UNIVERSITY OF CAPE COAST

EFFECTS OF MALARIA ON GALECTIN-3 AND INSULIN RESISTANCE IN DIABETIC AND NON-DIABETIC RESPONDENTS WITHIN THE GREATER ACCRA REGION OF GHANA

EMMANUEL NORTEY

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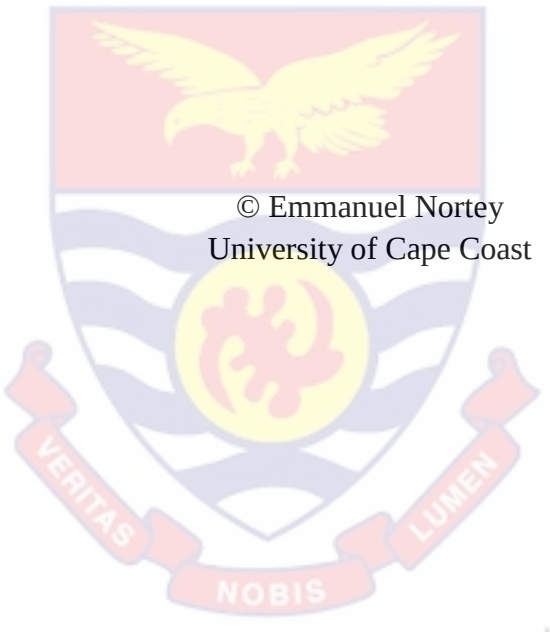

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BY

EMMANUEL NORTEY

Thesis presented to the University of Cape Coast's Department of Microbiology and Immunology, School of Medical Sciences, College of Health and Allied Sciences, in partial satisfaction of the requirements for the award of a Master of Philosophy degree in Infection and Immunity

MARCH, 2024

DECLARATION

I, Emmanuel Nortey, certify that the thesis presented to fulfill the prerequisites for the Master of Philosophy degree is my own original research. To the best of my awareness, it does not incorporate any previously published material or content that has been acknowledged for the granting of another degree, in this or any other university except where appropriate citations have been included made in text.

Candidate's Signature: …… Date: ……

Name: EMMANUEL NORTEY

We affirm that the thesis preparation and presentation were overseen according to the University of Cape Coast thesis supervision criteria**.**

Principal Supervisor's Signature: …… Date: ……

Name: PROF. SAMUEL ACQUAH

Co-Supervisor's Signature: …….. Date: ……

Name: DR. DANIEL AMOAKO – SAKYI

ABSTRACT

Malaria stands as the primary cause of mortality in sub-Saharan Africa. Besides, Sub-Saharan Africa also has the largest type 2 diabetes mellitus rate growth. Malaria causes insulin resistance in adults. Galectin-3 on the other hand has been explored in numerous conditions such as diabetes, inflammation, fibrosis, rheumatoid arthritis, asthma, certain cancers and heart failure. Considering the many pathophysiological processes associated with galectin-3, it might play a vital role in malaria infection. However, scientific information on the impact of malaria on circulating gelactin-3 levels and its relationship with insulin resistance in the context of development of T2DM is unknown. Hence, this study aimed at investigating the effect of malaria on galectin-3 and insulin resistance in 160 patients with and without T2DM who had malaria or not within the Tema metropolis in the Greater Accra region.

Under fasting conditions, body measurements of weight and height were taken to calculate the individual's body mass index (BMI). Additionally, blood pressure, waist circumferences (WC) and hip circumferences (HC) of each participant was measured following the standard protocol. Above all, blood glucose (FBG), full blood count (FBC), lipid profile, serum insulin and galectin-3 of each patient were measured. Homeostatic models assessment of insulin resistance (HOMAIR) and beta cell function (HOMAB) formulas were utilized to arrive at the aforementioned results

Compared to controls, diabetics without malaria exhibited statistically significant ($P < 0.05$) increases in mean age, BMI, WC, HC, SBP, DBP, FBG, insulin, galectin-3, HOMAIR and HOMAB. Diabetics with malaria were significantly ($P < 0.05$) of high age with higher mean values of FBG, SBP, DBP, galectin-3 and HOMAIR but decreased mean values of insulin and HOMAB compared to controls. Malaria was associated with dyslipidemia, characterized by low total cholesterol, HDL, and LDL but high levels of triglycerides in both T2DM and non-diabetic respondents.

Insulin resistance within the study population was aggravated by malaria in both study groups. Malaria was associated with high serum galectin-3 levels in both study group.

KEY WORDS

Malaria

Insulin resistance

Galectin-3

Type II diabetes mellitus (T2DM)

Metabolic syndrome

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DEDICATION

I offer this endeavor to my loved ones and companions, acknowledging their significant role in supporting my well-being.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ACRONYMS

T2DM	Type 2 Diabetes Mellitus
ADA	American Diabetes Association
CRD	Carbohydrate-recognition Domains
IDF	International Diabetes Federation
FBG	Fasting Blood Glucose
WHO	World Health Organization
BMI	Body Mass Index
IFG	Impaired Fasting Glucose
CVD	Cardiovascular Diseases
DM	Diabetes Mellitus
HDL	High-density Lipoprotein Cholesterol
LDL	Low-density Lipoprotein Cholesterol
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
ELISA	Enzyme-linked Immunosorbent Assay
HOMAIR	Homeostatic Model Assessment of Insulin Resistance
HOMAB	Homeostatic Model Assessment of β-Cell Function
iRBCs,	infected Red blood Cells
TLR	Toll-Like Receptors
CD36	Cluster of Differentiation 36
CIDR	Cysteine-Rich Inter-Domain Regions
DBL-CIDR	Duffy-Binding-Like – Cysteine-Rich Inter-Domain Regions
PfEMP1	Plasmodium falciparum Erythrocyte Membrane Protein 1
FGF	Fibroblast Growth Factor
TNF	Tumor Necrosis Factor
EGFR	Epidermal Growth Factor Receptor
VEGF	Vascular Endothelial Growth Factor
TGF	Transforming Growth Factor

CHAPTER ONE

INTRODUCTION

Background of the Study

Danquah, Bedu-Addo, and Mockenhaupt (2010) reported that in sub-Saharan Africa, infectious illnesses remain the greatest cause of mortality and disability. There are approximately one million deaths a year due to Plasmodium falciparum malaria alone (Lopez *et al.*, 2006). According to the World Health Organization (2020), the sub-Saharan Africa region saw a significant burden of malaria infections and fatalities in 2019 accounting for around 94% of the global cases. This observation highlights the disproportionate distribution of malaria within this specific geographical area. A substantial decline in malaria morbidity and mortality has been observed in numerous African nations following the implementation of WHO's Global Technical Strategy for Malaria 2016-2030 (Pradines & Robert, 2019; World Health Organization, 2020). Nevertheless, in Ghana, malaria remains a major health issue, contributing significantly to the country's disease burden and mortality rates (Kawaguchi *et al.,* 2022). WHO identified Ghana as one of the ten countries globally with the utmost malaria burden. In 2018, Ghana was one of two African nations that saw the maximum absolute rise in malaria cases, with an 8% increase (Heinemann *et al.*, 2020).

In addition to the highest global malaria burden, Sub-Saharan Africa is currently witnessing the most significant upsurge in the incidence of type 2 diabetes mellitus (T2DM) globally, which can be attributed to the adoption of Western lifestyles and genetic predispositions (Agyemang *et al*., 2016; IDF, 2021; Ojuka & Goyaram, 2014). In the year 2011, a total of 14.7 million

individuals residing in the sub-Saharan Africa region were officially diagnosed with diabetes (IDF, 2011). The International Diabetes Federation (IDF) projects this figure would rise to 28.0 million by 2030, with the sub-Saharan Africa Region having the highest percentage increase in diabetes prevalence followed by Middle East Region of 83% (International Diabetes Federation, 2011). As a matter of fact, approximately 24 million adults, which translates to one in twenty-two people, are presently living with diabetes in Africa (*IDF*, 2021), and this number is expected to by 134% to 55 million by the year 2045. The prevalence of T2DM in Ghana is 1.8% (Lindstrom & Tuomilehto, 2020). Individuals diagnosed with type 2 diabetes exhibit an increase vulnerability to infections because their immune systems are weakened (Alves *et al.*, 2012; Muller *et al.*, 2005). Higher rates of *Plasmodium falciparum* infection were found in T2DM in a case-control study of 1,466 urban people in Ghana (Danquah *et al.*, 2010). The detection and monitoring of severe malaria cases remains key during patient treatment (Hatz, 2001).

Increased levels of galectins have been associated with both malaria infection (Dembele *et al*., 2016; Oakley *et al.*, 2009) and T2DM (He *et al*., 2017; P. Li *et al.*, 2016; Y. Li, Li, Zhou, & Xiao, 2022; Lin *et al*., 2021). Galectins are a set of proteins that have been conserved throughout evolution and possess the capability to attach to β-galactosides via unique carbohydrate-recognition domains (CRD) (Díaz-Alvarez & Ortega, 2017; Vasta *et al*., 2001). Galectins have been identified across a wide range of organisms, from sponges as well as fungi to nematodes, insects, mammals (including humans), and even some viruses (Cooper, 2002). Plant species also contain galectin

homologues (Letunic *et al.*, 2004), though these proteins are absent in yeasts. Mammals collectively possess 16 galectins, however, the human genome contains only 12 galectin genes (Brinchmann, Patel, & Iversen, 2018), including two for galectin-9 (Lipkowitz et al., 2001). Galectins play numerous significant roles including the innate and adaptive immune response, inflammations, wound healing, infections, cancers (Henderson & Sethi, 2009; Liu & Stowell, 2023; Newlaczyl & Yu, 2011; Yang *et al* 2008).

Galectin-3 is distinct in its structure from all other galectins due to the fact that it has a carbohydrate-recognition domain at the C-terminus that is connected to a protein-binding domain at the N-terminus. This makes it the sole chimeric galectin found in vertebrates (Díaz-Alvarez & Ortega, 2017; Nio-Kobayashi, 2017). Inflammatory cells including mast cells, neutrophils, and macrophages express galectin-3 as well as other tissues such the gut, spleen, colon, and kidney. (Díaz-Alvarez & Ortega, 2017). Diabetes, inflammation, fibrosis, rheumatoid arthritis, asthma, some malignancies, and heart failure are only some of the pathophysiological processes in which galectin-3 plays a role (De Boer *et al*., 2009; Henderson & Sethi, 2009; Newlaczyl & Yu, 2011).

According to He *et al.* (2017), individuals diagnosed with T2DM exhibited markedly elevated galectin-3 levels in comparison to individuals without any known health conditions. The study also revealed that galectin-3 is connected to insulin resistance and glycemic control, suggesting that it may have a role in the development of T2DM. Some proposed mechanisms to explain the association between galectin-3 and diabetes include its possible contribution to insulin resistance by interfering with insulin signaling. A study

showed that galectin-3 overexpression in skeletal muscle cells inhibited insulin signaling and glucose uptake (P. Li *et al*., 2016).

Plasmodium-infected erythrocytes display altered surface glycosylation patterns compared to uninfected erythrocytes (Chan *et al*., 2014). Galectin-3 has been shown to bind to glycosylated molecules (Iacobini *et al*., 2003) and may influence the altered surface glycosylation of infected erythrocytes. This study hypothesized that these interaction may facilitate parasite sequestration, adhesion to endothelial cells, and immune evasion strategies employed by the parasite. However, experimental models of galectin-3 on the effect of malaria infection showed that levels of galectin-3 is enhanced in mice showing symptoms of experimentally-induced cerebral malaria (ECM). From the study galectin-3 deficient mice "(gal3¯/¯)" display partial protection against ECM induced by P. berghei ANKA infection (Oakley *et al*., 2009). In addition, the study showed that the absence of galectin-3 leads to a significant reduction in P. yoelii 17XNL parasitaemia, suggesting a potential impact of galectin-3 on the replication or infectivity of P. yoelii 17XNL.

However, information on serum levels of galectin-3 in human malaria patients (with/without) diabetes is limited. In this study, serum levels of Galectin-3 was evaluated in T2DM and non-diabetics with/without malaria infection.

Access to this information may deepen our understanding of malaria-induced insulin resistance and contribute to improvement in measures aimed at curbing the menace of metabolic syndrome (Alberti *et al*., 2009; Zimmet *et al*., 2006; McCracken *et al*., 2018) in the Ghanaian context.

Statement of the Problem

Non-communicable diseases significantly contribute to mortality rates and the global disease burden (Danquah *et al*., 2010). Malaria, a severe and life-threatening infection, leads to a substantial loss of healthy life years and prolonged disability worldwide (Lopez *et al.*, 2006). Countries with low to intermediate income levels bear a disproportionate high malaria burden. The recent multi-morbidity and syndemics pattern calls for the study of diseases as clusters and not in isolation (MacMahon & The Academy of Medical Sciences, 2018; Mendenhall, 2017) because new links between diseases and their effects on biomarkers/biochemical parameters could signal innovative prevention and management approach. Therefore, it is vital to investigate the possible connections between non-communicable diseases and malaria, especially for conditions like diabetes that have experienced a rapid increase in incidence over recent decades (Kengne et al., 2017; van Crevel, van de Vijver, & Moore, 2017).

Scientific information on the impact of malaria on circulating galectin-3 levels and its connection with insulin resistance among T2DM patients is unknown. As a result, this study is aimed at determining the effects of malaria on galectin-3 levels and insulin resistance in T2DM patients and non-diabetics within the Tema metropolis.

Aim

To determine the effect of malaria on the levels of galectin-3 and insulin resistance in T2DM patients and non-diabetic controls within the Tema metropolis in the Greater Accra region.

Specific Objectives

i. compare BMI, waist and hip circumference, serum insulin, galectin-3, and lipid profile in T2DM and non-diabetics with or without malaria;
ii. determine the correlation between galectin-3, insulin resistance, lipid profile and malaria parasitaemia in respondents;
iii. explore the relationship between anthropometric measures and blood-based biomarkers in respondents; and
iv. examine the role of gelactin-3 in the progression of insulin resistance caused by malaria.

Hypothesis

T2DM respondents with malaria have greater levels of galectin-3 than non-diabetic patients.

Significance of the study

Knowing the effect of malaria on galectin-3 and insulin resistance may escalate our apprehension of malaria-induced insulin resistance in the development of T2DM. Access to this information may provide useful data to modify policies targeted at curbing the menace of metabolic syndrome in Ghana. Though the policy provides preventive measures and essential procedure for the management of uncomplicated and complicated malaria (Ghana Health service, 2022), it does not elaborate on the management of malaria among T2DM or individuals with insulin resistance. It may also provide a basis for further research to understand the pathophysiological significant of galectin-3 in the context of insulin resistance and development of T2DM in malaria-prevalent regions of the globe.

Delimitation of the study

The study is limited to T2DM patients only (without those with other types of the disease as well as newly diagnosed or undiagnosed T2DM). Also, adults aged 20 years and above were the target respondents for the study, because this age group is considered to have increased risk of developing the condition**.** Also, individuals with diagnosed health conditions such as pancreatitis, fibrosis, HIV, viral and bacterial infections, rheumatoid arthritis, hepatitis, asthma and heart failure were excluded from the study based on their health records because these conditions affect serum galectin-3 levels.

Limitation of the study

The use of cross-sectional study design implies that causality cannot be established within the study. Also, glycated haemoglobin (HbA1c) of respondent was not measured hence the study did not measure the glycemic control of respondents.

Definition of terms

1. Metabolic syndrome refers to group of metabolic disorders like insulin resistance, high blood pressure throughout the body, low good cholesterol (HDL), high bad cholesterol (LDL), and central obesity**.**
2. Insulin resistance refers to a chronic metabolic disorder characterized by high blood glucose levels due to defects in insulin secretion, insulin action, or both.
3. Type 2 Diabetes Mellitus (T2DM): A state of hyperglycaemia which stem primarily from insulin resistance, which prevents cells from responding normally to insulin.

4. Diabetics/T2DM respondent refers to participants who have been already diagnosed of T2DM and are taking medications for the condition.
5. Non-Diabetics refers to individuals who have not been diagnosed of any form of diabetes.
6. HOMAIR (Homeostatic Model Assessment of Insulin Resistance) refers to a mathematical model which is used to predict/detect insulin resistance.
7. HOMAB (Homeostatic Model Assessment of β-Cell Function) refers to a mathematical model which is used to assess the pancreas β-cell function.
8. Galectins are a set of proteins that have been conserved throughout evolution and possess the capability to attach to β-galactosides via unique carbohydrate-recognition domains
9. Galectins-3: A unique type of galectins due to the fact that it possess a carbohydrate-recognition domain at the C-terminus that is connected to a protein-binding domain at the N-terminus.
10. Malaria infection: An acute, recurrent and sometimes chronic vector borne protozoan disease, which is common in tropical and subtropical areas around the world.

Organization of the Study

The current research work encompasses five different chapters. First and foremost, the initial chapter in this study is chapter one, which happens to be an introductory chapter. This section encompasses background information of the study, problem statement, goal, hypothesis, importance of the research,

delimitation as well as limitation of the research. The next section is chapter two which review the literature pertaining to T2DM, malaria infection as well as metabolic syndrome. Therefore, relevant information was obtained from scholarly journals detailing previous studies of T2DM, malaria infection as well as metabolic syndrome. Chapter three (research methods), comes after chapter two and it elaborate on the research design, target population, study site, sampling techniques, data collection tools, data collection process, as well as data processing and analysis. Subsequent section, chapter four presents the study's results along with the discussion of the research results/findings. The final section is chapter five and contains the summary of the research, conclusions, as well as recommendations.

Chapter Summary

Infectious diseases like malaria remain the predominant cause of morbidity and mortality within sub-Saharan Africa. Besides, Besides, Sub-Saharan Africa also has the largest type 2 diabetes mellitus rate growth. Malaria infection has been shown to induce insulin resistance in adults. Galectin-3 on the other hand has been explored in numerous conditions such as diabetes, inflammation, fibrosis, rheumatoid arthritis, asthma, certain cancers and heart failure. Considering the many pathophysiological processes associated with galectin-3, it might play a vital role in malaria infection. However, scientific information on the impact of malaria on human gelactin-3 levels and its connection with insulin resistance in the context of development of T2DM is unknown. Hence, this study aimed at examining the effect of malaria on galectin-3 and insulin resistance in 160 patients with and without

T2DM who had malaria or not within the Tema metropolis in the Greater Accra region.

CHAPTER TWO

LITERATURE REVIEW

Introduction

The rational of this current study was to determine the effects of malaria on human galectin-3 levels and insulin resistance in T2DM and non-diabetic controls within the Tema metropolis. This was aimed at deepening our understanding of malaria-induced insulin resistance and measures aimed at curbing the menace of metabolic syndrome in the Ghanaian context. Relevant information was obtained from scholarly journals detailing previous studies of T2DM, malaria infection, metabolic syndrome and the various component of metabolic syndrome. This chapter therefore is a review of the literature pertaining to T2DM, malaria infection as well as metabolic syndrome.

Metabolic syndrome (MetS)

Other names for MetS include the Insulin Resistance Syndrome, the Deadly Quartet, Reaven's Syndrome, Dysmetabolic Syndrome, and Syndrome X. (Belete *et al*., 2021; Gyakobo *et al*, 2012). It's characterized by group of metabolic disorders like insulin resistance, high blood pressure throughout the body, low good cholesterol (HDL), high bad cholesterol (LDL), and central obesity (Alberti *et al*., 2009, 2006; McCracken *et al.*, 2018). Having MetS raises the odds of developing T2DM by three to five times (Ford, 2005; Ford *et al.,* 2008) and of developing cardiovascular disease (CVD) by twice as compared to individuals without the syndrome (Mottillo *et al.*, 2010). Studies pertaining to MetS in sub-Saharan Africa suggest that MetS is of greater concern. Prevalence estimates for MetS in urban areas of sub-Saharan Africa vary widely, from 21.0% in Ghana (Ofori-Asenso *et al.*, 2017) to 34.6% in

urban Kenya (Kaduka *et al*., 2012) to 13.7% in rural Uganda (Murphy *et al*., 2013). Different investigations of subsets of the Ghanaian population have yielded widely contrasting incidence rates (Gyakobo *et al.*, 2012; Ofori-Asenso *et al.*, 2017; Osei-Yeboah *et al*., 2017). For example Gyakobo *et al.* (2012) found a prevalence of 35.9% when using criteria from the International Diabetes Federation (IDF) and a prevalence of 15.0% when using criteria from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).

MetS prevalence was reported to be 8.3% among rural Ghanaian men, 23.6% among urban Ghanaian men, and 31.4% among Ghanaian migrants in Amsterdam. The study found that the prevalence of MetS among women, as measured by the age-standardized definition, rose from 25% in rural regions to 34.4% in urban areas (van der Linden *et al*., 2019). Nonetheless van der Linden *et al*. (2019) found that among urban Ghanaian women, the prevalence of MetS was 38.4% in Amsterdam and 38.2% in London. Lifestyle changes associated with urban centers have been proposed as a main contributor to this rural–urban difference (Mbanya *et al.*, 2010; van der Linden *et al*., 2019).

According to NCEP-ATP III, WHO, and IDF criteria, the prevalence of MetS in T2DM patients in Ghana was 43.83 percent, 63.58 percent, and 69.14 percent, respectively (Osei-Yeboah *et al*., 2017). In women, abdominal obesity was the primary contributor to the syndrome, while hypertension was the primary contributor in men (Osei-Yeboah *et al*., 2017).

Diabetes Mellitus

Diabetes mellitus, more generally referred to as diabetes, is a chronic condition characterized by elevated levels of blood sugar triggered through

lack of insulin production or an inability to properly utilize the insulin that is produced (World Health Organization, 2019; American Diabetes Association, 2019; Banday *et al.*,2020). A growing global public health concern, diabetes, as stated by the new report from International Diabetes Federation (*IDF*, 2021) suggested that currently, 537 million people, which accounts for 10.5% of the world's adult population, have diabetes, and this figure is anticipated to increase up to 643 million by 2030 and 783 million by 2045. Ninety-four percent of these occurrences will be in countries with low or intermediate incomes (*IDF*, 2021). In a world where 240 million individuals have diabetes but don't know it, nearly half of all adults with the disease are in denial. The number of people with impaired glucose tolerance is expected to rise to 541 million by 2021 (*IDF*, 2021). According to a document by the International Diabetes Federation, about 6.7 million persons aged 20-79 would die as a direct result of diabetes in 2021 (*IDF*, 2021).

One in every twenty-two adults in Africa currently has diabetes, and that number is projected to rise to 55 million by 2045, a whopping 134 percent increase. It is quite worrying that more than half of persons with diabetes (54%) have never been diagnosed. IDF estimates that in 2021, diabetes would have been responsible for around 416,000 deaths in Africa (*IDF*, 2021).

Types of Diabetes

Several types of the condition have been reported in literature based on the pathogenesis.

Type 1 Diabetes

The beta cells in the pancreas that produce insulin are attacked by the immune system, leading to type 1 diabetes. This results in inadequate insulin

production in the body. An autoimmune response, which causes this destructive process, is likely caused by a combination of genetic predisposition (resulting from many genes) and an environmental trigger, such as a viral infection (Atkinson *et al.*, 2014; Craig *et al*., 2014). Type I diabetes, which typically manifests in childhood, was formerly referred to by the names juvenile-onset diabetes and insulin-dependent diabetes (Engelgau *et al*., 2004). The disease can emerge at any stage of life, although type 1 diabetes is more commonly found in children and young adults. It ranks among the prevalent long-term illnesses during childhood (Engelgau *et al*., 2004). Individuals afflicted with this kind of diabetes require regular administration of insulin through injections to retain their blood sugar levels within the desired range (Hirsch *et al*., 2020).

Type 2 Diabetes Mellitus (T2DM)

Greater than 90% of all cases of diabetes in the world are attributable to T2DM (IDF, 2021). In T2DM, hyperglycaemia is the outcome and stem primarily from insulin resistance, which prevents cells from responding normally to insulin (Banday *et al.*, 2020). When insulin resistance occurs, the effectiveness of the hormone decreases and eventually insulin production increases. Gradually, the pancreatic beta cells may fail to meet the body's demand for insulin, resulting in insufficient insulin production. Some people with T2DM experience symptoms comparable to those with type 1 diabetes, but these symptoms are typically milder, and in some cases, people with T2DM may not experience any symptoms at all. In most cases, pinpointing the precise moment when T2DM was first diagnosed is also impossible. This means that many patients with T2DM go misdiagnosed, and that the average

time from first symptoms to diagnosis might be rather protracted (*IDF*, 2021). Vision loss, slow-healing lower-limb ulcers, heart disease, and stroke are just some of the consequences that can occur if a diagnosis is delayed for too long (Gregg *et al*., 2014; Donnelly *et al*., 1999).

Hyperglycaemia in pregnancy (HIP)

(WHO, 2013; Hod *et al*., 2015) The World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) have determined that hyperglycemia in pregnancy can be broken down into three distinct subtypes. These subtypes are pre-gestational diabetes, gestational diabetes mellitus (GDM), and diabetes in pregnancy (DIP). Pre-gestational diabetes include women who have been diagnosed with type 1, type 2, or less common variants of diabetes before to becoming pregnant. GDM has the potential to occur at any stage throughout the prenatal period and is often not observed to remain beyond the period of childbirth (Immanuel & Simmons, 2017). DIP refers to pregnant women with a first diagnosis of hyperglycemia during pregnancy who meet the WHO's outline criteria for diabetes diagnosis in the non-pregnant individual. According to Guariguata *et al.*, (2014), the optimal time for detecting DIP is during the initial trimester. The American Diabetes Association documented that most (75%–90%) cases of HIP are GDM (American Diabetes Association, 2014).

In addition to women who experience hyperglycemia during the early stages of pregnancy, gestational diabetes mellitus (GDM) also manifests in women who have inadequate insulin secretion to counteract the impaired insulin action, known as insulin resistance, caused by hormonal fluctuations induced by the placenta as the pregnancy advances (WHO, 2013).

Factors that put a woman susceptible to developing GDM encompass advanced maternal age, elevated body mass index (BMI) indicating overweight or obesity, previous occurrence of GDM, excessive gestational weight gain, familial predisposition to diabetes, habitual smoking ,presence of polycystic ovary syndrome (PCOS), and a history of stillbirth or delivering an infant with a congenital abnormality (*IDF* , 2021). Certain ethnic populations have a greater prevalence of gestational diabetes mellitus (GDM) in comparison to other groups. It is commonly observed that GDM is a transient illness that manifests during pregnancy and typically resolves postpartum (*IDF*, 2021). Nonetheless, pregnant women with elevated blood sugar levels are more susceptible to developing GDM in future pregnancies. Furthermore, the likelihood of developing T2DM significantly increases within 3-6 years following GDM, even before the age of 40 (*IDF*, 2021). Moreover, infants born to mothers diagnosed with GDM encounter an elevated long-term likelihood of developing obesity and eventually developing T2DM *(*Fetita *et al.*, 2006).

Other types of diabetes

The recent WHO publication introduces a revised categorization of diabetes mellitus that includes the inclusion of "specific forms" of diabetes (WHO, 2019).. These particular forms comprise monogenic diabetes as well as the previously categorized "secondary diabetes." Monogenic diabetes, as its nomenclature suggests, arises from the influence of a solitary gene rather than the combined impact of many genes and environmental variables, as observed in type 1 and T2DM. Monogenic diabetes is a far less common form of diabetes, comprising approximately 1.5-2% of cases. However, it is plausible

that this number underrepresents the true prevalence due to frequent misdiagnosis as either type 1 or T2DM (Hattersley *et al*., 2018). The monogenic forms of diabetes exhibit a wide range of manifestations, including neonatal diabetes mellitus, maturity onset diabetes of the young (MODY), and unusual syndromic disorders connected with diabetes (Vaxillaire *et al.*, 2012).

Though monogenic diabetes is uncommon, these can serve as 'human knockout models', offering insights into the pathogenesis of diabetes (Cnop *et al.*, 2017). Precise identification of the monogenic forms of diabetes is crucial from a medical viewpoint, as tailored treatments can sometimes be directed at the specific genetic defect (Hattersley *et al*., 2018). The differentiation among the 14 various subcategories of MODY not only results in variations in clinical care but also different predictions regarding the risk of complications. The discovery of a growing number of monogenic diabetes types has been facilitated by the accumulation of genome-wide association studies in recent times (Cnop *et al*., 2017; Flannick *et al.*, 2016; Hattersley *et al*., 2018; Vaxillaire *et al.*, 2012). Hence, it is possible that the actual prevalence of these variations is underrated. Diabetes may also manifest as a consequence of other underlying diseases. The subsequent diabetes kinds are delineated below, in accordance with recent diabetes classification established by the WHO (WHO, 2019).

Diabetes can manifest as a result of several pancreatic disorders, including pancreatitis, trauma, infection, pancreatic cancer, and pancreatectomy.

Diabetes resulting from endocrine abnormalities characterized by the excessive release of hormones that counteract the effects of insulin, such as Cushing's syndrome.

Drug-induced diabetes mellitus refers to the development of diabetes as a result of the use of certain medications that interfere with either the secretion of insulin or the action of insulin.

Infection-induced diabetes refers to a form of diabetes mellitus that arises as a consequence of viral infection, specifically characterized by the death of beta cells.

Apart from the etiology of type 1 diabetes, there exist less prevalent variants of immune-mediated diabetes characterized by distinct immunological abnormalities.

There are additional genetic syndromes that have been seen to be occasionally linked with diabetes, including Prader-Willi syndrome, Down's syndrome, and Friedreich's ataxia.

Risk Factors for T2DM

The American Diabetes Association (ADA) has delineated several risk factors linked to the onset of T2DM, as expounded upon in the following sections.

Age: T2DM prevalence exhibits an age-dependent pattern, characterized by a low occurrence prior to the age of 30 years, followed by a notable and consistent rise as individuals grow older (Yan et al., 2022). It is recommended that individuals receive medical testing no later than the age of 45.

Race/ethnicity: The ethnic background of an individual can contribute to their heightened vulnerability to Type 2 Diabetes Mellitus (T2DM). Several ethnic groups, including Non-Hispanic Black, Hispanic/Latino American, Asian American, Pacific Islander, American Indian, and Alaskan native communities, exhibit a heightened susceptibility to diabetes, with prevalence rates ranging from two to four times higher compared to the majority population (Engelgau *et al*., 2004).

Overweight: Being overweight and/or obese is a key contributing factor for T2DM. If BMI falls between 25.0 and less than 30, it is categorized as overweight. But if BMI is 30.0 or above, it is categorized as obese. (World Health Organization, 2000). It is advisable to perform screening for diabetes in adults who are overweight or obese, irrespective of their age, and who have one or more risk factors associated with the disease (ADA, 2019). Approximately 90% of people diagnosed with T2DM are overweight (Whitmore, 2010).

Low physical activity: Participating in physical activity has been shown to improve the body's cellular sensitivity to insulin, facilitate the utilization of glucose as an energy source, and play a role in weight management. As a result, persons who engage in lower levels of physical activity face an increased susceptibility to the development of T2DM (ADA, 2019). As per the guidelines set forth by the American Diabetes Association (ADA), low physical activity is operationally defined as engaging in exercise for a duration of less than 30 minutes, on fewer than five days during a week.

Hypertension: Hypertension, sometimes referred as high blood pressure, is regarded as by a systolic blood pressure equal to or exceeding 130

mmHg and/or a diastolic blood pressure equal to or exceeding 80 mmHg. This condition arises when blood circulates through the vasculature with excessive power. According to Whelton *et al*. (2018) stage 2 hypertension is characterized by a blood pressure measurement equal to or exceeding 140/90 mmHg. According to a study conducted by Ostchega, Fryal, Nwankwo *et al.* (2017) approximately 45.4% of adults in the United States are affected with hypertension. Unfortunately, just around a quarter of adults (24%) suffering from hypertension effectively manage their condition (Ostchega *et al*., 2017). Elevated blood pressure necessitates the heart to work harder, leading to an increased vulnerability to diabetes and heart disease (American Diabetes Association, 2019). In Ghana, hypertension is diagnosed at blood pressure above 90/140 mmHg.

Cholesterol: There exists an interconnection between blood glucose, blood pressure, and cholesterol levels. Dyslipidemia, characterized by abnormal levels of cholesterol, particularly a decrease in high-density lipoprotein cholesterol and an increase in tiny, dense, low-density lipoprotein particle size and triglycerides, is associated with an greater risk of developingT2DM (Thambiah & Lai, 2021; Hirano, 2018). In order to mitigate the possibility of developing T2DM, the American Diabetes Association (ADA) provides a set of recommended guidelines:

I. Low-density lipoprotein (LDL, commonly referred to as “bad” cholesterol) ought to be less than 100 mg/dL
II. High-density lipoprotein (HDL, commonly referred to as “good” cholesterol) ought to be greater than 50 mg/dL
III. Triglycerides ought to be less than 150 mg/dL (ADA, 2004).

The management of cholesterol levels can be achieved through lifestyle alterations, such as the adoption of a nutritious diet, engagement in regular physical activity, avoidance of smoking, and the reduction of excess body weight. However, if lifestyle adjustments prove to be ineffective, pharmaceutical therapy is necessary (ADA, 2004).

Family history: Having a first degree relative with T2DM is a major risk factor increasing one's odds of developing the disease (Ismail *et al.,* 2021; van 't Riet et al., 2010). This elevated risk of T2DM has been attributed to genetic as well as shared environmental components amongst family members (van 't Riet *et al*., 2010)

Prevention of T2DM

Multiple research studies have shown evidence that the prevention of diabetes among persons who are at a heightened risk can be achieved by lifestyle modifications. These interventions, particularly focusing on dietary adjustments and increased physical activity to facilitate weight reduction, have been found to be both practical and cost-efficient (Berthezène, 2002; Kosaka *et al*., 2005; Mensink *et al.*, 2003; Neumann *et al*., 2017). Moreover, empirical studies have demonstrated that lifestyle interventions have the potential to decrease the occurrence of diabetes in patients with impaired glucose tolerance (Schwarz *et al.*, 2007). Given the substantial likelihood of developing early onset T2DM and the association between previous GDM and increased risk of Cardiovascular Disease (CVD), both with and without T2DM, it is recommended that all lifestyle changes be implemented within a three-year timeframe following pregnancy in order to optimize the potential benefits in preventing diabetes (Bellamy *et al.,* 2009; C. Song *et al.,* 2018).). Pregnant

women with hyperglycemia have the ability to regulate their blood glucose levels by the implementation of a nutritious diet, effective weight management, engaging in moderate physical activity, and regularly monitoring their blood glucose levels. Effective communication with healthcare providers is crucial for individuals to effectively manage their own health and to identify the need for medical interventions like as insulin or oral drugs, as well as maternity care (*IDF*, 2021)**.**

Treatment/management for T2DM

The results of diabetes are influenced by psychosocial and educational aspects, given that it is primarily a disease that requires self-management (Ernawati *et al.*, 2021; Ghisi *et al.*, 2020; Hailu *et al.* 2019). Hence, it is imperative that diabetes education programs offer consistent and evidence-based instruction that aligns with established treatment guidelines, self-management education standards, and patient objectives (Ernawati *et al.*, 2021; Ghisi *et al.*, 2020). In individuals diagnosed with T2DM, implementation of dietary modifications and engagement in physical activity are considered crucial primary treatment approaches. Moreover, numerous professional organizations currently advocate for the initiation of metformin therapy upon diagnosis (Richardson *et al.*, 2021). Meal planning is highly suggested for individuals at all stages of diabetes. Moreover, the management of obesity plays a pivotal role in the holistic management of T2DM in numerous instances (Richardson *et al.*, 2021). Women who have diabetes before getting pregnant and are in their child-bearing age should be provided with pre-conception guidance (*IDF*, 2021). The recommended course of action entails administering an increased dosage of folic acid treatment, doing a

thorough evaluation of the patient's pharmaceutical regimen, implementing a comprehensive diabetes management strategy, and adopting a meticulously devised approach to pregnancy (*IDF*, 2021). The maintenance of blood lipids in conjunction with blood pressure is vital during the management of diabetes.

Complications of Diabetes

Diabetes has the potential to result in serious undesirable outcomes including fatality, CVD like heart disease and stroke, high blood pressure, loss of vision, kidney disease, disorders of the nervous system, disease of the lower extremities, dental complications, complications during pregnancy, diabetic ketoacidosis, and disability (Mezil, & Ahmed, 2021). However, the majority of the aforementioned issues can be mitigated by effectively managing blood glucose, blood lipids, and blood pressure levels (CDC, 2020).

Diabetes is a major contributor to global mortality, albeit with varying effects across different countries (*IDF*, 2021), it is anticipated that around 6.7 million individuals amongst the age range of 20 and 79 succumbed to diabetes or its associated consequences in 2021, excluding the mortality risks attributed to the COVID-19 pandemic induced by the novel coronavirus SARS-CoV-2 (*IDF*, 2021). This figure represents approximately 12.2% of the total mortality rate within this specific age cohort on a global scale. Approximately 32.6% of mortality cases associated with diabetes occur in individuals who are younger than 60 years old, constituting 11.8% of the overall global deaths within this specific age cohort. The lifespan of middle-aged individuals with diabetes is shortened by five to ten years, while the overall population of people with diabetes experiences a reduction in life expectancy of around 13 years. This

increased risk of death is even more pronounced among younger individuals (Emerging Risk Factors Collaboration, 2023).

The occurrence of diabetic adults' heart disease is significantly high, with a two to fourfold increase compared to individuals without diabetes and the likelihood of stroke is also amplified by a factor of two to four in diabetic individuals (CDC., 2011; Matheus et al., 2013). Among those aged 18 to 44 with diabetes, the occurrence of ischemic heart disease is almost 14 times greater compared to their counterparts without the condition (Engelgau *et al*., 2004). In 2016, a total of 7.8 million individuals discharged at hospitals in U.S. were associated with diabetes out of which 1.7 million were for major CVD with 438,000 cases associated with ischemic heart disease and 313,000 cases related to stroke. This represents a rate of 75.3 per 1,000 adults with diabetes (CDC, 2020).

Hypertension is a well-known significant and amendable risk factor for both macrovascular as well as microvascular problems associated with diabetes (I. H. de Boer et al., 2017). According to a study conducted between 2003 and 2004, it was found that 75% of individuals who self-reported having diabetes either had hypertension or were taking prescription drugs for hypertension (CDC, 2007). The recommended blood pressure target for individuals with diabetes is less than 130/80 mmHg, which is different from the target for the general population. This distinction is made because of the increased risks associated with high blood pressure in individuals with diabetes (Arauz-Pacheco, Parrott, Raskin, & ADA, 2003; I. H. de Boer *et al*., 2017).

The occurrence of blindness and visual impairment is a common phenomenon among those diagnosed with diabetes (Kropp et al., 2023). Diabetic retinopathy represents the leading etiology of incident visual impairment in individuals between the ages of 20 and 74. An estimated 212,000 to 240,000 individuals experience blindness each year as a result of this particular illness (CDC, 2007). According to a comprehensive study conducted across the United States, it was found that nearly 25% of patients diagnosed with diabetes encountered notable visual impairment. This percentage is roughly twice as high as the prevalence reported among individuals without diabetes (Shukla & Tripathy, 2024).

Nephropathy is a persistent condition that is distinguished by heightened excretion of urine albumin (proteinuria) or diminished glomerular filtration rate (GFR) in individuals with diabetes mellitus (Alicic, Rooney, & Tuttle, 2017). Diabetes stands as the primary cause of kidney failure, contributing to 44% of newly reported cases (de Boer *et al.*, 2014). According to Orlando, et al, 2011, individuals diagnosed with diabetes represent the demographic experiencing the most rapid increase in the number of individuals requiring dialysis and kidney transplants. In 2005, a cohort of 46,739 adults diagnosed with diabetes initiated therapeutic interventions for severe renal disease in the United States and Puerto Rico. According to data from the Centers for Disease Control and Prevention (CDC) in 2007, there were a total of 178,689 individuals in the United States and Puerto Rico who suffered from end-stage kidney disease caused by diabetes. These individuals were either receiving kidney transplants or undergoing chronic dialysis treatment (CDC, 2007).

According to the National Diabetes Information Clearinghouse (n.d.)., a significant proportion, ranging from 60% to 70%, of individuals diagnosed with diabetes experience varying degrees of neuropathic complications. Impairment of the nervous system gives rise to several disorders, including erectile dysfunction, carpal tunnel syndrome, delayed gastric digesting, and diminished tactile sensation in the extremities. Diabetic neuropathy has a key role in a considerable proportion of lower limb amputations Diabetic neuropathy, a frequently encountered yet rather obscure condition in individuals with chronic diabetes, has been found to afflict over 15% of patients (Herat et al., 2018).

Lower extremity disease contribute to higher incidence of amputations in the lower extremities for individuals with diabetes (Walicka *et al*., 2021). Diseases affecting the lower extremities encompass peripheral arterial disease, peripheral neuropathy, or a combination of both conditions. According to studies, around 48% of individuals diagnosed with diabetes encountered various lower extremities complications, including but not limited to lower extremity amputation, numbness in the feet, ulcers, peripheral neuropathy, and peripheral artery disease (Engelgau *et al*., 2004; Hicks & Selvin, 2019). In the year 2004, over 71,000 individuals with diabetes in U.S underwent non-traumatic lower-limb amputation, comprising over 60% of the total cases of non-traumatic lower-limb amputations. (CDC, 2007).

Individuals with diabetes are more susceptible to developing periodontal disease (Casanova, Hughes, & Preshaw, 2015; Genco & Borgnakke, 2020). According to the CDC, those who are younger and diagnosed with diabetes are approximately twice as likely to acquire

periodontal disease in comparison to those without diabetes (CDC, 2007). According to CDC, individuals with uncontrolled diabetes have a nearly threefold increased risk of developing severe periodontitis compared to persons without the condition (CDC, 2007). Individuals with diabetes are at an elevated susceptibility to periodontal disease, a condition that poses challenges in managing diabetes through blood sugar regulation (Genco & Borgnakke, 2020; Sanz *et al*., 2018).

GDM exerts its impact on the mother throughout the latter stages of pregnancy, which aligns with the period of fetal growth. When diabetes is inadequately controlled or not treated, it consequently lead to elevated levels of blood glucose in the infant. The increase in glucose levels stimulates the pancreas of the infant to produce extra insulin in an effort to maintain blood sugar homeostasis. As a result, the infant accumulates an excessive amount of energy, leading to the storage of adipose tissue. The presence of surplus adipose tissue can lead to the occurrence of macrosomia, a condition characterized by fetal growth beyond the expected range for the corresponding gestational period. Macrosomia frequently gives rise to health concerns, such as the possibility of nerve and shoulder injury during the birthing process (ADA Gestational Diabetes, n.d.; *IDF*, 2021; Karen Gill & Stephanie Watson, 2017). The much larger size of the infant presents a potential health hazard for both the maternal figure and the offspring (CDC, 2007). Newborn infants may present with hypoglycemia shortly after delivery, potentially leading to an elevated risk of respiratory complications as a result of hyperinsulinemia stemming from excessive pancreatic insulin secretion. GDM places infants

susceptible to future obesity and T2DM (ADA Gestational Diabetes, n.d.; *IDF*, 2021; Karen Gill & Stephanie Watson, 2017).

When the cells in the body don't receive sufficient glucose for energy, they start to utilize fat for energy, generating ketones. The aforementioned ketones possess acidic properties and accumulate in the bloodstream, becoming detectable in urine under conditions of insufficient insulin levels within the body. The occurrence of excessive amount of ketones in the body has the potential to lead to a diabetic coma or fatality (ADA Diabetes & Ketoacidosis, n.d.). The frequency of hospitalizations resulting from diabetes-ketoacidosis in 1980 was 61,000, and subsequently rose to 99,913 by the year 2001 within the U.S. (Engelgau *et al.*, 2004).

Primarily, individuals diagnosed with diabetes experience a greater prevalence of both physical and cognitive problems (Engelgau *et al.*, 2004). According to a study conducted by Engelgau *et al.*, (2004)., the National Health Interview Survey (1998) in the United States found that those with diabetes have a significantly higher prevalence of physical handicap compared to those without diabetes, with the frequency being nearly twice as high. In addition, those with diabetes face a twofold increased chance of developing dementia in later life as compared to those without diabetes, as indicated by research conducted by Engelgau *et al.*, (2004).

Cost of T2DM

It is estimated that diabetes-related expenditure worldwide in 2021 totals USD 241 billion, representing 25% of global expenditure and this amount is projected to reach 262.4 billion by 2030, and 269.5 billion by 2045.

In 2021, the average amount of money spent on diabetes-related expenses per person aged 20-79 with diabetes in Ghana was 279.4 USD (*IDF*, 2021).

Malaria Infection

Malaria is an acute, recurrent and sometimes chronic vector borne protozoan disease, which is common in tropical and subtropical areas around the world (Chou, 2007). Malaria cases worldwide decreased from 238 million in 2000 to an expected 229 million in 2019 in 87 malaria endemic countries (WHO, 2020). The occurrence of malaria cases (meaning the number of cases per 1000 people at risk) decrease from 80 cases in 2000 to 58 cases in 2015, followed by a further decrease to 57 cases in 2019 worldwide. The period from 2000 to 2015 witnessed a significant drop of 27% in the global incidence of malaria cases but the decline between 2015 and 2019 was minimal, measuring less than 2%, signifying a noticeable slowdown in the rate of reduction since 2015(World Health Organization, 2020). The implementation of WHO's Global Technical Strategy for Malaria 2016-2030 by most African countries has resulted in a significant waning in malaria morbidity and mortality (Pradines & Robert, 2019; WHO, 2020). The occurrence of malaria within sub-Saharan Africa is significantly elevated compared to other regions, with statistics showing that in 2019, the sub-Saharan region recorded 94% of all reported cases and deaths related to malaria worldwide (WHO, 2020). According to the WHO's malaria report in 2020, nearly all (95%) of the total malaria cases worldwide were concentrated in 29 countries. Approximately 51% of all malaria cases can be traced back to just five countries in sub-Saharan Africa: Nigeria (27%), Democratic Republic of the Congo (12%), Uganda (8%), Mozambique (6%), and Niger (3%) (WHO, 2020). Worldwide,

the death rate due to malaria (expressed as the number of fatalities per 100,000 people at risk) decreased from approximately 25 in the year 2000 to 12 in 2015, and further declined to 10 in 2019. However, the pace of this reduction slowed down during the later years. Almost 95% of malaria fatalities globally were in 31 countries. In 2019, approximately 51% of worldwide malaria fatalities were attributed to six nations within sub-Saharan Africa. These nations are Nigeria, Democratic Republic of Congo, United Republic of Tanzania Mozambique, Niger and Burkina Faso with a death rate of 23%, 11%, 5%, 4%, 4% and 4% respectively (WHO, 2020).

Causative agents of malaria infection

Infection with a parasitic protozoan of the genus Plasmodium results in the sickness known as malaria. The most prevalent species causing human malaria consist of *P. falciparum*, *P. ovale*, *P. vivax*, *P. knowlesi, and P. malariae*. *Plasmodium falciparum* is often regarded as the most dangerous and aggressive form of malaria parasite. The haematological changes associated with malaria are believed to stem from the noticeable biochemical shifts that happen during the asexual phase of the parasite's life cycle.

Upon invasion of erythrocytes, *P. falciparum* commonly induces a substantial increase in the synthesis of inflammatory cytokines, including TNFα, IL-1, IL-10, and IFNγ. Also, an increase in endothelial cell activation occurs on account of several factors, including excessive expression of cell adhesion molecules (such as ICAM-1 and VCAM-1), initiation of the coagulation process (down to both platelet usage and damage to endothelial cells), and the sequestration of parasitized red blood cells. This sequestration is a consequence of the overexpression of cell adhesion molecules, pfEMP, and

iNOS, as indicated by previous studies (B. C. Clark *et al.*, 2011; Ghosh *et al*., 2001).

Geographical distribution of malaria parasite

Plasmodium falciparum

P. falciparum is predominantly found in geographical areas that exhibit elevated levels of temperature and humidity. It is predominantly present in tropical and subtropical areas of Africa, Central America, South America, as well as countries like Bangladesh, Pakistan, Afghanistan, Nepal, Sri Lanka, Southeast Asia, Indonesia, Philippines, Haiti, Solomon Islands, Papua New Guinea, and various Melanesia islands. Additionally, it is evident that this phenomenon is present in specific regions of India, the Middle East, and the eastern Mediterranean (Cheesbrough, 2006). *P. falciparum* exhibits various 'variants' that display variances in their geographic prevalence, susceptibility to vectors, patterns of human infection, susceptibility to drugs, antigenic makeup and morphology.

Plasmodium vivax

P. vivax, a kind of malaria parasite, demonstrates the capacity to undergo maturation within mosquitoes even under colder temperature conditions in comparison to *P. falciparum*. As a result, *P. vivax* has a broader presence in regions with temperate and sub-tropical climates. It serves as the predominant *Plasmodium species* across diverse locations including South America (extending to northern Argentina), Mexico, the Middle East, northern Africa, India, Pakistan, Sri Lanka, Papua New Guinea, and the Solomon Islands. Additionally, *P. vivax* is detected in parts of South East Asia, Indonesia, Philippines, Madagascar, tropical and subtropical Africa, Korea,

and China (Cheesbrough, 2006). Within *P. vivax*, numerous strains exist, showcasing variations in factors such as incubation period, relapse pattern, parasite count within red blood cells, and sensitivity to anti-malarial medications.

Plasmodium malariae

P. malariae exhibits a significantly lower prevalence in comparison to *P. falciparum* and *P. vivax*. The existence of it is detected in regions characterized by tropical and subtropical climates. Within the tropical regions of Africa, Plasmodium infections account for around 25% of the total cases. Moreover, the presence of this particular strain has been observed in several countries such as Guyana, India, Sri Lanka, and Malaysia, where its contribution to Plasmodium infections is less than 10% (Cheesbrough, 2006).

Plasmodium ovale

P. ovale demonstrates a comparatively low prevalence rate. Its presence is primarily observed in West Africa, contributing to around 10% of malaria cases in the region and has also been documented in various regions across Africa, as well as in the Philippines, Indonesia, China, and multiple areas within the Far East, Southeast Asia, and South America. (Cheesbrough, 2006)

Plasmodium knowlesi

Cases of human malaria resulting from the *P. knowlesi* parasite, which primarily affects monkeys (specifically macaques), have been documented in both Malaysia and Thailand. While *P. knowlesi* shares similarities in appearance with *P. malariae*, it stands apart due to the notably elevated levels

of parasites and more intense clinical manifestations, which contrasts with the characteristics of *P. malariae* infections. (Singh *et al*., 2004)

Transmission of malaria infections.

Malaria parasites spread through the bite of a female Anopheles mosquito that carries the infection. When the mosquito feeds on a human, it injects sporozoites, which are the parasite's early forms, into the bloodstream through its saliva. Apart from mosquito bites, infection can also happen through receiving contaminated blood via transfusion, injection with needles or syringes tainted by infected blood, and in rare cases, from a non-immune mother to her child during pregnancy.

Strategies to control and prevent malaria

Supplying available facilities for diagnosing malaria and offering affordable and efficient medications to promptly address ongoing infections has shown effectiveness. This approach also extends to preventing malaria in vulnerable groups like pregnant women and individuals lacking immunity who travel to or reside in areas where the disease is prevalent (WHO, 2012). Moreover, enhancing the general understanding of malaria's risks and ways to minimize exposure to mosquitoes can play a crucial role in curbing its transmission.

Another strategy involves steering clear of mosquito bites through measures such as employing long-lasting bed nets treated with insecticides, installing mosquito netting on windows and doors, donning protective attire, and applying mosquito repellents (World Health Organization, 2020).

An essential component of a mosquito control program involves various measures such as eliminating standing water, filling ponds and ditches,

modifying potential breeding areas, applying pesticides to breeding sites, and using effective chemicals to eradicate adult mosquitoes.

Above all, expedite actions to effectively control epidemics in complex emergency situations will minimize derails in gains made in the control efforts.

Treatment of malaria infection

WHO has provided guidelines for malaria treatment based on factors such as the infection's severity, specie responsible for the infection, age of the individual, whether pregnant or not (WHO, 2015).

Malaria Pathogenesis

Host immune response, direct receptor–ligand interactions and parasite factors contributes to the pathogenesis of malaria (Moxon, Gibbins, McGuinness, Milner, & Marti, 2020).

Inflammatory Parasite Factors

The phenomenon of cytoadherence in infected red blood cell (iRBCs) and the growth of mature schizonts, where various parasite component accumulate, might offer a mechanism for concentrating harmful or immune-stimulating components on the endothelial surface at sequestration sites (Moxon et al., 2020). The aforementioned procedure has the potential to cause localized disturbances in the endothelium barrier or impair anticoagulant function, which may subsequently lead to the occurrence of leaks or coagulation disorders, or both (Moxon et al., 2020). Parasite-derived factors have the potential to trigger the production of inflammatory cytokines, which can subsequently activate the endothelial cells. Additionally, factors like the attachment of iRBCs have the ability to directly stimulate endothelial cells ex

vivo (Jambou et al., 2010; Viebig et al., 2005). All of these processes can activate endothelial receptors like intercellular adhesion molecule 1 (ICAM-1) to attach iRBCs and increase their sequestration (Moxon et al., 2020). Certainly, activation of these processes might serve as a beneficial technique for the parasite to enhance its survival by facilitating sequestration, even though the negative effects on the host's health are unintentional. Pathogen-recognition receptors serve as a traditional channel for the host's immune system to detect the presence of an external intruder (Moxon et al., 2020).

The recognition of pathogens through Toll-like receptors (TLRs), found on both exterior and interior of host cells', is a widely explained approach which is known to trigger various reactions downstream, one of which involves the discharge of inflammatory signaling molecules like interleukin (IL)-1β and tumor necrosis factor (TNF). Research has brought to light that the release of hemozoin from iRBCs is connected with the activation of endothelial cells (Griffith *et al.,* 2009). This phenomenon of activation is probably induced by DNA originating from parasites, which is linked to hemozoin and this combination interacts with and triggers the activation of TLR9 (Parroche *et al.,* 2007). Moreover, it has been observed in in vitro studies that macrophages are activated by both DNA and hemozoin, leading to the activation of the NLRP3 and AIM2 inflammasomes subsequent to the phagolysosome breakdown. This activation enables them to enter the cytosol and initiate the release of IL-1β (Kalantari *et al.,* 2014). (Griffith *et al.,* 2009). Nucleosomes have the ability to trigger dendritic cells via TLR9, leading to the release of TNF and IL-12 (Gowda, Wu, & Gowda, 2011). On the other hand, heme can prompt the release of TNF in both murine and human

macrophages by utilizing the TLR4 pathway (Figueiredo et al., 2007). Certain factors produced by parasites have a direct impact on endothelial cells. Laboratory studies have demonstrated that histones derived from *P. falciparum* can stimulate the production of IL-8 by interacting with TLR2 receptors located on endothelial cells. Furthermore, these histones can also augment vascular permeability through a mechanism associated with their charge (Gillrie *et al.*, 2012).

Interactions between Receptors and Ligands in Malaria Pathogenesis

Apart from the impacts of inflammation caused by parasites, the involvement of malaria's progression is attributed to the direct interaction between the parasite and host cells via receptor-ligand interactions (Moxon *et al.,* 2020). Detailed examinations at the ultrastructural level have shown significant changes in iRBCs during *P. falciparum* malaria such as creation of electron-dense protrusions on cellular membrane, which are referred to as 'knobs' (Leech, Barnwell, Miller, & Howard, 1984). The examination of infected tissue acquired from postmortem examinations of human subjects has shown evidence that parasites within the tissue interact with the endothelium through the utilization of these protrusions known as knobs (Silamut *et al.*, 1999). In addition, the predominant immunodominant and variant forms of *P. falciparum* erythrocyte membrane protein 1 *(Pf*EMP1) have been identified and localized on knobs (Marsh & Howard, 1986). The sequestration of parasites serves as a mechanism of avoiding spleen clearance, causing various pathologies specific to certain tissues (Moxon *et al.,* 2020). While multiple parasite-originating surface ligands on erythrocytes have been suggested to participate in this sequestration process, PfEMP1 is the sole ligand that has

been demonstrated to stably bind with host cell receptors (primarily endothelial cells) and it has been linked to disease outcomes. The var gene family in each genome has around 60 copies of the genetic coding for PfEMP1, which is a prominent antigen in the context of *P. falciparum* (Chan *et al.*, 2012). *Var* genes display allelic expression, allowing a single copy to be active in a cell at any given moment, which preserves the diversity in traits and antigens within the population (Dzikowski et al., 2006). The var gene repertoire exhibits variation among different strains, although it can be categorized into three main categories (A, B, C) in accordance to the upstream sequences and chromosome locations. Each PfEMP1 protein has a shorter acidic terminal segment inside and multiple tandem Duffy-binding-like (DBL) domains as well as cysteine-rich interdomain regions (CIDRs) on its outer part. (Smith *et al.,* 1995). Research involving binding and structural analyses has begun to elucidate how DBL and CIDR domains specifically attach to host receptors, thus influencing malaria's progression (Baruch *et al.,* 1997; Lennartz *et al.,* 2017). Initial adhesion experiments pinpoint CD36 as the receptor for the most N-terminal DBL–CIDR domain sets in various *Pf*EMP1 versions (Baruch *et al.*, 1997). Notably, CD36 binding is a prevalent trait in the majority of *Pf*EMP1 variations (including group B and C types) (Smith, 2014). ICAM-1 is identified as a common receptor binding characteristic among some types of group A and B (Smith *et al.*, 2000).

Malaria and Diabetes Interaction

Several studies have investigated the relationship between malaria and diabetes, with evidence suggesting that diabetes may augment the risk of malaria infection (Acquah *et al.,* 2014; Danquah *et al.,* 2010). Increase

vulnerability *to P. falciparum* infection among individuals with diabetes may suggest a compromised immune response in diabetics when compared to those without diabetes (Acquah, 2019). Generally, T2DM is believed to represent an immune-compromised state, potentially exposing individuals to a higher susceptibility to infections (Alves *et al.,* 2012; Muller *et al.,* 2005). Diabetics have compromised immune response against liver and/or blood-stage parasites which is likely a result of a diminishing T cell-mediated immune response (Muller *et al.*, 2005), allowing malaria parasites to flourish swiftly when excess glucose is present (Jensen *et al.,* 1983). There is also a viewpoint suggesting that individuals with diabetes might be more prone to attracting mosquito bites carrying infections due to olfactory signaling system (Takken & Knols, 1999).

The exact mechanisms underlying the interaction between malaria and diabetes are yet to be completely understood, nevertheless numerous factors have been suggested. For instance, malaria infection causes inflammation, oxidative stress, and altered lipid metabolism, which could exacerbate insulin resistance and lead to development of diabetes (Acquah *et al.,* 2014; Vasquez *et al.,*2021). Additionally, some antimalarial drugs have been shown to affect glucose metabolism, potentially exacerbating diabetes in patients with pre-existing diabetes (Davis *et al.*, 1996; Warrel, 1990)

Galectin

Galectins are a set of proteins that have been conserved throughout evolution and possess the capability to attach to β-galactosides via unique carbohydrate-recognition domains (CRD) (Díaz-Alvarez & Ortega, 2017; Vasta *et al*., 2001). The galectin family has been detected in several forms of

organisms, including sponges, fungi, nematodes, insects, mammals (including humans), and even viruses have been found to have galectins. (Cooper, 2002). Their homologues are also found in plants (Letunic *et al*., 2004), but not in yeasts Mammals collectively possess 16 galectins, yet the human genome contains only 12 galectin genes, but only 12 galectin genes are found in humans (Brinchmann et al., 2018), including two for galectin-9 (Lipkowitz et al., 2001). Galectins have been categorized into three main groups (Hirabayashi & Kasai, 1993).

Prototypical galectins, which have a single CRD which might link up as homodimers;

On the other hand, the chimeric galectins are characterized by galectin-3, which is currently the sole known species found in vertebrates. Typically, these proteins possess a solitary collagenous repeat domain (CRD) and an N-terminal region containing many iterations of peptide sequences that are abundant in proline, glycine, and tyrosine residues. The domain's recurrence resembles synexin and synaptophysin, suggesting self-aggregation (Massa *et al.*, 1993).

The tandem-repeat galectins, which contain a minimum of two CRDs in a polypeptide and are linked by a short peptide domain.

Galectin-3

Galectin-3 is distinct in its structure from all other galectins due to the fact that it has a carbohydrate-recognition domain at the C-terminus that is connected to a protein-binding domain at the N-terminus. This makes it the sole chimeric galectin found in vertebrates (Díaz-Alvarez & Ortega, 2017; Nio-Kobayashi, 2017). Inflammatory cells including mast cells, neutrophils,

and macrophages express galectin-3 as well as other tissues such the gut, spleen, colon, and kidney (Díaz-Alvarez & Ortega, 2017). Galectin-3 has the ability to localize within many cellular compartments, including the cytoplasm, nucleus, and cellular membranes. Moreover, the extracellular detection of this substance occurs subsequent to its release from cells in response to numerous stimuli, including lipopolysaccharide (LPS) and interferon-γ, under both healthy and pathological circumstances (Fritsch *et al*., 2016; Kang *et al.*, 2016). Diabetes, inflammation, fibrosis, rheumatoid arthritis, asthma, some malignancies, and heart failure are only some of the pathophysiological processes in which galectin-3 plays a role (De Boer *et al*., 2009; Henderson & Sethi, 2009; Newlaczyl & Yu, 2011).

Physiological functions of galectin-3

Importance of Galectin-3 in angiogenesis became evident when studies showed its ability to impact chemotaxis and differentiation of human umbilical vein endothelial cells (HUVECs) (P Nangia-Makker *et al.*, 2000). The research findings demonstrated that Galectin-3 possesses chemotactic properties and promotes the development of capillary tubules in both in vitro and in vivo experiments using HUVECs. The role of Galectin-3 in angiogenesis relies on its ability to recognize carbohydrates and its oligomerization process (Markowska *et al.*, 2010; Naghavi *et al*., 2017). A research conducted using mice demonstrated that galectin-3's participation in the process of angiogenesis is triggered by vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (Markowska *et al.*, 2010). The study found that using small interfering RNA to lower galectin-3 levels in HUVECs resulted in a decrease in migration and capillary tubule formation

triggered by VEGF and bFGF. Also, the study reported that Galectin-3-deficient mice did not experience neovascularization in response to either of the growth factors.

Notably, galectin-3 is involve in kidney development. The presence of galectin-3 has been established in hamster metanephroi (Foddy & Hughes, 1986) as well as during human nephrogenesis (Winyard, Bao, Hughes, & Woolf, 1997). In organ culture of developing mouse kidney Bullock *et al.*, (2001) suggest it affects ureteric bud branching. The early mouse metanephric growth showed that galectin-3 was mostly found in the renal pelvis' bud derivatives, urothelium and collecting ducts and that the introduction of external galectin-3 was observed to disrupt branching in explants at embryonic days E11 and E12. The function of galectin-3 in kidney development was studied extensively using in vitro model system involving Madin-Darby canine kidney (MDCK) tubulogenesis (Bao & Hughes, 1995). The study reported that, when a high concentration of external galectin-3 was added, the growth of MDCK cysts hindered while introduction of galectin-3 blocking antibodies and inhibitors enhanced the growth of cysts. The experimental system operates under the assumption that galectin-3 facilitates robust adhesive interactions, impeding the mobility at locations where cells undergo migration and reorganization during the processes of sprouting and tubule formation (Bao & Hughes, 1995). Conversely galectin-3 is thought to maintain cellular polarity by forming tight junctions.

This phenomenon also appears to occur with regular breast epithelial cells cultivated in matrigel where these cells develop a well define cysts while preserving their polarity (Howlett & Bissell, 1993). Galectin-3 has been

directly linked to the final maturation process of epithelial cells where it attaches to and forms a complex structure with a high molecular weight glycoprotein called hensin, which retains cellular polarity during differentiated (Hikita *et al.,* 2000).

Galectin-3 affects immune cell differentiation and proliferation. It induce T cells and neutrophils apoptosis and activates mast cells, neutrophils, monocytes, and T cells. Mediators release, superoxide anion creation, and cytokines synthesis result from this activation (Liu, 2005; Rabinovich *et al.,* 2007). The recombinant galectin-3 facilitates human monocytes and macrophages like chemokine. A G-protein-coupled pertussis toxin (PTX)-sensitive pathway mediated this action. The activity is also connected to calcium ions influx, suggesting chemokine receptors involvement (Liu, 2005; Rabinovich *et al.,* 2007). Cortegano *et al.,* (1998) found that Galectin-3 suppress myeloid cells by hindering IL-5 production in human eosinophils. The study conducted by Kuwabara & Liu, (1996) shown that the introduction of recombinant galectin-3 resulted in the promotion of adhesion between human neutrophils and laminin. Additionally, Sato *et al.,* (2002) found that same recombinant protein also facilitated adhesion between human neutrophils and endothelial cell lines.

Other physiological roles of galectin-3 include endocytosis (Crider-Pirkle *et al.,* 2002; Zhu & Ochieng, 2001), exocytosis (Furtak *et al.,*2001) and cellular signaling (Dennis *et al.,*2002) as well as cellular adhesion (Dong & Hughes, 1997; Hughes, 2001).

Pathophysiological roles of galectin-3

Within the heart, galectin-3 is predominantly present in activated macrophages and pathologically damaged cardiomyocytes, and is significantly involved in cardiac remodeling, including myocardial fibrogenesis, and also involve in pathogenesis of heart failure (Ho *et al.,* 2012; Ueland *et al.,* 2011; Yu *et al.,* 2013). According to Sharma *et al.* (2004) and Song *et al.* (2015) galectin-3 causes fibroblasts proliferation and heterogeneous collagen deposition which worsens heart function. Research indicated that recombinant galectin-3 has the ability to transform naive fibroblasts to myofibroblasts in addition to enhancing cardiac fibroblast proliferation, synthesis of TGF-β, production of collagen, as well as cyclin D1 expression (Sharma *et al.,* 2004). A research conducted by MacKinnon *et al.* unveiled that galectin-3 attaches to the macrophages membrane protein CD98. This interaction activates PI3K via a different route. IL-4 and IL-13 as well as ECM deposition is enhanced when macrophages are stimulated (MacKinnon *et al.*, 2008). Song *et al.* (2015) found that upregulating the galectin-3 gene boosted collagen I synthesis in HL-I cardiomyocytes, accelerating cardiac degeneration. Recent investigations have shown that galectin-3 can induce oxidative stress in human cardiac fibroblasts, as well as various animal and human heart diseases models (Ibarrola, Arrieta, *et al.*, 2018; Ibarrola, Sádaba, *et al.*, 2018). This discovery suggest a new in which galectin-3 causes heart damage.

Cancer persistence and prognosis are affected by many factors, including the tumor microenvironment (TME). The TME includes cancer cells, stromal cells, immunological cells, the extracellular matrix (ECM) in addition to other constituents (Guo *et al.,* 2020). The TME intracellular

galectin-3 in the TME has many functions. Galectin-3 is found in several cancers, and varies in expression (Haudek *et al.*, 2010). For instance, galectin-3 expression increases in thyroid, liver, stomach, and central nervous system cancers, while it decreases in breast, ovarian, uterine, and prostate cancers (Nakahara *et al.*, 2002). During the progression of tumors, galectin-3 is commonly found in the cytoplasm, as observed in cases of tongue and prostate cancer (Haudek *et al.*, 2010), and its weakly expressed when found in nucleus during the switching of tongue tissue from normal stage to malignant (Haudek *et al.*, 2010). Thus galectin-3 localization affects its biological effects; nuclear galectin-3 has anti-tumor effects, however, cytoplasmic galectin-3 has tumorigenic effects (Califice *et al.*, 2004; Dumic *et al.*, 2006; Haudek *et al.*, 2010). Galectin-3 expression changes from healthy to malignant cells with the nucleus expression decreasing and cytoplasm expression increasing (Radosavljevic *et al.*, 2011). The phenomenon matches prior study on melanoma patients, where those with lower survival rates exhibit higher cytoplasmic galectin-3 expression compared to nuclear expression (Prieto *et al.*, 2006).

Multiple studies have shown that extracellular galectin-3 affects endothelial cells, immunological cells, cancer-related fibroblasts, myofibroblasts, and MSCs. Research indicate that these cells can release galectin-3 (Fortuna-Costa *et al.*, 2014; Henderson *et al.*, 2008; Nangia-Makker *et al.*, 2000). Galectin-3 upregulation enhances cancer cells migration and invasion in breast, melanoma, lung, sarcoma, gastric cancer, and chronic myeloid leukemia (Henderson *et al.*, 2008; Honjo *et al.*, 2001; O'Driscoll *et al.*, 2002; Yamamoto-Sugitani *et al.*, 2011). Furthermore, galectin-3 binds

with ECM glycoproteins, such as fibronectin, collagen IV, elastin and laminin, essential in facilitating cell migration (Hughes, 2001; Nangia-Makker *et al.*, 2008; Ochieng *et al.*, 1999). Research shows that galectin-3 can interact with the epidermal growth factor receptor (EGFR), phosphorylation it and translocating it from the cell membrane to the cytoplasm. Wu *et al.* (2018), found that extracellular galectin-3 and EGFR interact to affect EGFR dynamics in colon cancer cell migration.

Galectin-3 and diabetes

Numerous research works have revealed that individuals with diabetes have increased levels of galectin-3, which is linked to insulin resistance, inflammation, and fibrosis (P. Li *et al.*, 2016; Y. Li, *et al.*, 2022; Lin et al., 2021; Souza *et al.*, 2021). He *et al.*, (2017) discovered that people with T2DM had significantly higher levels of galectin-3 compared to healthy individuals. The study also revealed that galectin-3 is connected to insulin resistance and glycemic control, suggesting that it may have a role in the development of T2DM. Some proposed mechanisms to explain the association between galectin-3 and diabetes include its possible contribution to insulin resistance by interfering with insulin signaling. A study showed that galectin-3 overexpression in skeletal muscle cells inhibited insulin signaling and glucose uptake (P. Li *et al.*, 2016). The study consequently suggests that galectin-3 may contribute to insulin resistance by interfering with the insulin signaling pathway. Another proposed mechanism is that galectin-3 can promote inflammation and fibrosis, both of which are implicated in the aetiology of T2DM and its complications. A study (Y. Li *et al.*, 2022) found that galectin-3 may account for the development of diabetic nephropathy by promoting renal

fibrosis, inflammation, and oxidative stress. Hence, the study suggested that targeting galectin-3 could be a potential therapeutic strategy for preventing or treating diabetic nephropathy.

Galectin-3 and malaria

Plasmodium-infected erythrocytes display altered surface glycosylation patterns compared to uninfected erythrocytes (Chan *et al.*, 2014). Galectin-3 has been shown to bind to glycosylated molecules (Iacobini *et al.*, 2003) and may influence the altered surface glycosylation of infected erythrocytes. This study hypothesized that these interactions may facilitate parasite sequestration, adhesion to endothelial cells, and immune evasion strategies employed by the parasite. A study involving plasma levels of galectin-9 (Gal‑9) in malaria infected individuals revealed that during the onset of malaria, Gal-9 is secreted and its levels are indicative of the intensity of the infection (Dembele *et al*., 2016). However, information on serum levels of galectin-3 in human malaria patients (with/without) diabetes is limited. However, experimental models of galectin-3 on the effect malaria infection showed that levels of galectin-3 is enhanced in mice showing signs of experimentally-induced cerebral malaria (ECM). Galectin-3 deficient mice (gal3$^{-/-}$) display partial protection against ECM induced by P. berghei ANKA infection (Oakley *et al.,* 2009). In addition, the study showed that absence of galectin-3 leads to a significant decline in P. yoelii 17XNL parasitaemia, suggesting a potential impact of galectin-3 on the replication or infectivity of P. yoelii 17XNL.

On the other hand, Toscano et al. (2012), showed no disparity in parasitaemia between galectin-3 deficient (Lgals3$^{-/-}$) and wild-type (WT)

mice infected with either P. berghei ANKA or P. chabaudi AS proposing that the role of galectin-3 in controlling parasitaemia may be variable and/or inconclusive. The observed differences in the effects of galectin-3 on disease outcomes following infections with P. berghei and P. chabaudi could stem from variations in both the genetic makeup of the host and the parasite.

In this study, serum levels of Galectin-3 was evaluated in T2DM and non- diabetics with/without malaria infection. The findings of this can provide baseline knowledge to trigger further studies into interaction between galectin-3 and malaria.

Insulin

Insulin is an essential hormone for maintaining energy homeostasis and is synthesized, secreted, and stored by pancreatic β-cells. This peptide hormone is instrumental in regulating the metabolism of carbohydrates, lipids, and proteins. Its secretion is intricately tied to even minor shifts in glucose levels, working to keep glucose within the normal range. (Pattaranit *et al.,*2008). The principal targets of insulin's effects are the muscles, adipose tissue, and liver. It curbs glucose production in the liver and encourages glucose uptake, utilization, and storage in muscles as well as fat cells. Conversely, low plasma glucose levels prompt pancreatic α-cells to release glucagon, which stimulates liver glucose production (Pattaranit *et al*., 2008). Adipose tissue also influences glucose metabolism by releasing non-esterified fatty acids (NEFAs) and producing hormones called 'adipokines,' including leptin, adiponectin, and tumor necrosis factor (TNF-α). NEFAs hinder glucose uptake in muscle (Bergman & Ader, 2000; Boden *et al.,* 1994), promote glucose production in liver (Bergman & Ader, 2000; Mlinar *et al.,* 2007),

inhibit lipoprotein lipase activity in adipose tissue (Mlinar *et al*., 2007) and reduce secretion of insulin from the pancreas (Bergman & Ader, 2000; Boden *et al*., 1994; Mlinar *et al*., 2007).

Leptin indirectly enhances insulin sensitivity by reducing food intake and boosting energy expenditure (Webber, 2003). These impacts are facilitated through the influence of leptin on the hypothalamus. Adiponectin increase insulin sensitivity by encouraging the oxidation of glucose and NEFA in muscles, thereby reducing levels of plasma glucose and NEFA (Kershaw & Flier, 2004; Mlinar *et al*., 2007). Moreover, in liver cells, adiponectin stimulates the oxidation of fatty acids, curbs glucose production, and reduces the uptake of NEFA as well as the synthesis of lipids. In contrast, TNF-α undermines insulin signaling in tissues responsive to insulin by reducing gene expression associated with glucose uptake and β-oxidation in the liver. TNF-α also prompts alterations in gene expression that may lead to insulin resistance in adipocytes (Cawthorn & Sethi, 2008). In muscles, TNF-α diminishes the uptake and storage of NEFA and glucose, thereby impairing insulin signaling (Mlinar *et al*., 2007).

Insulin resistance

Insulin resistance is a key feature of T2DM, a chronic metabolic disorder characterized by high blood glucose levels due to defects in insulin secretion, insulin action, or both. Various factors at multiple levels can serve as the main contributors to insulin resistance. These factors encompass reduced receptor density and kinase activity, alterations in insulin receptor substrate (IRS) concentration and phosphorylation due to phosphatidylinositol 3-kinase (PI3K) activity, translocation of glucose transporters, functioning of

intracellular enzymes, as well as a combination of genetic and environmental influences (Saltiel & Kahn, 2001). Hence, the etiology of insulin resistance is complex. Insulin resistance holds significant importance. Not only is it the most powerful predictor of future development of T2DM., it also becomes a focal point for treatment once hyperglycemia manifests (Taylor, 2012).

Galectin-3 and insulin resistance

A study on galectin-3 and insulin resistance P. Li *et al.,* (2016)., they found that galectin-3 could induce cellular insulin resistance in fat cells, muscles, and the liver and that mice with diet-induced obesity and insulin resistance had higher galectin-3 expression. Furthermore, they also found that galectin-3 inhibition increase insulin sensitivity and glucose tolerance, suggesting a potential therapeutic target for the treatment of insulin resistance. P. Li et al., further illustrated that galectin-3 originating from macrophages had a direct interaction with the insulin receptor. This interaction hindered crucial stages of the insulin signaling pathway, ultimately leading to reduced sensitivity to insulin in adipose tissue, liver, and muscle

Malaria-induced Insulin Resistance

Several studies have indicated that malaria infection may induce insulin resistance, potentially increasing the risk of developing T2DM (Eltahir et al., 2010; Acquah et al., 2014; Udoh *et al.*, 2020). A Ghanaian based study reported the presence of insulin resistance in adult uncomplicated malaria (Acquah *et al.*, 2014). In this study, serum levels of insulin was evaluated in diabetics and non- diabetics with/without malaria infection. The inflammatory response associated with malaria infection could impair insulin signaling pathways and promote insulin resistance.

The precise mechanisms that underlie the association between malaria and insulin resistance remain incompletely elucidated, while multiple causes have been proposed. Malaria infection is associated with inflammation (Clark *et al.*, 2006; Issifou *et al.*, 2003), oxidative stress (Acquah *et al.*, 2016; Griffiths *et al.*, 2001; Huber, 2002), and altered lipid metabolism (Kluck et al., 2019; Labaied et al., 2011; Visser, Wieten, Nagel, & Grobusch, 2013), all of which can primary lead to the development insulin resistance. The inflammatory reactions to malaria is regulated by several markers including specific IL, TNFα, C-reactive protein as well as IFNγ (Abdel-Hamid *et al.*, 2013; Bousema *et al.*, 2014; Mbengue *et al.*, 2016). These aforementioned alterations have been implicated as potential mechanisms underlying the development of insulin resistance in malaria-infected individuals.

Malaria-induced dyslipidemia has been documented by numerous studies in humans (Baptista *et al*, 1996; Maurois *et al.*, 1979; Visser *et al*., 2013) and mouse model (Kluck *et al*., 2019), and has been link to malaria-induce insulin resistance (Labaied *et al., 2*011). Malaria-infected individuals are reported to have higher than normal levels of triglycerides (Davis *et al.*, 1993; Sirak *et al*, 2016; Visser *et al.*, 2013) but lower levels of high-density lipoprotein (HDL) cholesterol, low density-lipoprotein cholesterol (LDL) and total cholesterol (Sirak *et al.*, 2016; Visser *et al.*, 2013). *Plasmodium* species are unable to synthesize cholesterol on their own (Labaied *et al.*, 2011; Sherman, 1979; Sirak *et al.*, 2016), hence, it has been proposed that malaria parasite utilize host cholesterol for replication within the host (Labaied *et al.*, 2011). In addition, *Plasmodium* can acquire cholesterol from hepatocytes by inhibiting host squalene synthase (Labaied *et al.*, 2011), which is an enzyme

involved in the initial stage of sterol synthesis. Additionally, some antimalarial drugs, such as chloroquine, have been shown to affect glucose metabolism and insulin sensitivity (Powrie *et al.*, 1991; Smith *et al.*, 1987; Warrel, 1990)

Chapter summary

Malaria and diabetes are two of the most pressing health challenges globally, with significant impacts on human health and economic development (*IDF*, 2021; WHO, 2020). Despite sub-Saharan Africa carrying the global malaria burden (World Health Organization, 2020), it has been projected that by 2045, the number of individuals with T2DM will increase to 134% within the sub-Saharan Africa region (*IDF*, 2021). Although malaria and diabetes are distinct conditions, recent studies have suggested a potential interaction between malaria and diabetes (Danquah *et al.*, 2010; Acquah *et al.*, 2014; Vos *et al.*, 2017)

Metabolic syndrome characterized by impaired glucose metabolism, insulin resistance, systemic hypertension, low levels of HDL, high triglycerides, and central obesity (Alberti *et al.*, 2009, 2006; McCracken *et al.*, 2018) is on a rise. Individuals with MetS have a 3-5-fold increased risk for developing T2DM (Ford, 2005; Ford *et al.*, 2008). In view of this, in malaria endemic countries, persistence malaria infection may results in T2DM (Acquah, 2019) and may results in adverse outcomes in diabetics.

Adults with uncomplicated malaria infection have been documented to have developed insulin resistance (Acquah *et al.*, 2014). Besides, a study conducted in Sudan revealed that children with severe complicated malaria had insulin resistance (Eltahir *et al.*, 2010). However, to the best of my knowledge, the role galectin-3 is malaria infection still underdeveloped though

diabetics are known to have high levels of serum galectin-3 as compared to non-diabetics (P. Li *et al.*, 2016; Y. Li *et al.*, 2022; Lin *et al.*, 2021; Souza *et al.*, 2021).

This study therefore seeks to determine serum insulin and galectin-3 levels in T2DM and non-diabetics within the Tema metropolis in the Greater Accra region.

CHAPTER THREE

RESEARCH METHODS

Introduction

The rational of this current study was to determine the effects of malaria on galectin-3 levels and insulin resistance in T2DM and non-diabetic controls within the Tema metropolis. This was aimed at deepening our understanding of malaria-induced insulin resistance and measures aimed at curbing the menace of metabolic syndrome in the Ghanaian context. This chapter therefore explains the study design, study population, study site, sampling method, inclusion and exclusion criteria, experimental protocols, data collection and analysis procedures used during the study.

Research design

The research utilized a hospital-based cross-sectional study design to recruit non-diabetics with or without malaria and T2DM patients with or without malaria. This study design was employed to establish the link or association between galectin-3, insulin resistance and human malaria.

Study Area

The research was conducted from October, 2021 to December, 2022 at the Tema General Hospital.

Study population

The study population comprised of diabetics and the non-diabetics who sought healthcare at the Tema General Hospital within the Greater Accra Region of Ghana.

Sample Size Estimation

An estimated number of one hundred and sixty (160) participants were recruited for the study. Sample size was calculated from the formula below (Wayne W. Daniel & Chad L. Cross, 2018):

$$p_1 = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \times F_1(1 - F_1) + F_2(1 - F_2) \over (F_1 - F_2)^2$$

F_1	Fraction of outcome from group-1
F_2	Fraction of outcome from group-2
α	Degree of significance
$1-\beta$	Power of test
$Z_{1-\alpha/2}$	Z value matching the degree of significance
$Z_{1-\beta}$	Z value matching the degree of power
P_1	Sample size for one group
$P = P_1 + P_2$	

F_1 = estimated proportion of malaria in Ghana

Malaria patient population in Ghana = 4,911,921 (WHO 2020)

Ghana's population = 31,072,940 (Worldometer, 2020)

$$\Rightarrow F_1 = \frac{4,911,921}{31,072,940} = 0.16$$

F_2 = estimated proportion of diabetics in Ghana = 1.8% = 0.018 (International Diabetic Federation, 2020)

$\alpha = 0.05$

$1 - \beta = 0.80$

$Z_{1-\alpha/2} = 1.96$ (Two tailed/sided test)

$Z_{1-\beta} = 0.842$

$$\Rightarrow P_1 = (1.96+0.842)^2 \times 0.16(1-0.16) + 0.018(1-0.018)$$

$$(0.16 - 0.018)^2$$

$$= \frac{7.85 \text{ X } (0.1344 + 0.0177)}{0.0202} \quad = \quad 7.85 \text{ X } 7.53$$

$$\Rightarrow \quad P_1 = 59.1$$

Therefore, $P = P_1 \text{ x } 2 = 118$

Addition of 36% non – response rate

Effective sample size = 118

Non-response rate =36%,

Final sample size = (118 X 0.36) + 118 = 160

Hence, one hundred and sixty (160) participants were targeted for the study. It was comprised of 80 diabetes patients with or without malaria and 80 non-diabetics with or without malaria. A non-response rate of 36% was selected due to expected COVID-19-induced apathy which could affect participation in research and most importantly, Tema, being an epi-centre during Ghana's share of the COVID-19 pandemic. This sample size was selected to provide us with adequate numbers for statistical analysis.

Inclusion Criteria

All consenting non-pregnant diabetic and non-diabetic patients aged 20 years and above attending the Tema General Hospital with or without malaria qualified to be included in the study. T2DM participants includes individuals who have been already diagnosed of diabetes and are taking medications for the condition.

Exclusion criteria

Any individual aged below 20 years was excluded from the study. Those above 20 years who refused to consent to the study were also excluded.

Newly diagnosed diabetics and undiagnosed diabetics were excluded from the study. Above all, individuals who have been diagnosed with health conditions such as fibrosis, hepatitis, HIV, pancreatitis, viral and bacterial infections, rheumatoid arthritis, asthma and heart failure were excluded from the study based on their health records because these conditions affect serum galectin-3 levels. In addition, expectant mothers were not included in the research due to the fact that the initial stages of pregnancy, including implantation, placentation, and the first and early second trimester, bear a resemblance to an "open wound" that necessitates a robust inflammatory reaction.

Sampling procedure

Simple random sampling method was used to recruit participants for the study. The randomization was done by dividing the total adult population of patients visiting the Tema General Hospital into diabetics and non-diabetics on daily basis. On every visit to the hospital, all individuals at the OPD or the diabetes clinic were educated appropriately on the study regarding its rationale, broad objective, risk and benefits for participation. After this, those who showed an interest to partake in the study were given the chance to select a folded piece of paper from properly mixed pull with an inscription YES or NO in an appropriate container. The inscription on the papers was only known by the researcher but not the potential participant. A total of 40 pieces of such folded papers were prepared with 20 ‘YES’ and 20 ‘NO’ on each day of the visit. Each individual was then offered the chance to select only one of the folded papers till all folded papers were selected. All those who selected ‘YES’ were then invited to participate in the study if they satisfy the inclusion criteria. Those who selected the NO were politely urged to try again at the

next opportune period. Anyone who selected YES but still declined or did not meet the inclusion requirement was not replaced on the day. This procedure was repeated on daily basis during the course of sample collection until the required sample size was attained for all categories of respondents.

Data collection Instruments

Apart from the laboratory, anthropometric and blood pressure measurements, demographic data were collected. Sociodemographic and clinical data were collected using questionnaires. A sample of the questionnaire is attached as appendix 1.

Blood pressure

An experienced nurse measured blood pressure with an electronic sphygmomanometer (Mindray VS-900C, Salvin Dental Specialties, Inc, USA) on three consecutive occasions. During the measurements, the individual was in a seated position, and their left arm was placed comfortably on a flat surface at the level of their heart. The initial reading was taken after the person had been seated for a minimum of 5 minutes. Subsequent measurements were then taken every 5 minutes. If there was a difference of more than 10 mmHg between the second and third readings, a fourth reading was obtained. The average of the second and third readings was used as the reported value. In instances where a fourth reading was necessary, the two readings closest in value were averaged.

Anthropometric measurements

The body weight, height, and waist plus hip circumferences were measured twice, following the World Health Organization guidelines (WHO, 2011). If the difference between the two initial readings exceeded 0.5 units, a

supplementary measurement was obtained. The measurements of weight, height, and body mass index (BMI) were obtained using a height, weight, and BMI measuring scale (Soehnle 7831, Soehnle Professional, Germany) that display the results on a digital screen with the subject wearing his or her usual clothes, shoeless, and without any objects in the pockets.

Experimental protocol

A total of 10 ml venous blood sample was taken from each respondent who consented to take part in the study for measurement of the various biomarkers by standardized venipuncture. A volume of four milliliters of venous blood was extracted and subsequently placed into a serum separator tube and was then used for galectin-3 and insulin measurement using an enzyme-linked immunoassay (ELISA) technique. A volume of 3 ml of venous blood was collected into a serum separator tube for the purpose of lipid profile analysis. The test was performed using AU 480 Beckman coulter chemistry analyzer (Beckman coulter, Ireland Inc., Ireland). The residual 3 ml of venous blood was obtained and placed into an anticoagulant tube containing ethylenediaminetetraacetic acid (EDTA) for the purpose of conducting a full blood count and diagnosing malaria.

Enzyme-linked immunoassay (ELISA) test

The levels of serum insulin and galectin-3 were quantified utilizing the ELISA technique. The quantitative assessment of serum galectin-3 in participants was performed using the Human Galectin-3 Quantikine ELISA Kit (R&D Systems Inc., USA) following the manufacturers' protocol. Serum levels of insulin was measured at University of Cape Coast, School of Medical Sciences (UCC-SMS) laboratory while galectin-3 levels were measured at the International Maritime Hospital laboratory, Tema. This occurred due to very late delivery of Human Galectin-3 Quantikine

ELISA test Kit from abroad. Insulin on the other hand was measured by PerkinElmer ELISA Kits (PerkinElmer Health Sciences Inc., USA) following the manufacturers' protocol.

Insulin measurement

The insulin quantitative ELISA test kit is based on sandwich solid phase type. The experimental setup involved the utilization of microplates containing 96 wells, which were coated with an anti-insulin antibody as the solid phase. Additionally, another anti-insulin antibody was introduced into the antibody-enzyme conjugate solution. Prior to testing, the samples, standards, and reagents were equilibrated at room temperature. Fifty microlitres of insulin standards, controls, and specimens were aliquoted into appropriate wells. Exact volume of 100 μL of enzyme conjugate was added to each well. Following a thorough mixing procedure, the experimental apparatus was subsequently subjected to an incubation period of one hour. Five rounds of washing were performed on the microplate wells with the help of an automated microplate washer (Thermo Electron Co-operation, Finland). Each wash cycle involved the utilization of 300 μL of 1X wash buffer. Hundred microlitres of TMB substrate was then added to each well and subsequently incubation at room temperature without illumination for a duration of 20 minutes. Afterwards, the reaction was terminated via adding 100 μL of stop solution to each well and thoroughly mixed until the blue color turns yellow**.** Using a Multiscan microplate reader, the absorbance at 450 nm was promptly measured. A suitable standard curve was created using the absorbance values obtained from the insulin standards. The standard curve then determined insulin concentration in the samples.

Galectin-3 measurement

The galectin-3 ELISA test utilizes a quantitative sandwich enzyme method. A human galectin-3 monoclonal antibody pre-coated a 96 well microplate. At room temperature, samples, standards, and reagents were equilibrated before testing. After depensing 100 μL of assay diluent RD1W into each, 50 μL of insulin standards, controls and specimens of various concentration were added. Following a 2-hour incubation period at ambient temperature, each well underwent four washes using a multiwell plate washer/dispenser manifold (Sigma-Aldrich, Merck M2656, Germany) with 400 μL of wash buffer. The plate was inverted and gently pressed on permeable paper towels. A volume of precisely 200 μL of human galectin-3 conjugate was introduced into every well, followed by an incubation period of 2 hours at ambient temperature. After the initial washing steps, as mentioned earlier, each well was subjected to an additional wash. Subsequently, 200 μL of substrate solution was added to each well, and the plate was incubated at room temperature for a duration of 30 minutes, devoid from light. A volume of 50 μL of stop solution was subsequently introduced into each well until the observed color transitioned from blue to yellow. With a fully automated microplate reader (PKL PPC 142, Italy), the absorbance was then measured immediately at 450 nm and 570 nm. The measurements obtained at a wavelength of 570 nm were deducted from the measurements obtained at a wavelength of 450 nm. Fully automated (PKL PPC 142) ELISA microplate reader was used to generate galectin-3 concentration by transforming the data to a log/log curve fit.

Full blood count (FBC)

A fully automated five-part differential sysmex haematology analyser (XN 1000, Sysmex Corporation, Japan) was used to determine the full blood count parameters of each sample in accordance with manufacturer's protocol within 30 minutes of blood collection.

Malaria Diagnosis

Malaria infection was detected using Carestart Malaria-Ag-Pf rapid diagnostic test kits specific for *Plasmodium falciparum* histidine-rich proteins 2 (*Pf*HRP2) (Access Bio Inc., USA) and light microscopy. Results of the test was interpreted following WHO guidelines (WHO, 2016). Two clean slides were used for each sample to make both thick and thin blood films. Afterward, the slides were stained using a 10% Giemsa stain solution (Cheesbrough, 2006). Slides were examined under oil immersion without knowledge about HRP2-RDT results. Parasitemia quantification was estimated following standard protocol. Thick blood films were used for malaria diagnosis and quantification of malaria parasites if present. Thin blood films on the other hand were used for malaria specie identification; however, in cases of hyper-parasitemia, thin blood films were used for quantification.

Data Processing and Analysis

The data were inputted into Microsoft Excel, thereafter examined for any input errors, modified as necessary, and subsequently transferred to the Statistical Package for the Social Sciences (SPSS IBM, USA) version 25 for the purpose of conducting the analysis. The data were given in the form of proportions and expressed as mean values accompanied by their corresponding standard deviations. The comparison of proportions of

measurable parameters between research groups was conducted using the chi-square test of independence. An independent samples t-test evaluated mean parameter levels between research groups and genders. The study compared the average parameters of malaria-infected and malaria-free groups using a one-way ANOVA and Tukey post hoc test. The Pearson bivariate correlation test was employed to evaluate the linear association between various measured parameters. Subsequently, a stepwise linear regression model was utilized to determine the independent factors predicting malaria-associated HOMAIR and galectin-3 levels. A p-value less than 0.05 was considered significant.

Ethical Consideration

Ethical approval was obtained from the Institutional Review Board of University of Cape Coast (UCCIRB/CHAS/2022/146). Approval was obtained from the Laboratory Manager of the Tema General Hospital before the commencement of sampling and data collection. Procedures used for the study were explained to the patients and written informed consent was obtained from each patient. Also, patients were given the opportunity to withdraw their consent and discontinue participation from the study at any time. Above all, procedures employed were strictly in line with the ethical standards of the Ghana Health Service

Chapter summary

The research utilized a hospital-based cross-sectional study design to recruit non-diabetics with or without malaria and T2DM patients with or without malaria. Simple random sampling method was used to recruit one hundred and sixty (160) participants for the study. Apart from the laboratory, anthropometric and blood pressure measurements, demographic data were

collected. Sociodemographic and clinical data were collected using questionnaires. Ethical approval was appropriately sought before commencement of study. Obtained data were appropriately analysed statistically to attain the study objectives.

CHAPTER FOUR

RESULTS AND DISCUSSIONS

Introduction

The significance of this current study was to determine the effects of malaria on galectin-3 levels as well as insulin resistance in T2DM and non-diabetic controls within the Tema metropolis. This was aimed at deepening our understanding of malaria-induced insulin resistance and measures aimed at curbing the menace of metabolic syndrome in the Ghanaian context. This chapter therefore describe how the data obtained from the study was analyzed and presented (results) as a well as the significance of these results presented (discussions).

Results

Socio-demographic Characteristics of Participants

The one hundred and sixty (160) participants for the study comprised of 80 diabetes patients of which half of them had malaria and 80 patients without diabetes with 40 of them presenting with malaria.

Study participants in the group with diabetes were significantly older than non-diabetics ($P < 0.001$). Female respondents constituted 61.3% of the total respondents with diabetes. Most of the T2DM respondents were taking medication for hypertension as compared to their non-diabetic counterparts (80% versus 25%; $P < 0.001$; Table 1). In addition, Most of the non-diabetic patients engaged in regular exercise compared to diabetic group ($P <0.001$).

Table 1.0: Socio-demographic characteristics of participants using test of Independence Chi-square test

Parameters	Patients with Diabetes	Patients without Diabetes	*P Value*
Age (years)	N (%)	N (%)	
20 – 29	3 (3.8)	17 (21.3)	
30 – 39	7 (8.8)	15 (18.8)	
40 – 49	18 (22.5)	30 (37.5)	
50 – 59	23 (28.7)	15 (18.8)	< 0.001*
60 – 69	25 (31.3)	3 (3.8)	
≥ 70	4 (5)	0 (0)	
Gender			
Male	31 (38.8)	50 (62.5)	0.003*
Female	49 (61.3)	30 (37.5)	
Takes Hypertension Medication			
Yes	64 (80)	20 (25)	< 0.001*
No	16 (20)	60 (75)	
Takes Cholesterol Medication			
YesNo	2 (2.5)	7 8.8	0.087
	78 (97.5)	73 91.2	
Regular exercise			
Less oftenOften	55 (68.8)	17 (21.3)	
	25 (31.3)	62 (77.5)	< 0.001*
Very often	0 (0.0)	1 (1.3)	

Source: Field work, 2022

Anthropometric Measures of Participants

Most of the respondents (both diabetics and non-diabetics) of the study had high BMI (Table 2), however, diabetes patients were more obese than their counterparts without the condition. Participants with diabetes recorded higher mean waist and hip circumference compared to those without diabetes ($P < 0.05$). Majority of T2DM respondents presented with hypertension as compared to their non-diabetic counterpart (Table 2) even though most of the T2DM respondents were taking medications for hypertension (Table 1). Though comparable, mean weight of non-diabetics and T2DM respondents was not statistically significant ($P > 0.05$).

Table 2.0: Comparison of Mean Parameters of Anthropometric measures of Participants using Independence sample T-test

Parameters	Diabetics	Non-diabetics	*P* value
BMI (kg/m²)	29.47 ± 6.16	27.35 ± 5.78	0.026*
Height (m)	1.68 ± 0.04	1.69 ± 0.06	0.142
Weight (kg)	83.51 ± 18.57	78.19 ± 15.55	0.051
Waist circumference (cm)	91.77 ± 11.49	87.83 ± 12.59	0.040*
Hip circumference (cm)	107.34 ± 12.53	102.87 ± 13.31	0.030*
Waist-hip ratio	0.86 ± 0.06	0.86 ± 0.08	0.866
SBP (mmHg)	143.61 ± 17.92	127.76 ± 17.65	< 0.001*
DBP (mmHg)	84.54 ± 12.91	75.40 ± 13.58	< 0.001*

Source: Field work, 2022

Clinical parameters of Participants

Predominantly, higher ($P < 0.05$) proportion of the diabetes patients presented with higher levels of FBG, serum insulin and HOMAIR compared to the non-diabetic patients (Table 3). In the malaria group, none of the diabetics had normal FBG but the non-diabetics with malaria recorded higher proportion of normal FBG. Diabetes patients without malaria recorded the highest proportion of individuals with high serum insulin level, followed by non-diabetic with malaria ($P < 0.001$; table 3). Generally, T2DM respondents presented with higher proportion of high levels of HOMAIR (Table 3), with diabetes patients without malaria having the highest proportion of individuals with high HOMAIR levels, followed by diabetes with malaria, non-diabetics with malaria and their counterpart without malaria in that order ($P < 0.001$). In terms of HOMAB levels, diabetes with malaria presented with the highest proportion of low HOMAB score while diabetics without malaria presented with the highest proportion of high levels of HOMAB (Table 3). In the presence of malaria, both T2DM and non-diabetics presented with relatively higher proportion of high levels of galectin-3 as well as higher proportion of

low platelets and lymphocyte but low proportion of low neutrophil. Total WBC and HB was statistically insignificant.

Table 3.0: Clinical Data of Participants using test of Independence Chi-square test

Parameters	Non-diabetic with malaria	Non-diabetic without malaria	Diabetics with malaria	Diabetics without malaria	P Value
FBS	N (%)	N (%)	N (%)	N (%)	
(mmol/L)	23 (57.5)	15 (37.5)	0 (0.0)	1 (2.5)	
Normal	14 (35.0)	19 (47.5)	1 (2.5)	10 (25.0)	< 0.001*
Pre-diabetes (5.6-6.9)	3 (7.5)	6 (15.0)	39 (97.5)	29 (72.5)	
Hyperglycemia (≥7.0)					
Total WBC					
Low	5 (12.5)	2 (5.0)	2 (5.0)	4 (10.0)	
Normal	35 (87.5)	37 (92.5)	37 (92.5)	34 (85.0)	0.652
High	0 (0.0)	1 (2.5)	1 (2.5)	2 (5.0)	
HB					
Low	10 (25.0)	6 (15.0)	13 (32.5)	4 (10.0)	0.059
Normal	30 (750)	30 (85.0)	27 (67.5)	36 (90.0)	
Platelet					
Low	32 (80.0)	1 (2.5)	28 (70.0)	0 (0.0)	< 0.001*
Normal	9 (20.0)	39 (97.5)	12 (30.0)	40 (100)	
Neutrophil					
Low	6 (15.0)	14 (35.0)	1 (2.5)	8 (20.0)	
Normal	34 (85.0)	25 (62.5)	38 (95.0)	30 (75.0)	0.01*
High	0 (0.0)	1 (2.5)	1 (2.5)	2 (5.0)	
Lymphocyte					
Low	24 (60.0)	1 (2.5)	19 (47.5)	2 (5.0)	
Normal	16 (40.0)	39 (97.5)	18 (45.0)	37 (92.5)	< 0.001*
High	0 (0.0)	0 (0.0)	3 (7.5)	1 (2.5)	
Insulin					
Low	11 (27.5)	11 (27.5)	14 (35.0)	12 (30.0) 2	
Normal	22 (55.0)	27 (67.5)	24 (60.0)	(5.0)	< 0.001*
High	7 (17.5)	2 (5.0)	2 (5.0)	26 (65.0)	
HOMAIR					
Low	21 (52.5)	20 (50.0)	13 (32.5)	4 (10.0)	
Normal	2 (5.0)	6 (15.0)	2 (5.0)	1 (2.5)	< 0.001*
High	17 (42.5)	14 (25.0)	25 (62.5)	35 (87.5)	
HOMAB					
Low	8 (20.0)	10 (25.0)	34 (85.0)	7 (17.5)	
Normal	11 (27.5)	9 (22.5)	4 (10.0)	6 (15.0)	< 0.001*
High	21 (52.5)	21 (52.5)	2 (5.0)	27 (67.5)	
Galectin-3					
Normal	27 (67.5)	39 (97.5)	28 (70.0)	37 (92.5)	< 0.001*
High	13 (32.5)	1 (2.5)	12 (30.0)	3 (7.5)	

Fasting Lipid Profile of Respondents

Malaria patients presented with higher proportion of low and optimal levels of total cholesterol ($P < 0.001$) as well as higher proportion of high

levels of triglycerides as compared to their counterparts without malaria infection (Table 4). In addition, respondents with malaria presented with higher ($P < 0.001$) proportion of optimal and near optimal levels of LDL cholesterol compared to their counterparts without malaria. In terms of HDL cholesterol, respondents malaria presented with a very high ($P < 0.001$) proportion of low levels of HDL compared to their counterparts without malaria.

Table 4.0: Fasting Lipid Profile of Respondents using test of Independence Chi-square test

Parameters	Non-diabetic with malaria	Non-diabetic without malaria	Diabetics with malaria	Diabetics without malaria	P value
Cholesterol	N (%)	N (%)	N (%)	N (%)	
Low	19 (47.5)	4 (10.0)	13 (32.5)	5 (12.5)	
Desirable	18 (45.0)	10 (25.0)	15 (37.5)	15 (37.5)	< 0.001*
Borderline high	2 (5.0)	15 (37.5)	7 (17.5)	12 (30.0)	
High	1 (2.5)	11 (27.5)	5 (12.5)	8 (20.0)	
HDL					
Low	34 (85.0)	11 (27.5)	30 (75.0)	12 (30.0)	
Normal	6 (15.0)	13 (32.5)	10 (25.0)	18 (45.0)	< 0.001*
High	0 (0.0)	16 (40.0)	0 (0.0)	10 (25.0)	
LDL					
Optimal	24 (60.0)	5 (12.5)	20 (50.0)	8 (20.0)	
Near optimal	10 (25.0)	9 (22.5)	9 (22.5)	12 (30.0)	
Borderline high	5 (12.5)	16 (40.0)	5 (12.5)	11 (27.5)	< 0.001*
High	1 (2.5)	8 (20.0)	6 (15.0)	4 (10.0)	
Very high	0 (0.0)	2 (5.0)	0 (0.0)	5 (12.5)	
Triglycerides					
Normal	24 (60.0)	36 (90.0)	16 (40.0)	29 (72.5)	
Borderline high	3 (7.5)	2 (5.0)	11 (27.5)	7 (17.5)	< 0.001*
High	13 (32.5)	2 (5.0)	13 (32.5)	4 (10.0)	

Source: Field work, 2022

Comparison of mean levels of measured parameters in different densities of malaria parasitemia in respondents with malaria.

Mean levels of selected measured parameters in different densities of malaria parasitemia in respondents with malaria showed a statistically significant difference ($P < 0.05$) in mean levels of platelet, cholesterol, LDL and triglyceride in T2DM respondents (Table 5). In non-diabetics with

malaria, statistical difference was only observed in levels of platelet (P < 0.05).

Table 5.0: Mean levels of selected parameters in different densities of malaria parasitemia in respondents with malaria using oneway ANOVA

Parameters	Low	Moderate	High	F-value	P-value
NON-DIABETICS					
Cholesterol	4.95 ± 1.52	3.96 ± 0.93	3.82 ± 0.60	1.249	0.299
HDL	0.86 ± 0.04	0.67 ± 0.40	0.57 ± 0.38	0.468	0.630
LDL	3.70 ± 1.41	2.37 ± 0.72	2.44 ± 0.48	3.233	0.051
TRIG	0.81 ± 0.03	2.05 ± 1.91	2.10 ± 1.67	0.439	0.648
Platelet	178.00 ± 98.99	120.90 ± 48.48	81.00 ± 43.36	3.430	0.043*
Insulin	8.50 ± 6.36	14.34 ± 15.78	26.91 ± 37.17	1.206	0.311
HOMAIR	2.16 ± 1.69	4.17 ± 5.04	7.33 ± 10.41	0.909	0.412
HOMAB	77.55 ± 50.13	128.82 ± 105.70	215.09 ± 272.35	1.207	0.311
Galectin-3	15.95 ± 3.76	12.33 ± 5.65	14.15 ± 6.05	0.613	0.547
T2DM					
Cholesterol	5.34 ± 1.20	4.41 ± 0.99	3.60 ± 0.34	2.467	0.009*
HDL	1.03 ± 0.31	0.93 ± 0.56	0.60 ± 0.29	1.304	0.284
LDL	3.40 ± 0.87	2.67 ± 1.00	1.38 ± 0.37	7.658	0.002*
TRIG	1.98 ± 1.02	1.77 ± 0.66	3.52 ± 0.57	11.643	< 0.001*
Platelet	145.00 ± 47.30	148.77 ± 45.65	83.60 ± 39.75	4.395	0.019*
Insulin	6.56 ± 3.94	8.50 ± 7.38	7.80 ± 5.50	0.293	0.748
HOMAIR	3.14 ± 1.96	4.50 ± 4.00	5.08 ± 4.77	0.572	0.569
HOMAB	21.87 ± 19.10	27.47 ± 37.03	17.18 ±13.62	0.269	0.765
Galectin-3	16.49 ± 5.03	12.50 ± 4.83	15.37 ± 5.40	2.483	0.097

Figures represent mean ± standard deviation; HDL; high density lipoprotein (mmol/L), LDL: low density lipoprotein (mmol/L), TRIG: triglycerides (mmol/L), ∗significant *p* value.

Source: Field work, 2022

Tukey's post hoc HSD test showed a significant change in mean levels of cholesterol, LDL and triglycerides at low and high malaria parasitemia. In addition, between moderate and high malaria parasitemia, Tukey's post hoc HSD test showed a significant change in mean levels of LDL, triglycerides and platelet. However, no significant change in mean levels of parameters was observe at low and moderate malaria parasitemia.

Table 6.0: Comparison of mean levels of parameters among participants using one-way ANOVA

Parameters	Non-diabetic with malaria	Non-diabetic without malaria	Diabetics with malaria	Diabetics without malaria	F value	P value
Age	37.45 ± 11.85	44.15 ± 9.37	53.13 ± 12.44	53.95 ± 11.86	18.852	< 0.001*
BMI	27.20 ± 6.03	27.50 ± 5.60	28.85 ± 5.29	30.09 ± 6.94	1.975	0.120
Height	1.70 ± 0.06	1.68 ± 0.05	1.68 ± 0.04	1.69 ± 0.04	2.476	0.064
Weight	78.96 ± 17.31	77.43 ± 13.75	81.54 ± 16.46	85.47 ± 20.29	1.690	0.171
WC	88.98 ± 14.51	86.69 ± 10.37	91.44 ± 12.55	92.08 ± 10.48	1.669	0.176
HC	103.20 ± 15.16	102.57 ± 11.34	107.52 ± 12.70	107.19 ± 12.51	1.600	0.192
WHR	0.87 ± 0.09	0.85 ± 0.08	0.95 ± 0.06	0.87 ± 0.07	0.970	0.408
SBP	127.63 ± 17.00	127.90 ± 18.49	141.88 ± 18.55	145.35 ± 17.32	10.764	< 0.001*
DBP	75.08 ± 15.38	75.73 ± 11.70	86.85 ± 14.05	82.23 ± 11.38	7.189	< 0.001*
FBG	5.66 ± 1.01	5.93 ± 1.22	12.59 ± 3.46	9.96 ± 3.94	59.441	< 0.001*
Insulin	16.25 ± 20.77	10.64 ± 9.56	7.98 ± 6.47	36.78 ± 24.61	23.251	< 0.001*
HOMAIR	4.62 ± 6.17	3.14 ± 4.04	4.27 ± 3.71	17.77 ± 15.11	25.785	< 0.001*
HOMAB	141.36 ±146.21	88.83 ± 73.23	24.92 ± 31.42	137.0 ± 100.41	12.488	< 0.001*
Galectin-3	12.66 ± 5.21	7.72 ± 3.57	13.76 ± 5.12	10.36 ± 4.77	12.871	< 0.001*
Total WBC	4.99 ± 1.55	5.67 ± 1.97	5.66 ± 1.81	6.52 ± 2.19	4.365	0.006*
Haemoglobin	12.19 ± 1.76	13.06 ± 1.63	12.52 ± 1.89	13.29 ± 1.48	1.665	0.179
Neutrophil	3.34 ± 1.46	2.82 ± 1.78	3.97 ± 1.38	3.27 ± 1.87	3.374	0.020*
Lymphocytes	1.06 ± 0.66	2.15 ± 0.70	1.28 ± 0.99	2.49 ± 0.87	28.133	< 0.001*
Monocytes	0.52 ± 0.30	0.50 ± 0.21	0.45 ± 0.32	0.57 ± 0.25	1.365	0.255
Eosinophils	0.04 ± 0.07	0.19 ± 0.17	0.05 ± 0.08	0.15 ± 0.13	15.448	< 0.001*
Basophils	0.03 ± 0.06	0.08 ± 0.12	0.03 ± 0.03	0.06 ± 0.11	2.861	0.039*
Platelets	116.78 ± 52.77	241.02 ± 54.29	139.78±49.21	254.58 ± 46.94	75.414	< 0.001*
Cholesterol	3.99 ± 0.91	5.53 ± 1.17	4.52 ± 1.10	5.29 ± 1.36	15.423	< 0.001*
LDL	2.45 ± 0.76	3.63 ± 0.90	2.67 ± 1.07	3.40 ± 1.12	13.522	< 0.001*
HDL	0.66 ± 0.38	1.36 ± 0.36	0.91 ± 0.50	1.30 ± 0.34	27.252	< 0.001*
Triglycerides	2.0 ± 1.82	1.02 ± 0.54	2.03 ± 0.93	1.34 ± 0.71	8.078	< 0.001*

Figures represent mean ± standard deviation; BMI: body mass index(kg/m²); FBG: fasting blood glucose(mmol/L); SBP: systolic blood pressure(mmHg); DBP: diastolic blood pressure(mmHg); WBC: white blood cell; HB: haemoglobin(g/dL); HOMAIR: homeostatic model assessment of insulin resistance; HOMAB: homeostatic model assessment of beta cell secretion; LDL: low density lipoprotein(mmol/L), HDL: high density lipoprotein(mmol/L), ∗significant p value.

Source: Field work, 2022

Comparison of means of measured parameters with one-way ANOVA

Analysis of variance showed that the mean values of numerous measured parameters were significantly different ($P < 0.05$) between groups with and without malaria, except for BMI, height, weight, waist-to-hip ratio, hemoglobin, and monocytes, as presented in Table 6.

Parameter mean values in diabetic respondents with and without malaria infection were compared using Tukey's HSD

Tukey's post hoc test showed that, diabetics with malaria maintained higher mean levels of FBG ($P < 0.001$) despite lower mean values of serum insulin and HOMAIR ($P < 0.001$) as compared to their counterparts without malaria as shown in Table 7 below. In addition, diabetics with malaria had lower mean levels of HOMAB ($P < 0.05$) platelets, cholesterol, LDL, and HDL but higher mean levels of triglycerides and galectin-3 compared to those without malaria (Table 7).

Table 7.0: Mean comparison of parameters in T2DM respondents with and without malaria infection using Tukey's HSD

Parameters	Diabetics		P value
	With malaria	Without malaria	
Age	53.13 ± 12.44	53.95 ± 11.86	0.988
SBP	141.88 ± 18.55	145.35 ± 17.32	0.820
DBP	86.85 ± 14.05	82.23 ± 11.38	0.403
FBG	12.59 ± 3.46	9.96 ± 3.94	< 0.001*
Insulin	7.98 ± 6.47	36.78 ± 24.61	< 0.001*
HOMAIR	4.27 ± 3.71	17.77 ± 15.11	< 0.001*
HOMAB	24.92 ± 31.42	137.0 ± 100.41	< 0.001*
Galectin-3	13.76 ± 5.12	10.36 ± 4.77	0.008*
Total WBC	5.66 ± 1.81	6.52 ± 2.19	0.186
Neutrophil	3.97 ± 1.38	3.27 ± 1.87	0.227
Lymphocytes	1.28 ± 0.99	2.49 ± 0.87	< 0.001*
Eosinophils	0.05 ± 0.08	0.15 ± 0.13	0.001*
Platelets	139.78±49.21	254.58 ± 46.94	< 0.001*
Cholesterol	4.52 ± 1.10	5.29 ± 1.36	0.015*
LDL	2.67 ± 1.07	3.40 ± 1.12	0.005*
HDL	0.91 ± 0.50	1.30 ± 0.34	< 0.001*
Triglycerides	2.03 ± 0.93	1.34 ± 0.71	< 0.001*

Figures represent mean ± standard deviation; FBG: fasting blood glucose (mmol/L); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); WBC: white blood cell; HOMAIR: homeostatic model assessment of insulin resistance; HOMAB: homeostatic model assessment of beta cell secretion; LDL: low density lipoprotein (mmol/L); HDL; high density lipoprotein (mmol/L), *significant *p* value.

Source: Field work, 2022

Mean values of parameters in malaria infected respondents with and without T2DM were compared using Tukey's HSD

As showed in table 8 below, Tukey's post hoc test indicated that malaria patients with diabetes were older with higher mean levels of SBP, DBP, FBG, HDL, but lower levels of HOMAB ($P < 0.05$) as compared to their counterparts without diabetes. Mean values of some estimated parameters were comparable ($P > 0.05$) among respondents (table 8.0).

Table 8.0: Mean comparison of parameters in malaria infected respondents with and without T2DM using Tukey's HSD

Parameters	Malaria infection		P value
	Patients with diabetes	Patients without diabetes	
Age	53.13 ± 12.44	37.45 ± 11.85	< 0.001*
SBP	141.88 ± 18.55	127.63 ± 17.00	0.003*
DBP	86.85 ± 14.05	75.08 ± 15.38	0.001*
FBG	12.59 ± 3.46	5.66 ± 1.01	< 0.001*
Insulin	7.98 ± 6.47	16.25 ± 20.77	0.138
HOMAIR	4.27 ± 3.71	4.62 ± 6.17	0.998
HOMAB	24.92 ± 31.42	141.36 ±146.21	< 0.001*
Galectin 3	13.76 ± 5.12	12.66 ± 5.21	0.721
Total WBC	5.66 ± 1.81	4.99 ± 1.55	0.388
Neutrophil	3.97 ± 1.38	3.34 ± 1.46	0.309
Lymphocytes	1.28 ± 0.99	1.06 ± 0.66	0.631
Eosinophils	0.05 ± 0.08	0.04 ± 0.07	0.997
Platelets	139.78±49.21	116.78 ± 52.77	0.184
Cholesterol	4.52 ± 1.10	3.99 ± 0.91	0.169
LDL	2.67 ± 1.07	2.45 ± 0.76	0.736
HDL	0.91 ± 0.50	0.66 ± 0.38	0.029*
Triglycerides	2.03 ± 0.93	2.0 ± 1.82	0.999

Figures represent mean ± standard deviation; FBG: fasting blood glucose (mmol/L); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); WBC: white blood cell; HOMAIR: homeostatic model assessment of insulin resistance; HOMAB: homeostatic model assessment of beta cell secretion; LDL: low density lipoprotein (mmol/L); HDL; high density lipoprotein (mmol/L), ∗significant *p* value.

Source: Field work, 2022

Mean comparison of parameters in participants without malaria infection using Tukey's HSD

As shown in table 9, Tukey's post hoc test indicated that diabetes patients without malaria were older with higher mean levels of SBP, FBS, serum insulin and HOMAIR (all $P < 0.001$) as compared to non-diabetics without malaria infection. Mean values of some estimated parameters were comparable ($P > 0.05$) among respondents (table 9.0).

Table 9.0: Mean comparison of parameters in both T2DM and non-diabetic respondents without malaria infection using Tukey's HSD

Parameters	Without malaria infection		P value
	Diabetics	Non-diabetics	
Age	53.95 ± 11.86	44.15 ± 9.37	0.001*
SBP	145.35 ± 17.32	127.90 ± 18.49	< 0.001*
DBP	82.23 ± 11.38	75.73 ± 11.70	0.129
FBG	9.96 ± 3.94	5.93 ± 1.22	< 0.001*
Insulin	36.78 ± 24.61	10.64 ± 9.56	< 0.001*
HOMAIR	17.77 ± 15.11	3.14 ± 4.04	< 0.001*
HOMAB	137.0 ± 100.41	88.83 ± 73.23	0.123
Galectin-3	10.36 ± 4.77	7.72 ± 3.57	0.062
Total WBC	6.52 ± 2.19	5.67 ± 1.97	0.191
Neutrophil	3.27 ± 1.87	2.82 ± 1.78	0.366
Lymphocytes	2.49 ± 0.87	2.15 ± 0.70	0.244
Eosinophils	0.15 ± 0.13	0.19 ± 0.17	0.504
Platelets	254.58 ± 46.94	241.02 ± 54.29	0.633
Cholesterol	5.29 ± 1.36	5.53 ± 1.17	0.784
LDL	3.40 ± 1.12	3.63 ± 0.90	0.731
HDL	1.30 ± 0.34	1.36 ± 0.36	0.906
Triglycerides	1.34 ± 0.71	1.02 ± 0.54	0.558

Figures represent mean ± standard deviation; FBG: fasting blood glucose (mmol/L); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); WBC: white blood cell; HOMAIR: homeostatic model assessment of insulin resistance; HOMAB: homeostatic model assessment of beta cell secretion; LDL: low density lipoprotein (mmol/L); HDL; high density lipoprotein (mmol/L), ⁎significant *p* value.

Source: Field work, 2022

Mean comparison of parameters in non-diabetic respondents using Tukey's HSD

Tukey's post hoc test also indicated that non-diabetics with malaria were younger with higher mean values of galectin-3 and triglycerides ($P < 0.05$) but lower mean levels of platelets, cholesterol, HDL and LDL (all $P < 0.001$) compared to their counterparts without malaria as shown in table 10.

Table 10.0: Mean comparison of parameters in non-diabetics respondents who have malaria and non-diabetics respondents without malaria using Tukey's HSD

Parameters	Non-diabetics		P value
	Without malaria	With malaria	
Age	44.15 ± 9.37	37.45 ± 11.85	< 0.001*
SBP	127.90 ± 18.49	127.63 ± 17.00	1.00
DBP	75.73 ± 11.70	75.08 ± 15.38	0.996
FBG	5.93 ± 1.22	5.66 ± 1.01	0.971
Insulin	10.64 ± 9.56	16.25 ± 20.77	0.460
HOMAIR	3.14 ± 4.04	4.62 ± 6.17	0.867
HOMAB	88.83 ± 73.23	141.36 ±146.21	0.078
Galectin-3	7.72 ± 3.57	12.66 ± 5.21	< 0.001*
Total WBC	5.67 ± 1.97	4.99 ± 1.55	0.380
Haemoglobin	13.06 ± 1.63	12.19 ± 1.76	0.987
Neutrophil	2.82 ± 1.78	3.34 ± 1.46	0.487
Lymphocytes	2.15 ± 0.70	1.06 ± 0.66	< 0.001*
Eosinophils	0.19 ± 0.17	0.04 ± 0.07	< 0.001*
Platelets	241.02 ± 54.29	116.78 ± 52.77	< 0.001*
Cholesterol	5.53 ± 1.17	3.99 ± 0.91	< 0.001*
LDL	3.63 ± 0.90	2.45 ± 0.76	< 0.001*
HDL	1.36 ± 0.36	0.66 ± 0.38	< 0.001*
Triglycerides	1.02 ± 0.54	2.0 ± 1.82	0.001*

Figures represent mean ± standard deviation; FBG: fasting blood glucose (mmol/L); SBP: systolic blood pressure (mmHg); DBP: diastolic blood pressure (mmHg); WBC: white blood cell; HOMAIR: homeostatic model assessment of insulin resistance; HOMAB: homeostatic model assessment of beta cell secretion; LDL: low density lipoprotein (mmol/L); HDL; high density lipoprotein (mmol/L), ∗significant *p* value.

Source: Field work, 2022

Table 11.0: Pearson's Bivariate Correlation of measured parameters among non-diabetics with malaria

	AGE	BMI	WC	HC	WHR	FBG	SBP	DBP	WBC	HB	PLT	NEU	LYM	MON	EOS	BAS	MP	CHO	HDL	LDL	TG	INSU	HMIR	HMB	GAL3
AGE	1																								
BMI	-0.07	1																							
WC	0.09	0.90	1																						
HC	0.05	0.81	0.80	1																					
WHR	0.06	0.26	0.46	-0.16	1																				
FBG	0.41	0.15	0.16	0.14	0.04	1																			
SBP	0.32	0.12	0.13	0.08	0.11	0.13	1																		
DBP	0.30	0.20	0.20	0.15	0.09	0.10	0.86	1																	
WBC	0.03	0.28	0.32	0.33	0.05	-0.02	-0.16	-0.06	1																
HB	-0.23	0.05	0.03	-0.24	0.35	-0.02	0.12	0.23	-0.11	1															
PLT	-0.19	0.07	0.14	0.05	0.19	-0.30	0.04	-0.01	0.24	-0.10	1														
NEU	-0.07	0.38	0.37	0.46	-0.04	0.09	-0.12	-0.08	0.83	-0.10	-0.05	1													
LYM	0.12	-0.09	-0.02	-0.12	-0.12	-0.15	-0.07	0.03	0.36	-0.08	0.53	-0.20	1												
MON	0.24	-0.28	-0.18	-0.28	0.12	-0.16	-0.11	-0.01	0.48	0.05	-0.01	0.24	0.23	1											
EOS	0.07	0.22	0.26	0.12	0.23	-0.09	0.17	0.34	0.09	0.09	0.35	-0.15	0.32	0.071	1										
BAS	0.08	-0.03	0.12	-0.11	0.44	0.14	-0.02	-0.09	0.12	0.02	0.04	0.06	0.11	0.072	0.14	1									
MP	-0.36	0.11	0.01	0.08	-0.09	0.02	-0.08	-0.09	-0.27	0.10	-0.46	-0.05	-0.33	-0.28	-0.28	-0.15	1								
CHO	-0.03	0.24	0.23	0.10	0.29	0.27	0.09	-0.02	0.20	-0.14	0.18	0.26	-0.06	-0.10	-0.06	0.41	-0.11	1							
HDL	-0.37	-0.03	-0.11	-0.10	-0.02	-0.07	0.04	-0.07	-0.13	0.18	0.59	0.02	-0.31	-0.09	-0.16	-0.08	-0.19	0.35	1						
LDL	-0.16	0.21	0.17	0.14	0.12	0.16	0.10	0.03	0.09	-0.01	0.44	0.23	-0.20	-0.19	-0.07	-0.08	-0.01	0.797	0.48	1					
TG	0.25	0.22	0.25	0.08	0.30	0.24	-0.06	-0.04	0.26	-0.23	-0.61	0.11	-0.36	0.03	-0.10	0.58	0.02	0.19	-0.58	0.33	1				
INSU	0.10	0.19	0.11	0.22	-0.18	0.41	-0.01	-0.01	-0.22	-0.04	-0.44	-0.08	-0.15	-0.37	-0.21	-0.17	0.43	0.09	-0.25	0.12	0.17	1			
HMIR	0.14	0.19	0.12	0.22	-0.17	0.47	-0.04	-0.02	-0.18	-0.01	-0.44	-0.05	-0.16	-0.30	-0.18	-0.15	0.39	0.11	-0.19	0.11	0.18	0.973	1		
HMB	-0.07	0.11	0.01	0.13	-0.23	0.15	-0.06	-0.07	-0.29	-0.08	-0.33	-0.16	-0.13	-0.38	-0.24	-0.20	0.42	0.06	-0.14	0.14	0.04	0.923	0.844	1	
GAL3	-0.10	0.16	0.16	0.30	-0.15	-0.10	0.11	-0.07	0.20	-0.22	0.16	0.15	0.14	0.07	-0.25	0.01	0.12	0.29	0.13	0.27	-0.08	0.01	-0.02	0.05	1

WBC stands for white blood cell; WC stands for waist circumference; HB stands for hemoglobin; HC stands for hip circumference, PLT stands for platelets; WHR stands for waist-hip ratio; NUE stands for neutrophils; BMI denote body mass index; LYM stands for lymphocytes; MON stands for monocytes; EOS stands for eosinophils; BAS stands for basophils; MP stands for malaria parasitemia; HMIR signifies Homeostatic Model Assessment of Insulin Resistance; CHO stands for Cholesterol; HMB signifies Homeostatic Model Assessment of Beta Cell Secretion; HDL stands for high density lipoprotein; GAL3 stands for Galectin-3, LDL refers to low density lipoprotein; INSU stands for Insulin while TG stands for triglyceride. The coloured portion yellow signifies the correlation is considered significant at the 0.01 threshold. The coloured portion pink signifies the correlation is considered significant at the 0.05 threshold. The coloured portion blue signifies correlation is not considered significantly significant.

Source: Field work, 2022.

Pearson's Bivariate Correlation of measured parameters among non-diabetics with malaria

Malaria-associated HOMAIR correlated positively as well as strongly; with insulin (r = 0.973; P < 0.001) and HOMAB (r = 0.844; P < 0.001) in non-diabetics as shown in Table 10. Also, malaria-associated HOMAB in non-diabetics correlated positively as well as strongly (r = 0.923, P < 0.001) with serum insulin. Malaria parasitemia correlated positively and moderately with malaria- associated insulin (r = 0.434; P = 0.005), HOMAB (r = 0.422; P = 0.007) and HOMAIR; (r = 0.387; P = 0.014) but negatively with platelet (r = -0.459, P < 0.001). Surprisingly, malaria-associated levels of galectin-3 in non-diabetics did not yield a significant correlation between any of the measured parameters as shown in table 11 above.

Predictors of malaria associated HOMAIR and cholesterol in non-diabetics using regression models

Applying a stepwise linear regression model in malaria patients without diabetes, HOMAB as well as insulin were considered significant (R^2 = 0. 973; adjusted R^2 = 0.947; P < 0.001) independent prognosticators of HOMAIR, jointly accounting for about 95% of the detected changes in HOMAIR levels. Also, LDL, triglycerides and HDL were significant (R^2 = 0.926, Adjusted R^2 = 0.919 P < 0.001,) predictors of total cholesterol and accounted for about 92% of the observed variation in total cholesterol levels.

Pearson's Correlation of measured parameters among T2DM

In T2DM patients with malaria, galectin-3 correlated negatively and moderately; with HOMAB (r = -0.391, P < 0.013) and monocyte (r = -0.347, P < 0.028) but positively and moderately with platelet (r = 0.441, P = 0.004) levels as shown in table 12 below.

Table 12.0: Pearson's Bivariate Correlation of measured parameters among T2DM with malaria

	AGE	BMI	WC	HC	WHR	FBG	SBP	DBP	WBC	HB	PLT	NEU	LYM	MON	EOS	BAS	MP	CHO	HDL	LDL	TG	INSU	HMIR	HMB	GAL3
AGE	1																								
BMI	-0.24	1																							
WC	-0.24	0.87	1																						
HC	-0.24	0.73	0.86	1																					
WHR	-0.02	0.52	0.52	0.05	1																				
FBG	0.19	0.25	0.21	0.08	0.30	1																			
SBP	0.03	0.10	0.03	-0.02	0.05	0.12	1																		
DBP	-0.03	0.15	0.06	0.01	0.03	0.06	0.82	1																	
WBC	0.22	-0.07	0.03	0.01	0.10	-0.03	-0.04	-0.01	1																
HB	0.03	0.16	0.18	-0.18	0.60	0.16	-0.09	-0.11	0.13	1															
PLT	-0.07	0.08	0.18	0.04	0.25	-0.02	0.07	-0.01	0.06	0.39	1														
NEU	0.19	-0.12	-0.17	-0.16	-0.01	0.04	-0.15	-0.19	0.81	0.01	-0.19	1													
LYM	0.03	0.04	0.14	0.17	0.02	-0.16	-0.07	0.06	0.47	0.08	0.15	0.12	1												
MON	-0.01	0.12	0.25	0.13	0.30	-0.17	0.15	0.13	0.54	0.39	0.39	0.07	0.42	1											
EOS	-0.19	0.26	0.37	0.31	0.20	0.02	-0.07	-0.05	0.09	0.35	0.28	-0.05	0.03	0.29	1										
BAS	-0.15	0.58	0.49	0.35	0.29	0.06	-0.16	-0.05	0.18	0.34	0.02	0.11	0.08	0.21	0.45	1									
MP	-0.11	0.22	0.22	0.24	0.02	0.29	0.05	0.04	0.07	-0.36	-0.48	0.13	-0.08	-0.09	-0.01	0.22	1								
CHO	-0.13	-0.11	-0.04	0.04	-0.20	-0.24	0.10	0.27	-0.06	0.12	0.21	-0.26	0.25	0.24	0.24	-0.11	-0.39	1							
HDL	-0.06	-0.17	-0.09	0.06	-0.32	-0.37	-0.08	0.04	-0.15	0.14	0.16	-0.26	0.23	0.10	0.22	-0.12	-0.54	0.86	1						
LDL	-0.13	-0.10	-0.14	-0.29	0.18	0.01	0.28	0.40	0.03	0.12	0.46	-0.14	0.05	0.27	0.10	-0.18	-0.28	0.43	0.07	1					
TG	-0.01	0.28	0.30	0.31	0.10	0.30	0.14	0.17	0.20	-0.17	0.41	0.16	0.04	0.07	-0.06	0.25	0.67	-0.09	-0.40	-0.22	1				
INSU	-0.10	-0.11	0.05	0.03	0.06	-0.20	0.13	-0.03	-0.10	-0.08	0.08	0.14	-014	0.04	0.21	-0.04	0.14	-0.10	-0.04	-0.10	-0.04	1			
HMIR	0.02	-0.01	0.16	0.13	0.11	0.20	0.23	0.04	0.09	-0.11	-0.02	0.17	-0.16	-0.07	0.12	-0.05	0.30	-0.20	-0.18	-0.20	0.16	0.875	1		
HMB	-0.21	-0.17	-0.04	-0.10	0.11	-0.43	0.03	-0.06	0.11	0.02	0.19	0.10	-0.09	0.19	0.31	0.02	-0.03	-0.01	0.02	0.14	-0.25	0.861	0.54	1	
GAL3	0.22	-0.04	0.10	0.25	-0.23	0.06	-0.30	-0.09	0.07	-0.35	-0.14	-0.07	0.44	-0.14	-0.22	-0.04	0.12	-0.02	-0.03	-0.23	0.31	-0.24	-0.11	-0.39	1

WBC stands for white blood cell; WC stands for waist circumference; HB stands for hemoglobin; HC stands for hip circumference, PLT stands for platelets; WHR stands for waist-hip ratio; NUE stands for neutrophils; BMI denote body mass index; LYM stands for lymphocytes; MON stands for monocytes; EOS stands for eosinophils; BAS stands for basophils; MP stands for malaria parasitemia; HMIR signifies Homeostatic Model Assessment of Insulin Resistance; CHO stands for Cholesterol; HMB signifies Homeostatic Model Assessment of Beta Cell Secretion; HDL stands for high density lipoprotein; GAL3 stands for Galectin-3, LDL refers to low density lipoprotein; INSU stands for Insulin while TG stands for triglyceride. The coloured portion yellow signifies the correlation is considered significant at the 0.01 threshold. The coloured portion pink signifies the correlation is considered significant at the 0.05 threshold. The coloured portion blue signifies correlation is not considered significantly significant.

Source: Field work, 2022.

HOMAIR correlated positively and strongly with insulin (r = 0.875, P < 0.001) and HOMAB (r = 0.861, P < 0.001). Triglyceride correlated negatively with WBC (r = -0.412; P < 0.001) and BMI (r = -0.396; P < 0.05). Malaria parasitemia correlated moderately and positively with triglyceride (r = 0.673; P < 0.001) but negatively with haemoglobin (r = -0.362; P < 0.05), platelet (r = -0.481; P < 0.001), total cholesterol (r = -0.388; P < 0.05) and LDL (r = -0.542; P < 0.001). Also, total cholesterol correlated positively as well as strongly with HDL but moderately with LDL and negatively and moderately with triglycerides.

Predictors of malaria associated HOMAIR, and galectin-3 in T2DM using regression models

Applying a stepwise linear regression model, among T2DM, HOMAB as well as insulin were considered significant (R^2 = 0.939; adjusted R^2 = 0.935; P < 0.001) independent prognosticators of HOMAIR, jointly accounting for more than 93% of the detected changes in HOMAIR levels.

Also, HOMAB, lymphocytes and haemoglobin were significant (R^2 = 0.459; adjusted R^2 = 0.414; P < 0.001) predictors gelactin-3 but the model could account for just 41.4% of the observed variation in gelactin-3 levels. Expectedly, LDL, HDL and triglycerides jointly predicted total cholesterol levels (R^2 = 0.999, Adjusted R^2 = 0.999; P < 0.001) with the model explaining almost the entire variation in the observed cholesterol levels in this group of participants.

Discussion

Malaria and diabetes are two of the most pressing health challenges globally, with significant impacts on human health and economic development (*IDF*, 2021; WHO, 2020). Despite sub-Saharan Africa carrying the global malaria burden (World Health Organization, 2020), it has been projected that by 2045, the occurence of individuals with T2DM will increase by 134% within the sub-Saharan Africa region (*IDF*, 2021). Although malaria and diabetes are distinct conditions, recent studies have suggested a potential interaction between malaria and diabetes (Danquah *et al.*, 2010; Acquah *et al*., 2014; Vos *et al.*, 2017). This study therefore investigated effects of malaria on galectin-3 as well as insulin resistance in diabetics and non-diabetic respondents within the Tema metropolis.

Not surprisingly, T2DM respondents presented with higher mean age and is because T2DM incidence is widely known to increase with age (Danquah *et al.*, 2010; Geiss *et al.*, 2006; Gonzalez *et al.*, 2009; IDF, 2021; Zhang *et al.*, 2017). In addition, T2DM respondents recruited for the study were know T2DM patients who have been receiving medication for the condition, some of which have lived with the condition over a decade.

T2DM respondents recorded higher BMI than the non-diabetics in this current study as previously documented (Acquah *et al.*, 2014; Chen *et al.*, 2018; Medhi *et al.*, 2021; Whitmore, 2010). This is because T2DM respondent recorded higher mean weight, as well as higher waist and hip circumference. Inadequate regular exercise on the parts of T2DM respondents could in part contribute to the higher BMI. According to Whitmore et al. (2010), virtually 90% of individuals with T2DM are overweight. In addition, waist

circumference of the current study is in agreement with previous studies that examined waist circumference in T2DM and non-diabetics (Abe *et al.,* 2021; Bai *et al.*, 2022; Kaur, Kaur *et al.*,2020) establishing that T2DM have higher waist circumference than non-diabetics especially in men (Kaur *et al.*, 2020). This could be ascribed to increased central obesity resulting from inadequate regular exercise, dietary factors, and genetic predispositions. A significantly higher mean levels of hip circumference was observed among T2DM in the current study as compared to non-diabetes (107.34 ± 12.53 to 102.87 ± 13.31 respectively, P = 0.030), however, a Shanghai-based study (Conway *et al*., 2011) reported that higher hip circumference for a given waist circumference and BMI is associated with a reduced risk of T2DM. The variation between this study and Conway *et al.*, may possibly be attributed to variation in respondents demography, sample size and study design. Whereas only 160 adults aged 20 years and above were investigated in the current study, Conway *et al*. investigated 56,100 men and 68,273 women, aged 40 to 74. In addition, majority of the diabetic respondent were female and generally, females have a higher hip circumference than males (Eghan *et al.*, 2019; WHO., 2011).

In this study both systolic and diastolic blood pressures were significantly elevated in diabetics as expected and has been previously reported in other studies (Bakris *et al.*, 2000; Banegas *et al.*, 2012; I. H. de Boer *et al.*, 2017; Hanefeld *et al.*, 1996). In the current study, inadequate regular exercise and high BMI among T2DM could partly account for the hypertension observe among T2DM respondent. Nevertheless, hypertension as a metabolic syndrome is on a rise in Ghana (Osei-Yeboah *et al.*, 2017) and the current study supports the previous finding in that even non-diabetic

respondents presented with elevated systolic blood pressure (table 2) and despite most diabetics taking medication for hypertension, this condition still persists. The increase in blood pressure could be ascribed to urban lifestyle and socioeconomic status of respondents.

In both T2DM and non-diabetics with malaria, thrombocytopenia was the predominant haematological abnormality noted. Increasing malaria parasitemia in both groups resulted in decreasing levels of platelets. The noticeable decrease could be attributed to hyper-reactive splenomegaly (Sirak *et al.,* 2016), splenic pooling (Karanikas *et al.,* 2004), immunologically-mediated reduction in platelet count (Tyagi & Biswas, 1999), and increased consumption of the platelets in the periphery (Horstmann & Dietrich, 1985) Mature parasitized red blood cells and cytokines have the potential to trigger the coagulation process. In malaria, various factors such as decreased levels of anti-thrombin III, higher concentrations of fibrin degradation products, and enhanced splenic removal of platelets collectively contribute to the development of coagulation disorders and low platelet count (Weatherall *et al.,* 2002). Total WBC of non-diabetics with malaria was significantly lower than their counterparts without malaria in the current study. Similarly, total WBC was higher in T2DM without malaria than in those with malaria. The lower total WBC count in this study could be ascribed to the localization of leukocytes away from the peripheral circulation and to the spleen and other marginal pools (Leoratti *et al.,* 2012; McKenzie *et al.,* 2005), rather than actual depletion or stasis (McKenzie *et al.,* 2005). However, neutrophils were significantly higher in non-diabetics with malaria than non-diabetics without malaria. Likewise, T2DM with malaria presented with higher neutrophils than

T2DM without malaria. Neutrophils play a crucial role in the immune response against the malaria parasite through phagocytosis, the process of engulfing and destroying pathogens, as well as by generating reactive oxygen species (ROS) (Babatunde & Adenuga, 2022). The lower mean levels of lymphocytes observed in the current study may be induced by lymph nodes sequestration (Borges *et al.*,2013) and/or death by apoptosis (Riccio *et al.*, 2003). In contrast to previous study (Kurtzhals *et al.*, 2001) that reported eosinophilia in malaria, both T2DM and non-diabetic with malaria presented with low level of eosinophils. This could be as a result of the increase in neutrophils in response to malaria, observe in the study. The degree of reduced haemoglobin levels in malaria respondent was not statistically significant. This could be as a result of immunity against malaria obtained from multiple malaria infection (Doolan *et al.*, 2009) in endemic areas like Ghana.

Not surprisingly, T2DM respondents recorded greater mean values of FBG than non-diabetics as previously reported (Acquah *et al.*, 2014). The higher FBG in T2DM with or without malaria in this study demonstrates sub-optimal effectiveness of the treatment regimen for these patients and calls for the need to re-examine the treatment plans for improved glycemic control (Abera *et al.*, 2022; Bin Rakhis *et al.*, 2022). Also, the observed hyperglycemia could be ascribed to the higher degree of insulin resistance which was unduly heightened among T2DM patients without malaria in the current study as determine by HOMAIR (Acquah *et al.*, 2014).

The increase in FBG in T2DM with malaria is as a result of low levels of serum insulin among T2DM with malaria. Insulin is responsible for regulating blood sugar by facilitating glucose uptake into body cells, hence,

inadequate levels will result in high blood glucose as observed in T2DM with malaria (Rahman *et al.,* 2021; Vasiljević *et al.,* 2020). It was noted that T2DM respondents with malaria who recorded very low levels of serum insulin presented with severe malaria. In spite of this, non-diabetics with malaria accounted for the youngest mean age group and this could contribute to the different in FBG observed between the two groups. It is plausible that the significant increase in FBG in diabetic patients with malaria could suggest that they responded to malaria infection via increasing blood glucose level.

Insulin resistance is a key feature of T2DM, resulting from defects in insulin secretion, insulin action, or both. According to research done by Amoah *et al.,* (2002), the Ghanaian population has been found to have insulin resistance as well as impaired beta cell secretory activity. Various factors at multiple levels can serve as the main contributors to insulin resistance. These factors encompass reduced receptor density and kinase activity, alterations in insulin receptor substrate (IRS) concentration and phosphorylation due to phosphatidylinositol 3-kinase (PI3K) activity, translocation of glucose transporters, functioning of intracellular enzymes, as well as a combination of genetic and environmental influences (Saltiel & Kahn, 2001). The most accurate method to determine this is the hyperinsulinemic-euglycemic clamp technique, which was developed by DeFronzo, Tobin, and Andres more than 30 years ago (DeFronzo *et al.,* 1979) which has gain acknowledgement as the gold standard. However, this technique is expensive, time-consuming, and requires specialized technical knowledge (Muniyappa *et al.,* 2008), making it impractical for routine clinical and research use when insulin resistance is not the primary focus. Therefore, several indirect mathematical models have been

created, among which are the HOMAIR and HOMAB models which was developed by Matthews and colleagues (Matthews *et al.*, 1985) and have gained significant acceptance in the scientific discipline.

The HOMAIR model, which utilizes insulin and glucose levels in the blood, demonstrates a strong correlation with the gold standard method. While the cutoff values for using the HOMAIR model to diagnose insulin resistance may differ among different populations (Esteghamati *et al.*, 2010; Lee *et al.*, 2006; McCormick *et al.*, 2011), a threshold of 2.6 is generally considered acceptable for identifying insulin resistance (Ascaso *et al.*, 2003). Typically, individuals with diabetes have higher HOMAIR values than those without diabetes (Esteghamati *et al.*, 2010; Lee *et al.*, 2006) and the current study supports the previous finding including higher HOMAIR value for diabetics with malaria infection. Hence, a significantly higher mean HOMAIR value was recorded for T2DM as compare to non-diabetic group in the current study similar to the previous study (Acquah *et al.*, 2014) only that the mean values obtained for T2DM (both those with malaria and without malaria) in the current study is much higher than that reported by the previous study. To the best of my knowledge, there have been no reports in adult populations of malaria-associated mean HOMAIR values above 4.2 in both diabetic and non-diabetic individuals, as observed in the present study. A study conducted in Sudan revealed that children with severe complicated malaria had insulin resistance (Eltahir *et al.*, 2010), a condition which according to Acquah *et al*., is usually not observed in semi-immune adults residing in malaria-prevalent areas such as Ghana (Acquah *et al.*, 2014). Acquah et al. established that uncomplicated malaria among adults might increase HOMAIR by more than

120% and 200% in T2DM and non-diabetic individuals respectively, surpassing the acknowledged threshold of 2.6 in a longitudinal study. Hence, they concluded that falciparum malaria can cause overt insulin resistance (Acquah *et al.*, 2014). Although the current study is cross-sectional in nature, the observed mean HOMAIR values are generally higher than those in a previous study (Acquah *et al.*, 2014), the trend of increase in HOMAIR particularly for malaria patients without T2DM appear to affirm the previous study that falciparum malaria can cause overt insulin resistance. Though not statistically significant, increasing malaria parasitemia in the current study resulted in an increase in serum insulin and HOMAIR in non-diabetics. A higher HOMAIR value in non-diabetics without malaria indicates the presence of already existing insulin resistance among individuals within the Tema metropolis. This could be attributed to the urban lifestyle of the respondents and the rapid alarming increase in the incidence of metabolic syndrome within the Ghanaian population (Gyakobo *et al.*, 2012; Ofori-Asenso *et al.*, 2017) especially in urban centers like Tema. If someone experiences several instances of clinical malaria, they may become more prone to developing overt T2DM due to the insulin resistance that occurs with each episode (Acquah *et al.*, 2014). This means, in malaria endemic countries like Ghana, urbanization and frequent malaria episode may be major risk factors in the development of T2DM.

In this study, T2DM patients with malaria demonstrated a reduced beta cell secretory function as determined by HOMAB. Hence**,** T2DM patients with malaria recorded lower mean level of serum insulin which could further explain the higher mean levels of FBG observed in T2DM patients with

malaria compared to their counterparts without malaria. In addition, decreased mean level of insulin among T2DM with malaria may be attributed to the activation of insulin-induced protein phosphorylation and cytoskeleton remodeling which facilitates the invasion of newly egressed merozoites to the red blood cells (Balaj *et al.*, 2020; Warncke & Beck, 2019).

As previously reported (P. Li *et al.*, 2016; Y. Li *et al.*, 2022; Lin *et al.*, 2021; Souza *et al.*, 2021), T2DM recorded significantly higher mean levels of serum galectin-3 compared to their non-diabetic controls. A study by He *et al.* (2017) found that galectin-3 levels were significantly higher in individuals with T2DM compared to healthy controls and galectin-3 was associated with insulin resistance and glycemic control, a phenomena also observed within the current study. To the best of our knowledge, the current study is the first to report mean galectin-3 levels above 12.6 in both diabetic and non-diabetic individuals with malaria. This novel finding in the current study with regard to malaria-associated galectin-3 levels is also found in malaria-associated insulin resistance within both study groups. However, galectin-3 levels were not associated with malaria parasitimea in both T2DM and non-diabetics.

In the T2DM patients with malaria, HOMAB, lymphocytes and haemoglobin accounted for 41.4% change in galectin-3 levels. In view of this, galectin-3 may play a significant role in the pathogenesis of malaria and insulin resistance by possibly inhibiting the production or secretion of insulin as galectin correlated negatively with HOMAB. Another potential mechanism is by enhancing malaria induce anaemia as galectin correlated negatively with haemoglobin level. Moreover, by stimulating immunological response via lymphocytes production, galeactin-3 may contribute to the pathogenesis of

malaria and insulin resistance as galectin correlated positively with lymphocytes.

Surprisingly, non-diabetics without malaria recorded a higher mean levels of galectin-3 compared with previous studies (Lin *et al.,* 2021; Weigert *et al.,* 2010). This could be ascribed to the rapid alarming increase in the incidence of metabolic syndrome within the Ghanaian population (Gyakobo *et al.*, 2012; Ofori-Asenso *et al.*, 2017) especially in urban centers like Tema.

Several research have been conducted to explore the association between malaria and lipid levels involving humans (Baptista *et al.,* 1996; Maurois *et al.,* 1979; Visser *et al.*, 2013) and mice model (Kluck *et al.*, 2019). The later reported hypocholesterolemia and hypertriglyceridemia in malaria infected mice. The current research found that individuals with malaria (both diabetics and non-diabetics) had reduced mean serum levels of cholesterol, HDL, and LDL but higher mean serum levels of triglycerides in comparison to the control group. This finding supports findings in previously studies in Ethiopia (Sirak *et al*., 2016), Gabon (Mens *et al.,* 2017) and Belgium (Visser *et al.,* 2013). These similarities could be as a result of the metabolic needs of malaria parasites and host immune response to malaria. This finding of the current study, however, differs from previous studies that showed no significant difference in total cholesterol and triglycerides level between malaria patient and their controls (Cuisinier-Raynal *et al.,* 1990; Onongbu & Onyeneke, 1983). The differences could be as a result of confounding factors such as ethnicity, socioeconomic conditions, lifestyle, eating habits, and the severity of malaria infection.

The liver is responsible for the synthesis of lipids (Alves-Bezerra & Cohen, 2017; Sirak *et al.*, 2016) and the site where infectious malaria sporozoites travel via the bloodstream, invade and settle in hepatocytes (Vaughan & Kappe, 2017). *Plasmodium* species are known to be incapable of synthesizing cholesterol on its own (Labaied *et al.*, 2011; Sherman, 1979; Vial & Ancelin, 1992), hence, it has been proposed that malaria parasite utilizes host cholesterol for replication within the host (Labaied *et al.*, 2011). However, recent cellular and molecular evidence in *P. falciparum* and *P. yoelii* have demonstrated the ability to produce fatty acids (FAs). These parasites contain the genes responsible for encoding type II FA synthase (FAS), which is presumed to facilitate the de novo synthesis of FAs (Carlton *et al.*, 2002; Gardner *et al.*, 2002; Surolia & Surolia, 2001; R. F. Waller, 2000; Ross F. Waller *et al.*, 1998). Nevertheless, *Plasmodium* can acquire cholesterol from hepatocytes by inhibiting host squalene synthase (Labaied *et al.*, 2011), which is an enzyme involved in the initial stage of sterol synthesis. Alternatively, reducing the expression of this enzyme by 80% can also decrease the cholesterol content of merozoites without affecting parasite growth (Labaied *et al.*, 2011) and this may account for the decrease in total cholesterol and LDL. Studies have indicated that HDL plays a crucial role in supporting the survival of *P. falciparum* in vitro culture (Imrie *et al.*, 2004; Trager & Jensen, 1976). According to Imrie *et al.* (2004) a research investigation revealed that HDL, when present in low concentrations (0.75 mg/ml protein) facilitates the growth and reinvasion of the parasite in a serum-free system. Conversely, when HDL concentrations are higher (2.4 mg/ml protein), it exhibit toxicity towards the parasite within infected erythrocytes

after invasion. This toxicity leads to aberrant maturation and subsequent demise of trophozoites. In view of this, the low HDL observed in this study can be attributed to parasite decreasing host HDL to promote growth and reinvasion of the parasites within host. It has been reported that malaria stimulates the production of cytokines and other inflammatory mediators, which can lead to a decrease in HDL cholesterol levels (Das *et al.,* 1993), The exact cause of hypertriglyceridemia in malaria is not completely comprehended, but there are proposed theories. One suggests that it might result from the inflammatory reaction initiated by the parasite. Another possibility is that triglyceride could originate from the phospholipids of red blood cell membranes after they rupture as hypertriglyceridemia is describe in disease with hemo-phagocytosis though not investigated.

Chapter Summary

The one hundred and sixty (160) participants for the study comprised of 80 diabetes patients of which half of them had malaria and 80 patients without diabetes with 40 of them presenting with malaria. T2DM respondents presented with ($P < 0.05$) higher mean age, BMI, WC, HC, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, insulin, galectin-3 as well as HOMAIR but decreased levels of HOMAB as compared to their non-diabetics' controls. In addition, diabetics with malaria were significantly ($P < 0.05$) of high age with higher mean values of FBG, SBP, DBP, galectin-3 and HOMAIR but decreased values of insulin as well as HOMAB than non-diabetics. Malaria was associated with dyslipidemia characterized by low total cholesterol, HDL, and LDL but high levels of triglycerides in both study groups. Insulin resistance within the study population was aggravated by

malaria in both study groups. Malaria was associated with high serum galectin-3 levels in both study group.

CHAPTER FIVE

SUMMARY, CONCLUSION AND RECOMMENDATIONS

Summary

Malaria and T2DM are two diseases that affect millions of people worldwide. Several studies have reported an association between malaria and T2DM (Acquah *et al.*, 2014; Danquah *et al.*, 2010). This current study investigated the effects of malaria on galectin-3 levels and insulin resistance in type 2 diabetics and non-diabetic controls within the Tema metropolis. A cross-sectional study design was used to recruit 80 patients with T2DM and 80 non-diabetics, with half of each group presenting with malaria.

T2DM respondents were significantly older and recorded higher mean, BMI, waist circumference, hip circumference, FBG, SBP, DBP, galectin-3, as compared to their non-diabetic counterparts. In the presence of malaria, both T2DM respondents and non-diabetics had high HOMAIR, however, T2DM respondents had a much higher FBG with a low serum insulin and HOMAB as compared to their non-diabetic counterparts. Malaria-associated insulin resistance was observed in both groups, while non-diabetics were able to respond to insulin resistance induced by malaria, diabetics were unable to respond adequately as determined by the mean HOMAB values. Furthermore, mean levels of serum galectin-3 increased in patients with malaria irrespective of diabetes status. Malaria was associated with dyslipidemia characterized by low total cholesterol, HDL, and LDL but high levels of triglycerides in both study groups. Malaria associated dyslipidemia was significantly associated with malaria parasitemia in diabetics with malaria.

Conclusion

The current study established the presence of insulin resistance within the study population. Insulin resistance was aggravated by malaria in both study groups. T2DM individuals are at increased risk of malaria associated insulin resistance as they were unable to adequately respond to insulin resistance induced by malaria unlike the non-diabetics with malaria.

The study also demonstrated novel findings that malaria is associated with increased serum galectin-3 levels in both study group though not associated with parasitemia. Galectin-3 may play a significant role in the pathogenesis of malaria and insulin resistance by possibly inhibiting the production or secretion of insulin, enhancing malaria induce anaemia and/or by stimulating immunological response via lymphocytes production during malaria.

Furthermore, malaria induced dyslipidemia characterized by low total cholesterol, HDL, and LDL but high levels of triglycerides. Malaria associated dyslipidemia was associated with the severity of malaria infection.

The discovery has consequences for the development of T2DM in areas of the world where malaria is prevalent.

Recommendations

Further research concerning malaria and galectin-3 interaction should be done to understand the mechanism of malaria-associated increased galectin-3 levels. This might lead to avenues to explore novel anti-malarial interventions and help curb the menace associated with T2DM especially in malaria regions. Also, from the study, respondent appeared to have developed insulin resistance prior, to malaria infection. Therefore, public anti-diabetic

educational campaigns targeting the entire population should be intensified to educate the populace against the lifestyles that increase the risk of insulin resistance and metabolic syndrome in general.

Suggestions for Further Studies

Further studies concerning malaria and galectin-3 interaction should be conducted to understand the mechanism of malaria-associated increased galectin-3 levels. In addition, further studies regarding malaria and diabetes should be conducted to understand the mechanism of malaria-associated insulin resistance. This might lead to avenues to explore novel anti-malarial interventions and help curb the menace associated with T2DM especially in malaria regions.

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APPENDIX

Appendix 1: Questionnaire

1. Pathology number ☐
2. Gender Male ☐ Female ☐
3. Age: 20-29 ☐ 30-39 ☐ 40-49 ☐ 50-59 ☐ 60-69 ☐ ≥ 70 ☐
4. Region ..... Ethnicity .....
5. Ward; OPD ☐ ANC ☐ Emergency ☐

   Others .....
6. Weight ☐
7. Height ☐
8. Waist circumference ☐
9. Hip circumference ☐
10. Blood pressure ☐
11. Random blood sugar ☐
12. On a weekly basis, how often do you engage in physical activities or exercises like running, golfing, or walking for a duration of 30 minutes or longer? _____days/per week

Questions related to diabetes

13. Have you ever had a test of glucose, or sugar, in blood? Yes ☐ No ☐
14. When was the last time that you had a blood sugar test?

    Less than 6 months ago ☐ 6 to 11 months ago ☐ 1 to 2 years ☐

    More than 2 years ago ☐ Unsure ☐
15. Has any health professional told you that you have diabetes or excess sugar in blood?

    Yes ☐ No ☐

16. If yes, how long have you been diagnose as diabetic ☐ year(s)

17. How old were you when they told you that you have diabetes?
    Years ☐

18. What treatment or medical recommendation have you been prescribed for diabetes or to lower the blood sugar?
    Drugs ☐ Special diet ☐ Weight lose ☐ Regular exercise ☐
    Avoiding alcoholic beverages in excess ☐ Home remedies ☐ Others ☐

19. Do you usually find the drugs that the doctor prescribes for diabetes?
    Yes ☐ No ☐ Sometimes ☐

20. Do you usually have money or the means for obtaining the drugs that your doctor prescribes for diabetes?
    Yes ☐ No ☐ Sometimes ☐

21. If female has any doctor told you had diabetes only during some of your pregnancies?
    Yes ☐ No ☐ Never been pregnant ☐ Not sure ☐

22. The way I currently live including what I eat and how active I am reduces the likelihood of me developing T2DM.
    Highly agree ☐ Agree ☐ Unsure ☐ Disagree ☐
    Highly disagree ☐

Questions related to hypertension

23. Has your blood pressure ever been taken? Yes ☐ No ☐

24. When was the last time that your blood pressure was taken?
    Less than 6 months ago ☐ 6 to 11 months ago ☐ 1 to 2 years ago ☐
    More than 2 years ago ☐ Unsure ☐

25. Has a doctor, nurse, or other health professional ever told you that you have high blood pressure? Yes ☐ No ☐ Unsure ☐

26. How old were you when they told you that you have high blood pressure?
    ☐ Years

27. What treatment have they prescribed you for high blood pressure?

Drugs ☐ Reduce salt in diet ☐ Weight lose ☐ Regular exercise ☐

Others ☐

Avoiding alcoholic beverages in excess ☐ Home remedies ☐

Prevent stress ☐

28. Do you usually find the drugs that the doctor prescribes for high blood pressure?

Yes ☐ No ☐ Sometimes ☐

29. Do you usually have money or the means for obtaining the drugs that your doctor prescribes for high blood pressure?

Yes ☐ No ☐ Sometimes ☐

30. The way I currently live, including my eating patterns and how active I am, lowers the likelihood of me developing high blood pressure.

Strongly agree ☐ Agree ☐ Unsure ☐ Disagree ☐

Strongly disagree ☐

Questions related to cholesterol

42 Have you ever had your blood cholesterol measured? Yes ☐ No ☐

43 When was the last time that you had a cholesterol test?

Less than 6 months ago ☐ 6 to 12 months ago ☐ 1 to 2 years ☐

3 to 4 years ago ☐ More than 5 years ago ☐ Unsure ☐

43 Has a health professional ever told you that your blood cholesterol is high?

Yes ☐ No ☐ Unsure ☐

44 How old were you when they first told you that you had high cholesterol?

☐ Years

45 What treatment or program have they prescribed you for lowering cholesterol?

Drugs ☐ Special diet ☐ Weight lose ☐ Regular exercise ☐

Home remedies ☐ Others ☐

46 Do you usually find the drugs that the doctor prescribes for high cholesterol?

Yes ☐ No ☐ Sometimes ☐

47 Do you usually have money or the means for obtaining the drugs that your doctor prescribes for high cholesterol?

Yes ☐ No ☐ Sometimes ☐

48 The way I currently live, including my eating patterns and how active I am, lowers the likelihood of me developing high cholesterol.

Highly agree ☐ Agree ☐ Unsure ☐ Disagree ☐

Highly disagree ☐

Appendix 2 Ethical Clearance

UNIVERSITY OF CAPE COAST
INSTITUTIONAL REVIEW BOARD SECRETARIAT
TEL: 0558093143 / 0508878309
E-MAIL: irb@ucc.edu.gh
OUR REF: UCC/IRB/A/2016/1662
YOUR REF:
OMB NO: 0990-0279
IORG #: IORG0011497

21ST DECEMBER 2022

Mr Emmanuel Nortey
School of Medical Sciences
University of Cape Coast

Dear Mr Nortey,

ETHICAL CLEARANCE – ID (UCCIRB/CHAS/2022/146)

The University of Cape Coast Institutional Review Board (UCCIRB) has granted Provisional Approval for the implementation of your research on **Effects of Malaria on Galectin-3 and Insulin Resistance in Diabetics and Non-Diabetic Respondents in Tema General Hospital.** This approval is valid from 21st December 2022 to 20th December 2023. You may apply for a renewal subject to the submission of all the required documents that will be prescribed by the UCCIRB.

Please note that any modification to the project must be submitted to the UCCIRB for review and approval before its implementation. You are required to submit a periodic review of the protocol to the Board and a final full review to the UCCIRB on completion of the research. The UCCIRB may observe or cause to be observed procedures and records of the research during and after implementation.

You are also required to report all serious adverse events related to this study to the UCCIRB within seven days verbally and fourteen days in writing.

Always quote the protocol identification number in all future correspondence with us in relation to this protocol.

Yours faithfully,

Kofi F. Amuquandoh
Ag. UCCIRB Administrator

ADMINISTRATOR
INSTITUTIONAL REVIEW BOARD
UNIVERSITY OF CAPE COAST