PRINT ISSN 1119-8362
Electronic ISSN 2659-1499

Full-text Available Online at
https://www.ajol.info/index.php/jasem
https://www.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 28 (11) 3631-3637 November, 2024

Assessment of the Levels of Immune Cells Ratios, Malaria Parasite Density, Anthropometric and Blood Pressure in Individuals with Type 2 *Diabetes mellitus* and Malaria Co-Morbidity attending Diabetic Clinic at a Tertiary Hospital in Nnewi, Anambra State, Nigeria

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ABSTRACT: Type 2 *Diabetes mellitus* (T2DM) is caused by defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond appropriately to insulin. Hence, the objective of this paper was to investigate the levels of immune cells ratios, malaria parasite density, anthropometric and blood pressure levels in individuals with T2DM and malaria co-morbidity attending the diabetic clinic at a tertiary Hospital in Nnewi, Anambra State, Nigeria using appropriate standard techniques for a total of 200 participants aged between 30 and 75.Results showed the mean BMI was significantly lower ($p<0.05$) in T2DM with and without MP and control group than in MP group alone while there was significantly higher mean SBP, DBP levels in T2DM with and without MP compared to MP group alone and control group ($p<0.05$) respectively. Furthermore, the mean PD was significantly higher in T2DM with MP compared to T2DM without MP, MP group alone and control group ($p<0.05$) while neutrophil-lymphocyte ratio and platelet-lymphocyte ratio was higher in T2DM with and without MP and MP alone than in control group ($p<0.05$) respectively. Thus, this study revealed that MP could worsen the severity of T2DM via alteration in immune cell ratios and blood pressure.

DOI: https://dx.doi.org/10.4314/jasem.v28i11.17

Cite this Article as: CHUKWUANUKWU, R. C; EHIAGHE, F. A; OKAFOR, V. C; MANAFA, P. O; EHIAGHE, J. I; IGIEBOR, F. A; EMEJE, P. I. (2024). Assessment of the Levels of Immune Cells Ratios, Malaria Parasite Density, Anthropometric and Blood Pressure in Individuals with Type 2 *Diabetes mellitus* and Malaria Co-Morbidity attending Diabetic Clinic at a Tertiary Hospital in Nnewi, Anambra State, Nigeria. *J. Appl. Sci. Environ. Manage.* 28 (11) 3631-3637

Dates: Received: 21 September 2024; Revised: 27 October 2024; Accepted: 04 November 2024 Published: 10 November 2024

Keywords: Immune cell ratio; Type 2 *Diabetes mellitus*; Malaria parasite density; Blood pressure

Diabetes mellitus (DM) is a chronic metabolic condition caused by decreased or absent insulin production or possibly by decreased tissue sensitivity to insulin (Ogbodo *et al*., 2019; Galicia-Garcia *et al*., 2020).The prevalence of diabetes is rising rapidly in developing nations like Nigeria, and Type 2 *Diabetes mellitus* is one of the leading causes of death that can be prevented globally (Maduka *et al*., 2021). Type 2 *Diabetes mellitus* (T2DM) has as its main pathophysiological characteristics impaired insulin

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secretion and increased insulin resistance (Olaogun *et al*., 2020). According to International Diabetes Federation (IDF), twenty-four million adults were living with diabetes in African in the year 2021 confirming diabetes as a significant global challenge to the health and well-being of individuals, families and societies (IDF, 2024). A systemic review and meta-analysis of studies on the prevalence of *Diabetes mellitus* in Nigerians showed that the overall pooled prevalence was 5.77 % (Uloko *et al*., 2018; Ademola *et al*., 2023).Immune cell ratios are emerging markers of the relationships between the immune system and diseases (Buonacera *et al*., 2022). Some important immune cell ratios of clinical importance include neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to lymphocyte ratio (PLR). These immune ratios are determined as a straightforward ratio between the counts of neutrophils and lymphocytes; monocytes and lymphocytes and platelets and lymphocytes respectively in peripheral blood. These immune cell ratios have been implicated in numerous conditions associated with inflammations including *Diabetes mellitus* and malaria parasitemia. These immune biomarkers combine the innate immune response, which is primarily supported by neutrophils, and adaptive immunity, which is supported by lymphocytes (Song *et al*., 2021). Neutrophils are the primary effector cells during the systemic inflammatory response and serve a crucial regulatory function in adaptive immunity (Buonacera *et al*., 2022). Conditions characterized by tissue damage that activates systemic inflammatory responses (SIRS), can result in an increase in ratios of these immune cells (Li *et al*., 2021; Adamstein *et al*., 2021; Lee *et al*., 2021; Niu *et al*., 2021). This is due to the proinflammatory state that is defined by the early hyperdynamic phase of infection and is driven by neutrophils and other inflammatory cells (Lowsby *et al*., 2015). Decreased levels of PLR have been documented in malaria infected persons (Asmerom *et al*., 2023). The primary mechanisms of thrombocytopenia in malaria are peripheral destruction, excessive platelet sequestration in the spleen, and excessive platelet consumption due to the disseminated intravascular coagulation process (Leal-Santos *et al*., 2013). The entry of the malaria parasite is frequently accompanied by increased secretion of inflammatory cytokines, including tumor necrosis factor alpha (TNF), interleukin-1, and interleukin-10, endothelial cell activation brought on by excessive expression of cell adhesion molecules, such as ICAM-1 and vascular adhesion molecule-1, the start of the coagulation pathways as a result of platelet consumption, and endothelial damage (D'souza *et al*., 2017). This may exacerbate the clinical outcome in individuals with *Diabetes mellitus* co-morbidity with malaria infection. Hence, the objective of this paper was to investigate the levels of immune cells ratios, malaria parasite density, anthropometric and blood pressure levels in individuals with Type 2 *Diabetes mellitus* (T2DM) and malaria co-morbidity attending the diabetic clinic at a tertiary Hospital in Nnewi, Anambra State, Nigeria.

MATERIALS AND METHODS

Study Site: This study was carried out at the diabetics' clinic, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria.

Study Population: The study population involved apparently healthy individuals (control group), individuals with type 2 *Diabetes mellitus*, individuals with malaria parasitemia as well as individuals with type 2 *Diabetes mellitus* and malaria parasitemia co-morbidity. All participants were between the ages of 30-75 years. Both male and female participants were recruited in this study.

Participants Recruitment: A total of 200 participants were recruited for this study and participants were divided into four groups: Group A (Individuals with type 2 *Diabetes mellitus* and malaria parasitemia co-morbidity, n=50); Group B (Individuals with type 2 *Diabetes mellitus* without malaria parasitaemia, n=50), Group C (Individuals with malaria parasitaemia only, n=50), Group D (Individuals without type2 *Diabetes mellitus* and malaria parasitaemia (control group, n=50). Participants were between the ages of 30 and 75 years and were recruited in this study using simple random sampling.

Sample size and Sample size calculation: The sample size for this study was calculated using G-Power Software Version 3.1.9.4. Following the above calculation, a total of 180 participants were obtained. Assuming an attrition rate of 10 %, a total of 198 participants were obtained and this was approximated to 200 participants. Thus, a total of 200 participants were recruited for the study using simple random sampling method.

Inclusion Criteria: Apparently healthy individuals (control), individuals with T2DM only, individuals with malaria parasitaemia only and those with both type 2 *Diabetes mellitus* and malaria parasitaemia co-infection were recruited for the study. All the participants were between the ages of 30 and 75 years

Exclusion Criteria: The study excluded people who were under the age of 30 or who were above the age of 75, pregnant women, breastfeeding mothers, people

with known immunological problems, people with other metabolic disorders except *Diabetes mellitus*. All those who refuse to give informed consent to the study were also excluded from the study.

Ethical Considerations: Ethical clearance for the study was sought and obtained from Nnamdi Azikiwe University Teaching Hospital Ethics Committee (NAUTH/CS/66/VOL.16/VER. 3/07/2023/07). The procedures involved in the study was explained to the subjects and written informed consent obtained from each subject before enrolling in the study. They were assured of the confidentiality of the information obtained from them during and after the study.

Sample Collection: Six milliliters (6ml) of venous blood was collected from each of the subjects. 2ml each was dispensed into well labeled fluoride oxalate container and ethylenediaminetetraacetic acid (EDTA) container for the determination of fasting plasma glucose, as well as full blood count and malaria parasite determination using thick and thin film respectively. The remaining 2ml of the venous blood was dispensed into a well-labeled plain container and allowed to clot. The sample was centrifuged at 3000 RMP for 10min. The serum was then separated and dispensed into plain containers and stored at −20°C in the Chemical Pathology Department of Nnamdi Azikiwe University Teaching Hospital, Nnewi until assayed. Thick and thin films making was done immediately without storage while glycated hemoglobin estimation was determined immediately also.

Anthropometric Indices Measurements: Body mass index (BMI) was calculated using the equation 1 (WHO, 1995):

$$BMI = \frac{Weight\ (kg)}{Height^2 (m^2)} \quad (1)$$

A measuring tape was fastened to a piece of wood to determine height, and an electronic weighing scale (Peace Sky model PH-2015A made in China, which can measure up to 180kg of weight) was used to determine weight. BMI of 25 and 30 kg/m^2 was used to classify overweight and generalized obesity, respectively. Waist circumference was measured with the participant in the standing position, at the midpoint between the upper margins of the iliaccre stand the lower margin of the last rib, using a metric tape (cm). The hip circumference in turn was determined with the patient in the standing position as the greatest distance between the major trochanters. The waist/hip ratio was calculated by dividing the waist circumference (in cm) by the hip circumference (in cm).

Blood Pressure Measurement Principle: This is based on the fact that most sphygmomanometers compress (usually) the brachial artery at the same level as the heart, until blood flow ceases. At this point, the cuff pressure equals the systolic pressure. Then the occluding pressure is slowly reduced until proximal blood flow starts. Significant cuff pressures are noted during this process. The operator of the manual sphygmomanometer pumps a bulb to inflate the cuff. After a 10-minute rest period, the subject's systemic blood pressure was measured using an automatic digital blood pressure monitor (Kris-Aloy Mercurial Sphygmomanometer made in China) and a Kris-Aloy Dual Head Stethoscope (Mercury Barometer method) with the subject seated. Systolic and diastolic rates were used to express blood pressure.

RESULTS AND DISCUSSION

The mean BMI of the diabetic participants with malaria parasitemia did not differ significantly when compared to their counterpart without malaria parasitemia and control group ($p>0.05$), but it was significantly lower in the diabetic participants with malaria parasitemia compared to the participants with malaria parasitemia only (21.60±2.66 Vs 24.94±4.22; $p=0.000$). Also, the mean BMI was significantly lower in the diabetic participants without malaria parasitemia compared to the participants with malaria parasitemia only (21.75±2.75 Vs 24.94±4.22; $p=0.000$), although the mean BMI was significantly higher in the participants with malaria parasitemia only compared to the control group (24.94±4.22 Vs 22.83±4.56; $p=0.038$). However, the mean BMI of the diabetic participants with and without malaria parasitemia did not differ significantly when compared to the control group ($p>0.05$) respectively. Furthermore, paired wise comparison showed the mean waist-hip ratio (WHR) in the participants studied did not differ significantly when compared between the various groups studied ($p>0.05$). There was significantly lower mean systolic blood pressure (SBP) observed in the diabetic participants with malaria parasitemia compared to the corresponding values observed in their counterpart without malaria parasitemia (157.09±12.31 Vs 183.24±10.79; $p=0.000$), but it was significantly higher than in the participants with malaria parasitemia only (157.09±12.31 Vs 115.39±5.83; $p=0.000$) and control group (157.09±12.31 Vs 114.96±5.91; $p=0.000$) respectively. Furthermore, the mean SBP values observed in the diabetic participants without malaria parasitemia was significantly higher when compared to the values observed in the participants with malaria parasitemia only (183.24±10.79 Vs 115.39±5.83; $p=0.000$) and control group (183.24±10.79 Vs 114.96±5.91; $p=0.000$) respectively. However, the

SBP values in the participants with malaria parasitemia only did not differ significantly when compared to the control group (p=1.000).There was significantly lower mean diastolic blood pressure (DBP) observed in the diabetic participants with malaria parasitemia compared to the corresponding values observed in their counterpart without malaria parasitemia (90.98±3.72 Vs 95.91±4.99; p=0.000), but it was significantly higher than in the participants with malaria parasitemia only (90.98±3.72 Vs 81.09±3.14; p=0.000) and control group (90.98±3.72 Vs 81.48±5.74; p=0.000) respectively. Furthermore, the mean DBP values observed in the diabetic participants without malaria parasitemia was significantly higher when compared to the values observed in the participants with malaria parasitemia only (95.91±4.99 Vs 81.09±3.14; p=0.000) and control group (95.91±4.99 Vs 81.48±5.74; p=0.000) respectively. However, the DBP values in the participants with malaria parasitemia only did not differ significantly when compared to the control group (p=1.000). Furthermore, there was no statistically significant difference observed in the mean Neutrophil- lymphocyte ratio (NLR) in the diabetic participants with malaria parasitemia when compared to the corresponding values observed in their counterpart without malaria parasitemia (p=1.000) and participants with malaria parasitemia only (p=1.000), but there was significantly higher mean Neutrophil-lymphocyte ratio observed in the male diabetic subjects with malaria parasitemia when compared to the corresponding values observed in the control group (2.33±1.04 Vs 0.74±0.20; p=0.000). The mean Neutrophil-lymphocyte ratio did not differ significantly when compared between the values observed in the diabetic participants without malaria parasitemia and the participants with malaria parasitemia only (p=1.000), but there was significantly higher mean Neutrophil-lymphocyte ratio observed in the diabetic participants without malaria parasitemia when compared to the observed values in the control group (2.46±0.76 Vs 0.74±0.20; p=0.000). Also, there was significantly higher mean Neutrophil-lymphocyte ratio observed in the participants with malaria parasitemia only when compared to the observed values in the control group (2.27±0.63 Vs 0.74±0.20; p=0.000).There was significantly lower mean platelet-lymphocyte ratio (PLR) observed in the diabetic participants with malaria parasitemia when compared to the corresponding values observed in their counterpart without malaria parasitemia (170.25±44.56 Vs 205.15±60.47; p=0.005). There was no statistically significant difference observed in the mean platelet-lymphocyte ratio in the diabetic participants with malaria parasitemia when compared to the values observed in the participants with malaria parasitemia only (p=0.588), but it was significantly higher compared to the values observed in the control group (170.25±44.56 Vs 97.12±46.21; p=0.000). The mean platelet- lymphocyte ratio did not differ significantly when compared between the values observed in the diabetic participants without malaria parasitemia and the participants with malaria parasitemia only (p=0.471), but there was significantly higher mean platelet-lymphocyte ratio observed in the diabetic participants without malaria parasitemia when compared to the observed values in the control group (205.15±60.47 Vs 97.12±46.21; p=0.000). Also, there was significantly higher mean platelet-lymphocyte ratio observed in the participants with malaria parasitemia only when compared to the observed values in the control group (187.26±40.10 Vs 97.12±46.21; p=0.000).

Table1: Anthropometric Parameters and Blood Pressure Level in the participants Studied and Control group (Mean± SD).

Groups	Age(Year)	BMI(kg/m^2)	WHR	SBP(mmHg)	DBP(mmHg)
DM subjects with MP$^+$(Group A; n=50)	35.75±3.93	21.60±2.66	0.80±0.03	157.09±12.31	90.98±3.72
DM subjects without MP (Group B; n=50)	33.85±2.74	21.75±2.75	0.79±0.06	183.24±10.79	95.91±4.99
MP$^+$ subjects (Group C; n=50)	24.28±6.52	24.94±4.22	0.81±0.04	115.39±5.83	81.09±3.14
Control (Group D; n=50)	22.28±2.65	22.83±4.56	0.76±0.11	114.96±5.91	81.48±5.74
F-value	113.515	8.090	1.031	616.182	119.425
p-value	0.000	0.000	0.380	0.000	0.000
AVsB	0.214	1.000	1.000	0.000	0.000
AVsC	0.000	0.000	0.961	0.000	0.000
AVsD	0.000	0.673	1.000	0.000	0.000
B VsC	0.000	0.000	0.924	0.000	0.000
B VsD	0.000	0.948	1.000	0.000	0.000
CVsD	0.154	0.038	0.882	1.000	1.000

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

This study observed significantly lower mean body mass index (BMI) in the diabetics with and without malaria parasitemia than in participants with malaria parasitemia alone. The reason for the lower BMI may be due the changes in dietary pattern commonly associated with diabetic subjects. This is in contrast with the reports of some previous similar studies that found higher BMI in diabetics compared to control

group (Arkew *et al*., 2021; Babandina *et al*., 2019; Ch'ng *et al*., 2021; Sharahili *et al*., 2023). The disparity in results may be due to the differences in the number of participants used as well as the duration of *Diabetes mellitus* among the selected participants. However, this study found higher BMI in the malaria infected persons alone compared to control group. The reason for the present result is not clear. Perhaps, malaria infection may predispose to overweight and obesity. Nevertheless, according to World Health Organization (WHO) classification of BMI into four categories: underweight (18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9kg/m^2), and obese (>30kg/m^2) (WHO, 2000), the BMI of the participants in the present study were within normal range. However, the present study observed no significant difference in the mean waist-hip ratio (WHR) in the participants studied when compared to control group. WHR measures abdominal obesity and according to WHO guidelines, waist-to-hip ratio (WHR) ≥0.90 in men and ≥0.85 in women (Ashwell and Gibson, 2009) is classified as having abdominal obesity which is not the case in this current study as the WHR was within the normal range. In the present study, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) was significantly lower in the diabetics with malaria parasitemia compared to their counterpart without malaria parasitemia, but significantly higher the diabetics with malaria parasitemia than in the participants with malaria parasitemia alone and control group.

Table 2: Levels of Parasite density (PD), Neutrophil-Lymphocyte ratio (NLR) and Platelet-Lymphocyte ratio (PLR) in the Participants Studied and Control group (Mean± SD).

Groups	Parasite density (/µl)	MCV (fl)	NLR	PLR
$DSMP^+$ (Group A; n=50)	2811.36±978.31	79.33±6.29	2.33±1.04	170.25±44.56
DSMP-(Group B; n=50)	63.04±313.65	78.03±6.22	2.46±0.76	205.15±60.47
MP^+ subjects (Group C; n=50)	1940.84±803.58	77.85±5.89	2.27±0.63	187.26±40.10
Control (Group D; n=50)	0.00±0.00	84.78±4.80	0.74±0.20	97.12±46.21
F-value	210.782	14.333	57.369	43.968
p-value	0.000	0.000	0.000	0.000
A Vs B	0.000	1.000	1.000	0.005
A Vs C	0.000	1.000	1.000	0.588
A Vs D	0.000	0.000	0.000	0.000
B Vs C	0.000	1.000	1.000	0.471
B Vs D	1.000	0.000	0.000	0.000
C Vs D	0.000	0.000	0.000	0.000

**Statistically significant at p<0.05.*

Key: $DSMP^+$=Diabetic subjects with malaria parasitemia; $DSMP^-$ = Diabetic subjects without malaria parasitemia; MP+= Subjects with Malaria parasitemia only

Also, the mean SBP and DBP was significantly higher in the diabetics without malaria parasitemia compared to the values observed in the participants with malaria parasitemia alone and control group. This suggests that the hypertension observed in the diabetics in this study may not be secondary to malaria parasitemia. The mechanism for this increased blood pressure in diabetics may be due to several factors such as inappropriate activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, mitochondria dysfunction, excessive oxidative stress, and systemic inflammation(Jia and Sowers, 2021; Ohishi, 2018). First, angiotensin II and aldosterone increase serine phosphorylation of insulin receptor substrate proteins, leading to decreased activity of insulin downstream signaling pathways in PI3K (phosphatidylinositide3-kinase) and Akt (protein kinase B), which leads to reduced eNOS (endothelial nitric oxide synthase) activation by insulin and reduced nitric oxide (NO) mediated vasodilation (Sowers, 2013).The hyperinsulinemia associated with metabolic insulin resistance stimulates production of the vasoconstrictor ET-1 (endothelin-1) via a mitogen-activated protein kinase-dependent signaling pathway which contributes to vascular insulin resistance, excessive arterial stiffening, and ultimately hypertension (Sowers, 2013). Secondly, in diabetes, excessive reactive oxygen species (ROS) production can induce damage to DNA, proteins, and lipids, leading to mitochondrial dysfunction. NADPH oxidases are important source of excess ROS production in the vasculature in insulin resistance and hypertension (Montezano and Touyz, 2014). Insulin resistance and diabetes are associated with increased activation of vascular NADPH oxidases thereby inducing excessive ROS production which causes an imbalance between endothelium-derived relaxing factors and endothelium-derived contractile factors leading to associated increases in vascular tone (Jia and Sowers, 2021). Excessive ROS reduce NO production and increase destruction of NO leading to diminished bioavailable NO, which contributes to arterial stiffness and hypertension (Jia and Sowers, 2021). Moreso, enhanced TLR (Toll-like receptor)-mediated proinflammatory signaling induces activation of nuclear factor kappa B and c-Jun N-

terminal kinase that promote release of inflammatory cytokines, including tumor necrosis factor alpha, interleukin-6, vascular cell adhesion molecular 1, and monocyte chemo-attractant protein-1 (Sowers, 2013). These proinflammatory cytokines can impair insulin metabolic signaling and reduce insulin-mediated NO production, leading to arterial stiffness and hypertension. The present findings agree with the results of previous similar studies that found higher blood pressure in diabetic patients compared to control group (Arkew *et al*., 2021; Bhowmik *et al*., 2018; Sharahili *et al*., 2023).

*Conclusion***:** This study revealed that malaria parasite could worsen the severity of T2DM via alteration in immune cell ratios and blood pressure.

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

Data Availability Statement: Data are available upon request from the corresponding author.

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