UNIVERSITY OF CAPE COAST

DIABETOGENIC RISK OF MALARIA IN RECOVERED COVID-19 RESPONDENTS COMPARED TO UNINFECTED COVID-19 RESPONDENTS IN THE TAMALE METROPOLIS

ADATSI RICHARD KUJO

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BY

ADATSI RICHARD KUJO

Thesis submitted to the Department of Microbiology and Immunology, of the School of Medical Sciences, of the College of Health and Allied Sciences of the University of Cape Coast in partial fulfilment of the requirement for the award of a Master of Philosophy degree in Infection and Immunity

AUGUST 2023

DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own original research and that no part of it has been presented for another degree in this university or elsewhere.

Candidate's Signature: …….. Date: ……

Name: Adatsi Richard Kujo

Supervisors' Declaration

We hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

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

Name: Prof. Samuel Acquah

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

Name: Dr. Faustina Pappoe

ABSTRACT

The emergence of COVID-19 has heightened interest in how the illness interacts with common comorbidities including malaria and type 2 diabetes mellitus (T2DM). COVID-19 infection has been associated with new-onset hyperglycaemia and T2DM, as well as a worsening of glycaemic control in non-diabetics without a history of diabetes and diabetics due to direct pancreatic damage and the cytokine onslaught in response to the infection. This cross-sectional study evaluated COVID-19 recovered persons with or without malaria for their likelihood of developing T2DM. Two hundred and ninety non-COVID-19 and COVID-19 confirmed participants with or without malaria were recruited from the public health reference laboratory database in the Northern region of Ghana. Respondents were assessed for fasting blood glucose (FBG), beta cell function, C-reactive protein (CRP), insulin resistance (IR), malondialdehyde (MDA), and malaria parasitaemia. Beta cell function and IR were calculated using the Homeostatic models for assessment of IR (HOMA-IR) and beta cell function (HOMA-B) formulae. COVID-19 recovered respondents exhibited significantly higher mean levels for HOMA-IR (7.1 ± 8.1 vs 3.7 ± 2.9 mIU/L; $P<0.001$), FBG (4.95 ± 1.13 vs 4.26 ± 0.58 mmol/l; $P<0.001$**),** and CRP (1.35 ±1.41 vs 0.99 ± 0.88 mg/dl; $P=0.0098$) compared to the control respondents. The total prevalence of HOMA-IR in cases was 38.3% compared to 32.4% in the control respondents. A binary logistic regression analysis of beta cell activity, insulin, CRP, MDA, and malaria found that study participants with malaria had a greater risk of developing hyperinsulinemia than participants without malaria in both groups. Mean values of the other indices were comparable between the groups. The findings of the study demonstrate that COVID-19, through insulin resistance, can contribute to the risk of T2DM development in recovered COVID-19 respondents.

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DEDICATION

Through this work, I give praise to the all-powerful God, who has protected, favoured, and shown me provisional mercies during all of my struggles. And to my wife, whose constant support and prayers kept me going when I was ready to give up the work.

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LIST OF ABBREVIATIONS

8-OHdG - 8-hydroxy-2'-deoxyguanosine

ARDS – Acute respiratory disease syndrome

ASK-1 - apoptotic signal-regulating kinase 1

ATP - Adenosine triphosphate

COVID-19 – Coronary virus disease, 2019

CRP – C-reactive protein

DNA – Deoxyribonucleic acid

HIV – Human immunodeficiency virus

HOMA-B – Homeostasis model assessment for beta cell function

HOMA-IR – Homeostasis model assessment for insulin resistance

HSV - Herpes Simplex Virus

IkB - Inhibitor kappa beta

IL – Interleukin

IR – Insulin resistance

JNK - Jun N-terminal kinase

MAPK - mitogen-activated protein kinase (MAPK)

NADPH – Nicotinamide adenine dinucleotide phosphate

NIDDM – Non-insulin-dependent diabetes mellitus

NLRP3 - Nucleotide-binding oligomerization domain-like receptor having pyrin domain 3

OGTT - Oral glucose tolerance test

PAMPs - Pathogen-associated molecular patterns

PRRs - Pathogen recognition receptors

RNA – Ribonucleic acid

RNS – Reactive nitrogen species

ROS – Reactive oxygen species

SARS-COV-2 – Severe acute respiratory coronary virus 2

T1DM – Type 1 diabetes mellitus

T2DM – Type 2 diabetes mellitus

TBARS - Thiobarbituric acid-reactive substances

TLRs - Toll-like receptors

TNF – Tumour necrosis factor

TNF-α - Tumour necrosis factor-alpha

WHO – World Health Organization

FI – Fasting Insulin

HTN – Hypertension

ESR – Erythrocyte Sedimentation Rate

MDA – Malondialdehyde

FBG – Fasting Blood Glucose

BMI – Body Mass Index

WHT – Waist to Hip Ratio

WHtR – Waist to Height Ratio

ICU – Intensive Care Unit

HHT – Human to Human Transmission

TMPRSS2 – Transmembrane Serine Protease 2

Ang I – Angiotensin I

AngII – Angiotensin II

RAAS – Renin-angiotensin-aldosterone system

ACE2 – Angiotensin-converting enzyme 2

ACE – Angiotensin converting enzymes.

TLR4 – Toll-like receptor 4

TLR9 – toll-like receptor 9

NF-kB – nuclear factor kappa beta

MCP-1– Monocyte chemoattractant protein-1

IFN-ɤ – interferon-gamma

IFP – infrapatellar fat pad

ATR1– Angiotensin II receptor type 1

FFA – Fatty acids

GLUT4 – Glucose transporter 4

IDF– International Diabetes Federation

Nrf2 – nuclear factor erythroid-related factor 2

TTH – Tamale Teaching Hospital

PHRL – Public Health Reference Laboratory

EDTA – Ethylenediamine tetraacetic acid

CHAPTER ONE

INTRODUCTION

The chapter describes coronavirus disease-2019 (COVID-19) and its mode of transmission, and its effect on society. It also considers how COVID-19 may relate to other prevailing medical conditions such as diabetes and malaria and their effects on the infected population. It summarizes the research question for this thesis and the scientific approaches employed to accomplish the goals and objectives. It also touches on the importance of the research.

Background of the Study

The emergence and rapid spread of the COVID-19 pandemic around the world have heightened interest in the impact of common comorbidities like diabetes and malaria on the cause and outcomes of the infection. Although diabetes does not appear to raise the possibility of COVID-19 infection per se, it has been conclusively demonstrated that hyperglycaemia to any degree increases the likelihood of poorer outcomes, such as more severe respiratory involvement, intensive care unit (ICU) admissions, the need for mechanical ventilation, and mortality (Unnikrishnan & Misra, 2021a). COVID-19 infection has been linked to new-onset hyperglycaemia and diabetes, as well as a worsening glycaemic control in already diabetics due to pancreatic damage caused by viral entry and the body's stress response to the infection including the cytokine onslaught (Unnikrishnan & Misra, 2021b).

A new strain of the severe acute respiratory syndrome-related coronavirus (SARS-COV) known as the severe acute respiratory syndrome-related coronavirus 2 (SARS-COV-2) is responsible for COVID-19, a respiratory illness (Jin et al., 2020). After emerging in Wuhan, China at the

end of December 2019, COVID-19 rapidly expanded its host range, prompting the World Health Organization (WHO) to proclaim it a pandemic on March 11, 2020 (Jin et al., 2020).

SARS-COV-2 is a beta coronavirus that is enveloped and has a single-stranded positive-sense RNA (23-32 kb) as its genetic material (Perrotta et al., 2020). COVID-19 is distributed primarily through human-to-human transmission (HHT) via respiratory droplets, fomite, and aerosols (Adhikari et al., 2020). Regarding symptoms, recovery, and fatality rates, COVID-19 has a varied pattern over the world. The majority of COVID-19 persons (Richardson et al., 2020; Y. Zhang et al., 2020) had shortness of breath, mild flu-like symptoms, and a diminished smell and sense of taste; however, some had no symptoms at all, while others developed more severe clinical complications such as pneumonia (Liguori et al., 2020; X. Sun et al., 2020). The possibility of an age-related risk factor in the case of COVID-19 is yet unknown, as the illness has been found in populations of practically all age groups. It seems that a sizable section of the global population will become afflicted in the future. To better predict and manage the effects on one another, it is necessary to examine how COVID-19 interacts with other common medical illnesses.

Diabetes is one such comorbidity that affected over 430 million individuals worldwide as of 2019 (Unnikrishnan & Misra, 2021b) and has the potential to alter COVID-19's natural history unfavourably. COVID-19, on the other hand, has been associated with the development of diabetes and the worsening of glycaemic control in people who already have diabetes (Pal & Bhadada, 2020). Several narratives and reviews examining the relationship between diabetes and COVID-19 have been published (Apicella et al., 2020;

Unnikrishnan & Misra, 2021b). However, the long-term effect of COVID-19 recovered individuals is yet to be fully examined.

Problem Statement

COVID-19's diabetogenic effects constitute a completely new idea, based on detailed observations of COVID-19 individuals from December 2019 to the present. It has been hypothesized that COVID-19 may cause diabetes in non-diabetics by exploiting many organs, resulting possibly in increased stress and depression, beta cell failure, glycaemic variability, endothelial dysfunction, reduced microbiome diversity, increased intestinal permeability, hepatic manifestations, and alterations in the pancreas-liver-gut-brain axis (Balasubramanyam, 2020). COVID-19 is a novel infection with little knowledge of post-infection complications with regards to diabetes. COVID-19 being an infectious disease like malaria has the potential to cause insulin resistance (IR). However, the nature of COVID-19-induced insulin resistance post infection is unknown and most importantly in the presence of malaria. In a region of Ghana where malaria is common, conducting a study that looks at post COVID-19 induced insulin resistance is relevant. This study compares recovered COVID-19 individuals with and without malaria to non-infected colleagues in order to determine which group has a higher chance of acquiring diabetes.

Aim and Objectives

This work aims to assess the risk of development of type 2 diabetes mellitus (T2DM) in COVID-19 recovered patients with or without malaria compared with their non-COVID-19-infected counterparts.

Specific objectives

The specific objectives of the study are to:

1. Determine the prevalence of insulin resistance (IR) in recovered COVID-19 patients with or without malaria compared with non-COVID-19 individuals;
2. Investigate the extent of inflammation and oxidative stress associated with malaria in recovered COVID-19 patients compared with non-COVID-19 individuals;
3. Examine the relationship between the measured markers of IR, inflammation, and oxidative stress in the various categories of respondents.

Research Questions

1. Can COVID-19 increase the risk of development of diabetes after recovery.
2. Which of the predisposing factors of diabetes is significantly associated to COVID-19 after recovery
3. Will the presence of malaria contribute to the risk of developing diabetes?

Hypothesis

COVID-19 can increase the risk of developing diabetes through insulin resistance.

Significance of the Study

COVID-19 and its devastating ravage on multiple organs could be causally linked to new-onset diabetes during and after the infection. The bidirectional relationship between COVID-19 and diabetes needs to be studied

further. The control and management of malaria infection and its related complications in sub-Saharan Africa has been a challenge due to limited resources in the area of research and health infrastructure. Previous work on malaria in Ghana showed a degree of IR in individuals with malaria (Acquah et al., 2014a). This suggests that the presence of malaria in COVID-19 recovered individuals could potentially heighten insulin resistance compared with non-COVID-19 infected counterparts with or without malaria. This work seeks to assess the risk of new-onset diabetes in recovered COVID-19 patients and non-COVID-19 individuals with or without malaria. This information may be necessary for appropriate policy measures to slow the pace of development of T2DM. It may prepare the ground for further research in malaria-COVID-19-related diabetes in sub-Saharan Africa.

Organisation of the Thesis

The thesis is made up of five chapters. Chapter one covers the chapter introduction, background, problem statement, aim and objectives, the significance of the study as well as the structure of the complete thesis. Likely keywords encountered are SARS-COV-2 and COVID-19. Chapter two covers the chapter introduction, epidemiological characteristics, entry mechanism of SARS-COV-2 into host cells, effects of COVID-19 on the renin-aldosterone system, and possible mechanisms for new-onset type 2 diabetes mellitus**.** Chapter three covers the introduction to the chapter, study design, study site, ethical clearance, participants selection, and sample size, population and sampling, sample size calculation, sampling technique, inclusion criteria, exclusion criteria, sample, and data collection procedure, questionnaire, anthropometric measurements, blood collection and laboratory measurements

of biomarkers. Chapter four covers the introduction to the chapter, results in the form of tables and figures, and discussions of findings made in the study. Chapter five covers the summary, conclusions, and recommendations of the work.

CHAPTER TWO

LITERATURE REVIEW

Introduction

The epidemiology and mechanism of the bidirectional association between SARS-COV-2 infection and diabetes as well as the molecular markers that may be used to predict or find the emergence of new-onset diabetes and IR, are critically reviewed in this section. It also emphasizes the knowledge gaps found.

COVID-19 infection is a worldwide pandemic with about 216 million cases and resulted in 4.49 million fatalities as at June 2021 (WHO, 2021). This virus was discovered in Wuhan, China, in 2019 (Ralph *et al.*, 2020). Transmission is through droplets, fomites, and aerosol resulting in a variety of symptoms in infected people ranging from mild or absence of respiratory ailment to critical organ malfunction and death (Y. Wang *et al*., 2020). Comorbid conditions like high blood pressure, excess weight gain, and cardiac ailment usually connected to type 1 and 2 diabetes mellitus (T1DM and T2DM) are linked to a higher death rate from COVID-19 (L. Zhu et al., 2020a). The surge in glucose concentration states and problems in COVID-19 infected individuals is comparable to the Coronavirus 1 occurrence in 2003 (J. K. Yang *et al*., 2010a) and respiratory syncytial virus infections (Broor *et al*., 2018; W. Liu *et al*., 2016).

Given the dynamic behaviour of the COVID-19 outbreak, it is not clear if new-onset COVID-19-induced diabetes comes from recognized pathways in diabetes or a unique type of diabetes. Whether COVID-19 infected persons are more prone to experiencing permanently elevated glucose

concentration or other complications after recovery from the virus is not clear at this point. This calls for more attention on glucose-related problems after COVID-19 diagnosis and recovery due to circulating COVID-19 genetic variants and ongoing cases and spread rates, despite extensive worldwide immunization efforts to control the pandemic.

COVID-19 and Diabetes Complications

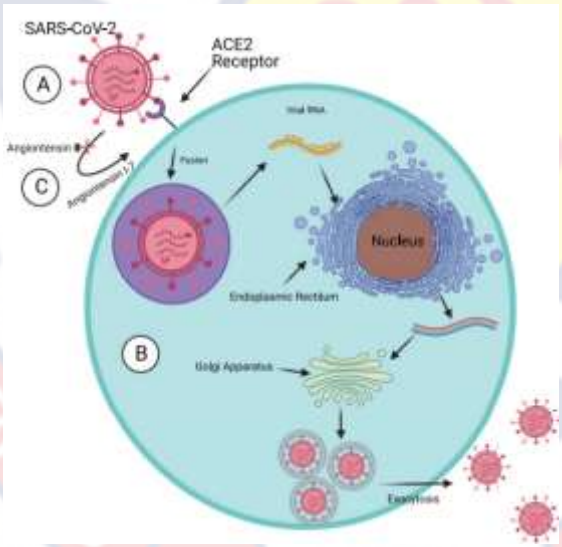
Pre-existing medical situations such as high blood pressure, higher than normal glucose concentrations, and cardiac disease are mostly coupled with severe illness and mortality in COVID-19 persons (Barbu *et al*., 2020). Pneumonia, diabetes-related renal ailment, and coronary artery disease (CAD) are commonly found in COVID-19 individuals with comorbid diabetes, and this can result in renal or heart failure (Erener, 2020). COVID-19 infected diabetics are more prone to death and admissions than their cohorts without diabetes. The onset of sudden respiratory difficulties in diabetics with COVID-19 infection is more likely to happen compared to non-diabetics with COVID-19 (Selvin & Juraschek, 2020). Diabetes-related death rates in COVID-19 individuals vary from 22% to 31% (Singh et al., 2020). When a study examined the deaths of COVID-19 hospitalized persons, it found 33.1% T2DM and 1.5% T1DM (Barron *et al*., 2020a). Obesity was found as a factor connected to COVID-19 disease admissions and dire consequences in a New York research of 2,741 hospitalized persons (Petrilli *et al*., 2019). This is revealing because obesity contributes to the onset of T2DM and is significantly connected to complications in COVID-19 illness (Norouzi *et al*., 2021).

Morbid obesity was seen to be a contributory factor to ICU admissions in a retrospective study of 1,158 COVID-19 infected persons in Kuwait (Al-Sabah et al., 2020). Coronavirus type 1 and human herpes 8 viruses have been proven to cause acute hyperglycaemia and IR due to normal response to the virus in the infected patients (Sobngwi *et al.*, 2008). This situation could raise the likelihood of T1DM or T2DM development (Sobngwi et al., 2008; J. K. Yang et al., 2010a). A 2003 study of 39 Coronavirus type 1 patients who had no history of diabetes found that 20 of them developed new-onset diabetes on admission and it persisted in two other participants over three years of follow-up having received glycaemic management after recovery from the viral infection (J. K. Yang et al., 2010b). SARS-COV-2 related diabetes may arise due to the virus's ability to disrupt insulin production, which is itself a solitary predictor of COVID-19 death (Mine et al., 2021).

Entry Mechanism of SARS-COV-2 into Host Cells

SARS-COV-2 is a positive-sense virus with a single-stranded RNA as its genetic material and is largely made up of membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins. For the virus to invade host cells, S proteins interact with angiotensin-converting enzyme 2 (ACE2), a membrane-bound receptor present in all respiratory system cells. Transmembrane serine protease 2 (TMPRSS2) cleaves bound S proteins, triggering the endocytic system to allow the virus into the cell for subsequent replication (Jackson *et al.*, 2022). The ACE2, a receptor that is present on surfaces of respiratory epithelial cells as well as in the kidneys, gastrointestinal tract, and pancreas aids as a vehicle for SARS-COV-2 into the host body (see Fig. 1). It has been proven that the virus can invade and multiply in human endocrine and exocrine pancreatic cells (Müller *et al.*, 2021).

Onset of insulin-dependent diabetes in some COVID-19 persons has been related to pancreatic beta cell destruction brought on by SARS-COV-2 penetration into host cells. A similar scenario with coronavirus type 1 enforces this theory in SARS-COV-2 infection (J. K. Yang *et al*., 2010b). About 90% of pancreatic beta cells must be damaged for this type of non-autoimmune new-onset T2DM to develop after a viral infection. This is clearly in sharp contradiction to the case of Coronavirus type 1 infection as SARS-COV-2 appears to be linked to acute pancreatitis according to literature (de-Madaria & Capurso, 2021; Y. Wang et al., 2020). This, however, calls for more research into the causes of the onset of an acute surge of glucose concentration and T2DM during and post COVID-19 infection as the clinical cause stays unclear.



A. **CoV-2 binds with ACE2 surface receptors**

B. **ACE2 receptors downregulate through endocytosis.**

C. **Excess accumulation of Ang II can lead to inflammation, oxidative stress, beta cell injury, insulin resistance, diabetic ketoacidosis, T2DM.**

Mechanism of CoV-2 entry to the cell through ACE2 receptors and interaction with the renin-angiotensin-aldosterone system. CoV-2 binds to ACE2 receptors commonly found on the surface of organs and tissue cells. The virus fuses through the host cell membrane by endocytosis and exits the host cell through exocytosis for further infection. ACE2 downregulates in the process and inhibits the conversion of angiotensin II to angiotensin (1–7). The overaccumulation of angiotensin II can lead to inflammation, oxidative stress, beta cell dysfunction, insulin resistance, diabetic ketoacidosis, and the onset of type 2 diabetes mellitus in exposed CoV-2 patients.

Figure 1: Mechanism of SARS-CoV-2 entry into host cell
Source: Metwally *et al*., 2021

Effects of COVID-19 on the Renin-Angiotensin-Aldosterone System and T2DM

There is an ongoing debate on how COVID-19 interacts with the hyperinflammatory environment, the renin-angiotensin-aldosterone system (RAAS), and the hypercoagulation loop, even though the science of the virus and diabetes stays unclear at this point (Domingo *et al*., 2020a). Angiotensinogen is broken down by the protease, renin, to angiotensin I (Ang I) and further broken down into angiotensin II (AngII) by the angiotensin converting enzymes (ACE) in the RAAS route (C. Huang et al., 2020). Angiotensin II activation occurs through its receptor type 1 and 2 channels. The type 1 receptor channel causes pro-inflammatory, proliferative, profibrotic, and vasoconstrictive effects by activating nuclear factor kappa beta (NF-kB), nicotinamide adenine dinucleotide oxidase (NADH), and toll-like receptor 4 (TLR4) (Liang & Acharya, 2020). ACE2, a variant of ACE initiates the alteration of angiotensin 2 (Ang II) to produce angiotensin (1–7) (Ang 1-7), to reduce inflammation by attaching to and stimulating the angiotensin receptor types 1, 2, and Mas receptor (Tan et al., 2018). Through the ACE2 receptor, SARS-COV-2 invades host cells where it quickly spreads and multiplies (Varga *et al*., 2020).

ACE2-Ang (1-7) Mas receptor route neutralizes the pathophysiological properties of the ACE-AngII-ATR1(angiotensin receptor type 1) path through its anti-inflammatory and anti-fibrotic properties. SARS-COV-2 binding to ACE2 reduces the expression of these receptors on the alveolar epithelial cells' increasing the concentration of angiotensin II which continues to stimulate the host's adaptive immunological response (Domingo *et al*., 2020b). Monocyte

chemoattractant protein-1 (MCP-1), interferon-gamma (IFN), infrapatellar fat pad (IFP), interleukins-1β, 1, 4, and 10 are released due to a heightened inflammatory response (X. Yang *et al*., 2020) which is key to the consequences of sudden respiratory difficulties caused by COVID-19 infection (Rajpal *et al*., 2020). Hyperinflammatory and hypercoagulation responses due to this resultant cytokine storm disturb endothelial cell function and the alveolar-capillary membrane resulting in severe hypoxia (L. Li *et al*., 2020). RAAS signalling is affected by reduced concentrations of ACE2 in COVID-19 infected persons (Valencia *et al*., 2020).

During hypoxia, Ang II action with AT1 receptors stimulates the activation of the anti-angiogenic factor sFlt-1 (C. C. Zhou et al., 2007). This increases oxidative stress by lowering endothelial nitric oxide synthase phosphorylation (Burke *et al*., 2016). Critically ill COVID-19 persons have higher plasma concentrations of sFlt-1 showing that stress from respiratory-related complications has created an anti-angiogenic environment that increases the likelihood of organ failure (Dupont *et al*., 2021). Pancreatic islet cells have been found to express ACE2 receptor, while the extent of the complication of COVID-19 on the functions of ACE2 in diabetic individuals is unknown currently (Somasundaram *et al*., 2020). According to an animal study, diabetes mellitus significantly raises the level of ACE2 in organs such as the lungs, pancreatic cells, and other tissues, making diabetics prone to COVID-19 (Roca-Ho *et al*., 2017). In a favourable environment, ACE2 controls the pressure of the blood by turning Ang II into Ang (1–7), minimizing IR and oxidative stress, and improving the activity of glucose transporter 4 (Takeda *et al*., 2013).

Reduced insulin sensitivity, oxidative stress, inflammation, high blood pressure, and congestive heart failure occur due to a reduced expression of ACE2 during COVID-19 infection (Finucane & Davenport, 2020). Particularly in people with elevated body mass index, inflammation and oxidative stress are essential components of T2DM manifestation (Vikram *et al*., 2014). Insulin activity is disrupted by inflammation and oxidative stress resulting in reduced insulin sensitivity, a predisposing factor to the onset of T2DM (Vikram et al., 2014). Increased inflammation worsens COVID-19 pathophysiology, increasing the likelihood of terrible consequences (C. Zhang *et al*., 2020). Increased concentration of IL-6 is found in diabetic persons with COVID-19 compared to non-diabetic and diabetic persons without the disease (C. Zhang *et al*., 2020).

Malaria and the Angiotensin System

One of the key elements of the RAAS is the ACE which controls blood pressure mechanisms in the human body. ACE is a 21-kb gene in length situated on chromosome 17 with 26 exons in human beings. It converts angiotensin I (Ang I) by breaking the amino acid at the C-terminal end into Ang II which primarily controls blood pressure. According to Fumagalli and Sironi (2014), the largest evolutionary pressure on the human genome is malaria, which was first suggested by Haldane as one of the key selection pressures on human evolution (Hedrick, 2011). Although it is well known that many human hemoglobinopathies, including sickle cell disease, glucose 6-phosphate dehydrogenase deficiency, and alpha-thalassemia, are positively selected by malaria, Miller was the first to wonder whether this selection might also affect genes that control blood pressure (Chiabi *et al*., 2014). Miller

hypothesized that mutations in angiotensin genes might prevent malaria parasite from growing and confer survival advantages against the parasite.

The D allele of the ACE gene is linked to a reduced risk of cerebral malaria according to a genetic analysis that was conducted on admitted severe malaria cases in Odisha and India (Dhangadamajhi *et al.*, 2010). Another study conducted in Nigeria found that moderate malaria sufferers had a higher ACE activity than severe malaria cases (Abdulazeez et al., 2017). The total genotype frequencies of the ID and DD genotypes are much higher than the II genotype of ACE in a small number of studies from malaria-endemic nations like Nigeria and India (Dhangadamajhi *et al.*, 2010; Kooffreh *et al.*, 2014; Patnaik *et al.*, 2014). Gallego-Delgado and Rodriguez proposed that malaria and hypertension (HTN) may be an example of a co-evolved adaptation because of the higher frequency of HTN in Africans and south Asians compared to Caucasians irrespective of their socioeconomic status (Gallego-Delgado & Rodriguez, 2014).

It is difficult to establish whether ACE I/D polymorphism is an indication of malaria-induced mutation that may have developed to protect against malaria due to a lack of evidence. Studies on molecular epidemiological relations are required to further investigate this concept.

Diabetics with COVID-19 are Prone to Complications Compared to Non-Diabetics

Many organs in the human body express ACE2 (Hikmet et al., 2020) but that of the pancreas has attracted attention due to accounts suggesting an occurrence of T2DM and ketoacidosis in COVID-19 infections through beta cell dysfunction (Fadini *et al.*, 2020; Rubino *et al.*, 2020). Many scholars have

examined the expression of TMPRSS2 and ACE2 SARS-COV-2 entry mechanisms in diabetics, non-diabetics, and COVID-19 pancreatic tissue to figure out its ability to cause diabetes (Drucker, 2021; Ibrahim & Monaco, 2021).

Most scientists agree with the fact that anomalies of pancreatic islet activity in COVID-19 persons may be caused by the presence of ACE2 and TMPRSS2 protein in pancreatic and endothelial cells of the micro-vascular (Metwally *et al*., 2021). Researchers who did not consider beta cell invasion factors did not find SARS-COV-2 core protein in pancreatic samples (Drucker, 2021; Ibrahim & Monaco, 2021) but studies that considered entry factors in the beta cell found nucleocapsid at concentrations that could infect human islets externally. This could alter insulin regulation and trigger beta cell death, resulting in widespread pathology that could promote T1DM-related hyperglycaemia (Drucker,2021; Ibrahim & Monaco, 2021).

The widespread beta cell damage by penetrating SARS-COV-2 is not exact with several post-mortem analyses, which normally report usual morphologies in pancreatic autopsy samples with T1DM or T2DM. The data are still uncertain and require further research for resolution. Similar epidemiological studies suggest that the prevalence of T1DM will not significantly rise between 2020 and the preceding years (Drucker, 2021; Fadini *et al*., 2020; Tittel *et al*., 2020). COVID-19 and exocrine beta cell degradation appear doubtful to be the cause of the present rates of new-onset T2DM, but this could alter over time due to the slower onset of autoimmune T1DM and calls for continuous surveillance. Adipose tissue expresses high ACE2 levels and may attract SARS-COV-2. Ageing, T2DM,

IR, and obesity are all associated with serious COVID-19 (Metwally et al., 2021). SARS-COV-2 may damage lipocytes and increase lasting inflammation, worsen IR, hyperglycaemia, and COVID-19 consequences for persons with diabetes. Concentrations of indicators of inflammation like C-reactive protein (CRP), ferritin, and IL-6 were higher in COVID-19 participants with diabetes compared to their cohorts without diabetes (L. Zhu et al., 2020b).

The development of immunosuppressive Tregs connected to cytokine outbursts, which are often used as a marker for COVID-19 severity, is suppressed by IL-6, which also raises neutrophil numbers, peripheral trafficking, and hyperactivates cluster of differentiation 4 T helper cell type 1($CD4^+$ Th1) capable of causing inflammation (X. Chen et al., 2020). Prolonged exposure to IL-6 reduces the liver's sensitivity to insulin in COVID-19 infected persons with diabetes leading to hyperglycaemia and ketosis (Torres-Tamayo *et al*., 2020).

Possible Mechanisms for New-Onset Type 2 Diabetes Mellitus

Although the correct circumstances causing the onset of T2DM in COVID-19 infections are still unclear at this point, there is the possibility of intricately interconnected pathophysiology such as insulin secretion difficulties and glucose disposal, transient increase in glucose level during the infection and existing diabetes before admission and drug-induced diabetes (see fig.2). New-onset T2DM may have developed due to undiagnosed diabetes before admission, possibly due to recent excess weight gained brought on by lifestyle modifications, and hyperglycaemia that deteriorated primarily due to self-isolation, social withdrawal, decreased regular exercise,

and poor diets (Khunti *et al*., 2021a; Xu *et al*., 2020). Alterations in behaviour may result in IR which could set off inflammatory pathways resulting in the onset of T2DM (Khunti *et al*., 2021b). The World Health Organization surveyed 155 countries that showed a 53% reduction in preventive and access to non-communicable diseases services among the participants either totally or partially (WHO, 2020).

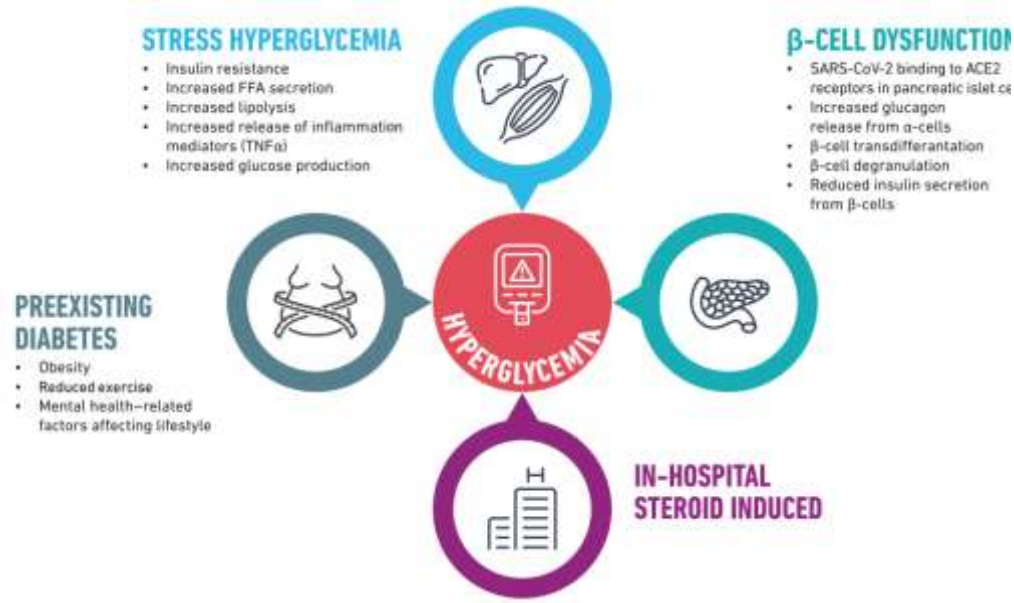


Figure 2: Some Potential Risk Factors for the Onset of T2DM. Adopted from (Khunti et al., 2021b)

The occurrence of a sudden increase in plasma glucose concentration and the onset of diabetes due to hospitalization following an illness is a known phenomenon (J. K. Yang *et al*., 2006). Stress-related hyperglycaemia is a symptom of insulin insufficiency connected to raised lipolysis and the presence of free fatty acids (FFA) in conditions like myocardial infarction and serious infections (Capes et al., 2000). The cytokine onslaught in COVID-19 infection may worsen stress hyperglycaemia. Elevated concentration of inflammatory biomarkers like CRP, erythrocyte sedimentation rate (ESR), and leukocytes are seen in recently detected T2DM patients (H. Li *et al*.,

2020). Studies have shown much higher levels of neutrophils, D dimer, and markers for inflammation in increased glucose concentrations than was seen in normal glucose concentrations in persons with COVID-19 infections suggesting worsening IR due to the acute inflammation seen in the cytokine onslaught (Accili, 2021a; Coppelli *et al*., 2020).

Excess weight gain is a predisposing influence for T2DM and critical COVID-19 complications and as well contributes to poor glucose use, immunological responses, and inflammation (Accili, 2021a; Chudasama *et al*., 2020). Data on new-onset diabetes prevalence brought on by COVID-19 infection paints an unclear picture when compared to facts from individuals admitted with similar acute diseases (Sathish *et al*., 2021). Few researchers have followed these individuals after they were discharged from the hospital to assess if the stress-related hyperglycaemia is temporary or develops into T2DM. Acute pancreatic inflammation caused by different viruses like the cytomegalovirus, herpes simplex virus, HIV, mumps, measles, and hepatitis virus has been documented in earlier research (Rawla *et al*., 2017).

Enterovirus infection has substantially been linked to both clinical T1D and T1D-related autoimmunity in 24 case-control studies (Yeung *et al*., 2011). According to this idea, limited virus-facilitated destruction of beta cells releases previously hidden antigens, which activate autoreactive T cells, triggering an immune mechanism that destroys the remaining beta-cell population, resulting in insulin-dependent T1DM (Boddu *et al*., 2020). This phenomenon takes weeks and cannot clarify how diabetes develops in the active phase of COVID-19 but it may be the mechanism behind how some people get diabetes weeks to months after the infection has cleared up.

Coronavirus type 1 infected persons with pneumonia have shown a higher incidence of acute-onset diabetes and fasting glycemia in the past (J. K. Yang et al., 2010c). Environmental variables like viruses and some pathogens may be significant predisposing factors according to several studies (Eslami & Jalili, 2020; Schneider & von Herrath, 2014) either by direct cytolytic action and progressive beta-cell loss or by-stander immune system activation (Rodriguez-Calvo *et al*., 2016). Another meta-analysis of 34 kinds of research in both retrospective and prospective studies significantly saw an elevated incidence of T2DM in persons infected with hepatitis C virus compared to others without the infection. A higher risk was seen when compared to control participants who had the hepatitis B virus (D. L. White *et al*., 2008).

Coxsackie B viruses have been proven to cause β-cell death or functional impairment in human islet cells resulting in new-onset T2DM (Geravandi *et al*., 2020). A sudden increase in glucose concentration in COVID-19 infections has been related to the virus binding to the ACE2 in the pancreas (Ali Abdelhamid *et al*., 2016; Drucker, 2020; Govender *et al*., 2020). It has been demonstrated that ACE2 expression is more in the pancreas than in the respiratory organs and is present in both exocrine glands and the pancreatic islets, including beta cells (Fignani *et al*., 2020; F. Liu *et al*., 2020a). Studies reveal that small subset of beta cells express ACE2, which makes the evidence for ACE2 expression in pancreatic cells unclear (Atkinson & Powers, 2021; F. Liu *et al*., 2020b).

SARS-COV-2 invasion of pancreatic endocrine cells, particularly beta cells, is not likely a major cause of diabetes, according to a research on human pancreatic samples that found ACE2 expression in the pancreatic ductal

epithelium and micro-vasculature (Kusmartseva *et al*., 2020). Other pathways may be direct pancreatic beta cell inflammation and damage from COVID-19's cytokines capable of promoting inflammation and acute-phase reactants (Wu *et al*., 2021a). COVID-19 infected persons experience cytokine onslaught which is a highly inflammatory clinical condition that can affect pancreatic beta-cells directly or indirectly. Three infected COVID-19 persons who died in China were found to have islet degeneration during an autopsy analysis (Yao *et al*., 2020). Presence of genes and proteins in autopsy pancreatic samples from COVID-19 infected persons and live human pancreatic cultures from a recent study suggests that the virus can invade pancreatic cells. It also showed that endocrine islets, exocrine acinar, and ductal cells in the pancreas aided SARS-COV-2 invasion of host cells (Shaharuddin *et al*., 2021). The COVID-19 infection causes beta cells to undergo apoptosis leading to a reduction in pancreatic insulin production and concentration (Wu *et al*., 2021b).

Hepatic symptoms and cell malfunction brought on by amyloid due to COVID-19 effects on several organs may have a part in the progress of new-onset T2DM. It has been proven that persons infected with COVID-19 undergo liver dysfunction marked by mildly raised serum aspartate aminotransferase levels (Amin, 2021). An increase in glucose concentration brought on by steroids is frequent in hospitalized patients (Choudhry *et al*., 2016). Study participants being 53-70% without a history of diabetes get hyperglycaemia by steroid administration according to an earlier study (Cheung, 2016). Seventy percent of participants in a study conducted in Australia among 80 hospitalized adults without a history of diabetes had at

least a blood glucose reading of 10 mmol/L (Fong & Cheung, 2013). In an analysis of 13 studies, a total of 32.3% of participants got hyperglycaemia by glucocorticoid administration, and 18.6% developed diabetes (X. X. Liu *et al*., 2014). The use of steroids may be a predisposing factor for T2DM development which is largely connected with drug-induced anomalies with slowed or impaired recovery of β-cell damage (Accili, 2021b).

Insulin Resistance and Diabetes Mellitus

Diminished tissue sensitivity to insulin results in IR (Tam *et al*., 2012a). Pancreatic islets of Langerhans produce insulin which promotes the transport of glucose to the muscle, liver, and adipose tissue, (Davids *et al*., 2020). Diabetes and cardiovascular disorders result from improper glucose regulation (Lauterbach & Wunderlich, 2017). IR affects around 46.5% of the global adult population, with the highest occurrence seen in Lebanon, and Asia, the second highest in Thailand, and the lowest in Europe (Tam *et al*., 2012b). There is little information on the incidence of IR in Africa, although a South African study saw a reduction from 24.8% in 2009 to 16.9% in 2016 (Davids *et al*., 2020).

When insulin does not adequately regulate blood glucose levels, diabetes mellitus develops (Prabhakar & Doble, 2011). T1DM and T2DM are the two most prevalent varieties (Ndisang *et al*., 2017). When the genes responsible for activating the pancreatic beta cells are genetically mutated or when an autoimmune response destroys the beta cells, T1DM results (Mishra & Ndisang, 2014). This could be related to cell death and oxidative stress brought on by hyperglycaemia, endothelial dysfunction, or a change in lipid metabolism (Petersen *et al*., 2017). In subgroups of very unwell COVID-19

infected persons, the exocrine and endocrine pancreatic production of ACE2 was reported to be likely related to an increased incidence of diabetes (Drucker, 2020). By attaching to the ACE2 receptor, the SARS-COV-2 causes pancreatic islet impairment and the onset of acute hyperglycaemia (L. Yang *et al*., 2020) which follows the same signalling pathways as coronavirus type 1 (J. K. Yang et al., 2010c). T1DM cases are more common in infected COVID-19 persons who are genetically susceptible to diabetes (Marchand *et al*., 2020), as shown by a 1.5% increased rate in admitted COVID-19 English patient group compared to non-infected patients (Barron et al., 2020).

T2DM is defined as glucose intolerance from an imbalance in the breakdown of carbohydrates and lipids (Z. Yang *et al*., 2021). The physiological role of beta cells and insulin sensitivity are both affected by hereditary, lifestyle, and environmental variables, which are often linked to this condition (Murea *et al*., 2012). Obese people are predisposed to the development of T2DM due to altered metabolism of leptin and adiponectin and the production of resistin and tumour necrosis factor (TNF) by the adipose tissue all of which disturb glucose breakdown by promoting insulin insensitivity (Duvnjak & Duvnjak, 2009). Additionally, the presence of glucose transporter 4 (GLUT4), needed for glucose translocation, is significantly suppressed by TNF. A decreased insulin production and function cause an excessive blood glucose concentration, while a surge in insulin insensitivity results in IR, one of T2DM's characteristics (Chadt & Al-Hasani, 2020). COVID-19 significantly worsens diabetic ketoacidosis, resulting in a pro-inflammatory environment with raised levels of IL-6, IL-1β, and TNF (Trevisani *et al*., 2020).

SARS-CoV-2 and Insulin Resistance

IR is rarely assessed in standard clinical care in our setting, masking its influence on COVID-19 outcomes. IR measures that may show adipose tissue dysfunction in COVID-19 are currently being evaluated in studies. A study of 4,102 COVID-19 persons in the United States saw respondents with acute respiratory disease syndrome (ARDS) presented an increased incidence of elevated plasma glucose concentration with worse consequences compared to those without ARDS (Reiterer *et al*., 2021). Higher concentrations of serum C-peptide and amylin in COVID-19 infected persons show a higher secretory beta cell activity inconsistent with common beta cell malfunction concepts. In addition to having elevated C-peptide-to-glucose ratios, COVID-19 patients with ARDS showed concentrations of IR that were three to six times greater than those of control participants, and 62% of them had no history of diabetes. Leptin concentrations were higher and serum adiponectin concentrations were lower in COVID-19 persons with respiratory difficulties leading to ratios of adiponectin and leptin that might promote adipose tissue failure in IR.

Scientific evidence from COVID-19 infected hamsters in Syria supports lower adiponectin levels in serum, hypodermal, and abdominal adipose tissue. Despite the lack of SARS-COV-2 nucleocapsid immunohistochemistry to support viral copying within adipose tissue cell types, adipose tissues were shown to have nucleocapsid copies, raising the possibility of SARS-COV-2 infecting adipose tissues within the host. Related findings into COVID-19 and IR were provided by Montefusco *et al* (2020), who examined prolonged alterations in glucose metabolism preceding acute COVID-19. Forty-six percent of Italian participants with no earlier

records of diabetes developed new-onset diabetes during the acute phase. Six months following COVID-19 recovery, 35% of this group remained hyperglycaemic, while another 2% were identified with T2DM, proving that the onset of hyperglycaemia can subject people to prolonged glucose-related problems.

In reaction to arginine activation, persons with T2DM, active COVID-19, or those who recovered from the infection showed greater concentrations of insulin and C-peptide secretion, which is in line with both short- and prolonged increased beta-cell secretion activity and IR after COVID-19 according to Reiterer *et al*, (2021). This calls for broader studies to see if these long-term undercurrents have a significant impact on new-onset diabetes rates. Metabolomic techniques used in measuring lipid biomarkers in COVID-19 persons have proven IR in COVID-19 persons (Barberis *et al*., 2020). Higher than normal concentrations of free fatty acids or triglycerides in COVID-19 persons show fat and energy metabolic abnormalities. Insulin and adiponectin hinder the liver from absorbing circulating fatty acids and releasing adipocyte-stored fatty acids into the blood, which is necessary to produce triglycerides in the liver to support glucose production from fats or proteins. Hyperglycaemia and IR may worsen because of an elevated free fatty acids and triglycerides by adipose tissue lipolysis in COVID-19 infection. Elevated free fatty acids and triglycerides concentrations may point to stress-related hyperglycaemia and temporary IR that typically occur in critical illness because samples were taken within 24–48 hours (about 2 days) of hospital admission. However, the persistence increased glucose concentration and IR which may subject people

to T2DM after COVID-19 resolution (Montefusco *et al*., 2021) calls for a longitudinal study.

Malaria and Insulin Resistance

IR, or a decreased sensitivity of cells to the effects of insulin, is one of the primary risk factors for T2DM. Before the onset of full-blown T2DM, reduced insulin sensitivity typically coexists with beta cell failure. The prevalence of T2DM is rising globally, with the sub-Saharan Africa region expected to have the biggest increase. The International Diabetes Federation (IDF) estimates that by 2040, there will be 642 million adults with T2DM, up from 415 million in 2015 (IDF, 2015). By 2040, there will be 34.2 million adult cases of the disease in sub-Saharan Africa, up from 14.2 million in 2015 (IDF, 2015). Compared to the expected global growth of 54.7%, this shows an increase of 140.85% in Africa. Additionally, sub-Saharan Africa has the largest percentage of untreated T2DM cases, putting the area at risk for complications from diabetes. The depressing forecast of rising T2DM incidence for sub-Saharan Africa is based on expected increases in obesity prevalence in the area. Obesity, which is characterized as the accumulation of extra body fat, is quite common in Ghana (Bosu, 2015; Cuong *et al*., 2007) and may aid in the start of T2DM via IR. As a result, several T2DM risk factors and IR appear to be related. Interestingly, different communicable diseases produced by many infectious organisms are a threat in Africa, particularly in the sub-Saharan region. An example is malaria which is a primary cause of morbidity and mortality in Africa compared to other continents worldwide (WHO, 2012).

Despite concerted attempts to reduce its spread and disease drain, malaria still accounts for most outpatient visits in Ghanaian healthcare institutions. These findings explain why there is a belief of a dual illness load on the African continent, which includes the burdens of both communicable and non-communicable diseases. To do this, it may be worthwhile to investigate the connection between contagious illnesses like malaria and their non-contagious counterparts, such as T2DM. There is little question that hypoglycaemia is a serious complication of severe malaria, which is more common in children, though few studies have documented hyperinsulinemia and hypoglycaemia in such circumstances in adults (N. J. White *et al*., 1983) and animal models (Elased *et al*., 1995; Elased & Playfair, 1994; Taylor & Molyneux, 2015).

Hypoglycaemia may be brought on by a blend of insulin action, increased host glucose consumption by malaria parasites, and impaired glucose anabolism. Mild, uncomplicated malaria is more common in semi-immune adults and is connected to accelerated gluconeogenesis (Esan, 2014) and elevated blood glucose levels (Acquah et al., 2014b). These findings imply that malaria's impact on glucose metabolism may be complicated. New evidence from human research appears to show the possibility of malaria causing IR in both children and adults (Acquah et al., 2014b; Eltahir et al., 2010), most likely by interaction with indicators of inflammation, oxidative stress, and lipid metabolic processes (Acquah *et al*., 2016; Jensen et al., 2012). The discovery made in both critical (Eltahir *et al*., 2010) and moderate (Acquah *et al*., 2014) types of human malaria, enforces the possible link between malaria and T2DM. In 2017, a study examining the relationship

between insulin resistance and parasitaemia in rats found that repeated cases of malaria could induce afflicted cells to acquire insulin resistance, raising the chance of the affected developing T2DM (Acquah et al., 2017).

The link between the two conditions can poses a novel challenge that calls for a careful investigation to avoid the likely associated negative outcome. This is because of the prevalence of malaria on the African continent, the predicted incidence of T2DM, and the possibility of multiple episodes of the malarial condition.

COVID-19 Pathogenesis and Oxidative stress

Oxidative stress occurs when the circulating concentration of reactive oxygen species (ROS) exceeds the limits of the cell's antioxidant reserve, possibly due to inflammation and injury to cellular macromolecules (Alkadi, 2018). Free radicals and ROS are created during typical cellular metabolism. ROS contributes favourably to significant signalling pathways necessary for vital cellular activities under normal physiological circumstances (Alpay *et al*., 2015). When dioxygen is converted to superoxide anion (O_2^-) in the electron carriers, the mitochondria produce ROS during an enzymatic reaction that results in the formation of ATP.

Some radicals, including hydroxyl (OH•), organic peroxides, and hydrogen peroxide (H_2O_2), can be produced when superoxide anion interacts with d-block elements like iron (Fe) and copper (Cu) which is likely to form other ROS by the mitochondrial respiratory chain (Valko *et al*., 2007). In typical cell physiology, ROS play many significant roles. Angiotensin II promotes superoxide anion synthesis in endothelial cells via activating nicotinamide adenine dinucleotide oxidase (Nguyen Dinh Cat et al., 2013).

Proteins that regulate cell proliferation are stimulated because of superoxide anion triggering the Raf-1 mitogen-activated protein kinase (MAPK) in the lower region (Harijith *et al*., 2014a). Superoxide anion increases the blood pressure-regulating hormone, vasopressin, generation in the central nervous system (CNS) (Gonzalez *et al*., 2020).

Nitric oxide, a signalling chemical produced by the isoform of nitric oxide synthase in reduced levels in vascular endothelial cells, proves the significance of ROS in vasodilation (Pisoschi & Pop, 2015). Nitric oxide synthase is also employed by macrophages to produce nitric oxide, which is used to destroy invasive infections. Nitric oxide stimulates relaxation of the corpora cavernosa, which increases blood flow and supports the penile function necessary for reproduction in smooth muscle tissue (Cecchini & Cecchini, 2020).

Tumour necrosis factor alpha (TNF-α) is a cytokine that also enhances the production of mitochondrial ROS, which are linked to programmed cell death (Doss C *et al*., 2014). This instance shows how ROS plays a helpful role in healthy cell physiology. On the other hand, ROS have negative effects on cells by oxidizing macromolecules including lipids, proteins, and carbohydrates, which alter how they function. With its short half-life and high reactivity, the hydroxyl radical can generate adducts through interaction with DNA bases to change transcription and affect how proteins function (Thimmulappa *et al*., 2019). Due to their capability to synergistically increase DNA damage and, DNA breakage, protein backbone alteration is promoted by peroxyl radicals (Liou & Storz, 2010). The likelihood of mutation is increased

when this kind of oxidative destruction to DNA leads to the generation of 8-hydroxy deoxyguanosine (8-OHdG) (Matsui *et al*., 2000).

Although much is not known about the levels of DNA adducts in COVID-19 persons, likely, the elevated concentrations of indicators of oxidative stress seen in these clients could lead to DNA oxidation and most resultant effects (Cecchini and Cecchini, 2020). Malondialdehyde (MDA) and 4-hydroxynonenal, which have an impact on the density and viability of cell membranes, are produced when membrane lipids are oxidized (Niki, 2014). When membrane lipids are oxidized by ROS, the internal mitochondrial membrane structure is altered, which leads to the widening of the mitochondrial permeability transition pore, diminished mitochondrial membrane permeability, leakage of cytochrome C, and ultimately cell death (Yadav *et al*., 2015). Lipids are extremely vulnerable to peroxidation from free radicals particularly polyunsaturated fatty acids which have many double bonds. Since lipids make up the membrane bilayer, any action by radicals results in lipid peroxidation (Ray *et al*., 2000). The resistance of the cell and the organism together is affected, as well as the permeability and functionality of the membrane.

Because peroxidation is a major pathway cell injury, several illnesses, like diabetes, cancer, heart problems, ischemia-reperfusion, artery disorders, vascular dementia, immunological disorders, and rheumatoid arthritis are linked to higher lipid peroxide and aldehyde production (Zarrini *et al*., 2016). Higher MDA concentration reported in an investigation of COVID-19 persons was related to stress from peroxidation (Muhammad *et al*., 2021).

Proteins that are oxidized, particularly those high in cysteine residues, undergo changes that lead to conformational changes and disrupted function because of detrimental metabolic effects on the three-dimensional structure of the protein (Höhn *et al*., 2014). It has been proven that the hydroxyl radical causes an oxidative attack on the polypeptide backbone by removing hydrogen from amino acid residues. This causes the production of carbon-centered radicals, that quickly interact with dioxygen to produce alkoxyl radicals that can break up and cross-link proteins (Höhn *et al*., 2014).

ROS can further oxidize other cellular macromolecules by forming alkoxyl radicals from the oxidation of proteins. Aging-related diseases like vascular dementia, respiratory difficulties, cataract development, and muscular-related diseases are strongly linked to the build-up of oxidized proteins, which causes a decline in the activity of enzymes crucial for vital physiological processes (Garcia-Garcia *et al*., 2012). There is insufficient data on the levels of oxidized proteins in COVID-19 patient populations, but the elevated ROS levels seen in COVID-19 infected persons may be causing protein oxidation because of increased cell death, necrotic cell reminants, and pulmonary interstitial fibrosis shown during the evaluation of histopathologic lung samples from COVID-19 persons who died (Donia & Habib Bokhari, 2021).

Particularly prone to ROS-induced oxidation via disulphide production are cysteine and methionine (Bin *et al*., 2017). This has a noticeable impact on receptors with lots of cysteine residues, such as the MAPK, insulin-like growth factor and insulin receptors, and ionotropic receptors, which dimerize and activate on their own without signalling molecules, leading to

dysfunctional activity (Bin *et al*., 2017). ROS enhances the activation of the NF-kB, a transcription factor that controls cytokine secretion, inflammation, and intrinsic immune regulation (Karin & Greten, 2005). Inhibitor kappa beta (IkB), an inhibitory protein of the chaperone family of proteins, hides NF-kB in the cytoplasm in normal circumstances (T. Liu *et al*., 2017).

In response to the right stimulus, inhibitor kappa kinase phosphorylates IkB, releasing NF-kB, which then translocate to the nucleus to ensure a regulated reaction to the stimulatory signal (T. Liu et al., 2017). H_2O_2 and other ROS can oxidize the cysteine residues in NF-kB. This strict regulatory mechanism may be compromised during oxidative stress, leading to altered stimulation of NF-kB by pathways other than IkB phosphorylation (S. C. Sun, 2011). Because of the function of NF-kB as a transcription factor, altered NF-kB activity has several downstream effects (S. C. Sun, 2011).

By inhibiting the apoptosis brought on by the stimulation of Jun N-terminal kinase (JNK) by TNF-α, NF-kB regulates immunological and inflammatory responses as well as inflammation (Darnay *et al*., 1998). One of the MAPK signalling pathways, the JNK pathway, regulates apoptosis, cytokine secretion, and cell proliferation (Mehan *et al*., 2011). In response to stressful situations, the apoptotic signal-regulating kinase 1 (ASK-1) triggers JNK upstream (Kanamoto *et al*., 2000). Stress, such as radiation that damages DNA, exposes cells to stress, which activates proteins that repair DNA damage.

However, when such DNA damage is permanent, the JNK pathway either activates the cell death pathway or inhibits the cell survival route, which causes the cell to be destined for death (Matsuzawa *et al*., 2002). The

oncogenic alteration, neurodegenerative ailments, cell death due to lack of oxygen, and reperfusion injury are all known to cause dysregulated JNK activity (Kanamoto *et al*., 2000). Since COVID-19 pathophysiology prominently involves cell death, which is mediated by NF-kB, it has been proposed that aiming for NF-kB may have clinical benefits for clients (Guisado-Vasco *et al*., 2020). The creation of reactive species by innate and adaptive immune systems that target pathogen penetration into the host system further shows the physiological role of reactive species (Lam *et al*., 2010). To combat infections when exposed to them, phagocytes produce ROS through an oxidative burst (H. Li *et al*., 2021).

The adaptive immune response, which uses antigenic peptides obtained from pathogens through phagocytosis and breakdown and delivered to T cells, is then launched if some pathogens manage to evade this response (Gasteiger & Rudensky, 2014). The immunological effector cells produced by the proliferating and differentiating activated T lymphocytes can show an effective immune response specific to an antigen (Brownlie & Zamoyska, 2013). Reduced T cell numbers, particularly of CD8+ T cells, have been found in COVID-19 persons and linked to the severity of the disease aetiology (J. Liu *et al*., 2020).

A benefit of using the favourable host cellular environment for viral replication and growth is conferred by viruses' small genome sizes since the host metabolic machinery already meets all the needs for viral metabolism (Chaitanya, 2019). Viral pathogenesis is accelerated by the redox imbalance that viruses create to promote replication and proliferation (Reshi *et al*., 2014). According to a report, many viral proteins can manipulate nuclear factor

erythroid-related factor 2 (Nrf2) to produce ROS and keep the host cell's redox state favourable for viral activity (Ivanov *et al*., 2011). The antioxidant response elements in the promoter region of genes for heme oxygenase-1, glutathione-S-transferase, glutathione peroxidase-1, and catalase are bound by Nrf2, an antioxidative transcription factor. The viral gp120 protein in human immunodeficiency virus type one has been connected to the activation of the Nrf2 pathway through the generation of oxidative stress, showing that manipulating the Nrf2 pathway may offer potential methods to antiviral action (Reshi *et al*., 2014).

Hepatocellular damage caused by the hepatitis C virus has been related to viral non-structural protein 3 and non-structural protein 5A that cause oxidative stress in human liver cells (Ivanov *et al*., 2011). Higher ROS generation has been noticed as well in lung damage brought on by the flu virus. There was a decrease in the quantity of active Nrf2 in the nucleus of bronchial adenocarcinoma cells of humans infected with the virus, pointing to viral manipulation of the antioxidant response of the infected humans (Reshi *et al*., 2014).

NrF2 antioxidant gene suppression was seen from biopsies taken from COVID-19 infected persons (Olagnier *et al*., 2020). The authors also noted that SARS-COV-2 replication was restricted after cells were treated with NrF2 agonists, revealing that Nrf2 could play a role in controlling COVID-19 disease (Olagnier *et al*., 2020). Given the specific preconditions for the structural modifications that guarantee the adherence and penetration of an enveloped virus into the host organism, the redox state of the cell is a significant determinant for the entry of the virus (Fenouillet *et al*., 2007).

Disulphide-thiol stability essentially controls a cell's redox state and has an impact on pH and protein stability. A Study has revealed that pathogenesis of COVID-19 is greatly impacted by changes to the natural disulphide state, particularly at a target cell's surface (Suhail *et al*., 2020). Elevated thiol concentration at the SARS-COV-2 spike protein-host cell surface has been found to limit viral adhesion, specifically indicating that a thiol amount is essential for virus entry into cells of the infected organism (Suhail *et al*., 2020). The structural alterations that permit viral attachments and invasion of host cells at the virus-host cell interface may need the action of thiol and disulfide groups as electron donors or acceptors (Suhail *et al*., 2020).

ACE2 activity, which is vital for SARS-COV-2 host entrance, amplification, and later pathogenesis, can also influence oxidative stress in the disease's aetiology (Suhail *et al*., 2020). Cells from several organs express the membrane-bound receptor ACE2. This protein mainly breaks down the vasoconstrictor angiotensin II, which can raise superoxide and ROS concentrations. According to a report, the SARS-COV-2 spike protein must attach to ACE2 which serves as a receptor to enable the virus through the host cell (Suhail *et al*., 2020). Because ACE2 no longer degrades Ang II because of binding to the spike protein, the cellular quantity of Ang II increases. Because of the elevated amounts of Ang II in this circumstance, the patients may experience oxidative stress, oxygen deprivation, and cellular damage that propels the course of COVID-19 and necessitates oxygen treatment.

Oxidative stress and Pathogenesis of Type 2 Diabetes Mellitus

The terms "ROS" and "RNS" refer to pro-oxidants and other non-radical reactive species that are classified as oxidants. Biochemical free radicals are substances created by normal cellular metabolism that are extremely unstable. They possess electrons that are able to interact chemically with a number of different organic substrates, such as lipids, proteins, and deoxyribonucleic acid (DNA). Free radicals are recognized to be both harmful and advantageous to humans (Abid et al., 2013). Free radicals (ROS and RNS) have positive effects at low to moderate concentrations, including mitogenic response activation, defence against pathogenic agents, and cell structure maturation (Rahal et al., 2014). RNS comprises peroxynitrite (OONO), nitrogen dioxide (NO_2), and nitric oxide (NO), whiles ROS comprises hypochlorous acid (HOCl), superoxide anion (O^-_2), hydrogen peroxide (H_2O_2), and hydroxyl (OH). Elevated levels of free radicals cause harmful reactions that lead to oxidative stress, which can harm cell structures (Halliwell, 2009).

An experimental study of diabetic persons and rats has proven a distinct connection between oxidative stress and diabetes. A hyperglycaemic state can reduce the functions of antioxidant enzymes and cause a rise in DNA damage indicators like 8-oxo-7, 8-dihydro-2'-deoxyguanosine, and 8-hydroxy-2'-deoxyguanosine (8-OHdG), nitro tyrosine and carbonyl levels, and thiobarbituric acid-reactive substances (TBARS) due to an increase oxidative destruction of cells (Halliwell, 2009).

A Study in cell culture using endothelium, aortic smooth muscle, and pancreatic beta cells have also proven a stimulated ROS generation in diabetes (Lee et al., 2010). Another study reported that oxidative stress causes insulin

gene promoter activity and mRNA expression to be inhibited in beta cell lines and isolated pancreatic islet cells leading to a reduction in insulin gene expression (Kawahito et al., 2009a). There is a substantial likelihood that oxidative stress contributes to IR brought on by long-term hyperglycaemia (Kawahito *et al*., 2009b).

Experimental and clinical observations have shown that oxidative stress contributes to the pathogenesis of illnesses, such as cardiac diseases and cancers. The biology and aetiology of diabetes are both known to include it as a contributing factor (Halliwell, 2009). This is because persistent hyperglycaemia causes non-enzymatic protein glycation, which produces ROS in the form of Schiff base and Amadori products in human cells and tissues (Kumar Pasupulati et al., 2016; Rehman & Akash, 2017). Chronic hyperglycaemia seems to play a key part in the progress of micro-vascular and macro-vascular difficulties in T2DM.

Hyperglycaemia has also been confirmed to destroy deoxyribonucleic acid, proteins, and lipids, with the magnitude of the destruction being correlated with the amount of ROS production caused by hyperglycaemia, which leads to oxidative stress (Butkowski & Jelinek, 2017a). According to a study on concentration of 8-hydroxy-deoxyguanosine altered peptides in GK-rats and Tucker diabetic rats, hyperglycemia is a key contributor to oxidative stress in pancreatic beta cells, which explains the mechanism behind glucotoxicity (Rehman & Akash, 2017b). Butkowski and Jelinek (2017), engaged 309 diabetic participants from the Diabetic Clinic at Charles Sturt University, Australia, to examine the impact of oxidative stress on T2DM. The control group had normoglycemia and normotension with no outward signs of

heart disease. Blood plasma and urine samples were also examined for oxidative stress biomarkers, lipids, and blood sugar levels. The researchers found that diabetics had higher levels of glycated haemoglobin, lipids, and oxidative stress indicators than non-diabetics. The findings support the interaction between T2DM and oxidative stress brought on by hyperglycaemia and could be used as an additional diagnostic tool to determine the diabetogenic risk in persons with mild to moderate hyperglycaemia.

Oxidative stress causes proteins or enzymes like superoxide dismutase, glutathione peroxidase, catalase, and reduced glutathione to become inactive, and a decrease in these proteins makes oxidative stress worse (Halliwell, 2009). Using the criteria of having undergone glucose tolerance test (OGTT) or been prescribed an anti-hyperglycaemic medication, diabetics were chosen for a study (Maciej Serda, 2013) to review the function of oxidative stress. Individuals in the control group did not have diabetes, cardiovascular disease, renal illness, or respiratory difficulties, but all participants had similar age, sex, smoking, alcohol intake, dietary habits, and levels of activity. According to the scientist, diabetics showed oxidative stress, which also aided the emergence of related diseases.

It might be beneficial to lessen oxidative stress in T2DM persons by reducing daily acute glucose swings. Dysglycaemia (chronic sustained hyperglycaemia and acute glycaemic fluctuations) has a strong connection to the emergence of diabetic complications. These types of dysglycaemia have been linked to two main pathways that involve stimulation of oxidative stress and enhanced stimulation of the inborn immune system, which can result in

diabetic complications (Z. Huang et al., 2012; B. Zhu & Qu, 2022). Glycaemic swings during the day have been positively related to oxidative stress.

Rizzo *et al*. (2013), conducted a randomized controlled trial to assess the influence of glucose fluctuations daily on plasma oxidative stress concentrations (Rizzo et al., 2013). During the first and third visits, each participant underwent a 48-hour continuous subcutaneous glucose monitoring. The scientists concluded that treating type 2 diabetic patients' daily acute glucose variations can lessen the activation of oxidative stress.

The primary culprit of arteriosclerosis progression in T2DM is oxidative stress, which may also raise the frequency of T2DM clinical presentation in patients (Dia et al., 2021). Dia *et al.* (2021), studied and assessed oxidative biomarkers in 45 non-smoking participants with T2DM who were aged 35 to 65 years to find out the association between oxidative stress and T2DM onset or development. According to the study, the level of MDA, a marker of oxidative stress, did not significantly correlate with fasting blood glucose levels. Further research using a bigger sample size is advised because it is probable that the study's results were influenced by the study's limited sample size.

The activation of complexes in the respiratory chain because of alterations in the mitochondrial membrane has been proven to occur in diabetes, which helps to produce oxygen radicals. Also known to produce ROS is, NADPH oxidase which is seen to be the main catalyst for the formation of glucose-induced ROS in the cells of diabetic models. It is essential to remember that xanthine oxidase assists to produce ROS, which contributes to the increased risk of developing hyperglycaemia and associated

complications. It has been observed that during auto-oxidation in diabetes, glucose and its metabolites combine with hydrogen peroxide to create a hydroxyl radical in the presence of iron and copper ions, which increases the production of ROS and advances diabetic complications (Dia *et al*., 2021).

The Impact of Inflammation on the Pathogenesis of COVID-19

Cells have the exceptional capability to recognize infections and prevent their reproduction to defend the body against them. According to Gasteiger and Rudensky (2014), the immune system is generally split into the innate and adaptive immune systems, with the innate serving as the primary line of defence. In an immune reaction, the host cells find the genome of the infection and target it for eradication. This is possible because microbes produce pathogen-associated molecular patterns (PAMPs), which are detected by pathogen recognition receptors (PRRs) in the cells of the host by a special mechanism defined by uniqueness (Muralidharan & Mandrekar, 2013).

A variety of anti-pathogen immune responses are launched after PAMPs are detected by PRRs. Various inflammatory cytokines, chemokines, and type I interferons are produced and secreted more often during the sequence of events (Kumar *et al*., 2011). Toll-like receptors (TLRs), which are essential glycoproteins with exterior luminal ligand binding sites and cytoplasmic activating receptor homology motifs, are one recognized subset of PRRs (Prince et al., 2011). As soon as a ligand attaches to the surface portion of the receptor, a pro-inflammatory response is initiated to attack the pathogen. The oligomerization of receptors initiates this intracellular signalling loop (Prince *et al*., 2011).

TLRs are present on the surfaces of cells and organelles, which limits their ability to detect intracellular cytosolic invaders. As a result, there are cytosolic PRRs that undertake TLR-independent pathogen identification. For instance, oral and genital herpes are caused by the Herpes Simplex Virus (HSV-1 and 2) subtypes (Govindan, 2014). HSV viral particles interact with TLR2 on cell surface membrane during infection leading to an increase in the generation of cytokines (Govindan, 2014).

Interferons are also produced during infection, following toll-like receptor 9 (TLR9) action. The efficiency of PRR-mediated immune responses has been altered by virus-developed strategies. Certain viruses, including those that cause HIV and rabies, include NF-kB binding sites in their promoter regions. These sites help activate NF-kB and control cellular development and programmed cell death (Kammouni *et al*., 2012).

The significant association between the SARS-COV-2 spike protein and toll-like receptors, particularly TLR4, reported by an in silico molecular docking research has raised questions about the prospective role of toll-like receptors in the pathophysiology of COVID-19 infection (Choudhury & Mukherjee, 2020). When pathogens alter a distinguishable chemical trait, such as the arrangement of the monomers in their polymers, the immune response's recognition mechanism is occasionally limited and they can elude detection (Nathan & Shiloh, 2000). A significant increase in apoptosis may prevent lymphocytes from growing and differentiating, which would change immunological responses and improve parasite survival. This is another drawback of the immune response to parasitic invasion (Guillermo *et al*., 2009). Due to these restrictions, cells of the host also employ reactive species

as a defence strategy to neutralize disease-causing microbes and stop infection. The correlation between elevated ROS levels and increased plasma cytokines capable of causing inflammation including TNF-α, IL-6, and IL-8 during infections further supports the idea that an oxidative component is included in the immunological reaction (Gasteiger & Rudensky, 2014).

The innate immune response includes neutrophils, monocytes, and macrophages, each of which performs specific tasks needed for infection defence. Most innate immune effector cells such as neutrophils phagocytose, or use oxidizing agents like NADPH oxidase to eliminate evasive microorganisms (Muralidharan & Mandrekar, 2013). COVID-19 persons may experience oxidative stress and thrombotic events due to reactive species produced by NADPH oxidase 2 (NOX-2) (Beltrán-García *et al*., 2020; Violi *et al*., 2020). The pathophysiology of SARS-COV-2 is also related to increased cytokine levels (J. Liu *et al*., 2020). The intrinsic immune system responds to SARS-COV-2 replication in respiratory system cells by generating macrophages and dendritic cells, which leads to inflammation. On histological inspection, the presence of inflammatory lymphocytic infiltration in the patients' lungs serves as proof of this (Costela-Ruiz *et al*., 2020). Cytokine onslaught with increased concentrations and activity of IL-1β, IL-6, and TNF-α is linked to the illness development (Cecchini & Cecchini, 2020; Delgado-Roche & Mesta, 2020; Suhail *et al*., 2020). A study has proven that the pathogenesis of COVID-19 is caused by the activity and secretion of IL-1β, which then activates IL-6 and TNF-α (Costela-Ruiz *et al*., 2020).

Inflammasomes that are stimulated by the production of ROS are also assembled and activated during the immune response (Harijith *et al*., 2014b).

Inflammasome stimulation leads to the production of caspase-1 and the subsequent activation of IL-1β and IL-18, which are primarily associated with injury to the lungs (Masters, 2013). The nucleotide-binding oligomerization domain-like receptor having pyrin domain 3 (NLRP3) is a familiar member of the inflammasome family (Abais *et al*., 2015).

T2DM and neurodegenerative ailments are both accompanied by excessive ROS production, which activates the NLRP3 inflammasome and other cytokines (Abais *et al*., 2015). NLRP3 was studied in post-mortem patient tissues and human mononuclear cells from peripheral blood in a research on the function of inflammasomes in COVID-19 (Rodrigues *et al*., 2021). The findings showed that the samples included active NLRP3, which was linked to caspase 1 activity, IL-18 activity, the extent the of illness, and bad outcome (Rodrigues *et al*., 2021), showing that NLRP3 may be a viable treatment target for COVID-19.

The Function of Inflammation in T2DM Pathogenesis

Understanding the mechanisms involved in the onset of T2DM is thought to be aided by the notion that the condition is an inflammatory disease. According to an earlier study (Sam & Mazzone, 2014), the presence of inflammatory activators predicts potential for future occurrence of T2DM in individuals. Raised blood concentrations of sialic acid, IL-6, and CRP were found to be predictive of the onset of T2DM, according to another study (Duncan et al., 2017). Elevated inflammatory biomarkers predicted IR and the onset of T2DM, according to a 2017 work by Fizelova *et al*. (2017). Additionally, research that studied the link between fasting insulin (FI) and CRP levels in the blood plasma of diabetics revealed a connection between

inflammatory processes and insulin insensitivity (Gelaye et al., 2010). According to other studies (Rodríguez-Hernández et al., 2013; W. L. Sun et al., 2011) chronic sub-clinical inflammation aid IR syndrome, a prominent hallmark of metabolic syndrome, and mild inflammation have been a predisposing factor for T2DM development.

Researchers have discovered that adipose tissue can release the primary cytokines capable of inducing inflammation, including TNF and IL-1 and 6, however the precise method by which the inflammatory process drives the progression of T2DM is yet unknown. These inflammatory markers are related to body weight gain, implying that stimulated innate immunity and inflammation are biologically principal factors in the pathophysiology of T2DM (Donath et al., 2019). For instance, diabetic neuropathy is thought to develop because of metabolic, enzymatic, and microvascular changes brought on by hyperglycemia that are connected to the production of local and infiltrating cytokines that can cause inflammation and have an impact on neurons in the central, peripheral, and nervous systems.

Animal research has also proven that mRNA expression in diabetic retinopathy for IL-1 and TNF-α is markedly raised in the retina of diabetic animals, while suppression of TNF-α enhanced diabetic retinopathy prevention (Pickup, 2004). persons with T2DM who had developed nephropathy had elevated levels of CRP, serum amyloid A, interleukin 6, and fibrinogen (Dalla Vestra et al., 2005). Another study discovered that mice with T2DM and diabetic nephropathy had greater levels of intracellular adhesion molecule 1(ICAM-1), a known inflammatory trigger that increases leucocyte

and macrophage influx and attachment in glomeruli and tubules (Chow et al., 2005).

Mice with diabetes were shown to have significantly higher TNF- mRNA expression levels in their kidneys than non-diabetic ones (Navarro & Mora-Fernández, 2006). Cytokines are thought to be toxic to epithelial cells, mesangial, and glomerular and may cause serious kidney damage. Another sign that inflammation contributes to the progression of T2DM is the discovery of a new gene, Tanis, whose activity is evidently affected by glucose and is disrupted after fasting in the diabetic state. Tanis is thought to be a receptor that attaches to the acute-phase inflammatory response protein known as serum amyloid A which has been related to the onset of T2DM (S. Huang et al., 2022). Donath and Shoelson (2011), found that T2DM patients have higher blood levels of fibrinogen, leukocyte count, CRP, serum amyloid A and cytokines capable of causing inflammation like IL-1β and IL-6, and chemokines like MCP-1. However, when type 2 diabetes mellitus patients make significant lifestyle adjustments that result in weight loss, these characteristics are reduced.

Adipose tissue, pancreatic cells, and muscle are inflammatory spots in the existence of obesity and T2DM, and these cells are central in the generation of cytokines capable of causing inflammation, according to many experts. The c-Jun N-terminal kinases (JNKs) and nuclear factor-kappa B routes are stimulated in more tissues in T2DM, playing a crucial role in increasing tissue inflammation. This disruption of insulin signalling in peripheral tissues allow cells to promote IR through the autocrine and paracrine pathways (Esser et al., 2014; Shoelson et al., 2006).

Inflammasome NLRP3 is an essential multi-protein oligomer found to trigger inflammatory responses (Kelley *et al*., 2019). The progression of metabolic syndrome and T2DM is aided by the maturation and release of cytokines that can cause inflammation such as IL-1 and IL-18. Beta cell failure, apoptosis, insulin insufficiency, and the progress of T2DM were because of the NLRP3 inflammasome activation in the pancreas by elevated glucose and fatty acid levels and the ensuing production of IL-1β (R. Zhou et al., 2010).

The innate immune system is thought to be activated by factors like obesity, physical inactivity, smoking, poor diet, mental stress, and infections, which cause chronic low-grade inflammation. Proinflammatory cytokines are then released, which increase IR, which in turn causes T2DM (Kavouras et al., 2007) Sedentary adults showed an increase in glucose and insulin concentrations than active people in the same weight group (Martinez-Ferran et al., 2020), while smoking has been positively related to many inflammatory biomarkers (M. Li et al., 2020). On the other hand, dietary practices have been linked to the treatment and averting of diabetes and IR (Sami et al., 2017). For instance, increasing ingestion of red meat may result in non-diabetic individuals developing IR (Kim et al., 2015).

Kavouras et al., (2007b). engaged 3042 participants for randomized controlled research to examine the effect of lifestyle on inflammatory markers in T2DM (Kavouras et al., 2007). The authors proved a relationship between mild inflammatory indicators and glycemia control variables independent of demographic and lifestyle indicators such as dietary components. Diabetics had higher concentrations of CRP, IL-6, and TNF than people without

diabetes. Following multi-adjustments analysis, the findings also revealed a positive association between blood glucose, insulin, CRP, and IL-6 concentrations, supporting the idea that low-grade inflammation is a key player in developing T2DM. Inflammatory biomarkers may be more prevalent due to IR (Kim *et al*., 2015). This correlation may be due to cytokines capable of causing inflammation, leptin, and tumour necrosis factor that influence insulin sensitivity or production.

TNF may cause IR by reducing the insulin receptor's ability to phosphorylate on its own, turning the insulin-receptor substrate-1 into an inhibitor of the insulin receptor tyrosine kinase activity, decreasing the glucose transporter in muscle cells, and raising blood lipids concentration (L. Chen et al., 2015; Medina-Urrutia et al., 2015). TNF and IL-6 may influence beta cell activity directly or indirectly by promoting the synthesis of free fatty acids. These mechanisms either promote or encourage the development of T2DM, establishing the link between inflammation and IR and explaining how these factors work together to cause type 2 diabetes mellitus. We can learn more about the role of inflammation and how it interacts with other components to cause T2DM from this interaction.

IR and T2DM occurrence are mostly influenced by elevated proinflammatory cytokines and the activation of the inflammatory processes. With this information and understanding, researchers should be motivated to develop a method that can lessen inflammation as a prophylactic approach mostly in the treatment of diabetes mellitus.

The Interrelationship of Oxidative stress, Inflammation, and Hyperglycaemia in T2DM

T2DM does occur due to disturbances in glucose metabolism and the ensuing hyperglycaemia. According to reports, chronic sustained elevated plasma glucose contributes to the occurrence of micro- and macro-vascular problems that are caused by several processes involving oxidative stress and inflammation (Butkowski & Jelinek, 2017b; Rehman & Akash, 2017b). T2DM which is linked to the elevated oxidative stress and ongoing subclinical inflammation may develop due to impaired fasting glucose (Belalcazar et al., 2013).

ROS is found to destroy DNA, lipids, and proteins because of hyperglycaemia-induced oxidative stress, and the severity of the destruction is linked to the length of hyperglycaemia (Tatsch et al., 2012). Elevated free radicals' concentrations are the cause of the oxidative stress brought on by hyperglycaemia. Hyperglycaemia may stimulate a rise in ROS numbers due to reduced concentration or functions of vitamins (vitamin C, E, and A), antioxidant proteins (glutathione), micronutrients (selenium and zinc), and enzymes (catalase, glutathione peroxidase, superoxide dismutase). Oxidative stress may then promote the release of cytokines and chemokines associated with inflammation (Salazar et al., 2014).

Research by Soleiman *et al.*(2013) on the connection between oxidative stress, inflammation, and T2DM observed that reducing oxidative stress and inflammation is essential for hastening the healing process and preventing diabetic complications (Azizi Soleiman et al., 2013). Butkowski and Jelinek (2017b), engaged 309 respondents from the Diabetes Health Clinic

in Australia to examine the connection between oxidative stress, hyperglycaemia, and inflammatory biomarkers. The study emphasized the potential benefit that the biomarkers of inflammatory and oxidative stress may offer in the screening of patients with hyperglycaemia. The findings highlighted the potential involvement of inflammation and oxidative stress in the development of T2DM by demonstrating a relationship between hyperglycaemia, oxidative stress, and inflammatory markers in a population. This association was supported by a review of the patient's clinical status which revealed an elevated risk of heart disease due to the link between T2DM, inflammation, and oxidative stress. Diabetes was linked to oxidative stress and inflammatory reactions and reported hyperglycaemia as a predisposing factor for the onset of T2DM. Between the normoglycemic and hyperglycaemic groups, they noticed changes in the leucocyte count, blood plasma glucose concentration, triglyceride, high-density lipoprotein cholesterol, and glycosylated haemoglobin.

Elevated concentrations of IL-6 and IL-1β have been linked to a triple increase in the risk of T2DM, although low levels of IL-1β were not linked to a higher rate of the disease (Al-Aubaidy & Jelinek, 2011; Donath et al., 2013). It is critical to recognize that greater levels of monocyte chemoattractant protein-1 and a decrease in insulin-like growth factor-1 complement the production of cytokines during hyperglycemia (Dia et al., 2021; Elmarakby & Sullivan, 2012; Esser *et al*., 2014b). According to studies, increased levels of monocyte chemoattractant protein-1 can stimulate macrophage infiltration into adipose tissue, which results in induced adipose de-differentiation and contributes to IR, hyperinsulinemia, and T2DM (Al Hannan & Culligan,

2015). It is believed that the interaction between oxidative stress and inflammation contributes to the evolution of chronic diseases.

Superoxide radicals and oxidative stress are reportedly promoted by elevated interleukin 6, which has a detrimental influence on the efficient utilization of liberated fatty acids. Thus, increase peroxidation results in mitochondrial uncoupling and increases ROS production. Enhanced production of ROS triggers a chain of reactions that results in increased oxidative stress and inflammation.

According to the pathophysiology of T2DM, oxidative stress is among the factors that contribute to the pathophysiology of IR, diminished insulin secretion, reduced glucose uptake, impaired hepatic glucose metabolism, and activated cytokines that can cause inflammation, all of which led to T2DM (Rehman & Akash, 2017b). High glucose levels, hyperlipidaemia, and inflammatory reactions are known to cause oxidative stress in pancreatic beta cells (Dinarello et al., 2010). The production of cytokines capable of causing inflammation such as TNF is increased under a prevailing oxidative stress condition.

Adipocytes have also been seen to produce more ROS, and inflammation-induced oxidative stress is a key contributing factor to the occurrence of T2DM (Donath *et al*., 2013). According to research by Oh *et al.* (2018), an increased oxidative destruction of cells is the main part that causes apoptosis in pancreatic beta cells when they are subjected to a higher number of fatty acids and hyperglycaemia. Additionally, in type 2 diabetic volunteers, a correlation between oxidative stress markers and the existence of pancreatic beta cell lesions has been seen, and patients with increased oxidative stress

have been discovered to have a substantial reduction in antioxidant enzyme activity (Oh et al., 2018). The aetiology of T2DM is related to oxidative stress-induced autophagy. Free fatty acids are one of the variables that cause lipid peroxidation, which leads to peripheral IR in T2DM, which in turn leads to oxidative stress-induced autophagy in pancreatic beta cells.

Possible Link of T2DM to Recovered COVID-19 Patients

Acute hyperglycaemia and IR are known side effects from viral infections such as human herpes virus and severe acute respiratory syndrome coronaviruses due to antiviral responses from host cell defensive mechanisms during infection periods (Sobngwi *et al*., 2008). These conditions may affect glucose metabolism which could increase the risk of developing T1DM or T2DM (Sobngwi *et al*., 2008; J. K. Yang *et al*., 2010a). The penetration of SARS-COV-2 into pancreatic beta cells, followed by cell death, is one theory for the emergence of insulin-dependent diabetes in some COVID-19 infected individuals. The connection between SARS-CoV-1 and a comparable pattern backs up this theory (J. K. Yang *et al*., 2010b). Because the SARS-COV-1 virus prevents the islet cells from functioning properly, infection results in hyperglycaemia, IR, and newly formed T2DM (J. K. Yang *et al*., 2010b).

According to several studies (Eslami & Jalili, 2020; Schneider & von Herrath, 2014), environmental factors like viruses and other pathogens may be important causes of T2DM, either by direct cytolytic action or progressive beta cell loss by autoimmune destruction (Rodriguez-Calvo *et al*., 2016). Enterovirus infection was strongly associated with both clinical T1DM and T1DM-related autoimmunity in a meta-analysis of 24 case-control studies (Yeung *et al*., 2011). This concept proposes that a small amount of virus-

mediated beta cell damage liberates previously hidden antigens, which activate autoreactive T cells, causing self-destruction of the remaining beta cell population that leads to insulin-dependent type 1 diabetes (Boddu *et al*., 2020). This mechanism takes weeks and cannot explain how diabetes develops in the active phase of COVID-19 but may be the mechanism behind the onset of T2DM weeks after recovery from the virus.

Sialic acid, IL-6, and CRP are examples of inflammatory mediators that contribute to a higher risk of T2DM in the future (Sam & Mazzone, 2014; Duncan *et al*., 2017). A 2017 study by Fizelova *et al.* found that elevated inflammatory biomarkers predicted IR and the onset of T2DM. Following other studies (Rodríguez-Hernández *et al*., 2013; Sun *et al*., 2011), mild inflammation was attributed to the onset of T2DM whiles chronic sub-clinical inflammation was linked to IR syndrome, a prominent hallmark of metabolic syndrome. Tumour necrosis factor may cause IR by reducing the insulin receptor's ability to phosphorylate on its own, turning the insulin-receptor substrate-1 into an inhibitor of the insulin receptor tyrosine kinase activity, decreasing the glucose transporter in muscle cells, and raising the levels of free fatty acids in the blood (L. Chen *et al*., 2015; Medina-Urrutia *et al*., 2015).

ACE2 controls blood pressure by converting Ang II to Ang (1–7), reducing IR and oxidative stress, and increasing glucose transporter 4 activity in a healthy microenvironment (Takeda *et al*., 2013). Infection with COVID-19 decreases ACE2 expression, which causes a rise in Ang II activity, IR, oxidative stress, inflammation, high blood pressure, and cardiac malfunction (Finucane & Davenport, 2020). Despite significant global immunization

efforts to stop the COVID-19 pandemic, surviving SARS-CoV-2 genetic variants and continued case and transmission rates offer greater evidence that attention must be devoted to diabetes and diabetic implications after COVID-19 diagnosis and recovery.

Challenges in Researching New-Onset T2DM in COVID-19 Recovered Patients

Although the physiological responses and clinical diagnoses of COVID-19 persons with new-onset diabetes are similar, each person activates different molecular pathways when infected. This trend could result in the onset of T2DM at various points and for varying lengths of time both during and after the viral infection. In order to uncover pathways associated with the development of diabetes, experimental investigations must approach this subject utilizing comprehensive systems biology methodologies because underpinning mechanisms cannot be sufficiently addressed by a single clinical or molecular assay alone. People who are insulin-resistant before contracting SARS-COV-2 may be more prone to developing type 2 diabetes during or after the infection. The challenge of figuring out which of your participants had IR before contracting SARS-COV-2 could be difficult because our hospitals don't routinely screen for it due to the cost involved. Many individuals do not, assuming it is even available. Others may have had undiagnosed diabetes before admission due to a recent weight gain brought on by lifestyle modifications, and hyperglycaemia that is worsened predominantly because of self-isolation, social disengagement, decreased physical activity, and poor diets.

Another challenge that confronts the study of new-onset diabetes is hyperglycaemia brought on by steroids given to hospitalized patients. People without diabetes get steroid-related hyperglycaemia, according to an earlier study (Cheung, 2016). The use of steroids may also be linked to a considerable risk of developing new T2DM which is again connected to steroid-related anomalies with slow recovery of β-cell damage. This may account for T2DM in some recovered COVID-19 individuals.

Summary

This chapter gives a detailed account of SARS-COV-2 mechanism of entry into host cell with associated complications and effect on some metabolic processes. The aetiology of COVID-19 is described, along with links to diabetes, IR, malaria, inflammatory processes, and increased peroxidation. Challenges in studying the onset of T2DM in COVID-19 recovered individuals are discussed as well.

CHAPTER THREE

METHODOLOGY

Introduction

This cross-sectional study employed simple random technique in sampling participants to determine the risk of development of T2DM in COVID-19 recovered patients with or without malaria. Blood specimen and anthropometric measurements were collected for malaria microscopy, fasting blood glucose (FBG), FI, CRP, MDA, body mass index (BMI), waist to height ratio (WHtR) and waist to hip ratio (WHR). Detailed procedure on malaria, FBG, FI, CRP and MDA estimation is given. A brief explanation of the gathering, processing, and analysis of data is provided.

Study Design

This study is a cross-sectional study of confirmed COVID-19 recovered individuals and non-COVID-19 individuals with or without malaria at the Tamale Teaching Hospital. A cross-sectional study is relatively faster and inexpensive (X. Wang & Cheng, 2020). Data for this study were gathered using both qualitative and quantitative methodologies. A questionnaire was used in retrieving data on disease conditions, smoking, and drinking habits, age, sex and medication, occupation, and place of residents.

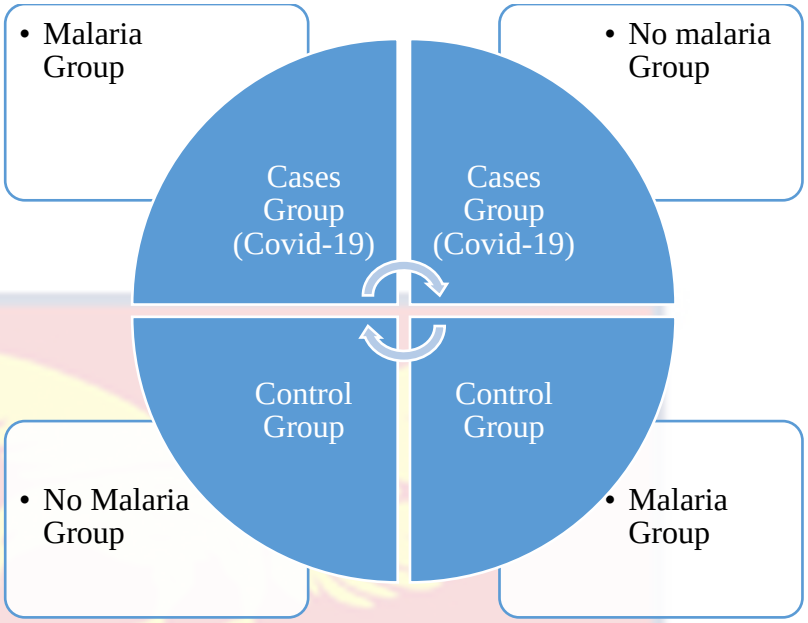


Figure 3: Study design showing the various group of respondents recruited for the study

Study Site

This cross-sectional study was carried out at the Tamale Teaching Hospital (TTH) and the Public Health Reference Laboratory (PHRL) in Tamale, Northern Region of Ghana. TTH and PHRL serve as the major referral hospital and Laboratory for the Upper East, Upper West, Oti, North-East and Savanna Regions, Bono East and Brong-Ahafo Regions. The Public Health Reference Laboratory in Tamale is accredited by International Organization for Standardization (ISO: 90001) and currently serves as the National Reference Bacterial Meningitis Laboratory for Ghana. PHRL is the major testing site for COVID-19 for the five northern regions of Ghana currently. Up until 2018 when the Savanna and the North-East Regions were formed from the Northern Region, it was the largest of the then 10 Regions of Ghana, covering an area of 70,384 square kilometres, or 31% of Ghana's total area. Northern region today has a total area of 26,524 square kilometres and a population of 2,320,939, with Tamale Metropolis having a population of

374,744 and a total area of 454 square kilometres, according to the 2021 Population and Housing Census (GSS, 2021).

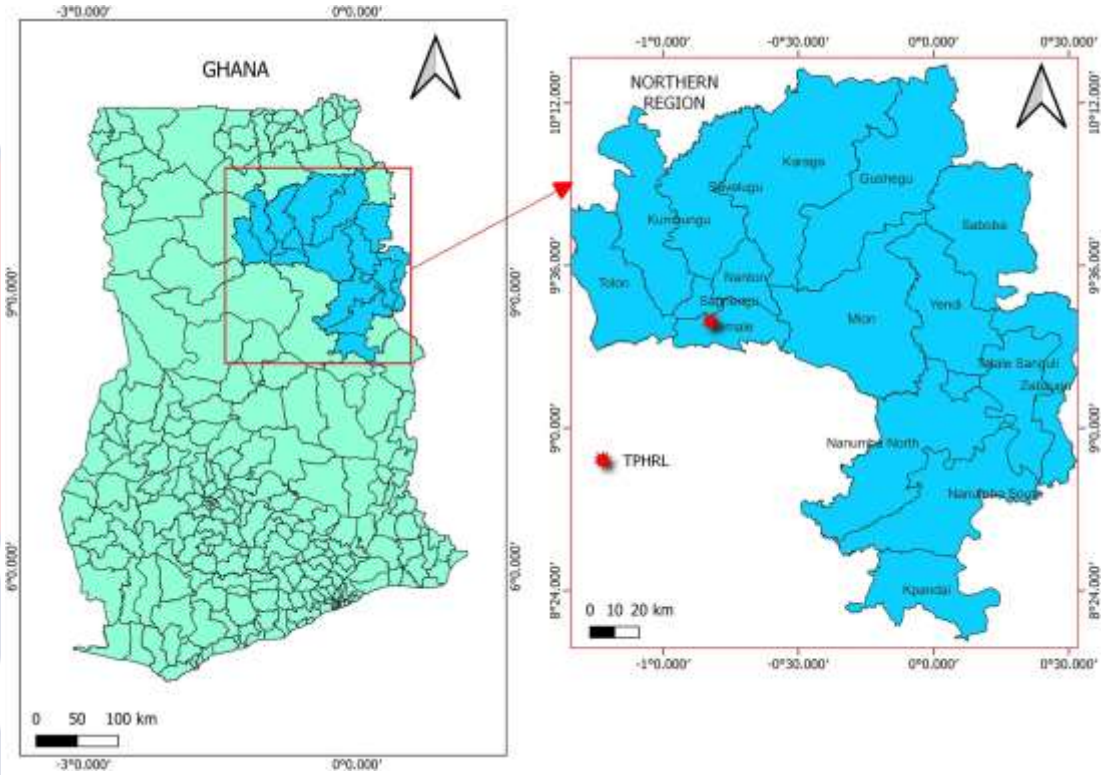


Figure 4: Geographical map of the study area

Ethical Approval

The Ethical Review Committee of the Research Department at the Tamale Teaching Hospital granted ethical clearance for the study. The Hospital administration gave permission to conduct the study at the facility. Participants who met the requirements for the study's eligibility were asked for their informed, written consent. Before obtaining participation consent, all participants were given a clear explanation of the study's goals, procedures, and relevance in a language they could understand. The highest standards of confidentiality were always upheld.

Participants Selection and Sample Size

Population and sampling

In this outpatient cross-sectional study, uninfected COVID-19 individuals and confirmed COVID-19 patients who had recovered from the illness with or without malaria were sampled from March to October 2022. Participants had to be 18 years or above, have never had diabetes before and at the time of sampling to be in the control group. Confirmed COVID-19 persons and negative cases (control group) were both randomly selected from the database of the PHRL for the study. The total number of participants recruited for the study was 290 consisting of 145 confirmed COVID-19 patients who had recovered and 145 uninfected individuals serving as the control group with or without malaria.

Sample size calculation

The study dealt with cases and control with qualitative outcomes of the history of their COVID-19 status. The formula by Charan and Biswas (Charan & Biswas, 2013) was ideal for the sample size calculation because the study involved comparison between two groups with a qualitative endpoints. The study looked at the risk outcomes in cases and control groups with respect to T2DM.

The total number of suspected cases of COVID-19 in the Tamale metropolis was 9658 with 561 testing positive in 2021 from Public Health Reference Laboratory, Tamale database. Using the formula by Charan and Biswas (Charan & Biswas, 2013), the sample size was calculated as follows;

- $Sample\ size = \frac{2(Z\alpha_{/2}+Z_{\beta})^2 P(1-P)}{(p_1-p_2)^2}$

- $P = \frac{Prevalence\ in\ case\ group\ (p_1) + Prevalence\ in\ case\ group\ (p_2)}{2} = \frac{0.058+0.014}{2}$

p_1 = Proportion of outcome from group – 1 = 5.8

p_2 = Proportion of outcome from group – 2 = 1.37

P = Pooled prevalence = 0.0360

α = Level of significance = 0.05

β = Power of the test = 0.20

$Z\alpha/_2$ = Z-score value corresponding level of significance = 1.96

Z_β = Z-score value corresponding level of power = 0.840

$$Sample\ size = \frac{2(1.96+0.840)^2 0.0360(1-0.0360)}{(0.058-0.014)^2} = 276.2 \approx 276$$

$$Attrition = \frac{5}{100} \times (276.2) = 13.81 \approx 14$$

Total sample size = 276 + 14 = 290

An attrition rate of 5.0 percent was calculated and added to the total sample size to carter for sampling bias. A total of 290 participants were selected from the sampling frame (PHRL Covid-19 database). Simple random sampling technique without replacement (SRSWOR) was used in recruiting study participants. Rstudio software was used to generate the randomly selected individual case identification codes for the cases and controls assigned. The total cases for Covid-19 group were 145 from 561 and 145 from 9097 for controls. Mathematical expression of the extractions for cases and controls are;

For cases (145 out of 561):

- Cases <- read.csv (file.choose())

- Sample (Cases, size = 145, replace = FALSE)

  For Controls (145 out of 9097);

- Controls <- read.csv (file. choose())
- Sample (Cases, size = 145, replace = TRUE)

Calls were made to the respondents after they had been randomly chosen. Houses, and places of work were visited for the sampling and anthropometric measurements. Others contacted also decided to visit the laboratory for the sampling. Each of the participants was interviewed based on a questionnaire.

Inclusion Criteria

All individuals who have been confirmed but recovered from COVID-19 and have tested negative after the infection with no history of diabetes before and during COVID-19 infection were included if aged 18 years as part of the case group with or without malaria. Individuals of 18 years and older without a confirmed history of COVID-19 or history of diabetes were recruited for the study as controls with or without malaria.

Exclusion Criteria

Known diabetics before or after COVID-19 infections and participants who tested positive to COVID-19 disease at the time of sampling were not added to the study. Above all, individuals below age 18 years, diabetic and those who did not agree to give consent to take part in the study were not added.

Sample and Data Collection Procedure

Questionnaire

The participants' demographic and socioeconomic information, as well as other harmful behavioural traits including smoking and drunkenness, were

collected via a closed-ended questionnaire. Data on their current clinical condition and medication were taken. Their places of residents and occupation were captured as well.

Anthropometric measurements

BMI, WHtR and WHR were determined for all the respondents. The respondents were instructed to stand straight with their arms at their sides, feet together, and their body weight uniformly distributed (WHO, 2008) before having their weight measured to nearest in 0.1 kg and height to the nearest 0.1 cm using a seca 213 stadiometer and a seca digital weighing scale (Seca Medical Measuring System and Scales Inc., Hamburg, Germany). Using a tape measure (Henan Huajiang Industry Co., Ltd, China), the width of the buttocks and the lower edge of the last palpable rib at the top of the iliac crest were the two points used to measure the waist and hip circumferences. These measurements were done to the nearest 0.1 cm (WHO, 2008). This was done in a relaxed state after normal expiration to reduce the inward pull of abdominal contents (WHO, 2008). The BMI was obtained by dividing the weight (kg) by height (m^2), WHtR by dividing waist circumference (cm) by height (cm), and WHR by dividing waist circumference (cm) by hip circumference (cm).

Blood Collection

About 10 ml of venous blood was collected after overnight fast into, ethylenediamine tetraacetic acid (EDTA), fluoride, and gel separator test tubes for the extraction of plasma and serum through centrifugation for determination of the various research parameters. About 4 ml each of whole blood was kept into the fluoride for plasma and the gel separator for serum

preparation specimen tubes, and the remaining 2 ml of whole blood was kept into the EDTA specimen tube. The whole blood in the EDTA and the plasma sample from the fluoride tubes were analysed the same day for malaria and fasting blood glucose whereas the serum was aliquoted and kept at −80∘ C for further analysis.

Laboratory Analysis

The laboratory analysis was done in line with standard operation procedure (SOP) of the Centre for Disease Control and Preventions. The tests conducted for the study include, malaria parasite identification and quantification, fasting blood glucose estimation, determination of MDA levels, insulin levels, insulin resistance, beta cell function determination, and c-reactive protein levels.

Malaria Parasite Identification and quantification

Thick blood films were prepared on grease-free slides per sample using 20 microliters of whole blood from the EDTA test tube immediately after sampling and followed by staining with 10% Giemsa stain (Capitol Scientific Inc., Austin Texas, USA) for 10 minutes. The slides were washed, dried and examined under oil immersion by a trained medical laboratory scientist. The parasites were identified and counted by multiplying the number of parasites observed per 200 leukocytes by 800 standard leucocytes per microliter of blood and divided by 200 leucocytes counted (Parasite Density = Number of asexual parasites × 800/Number of leucocytes counted). A slide was considered negative after examining 100 high-power fields without seeing a malaria parasite (Prairie, 2012).

Fasting Blood Glucose Estimation

FBG was estimated from plasma recovered by centrifugation of whole blood samples collected into fluoride oxalate using Mindray fully automated chemistry analyser (Mindray Diagnostics, Nanshan Shenzhen, China). The estimation followed the glucose oxidase peroxidase (GOD-POD) enzymatic method. The GOD-POD is the most common among the enzymatic methods that combines specificity with great simplicity and accuracy compared to other methods (Dandekar & Rane, 2004). In the presence of oxygen in the air, the enzyme glucose oxidase (GOD) transforms the glucose present in the specimen into gluconic acid and hydrogen peroxide. A red quinonimine dye that was detected calorimetrically at 540 nm was created when the resultant H_2O_2 oxidatively reacted with 4-aminoantipyrine and phenol in the presence of peroxidase (POD). The intensity of the colour is directly related to how much glucose is contained in the sample.

Determination of Malondialdehyde (MDA) level

MDA reagent meant for the quantitative determination of serum MDA concentration by TBARS ASSAY (thiobarbituric acid-reactive-substances assay) from Solarbio Life Sciences (Solarbio inc. China) was used. TBARS ASSAY is simple and fast, cheaper, versatile, reliable, and widely used by researchers for determining oxidative stress levels (Devasagayam et al., 2003). It followed a calorimetric method. Exactly 100 µl of serum was added to 300 µl of MDA working reagent diluent and 100 µl of thiobarbituric reagent (20% trichloroacetic acid, 0.5% thiobarbituric acid, and 2.5 *N* hydrochloric acid). The mixture was incubated at 100 °C for 60 minutes and tightly closed to prevent moisture lost. It was then cooled on ice for about 15 minutes and

centrifuged at 10000 g for 10 minutes at room temperature to remove insoluble materials. Two hundred microliters of supernatant were taken into a 96 well flat-bottom plate and measured at an absorbance of 532 nm and 600 nm with Apollo 11 LB 13 microplate reader (Montreal Biotech Inc, USA). In an acidic pH and at high temperatures, MDA and thiobarbituric acid (TBA) condense to form pink coloured TBARS with the peak absorbance at 532 nm. The concentration of MDA was determined by subtracting the change in concentration of blank absorbance from sample absorbance at 532 nm, and 600 nm and multiplied by a manufacturer provided factor.

Insulin, Insulin Resistance and Beta Cell Function Determination

Insulin reagent meant for quantitative determination of insulin in serum and plasma by immunoturbidimetric assay from Kamiya Biomedicals Company (K-ASSAY Seattle, USA) was used to measure the insulin concentrations. Immunoturbidimetric principle was chosen because interferences from haemolysis, bilirubin and lipemia is minimal and sensitivity, specificity, precision, and accuracy are better based on the performance characteristics provided by the manufacturer. All reagents, quality assurance materials and samples were brought to room temperature before the analysis was done on Mindray BS240 automated chemistry analyser (Mindray Diagnostics, Nanshan Shenzhen, China).

The insulin calibrators ranging from the concentrations 4.5, 10.6, 25, 49.8 and 105.5 µIU/mL were programmed with levels 1 and 2 controls. It was ensured that the calibrators and control met all quality assurance requirement before the analysis was done. The analyser was programmed to aspirate 16 µL of serum into 175 µL of reagent 1 (buffer reagent) and 65 µL of reagent 2

(Latex suspension) in a multi-point endpoint at 578 nm main and 800 nm sub reaction according to the reagent manufacturers specifications. Latex particles coated with antibodies specific to human insulin bind to insulin from the sample to create immunological complexes. When more complexes are produced, light scattering increases according to the level of serum insulin. Reading turbidity at 600 nm primary and 800 nm secondary allowed for the measurement of light scattering. Insulin calibrators with established concentrations were used to determine the sample insulin concentration.

The IR was calculated using the homeostasis model assessment (HOMA-IR) where the product of basal glucose and insulin levels is divided by 22.5 (HOMA=glucose × insulin)/22.5. The 22. 5 figure is a standard normal or normalizing factor obtained from multiplying normal fasting plasma insulin of 5 µIU/mL, and normal fasting plasma glucose of 4.5 mmol/L (Wallace et al., 2004a). HOMA of β-cell function was calculated using the formula: 20 × fasting insulin (µIU/ml)/ fasting glucose (mmol/ml) − 3.5 (HOMA-B= (20 × FPI)/(FPG - 3.5) and has been proposed to be a good measure of beta-cell function (Wallace et al., 2004a). The HOMA-IR and HOMA-B approach is simple, less expensive and a more reliable method of measuring IR and beta cell function respectively (Wallace et al., 2004b).

C-Reactive Protein

CRP reagent meant for quantitative determination of CRP in serum and plasma by immunoturbidimetric assay from Kamiya Biomedicals Company (K-ASSAY Seattle, USA) was used to measure the CRP concentrations. All reagents, quality control materials and samples were brought to room

temperature before the analysis was done on the Mindray BS240 automated chemistry analyser (Mindray Inc. Nanshan Shenzhen, China).

The analyser was programmed to aspirate 12 µL of serum into 280 µL of reagent 1 (buffer reagent) and 70 µL of reagent 2 (antiserum reagent) in a multi-point endpoint, 340 nm primary and 670 nm secondary wavelength's reaction according to the reagent manufacturers specifications. The CRP calibrators ranging from the concentrations 0.0, 1.0, 4.0, 7.7, 11.8, and 24.7 mg/dL and controls (level 1 and level 2) were programmed into the first 8 positions of the analyser. It was ensured that the calibrators and control met all quality assurance requirements by the manufacturer before the analysis was done.

Antibodies specific for human CRP forms immunological complexes with CRP in the patient's serum. This complex formation is accelerated and enhanced by the polyethylene glycol present in the reagent. The increased light scattering caused by the immunological complex formation correlates with the concentration of CRP in the serum. The light scattering was measured by reading turbidity at 340 nm and 700 nm to determine CRP concentration in the sample.

Reference Ranges for Laboratory Investigations

The reference ranges for the laboratory indices were acquired from reagents manufacturer and credible sources (Elsafty *et al*., 2018; Mas-Bargues *et al*., 2021; Nehring *et al*., 2022). The table below gives a breakdown of indices and their respective reference ranges used for analysis and interpretation.

Table 1: Reference ranges for laboratory tests

Indicators	Unit of measurement	Reference Ranges	
		Females	**Males**
Fasting Blood Glucose	mmol/L		
Low		< 3.4	< 3.4
Normal		3.4 - 6.4	3.4 - 6.4
High		≥ 6.4	≥ 6.4
Malondialdehyde	µmol/L		
Low		< 0.36	< 0.36
Normal		0.36 – 2.80	0.36 – 2.80
High		≥ 2.80	≥ 2.80
Insulin Levels	mIU/L		
Normal		2.6 - 24.9	2.6 - 24.9
Abnormal		< 2.60	< 2.60
		> 24.9	> 24.9
Insulin Resistance	mIU/L		
Normal IR		0.0 - 2.6	0.0 - 2.6
Moderate Elevated IR		2.6 - 5.8	2.6 - 5.8
Highly Elevated IR		> 5.8	> 5.8
C - reactive Protein	mg/dL		
Normal		0.3 - 1.0	0.3 - 1.0
Moderate Elevation		1.0 - 10.0	1.0 - 10.0
Marked Elevation		10 - 50.0	10 - 50.0
Severe Elevation		> 50.0	> 50.0
HOMA - B (Beta Cells function)	(%)		
Normal		> 48	> 48
Borderline		25.0 - 48	25 - 48
Non-insulin dependent diabetes mellitus		< 25.0	< 25.0

Source: Elsafty et al., 2018; Mas-Bargues et al., 2021; Nehring et al., 2022

Data Analysis

Data were collected using a paper based structured questionnaire, transcribed into a designed excel sheet in Microsoft Excel, version 2016, cleaned, edited, corrected for errors, and prepared for data analysis. Coding of dependent and independent variables of interest were done.

Subsequently, data was imported into RStudio, V4.2.2 software. The weighted sample characteristics, prevalence of IR in the COVID-19 recovered and Control groups, measured biomarkers, and anthropometric data were all described using descriptive statistics. In all instances, normality of the datasets was tested using Shapiro-wilks test. The chi square and fisher's exact tests were used, respectively, to determine the relationship between the prevalence of IR and risk factors. In order to investigate the relationships between socioeconomic and health behavioral variables and IR, MDA, and CRP, bivariate and multivariable logistic regression models were used. The socio-demographic, economical, behavioral, and anthropometric characteristics were considered in a binary logistic regression that was stratified by past COVID-19 status. The study conducted hierarchical models to examine the related effects of the numerous confounders on the connection between IR and socio-demographic, socioeconomic, behavioral and anthropometric parameters. Repeated models were adjusted for dependent variables, MDA and CRP with past COVID-19 status, socio-demographic, and anthropometric factors. Adjustments were made for past COVID-19 status in model I, past COVID-19 status, and socio- demographic factors (age and residence) in model II, past COVID-19 status, socio-demographic plus anthropometric factors in model III. Statistical significance level was determined at $P < 0.05$, for all analyses.

Summary

This cross-sectional study employed simple random sampling technique to recruit respondents from the data provided by the public health reference laboratory in Tamale. Participants numbering 290 and above 18 years of age were recruited for the study. Procedures for determination of IR status and other laboratory indices were covered as well as the statistical analyses of data.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

This chapter is made up of two sections, results and discussions with data presented in tables, and figures under the results section whiles the discussion section relates to key findings and observations made in in the context of previous knowledge. This cross-sectional comparative study aimed at determining the risk of development of T2DM in recovered COVID-19 patients with or without malaria. It employed simple random sampling technique in recruiting participants for the study. Serum sample was extracted from whole blood that was aseptically taken in accordance with all standard operating procedures for the analysis.

Results

Demographic Characteristics of Respondents

Young adults (18 – 39 years) dominated the respondents in the cases group with (68.1%: n = 98) and controls (64.1%: n = 93). Adults aged 40-59 years constituted the least age group in the cases group (4.9%: n=7), and controls (7.6%: n=11) with no statistically significant difference. Generally, females (51.7%: n=150) slightly dominated in the study compared to males (48.3%: n=140). However, males were the majority in the cases group (54.0%: n=79).

In table 2, majority of cases (93.0%: n=135) and the entire controls (100%: n=145) do not smoke neither do they drink alcohol (92.1%: n=267). Most of the respondents in the cases were health workers (49.0%: n=71) whiles generally health workers constituted (30.3%: n=88) in the study

population. Majority of the participants had no chronic medical disease (93.5%: n=271).

Table 2: Demographic characteristics of study respondents

Characteristics	Cases, N=145[1]	Controls, N=145[1]	Totals, N=290[1]	P-value
Age Grouping				0.4159
Young adult (18-39yrs)	98 (68.1%)	93 (64.1%)	191 (65.9%)	
Middle-aged (40-59yrs)	39 (27.0%)	41 (28.3%)	80 (27.6%)	
Old age (≥60yrs)	7 (4.9%)	11 (7.6%)	18 (6.2%)	
Mean age **35.7(±13.03)**	35.9 (±12.33)	35.3 (±13.94)	35.7 (±13.03)	
Gender				0.0347*
Female	66 (46.0%)	84 (58.0%)	150 (51.7%)	
Male	79 (54.0%)	61 (42.0%)	140 (48.3%)	
Residential status				0.0891.
Rural	15 (10%)	25 (17.0%)	40 (13.8%)	
Urban	130 (90%)	120 (83.0%)	250 (86.2%)	
Smoking status				0.0013**
Not smoking	135 (93.0%)	145 (100%)	280 (96.6%)	
Smoking	10 (7.0%)	0 (0.0%)	10 (3.4%)	
Alcohol status				<0.000***
Non-Alcoholic	122 (84.0%)	145 (100%)	267 (92.1%)	
Alcoholic	23 (16.0%)	0 (0.0%)	23 (7.9%)	
Occupation				0.0033**
Agric worker	5 (3.1%)	14 (9.7%)	19 (6.6%)	
Artisan	14 (9.7%)	26 (17.9%)	40 (13.8%)	
Health worker	71 (49%)	17 (11.7%)	88 (30.3%)	
Public servant	33 (23%)	26 (17.9%)	59 (20.3%)	
Student	16 (11%)	26 (17.9%)	42 (14.5%)	
Unemployed	6 (4.2%)	36 (24.8%)	42 (14.5%)	
Medical history				0.1063
Cardiovascular	5 (3.4%)	1 (0.7%)	6 (2.1%)	
Liver disease	1 (0.7%)	1 (0.7%)	2 (0.7%)	
Ulcers	9 (6.2%)	0 (0.0%)	9 (3.1%)	
Rheumatic disease	1 (0.7%)	0 (0.0%)	1 (0.3%)	
Tumour	1 (0.7%)	0 (0.0%)	1 (0.3%)	
None	128 (88%)	143 (98.6%)	271 (93.5%)	

[1]N (%)

Signif. codes: '*' < 0.001 '**' < 0.01 '*'< 0.05**

Source: Field data, 2022

Biomarkers of T2DM in cases and control

Majority (57.2%: n=166) of the participants had a normal BMI for both the control group (58.0%: n= 84) and cases (57.0%: n= 82). A total of 90 (31%) respondents were overweight with cases (32.0%: n= 46) slightly higher than that of the control group (30.0%: n= 44). Obesity in controls (12.0%: n= 17) and cases (12.0%: n= 17) were equal. The distribution of respondents for the outcomes, however, was not statistically significant (*p>0.05*) in cases and control. WHR was slightly lower in cases (73.0%: n= 106) compared to controls (74.0%: n= 107) with no statistically significant (*p>0.05*) difference observed between the groups. WHtR had no statistically significant (*p>0.05*) association between cases and controls likewise HOMA-ß *(p>0.05)* and MDA (*p>0.05*). However, CRP, FBG and IR recorded statistically significant (*p<0.05*) association in cases and controls (**Table 3**).

Table 3: Bi-variate analysis of biomarkers of Type 2 diabetes

Characteristics	**Cases,** N=145[1]	**Controls,** N=145[1]	**Totals,** N=290[1]	P-value
Body Mass Index (kg/m^2)				0.7974
Normal (18-24.9)	82 (57.0%)	84 (58.0%)	166 (57.2%)	
Obesity (>30)	17 (12.0%)	17 (12.0%)	34 (11.7%)	
Overweight (25-30)	46 (32.0%)	44 (30.0%)	90 (31.0%)	
Waist to Hip ratio (Cm)				0.8944
High risk	106 (73.0%)	107 (74.0%)	213 (73.4%)	
Low risk	39 (27.0%)	38 (26.0%)	77 (26.65)	
Waist to Height ratio (Cm)				0.5876
Normal	82 (57.0%)	87 (60.1%)	169 (58.3%)	
Increased risk	53 (36.1%)	48 (33.0%)	101 (34.8%)	
High risk	10 (6.9%)	10 (6.9%)	20 (6.9%)	
Homeostasis Model Assessment (HOMA–ß%)				0.2853
Normal (>48%)	126 (96.9.0%)	106 (88.3%)	232 (92.8%)	
Prediabetes (25-48%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
NIDDM (<25%)	4 (3.1%)	14 (11.7%)	18 (7.2%)	

Table 3 Continue

C-reactive protein (mg/dl)				<0.001***
Normal (0.3-1.0)	56 (39.3%)	88 (61.0%)	144 (49.7%)	
Abnormal (> 1.0)	89 (60.7%)	57 (39.0%)	146 (50.3%)	
Fasting Blood Glucose (mmol/L)				0.00547**
Normal (3.4-6.4)	134 (92.4%)	140 (96.6%)	274 (94.5%)	
Low (<3.4)	2 (1.4%)	5 (3.4%)	7 (2.4%)	
High (>6.4)	9 (6.2%)	0 (0.0%)	9 (3.1%)	
Malondialdehyde (nmol/L)				0.4491
Normal (0.36-2.8)	41 (28.6%)	50 (34.0%)	91 (31.4%)	
Low (<0.36)	2 (1.4%)	2 (1.4%)	4 (1.4%)	
High (>2.8)	102 (70.0%)	93 (63.6%)	195 (67.2%)	
Insulin Resistance (mIU/L)				<0.001***
Normal (0.0-2.6)	34 (23.0%)	51 (35.0%)	85 (29.3%)	
Moderate Elevated (2.6-5.8)	64 (44.0%)	78 (54.0%)	142 (49.0%)	
Highly Elevated (>5.8)	47 (32.0%)	16 (11.0%)	63 (21.7%)	
Malaria status				0.3964
Parasites not seen	116 (80.0%)	110 (76.0%)	226 (77.9%)	
Parasites seen	29 (20.0%)	35 (24.0%)	64 (22.4%)	
Mean parasitaemia	29.8 (±82.6)	50.8 (±118.1)	40.3 (±102.3)	

[1]N (%)

Signif. codes: '*' < 0.001 '**' < 0.01 '*'< 0.05**

Source: Field data, 2022

Generally, cases and controls had no statistically significant (*P>0.05*) difference with respect to BMI, WHR, WHtR, MDA, and HOMA-B levels. Statistically significant (*P<0.05*) differences were observed in IR, CRP levels and FBG as shown in table 4, where the cases showed higher levels.

Table 4: Assessment of measured biomarkers of T2DM and anthropometric parameters of cases and controls

Characteristics	Cases = 145[1] Mean(±SD)	Control = 145[1] Mean(±SD)	Total=290 Mean(±SD)	P-value
BMI	25.8 (±5.3)	25.7 (±5.4)	25.7(±5.35)	0.8136
WHR	0.9 (±0.05)	0.9 (±0.05)	0.88(±0.05)	0.9735
WH_tR	0.49 (±0.07)	0.48 (±0.08)	0.49(±0.08)	0.4913
HOMA–*ß*	748.6 (±2105.7)	258.5 (±3977.9)	503.5(±3186.5)	0.3424
Insulin Resistance	7.1 (±8.1)	3.7 (±2.9)	5.4(±6.28)	< 0.001***
C - reactive Protein	1.35 (±1.41)	0.99 (±0.88)	1.2(±1.19)	0.0098**
Fasting Glucose	4.95 (±1.13)	4.26 (±0.58)	4.6(±0.96)	< 0.001***
Malondialdehyde	6.54 (± 6.05)	6.27 (±5.91)	6.4(±5.97)	0.7052
Signif. codes:	**'***' < 0.001**	**'**' < 0.01**	**'*'< 0.05**	

Source: Field data, 2022

Prevalence of Insulin Resistance in the Study Population

Figure 5 indicates prevalence of IR amongst study respondents. Overall prevalence of IR in the study population was 70.7%(n=205). Findings revealed a 21.7% (n=63) highly elevated HOMAIR (*>5.8mIU/L*) prevalence in cases and controls and a 49.0% (n=142) for moderately elevated IR (*2.6 - 5.8 mIU/L*). However, majority (16.2%: n=47) of the cases had elevated IR levels compared to the controls (5.5%: n=16). Moderately elevated HOMAIR levels were more prevalent in controls (26.9%: n=78) compared to cases (22.1%: n=64).

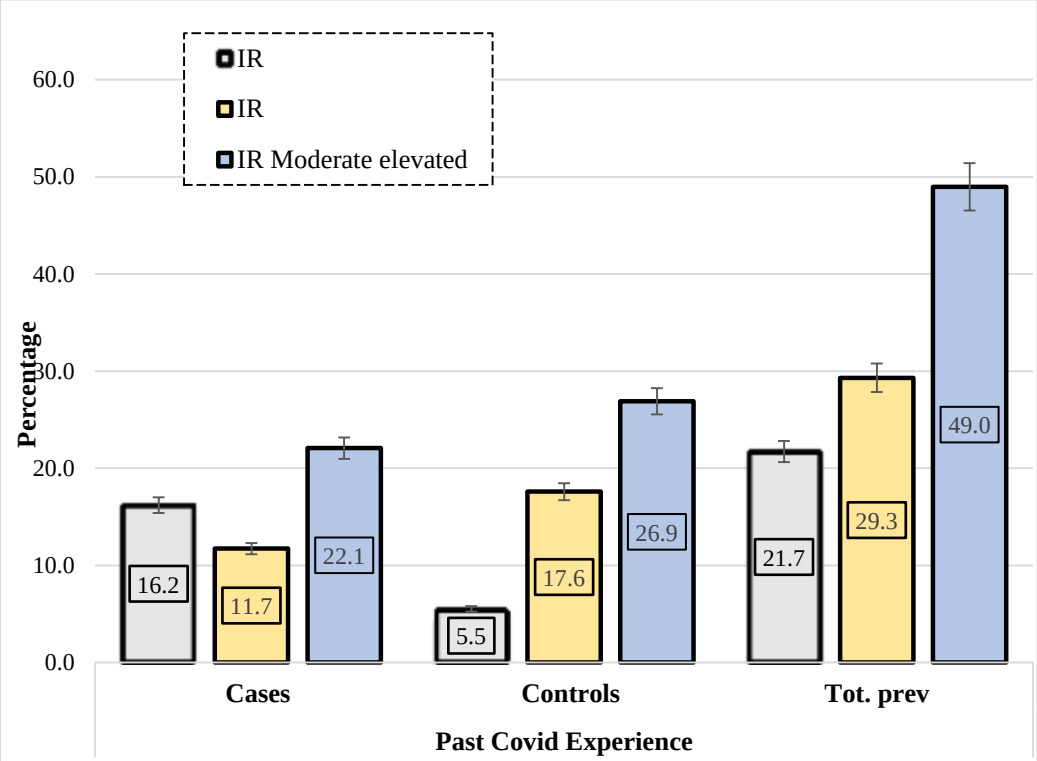


Figure 5: Prevalence of Insulin resistance in cases and controls
Source: Field data, 2022

The weighted prevalence of IR in cases with malaria was 3.4% (95% CI: 1.2–6.9) compared to controls with 11.2% (95% CI: 7.6-16.3). Female prevalence was generally high (37.7%, 95% CI: 32.2-43.3) with cases having high prevalence in males with statistically significant differences ($p<0.05$).

Table 5 illustrates the prevalence of IR in accordance with demographic, behavioural, anthropometric, and clinical characteristics. Respondents in urban areas had a comparable (P = 0.1254; table 5) prevalence with those in rural areas. Young adults (18-39 years) had the highest prevalence in both cases and controls (34.6%, 95% CI: 28.5-41.4 vs 27.85, 95% CI: 22.1-49.9) with no statistical significance difference in percentages (p > 0.05). A significant association between IR and occupation of participants was observed with prevalence in health workers being the highest (23.8%, 95% CI: 19.3-29.0) compared to the other occupation. Respondents with a waist to hip ratio in the high-risk zone (73.2%, 95% CI: 78.8) had higher prevalence in both cases and controls compared to their low-risk cohorts (26.8%, 95% CI: 21.2-33.3). Obese respondents who constituted 11.7% (n=34) of the study population had a prevalence of 9.3% (95% CI: 6.5–13.2) while overweight respondents had a 22.8% (95% CI: 18.3-27.9) prevalence with a total population of 31% (n=90). Respondents with normal BMI had a prevalence of 38.6% (95% CI: 33.2–44.3) with a total population of 57.2% (n= 166) in the study.

Table 5: Prevalence of insulin resistance according to demographic and health behavioural characteristics of respondents

Characteristics	Cases % (95% CI) [n=145]	Controls % (95% CI) [n=145]	Totals % (95% CI) [n=290]	*P-value*
Age categorization				0.0964.
Young adult(18-39yrs)	34.6 (28.5-41.4)	27.8 (22.1-34.3)	44.1 (38.5-49.9)	
Middle-aged(40-59yrs)	16.1 (11.7-21.7)	15.6 (11.3-21.2)	31.7 (25.7-38.4)	
Old age(>60yrs)	2.9 (1.3-6.2)	2.4 (1.1-5.6)	3.8 (2.1-6.7)	
Gender				0.0458*
Female	17.9 (13.9-22.8)	19.7 (15.6-24.6)	37.6 (32.2-43.3)	
Male	20.3 (16.1-25.4)	12.8 (9.4-17.1)	33.1 (22.9-38.7)	
Occupation				8.257e-13 ***
Agric worker	2.4 (1.1-5.6)	4.9 (2.7-8.7)	5.2 (3.2-8.4)	
Artisan	4.4 (2.3-8.1)	7.8 (4.9-12.3)	8.6 (5.9-12.4)	
Health worker	26.8 (21.2-33.3)	6.8 (4.1-11.1)	23.8 (19.3-29.0)	
Public servant	13.7 (9.6-19.0)	10.2 (6.8-15.2)	16.9 (13.0-21.6)	
Student	4.8 (2.7-8.7)	7.8 (4.9-12.3)	8.9 (6.2-12.8)	
Unemployed	1.9 (0.8-4.9)	8.3 (5.2-12.9)	7.2 (4.8-10.8)	
Residential stat				0.1254
Rural	5.4 (3.0-9.3)	3.4 (1.7-6.9)	6.2 (3.9-9.6)	
Urban	48.8 (42.0-55.6)	42.4 (35.9-49.3)	64.5 (58.8-69.8)	
Smoking status				0.0038***
Not smoking	50.7 (43.9-57.5)	45.9 (39.2-52.7)	68.3 (62.7-93.4)	
Smoking	3.4 (1.7-6.8)	0.0 (0.0-0.0)	2.4 (1.2-4.9)	
Alcohol status				1.746e-06***
Not Alcoholic	44.4 (37.8-51.2)	45.9 (39.2-52.7)	63.8 (58.1-69.1)	
Alcoholic	9.8 (6.4-14.6)	0.0 (0.0-0.0)	6.9 (4.5-10.4)	
Body Mass Index (kg/m^2)				0.9663
Normal (18-24.9)	27.3 (21.7-33.8)	27.3 (21.7-33.8)	38.6 (33.2-44.3)	
Obesity (>30)	7.8 (4.9-12.3)	5.4 (3.0-9.4)	9.3 (6.5-13.2)	
Overweight (25-30)	19.0 (14.2-24.9)	8.3 (5.2-12.9)	22.8 (18.3-27.9)	
Waist to Hip ratio (WHR)				0.9041
High risk	40.0 (33.5-46.8)	33.2 (22.1-39.9)	73.2 (66.7-78.8)	
Low risk	14.1 (10.0-19.6)	5.9 (3.4-10.0)	26.8 (21.2-33.3)	
Waist to Height ratio (WHtR)				0.8206
Normal	28.3 (22.6-34.8)	27.3 (21.7-33.8)	39.3 (33.9-45.0)	
Increased risk	21.5 (16.4-27.6)	16.1 (11.7-21.7)	26.6 (21.8-31.9)	
High risk	4.4 (2.3-8.1)	2.4 (1.1-5.6)	4.8 (2.9-7.9)	
Malaria status				0.4790
Parasites not seen	43.4 (36.8-50.3)	34.6 (28.5-41.4)	55.2 (49.4-60.8)	
Parasites seen	3.4 (1.2-6.9)	11.2 (7.6-16.3)	15.5 (11.8-20.1)	
Signif. codes:	**'***' < 0.001**	**'**' < 0.01**	**'*'< 0.05**	

Source: Field data, 2022

Association of Malaria to Malondialdehyde, Insulin resistance, and C-Reactive Protein in the Study Population

In table 6, the overall prevalence of malaria was 22.1%. The prevalence of malaria in cases was 10.0% (n=29) and control 12.1% (n=35). Malaria in high MDA levels in cases was 11.0% (n=16) compared to controls with high MDA levels 17.2% (n=25). Highly elevated IR levels in cases had 6.9% (n=10) prevalence of malaria compared to control with 5.5% (n=8) incidence. Respondents with high CRP concentration recorded 13.1% (n=19) prevalence of malaria in the cases compared to 11.7% (n=17) in the control. However, statistically significant difference in mean parasite count was observed between the cases and controls for MDA ($p<0.05$) and CRP ($p<0.01$).

Table 6: Prevalence of malaria in cases and controls for laboratory indices

Characteristics	**Cases** BF counts (n=29)	**Controls** BF counts (n=35)	**P-value**
Malondialdehyde ($\bar{x}$)	26.0	47.3	0.03618
Normal (0.36-2.8)	13 (9.0%)	10 (6.9%)	
Low (<0.36)	0 (0.0%)	0 (0.0%)	
High (>2.8)	16 (11.0%)	25 (17.2%)	
C-reactive protein ($\bar{x}$)	20.1	64.2	<0.001***
Normal (0.3-1.0)	10 (6.9%)	18 (12.4%)	
Abnormal (>1.0)	19 (13.1%)	17 (11.7%)	
Fasting Blood Glucose ($\bar{x}$)	40.9	22.9	0.3076
Normal (3.4-6.4)	27 (18.6%)	35 (24.1%)	
Low (<3.4)	0 (0.0%)	0 (0.0%)	
High (>6.4)	2 (1.4%)	0 (0.0%)	
Insulin Resistance ($\bar{x}$)	26.6	46.0	0.06438
Normal (0.0-2.6)	7 (4.8%)	12 (8.3%)	
Moderately Elevated(2.6-5.8)	12 (8.3%)	15 (10.3%)	
Highly Elevated(>5.8)	10 (6.9%)	8 (5.5%)	
Signif. codes:	**'***' < 0.001 '**' < 0.01 '*'< 0.05**		

Source: Field data, 2022

Association between Malaria, Malondialdehyde, and C-Reactive Protein in the cases group

There was no statistically significant evidence of an association between malaria and CRP levels (p=0.857) as well as oxidative stress of participants recovered from COVID-19. But AOR = 0.92 (95% CI: 0.36 – 2.35) for cases indicates reduced risk of inflammation without the presence of malaria compared to normal or high CRP levels as seen table 7.

Table 7: Bivariate and logistics regression of the association between malaria and laboratory markers of Cases

Characteristics	Model I: **COR [95% CI]**	Model II: **AOR [95% CI]**	**P-value**
C. reactive protein			
Normal	-	-	-
Abnormal	0.67 (0.29, 1.57)	0.92 (0.36, 2.35)	0.857
Malondialdehyde			
Normal	-	-	-
Low	5.50^{-07}(0.00, Inf)	9.34^{-07}(0.00, Inf)	0.997
High	2.50 (1.07, 5.82)	2.27 (0.94, 5.47)	0.067
Model I: Crude association of factors			
Model II: Adjusted for BMI, Smoking, and Ag			
Signif. codes:	**‘***’ < 0.001**	**‘**’ < 0.01**	**‘*’< 0.05**

Source: Field data, 2022

Association between malaria, Malondialdehyde, and C-reactive protein in the control group

Table 8 denotes the bivariate linear regression of biomarkers with the presence of malaria. There was no statistically significant association after adjusting for age, BMI, and smoking status of control and cases. A normal

CRP levels had inverse relationship with the presence and/or absence of malaria (AOR=0.47, 95% CI: 0.21-1.05) compared to abnormal CRP levels. The presence of malaria in the control and cases that had normal MDA levels introduced a reduced risk of T2DM compared to high MDA levels.

Table 8: Bivariate and logistics regression of the association between malaria and biomarkers of Controls

Characteristics	Model I: COR [95% CI]	Model II: AOR [95% CI]	P-value
C. reactive protein			
Normal	-	-	-
Abnormal	0.43 (0.20, 0.95)	0.47 (0.21, 1.05)	0.0667.
Malondialdehyde			
Normal	-	-	-
Low	4.70^{-07}(0.00, Inf)	8.30^{-07}(0.00, Inf)	0.989
High	0.68 (0.30, 1.56)	0.66 (0.29, 1.53)	0.335
Model I: Crude association of factors			
Model II: Adjusted for BMI, Smoking, and Age			
Signif. codes: 0.05	**'***' < 0.001**	**'**' < 0.01**	**'*'<**

Source: Field data, 2022

Risk factors associated with Insulin resistance, C-reactive protein, and Malondialdehyde.

A binary logistics regression showed statistical significance of HOMA-ß, CRP levels, FBG, and malaria for adjusted model III. It was revealed that, respondents with borderline HOMA- ß levels have a greater risk of elevated insulin resistance levels after adjusting for socio-demographic characteristics and anthropometric factors.

Also, a participant with normal levels of CRP has a lower risk of elevated insulin levels compared to those with abnormal CRP levels. Also, those with high FBG levels have lower risk of elevated insulin resistance levels compared with normal FBG levels. Notwithstanding that, participants who had malaria parasites after investigations had a higher risk of elevated

insulin levels compared to participants without malaria parasites in model III (Table 9).

Table 9: Binary Logistics regression analyses of the demographic and health related determinants of insulin resistance

Characteristics	Univariate COR (95% CI)	Model I AOR (95% CI)	Model II AOR (95% CI)	Model III AOR (95% CI)
Age Grouping				
Young adult	1	1	-	-
Middle-aged	2.13 (1.13-4.03)*	2.19 (1.15-4.16)*	-	-
Old-age	0.77 (0.29-2.09)	0.83 (0.30-2.26)		
Gender				
Female	1	1	1	1
Male	0.82 (0.49-1.36)	0.76 (0.45-1.26)	0.77 (0.45-1.33)	0.77 (0.45-1.33)
Residential status				
Rural	1	1	-	-
Urban	3.63 (1.83-7.20)*	3.43 (1.72-6.86)*	-	-
Smoking status				
Not smoking	1	1	1	1
Smoking	0.97 (0.24-3.83)	0.70 (0.16-2.85)	0.92 (0.20-4.19)	0.90 (0.20-4.11)
Alcohol status				
Alcoholic	1	1	1	1
Non-Alcoholic	0.34 (0.10-1.17)	0.44 (0.12-1.58)	0.44 (0.12-1.62)	0.46 (0.12-1.73)
Occupation				
Agric worker	1	1	1	1
Artisan	0.44 (0.12-1.59)	0.44 (0.12-1.56)	0.40 (0.11-1.50)	0.39 (0.11-1.47)
Health worker	0.97 (0.29-3.26)	0.86 (0.25-3.03)	0.61 (0.16-2.29)	0.60 (0.16-2.25)
Public servant	1.31 (0.36-4.77)	1.27 (0.33-4.54)	1.05 (0.27-4.04)	0.99 (0.26-3.89)
Student	0.43 (0.12-1.54)	0.42 (0.12-1.50)	0.38 (0.10-1.47)	0.36 (0.09-1.40)
Unemployed	0.27 (0.08-0.94)*	0.27 (0.08-0.96)*	0.35 (0.09-1.31)	0.35 (0.09-1.29)
Body Mass Index (BMI)				
Normal	1	1	1	-
Obesity	1.86 (0.76-4.54)	1.87 (0.76-4.60)	1.47 (0.58-3.70)	-
Overweight	1.33 (0.75-2.34)	1.32 (0.74-2.34)	1.04 (0.56-1.93)	-

Table 9: Continue

Waist to Hip ratio (WHR)				
High risk	1	1	1	1
Low risk	1.05 (0.59-1.87)	1.05 (0.59-1.87)	0.90 (0.49-1.64)	0.93 (0.50-1.72)
Waist to Height ratio (WHtR)				
Normal	1	1	1	1
High risk	0.15 (0.06-0.39)*	0.12 (0.04-0.35)*	0.13 (0.04-0.37)*	0.30 (0.07-1.33)
Increased risk	0.52 (0.28-0.97)*	0.53 (0.28-0.99)*	0.60 (0.31-1.16)	0.89 (0.39-2.02)
Homeostasis Model Assessment (HOMA–ß)				
Normal	1	1	1	1
Border line	18.6 (8.07-42.9)*	18.2 (7.84-42.4)*	20.9 (8.57-50.8)*	20.6 (8.46-50.02)*
Non-insulin diabetes	6.85^{07}(0.00-Inf)	8.90^{07}(0.00-Inf)	1.36^{08}(0.00-Inf)	1.42^{08}(0.00-Inf)
C-reactive protein				
Normal	1	1	1	1
Abnormal	0.50 (0.30-0.85)*	0.56 (0.32-1.96)*	0.49 (0.28-1.86)	0.48 (0.27-1.86)*
Fasting Blood Glucose				
Normal	1	1	1	1
Low	$3.93e^{06}$ (0.0-Inf)	$3.08e^{06}$ (0.0-Inf)	$3.29e^{06}$ (0.0-Inf)	$2.18e^{06}$ (0.0-Inf)
High	$3.14e^{-02}$(0.00-0.26)*	$5.13e^{-02}$(0.01-0.4)*	$6.42e^{-02}$(0.01-0.5)*	$7.94e^{-02}$(0.01-0.7)*
Malondialdehyde				
Normal	1	1	1	1
Low	0.44 (0.22-0.88)*	0.46 (0.23-0.93)*	0.46 (0.22-0.94)*	0.49 (0.24-1.03)
High	0.46 (0.04-4.75)	0.46 (0.04-5.27)	0.63 (0.05-8.11)	0.91 (0.07-11.17)
Malaria status				
Parasites not seen	1	1	1	1
Parasites seen	0.98 (0.53-1.79)	1.01 (0.55-1.87)	1.46 (1.06-5.70)*	2.53 (1.08-5.88)*
Model I: Adjusted for Past Covid-19 status				
Model II: Adjusted for socio-demographic factors (Age and residence) and Past Covid-19 status				
Model III: Adjusted for socio-demographic factors and anthropometric factors (BMI)				

Source: Field data, 2022

In the model, after adjusting for confounding variables (Past COVID-19 status, socio-demographic characteristic, and BMI), participants with a high MDA level had 53% lower risk of elevated CRP levels compared to the normal MDA (shown in Table 10).

Table 10: Binary Logistics regression analyses of the demographic and health related determinants of C-Reactive Protein

Characteristics	Univariate COR (95% CI)	Model I AOR (95% CI)	Model II AOR (95% CI)	Model III AOR (95% CI)
Age Grouping				
Young adult	1	1	-	-
Middle-aged	0.84 (0.50-1.42)	0.81 (0.47-1.39)	-	-
Old-age	1.00 (0.38-2.65)	0.88 (0.32-2.41)		
Gender				
Female	1	1	1	1
Male	0.72 (0.46-1.15)	0.81 (0.50-1.30)	0.86 (0.52-1.40)	0.86 (0.52-1.41)
Residential status				
Rural	1	1	-	-
Urban	1.53 (0.78-2.99)	1.84 (0.92-3.71)	-	-
Smoking status				
Not smoking	1	1	1	1
Smoking	0.35 (0.09-1.38)	0.57 (0.14-2.30)	0.75 (0.18-3.14)	0.74 (0.17-3.12)
Alcohol status				
Alcoholic	1	1	1	1
Non-Alcoholic	2.37 (0.97-5.77)	1.44 (0.57-3.65)	1.51 (0.59-3.87)	1.62 (0.62-4.25)
Occupation				
Agric worker	1	1	1	1
Artisan	1.10 (0.37-3.29)	1.24 (0.40-3.87)	1.13 (0.35-3.64)	1.11 (0.35-3.59)
Health worker	0.86 (0.32-2.32)	1.71 (0.58-5.02)	1.32 (0.42-4.10)	1.29 (0.41-4.03)
Public servant	1.51 (0.53-4.30)	2.31 (0.76-6.97)	2.10 (0.67-6.61)	2.01 (0.63-6.41)
Student	0.90 (0.30-2.66)	1.04 (0.34-3.21)	0.72 (0.21-2.41)	0.69 (0.20-2.34)
Unemployed	1.20 (0.40-3.56)	1.04 (0.34-3.21)	1.05 (0.32-3.43)	1.03 (0.31-3.37)
Body Mass Index (BMI)				
Normal	1	1	1	-
Obesity	1.47 (0.69-3.12)	1.51 (0.69-3.29)	1.31 (0.59-2.91)	-
Overweight	1.09 (0.65-1.82)	1.11 (0.65-1.89)	1.10 (0.63-1.93)	-
Waist to Hip ratio (WHR)				
High risk	1	1	1	1
Low risk	1.02 (0.61-1.73)	1.03 (0.60-1.77)	0.93 (0.54-1.62)	0.97 (0.55-1.69)

Table 10: Continue

Waist to Height ratio (WHtR)				
Normal	1	1	1	1
High risk	2.05 (0.75-5.58)	2.17 (0.77-6.08)	1.90 (0.66-5.42)	2.02 (0.49-8.36)
Increased risk	0.97 (0.59-1.59)	1.01 (0.61-1.68)	0.93 (0.55-1.59)	0.86 (0.45-1.67)
Homeostasis Model Assessment (HOMA–ß)				
Normal	1	1	1	1
Border line	1.68 (0.85-3.32)	1.51 (0.75-3.05)	1.44 (0.71-2.93)	1.47 (0.72-3.00)
Non-insulin diabetes	4.68 (0.54-40.65)	6.75 (0.76-59.98)	6.49 (0.73-57.96)	6.68 (0.74-60.03)
Fasting Blood Glucose				
Normal	1	1	1	1
High	1.06 (0.28-4.05)	1.78 (0.46-6.94)	2.05 (0.50-8.32)	1.96 (0.48-8.05)
Low	1.14 (0.25-5.17)	0.92 (0.19-4.37)	0.84 (0.18-4.01)	0.88 (0.18-4.23)
Malondialdehyde				
Normal	1	1	1	1
High	0.49 (0.29-0.82)*	0.51 (0.29-0.86)*	0.48 (0.28-0.83)*	0.47 (0.27-0.82)*
Low	0.52 (0.06-3.85)	0.52 (0.07-4.13)	0.47 (0.06-4.00)	0.42 (0.05-3.67)
Malaria status				
Parasites not seen	1	1	1	1
Parasites seen	0.58 (0.33-1.02)	0.53 (0.30-0.95)	1.60 (0.31-1.17)	0.61 (0.31-1.19)

Model I: Adjusted for Past Covid-19 status

Model II: Adjusted for socio-demographic factors (Age and residence) and Past Covid-19 status

Model III: Adjusted for socio-demographic factors and anthropometric factors (BMI)

Source: Field data, 2022

Table 11 denotes a binary logistics regression model indicating risk of developing high MDA with or without past Covid-19 infection, adjusting for confounding variables. Model III indicates an adjusted odd ratio of 0.37 indicating that, participants who do not take alcohol have a 63% lower risk of having high MDA levels compared to those who take alcohol.

Table 11: Binary Logistics regression analyses of the demographic and health related determinants of malondialdehyde

Characteristics	Univariate COR (95% CI)	Model I AOR (95% CI)	Model II AOR (95% CI)	Model III AOR (95% CI)
Age Grouping				
Young adult	1	1	-	-
Middle-aged	0.67 (0.38-1.20)	0.67 (0.37-1.20)	-	-
Old-age	1.52 (0.57-4.02)	1.47 (0.55-3.91)		
Gender				
Female	1	1	1	1
Male	0.78 (0.48-1.28)	0.81 (0.49-1.33)	0.79 (0.47-1.32)	0.80 (0.48-1.33)
Residential status				
Rural	1	1	-	-
Urban	0.61 (0.31-1.21)	0.64 (0.32-1.26)	-	-
Smoking status				
Not smoking	1	1	1	1
Smoking	0.88 (0.22-3.46)	1.02 (0.25-4.14)	0.92 (0.22-3.94)	0.92 (0.21-3.94)
Alcohol status				
Alcoholic	1	1	1	1
Non-Alcoholic	0.50 (0.21-1.18)	0.39 (0.16-0.97)*	0.39 (0.16-0.98)*	0.37 (0.14-0.95)*
Occupation				
Agric worker	1	1	1	1
Artisan	1.17 (0.36-3.74)	1.18 (0.37-3.79)	1.16 (0.36-3.76)	1.19 (0.37-3.89)
Health worker	0.91 (0.31-2.65)	0.98 (0.32-2.98)	1.04 (0.33-3.28)	1.08 (0.34-3.44)
Public servant	0.88 (0.28-2.69)	0.91 (0.29-2.83)	0.93 (0.30-2.95)	1.00 (0.31-3.21)
Student	0.97 (0.30-3.12)	0.99 (0.31-3.18)	0.90 (0.26-3.07)	0.95 (0.28-3.28)
Unemployed	1.79 (0.57-5.61)	1.76 (0.56-5.53)	1.46 (0.45-4.71)	1.52 (0.47-4.95)
Body Mass Index (BMI)				
Normal	1	1	1	-
Obesity	0.76 (0.34-1.69)	1.76 (0.34-1.69)	0.81 (0.36-1.85)	-
Overweight	0.74 (0.42-1.28)	0.74 (0.42-1.29)	0.78 (0.44-1.41)	-
Waist to Hip ratio (WHR)				
High risk	1	1	1	1
Low risk	0.83 (0.47-1.47)	0.84 (0.47-1.47)	0.86 (0.48-1.54)	0.81 (0.45-1.46)
Waist to Height ratio (WHtR)				
Normal	1	1	1	1
High risk	0.33 (0.09-1.17)	0.33 (0.09-1.17)	0.36 (0.10-1.28)	0.24 (0.05-1.23)
Increased risk	0.90 (0.54-1.53)	0.91 (0.54-1.54)	1.01 (0.59-1.75)	1.12 (0.57-2.21)

Table 11: Continue

Homeostasis Model Assessment (HOMA–ß)				
Normal	1	1	1	1
Border line	1.15 (0.58-2.28)	1.11 (0.56-2.21)	1.02 (0.50-2.07)	1.02 (0.50-2.05)
Non-insulin diabetes	0.41 (0.05-3.59)	0.45 (0.05-3.93)	0.51 (0.06-4.54)	0.53 (0.06-4.77)
Fasting Blood Glucose				
Normal	1	1	1	1
High	1.60 (0.42-6.14)	1.95 (0.49-7.64)	2.24 (0.54-9.31)	2.55 (0.60-10.9)
Low	$1.29e^{-08}$(0.00-Inf)	$1.20e^{-07}$(0.00-Inf)	$1.39e^{-07}$(0.00-Inf)	$1.24e^{-07}$(0.00-Inf)
Malaria status				
Parasites not seen	1	1	1	1
Parasites seen	1.19 (0.67-2.14)	1.18 (0.66-2.12)	0.95 (0.48-1.88)	0.93 (0.47-1.84)
Model I: Adjusted for Past Covid-19 status				
Model II: Adjusted for socio-demographic factors (Age and residence) and Past Covid-19 status				
Model III: Adjusted for socio-demographic factors and anthropometric factors (BMI)				

Source: Field data, 2022

Discussion of Results

Study Demographics and Prevalence of Insulin Resistance

This study examined the risk of development of T2DM after having recovered from COVID-19 in the Northern region of Ghana. Injurious effects of SARS-COV-2 infection on different organs have been documented in an increasing number of studies (Roca-Ho et al., 2020; Wiersinga et al., 2020). However, not enough research has looked at metabolic factors in COVID-19 recovered patients, like insulin sensitivity and secretion. Our research, to our knowledge, is the first to reveal that COVID-19 in the Northern region of Ghana may raise the risk of IR in people without a history of diabetes. This study was conducted in both rural (13.8%) and urban (86.2%) residents. A total of 290 respondents were recruited for this study with a mean age of 35.7 (± 13.03 years) with young adults (18-39 years) accounting for 65.9%, middle age (40-59 years), 27.6%, and old age (≥60 years) 6.2%. Alcohol consumers

and smokers accounted for 7.9% and 10% while the mean BMI among the participants was 25.7 (±5.35).

Although the circumstances causing the onset of T2DM in COVID-19 infections are still unclear at this point, there is the possibility of intricately interconnected pathophysiology such as insulin secretion difficulties and glucose disposal, transient increase in glucose level during the infection and existing diabetes before COVID-19 infection (Khunti et al., 2021b). IR which is defined as diminished tissue sensitivity to insulin (Tam et al., 2012a) and reduction in insulin production are the major characteristics of T2DM pathogenesis (Dedoussis et al., 2007; Reaven, 2011; Unger, 2008). The homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of beta cell function (HOMA-B) are mathematical models used to indirectly estimate IR and beta cell function. Although cut-offs affect how HOMAIR-dependent diagnoses of IR are used in various populations (Esteghamati et al., 2010; Lee et al., 2006), a value of 2.6 seems to be a widely accepted cut-off for diagnosing IR (Elsafty et al., 2018). The study found a significantly increased risk of IR with age in the middle-age group. Young adult between the ages of 18-39 years recorded the highest IR prevalence of 44.1% followed by the middle aged (40-59 years) with 31.7%, and 3.8% for 60 years and above. This finding is contrary to the findings of Pan et al. that related high risk of IR to increasing age due to lingering problems from obesity, diabetes, and hypertension (HTN) that become more pronounced with age (Pan et al., 2016). The evident age-specific disparity between the results of the present study and those of Pan et al. (Pan et al., 2016) may be due to the disparity in sample sizes, research designs, and

respondent characteristics between the two investigations. Young adults made up 33.75% of the substantially larger sample size of 3515 respondents in the Pan et al. (Pan et al., 2016) study. The current study, however, was limited to 290 participants, with young adults accounting for approximately 65.9% of the sample population.

The study did not find significant difference in IR risk associated with men and women but women accounted for the highest prevalence of IR in the study population indicating a probable high-risk group. This is in contrast to the findings of Pan et al, who associated men to a higher chance of developing IR because they produce much less adiponectin, an insulin-stimulating hormone (Cnop et al., 2003; Yamauchi et al., 2001).This in combination with lack of a possible estrogenic effect and greater amounts of visceral and hepatic adipose tissues may contribute to men's higher IR than women (Pan et al., 2016). The study did not observe significant association between IR and adiposity indices such as BMI, WHtR and WHR. This is not comparable to several studies conducted by Do et al, Gayoso-Diz et al, and Pan et al who associated BMI, WHtR, and WHR to an increased risk of IR (Do et al., 2010; Gayoso-Diz et al., 2011; Pan et al., 2016). However, the present investigation is comparable to one carried out at Cape Coast by Acquah et al. (Acquah et al., 2014), who did not detect a significant correlation between fat accumulation and the chance of developing IR.

As expected, mean FI, FBG, HOMA-B, and HOMA-IR were significantly higher in the cases as compared to the control group. However, a 3.1% of the cases had HOMA-B function of less than 25% compared to 11.7% in the control respondents. The higher incidence seen in the control

respondents may be due to an already existing problem prior to the recruitment. This could be due to loss of normal tissue sensitivity to insulin, a genetic defect affecting the beta cell function or an autoimmune destruction of the beta cells as observed in some viral infections. According to this idea, mild virus-mediated damage to beta cells releases previously hidden antigens that activate autoreactive T-lymphocytes, which then cause an autoimmune reaction that destroys the residual beta-cell mass, leading to insulin-dependent type 1 diabetes (Boddu et al., 2020). This process requires many weeks to several months and cannot account for the development of diabetes during the acute stage of COVID-19 infection, but it may be the cause of diabetes in some of the respondents following infection recovery after six months when recruitment was done. However, there was no evidence of hyperglycaemia in the control group suggesting that the secreted insulin level was able to regulate glucose level in this study group.

A 6.2% prevalence in hyperglycemia was observed in the cases compared to a 0.0% prevalence in the control group. This is comparable to a study by Montefusco et al. (2021) in Italy who found significantly higher FBG, HOMAI-R, and HOMA-B six months after recovery from COVID-19 compared to the healthy control group. They examined prolonged alterations in glucose metabolism preceding acute COVID-19. Forty-six percent of the participants with no earlier records of diabetes developed new-onset diabetes during the acute phase. Six months following COVID-19 recovery, 35% of this group remained hyperglycaemic, while another 2% were identified with T2DM (Montefusco et al., 2021). Reiterer et al. found that individuals who recovered from COVID-19 infection had higher insulin concentrations, which

is consistent with both short- and long-term increases in beta-cell secretion activity and IR after COVID-19 (Reiterer et al., 2021). Another study by Chen et al. examining the impact of COVID-19 on IR three and six months after recovery found a mean IR of 4.96 ± 4.46 at the sixth month compared to a baseline mean of 4.07 ± 2.20 (M. Chen et al., 2021).

This current study observed an IR mean of 7.1 (±8.1) in the cases compared to a 3.7 (±2.9) in the control group. To the best of our knowledge this is the first time an IR mean of 7.1 has been recorded in COVID-19 recovered patients in the Northern region of Ghana. In comparison to the control group, the cases had significantly higher mean HOMA-IR values, which translated to significantly higher beta cell secretory function. This hypersecretory beta cell function observed in the cases may be due to increasing tissue insensitivity to insulin because of remnants of angiotensin activity after recovering from COVID-19. Angiotensin - converting enzymes II (ACE2) controls blood pressure by converting Ang II to Ang (1–7), lowering IR and oxidative stress, and improving glucose transporter 4 function in a favourable environment (Takeda et al., 2013). Insulin insensitivity, oxidative destruction of cells, and inflammation have been associated to reduced ACE2 expression because of SARS-COV-2 entry during COVID-19 (Finucane & Davenport, 2020). The lack of a significant relationship between fasting blood glucose and insulin with BMI, WHtR, and WHR suggests that general and central fat accumulation did not significantly contribute to the IR levels seen in this investigation.

This study has demonstrated the presence of hyperglycaemia, IR, and beta cell hyperstimulation in cases without a history of diabetes compared to

the control group. This effect appears to be mediated by the abnormal secretome, which remained altered long after recovery from COVID-19 (Montefusco et al., 2021). Even though other viral infections have been linked to metabolic changes (Krogvold et al., 2015; Laitinen et al., 2014), COVID-19 may cause an inflammatory state that is similar to but more worsened than that seen in T2DM (Hollstein et al., 2020; Naguib et al., 2020; Solerte et al., 2020) in the long term. These outcomes could result in the depletion of beta cells and aggravation of diabetes brought on by islet hyperstimulation and glucose toxicity (Eguchi & Nagai, 2017; Hotamisligil, 2017).

Associations between oxidative stress, C-Reactive Protein, and Insulin Resistance

Oxidative stress occurs when the circulating concentration of ROS exceeds the limits of the cell's antioxidant reserve, possibly due to inflammation and injury to cellular macromolecules (Alkadi, 2018). Oxidative stress could be assessed by measuring serum MDA levels. Thiobarbituric acid-reactive-substances assay was used in measuring MDA levels in this study because it is fast and simple, cheaper, and widely used by researchers to measure oxidative stress levels. Oxidative stress level was not significantly associated with the cases compared to the control respondents but the cases saw a higher mean of 6.54 (± 6.05) compared to a mean of 6.27 (±5.91) in the control group.

The presence of some level of oxidative stress in the cases shows a positive association with FI levels. This is comparable to Meigs et al. in the Framingham Offspring study who demonstrated a positive association between the prevalence of IR and concentration of oxidative stress (Meigs et al., 2007).

Oxidative stress leads to impaired glucose uptake in muscle and fat cells and decreases insulin secretion from beta cells (Maddux et al., 2001; Rudich et al., 1998). This demonstrates that IR is associated with oxidative stress in non-diabetics with an increased risk of diabetes. The oxidative stress observed in this study may be due to a possible hyperglycaemia during the acute phase of COVID-19 and reduced expression ACE2 caused by direct virus entry into host cell. A hyperglycaemic state can reduce the functions of antioxidant enzymes and cause a rise in oxidative stress-induced DNA damage indicators like thiobarbituric acid-reactive substances (TBARS).

A study has confirmed that oxidative stress causes the insulin gene's promoter activity and mRNA expression to be inhibited in beta cell lines and isolated pancreatic islet cells leading to a reduction in insulin gene expression (Kawahito *et al*., 2009a). The high prevalence of IR observed in the cases could be due to the existing oxidative stress. There is a substantial likelihood that oxidative stress contributes to IR brought on by long-term hyperglycaemia (Kawahito *et al*., 2009b). Oxidative stress is widely identified as a contributory factor in the pathophysiology and aetiology of diabetes (Halliwell, 2009). This is because persistent hyperglycaemia causes non-enzymatic protein glycation, which produces ROS in the form of Schiff base and Amadori products in human cells and tissues (Kumar Pasupulati *et al*., 2016; Rehman & Akash, 2017a).

CRP, which is produced by the liver in response to IL-6, is the primary downstream mediator of the acute phase response. It is among the most well investigated epidemiological biomarkers of inflammation in prediabetes, diabetes, and its related cerebrovascular diseases (Brahimaj et al., 2017;

Donath & Shoelson, 2011; Maschirow et al., 2015; Pradhan et al., 2001). Its primary functions include controlling platelet activation, boosting leukocyte activity, and fixing complement (Luc et al., 2019). Those with prediabetes have been found to have significantly higher CRP levels than those with normoglycemia (Grossmannm et al., 2015). Diabetic patients showed a modest rise in CRP compared to those with prediabetes indicating a low-level inflammation in people with prediabetes (Luc et al., 2019). CRP was significantly associated with the cases compared to the control respondents. A mean of 1.35 was observed in the cases compared to a mean of 0.99 in the control respondents. A positive correlation of CRP and IR was observed in the cases. This is comparable to a study by Fizelova et al. (Fizelova et al., 2017) who found that elevated CRP is a predictor of IR and the onset of T2DM. According to other studies (Rodríguez-Hernández *et al*., 2013; Sun *et al*., 2011), chronic sub-clinical inflammation aid IR syndrome, a prominent hallmark of metabolic syndrome, and mild inflammation have been a predisposing factor for T2DM development.

A significant link between oxidative stress, inflammation, and IR has been observed in this current study but that of the cases is more significantly associated to these risk factors of T2DM. Previous work done by Montefusco et al and Chen et al. (M. Chen et al., 2021; Montefusco et al., 2021) demonstrated an increased risk of T2DM in recovered COVID-19 patients, due, probably, to SARS-COV-2 detrimental effect on multiple organs (Mao et al., 2020; Rodriguez-Morales et al., 2020). They showed that SARS-CoV-2 promotes IR and beta cell dysfunction as shown for T2DM (Daniele et al., 2014; Fiorentino et al., 2019) by impairing insulin signalling and beta cell

function. This proinflammatory environment is brought on by a cytokine storm, in which IL-6 plays a primary role. According to Rehman & Akash 2017b, oxidative stress is among the factors that contribute to the pathophysiology of IR, diminished insulin secretion, reduced glucose uptake, impaired hepatic glucose metabolism, and activated cytokines that can cause inflammation, all of which led to T2DM (Rehman & Akash, 2017b).

Extent of oxidative stress, C-reactive Protein, and Insulin Resistance Associated with Malaria Infection

Total malaria prevalence of 22.1% was observed in the study population with 10% prevalence in the cases and 12.1% in the control respondents. We speculate that remnants of stimulated angiotensin activity during SARS-COV-2 infection may be offering some protection to the cases against malaria but a larger sample size will be required in future studies to ascertain this. A study conducted in Nigeria found that moderate malaria sufferers had a higher angiotensin converting enzymes activity compared to severe malaria cases (Abdulazeez et al., 2017). Miller in a separate study hypothesized that mutations in angiotensin genes might prevent the growth of the malaria parasite and confer survival advantages against malaria (Chiabi et al., 2014). Although malaria could not be significantly associated with inflammation and oxidative stress between the study groups, an adjusted odd ratio of the cases revealed reduced risk of inflammation and oxidative stress without the malaria parasites in both groups.

The presence of malaria in the control and cases respondents that had normal MDA levels introduced a reduced risk of diabetes compared to high MDA levels. A similar observation was made between the presence of

malaria and insulin levels. Generally, a greater percentage of respondents with malaria parasite had higher insulin levels compared to their cohorts without malaria in both study groups. Higher incidence of hyperinsulinemia was observed in the cases with malaria compared to the respondents in the control group. Previous exposure to COVID-19 may be contributing largely to the higher incidence of IR observed in the cases. The increase in insulin level due to malaria was observed in both the case and control groups suggesting that malaria by itself can predispose one to T2DM.

Comparable research was conducted in Cape Coast by Acquah et al. who discovered that uncomplicated malaria in semi-immune adults might increase HOMA-IR levels by over 120% and 200% in diabetic and non-diabetic controls to levels above the conventional 2.6 (Acquah *et al*., 2014). The potential of repeated bouts of clinical malaria in the same person, according to Acquah et al. (2014), suggests that HOMA-IR values exceeding 2.6 in the respondents without diabetes may have consequences for the development of T2DM in malaria-endemic areas like Ghana.

Association between Measured Biomarkers in Study Respondents

A binary logistic regression analysis of beta cell function, insulin, CRP, MDA, and malaria revealed that, malaria infected respondents stood a higher risk of hyperinsulinemia compared to other respondents without malaria in the study. This finding is comparable to that of Acquah et al. who demonstrated that malaria caused an appreciable increase in insulin level among non-diabetic respondents in Cape Coast (Acquah et al., 2014a).

Borderline HOMA-B values was associated to hyperinsulinemia after adjusting for anthropometric and socio-demographic factors. HOMA-B mean

value of 748.6 was observed in the cases compared to a mean of 258.5 in the control group. This may be due to increasing tissue insensitivity towards insulin. This explains why a higher mean HOMA-IR of 7.1 was observed in the cases compared to a 3.7 mean in the control group. This finding in the current study predisposes the recovered COVID-19 respondents to a higher incidence of HOMA-IR and a greater risk of T2DM development as seen in a similar study by Chen et al. who observed a mean of 4.96 in recovered COVID-19 respondents compared to a baseline mean of 4.07 (M. Chen et al., 2021).

Normal CRP was linked to a lower risk of hyperinsulinemia indicating a positive correlation between elevated CRP levels and hyperinsulinemia in the study population whiles low MDA was linked to elevated levels of CRP indicating a negative correlation between the two. This observation may explain why elevated levels of CRP protein was observed in the study groups even though MDA was not significantly associated to the study groups. This study reveals an association between oxidative stress, an increased inflammation and the presence of IR in the study respondents especially in the cases. This is comparable to another study (Iddir et al., 2020) that emphasizes on the direct connection between inflammation and oxidative stress. According to Iddir et al. (2020), immune cells in COVID-19 respondents particularly macrophages, produce excessive amounts of free radicals at the site of infection, leading to oxidative stress.

Markers of excessive extracellular reactive oxygen species or reactive nitrogen species such as MDA and isoprostane can either oxidize biomolecules like RNA/DNA, lipids, or structurally modify proteins and genes to start signalling cascades that can start the inflammatory response (Lopresti

et al., 2014; Park *et al*., 2013). Fizelova et al. (2017), found that an elevated inflammatory biomarkers such as CRP predicted the onset of T2DM. Research by Soleiman *et al.* (Azizi Soleiman et al., 2013) on the connection between oxidative stress, inflammation, and T2DM observed that reducing oxidative stress and inflammation is essential for hastening the healing process and preventing diabetic complications.

Limitations of the Study.

The beta cell activity and insulin sensitivity of the respondents were not known prior to COVID-19 infection. Respondents were interviewed through questionnaire and medical records where available to determine their diabetogenic status prior to COVID-19 infection before sampling. Undue generalization of findings from the malaria respondents may be difficult due to the relatively small sample size although the randomisation in sample selection is expected to moderate this effect. Above all, the cross-sectional nature of the study made establishment of causality difficult. Notwithstanding the above limitations, the study has unveiled the potential of COVID-19 to contribute to the future burden of diabetes through insulin resistance, inflammation, and oxidative stress.

Summary

The current study has demonstrated significant association of hyperglycaemia, inflammation, oxidative stress, and IR in recovered COVID-19 respondents compared to their control respondents with or without malaria six months after COVID-19 infection. Prevalence of IR, extent of inflammation and oxidative stress associated with malaria, and the correlation

between the measured biomarkers (CRP, MDA, and insulin) in the various respondents have been demonstrated in this study.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

This study intended to identify the risk of acquiring T2DM by examining insulin sensitivity and beta-cell function, oxidative stress, and inflammatory activity in recovered COVID-19 patients with or without malaria in the northern region of Ghana.

Summary of Findings and Results

The total prevalence of highly elevated HOMA-IR in the cases was 16.2% compared to 5.5% in the control respondents in the total population. Moderately elevated IR prevalence of 22.1% was observed in the cases compared to a 26.9% in the control respondents. Mean HOMA-IR of 7.1 (±8.1) was obtained for the cases compared to a mean value of 3.7 (±2.9) in the control group. Hypersecretory beta cell activity was observed in the cases with a HOMA-B mean of 748.6 (±2105.7) compared to 258.5 (±3977.9) in the control group. Increased risk of HOMAIR and hypersecretory beta cell activity was significantly associated with the cases compared to the control respondents. Compared to the control group, the respondents in cases had significantly higher fasting blood glucose levels than the control group (4.95±1.13 vs 4.26±0.58 mmol/L; $P<0.01$). Binary logistic regression analysis of beta cell function, CRP, MDA, and malaria revealed that malaria infected respondents stood a higher risk of hyperinsulinemia compared to other respondents without malaria in the study although inflammation and oxidative stress was not significantly associated to malaria infection. BMI, WHtR and WHR were not significantly associated to the measured biomarkers (insulin, oxidative stress, and inflammation) in the study population.

Conclusion

The total prevalence of HOMA-IR in cases was 38.3% with a mean of 7.1 compared to 32.4% with a mean of 3.7 in the control respondents. Inflammation and oxidative stress were not significantly associated to malaria but an adjusted odd ratio of the cases showed a lower risk of an elevated inflammation and oxidative stress in both groups without the parasites. Normal CRP was linked to lower risk of hyperinsulinemia, demonstrating a positive correlation between raised CRP levels and hyperinsulinemia, whereas low MDA was associated with elevated CRP, indicating a negative correlation between the two. Normal HOMA-B values was associated to hyperinsulinemia and risk of insulin resistance.

Recommendation

The following suggestions are made considering the study's findings.

- An improved management regime for COVID-19 recovered patients that allows for continuous monitoring and testing for risk factors associated with T2DM development should be kept in place.
- Recovered COVID-19 clients should be educated on the need to voluntarily undertake regular routine investigations that includes fasting blood glucose and insulin levels.
- Recovered COVID-19 clients should be educated on the need for a healthy lifestyle that involve regular exercises and good nutrition to limit insulin insensitivity, inflammation, and oxidative stress.
- Public education on malaria prevention should be strengthened as part of the preventive measures against future development of T2DM.

- Future research should consider using longitudinal methodologies and a bigger sample size to examine the long-term implications of malaria associated with COVID-19 recovered individuals in particular and the general population at large.

REFERENCES

Abais, J. M., Xia, M., Zhang, Y., Boini, K. M., & Li, P. L. (2015). Redox regulation of NLRP3 inflammasomes: ROS as trigger or effector? *Antioxidants & Redox Signaling*, *22*(13), 1111–1129. https://doi.org/10.1089/ARS.2014.5994

Abdulazeez, A., Ya'u, M., & Kurfi, B. (2017). Association of hypertension and activity of angiotensin converting enzyme in malaria patients attending Sheik Muhammad Jidda General Hospital, Kano State, Nigeria. *Nigerian Journal of Basic and Clinical Sciences*, *14*(2), 121. https://doi.org/10.4103/NJBCS.NJBCS_6_17

Abid, A. L., Shaiq, A. G., Rayees, A. A., Hilal, A. B., Tauseef, A. B., & Imtiyaz, A. W. (2013). Free radicals and antioxidants: Myths, facts and mysteries. *African Journal of Pure and Applied Chemistry*, *7*(3), 91–113. https://doi.org/10.5897/AJPAC12.074

Accili, D. (2021a). Can COVID-19 cause diabetes? *Nature Metabolism*, *3*(2), 123–125. https://doi.org/10.1038/S42255-020-00339-7

Accili, D. (2021b). Can COVID-19 cause diabetes? *Nature Metabolism*, *3*(2), 123–125. https://doi.org/10.1038/S42255-020-00339-7

Acquah, S., Ameyaw, E., Derkyi-Kwarteng, L., Konja, D., & Boampong, J. (2017). Association of Insulin Resistance with Parasitaemia in Rat Malaria. *The International Annals of Medicine*, *1*(5). https://doi.org/10.24087/IAM.2017.1.5.130

Acquah, S., Boampong, J. N., & Eghan Jnr, B. A. (2016). Increased Oxidative Stress and Inflammation Independent of Body Adiposity in Diabetic and Nondiabetic Controls in falciparum Malaria. *BioMed Research*

International, *2016*. https://doi.org/10.1155/2016/5216913

Acquah, S., Boampong, J. N., Eghan Jnr, B. A., & Eriksson, M. (2014a). Evidence of insulin resistance in adult uncomplicated malaria: Result of a two-year prospective study. *Malaria Research and Treatment*, *2014*. https://doi.org/10.1155/2014/136148

Acquah, S., Boampong, J. N., Eghan Jnr, B. A., & Eriksson, M. (2014b). Evidence of insulin resistance in adult uncomplicated malaria: Result of a two-year prospective study. *Malaria Research and Treatment*, *2014*. https://doi.org/10.1155/2014/136148

Adhikari, S. P., Meng, S., Wu, Y.-J., Mao, Y.-P., Ye, R.-X., Wang, Q.-Z., Sun, C., Sylvia, S., Rozelle, S., Raat, H., & Zhou, H. (2020). Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infectious Diseases of Poverty 2020 9:1*, *9*(1), 1–12. https://doi.org/10.1186/S40249-020-00646-X

Al-Aubaidy, H. A., & Jelinek, H. F. (2011). Oxidative DNA damage: antioxidant response in postprandial hyperglycaemia in type 2 diabetes mellitus. *Undefined*, *11*(2), 87–91. https:// doi.org/10.1177/ 1474651 41 1405259

Al-Sabah, S., Al-Haddad, M., Al-Youha, S., Jamal, M., & Almazeedi, S. (2020). COVID-19: Impact of obesity and diabetes on disease severity. *Clinical Obesity*, *10*(6). https://doi.org/10.1111/COB.12414

Al Hannan, F., & Culligan, K. G. (2015). Human resistin and the RELM of Inflammation in diabesity. *Diabetology & Metabolic Syndrome*, *7*(1). https://doi.org/10.1186/S13098-015-0050-3

Ali Abdelhamid, Y., Kar, P., Finnis, M. E., Phillips, L. K., Plummer, M. P., Shaw, J. E., Horowitz, M., & Deane, A. M. (2016). Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. *Critical Care (London, England)*, *20*(1). https://doi.org/10.1186/S13054-016-1471-6

Alkadi, H. (2018). A Review on Free Radicals and Antioxidants. *Infectious Disorders - Drug Targets*, *20*(1), 16–26. https://doi.org/ 10.2174/ 18715 26518666180628124323

Alpay, M., Backman, L. R. F., Cheng, X., Dukel, M., Kim, W. J., Ai, L., & Brown, K. D. (2015). Oxidative stress shapes breast cancer phenotype through chronic activation of ATM-dependent signaling. *Breast Cancer Research and Treatment 2015 151:1*, *151*(1), 75–87. https:/ /doi.org / 10.1007/S10549-015-3368-5

Amin, M. (2021). COVID-19 and the liver: overview. *European Journal of Gastroenterology & Hepatology*, *33*(3), 309–311. https:// doi.org/ 10. 1097/MEG.0000000000001808

Apicella, M., Campopiano, M. C., Mantuano, M., Mazoni, L., Coppelli, A., & Del Prato, S. (2020). COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *The Lancet. Diabetes & Endocrinology*, *8*(9), 782–792. https://doi.org/10.1016/S2213-8587(20)30238-2

Atkinson, M. A., & Powers, A. C. (2021). Distinguishing the real from the hyperglycaemia: does COVID-19 induce diabetes? *The Lancet Diabetes and Endocrinology*, *9*(6), 328–329. https://doi.org/10.1016/S2213-8587(21)00087-5

Azizi Soleiman, F., Pahlavani, N., Rasad, H., Sadeghi, O., & Reza Gohari, M. (2013). The Relationship between Inflammation, Oxidative Stress, and Metabolic Risk Factors in Type 2 Diabetic Patients. *Iranian Journal of Diabetes and Obesity*, *5*.

Balasubramanyam, M. (2020). Does COVID-19 Warn Us to Revisit Virus-Induced Diabetes? *Exploratory Research and Hypothesis in Medicine*, *000*(000), 1–5. https://doi.org/10.14218/erhm.2020.00046

Barberis, E., Timo, S., Amede, E., Vanella, V. V., Puricelli, C., Cappellano, G., Raineri, D., Cittone, M. G., Rizzi, E., Pedrinelli, A. R., Vassia, V., Casciaro, F. G., Priora, S., Nerici, I., Galbiati, A., Hayden, E., Falasca, M., Vaschetto, R., Sainaghi, P. P., … Manfredi, M. (2020). Large-Scale Plasma Analysis Revealed New Mechanisms and Molecules Associated with the Host Response to SARS-CoV-2. *International Journal of Molecular Sciences*, *21*(22), 1–25. https://doi.org/10.3390/IJMS 21 228623

Barbu, M. G., Thompson, R. J., Thompson, D. C., Cretoiu, D., & Suciu, N. (2020). The Impact of SARS-CoV-2 on the Most Common Comorbidities–A Retrospective Study on 814 COVID-19 Deaths in Romania. *Frontiers in Medicine*, *7*. https://doi.org/ 10.3389/ FMED. 2020 .567199

Barron, E., Bakhai, C., Kar, P., Weaver, A., Bradley, D., Ismail, H., Knighton, P., Holman, N., Khunti, K., Sattar, N., Wareham, N. J., Young, B., & Valabhji, J. (2020). Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *The Lancet. Diabetes & Endocrinology*, *8*(10), 813–822. https://doi.org /10.

1016/S2213-8587(20)30272-2

Belalcazar, L. M., Haffner, S. M., Lang, W., Hoogeveen, R. C., Rushing, J., Schwenke, D. C., Tracy, R. P., Pi-Sunyer, F. X., Kriska, A. M., & Ballantyne, C. M. (2013). Lifestyle intervention and/or statins for the reduction of C-reactive protein in type 2 diabetes: from the look AHEAD study. *Obesity (Silver Spring, Md.), 21*(5), 944–950. https://doi.org/ 10.1002/OBY.20431

Beltrán-García, J., Osca-Verdegal, R., Pallardó, F. V., Ferreres, J., Rodríguez, M., Mulet, S., Sanchis-Gomar, F., Carbonell, N., & García-Giménez, J. L. (2020). Oxidative Stress and Inflammation in COVID-19-Associated Sepsis: The Potential Role of Anti-Oxidant Therapy in Avoiding Disease Progression. *Antioxidants, 9*(10), 1–20. https:// doi.org/10.3390/ANT IOX9100936

Bin, P., Huang, R., & Zhou, X. (2017). Oxidation Resistance of the Sulfur Amino Acids: Methionine and Cysteine. *BioMed Research International, 2017*. https://doi.org/10.1155/2017/9584932

Boddu, S. K., Aurangabadkar, G., & Kuchay, M. S. (2020). New onset diabetes, type 1 diabetes and COVID-19. *Diabetes & Metabolic Syndrome*, *14*(6), 2211–2217. https://doi.org/10.1016/J.DSX.2020.11.012

Bosu, W. K. (2015). An overview of the nutrition transition in West Africa: Implications for non-communicable diseases. *Proceedings of the Nutrition Society*, *74*(4), 466–477. https:// doi.org/10.1017/ S00296 65114001669

Brahimaj, A., Ligthart, S., Ghanbari, M., Ikram, M. A., Hofman, A., Franco, O. H., Kavousi, M., & Dehghan, A. (2017). Novel inflammatory markers

for incident pre-diabetes and type 2 diabetes: the Rotterdam Study. *European Journal of Epidemiology*, *32*(3), 217. https:// doi.org/ 10.1007/ S10654-017-0236-0

Broor, S., Parveen, S., & Maheshwari, M. (2018). Respiratory Syncytial Virus Infections in India: Epidemiology and Need for Vaccine. *Indian Journal of Medical Microbiology*, *36*(4), 458–464. https://doi.org/ 10.4103/ IJMM.IJMM_19_5

Brownlie, R. J., & Zamoyska, R. (2013). T cell receptor signalling networks: branched, diversified and bounded. *Nature Reviews. Immunology*, *13*(4), 257–269. https://doi.org/10.1038/NRI3403

Burke, S. D., Zsengellér, Z. K., Khankin, E. V., Lo, A. S., Rajakumar, A., DuPont, J. J., McCurley, A., Moss, M. E., Zhang, D., Clark, C. D., Wang, A., Seely, E. W., Kang, P. M., Stillman, I. E., Jaffe, I. Z., & Karumanchi, S. A. (2016). Soluble FMS-like Tyrosine Kinase 1 promotes angiotensin II sensitivity in preeclampsia. *Journal of Clinical Investigation*, *126*(7), 2561–2574. https://doi.org/10.1172/JCI83918

Butkowski, E. G., & Jelinek, H. F. (2017). Hyperglycaemia, oxidative stress and inflammatory markers. *Redox Report : Communications in Free Radical Research*, *22*(6), 257–264. https://doi.org/ 10.1080/ 13510002. 2016.1215643

Capes, S. E., Hunt, D., Malmberg, K., & Gerstein, H. C. (2000). Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet (London, England)*, *355*(9206), 773–778. https://doi.org/10.1016/S0140-6736(99)08415-9

Cecchini, R., & Cecchini, A. L. (2020). SARS-CoV-2 infection pathogenesis is related to oxidative stress as a response to aggression. *Medical Hypotheses*, *143*. https://doi.org/10.1016/J.MEHY.2020.110102

Chadt, A., & Al-Hasani, H. (2020). Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. *Pflugers Archiv European Journal of Physiology*, *472*(9), 1273–1298. https://doi.org/10.1007/S00424-020-02417-X

Chaitanya, K. V. (2019). Structure and Organization of Virus Genomes. *Genome and Genomics*, 1–30. https://doi.org/10.1007/978-981-15-0702-1_1

Charan, J., & Biswas, T. (2013). How to calculate sample size for different study designs in medical research? *Indian Journal of Psychological Medicine*, *35*(2), 121–126. https://doi.org/10.4103/0253-7176.116232

Chen, L., Chen, R., Wang, H., & Liang, F. (2015). Mechanisms Linking Inflammation to Insulin Resistance. *International Journal of Endocrinology*, *2015*. https://doi.org/10.1155/2015/508409

Chen, M., Zhu, B., Chen, D., Hu, X., Xu, X., Shen, W. J., Hu, C., Li, J., & Qu, S. (2021). COVID-19 May Increase the Risk of Insulin Resistance in Adult Patients Without Diabetes: A 6-Month Prospective Study. *Endocrine Practice*, *27*(8), 834–841. https://doi.org/ 10.1016 /j. eprac. 2021.04.004

Chen, X., Zhao, B., Qu, Y., Chen, Y., Xiong, J., Feng, Y., Men, D., Huang, Q., Liu, Y., Yang, B., Ding, J., & Li, F. (2020). Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in

Critically Ill Patients With Coronavirus Disease 2019. *Clinical Infectious Diseases*, *71*(8), 1937–1942. https://doi.org/10.1093/CID/CIAA449

Cheung, N. W. (2016). Steroid-induced hyperglycaemia in hospitalised patients: does it matter? *Diabetologia*, *59*(12), 2507–2509. https://doi.org/10.1007/S00125-016-4116-Z

Chiabi, A., Obadeyi, B., Désiré Mbassi, H., Nenwa, L., Mbuagbaw, L., Mah, E., Félicité, D., Zeh Meka, A., Walinjom, J., & Mbonda, E. (2014). Protection Against Malaria in Man: a Probe into some of the Implicated Mechanisms in Sub-Saharan Africa. *The Open Area Studies Journal*, *5*(1), 22–29. https://doi.org/10.2174/1874914320130806001

Choudhry, M. N., Malik, R. A., & Charalambous, C. P. (2016). Blood Glucose Levels Following Intra-Articular Steroid Injections in Patients with Diabetes: A Systematic Review. *JBJS Reviews*, *4*(3). https://doi.org/10.2106/JBJS.RVW.O.00029

Choudhury, A., & Mukherjee, S. (2020). In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. *Journal of Medical Virology*, *92*(10), 2105–2113. https://doi.org/10.1002/JMV.25987

Chow, F. Y., Nikolic-Paterson, D. J., Ozols, E., Atkins, R. C., & Tesch, G. H. (2005). Intercellular adhesion molecule-1 deficiency is protective against nephropathy in type 2 diabetic db/db mice. *Journal of the American Society of Nephrology : JASN*, *16*(6), 1711–1722. https:// doi.org/ 10. 1681/ASN.2004070612

Chudasama, Y. V., Gillies, C. L., Zaccardi, F., Coles, B., Davies, M. J., Seidu, S., & Khunti, K. (2020). Impact of COVID-19 on routine care for chronic

diseases: A global survey of views from healthcare professionals. *Diabetes & Metabolic Syndrome*, *14*(5), 965–967. https://doi.org/ 10.1016/J.DSX.2020.06.042

Cnop, M., Havel, P. J., Utzschneider, K. M., Carr, D. B., Sinha, M. K., Boyko, E. J., Retzlaff, B. M., Knopp, R. H., Brunzell, J. D., & Kahn, S. E. (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*, *46*(4), 459–469. https://doi.org/10.1007/S00125-003-1074-Z

Coppelli, A., Giannarelli, R., Aragona, M., Penno, G., Falcone, M., Tiseo, G., Ghiadoni, L., Barbieri, G., Monzani, F., Virdis, A., Menichetti, F., & Prato, S. Del. (2020). Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: The pisa COVID-19 study. *Diabetes Care*, *43*(10), 2345–2348. https://doi.org/10.2337/DC20-1380

Costela-Ruiz, V. J., Illescas-Montes, R., Puerta-Puerta, J. M., Ruiz, C., & Melguizo-Rodríguez, L. (2020). SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine & Growth Factor Reviews*, *54*, 62–75. https://doi.org/10.1016/J.CYTOGFR.2020.06.001

Cuong, T. Q., Dibley, M. J., Bowe, S., Hanh, T. T. M., & Loan, T. T. H. (2007). Obesity in adults: An emerging problem in urban areas of Ho Chi Minh City, Vietnam. *European Journal of Clinical Nutrition*, *61*(5), 673–681. https://doi.org/10.1038/sj.ejcn.1602563

Dalla Vestra, M., Mussap, M., Gallina, P., Bruseghin, M., Cernigoi, A. M., Saller, A., Plebani, M., & Fioretto, P. (2005). Acute-phase markers of

inflammation and glomerular structure in patients with type 2 diabetes. *Journal of the American Society of Nephrology*, *16*(3 SUPPL. 1). https://doi.org/10.1681/ASN.2004110961

Dandekar, S. P., & Rane, S. A. (2004). *Practicals and viva in medical biochemistry*. 242. https:// books.google. com/books/ about/ Practicals_and_Viva_in_Medical_Biochemis.html?id=s9HEoJquruwC

Daniele, G., Guardado Mendoza, R., Winnier, D., Fiorentino, T. V., Pengou, Z., Cornell, J., Andreozzi, F., Jenkinson, C., Cersosimo, E., Federici, M., Tripathy, D., & Folli, F. (2014). The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. *Acta Diabetologica*, *51*(1), 123–131. https://doi.org/ 10.1007/ S00592-013-0543-1

Darnay, B. G., Haridas, V., Ni, J., Moore, P. A., & Aggarwal, B. B. (1998). Characterization of the Intracellular Domain of Receptor Activator of NF-κB (RANK): INTERACTION WITH TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED FACTORS AND ACTIVATION OF NF-κB AND c-JUN N-TERMINAL KINASE *. *Journal of Biological Chemistry*, *273*(32), 20551–20555. https://doi.org/ 10.1074/ JBC.273.32.20551

Davids, S. F. G., Davids, S. F. G., Matsha, T. E., Peer, N., Peer, N., Erasmus, R. T., & Kengne, A. P. (2020). The 7-Year Change in the Prevalence of Insulin Resistance, Inflammatory Biomarkers, and Their Determinants in an Urban South African Population. *Journal of Diabetes Research*, *2020*. https://doi.org/10.1155/2020/3781214

de-Madaria, E., & Capurso, G. (2021). COVID-19 and acute pancreatitis: examining the causality. *Nature Reviews. Gastroenterology & Hepatology*, *18*(1), 3–4. https://doi.org/10.1038/S41575-020-00389-Y

Dedoussis, G. V. Z., Kaliora, A. C., & Panagiotakos, D. B. (2007). Genes, diet and type 2 diabetes mellitus: A review. *Review of Diabetic Studies*, *4*(1), 13–24. https://doi.org/10.1900/RDS.2007.3.13

Delgado-Roche, L., & Mesta, F. (2020). Oxidative Stress as Key Player in Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection. *Archives of Medical Research*, *51*(5), 384–387. https://doi.org/10.1016 / J.ARCMED.2020.04.019

Devasagayam, T. P. A., Boloor, K. K., & Ramasarma, T. (2003). Methods for estimating lipid peroxidation: An analysis of merits and demerits. *Indian Journal of Biochemistry and Biophysics*, *40*(5), 300–308.

Dhangadamajhi, G., Mohapatra, B. N., Kar, S. K., & Ranjit, M. (2010). Gene polymorphisms in angiotensin I converting enzyme (ACE I/D) and angiotensin II converting enzyme (ACE2 C-->T) protect against cerebral malaria in Indian adults. *Infection, Genetics and Evolution : Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases*, *10*(2), 337–341. https://doi.org/10.1016/ J.MEEGID. 2010.01. 009

Dia, D. G., Dia, A. D., Diagne, N., Ndao, A. C., Tall, C. T., & Ngouamba, B. M. (2021). Difficulties in the Management of Systemic Autoimmune Diseases in Saint-Louis Du Senegal through the Analysis of a Series of 70 Observations. *Open Journal of Internal Medicine*, *11*(04), 258–264. https://doi.org/10.4236/OJIM.2021.114022

Dinarello, C. A., Donath, M. Y., & Mandrup-Poulsen, T. (2010). Role of IL-1β in type 2 diabetes. *Current Opinion in Endocrinology, Diabetes and Obesity*, *17*(4), 314–321. https://doi.org/ 10.1097/MED. 0B013E32833 BF6DC

Do, H. D., Lohsoonthorn, V., Jiamjarasrangsi, W., Lertmaharit, S., & Williams, M. A. (2010). Prevalence of insulin resistance and its relationship with cardiovascular disease risk factors among Thai adults over 35 years old. *Undefined*, *89*(3), 303–308. https://doi.org/10.1016/ J. DIABRES.2010.04.013

Domingo, P., Mur, I., Pomar, V., Corominas, H., Casademont, J., & de Benito, N. (2020a). The four horsemen of a viral Apocalypse: The pathogenesis of SARS-CoV-2 infection (COVID-19). *EBioMedicine*, *58*. https:// doi. org/10.1016/j.ebiom.2020.102887

Domingo, P., Mur, I., Pomar, V., Corominas, H., Casademont, J., & de Benito, N. (2020b). The four horsemen of a viral Apocalypse: The pathogenesis of SARS-CoV-2 infection (COVID-19). *EBioMedicine*, *58*. https:// doi.org/10.1016/J.EBIOM.2020.102887

Donath, M. Y., Dalmas, É., Sauter, N. S., & Böni-Schnetzler, M. (2013). Inflammation in obesity and diabetes: islet dysfunction and therapeutic opportunity. *Cell Metabolism*, *17*(6), 860–872. https://doi.org /10.1016/ J.CMET.2013.05.001

Donath, M. Y., Dinarello, C. A., & Mandrup-Poulsen, T. (2019). Targeting innate immune mediators in type 1 and type 2 diabetes. *Nature Reviews. Immunology*, *19*(12), 734–746. https://doi.org/10.1038/S41577-019-0213-9

Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. *Nature Reviews. Immunology*, *11*(2), 98–107. https:// doi.org/ 10.1038/NRI2925

Donia, A., & Habib Bokhari, ·. (2021). Apoptosis induced by SARS-CoV-2: can we target it? *Apoptosis*, *26*, 7–8. https://doi.org/10.1007/s10495-021-01656-2

Doss C, G. P., Agoramoorthy, G., & Chakraborty, C. (2014). TNF/TNFR: drug target for autoimmune diseases and immune-mediated inflammatory diseases. *Frontiers in Bioscience (Landmark Edition)*, *19*(7), 1028–1040. https://doi.org/10.2741/4265

Drucker, D. J. (2020). Coronavirus Infections and Type 2 Diabetes-Shared Pathways with Therapeutic Implications. *Endocrine Reviews*, *41*(3), 457–469. https://doi.org/10.1210/ENDREV/BNAA011

Drucker, D. J. (2021). Diabetes, obesity, metabolism, and SARS-CoV-2 infection: the end of the beginning. *Cell Metabolism*, *33*(3), 479–498. https://doi.org/10.1016/J.CMET.2021.01.016

Duncan, B. B., Schmidt, M. I., Ewerton Cousin, Moradi-Lakeh, M., Passos, V. M. D. A., França, E. B., Marinho, F., & Mokdad, A. H. (2017). The burden of diabetes and hyperglycemia in Brazil-past and present: findings from the Global Burden of Disease Study 2015. *Diabetology & Metabolic Syndrome*, *9*(1). https://doi.org/10.1186/S13098-017-0216-2

Dupont, V., Kanagaratnam, L., Goury, A., Poitevin, G., Bard, M., Julien, G., Bonnivard, M., Champenois, V., Noel, V., Mourvillier, B., & Nguyen, P. (2021). Excess Soluble fms-like Tyrosine Kinase 1 Correlates with Endothelial Dysfunction and Organ Failure in Critically Ill Coronavirus

Disease 2019 Patients. *Clinical Infectious Diseases*, *72*(10), 1834–1837. https://doi.org/10.1093/CID/CIAA1007

Duvnjak, L., & Duvnjak, M. (2009). The metabolic syndrome - an ongoing story. *Journal of Physiology and Pharmacology : An Official Journal of the Polish Physiological Society*, *60 Suppl 7*, 19–24.

Eguchi, K., & Nagai, R. (2017). Islet inflammation in type 2 diabetes and physiology. *The Journal of Clinical Investigation*, *127*(1), 14–23. https://doi.org/10.1172/JCI88877

Elased, K., De Souza, J. B., & Playfair, J. H. L. (1995). Blood-Stage malaria infection in diabetic mice. *Clinical & Experimental Immunology*, *99*(3), 440–444. https://doi.org/10.1111/J.1365-2249.1995.TB05570.X

Elased, K., & Playfair, J. H. L. (1994). Hypoglycemia and hyperinsulinemia in rodent models of severe malaria infection. *Infection and Immunity*, *62*(11), 5157–5160. https://doi.org/10.1128/IAI.62.11.5157-5160.1994

Elmarakby, A. A., & Sullivan, J. C. (2012). Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. *Cardiovascular Therapeutics*, *30*(1), 49–59. https://doi.org/ 10.1111/ J. 1755-5922.2010.00218.X

Elsafty, A., Nabhan, S., Saad, M., Mahmoud, H., Azzazy, H., Nwadike, C., Nwanjor, H., Duru, M., Onyejiekwe, C., & Ezekwe, R. (2018). Specific Cutoffs for HOMA1-IR, HOMA2-IR, HOMA1-%B, and HOMA2-%B in Adult Egyptian Patients. *American Journal of Clinical Pathology*, *150*(suppl_1), S66–S66. https://doi.org/10.1093/AJCP/AQY092.162

Eltahir, E. M., ElGhazali, G., A-Elgadir, T. M. E., A-Elbasit, I. E., Elbashir, M. I., & Giha, H. A. (2010). Raised plasma insulin level and homeostasis

model assessment (HOMA) score in cerebral malaria: Evidence for insulin resistance and marker of virulence. *Acta Biochimica Polonica*, *57*(4), 513–520. https://doi.org/10.18388/ABP.2010_2437

Erener, S. (2020). Diabetes, infection risk and COVID-19. *Molecular Metabolism*, *39*. https://doi.org/10.1016/J.MOLMET.2020.101044

Esan A.J, I. M. . (2014). Dekker E, Romijn JA, Ekberg K, Wahren J, Van Thien H, Ackermans MT, et al., Glucose production and gluconeogenesis in adults with uncomplicated falciparum malaria. Am J Physiol; (1997) 272. E1059-1064. *International Journal of Hematological Disorders*, *1*, 31–34. http://www.sciepub.com/reference/80854

Eslami, H., & Jalili, M. (2020). The role of environmental factors to transmission of SARS-CoV-2 (COVID-19). *AMB Express*, *10*(1). https://doi.org/10.1186/S13568-020-01028-0

Esser, N., Legrand-Poels, S., Piette, J., Scheen, A. J., & Paquot, N. (2014). Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Research and Clinical Practice*, *105*(2), 141–150. https://doi.org/10.1016/J.DIABRES.2014.04.006

Esteghamati, A., Ashraf, H., Khalilzadeh, O., Zandieh, A., Nakhjavani, M., Rashidi, A., Haghazali, M., & Asgari, F. (2010). Optimal cut-off of homeostasis model assessment of insulin resistance (HOMA-IR) for the diagnosis of metabolic syndrome: third national surveillance of risk factors of non-communicable diseases in Iran (SuRFNCD-2007). *Undefined*, *7*. https://doi.org/10.1186/1743-7075-7-26

Fadini, G. P., Morieri, M. L., Boscari, F., Fioretto, P., Maran, A., Busetto, L., Bonora, B. M., Selmin, E., Arcidiacono, G., Pinelli, S., Farnia, F.,

Falaguasta, D., Russo, L., Voltan, G., Mazzocut, S., Costantini, G., Ghirardini, F., Tresso, S., Cattelan, A. M., … Vettor, R. (2020). Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. *Diabetes Research and Clinical Practice*, *168*, 108374. https://doi.org/10. 1016/J. DIABRES. 2020.108374

Fenouillet, E., Barbouche, R., & Jones, I. M. (2007). Cell entry by enveloped viruses: redox considerations for HIV and SARS-coronavirus. *Antioxidants & Redox Signaling*, *9*(8), 1009–1034. https://doi.org/ 10.1089/ARS.2007.1639

Fignani, D., Licata, G., Brusco, N., Nigi, L., Grieco, G. E., Marselli, L., Overbergh, L., Gysemans, C., Colli, M. L., Marchetti, P., Mathieu, C., Eizirik, D. L., Sebastiani, G., & Dotta, F. (2020). SARS-CoV-2 Receptor Angiotensin I-Converting Enzyme Type 2 (ACE2) Is Expressed in Human Pancreatic β-Cells and in the Human Pancreas Microvasculature. *Frontiers in Endocrinology*, *11*. https://doi.org/ 10.3389/ FENDO. 2020. 596898

Finucane, F. M., & Davenport, C. (2020). Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19 Infection? *Frontiers in Public Health*, *8*, 184. https://doi.org/ 10.3389 / FPUBH.2020. 00184/ BIBTEX

Fiorentino, T. V., Casiraghi, F., Davalli, A. M., Finzi, G., Rosa, S. La, Higgins, P. B., Abrahamian, G. A., Marando, A., Sessa, F., Perego, C., Guardado-Mendoza, R., Kamath, S., Ricotti, A., Fiorina, P., Daniele, G., Paez, A. M., Andreozzi, F., Bastarrachea, R. A., Comuzzie, A. G., …

Folli, F. (2019). Exenatide regulates pancreatic islet integrity and insulin sensitivity in the nonhuman primate baboon Papio hamadryas. *JCI Insight*, *4*(20). https://doi.org/10.1172/JCI.INSIGHT.93091

Fizelova, M., Jauhiainen, R., Kangas, A. J., Soininen, P., Ala-Korpela, M., Kuusisto, J., Laakso, M., & Stancáková, A. (2017). Differential Associations of Inflammatory Markers With Insulin Sensitivity and Secretion: The Prospective METSIM Study. *The Journal of Clinical Endocrinology and Metabolism*, *102*(9), 3600–3609. https://doi.org / 10.1210/JC.2017-01057

Fong, A. C., & Cheung, N. W. (2013). The high incidence of steroid-induced hyperglycaemia in hospital. *Diabetes Research and Clinical Practice*, *99*(3), 277–280. https://doi.org/10.1016/J.DIABRES.2012.12.023

Fumagalli, M., & Sironi, M. (2014). Human genome variability, natural selection and infectious diseases. *Current Opinion in Immunology*, *30*(1), 9–16. https://doi.org/10.1016/J.COI.2014.05.001

Gallego-Delgado, J., & Rodriguez, A. (2014). Malaria and hypertension. Another co-evolutionary adaptation? *Frontiers in Cellular and Infection Microbiology*, *4*(SEP). https://doi.org/10.3389/FCIMB.2014.00121

Garcia-Garcia, A., Rodriguez-Rocha, H., Madayiputhiya, N., Pappa, A., I. Panayiotidis, M., & Franco, R. (2012). Biomarkers of protein oxidation in human disease. *Current Molecular Medicine*, *12*(6), 681–697. https://doi.org/10.2174/156652412800792543

Gasteiger, G., & Rudensky, A. Y. (2014). Interactions between innate and adaptive lymphocytes. *Nature Reviews Immunology 2014 14:9*, *14*(9), 631–639. https://doi.org/10.1038/nri3726

Gayoso-Diz, P., Otero-Gonzalez, A., Rodriguez-Alvarez, M. X., Gude, F., Cadarso-Suarez, C., García, F., & De Francisco, A. (2011). Insulin resistance index (HOMA-IR) levels in a general adult population: curves percentile by gender and age. The EPIRCE study. *Diabetes Research and Clinical Practice*, *94*(1), 146–155. https://doi.org/10.1016/ J.DIABRES. 2011.07.015

Gelaye, B., Revilla, L., Lopez, T., Suarez, L., Sanchez, S. E., Hevner, K., Fitzpatrick, A. L., & Williams, M. A. (2010). Association between insulin resistance and c-reactive protein among Peruvian adults. *Diabetology & Metabolic Syndrome*, *2*(1). https://doi.org/10.1186/1758-5996-2-30

Geravandi, S., Liu, H., & Maedler, K. (2020). Enteroviruses and t1d: Is it the virus, the genes or both which cause t1d. *Microorganisms*, *8*(7), 1–20. https://doi.org/10.3390/MICROORGANISMS8071017

Gonzalez, A. A., Salinas-Parra, N., Cifuentes-Araneda, F., & Reyes-Martinez, C. (2020). Vasopressin actions in the kidney renin angiotensin system and its role in hypertension and renal disease. *Vitamins and Hormones*, *113*, 217–238. https://doi.org/10.1016/BS.VH.2019.09.003

Govender, N., Khaliq, O. P., Moodley, J., & Naicker, T. (2020). *Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . January*.

Govindan, B. (2014). Toll like receptors: Sensors for herpes simplex virus infection. *Indian Journal of Sexually Transmitted Diseases and AIDS*,

35(2), 170–171. https://doi.org/10.4103/0253-7184.142425

Grodsky, G. M. (1999). The importance of rapid insulin secretion: revisited. *Diabetes Technology & Therapeutics*, *1*(3), 259–260. https://doi.org/10.1089/152091599317161

Grossmannm, V., Schmitt, V. H., Zeller, T., Panova-Noeva, M., Schulz, A., Laubert-Reh, D., Juenger, C., Schnabel, R. B., Abt, T. G. J., Laskowski, R., Wiltink, J., Schulz, E., Blankenberg, S., Lackner, K. J., Münzel, T., & Wild, P. S. (2015). Profile of the Immune and Inflammatory Response in Individuals With Prediabetes and Type 2 Diabetes. *Diabetes Care*, *38*(7), 1356–1364. https://doi.org/10.2337/DC14-3008

GSS. (2021). Ghana Population and Housing Census, General Report 3A. In *Population of Regions and Districts* (Vol. 3A, Issue 3(A)).

Guillermo, L. V. C., Pereira, W. F., De Meis, J., Ribeiro-Gomes, F. L., Silva, E. M., Kroll-Palhares, K., Takiya, C. M., & Lopes, M. F. (2009). Targeting caspases in intracellular protozoan infections. *Immunopharmacology and Immunotoxicology*, *31*(2), 159–173. https://doi.org/10.1080/08923970802332164

Guisado-Vasco, P., Cano-Megías, M., Rodríguez-López, M., de-Luna-Boquera, I. M., & Carnevali-Ruiz, D. (2020). COVID-19 and Metabolic Syndrome: NF-κB Activation. Crossroads. *Trends in Endocrinology and Metabolism: TEM*, *31*(11), 802–803. https://doi.org/ 10.1016/ J.TEM. 2020.08.004

Halliwell, B. (2009). The wanderings of a free radical. *Free Radical Biology & Medicine*, *46*(5), 531–542. https://doi.org /10.1016/ J. FREERAD BIOMED.2008.11.008

Harijith, A., Ebenezer, D. L., & Natarajan, V. (2014a). Reactive oxygen species at the crossroads of inflammasome and inflammation. *Frontiers in Physiology*, *5*. https://doi.org/10.3389/FPHYS.2014.00352

Harijith, A., Ebenezer, D. L., & Natarajan, V. (2014b). Reactive oxygen species at the crossroads of inflammasome and inflammation. *Frontiers in Physiology*, *5*. https://doi.org/10.3389/FPHYS.2014.00352

Hedrick, P. W. (2011). Population genetics of malaria resistance in humans. *Heredity*, *107*(4), 283–304. https://doi.org/10.1038/HDY.2011.16

Hikmet, F., Méar, L., Edvinsson, Å., Micke, P., Uhlén, M., & Lindskog, C. (2020). The protein expression profile of ACE2 in human tissues. *Molecular Systems Biology*, *16*(7). https:// doi.org/10. 15252/ MSB. 20209610

Höhn, A., Jung, T., & Grune, T. (2014). Pathophysiological importance of aggregated damaged proteins. *Free Radical Biology & Medicine*, *71*, 70–89. https://doi.org/10.1016/J.FREERADBIOMED.2014.02.028

Hollstein, T., Schulte, D. M., Schulz, J., Glück, A., Ziegler, A. G., Bonifacio, E., Wendorff, M., Franke, A., Schreiber, S., Bornstein, S. R., & Laudes, M. (2020). Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. *Nature Metabolism*, *2*(10), 1021–1024. https://doi.org/10.1038/S42255-020-00281-8

Hotamisligil, G. S. (2017). Inflammation, metaflammation and immunometabolic disorders. *Nature*, *542*(7640), 177–185. https:// doi.org /10.1038/NATURE21363

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W.,

Li, H., Liu, M., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Huang, S., Wang, J., Zhang, L., Tian, S., Wang, Y., Shao, X., Zhou, S., & Yu, P. (2022). Ras guanine nucleotide-releasing protein-4 promotes renal inflammatory injury in type 2 diabetes mellitus. *Metabolism: Clinical and Experimental*, *131*, 155177. https://doi.org/ 10.1016/J.METABOL. 2022. 155177

Huang, Z., Rose, A. H., & Hoffmann, P. R. (2012). The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. *Antioxidants & Redox Signaling*, *16*(7), 705–743. https://doi.org/10.1089/ARS.2011.4145

Ibrahim, S., & Monaco, G. (2021). Not so sweet and simple: impacts of SARS- CoV-2 on the b cell. *Islets*, *13*, 66–67.

Iddir, M., Brito, A., Dingeo, G., Del Campo, S. S. F., Samouda, H., La Frano, M. R., & Bohn, T. (2020). Strengthening the immune system and reducing inflammation and oxidative stress through diet and nutrition: Considerations during the covid-19 crisis. *Nutrients*, *12*(6), 1–39. https://doi.org/10.3390/nu12061562

IDF. (2015). *7th edition | IDF Diabetes Atlas*. International Diabetes Atlas. https://diabetesatlas.org/atlas/seventh-edition/

Ivanov, A. V., Smirnova, O. A., Ivanova, O. N., Masalova, O. V., Kochetkov, S. N., & Isaguliants, M. G. (2011). Hepatitis C Virus Proteins Activate NRF2/ARE Pathway by Distinct ROS-Dependent and Independent Mechanisms in HUH7 Cells. *PLOS ONE*, *6*(9), e24957. https://doi.org

/10.1371/JOURNAL.PONE.0024957

Jackson, C. B., Farzan, M., Chen, B., & Choe, H. (2022). Mechanisms of SARS-CoV-2 entry into cells. *Nature Reviews. Molecular Cell Biology*, *23*(1), 3–20. https://doi.org/10.1038/S41580-021-00418-X

Jensen, M. K., Rimm, E. B., Furtado, J. D., & Sacks, F. M. (2012). Apolipoprotein C-III as a Potential Modulator of the Association Between HDL-Cholesterol and Incident Coronary Heart Disease. *Journal of the American Heart Association*, *1*(2). https://doi.org/ 10.1161/ JAHA . 111.000232.)

Jin, Y., Yang, H., Ji, W., Wu, W., Chen, S., Zhang, W., & Duan, G. (2020). *viruses Virology, Epidemiology, Pathogenesis, and Control of COVID-19*. https://doi.org/10.3390/v12040372

Kammouni, W., Hasan, L., Saleh, A., Wood, H., Fernyhough, P., & Jackson, A. C. (2012). Role of nuclear factor-κB in oxidative stress associated with rabies virus infection of adult rat dorsal root ganglion neurons. *Journal of Virology*, *86*(15), 8139–8146. https:// doi.org/ 10.1128/ JVI. 00550-12

Kanamoto, T., Mota, M., Takeda, K., Rubin, L. L., Miyazono, K., Ichijo, H., & Bazenet, C. E. (2000). Role of apoptosis signal-regulating kinase in regulation of the c-Jun N-terminal kinase pathway and apoptosis in sympathetic neurons. *Molecular and Cellular Biology*, *20*(1), 196–204. https://doi.org/10.1128/MCB.20.1.196-204.2000

Karin, M., & Greten, F. R. (2005). NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nature Reviews. Immunology*, *5*(10), 749–759. https://doi.org/10.1038/NRI1703

Kavouras, S. A., Panagiotakos, D. B., Pitsavos, C., Chrysohoou, C., Anastasiou, C. A., Lentzas, Y., & Stefanadis, C. (2007). Physical activity, obesity status, and glycemic control: The ATTICA study. *Medicine and Science in Sports and Exercise*, *39*(4), 606–611. https://doi.org/ 10.1249/ MSS.0B013E31803084EB

Kawahito, S., Kitahata, H., & Oshita, S. (2009). Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress. *World Journal of Gastroenterology*, *15*(33), 4137–4142. https://doi.org/ 10.3748 /WJG.15.4137

Kelley, N., Jeltema, D., Duan, Y., & He, Y. (2019). The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *International Journal of Molecular Sciences*, *20*(13). https:// doi.org/10.3390/IJMS20133328

Khunti, K., Prato, S. Del, Mathieu, C., Kahn, S. E., Gabbay, R. A., & Buse, J. B. (2021a). COVID-19, Hyperglycemia, and New-Onset Diabetes. *Diabetes Care*, *44*(12), 2645–2655. https://doi.org/10.2337/DC21-1318

Khunti, K., Prato, S. Del, Mathieu, C., Kahn, S. E., Gabbay, R. A., & Buse, J. B. (2021b). COVID-19, Hyperglycemia, and New-Onset Diabetes. *Diabetes Care*, *44*(12), 2645–2655. https://doi.org/10.2337/DC21-1318

Kim, Y., Keogh, J., & Clifton, P. (2015). A review of potential metabolic etiologies of the observed association between red meat consumption and development of type 2 diabetes mellitus. *Metabolism: Clinical and Experimental*, *64*(7), 768–779. https://doi.org/ 10.1016/ J.METABOL. 2015.03.008

Kooffreh, M., Anumudu, C., & Kumar, Pl. (2014). Insertion/deletion polymorphism of the angiotensin-converting enzyme gene and the risk of hypertension among residents of two cities, South-South Nigeria. *Advanced Biomedical Research*, *3*(1), 118. https://doi.org/10.4103/2277-9175.133184

Krogvold, L., Edwin, B., Buanes, T., Frisk, G., Skog, O., Anagandula, M., Korsgren, O., Undlien, D., Eike, M. C., Richardson, S. J., Leete, P., Morgan, N. G., Oikarinen, S., Oikarinen, M., Laiho, J. E., Hyöty, H., Ludvigsson, J., Hanssen, K. F., & Dahl-Jørgensen, K. (2015). Detection of a Low-Grade Enteroviral Infection in the Islets of Langerhans of Living Patients Newly Diagnosed With Type 1 Diabetes. *Diabetes*, *64*(5), 1682–1687. https://doi.org/10.2337/DB14-1370

Kumar, H., Kawai, T., & Akira, S. (2011). Pathogen recognition by the innate immune system. *International Reviews of Immunology*, *30*(1), 16–34. https://doi.org/10.3109/08830185.2010.529976

Kumar Pasupulati, A., Chitra, P. S., & Reddy, G. B. (2016). Advanced glycation end products mediated cellular and molecular events in the pathology of diabetic nephropathy. *Biomolecular Concepts*, *7*(5–6), 293–299. https://doi.org/10.1515/BMC-2016-0021

Kusmartseva, I., Wu, W., Syed, F., Van Der Heide, V., Jorgensen, M., Joseph, P., Tang, X., Candelario-Jalil, E., Yang, C., Nick, H., Harbert, J. L., Posgai, A. L., Paulsen, J. D., Lloyd, R., Cechin, S., Pugliese, A., Campbell-Thompson, M., Vander Heide, R. S., Evans-Molina, C., … Atkinson, M. A. (2020). Expression of SARS-CoV-2 Entry Factors in the Pancreas of Normal Organ Donors and Individuals with COVID-19. *Cell*

Metabolism, *32*(6), 1041-1051.e6. https://doi.org/10.1016 /J. CMET. 2020.11.005

Laitinen, O. H., Honkanen, H., Pakkanen, O., Oikarinen, S., Hankaniemi, M. M., Huhtala, H., Ruokoranta, T., Lecouturier, V., André, P., Harju, R., Virtanen, S. M., Lehtonen, J., Almond, J. W., Simell, T., Simell, O., Ilonen, J., Veijola, R., Knip, M., & Hyöty, H. (2014). Coxsackievirus B1 is associated with induction of β-cell autoimmunity that portends type 1 diabetes. *Diabetes*, *63*(2), 446–455. https://doi.org/10.2337/DB13-0619

Lam, G. Y., Huang, J., & Brumell, J. H. (2010). The many roles of NOX2 NADPH oxidase-derived ROS in immunity. *Seminars in Immunopathology*, *32*(4), 415–430. https://doi.org/10.1007/S00281-010-0221-0

Lauterbach, M. A. R., & Wunderlich, F. T. (2017). Macrophage function in obesity-induced inflammation and insulin resistance. *Pflugers Archiv*, *469*(3), 385. https://doi.org/10.1007/S00424-017-1955-5

Lee, Y. J., Suh, K. S., Choi, M. C., Chon, S., Oh, S., Woo, J. T., Kim, S. W., Kim, J. W., & Kim, Y. S. (2010). Kaempferol protects HIT-T15 pancreatic beta cells from 2-deoxy-D-ribose- induced oxidative damage. *Phytotherapy Research*, *24*(3), 419–423. https:// doi.org/ 10.1002/ PTR. 2983

Li, H., Tian, S., Chen, T., Cui, Z., Shi, N., Zhong, X., Qiu, K., Zhang, J., Zeng, T., Chen, L., & Zheng, J. (2020). Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes, Obesity & Metabolism*, *22*(10), 1897–1906. https://doi.org/10.1111/DOM.14099

Li, H., Zhou, X., Huang, Y., Liao, B., Cheng, L., & Ren, B. (2021). Reactive Oxygen Species in Pathogen Clearance: The Killing Mechanisms, the Adaption Response, and the Side Effects. *Frontiers in Microbiology*, *11*. https://doi.org/10.3389/FMICB.2020.622534

Li, L., Huang, Q., Wang, D. C., Ingbar, D. H., & Wang, X. (2020). Acute lung injury in patients with COVID-19 infection. *Clinical and Translational Medicine*, *10*(1), 20. https://doi.org/10.1002/CTM2.16

Li, M., Yang, T., He, R., Li, A., Dang, W., Liu, X., & Chen, M. (2020). The Value of Inflammatory Biomarkers in Differentiating Asthma–COPD Overlap from COPD . *International Journal of Chronic Obstructive Pulmonary Disease*, *15*, 3025–3037. https://doi.org/10.2147/COPD.S273422

Liang, H., & Acharya, G. (2020). Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow? *Acta Obstetricia et Gynecologica Scandinavica*, *99*(4), 439–442. https://doi.org/10.1111 / AOGS.13836

Liguori, C., Pierantozzi, M., Spanetta, M., Sarmati, L., Cesta, N., Iannetta, M., Ora, J., Mina, G. G., Puxeddu, E., Balbi, O., Pezzuto, G., Magrini, A., Rogliani, P., Andreoni, M., & Mercuri, N. B. (2020). Subjective neurological symptoms frequently occur in patients with SARS-CoV2 infection. *Brain, Behavior, and Immunity*, *88*, 11–16. https://doi.org/ 10.1016/J.BBI.2020.05.037

Liou, G. Y., & Storz, P. (2010). Reactive oxygen species in cancer. *Free Radical Research*, *44*(5), 479–496. https://doi.org/10.3109/107157 61003667554

Liu, F., Long, X., Zhang, B., Zhang, W., Chen, X., & Zhang, Z. (2020a). ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clinical Gastroenterology and Hepatology*, *18*(9), 2128-2130.e2. https://doi.org/10.1016/J.CGH.2020.04.040

Liu, F., Long, X., Zhang, B., Zhang, W., Chen, X., & Zhang, Z. (2020b). ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *18*(9), 2128-2130.e2. https://doi.org/ 10.1016/ J.CGH. 2020. 04.040

Liu, J., Li, S., Liu, J., Liang, B., Wang, X., Wang, H., Li, W., Tong, Q., Yi, J., Zhao, L., Xiong, L., Guo, C., Tian, J., Luo, J., Yao, J., Pang, R., Shen, H., Peng, C., Liu, T., … Zheng, X. (2020). Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine*, *55*. https://doi.org/ 10.1016/J.EBIOM.2020.102763

Liu, T., Zhang, L., Joo, D., & Sun, S. C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy 2017 2:1*, *2*(1), 1–9. https://doi.org/10.1038/sigtrans.2017.23

Liu, W., Chen, D., Tan, W., Xu, D., Qiu, S., Zeng, Z., Li, X., & Zhou, R. (2016). Epidemiology and clinical presentations of respiratory syncytial virus subgroups A and B detected with multiplex real-time PCR. *PLoS ONE*, *11*(10). https://doi.org/10.1371/JOURNAL.PONE.0165108

Liu, X. X., Zhu, X. M., Miao, Q., Ye, H. Y., Zhang, Z. Y., & Li, Y. M. (2014). Hyperglycemia induced by glucocorticoids in nondiabetic patients: a

meta-analysis. *Annals of Nutrition & Metabolism*, *65*(4), 324–332. https://doi.org/10.1159/000365892

Lopresti, A. L., Maker, G. L., Hood, S. D., & Drummond, P. D. (2014). A review of peripheral biomarkers in major depression: the potential of inflammatory and oxidative stress biomarkers. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *48*, 102–111. https://doi.org/10.1016/J.PNPBP.2013.09.017

Luc, K., Schramm-Luc, A., Guzik, T. J., & Mikolajczyk, T. P. (2019). Oxidative stress and inflammatory markers in prediabetes and diabetes. *Journal of Physiology and Pharmacology*, *70*(6). https://doi.org /10.26402/jpp.2019.6.01

Maciej Serda. (2013). Synteza i aktywność biologiczna nowych analogów tiosemikarbazonowych chelatorów żelaza. *Uniwersytet Śląski*, 343–354. https://doi.org/10.2/JQUERY.MIN.JS

Maddux, B. A., See, W., Lawrence, J. C., Goldfine, A. L., Goldfine, I. D., & Evans, J. L. (2001). Protection against oxidative stress-induced insulin resistance in rat l6 muscle cells by micromolar concentrations of α-lipoic acid. *Diabetes*, *50*(2), 404–410. https:// doi.org/ 10.2337 /DIABETES. 50 .2.404

Mao, R., Qiu, Y., He, J. S., Tan, J. Y., Li, X. H., Liang, J., Shen, J., Zhu, L. R., Chen, Y., Iacucci, M., Ng, S. C., Ghosh, S., & Chen, M. H. (2020). Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*, *5*(7), 667–678. https://doi.org/ 10.1016/S2468-1253(20)30126-6

Marchand, L., Pecquet, M., & Luyton, C. (2020). Type 1 diabetes onset triggered by COVID-19. *Acta Diabetologica*, *57*(10), 1265–1266. https://doi.org/10.1007/S00592-020-01570-0

Martinez-Ferran, M., de la Guía-Galipienso, F., Sanchis-Gomar, F., & Pareja-Galeano, H. (2020). Metabolic Impacts of Confinement during the COVID-19 Pandemic Due to Modified Diet and Physical Activity Habits. *Nutrients*, *12*(6). https://doi.org/10.3390/NU12061549

Mas-Bargues, C., Escrivá, C., Dromant, M., Borrás, C., & Viña, J. (2021). Lipid peroxidation as measured by chromatographic determination of malondialdehyde. Human plasma reference values in health and disease. *Archives of Biochemistry and Biophysics*, *709*. https://doi.org/ 10.1016/ j. abb.2021.108941

Maschirow, L., Khalaf, K., Al-Aubaidy, H. A., & Jelinek, H. F. (2015). Inflammation, coagulation, endothelial dysfunction and oxidative stress in prediabetes--Biomarkers as a possible tool for early disease detection for rural screening. *Clinical Biochemistry*, *48*(9), 581–585. https:// doi.org/10.1016/J.CLINBIOCHEM.2015.02.015

Masters, S. L. (2013). Specific inflammasomes in complex diseases. *Clinical Immunology (Orlando, Fla.)*, *147*(3), 223–228. https://doi.org/ 10.1016/ J.CLIM.2012.12.006

Matsui, A., Ikeda, T., Enomoto, K., Hosoda, K., Nakashima, H., Omae, K., Watanabe, M., Hibi, T., & Kitajima, M. (2000). Increased formation of oxidative DNA damage, 8-hydroxy-2'-deoxyguanosine, in human breast cancer tissue and its relationship to GSTP1 and COMT genotypes. *Cancer Letters*, *151*(1), 87–95. https://doi.org/10.1016/S0304-

3835(99)00424-3

Matsuzawa, A., Nishitoh, H., Tobiume, K., Takeda, K., & Ichijo, H. (2002). Physiological roles of ASK1-mediated signal transduction in oxidative stress- and endoplasmic reticulum stress-induced apoptosis: advanced findings from ASK1 knockout mice. *Antioxidants & Redox Signaling*, *4*(3), 415–425. https://doi.org/10.1089/15230860260196218

Medina-Urrutia, A., Posadas-Romero, C., Posadas-Sánchez, R., Jorge-Galarza, E., Villarreal-Molina, T., González-Salazar, M. del C., Cardoso-Saldaña, G., Vargas-Alarcón, G., Torres-Tamayo, M., & Juárez-Rojas, J. G. (2015). Role of adiponectin and free fatty acids on the association between abdominal visceral fat and insulin resistance. *Cardiovascular Diabetology*, *14*(1), 1–8. https://doi.org/10.1186/S12933-015-0184-5/TABLES/2

Mehan, S., Meena, H., Sharma, D., & Sankhla, R. (2011). JNK: a stress-activated protein kinase therapeutic strategies and involvement in Alzheimer's and various neurodegenerative abnormalities. *Journal of Molecular Neuroscience : MN*, *43*(3), 376–390. https://doi.org/ 10.1007/ S12031-010-9454-6

Meigs, J. B., Larson, M. G., Fox, C. S., Keaney, J. F., Vasan, R. S., & Benjamin, E. J. (2007). Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: the Framingham Offspring Study. *Diabetes Care*, *30*(10), 2529–2535. https://doi.org/10.2337/DC07-0817

Metwally, A. A., Mehta, P., Johnson, B. S., Nagarjuna, A., & Michael, P. (2021). *COVID-19 – Induced New-Onset Diabetes : Trends and Technologies*. *June*, 1–12.

Mine, K., Nagafuchi, S., Mori, H., Takahashi, H., & Anzai, K. (2021). SARS-CoV-2 Infection and Pancreatic β Cell Failure. *Biology 2022, Vol. 11, Page 22*, *11*(1), 22. https://doi.org/10.3390/BIOLOGY11010022

Mishra, M., & Ndisang, J. (2014). A critical and comprehensive insight on heme oxygenase and related products including carbon monoxide, bilirubin, biliverdin and ferritin in type-1 and type-2 diabetes. *Current Pharmaceutical Design*, *20*(9), 1370–1391. https://doi.org/10.2174/1381612811319999055 9

Montefusco, L., Ben Nasr, M., D'Addio, F., Loretelli, C., Rossi, A., Pastore, I., Daniele, G., Abdelsalam, A., Maestroni, A., Dell'Acqua, M., Ippolito, E., Assi, E., Usuelli, V., Seelam, A. J., Fiorina, R. M., Chebat, E., Morpurgo, P., Lunati, M. E., Bolla, A. M., … Fiorina, P. (2021). Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nature Metabolism*, *3*(6), 774–785. https://doi.org/10.1038 / S42255-021-00407-6

Muhammad, Y., Kani, Y. A., Iliya, S., Muhammad, J. B., Binji, A., El-Fulaty Ahmad, A., Kabir, M. B., Umar Bindawa, K., & Ahmed, A. (2021). Deficiency of antioxidants and increased oxidative stress in COVID-19 patients: A cross-sectional comparative study in Jigawa, Northwestern Nigeria. *SAGE Open Medicine*, *9*, 205031212199124. https://doi.org/10.1177/2050312121991246

Müller, J. A., Groß, R., Conzelmann, C., Krüger, J., Merle, U., Steinhart, J., Weil, T., Koepke, L., Bozzo, C. P., Read, C., Fois, G., Eiseler, T., Gehrmann, J., van Vuuren, J., Wessbecher, I. M., Frick, M., Costa, I. G., Breunig, M., Grüner, B., … Kleger, A. (2021). SARS-CoV-2 infects and

replicates in cells of the human endocrine and exocrine pancreas. *Nature Metabolism*, *3*(2), 149–165. https://doi.org/10.1038/S42255-021-00347-1

Muralidharan, S., & Mandrekar, P. (2013). Cellular stress response and innate immune signaling: integrating pathways in host defense and inflammation. *Journal of Leukocyte Biology*, *94*(6), 1167–1184. https://doi.org/10.1189/JLB.0313153

Murea, M., Ma, L., & Freedman, B. I. (2012). Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. *The Review of Diabetic Studies : RDS*, *9*(1), 6–22. https://doi.org/10.1900/RDS.2012.9.6

Naguib, M. N., Raymond, J. K., & Vidmar, A. P. (2020). New onset diabetes with diabetic ketoacidosis in a child with multisystem inflammatory syndrome due to COVID-19. *Journal of Pediatric Endocrinology & Metabolism : JPEM*, *34*(1), 147–150. https://doi.org/10.1515/JPEM-2020-0426

Nathan, C., & Shiloh, M. U. (2000). Reactive oxygen and nitrogen intermediates in the relationship between mammalian hosts and microbial pathogens. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(16), 8841. https://doi.org/ 10.1073/ PNAS.97.16.8841

Navarro, J. F., & Mora-Fernández, C. (2006). The role of TNF-alpha in diabetic nephropathy: pathogenic and therapeutic implications. *Cytokine & Growth Factor Reviews*, *17*(6), 441–450. https://doi.org/ 10.1016/ J.CYTOGFR.2006.09.011

Ndisang, J. F., Vannacci, A., & Rastogi, S. (2017). Insulin Resistance, Type 1 and Type 2 Diabetes, and Related Complications 2017. *Journal of Diabetes Research*, *2017*. https://doi.org/10.1155/2017/1478294

Nehring, S. M., Goyal, A., Bansal, P., & Patel, B. C. (2022). C Reactive Protein. *StatPearls*, *65*(5), 237–244. https:// www.ncbi. nlm.nih.gov /books/NBK441843/

Nguyen Dinh Cat, A., Montezano, A. C., Burger, D., & Touyz, R. M. (2013). Angiotensin II, NADPH oxidase, and redox signaling in the vasculature. *Antioxidants and Redox Signaling*, *19*(10), 1110–1120. https://doi.org/10.1089/ARS.2012.4641

Niki, E. (2014). Biomarkers of lipid peroxidation in clinical material. *Biochimica et Biophysica Acta (BBA) - General Subjects*, *1840*(2), 809–817. https://doi.org/10.1016/J.BBAGEN.2013.03.020

Norouzi, M., Norouzi, S., Ruggiero, A., Khan, M. S., Myers, S., Kavanagh, K., & Vemuri, R. (2021). *microorganisms Type-2 Diabetes as a Risk Factor for Severe COVID-19 Infection*. https:// doi.org/10.3390/ microorganisms9061211

Oh, Y. S., Bae, G. D., Baek, D. J., Park, E. Y., & Jun, H. S. (2018). Fatty Acid-Induced Lipotoxicity in Pancreatic Beta-Cells During Development of Type 2 Diabetes. *Frontiers in Endocrinology*, *9*(JUL). https://doi.org/10.3389/FENDO.2018.00384

Olagnier, D., Farahani, E., Thyrsted, J., Blay-Cadanet, J., Herengt, A., Idorn, M., Hait, A., Hernaez, B., Knudsen, A., Iversen, M. B., Schilling, M., Jørgensen, S. E., Thomsen, M., Reinert, L. S., Lappe, M., Hoang, H. D., Gilchrist, V. H., Hansen, A. L., Ottosen, R., … Holm, C. K. (2020).

SARS-CoV2-mediated suppression of NRF2-signaling reveals potent antiviral and anti-inflammatory activity of 4-octyl-itaconate and dimethyl fumarate. *Nature Communications*, *11*(1). https://doi.org/ 10.1038/ S41467-020-18764-3

Pal, R., & Bhadada, S. K. (2020). COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. *Diabetes & Metabolic Syndrome*, *14*(4), 513–517. https://doi.org/10.1016/J.DSX.2020.04.049

Pan, S. Y., De Groh, M., Aziz, A., & Morrison, H. (2016). Relation of insulin resistance with socialdemographics, adiposity and behavioral factors in non-diabetic adult Canadians. *Journal of Diabetes and Metabolic Disorders*, *15*(1), 1–11. https://doi.org/10.1186/s40200-016-0253-7

Park, J., Choi, H., Min, J. S., Park, S. J., Kim, J. H., Park, H. J., Kim, B., Chae, J. Il, Yim, M., & Lee, D. S. (2013). Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells. *Journal of Neurochemistry*, *127*(2), 221–232. https://doi.org/10.1111/JNC.12361

Patnaik, M., Pati, P., Swain, S. N., Mohapatra, M. K., Dwibedi, B., Kar, S. K., & Ranjit, M. (2014). Association of angiotensin-converting enzyme and angiotensin-converting enzyme-2 gene polymorphisms with essential hypertension in the population of Odisha, India. *Annals of Human Biology*, *41*(2), 145–152. https://doi.org/10.3109/03014460.2013.837195

Perrotta, F., Matera, M. G., Cazzola, M., & Bianco, A. (2020). Severe respiratory SARS-CoV2 infection: Does ACE2 receptor matter? *Respiratory Medicine*, *168*, 105996. https://doi.org/10.1016/ J.RMED. 2020.105996

Petersen, M. C., Vatner, D. F., & Shulman, G. I. (2017). Regulation of hepatic glucose metabolism in health and disease. *Nature Reviews. Endocrinology*, *13*(10), 572–587. https:// doi.org/ 10.1038/ NRENDO. 2017.80

Petrilli, C. M., Jones, S. A., Yang, J., Rajagopalan, H., O'donnell, L., Chernyak, Y., Tobin, K. A., Cerfolio, R. J., Francois, F., & Horwitz, L. I. (2019). Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ 2020;369:M1966*. https://doi.org/ 10.1136 /bmj.m1966

Pickup, J. C. (2004). Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care*, *27*(3), 813–823. https://doi.org/10.2337/DIACARE.27.3.813

Pisoschi, A. M., & Pop, A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review. *European Journal of Medicinal Chemistry*, *97*, 55–74. https://doi.org/10.1016/J.EJMECH.2015.04.040

Prabhakar, P. K., & Doble, M. (2011). Mechanism of action of natural products used in the treatment of diabetes mellitus. *Chinese Journal of Integrative Medicine*, *17*(8), 563–574. https://doi.org/10.1007/S11655-011-0810-3

Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*, *286*(3), 327–334. https:// doi.org/ 10.1001/ JAMA. 286. 3.327

Prairie, K. (2012). Methods Manual:Microscopy for the detection, identification and quantification of malaria parasites on stained thick and thin blood films in research settings. *World Health Organization*, *1*, 1–109.

Prince, L. R., Whyte, M. K., Sabroe, I., & Parker, L. C. (2011). The role of TLRs in neutrophil activation. *Current Opinion in Pharmacology*, *11*(4), 397–403. https://doi.org/10.1016/J.COPH.2011.06.007

Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S., & Dhama, K. (2014). Oxidative stress, prooxidants, and antioxidants: the interplay. *BioMed Research International*, *2014*. https://doi.org/ 10.1155/ 2014/761264

Rajpal, A., Rahimi, L., & Ismail-Beigi, F. (2020). Factors leading to high morbidity and mortality of COVID-19 in patients with type 2 diabetes. *Journal of Diabetes*, *12*(12), 895–908. https://doi.org/10.1111/1753-0407.13085

Ralph, R., Lew, J., Zeng, T., Francis, M., Xue, B., Roux, M., Ostadgavahi, A. T., Rubino, S., Dawe, N. J., Al-Ahdal, M. N., Kelvin, D. J., Richardson, C. D., Kindrachuk, J., Falzarano, D., & Kelvin, A. A. (2020). 2019-nCoV (Wuhan virus), a novel Coronavirus: Human-to-human transmission, travel-related cases, and vaccine readiness. *Journal of Infection in Developing Countries*, *14*(1), 3–17. https://doi.org/10.3855/jidc.12425

Rawla, P., Bandaru, S. S., & Vellipuram, A. R. (2017). Review of Infectious Etiology of Acute Pancreatitis. *Gastroenterology Research*, *10*(3), 153–158. https://doi.org/10.14740/GR858W

Ray, G., Batra, S., Shukla, N. K., Deo, S., Raina, V., Ashok, S., & Husain, S. A. (2000). Lipid peroxidation, free radical production and antioxidant status in breast cancer. *Breast Cancer Research and Treatment*, *59*(2), 163–170. https://doi.org/10.1023/A:1006357330486

Reaven, G. M. (2011). Insulin resistance: the link between obesity and cardiovascular disease. *The Medical Clinics of North America*, *95*(5), 875–892. https://doi.org/10.1016/J.MCNA.2011.06.002

Rehman, K., & Akash, M. S. H. (2017). Mechanism of Generation of Oxidative Stress and Pathophysiology of Type 2 Diabetes Mellitus: How Are They Interlinked? *Journal of Cellular Biochemistry*, *118*(11), 3577–3585. https://doi.org/10.1002/JCB.26097

Reiterer, M., Rajan, M., Gómez-Banoy, N., Lau, J. D., Gomez-Escobar, L. G., Ma, L., Gilani, A., Alvarez-Mulett, S., Sholle, E. T., Chandar, V., Bram, Y., Hoffman, K., Bhardwaj, P., Piloco, P., Rubio-Navarro, A., Uhl, S., Carrau, L., Houhgton, S., Redmond, D., … Lo, J. C. (2021). Hyperglycemia in acute COVID-19 is characterized by insulin resistance and adipose tissue infectivity by SARS-CoV-2. *Cell Metabolism*, *33*(11), 2174-2188.e5. https://doi.org/10.1016/j.cmet.2021.09.009

Reshi, M. L., Su, Y. C., & Hong, J. R. (2014). RNA Viruses: ROS-Mediated Cell Death. *International Journal of Cell Biology*, *2014*. https://doi.org/10.1155/2014/467452

Richardson, S., Hirsch, J. S., Narasimhan, M., Crawford, J. M., McGinn, T., Davidson, K. W., Barnaby, D. P., Becker, L. B., Chelico, J. D., Cohen, S. L., Cookingham, J., Coppa, K., Diefenbach, M. A., Dominello, A. J., Duer-Hefele, J., Falzon, L., Gitlin, J., Hajizadeh, N., Harvin, T. G., …

Zanos, T. P. (2020). Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*, *323*(20), 2052–2059. https://doi.org/10.1001/JAMA.2020.6775

Rizzo, M. R., Barbieri, M., Marfella, R., & Paolisso, G. (2013). Response to Comment on: Rizzo et al. Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. Diabetes Care 2012;35:2076-2082. *Diabetes Care*, *36*(1). https://doi.org/10.2337/DC12-1436

Roca-Ho, H., Riera, M., Palau, V., Pascual, J., & Soler, M. J. (2017). Characterization of ACE and ACE2 Expression within Different Organs of the NOD Mouse. *International Journal of Molecular Sciences*, *18*(3). https://doi.org/10.3390/IJMS18030563

Rodrigues, T. S., de Sá, K. S. G., Ishimoto, A. Y., Becerra, A., Oliveira, S., Almeida, L., Gonçalves, A. V., Perucello, D. B., Andrade, W. A., Castro, R., Veras, F. P., Toller-Kawahisa, J. E., Nascimento, D. C., de Lima, M. H. F., Silva, C. M. S., Caetite, D. B., Martins, R. B., Castro, I. A., Pontelli, M. C., … Zamboni, D. S. (2021). Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. *The Journal of Experimental Medicine*, *218*(3). https://doi.org/10.1084/JEM.20201707

Rodriguez-Calvo, T., Sabouri, S., Anquetil, F., & von Herrath, M. G. (2016). The viral paradigm in type 1 diabetes: Who are the main suspects? *Autoimmunity Reviews*, *15*(10), 964–969. https://doi.org/ 10.1016/

J.AUTREV.2016.07.019

Rodríguez-Hernández, H., Simental-Mendía, L. E., Rodríguez-Ramírez, G., & Reyes-Romero, M. A. (2013). Obesity and Inflammation: Epidemiology, Risk Factors, and Markers of Inflammation. *International Journal of Endocrinology*, *2013*, 11. https://doi.org/10.1155/2013/678159

Rodriguez-Morales, A. J., Cardona-Ospina, J. A., Gutiérrez-Ocampo, E., Villamizar-Peña, R., Holguin-Rivera, Y., Escalera-Antezana, J. P., Alvarado-Arnez, L. E., Bonilla-Aldana, D. K., Franco-Paredes, C., Henao-Martinez, A. F., Paniz-Mondolfi, A., Lagos-Grisales, G. J., Ramírez-Vallejo, E., Suárez, J. A., Zambrano, L. I., Villamil-Gómez, W. E., Balbin-Ramon, G. J., Rabaan, A. A., Harapan, H., … Sah, R. (2020). Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel Medicine and Infectious Disease*, *34*, 101623. https://doi.org/10.1016/J.TMAID.2020.101623

Rubino, F., Amiel, S. A., Zimmet, P., Alberti, G., Bornstein, S., Eckel, R. H., Mingrone, G., Boehm, B., Cooper, M. E., Chai, Z., Del Prato, S., Ji, L., Hopkins, D., Herman, W. H., Khunti, K., Mbanya, J.-C., & Renard, E. (2020). New-Onset Diabetes in Covid-19. *The New England Journal of Medicine*, *383*(8), 789–790. https://doi.org/10.1056/NEJMC2018688

Rudich, A., Tlrosh, A., Potashnik, R., Hemi, R., Kanety, H., & Bashan, N. (1998). Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes. *Diabetes*, *47*(10), 1562–1569. https://doi.org/10.2337/DIABETES.47.10.1562

Salazar, J., Martínez, M. S., Chávez, M., Toledo, A., Añez, R., Torres, Y., Apruzzese, V., Silva, C., Rojas, J., & Bermúdez, V. (2014). C-reactive

protein: clinical and epidemiological perspectives. *Cardiology Research and Practice, 2014*. https://doi.org/10.1155/2014/605810

Sam, S., & Mazzone, T. (2014). Adipose tissue changes in obesity and the impact on metabolic function. *Translational Research*, *164*(4), 284–292. https://doi.org/10.1016/J.TRSL.2014.05.008

Sami, W., Ansari, T., Butt, N. S., & Hamid, M. R. A. (2017). Effect of diet on type 2 diabetes mellitus: A review. *International Journal of Health Sciences*, *11*(2), 65. /pmc/articles/PMC5426415/

Sathish, T., Kapoor, N., Cao, Y., Tapp, R. J., & Zimmet, P. (2021). Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. *Diabetes, Obesity & Metabolism*, *23*(3), 870–874. https://doi.org/10.1111/DOM.14269

Schneider, D. A., & von Herrath, M. G. (2014). Potential viral pathogenic mechanism in human type 1 diabetes. *Diabetologia*, *57*(10), 2009–2018. https://doi.org/10.1007/S00125-014-3340-7

Selvin, E., & Juraschek, S. P. (2020). Diabetes Epidemiology in the COVID-19 Pandemic. *Diabetes Care*, *43*(8), 1690–1694. https://doi.org/ 10.2337 / DC20-1295

Shaharuddin, S. H., Wang, V., Santos, R. S., Gross, A., Wang, Y., Jawanda, H., Zhang, Y., Hasan, W., Garcia, G., Arumugaswami, V., & Sareen, D. (2021). Deleterious Effects of SARS-CoV-2 Infection on Human Pancreatic Cells. *Frontiers in Cellular and Infection Microbiology*, *11*. https://doi.org/10.3389/FCIMB.2021.678482

Shoelson, S. E., Lee, J., & Goldfine, A. B. (2006). Inflammation and insulin resistance. *The Journal of Clinical Investigation*, *116*(7), 1793–1801.

https://doi.org/10.1172/JCI29069

Singh, A. K., Gupta, R., Ghosh, A., & Misra, A. (2020). Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes & Metabolic Syndrome*, *14*(4), 303–310. https://doi.org/ 10.1016/J.DSX.2020.04.004

Sobngwi, E., Choukem, S. P., Agbalika, F., Blondeau, B., Fetita, L. S., Lebbe, C., Thiam, D., Cattan, P., Larghero, J., Foufelle, F., Ferre, P., Vexiau, P., Calvo, F., & Gautier, J. F. (2008). Ketosis-prone type 2 diabetes mellitus and human herpesvirus 8 infection in sub-saharan africans. *JAMA*, *299*(23), 2770–2776. https://doi.org/10.1001/JAMA.299.23.2770

Solerte, S. B., Di Sabatino, A., Galli, M., & Fiorina, P. (2020). Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. *Acta Diabetologica*, *57*(7), 779–783. https://doi.org/10.1007/S00592-020-01539-Z

Somasundaram, N. P., Ranathunga, I., Ratnasamy, V., Wijewickrama, P. S. A., Dissanayake, H. A., Yogendranathan, N., Gamage, K. K. K., De Silva, N. L., Sumanatilleke, M., Katulanda, P., & Grossman, A. B. (2020). The impact of SARS-Cov-2 virus infection on the endocrine system. *Journal of the Endocrine Society*, *4*(8), 1–22. https:// doi.org/ 10. 1210/jendso/bvaa082

Suhail, S., Zajac, J., Fossum, C., Lowater, H., McCracken, C., Severson, N., Laatsch, B., Narkiewicz-Jodko, A., Johnson, B., Liebau, J., Bhattacharyya, S., & Hati, S. (2020). Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: A Review. *The Protein Journal*, *39*(6), 644. https://doi.org/10.1007/S10930-020-09935-8

Sun, S. C. (2011). Non-canonical NF-κB signaling pathway. *Cell Research*, *21*(1), 71–85. https://doi.org/10.1038/CR.2010.177

Sun, W. L., Chen, L. L., Zhang, S. Z., Wu, Y. M., Ren, Y. Z., & Qin, G. M. (2011). Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis. *Internal Medicine (Tokyo, Japan)*, *50*(15), 1569–1574. https://doi.org/10.2169 / INTERNALMEDICINE. 50.5166

Sun, X., Wang, T., Cai, D., Hu, Z., Chen, J., Liao, H., Zhi, L., Wei, H., Zhang, Z., Qiu, Y., Wang, J., & Wang, A. (2020). Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine & Growth Factor Reviews*, *53*, 38–42. https://doi.org/10.1016/J.CYTOGFR.2020.04.002

Takeda, M., Yamamoto, K., Takemura, Y., Takeshita, H., Hongyo, K., Kawai, T., Hanasaki-Yamamoto, H., Oguro, R., Takami, Y., Tatara, Y., Takeya, Y., Sugimoto, K., Kamide, K., Ohishi, M., & Rakugi, H. (2013). Loss of ACE2 exaggerates high-calorie diet-induced insulin resistance by reduction of GLUT4 in mice. *Diabetes*, *62*(1), 223–233. https://doi.org/10.2337/DB12-0177

Tam, C. S., Xie, W., Johnson, W. D., Cefalu, W. T., Redman, L. M., & Ravussin, E. (2012a). Defining insulin resistance from hyperinsulinemic-euglycemic clamps. *Diabetes Care*, *35*(7), 1605–1610. https://doi.org/10.2337/DC11-2339

Tam, C. S., Xie, W., Johnson, W. D., Cefalu, W. T., Redman, L. M., & Ravussin, E. (2012b). Defining Insulin Resistance From Hyperinsulinemic-Euglycemic Clamps. *Diabetes Care*, *35*(7), 1605–

1610. https://doi.org/10.2337/DC11-2339

Tan, W. S. D., Liao, W., Zhou, S., Mei, D., & Wong, W. S. F. (2018). Targeting the renin–angiotensin system as novel therapeutic strategy for pulmonary diseases. *Current Opinion in Pharmacology*, *40*, 9–17. https://doi.org/10.1016/J.COPH.2017.12.002

Tatsch, E., Bochi, G. V., Piva, S. J., De Carvalho, J. A. M., Kober, H., Torbitz, V. D., Duarte, T., Signor, C., Coelho, A. C., Duarte, M. M. M. F., Montagner, G. F. F. S., Da Cruz, I. B. M., & Moresco, R. N. (2012). Association between DNA strand breakage and oxidative, inflammatory and endothelial biomarkers in type 2 diabetes. *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis*, *732*(1–2), 16–20. https://doi.org/10.1016/J.MRFMMM.2012.01.004

Taylor, T. E., & Molyneux, M. E. (2015). The pathogenesis of pediatric cerebral malaria: eye exams, autopsies and neuro-imaging. *Annals of the New York Academy of Sciences*, *1342*(1), 44. https://doi.org/10. 1111/ NYAS.12690

Thimmulappa, R. K., Chattopadhyay, I., Rajasekaran, S., Thimmulappa, R. K., Chattopadhyay, I., & Rajasekaran, S. (2019). Oxidative Stress Mechanisms in the Pathogenesis of Environmental Lung Diseases. *Oxidative Stress Mechanisms in the Pathogenesis of Environmental Lung Diseases*. https://doi.org/10.1007/978-981-32-9366-3_5

Tittel, S. R., Rosenbauer, J., Kamrath, C., Ziegler, J., Reschke, F., Hammersen, J., Mönkemöller, K., Pappa, A., Kapellen, T., & Holl, R. W. (2020). Did the COVID-19 Lockdown Affect the Incidence of Pediatric Type 1 Diabetes in Germany? *Diabetes Care*, *43*(11), e172–e173.

https://doi.org/10.2337/DC20-1633

Torres-Tamayo, M., Caracas-Portillo, N. A., Pena-Aparicio, B., Juarez-Rojas, J. G., Medina-Urrutia, A. X., & Martínez-Alvarado, M. del R. (2020). Coronavirus infection in patients with diabetes. *Archivos de Cardiologia de Mexico*, *90*(Supl), 67–76. https://doi.org/10.24875/ACM.M20000068

Trevisani, V., Bruzzi, P., Madeo, S. F., Cattini, U., Lucaccioni, L., Predieri, B., & Iughetti, L. (2020). COVID-19 and type 1 diabetes: Concerns and challenges. *Acta Biomedica*, *91*(3), 1–6. https://doi.org/ 10.23750/ ABM. V91I3.10366

Unger, R. H. (2008). Reinventing type 2 diabetes: pathogenesis, treatment, and prevention. *JAMA*, *299*(10), 1185–1187. https:// doi.org/ 10.1001/JAMA.299.10.1185

Unnikrishnan, R., & Misra, A. (2021a). Diabetes and COVID19: a bidirectional relationship. *European Journal of Clinical Nutrition*, *75*(9), 1332–1336. https://doi.org/10.1038/s41430-021-00961-y

Unnikrishnan, R., & Misra, A. (2021b). Diabetes and COVID19: a bidirectional relationship. *Nutrition & Diabetes 2021 11:1*, *11*(1), 1–5. https://doi.org/10.1038/s41387-021-00163-2

Valencia, I., Peiró, C., Lorenzo, Ó., Sánchez-Ferrer, C. F., Eckel, J., & Romacho, T. (2020). DPP4 and ACE2 in Diabetes and COVID-19: Therapeutic Targets for Cardiovascular Complications? *Frontiers in Pharmacology*, *11*. https://doi.org/10.3389/FPHAR.2020.01161

Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T. D., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell*

Biology, *39*(1), 44–84. https://doi.org/10.1016/J.BIOCEL.2006.07.001

Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., Mehra, M. R., Schuepbach, R. A., Ruschitzka, F., & Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. *Lancet (London, England)*, *395*(10234), 1417–1418. https://doi.org/10.1016/S0140-6736(20)30937-5

Vikram, A., Tripathi, D. N., Kumar, A., & Singh, S. (2014). *Editorial Oxidative Stress and Inflammation in Diabetic Complications*. https://doi.org/10.1155/2014/679754

Violi, F., Oliva, A., Cangemi, R., Ceccarelli, G., Pignatelli, P., Carnevale, R., Cammisotto, V., Lichtner, M., Alessandri, F., De Angelis, M., Miele, M. C., D'Ettorre, G., Ruberto, F., Venditti, M., Pugliese, F., & Mastroianni, C. M. (2020). Nox2 activation in Covid-19. *Redox Biology*, *36*. https://doi.org/10.1016/J.REDOX.2020.101655

Wallace, T. M., Levy, J. C., & Matthews, D. R. (2004a). *Use and Abuse of HOMA Modeling*. http://diabetesjournals.org/care/article-pdf/27/6/1487/645883/zdc00604001487.pdf

Wallace, T. M., Levy, J. C., & Matthews, D. R. (2004b). Use and Abuse of HOMA Modeling. *Diabetes Care*, *27*(6), 1487–1495. https:// doi.org/10.2337/DIACARE.27.6.1487

Wang, X., & Cheng, Z. (2020). Cross-Sectional Studies: Strengths, Weaknesses, and Recommendations. *Chest*, *158*(1S), S65–S71. https://doi.org/10.1016/J.CHEST.2020.03.012

Wang, Y., Wang, Y., Chen, Y., & Qin, Q. (2020). Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia

(COVID-19) implicate special control measures. *Journal of Medical Virology*, *92*(6), 568–576. https://doi.org/10.1002/JMV.25748

White, D. L., Ratziu, V., & El-Serag, H. B. (2008). Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *Journal of Hepatology*, *49*(5), 831–844. https://doi.org/10.1016/J.JHEP.2008.08.006

White, N. J., Warrell, D. A., Chanthavanich, P., Looareesuwan, S., Warrell, M. J., Krishna, S., Williamson, D. H., & Turner, R. C. (1983). Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *The New England Journal of Medicine*, *309*(2), 61–66. https://doi.org/ 10.1056/ NEJM198307143090201

WHO. (2012). *World malaria report : 2012*. World Malaria Report. https://apps.who.int/iris/handle/10665/78945

WHO. (2021). *WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data*. WHO Coronavirus (COVID-19)Dashboard With Vaccination Data. https://covid19.who.int/

Wiersinga, W. J., Rhodes, A., Cheng, A. C., Peacock, S. J., & Prescott, H. C. (2020). Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*, *324*(8), 782–793. https://doi.org/10.1001/JAMA.2020.12839

World Health Organisation. (2008). *WHO | Waist Circumference and Waist–Hip Ratio. Report of a WHO Expert Consultation. Geneva, 8-11 December 2008. December*, 8–11. http://www.who.int

Wu, C. T., Lidsky, P. V., Xiao, Y., Lee, I. T., Cheng, R., Nakayama, T., Jiang, S., Demeter, J., Bevacqua, R. J., Chang, C. A., Whitener, R. L., Stalder,

A. K., Zhu, B., Chen, H., Goltsev, Y., Tzankov, A., Nayak, J. V., Nolan, G. P., Matter, M. S., … Jackson, P. K. (2021a). SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metabolism*, *33*(8), 1565-1576.e5. https://doi.org/10.1016/J.CMET.2021.05.013

Wu, C. T., Lidsky, P. V., Xiao, Y., Lee, I. T., Cheng, R., Nakayama, T., Jiang, S., Demeter, J., Bevacqua, R. J., Chang, C. A., Whitener, R. L., Stalder, A. K., Zhu, B., Chen, H., Goltsev, Y., Tzankov, A., Nayak, J. V., Nolan, G. P., Matter, M. S., … Jackson, P. K. (2021b). SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment. *Cell Metabolism*, *33*(8), 1565-1576.e5. https://doi.org/10.1016/J.CMET.2021.05.013

Xu, Z., Wang, Z., Wang, S., Ye, Y., Luo, D., Wan, L., Yu, A., Sun, L., Tesfaye, S., Meng, Q., & Gao, L. (2020). The impact of type 2 diabetes and its management on the prognosis of patients with severe COVID-19. *Journal of Diabetes*, *12*(12), 909–918. https://doi.org/10.1111/1753-0407.13084

Yadav, N., Kumar, S., Marlowe, T., Chaudhary, A. K., Kumar, R., Wang, J., O'Malley, J., Boland, P. M., Jayanthi, S., Kumar, T. K. S., Yadava, N., & Chandra, D. (2015). Oxidative phosphorylation-dependent regulation of cancer cell apoptosis in response to anticancer agents. *Cell Death & Disease*, *6*(11), e1969. https://doi.org/10.1038/CDDIS.2015.305

Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., Mori, Y., Ide, T., Murakami, K., Tsuboyama-Kasaoka, N., Ezaki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M. L., Kagechika, H., Shudo, K., Yoda, M., Nakano, Y., … Kadowaki, T. (2001). The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy

and obesity. *Nature Medicine*, *7*(8), 941–946. https://doi.org/ 10.1038/ 90984

Yang, J. K., Feng, Y., Yuan, M. Y., Yuan, S. Y., Fu, H. J., Wu, B. Y., Sun, G. Z., Yang, G. R., Zhang, X. L., Wang, L., Xu, X., Xu, X. P., & Chan, J. C. N. (2006). Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. *Diabetic Medicine : A Journal of the British Diabetic Association*, *23*(6), 623–628. https://doi.org/10.1111/J.1464-5491.2006.01861.X

Yang, J. K., Lin, S. S., Ji, X. J., & Guo, L. M. (2010a). Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetologica*, *47*(3), 193–199. https://doi.org/10.1007/S00592-009-0109-4

Yang, J. K., Lin, S. S., Ji, X. J., & Guo, L. M. (2010b). Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetologica*, *47*(3), 193–199. https://doi.org/10.1007/S00592-009-0109-4

Yang, J. K., Lin, S. S., Ji, X. J., & Guo, L. M. (2010c). Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetologica*, *47*(3), 193–199. https://doi.org/10.1007/S00592-009-0109-4

Yang, L., Han, Y., Nilsson-Payant, B. E., Gupta, V., Wang, P., Duan, X., Tang, X., Zhu, J., Zhao, Z., Jaffré, F., Zhang, T., Kim, T. W., Harschnitz, O., Redmond, D., Houghton, S., Liu, C., Naji, A., Ciceri, G., Guttikonda, S., … Chen, S. (2020). A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells

and Organoids. *Cell Stem Cell*, *27*(1), 125-136.e7. https://doi.org/ 10.1016/J.STEM.2020.06.015

Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Wu, Y., Zhang, L., Yu, Z., Fang, M., Yu, T., Wang, Y., Pan, S., Zou, X., Yuan, S., & Shang, Y. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet. Respiratory Medicine*, *8*(5), 475–481. https://doi.org/10.1016/S2213-2600(20)30079-5

Yang, Z., Mi, J., Wang, Y., Xue, L., Liu, J., Fan, M., Zhang, D., Wang, L., Qian, H., & Li, Y. (2021). Effects of low-carbohydrate diet and ketogenic diet on glucose and lipid metabolism in type 2 diabetic mice. *Nutrition*, *89*. https://doi.org/10.1016/J.NUT.2021.111230

Yao, X.H., Li, T.Y., He, Z.C., et al. (2020). *Yao, X.H., Li, T.Y., He, Z.C., et al. (2020) A Pathological Report of Three COVID-19 Cases by Minimally Invasive Autopsies. Chinese Journal of Pathology, 49, 411-417. - References - Scientific Research Publishing*. Happy Hypoxia in COVID-19 Patients at Kinshasa University Hospital (Democratic Republic of the Congo): Frequency and Vital Outcome. https://www. scirp.org/(S(lz5mqp453edsnp55rrgjct55))/reference/referencespapers.aspx?referenceid=2922335

Yeung, W. C. G., Rawlinson, W. D., & Craig, M. E. (2011). Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. *BMJ*, *342*(7794), 421. https://doi.org/10.1136/BMJ.D35

Zarrini, A. S., Moslemi, D., Parsian, H., Vessa, M., Mosapour, A., & Kelagari, Z. S. (2016). The status of antioxidants, malondialdehyde and some trace elements in serum of patients with breast cancer. *Caspian Journal of Internal Medicine*, *7*(1), 31. /pmc/articles/PMC4761120/

Zhang, C., Wu, Z., Li, J. W., Zhao, H., & Wang, G. Q. (2020). Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *International Journal of Antimicrobial Agents*, *55*(5). https:// doi.org/ 10.1016/ j.ijantimicag. 2020.105954

Zhang, Y., Cui, Y., Shen, M., Zhang, J., Liu, B., Dai, M., Chen, L., Han, D., Fan, Y., Zeng, Y., Li, W., Lin, F., Li, S., Chen, X., & Pan, P. (2020). Association of diabetes mellitus with disease severity and prognosis in COVID-19: A retrospective cohort study. *Diabetes Research and Clinical Practice*, *165*, 108227. https://doi.org/ 10.1016/ J.DIABRES. 2020.108227

Zhou, C. C., Ahmad, S., Mi, T., Xia, L., Abbasi, S., Hewett, P. W., Sun, C., Ahmed, A., Kellems, R. E., & Xia, Y. (2007). Angiotensin II induces soluble fms-Like tyrosine kinase-1 release via calcineurin signaling pathway in pregnancy. *Circulation Research*, *100*(1), 88–95. https://doi.org/10.1161/01.RES.0000254703.11154.18

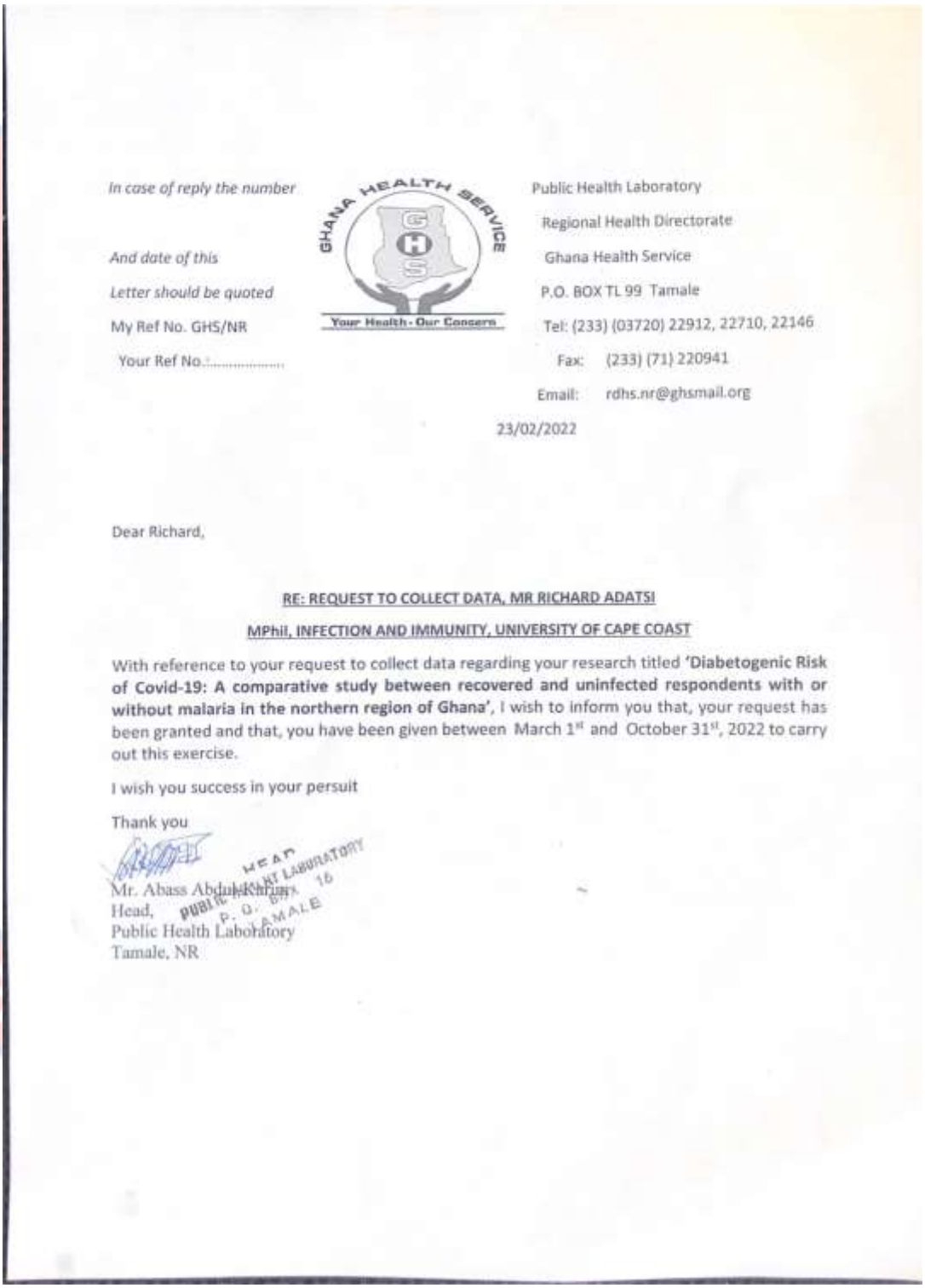
Zhou, R., Tardivel, A., Thorens, B., Choi, I., & Tschopp, J. (2010). Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nature Immunology*, *11*(2), 136–140. https://doi.org/ 10.1038/ NI.1831

Zhu, B., & Qu, S. (2022). The Relationship Between Diabetes Mellitus and Cancers and Its Underlying Mechanisms. *Frontiers in Endocrinology*, *13*, 75. https://doi.org/10.3389/FENDO.2022.800995/BIBTEX

Zhu, L., She, Z. G., Cheng, X., Qin, J. J., Zhang, X. J., Cai, J., Lei, F., Wang, H., Xie, J., Wang, W., Li, H., Zhang, P., Song, X., Chen, X., Xiang, M., Zhang, C., Bai, L., Xiang, D., Chen, M. M., … Li, H. (2020a). Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metabolism*, *31*(6), 1068-1077.e3. https://doi.org/10.1016/J.CMET.2020.04.021

Zhu, L., She, Z. G., Cheng, X., Qin, J. J., Zhang, X. J., Cai, J., Lei, F., Wang, H., Xie, J., Wang, W., Li, H., Zhang, P., Song, X., Chen, X., Xiang, M., Zhang, C., Bai, L., Xiang, D., Chen, M. M., … Li, H. (2020b). Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metabolism*, *31*(6), 1068-1077.e3. https://doi.org/10.1016/J.CMET.2020.04.021

APPENDIX



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Tel: (233) (03720) 22912, 22710, 22146
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23/02/2022

Dear Richard,

RE: REQUEST TO COLLECT DATA, MR RICHARD ADATSI

MPhil, INFECTION AND IMMUNITY, UNIVERSITY OF CAPE COAST

With reference to your request to collect data regarding your research titled **'Diabetogenic Risk of Covid-19: A comparative study between recovered and uninfected respondents with or without malaria in the northern region of Ghana'**, I wish to inform you that, your request has been granted and that, you have been given between March 1st and October 31st, 2022 to carry out this exercise.

I wish you success in your persuit

Thank you

Mr. Abass Abdul-Karim
Head,
Public Health Laboratory
Tamale, NR

HEAD PUBLIC HEALTH LABORATORY P. O. BOX TL 16 TAMALE

PARTICIPANT QUESTIONNAIRE

THESIS TITLE: DIABETOGENIC RISK OF ROCOVERED COVID-19 PATIENTS

PRINCIPAL INVESTIGATOR: MR. ADATSI RICHARD KUJO

Participant: _____

AGE**:** _____

Sex: □ Male □ Female **Place of Residence**: __-

_____

Please indicate if you smoke or take alcohol □ Smoke □ Alcohol

Any known Health Condition:

_____

Medication: _____ **Occupation:**

_____

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INFORMED CONSENT FOR PARTICIPATION IN MEDICAL RESEARCH

PARTICIPANT:

…….

PRINCIPAL INVESTIGATOR: MR ADATSI RICHARD KUJO

TITLE OF PROJECT: DIABETOGENIC RISK OF COVID-19 RECOVERED PATIENTS IN THE NORTHERN REGION OF GHANA, TAMALE.

I…… agree to participate in the research study being conducted by **Mr. Adatsi Richard Kujo** under the direction of **Prof. Samuel Acquah, Prof. leonard Derkyi-Kwarteng**, Dr. (Mrs) Faustina Pappoe, Dr. Sandy Ansumana Bockarie

2. The overall purpose of the research is:

To Determine the risk of developing diabetes post covid-19 recovery

3. My participation will involve the following:

- Provide required information about myself for the study
- Allow blood sample to be taken from me for the study
- Avail myself for any other procedure that will be required of me during the research

4. My participation in the study will be one day at the Public Health Reference Laboratory at the Tamale Teaching Hospital, Tamale.

5. I understand that the possible benefits to myself or society are:

- Better management of post exposure complications of covid-19 disease
- Assess the risk of developing diabetes post covid-19 infection

- Assess Insulin resistance, oxidative stress and inflammation post covid-19 infection

Participant…….. Investigator……

Date……. Date……