi*, with *P. falciparum* and *P. vivax* posing the greatest clinical danger. [11] Year-round transmissions across Nigeria are sustained by dominant vectors, including *Anopheles gambiae, A. funestus, A. arabiensis, A. coluzzii,* and *A. moucheti.* [12] Despite the deployment of targeted interventions like the Seasonal Malaria Control Strategy (SMCS), infection rates remain stubbornly high.[13, 14] Epidemiological data highlight severe regional burdens: Research indicates that up to 63.3% of adult febrile patients present with confirmed malaria parasitemia.[15] Studies in Abia State revealed a striking 73.39% prevalence in the rural communities of Umuchieze and Uturu, alongside rates of 74.40% in Umuahia and 58.67% in the Ibere community.[16, 17.] Globally, the World Health Organization (WHO) documented a rising trajectory in cases, climbing from 245 million infections in 2020 to 247 million in 2021[18]. The clinical intersection of T2DM and malaria is heavily mediated by cytokines signaling molecules that orchestrate inflammatory and immune responses.

TNF-alpha is a critical disease pathway bridging the two conditions, [7, 19-23] and plays a leading role in underlying physiology of both conditions throughout an infection. In malaria, the role of TNF-alpha is that of a double-edged sword: on the one hand, it provides protection at early stages of infection, on the other; it causes significant complications such as cerebral malaria in cases of high levels [24]. A high concentration of TNF-alpha has a direct effect on insulin sensitivity, which is a marker of metabolic health. It does this by lowering the amount of IRS-1 and GLUT4 protein in lipid-rich cells, which helps to cause insulin resistance and make it easier for T2DM to start [25]. Interleukin-10 (IL-10) is an anti-inflammatory counterweight, however. Malaria patients have been found to have significantly elevated state of IL-10 in their serum, and higher IL-10/TNF-alpha ratios, despite the absolute state of TNF-alpha in the serum seeming similar to control levels [24]. Other whole-blood donor assays, however, have reported significant boost in the amount of TNF-alpha in the bloodstream during active infection [26, 27]. There are several studies that showed that T2DM patients have significantly lower serum levels of IL-10 and have down-regulated levels of IL-10 receptor expression compared to healthy individuals [28-30]. Other results suggest increased IL-10 in the diabetic groups [31]. The significance of this increase in IL-10 in patients with T2DM is not fully understood, but may be compensatory, attempting to counteract, block and prevent tissue damage (particularly mediated by TNF-alpha), or may be a key protective mechanism against the progression of T2DM, by actively inhibiting the production of inflammatory cytokines. The pathophysiological mechanisms of malaria and T2DM add up when they are co-infecting a single individual. Symptomatic immune response to the malaria parasite is acute, and leads to hypercytokinemia. This inflammatory condition activates the endothelial cells, causing an over-expression of cell adhesion molecules (CAMs) including Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) [32]. At the same time, platelet activation leads to a hyperactivation of coagulation mechanisms that ultimately results in endothelial damage in a susceptible host with diabetes, further exacerbating clinical events.

MATERIALS AND METHODS

Study Design and Site: The study adopted the case-control study research design and was conducted at the Diabetic Clinic of Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State. The main aim was to assess and compare the levels of TNF-alpha, IL-10, glycated hemoglobin (HbA1c), and red blood cell (RBC) indices in various patient groups.

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Study Population and Cohort Allocation; Male and female subjects 30-75 years were recruited for the study. A total of 200 subjects were enlisted via a randomized selection process, and then divided into 4 distinct experimental arms – 50 subjects in each arm Group A (Co-infected): subjects with T2DM and concurrent malaria parasite. Group B (T2DM Only): People who were diagnosed with T2DM and were receiving anti-diabetic medication but who were not parasitaemic with malaria. Group "C" (Malaria Only): People who have been diagnosed with acute malaria parasitemia but not seen with diabetes. Group D (Control Group): Apparently healthy subjects with neither T2DM nor malaria parasite.

Sample Size Determination: A minimum sample size was determined with G*Power Software, version 3.1.9.4. A minimum sample size of 180 was determined by the power calculation. A 10% attrition rate was considered for possible data loss, and the total number of participants in the study was rounded up to an even number of 200, with a target of 198 participants.

Inclusion Criteria: Adults only age 30 to 75. Confirmed clinical diagnosis of T2DM (for Groups A and B) and/or active peripheral malaria parasitemia (for Groups A and C). A willingness to give clear documented informed consent.

Exclusion Criteria: People outside the age range (<30 or >75 years). Biological conditions that would affect hematological or immunological parameters in a physiological manner, such as pregnancy and lactation. Patients with known primary immunological disorders or with other metabolic disorder(s) in addition to T2DM. Any person who refuses to give informed consent.

Ethical Considerations and Data Collection: It was reviewed and received formal ethical clearance from Nnamdi Azikiwe University Teaching Hospital Ethics Committee (NAUTH/CS/66/VOL. 16/VER). 3/07/2023/07). Each candidate was given a detailed description of the clinical and experimental procedures before taking up the position. After this, a written informed consent was obtained from all participants. A strict workflow of data handling was enforced to ensure absolute anonymity of the participants and data confidentiality during the active trial and after the trial. Systematic collection of demographic data, medical histories and pertinent baseline clinical bio-data was done by using a structured questionnaire.

Biological Sample Collection: Venous blood (5 mL) was drawn from each subject and split in two for parallel hematological and biochemical analyses: Hematological Fraction (2 mL) was placed immediately in an ethylenediaminetetraacetic acid (EDTA) tube. These fractions were utilized for immediate blood count, automated RBC indices determinations and preparation of thick and thin blood films for microscopy screening of malaria parasite. Biochemical Fraction (3 mL): Collected in a plain tube without any anti-coagulant and clotted at room temperature. After the sample had coagulated, centrifuged at 3,000 rpm for 10 minutes to remove the serum. The separated serum was immediately aliquoted into sterile plain microtubes and placed directly in ultra-low temperature storage at -20^{0}C in the Department of Chemical Pathology at NAUTH until activated cytokine and biomarker assaying.

Laboratory Methods

Malaria Parasitemia Determination: The determination of malaria parasite was done by using Giemsa-stained thick blood film on which the malaria parasites were looked for as described by WHO [33].

Estimation of FBC: The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) is measured by using a three-part Biobase hematology analyzer (BK-6190, China).

Blood test to measure Glycosylated haemoglobin (HbA1c): The level of HbA1c was measured by the ion exchange resin method [34].

Estimation of TNF α: Human TNF-α immunoassay was done by enzyme immunoassay (EIA) as described in [35].

Human Interleukin 10 (IL-10) Estimation: The concentration of human IL-10 immunoassay was evaluated by enzyme immunoassay (EIA) method as described in [36].

Statistical Evaluation: The data interpretation was performed by using the SPSS version 26. To compare more than two groups for each variable in obtained data analysis of variance (ANOVA) was applied. Pearson correlation is used to correlate various parameters. Values obtained was considered statistically significant if p-value is <0.05.

RESULTS

The Analysis of Variance (ANOVA) revealed that the mean serum TNF-alpha, IL-10 and glycated hemoglobin HbA1c levels for all assessed groups were significantly

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different (P<0.05). In particular, the co-infected group (diabetic patients who had malaria parasitemia) had the highest level of serum TNF-alpha, which was markedly elevated than the diabetic group (p = 0.001) when compared directly to them. This baseline diabetic group had significantly higher TNF alpha levels than patients with only malaria (p = 0.001) and healthy controls (p = 0.001); and the acute malaria-only group had significantly higher levels of this pro-inflammatory marker than the control group (p = 0.000). The anti-inflammatory cytokine was on the other hand, profoundly depleted among nutritionally vulnerable sub-populations, the mean serum IL-10 level of malnourished diabetic participants with malaria parasitemia was significantly lower than malnourished diabetic participants who were not parasitized by malaria (p = 0.001), as well as the control group (p = 0.001). Within the broader groups, isolated diabetic patients had significantly higher levels of IL-10 than patients with malaria alone (p = 0.001) but there was no significant difference between IL-10 levels in isolated diabetic patients and IL-10 levels in healthy controls (p = 0.591), who had significantly higher IL-10 levels than the malaria-only group (p = 0.001). As far as metabolic control is concerned, the metabolic control defined as HbA1C levels did not get influenced by active parasitemia – no demonstrable statistical divergence was measured between observed between the diabetic participants with malaria and those without (p = 1.000). Both the co-infected and isolated diabetic group had markedly elevated HbA1c percentages than the malaria-only group and control subject (p = 0.001 for both) and that there was no significant difference between baseline HbA1c values of the malaria-only group and control subject (p = 1.000). In addition, there were significant differences between the mean values of all evaluated indices of RBCs (MCV, MCH and MCHC) between the structural groups (p < 0.05). The mean MCV of the co-infected group was not significantly different from either the malaria-only or diabetic-only groups (p > 0.05) but all three groups of diseased subjects had significantly smaller means compared to healthy controls (p = 0.001 for all groups) showing that there is consistent microcytosis among all three groups. No statistical difference was observed between the diabetic-only group as compared to the malaria-only group (p = 1.000). The values of MCH were similar among most study groups (p > 0.05), except for diabetic-only group where MCH was significantly elevated than controls (p = 0.011). By contrast, cellular HbC was shown to be variable according to co-morbidity status, with significantly higher cellular HbC in the co-infected group compared to the diabetic group without malaria (p = 0.011), the malaria group (p = 0.001) and the healthy group (p = 0.001). The isolated diabetic group was also significantly higher than the malaria-only group (p = 0.001), but not significantly different from the healthy controls (p = 1.000); the malaria-only group was significantly lower than the healthy controls (p = 0.001). Lastly, there were positive associations of MCV with MCH and of MCH with MCHC within the co-infected cohort, and a significant negative association of serum levels of TNF-alpha with MCH values, suggesting important pathophysiological relationships between the parameters, with increasing systemic inflammation (TNF-alpha) and decreasing individual erythrocyte hemoglobin content (MCH).

Table 1: Serum State of TNF-α, IL-10 and HbA1c in the Subjects Studied and Control Subject (Mean± SD).

Groups	TNF-α (pg/ml)	IL-10 (pg/ml)	HbA1c (%)
DM subjects with MP$^+$(Group A; n=50)	251.95±0.24	17.07±0.25	7.18±0.13
DM subjects without MP (Group B; n=50)	142.48±0.58	28.24±0.96	7.13±0.13
MP$^+$ subjects (Group C; n=50)	107.20±0.76	21.80±0.27	4.93±0.56
Control (Group D; n=50)	41.85±0.24	30.93±0.98	4.93±0.43
F-value	320.792	29.211	549.483
p-value	0.00	0.00	0.00
A against B	0.00	0.001	1.000
A against C	0.001	0.026	0.001
A against D	0.001	0.001	0.001
B against C	0.001	0.001	0.001
B against D	0.001	0.591	0.001
C against D	0.001	0.001	1.000

*Statistically significant at p<0.05. Key: DM=Diabetes Mellitus, MP= Malaria parasitemia

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Table 2: Levels of MCV, MCH, MCHC in the Subjects Studied and Control Subject (Mean± SD).

Groups	MCV (fl)	MCH (pg)	MCHC (g/l)
DSMP⁺ (Group A;n=50)	79.33±0.29	31.93±0.13	389.84±0.65
DSMP-(Group B;n=50)	78.03±0.22	33.28±0.71	346.02±0.53
MP⁺ subjects (Group C;n=50)	77.85±0.89	32.57±0.61	294.85±0.33
Control (Group D;n=50)	84.78±0.80	30.78±0.17	341.37±0.61
F-value	14.333	3.620	23.881
p-value	0.001	0.014	0.00
A against B	1.000	0.553	0.00
A against C	1.000	1.000	0.00
A against D	0.001	0.908	0.00
B against C	1.000	1.000	0.00
B against D	0.001	0.011	1.000
C against D	0.001	0.146	0.00

Table 3: Levels of association between parameters studied in diabetic subjects with malaria parasitemia

Variables	r-value	P-value
MCV against MCH	0.503	0.00
MCH against MCHC	0.555	0.00
TNF-α against MCH	- 0.330	0.003

*Statistically significant at $p<0.05$.

DISCUSSION

The result of this outcomes demonstrate that diabetic individuals co-infected with malaria present with significantly elevated mean serum TNF-alpha levels compared to diabetic patients without malaria, patients with malaria alone, and healthy controls. Due to the nature of both diabetes mellitus and malaria as inflammatory diseases, the co-existence of both diseases seems to exacerbate the systemic low grade chronic inflammatory status [37, 38]. This increased inflammatory state may lead to the worsening of type 2 diabetes mellitus (T2DM) and its clinical manifestations. TNF-alphas overproduction plays a major role in the pathophysiology of T2DM, interfering directly with insulin signaling in downstream pathways, which is an important characteristic of development of T2DM. Thus, this cytokine is a key pathogenic link between T2DM and the infection of malaria. TNF alpha levels were significantly higher in the subjects with diabetes alone compared to healthy controls and patients with isolated malaria infections in this cohort. This difference highlights the fact that T2DM is associated with a higher and sustained level of low-level inflammation than would be seen in malaria alone [39]. This finding is consistent with the previous reports that the baseline serum TNF}-alpha levels were elevated in the diabetic compared to the malaria infected groups [40,21-23,41-43]. In T2DM, this high level of cytokine also worsens hyperglycemia, promotes oxidative stress and further increases free radical production, maintaining a vicious circle of insulin resistance. So, T2DM have a much higher baseline chronic inflammation burden.

However, when considering the isolated malaria infections, the host's pro-inflammatory response to the malaria parasite was clearly seen since TNF-alpha was significantly raised in the malaria-only group compared to healthy controls. When the erythrocytes are ruptured, antigens and toxins enter the blood, stimulating monocytes, macrophages and T lymphocytes to release TNF alpha that will clear the parasitaemia. Under normal circumstances, however, when this response is dysregulated, too much TNF-alpha is produced and can change from a protective to a disease-promoting factor, potentially worsening the severity of malarial infection. The high level of TNF-alpha is consistent with several previous reports [44,45] but differs from studies reporting no difference in the level of TNF-alpha in malaria patients compared to controls [24,46].

Interleukin-10IL-10 has an important counter-regulatory function that regulates hyper-inflammation and tissue homeostasis, acts as an endogenous danger signal to prevent immune-mediated damage during severe inflammatory insults [47]. The mean level of serum IL-10 was significantly lower in the co-infected group (T2DM and malaria parasitaemia) when compared to the

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other groups. There was a clear gradient of decline in the level of IL-10:

This is a dramatic decrease in the proportion of those co-infected, presumably because IL-10 is being used up to combat such a huge inflammatory response that is being caused by the release of TNF alpha. This is in direct contrast to previous studies showing no difference in expression of IL-10 between diabetic patients and controls [43,48]. Interestingly, diabetic patients that did not have malaria showed a significant increase in IL-10 compared to patients with malaria alone. It indicates that, in the metabolic milieu of diabetes, upregulation of IL-10 production could be a protective, compensatory mechanism designed to be able to control chronic immune activation and avert the development of widespread tissue damage [49]. This is similar to the findings of Francisco *et al.* [50] and Samir *et al.* [51] who reported elevated serum of IL-10 in diabetic groups.

Malaria-only group, however, showed significantly lower levels of IL-10 compared to healthy control group. The result is systemic uncontrolled hyper-inflammation followed by tissue damage, further aggravating the course of the infection [52,53]. The result is contrary to that of Ibrahim *et al.*, [54] who reported a higher level of IL-10 in malaria patients, and that of Barkat *et al.* [46], who did not find any significant differences between malaria patients and healthy controls. This study showed that the glycated hemoglobin HbA1c level was significantly higher in the diabetic subjects compared to the other study subjects irrespective of their malaria status, indicating that chronic hyperglycemia is a stimulator of hemoglobin glycation, even in the absence of acute parasitic infection [55,56]. During periods of sustained hyperglycemia, there is an increase in the amount of blood glucose attached to erythrocytes by a non-enzymatic reaction, which reflects poor glycemic control, and is known as glycosylated hemoglobin. In addition, glycation changes red blood cell membranes, creating advanced glycation end-products (AGEs) that lead to cell adhesion to endothelial AGE receptors [57]. The raised HbA1c levels observed in co-infected and isolated diabetic groups aligned with those reported by Ch'ng *et al.* [55] and Abdulai *et al.* [58] who also found that the fasting blood glucose levels were concurrently raised. This study is also in keeping with the wide agreement of the literature showing that diabetic groups have high HbA1C levels compared to non-diabetic groups [59-62].

Average erythrocyte volume (MCV), a measurement of the size of the erythrocytes, is a very important parameter to help classify anemias, which are either microcytic, normocytic, or macrocytic [63]. MCV was significantly lower in all the patients compared to the control group, including diabetic only patients, malaria only patients and co-infected patients. It was in agreement with Elkhalifa *et al.* [64] who reported a decrease in MCV in malaria cases and contrary to Aggarwal *et al.* [65] who reported macrocytosis during malaria.

However, other recent reports have failed to show any significant MCV changes in diabetic patients [66-68] Also, the lower MCV values in the diabetic cohorts were in contrast to the results of Ebrahim et al. who reported that levels higher than 7% resulted in macrocytosis in diabetic patients due to the influx of water into the cells via insulin-independent GLUT-1 transporters [69]. This presentation may be caused by microcytosis (low MCV[70]); iron deficiency is the common cause of this, as well as anemia of chronic disease, sideroblastic anemia [71] or thalassemia [72].

The mean corpuscular hemoglobin (MCH) values did not differ significantly in most of the study groups, except in the diabetic-only group, which had significantly elevated MCH compared with the controls. This result corroborates the result of Asmamaw *et al.* [71] who attributed elevated MCH to HbA1c ≥ 7 which may be attributed to increased cytoplasmic viscosity in hyperglycemic milieu. Structural changes in the hemoglobin molecule have also been reported at high HbA1C levels, such as a decrease in \alpha-helices and increase in beta-pleated sheets [73].

In addition, some literature indicates that anemia in diabetes is due to the non-enzymatic glycosylation of the erythrocyte membrane proteins [81]. These proteins when oxidized contribute to the formation of lipid peroxide, which results in hemolysis or secondary anemic disorders [74]. On the other hand, the present study's MCH results are different from that of Arkew *et al.* [67] who did not observe any significance difference between diabetic patients and healthy controls.

The mean corpuscular hemoglobin concentration (MCHC) was significantly higher in the co-infected group than all other groups. In addition, there was a significant difference between the MCHC of diabetic-only and malaria-only patients as the former had higher MCHC compared to the latter who had lower MCHC than the healthy controls. An increased MCHC seen in T2DM is consistent with previous findings in India, [75] Libya, [76] and Ethiopia, [77] which are probably related to

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morphological and functional changes in the erythrocytes caused by chronic hyperglycemia.

As a result of sustained high blood glucose, hemoglobin binds to the internal erythrocyte membrane scaffold proteins (band 3 and spectrin proteins) causing the cells to become spherocytes and leads to changes in cell mechanics. The rise in intracellular viscosity leads to an increase in MCHC value in this spectrin binding [78]. Other studies, however, showed significantly lower [67, 79,80] or unchanged [71] MCHC in diabetic groups, which is in direct contradiction to the current study.

Correlational analysis in the T2DM and malaria co-infected group showed different relationships between inflammatory markers and haematological parameters: MCV vs MCH and MCH vs MCHC, with positive correlations between these parameters, suggesting that the increase in the volume of the erythrocytes is accompanied by an increase in the total content of hemoglobin, as well as an increase in the concentration of hemoglobin in erythrocytes.

The level of serum TNF-alpha was significantly and negatively correlated with the MCH level, demonstrating that patients with the highest individual pro-inflammatory profiles have erythrocyte hemoglobin concentrations that are lowest.

This inverse relationship is drawn attention to the role of pro-inflammatory cytokines in the disruption of hematopoiesis. Strong evidence shows that severe inflammation can inhibit erythropoiesis, impact systemic iron metabolism and reduce the life of the erythrocytes, all of which lead to a decrease in hemoglobin production and a reduction in MCH. If a person has malaria and diabetes, the inflammatory state of diabetes is exacerbated by the immune activation that occurs in the presence of malaria. This results in an additive increase in the production of the inflammatory cytokine, TNF-alpha, which has anti-MCH effects and indicates that long-standing, TNF-alpha-driven inflammation is a major contributor to anemia in the diabetics with malaria parasite.

CONCLUSION

HbA1c and TNF-α were significantly elevated in patients who were also diabetic relative to the diabetic without malaria, malaria-only and control subject. Additionally, the TNF-α level in the diabetic group without malaria was higher than the control group and the group who were only infected with malaria. Diabetics with co-infection had significantly lower levels of IL-10 when compared to malaria alone, and the control group. Non-malarial diabetics, by contrast, had elevated stated of IL-10 than the malaria-only group, and malaria-only group had lower levels than the control group. The diabetic participants and malaria-only patients group had significantly lower MCV values than the control group. There were positive correlation between MCV and MCH, and between MCH and MCHC, and negative correlation between TNF-α and MCH in the Type 2 diabetes mellitus co-infected patients with malaria. The significant alterations that were observed in the population studied, such as the increase in TNF-α, decrease in IL-10, and the increases in glycated hemoglobin, MCV, MCH, and MCHC, suggest a possible worsening of the severity and prognosis of T2DM associated with malaria parasitemia. Routine monitoring of malaria parasitemia in type 2 diabetes mellitus patients, as well as well the incorporation of cytokine assay and red blood cell indices in the diagnosis and management of diabetes mellitus is recommended. The present results require further studies to better understand the mechanisms.

Declarations

Authors' contribution: EFA, CRC, OVC were involved in all aspects of the work, EFA, CRC and MPO designed and supervised the work, EJI, ERU, EGO, OSI, ENN, OPA and DIN were involved in the acquisition, analysis and interpretation of data for the study, EJI, ERU, EGO, OSI, ENN and OPA and DIN were involved in Literature review and manuscript preparation. All authors read through and approved the final manuscript

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