EFFECT OF DEPO MEDROXYPROGESTERONE ACETATE (DMPA) INJECTABLE CONTRACEPTIVE ON CARDIOMETABOLIC RISK PROFILE AMONG WOMEN OF REPRODUCTIVE AGE IN KIGALI, RWANDA

A thesis submitted to fulfil the requirements for the award of a PhD. Degree in Biomedical Sciences, to the School of Health Sciences, College of Medicine, and Health Sciences, University of Rwanda

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Declaration

Declaration

I, KANTARAMA Evelyne, declare that this thesis is the result of my own work and has not been submitted for any other degree at the University of Rwanda or any other institution. It has been checked through the anti-plagiarism checker and found compliant. The following is the final version:

"Effect of Depo Medroxyprogesterone Acetate (DMPA) Injectable Contraceptive on Cardiometabolic Risk Profile Among Women of Reproductive Age in Kigali, Rwanda."

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Date: 29/06/2023 Signature: 

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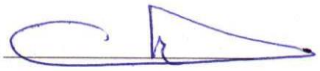
Date: 29/06/2023 Signature 

Dedication

To almighty God, the master of the time, all circumstances, and the author of my success!

Acknowledgment

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Abstract

Background

Depo medroxyprogesterone acetate (DMPA) injectable contraceptive is a reversible and effective hormonal contraceptive method many women in East Africa use. However, various studies suggest it might increase cardiometabolic disease risk due to its influence on cardiometabolic risk factors and call for a thorough evaluation of its effects on cardiometabolic risk profile to design proper prevention strategies. There is a need for further research to fully characterize the effects and make an informed decision on establishing measures for regular follow-up with users. This study responds to that need and explores the impact of DMPA use on lipid profile, waist circumference, blood pressure, glycated haemoglobin, and inflammatory markers among women of reproductive age in Rwanda. Three main objectives guided the study: (i) to explore the prevalence of central obesity and its association with other cardiometabolic risk factors in women of reproductive age in Kigali, Rwanda; (ii) to evaluate the effects of DMPA on lipid profile, waist circumference, blood pressure, glycated haemoglobin, and inflammatory markers among women of reproductive age in Kigali, Rwanda; and (iii) to analyse changes in cardiometabolic risk markers among abdominally obese women of reproductive age in Kigali, Rwanda during the use of DMPA.

Methods

The study used a cross-sectional design to explore the prevalence of central obesity and its correlates (objective 1). It also used a prospective cohort design to evaluate the effects of DMPA on cardiometabolic risk profile among the users (objective 2) and a pre-post design to analyse the changes in cardiometabolic risk markers among abdominally obese women.

The target population was women of reproductive age in Kigali city. To explore the prevalence of central obesity and its correlates, we conveniently selected 138 participants and analysed data by chi-square and logistic regression analyses. To evaluate the effects of DMPA on cardiometabolic risk profile, we randomly selected 45 DMPA users and 45 non-hormonal methods users and analysed data by the Manny Whitney test. To assess the changes in cardiometabolic risk markers among abdominally obese women during DMPA use, we selected a sample of 65 participants and analysed data using Wilcoxon signed-rank test.

Results

The thesis report is presented as a compilation of three complementary manuscripts, each responding to one of the objectives earlier described.

Study 1: The first study explored the prevalence of central obesity and its correlates using a cross-sectional design. Results indicate that the prevalence of central obesity was 48.5% and was significantly associated with age (OR=3.25, 95% CI: 1.11-9.47), alcohol use (OR=5.57, 95% CI: 1.91-16.20), meat consumption (OR=4.33, 95% CI: 1.49-12.59), hypertriglyceridemia (OR= 4.12, 1.01-14.76), and elevated diastolic blood pressure (OR=4.87, 95% CI: 1.47-16.13).

Study 2: The second study evaluates the effects of DMPA on cardiometabolic risk profiles among the users using a prospective design. Results indicate that DMPA users experienced a significant increase in waist circumference, TG, LDL, TC, hs-CRP, and glycated haemoglobin at twelve months of follow-up. In contrast, they experienced a significantly lower HDL than controls ($p = <0.05$). However, the study did not indicate a significant difference in blood pressure changes between DMPA users and the control group ($p > 0.05$).

Study 3: The third study analysed the changes in cardiometabolic risk markers among abdominally obese women during the use of DMPA. Results indicate that after twelve months, all cardiometabolic risk markers showed significant changes; there was a gradual decrease in HDL and an increase in TG, LDL, TC, hs-CRP, waist circumference, SBP, DBP, and glycated haemoglobin ($p = <0.05$).

Conclusions

The prevalence of central obesity was relatively high among women of reproductive age, and it was associated with older age, elevated diastolic blood pressure, high triglycerides levels, and meat and alcohol consumption. The study recommends an intensive awareness of health risks associated with central obesity and its associated factors to address the rising risk of cardiovascular diseases in this population. DMPA induces alteration in the cardiometabolic risk profile, where this alteration worsens when the user is abdominally obese. Considering the cardiometabolic health of individual users before initiating the method and providing a follow-up to the users of increased risk sounds essential.

Keywords: *central obesity, cardiometabolic risk, injectable contraceptives, women of reproductive age, follow-up.*

List of acronyms and abbreviations

AHA: American heart association

ATP: adult treatment panel

BMI: body mass index

CAD: coronary artery disease

CARTA: consortium for advanced research training in Africa

CI: confidence interval

CIC: combined injectable contraceptives

CMD: cardiometabolic disease

CMHS: college of medicine and health sciences

CMS: cardiometabolic syndrome

COCs: combined oral contraceptives

CVD: cardiovascular disease

DBP: diastolic blood pressure

DHS: demographic and health survey

DMPA: Depo medroxyprogesterone acetate

DVT: deep vein thromboembolism

HbA1C: glycated hemoglobin

HDL: high-density lipoprotein cholesterol

HIV: human immunodeficiency virus

hs-CRP: high sensitivity C-reactive protein

IDL: intermediate density lipoprotein cholesterol

IL-6: interleukin 6

IRB: institutional review board

IUDs: intrauterine devices

LDL: low-density lipoprotein cholesterol

MoH: ministry of health

NCDs: non-communicable diseases

NCEP: national cholesterol education program

NHANES: National Health and Nutrition Examination Survey

OR: odds ratio

PAD: peripheral artery disease

PCOS: polycystic ovary syndrome

PE: pulmonary embolism

POI: progestin-only injectable contraceptives

RBC: Rwanda biomedical centre

SBP: Systolic blood pressure

T2DM: type two diabetes mellitus

TC: total cholesterol

TG: triglycerides

TNF: tissue necrosis factor

VLDL: very low-density lipoprotein cholesterol

WC: waist circumference

WHO: world health organisation

WHR: waist-to-hip ratio

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Chapter One: General Introduction

1.1. Background

1.1.1. Definition of concepts

a. Cardiometabolic risk

Cardiometabolic risk represents the likelihood of an individual developing a cluster of conditions that increase the risk of cardiovascular disease (CVD) and metabolic disorders, such as type 2 diabetes [1]. The key factors that contribute to the development of cardiometabolic diseases, as indicated in Figure 1, include abdominal obesity, atherogenic dyslipidemia manifested by high triglycerides (TG) level and/or low high-density lipoprotein cholesterol (HDL), high blood pressure, insulin resistance, pro-inflammatory state primarily manifested by an abnormal level of high sensitivity C-reactive protein (hs-CRP), microalbuminuria, pro-thrombotic state, and endothelial dysfunction [2, 3]. Other factors influencing cardiometabolic health include family history, age, sex, unhealthy diet, smoking, and physical inactivity [3].

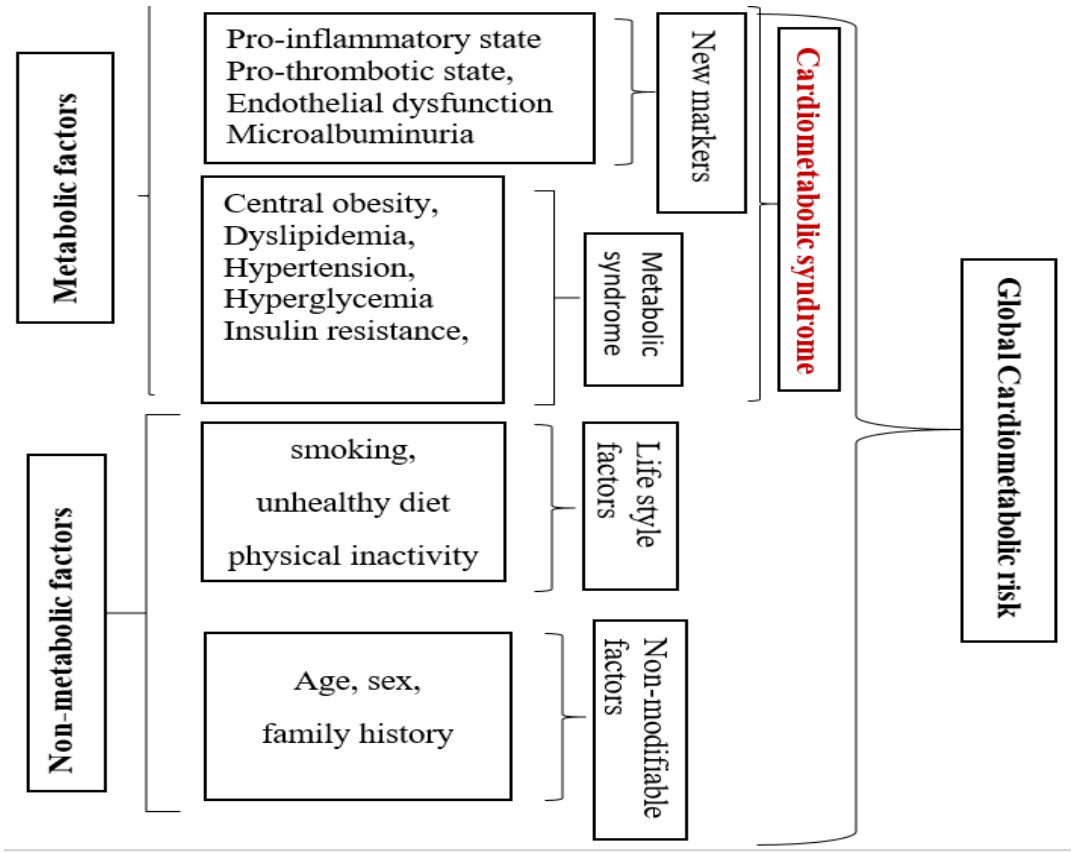

Figure 1.1: the components of global cardiometabolic risk with adaptation from Alkerwi et al. study [4].

b. Cardiometabolic syndrome and metabolic syndrome

Cardiometabolic and metabolic syndrome terms are mostly used interchangeably because they refer to similar health conditions and risk factor clusters [5]. Various bodies worked to define metabolic syndrome (MetS). They all have in common five primary metabolic risk factors: central obesity, insulin resistance, dyslipidemia (higher triglyceride and lower HDL levels), hyperglycemia, and hypertension, and it was defined by the simultaneous presence of more than two metabolic risk factors. According to the International Diabetes Federation (IDF), when an individual has central obesity plus any other two factors, he or she is diagnosed with MetS [6]. The Revised third report of the National Cholesterol Education Program (NCEP) adult treatment panel (ATP III) defines the MetS as the multi-morbidity of any three factors among those five factors [7]. However, the World Health Organization (WHO) insists first on insulin resistance/ diabetes/Impaired Glucose Tolerance (IGT)/oral glucose intolerance plus any other two factors on the list [8].

The term cardiometabolic syndrome (CMS) emerged more recently and is used to emphasize the strong link between metabolic factors and cardiovascular health [5]. Figure 1 indicates that, in addition to the core components of metabolic syndrome, the cardiometabolic syndrome may include other factors like a pro-inflammatory state (increased high sensitivity C-reactive protein levels), pro-thrombotic state (increased clotting tendency), endothelial dysfunction (problems with the inner lining of blood vessels), non-alcoholic steatohepatitis and microalbuminuria [3, 9]. An individual with clinical evidence of diabetes and insulin resistance plus any other two factors (central obesity, hypertension, dyslipidemia, pro-inflammatory state, pro-thrombotic state, endothelial dysfunction, fatty liver disease, or microalbuminuria) is said to have CMS [5].

CMS is recognized as a disease entity and a global epidemic that affects about 30% of adult people globally [10], and the prevalence varies within individual countries. The USA counts 33% of the general population [11], and Indonesia and the Dutch count 39% and 29%, respectively [12]. In African countries, the prevalence varies depending on the involved population; a systematic review in Nigeria reported a prevalence of 31% in the general population [13], and a study in Ghana reported a prevalence of around 43% in individuals with type 2 diabetes patients [14]. CMS was reported as a strong predictor for most CVD and type 2 diabetes. It was highly linked to increased incidence of coronary artery disease, peripheral vascular diseases, myocardial infarction, and ischemic stroke [15]. It was also revealed that

individuals having CMS are more than five times more likely to develop type two diabetes compared to those without it [5].

1.1.2. Central obesity as the primary contributor to CMS

Central obesity is considered one of the most critical components of CMS because it is associated with insulin resistance, inflammation, and other metabolic abnormalities that contribute to the development of cardiovascular disease and diabetes [14, 16]. Figure 2 highlights the importance of visceral fat deposition in the pathogenesis of cardiometabolic syndrome. Visceral fat deposition promotes the release of free fatty acids (the source of atherosclerotic dyslipidemia), pro-inflammatory cytokines, and the reduction of adipokines involved in regulating glucose and lipid metabolism. It induces insulin resistance, which influences the hyperlipolytic state, leading to high levels of FFA and hyperinsulinemia, a factor associated with a high risk of hypertension and type 2 diabetes [3, 17]. The literature indicated that most individuals with CMS also have central obesity. It is an example of a study done in Morocco, where the prevalence of central obesity was 97.6% among patients with cardiometabolic syndrome [18]. Another study conducted in Ghana found that the prevalence of central obesity was 61% among patients with cardiometabolic syndrome [19].

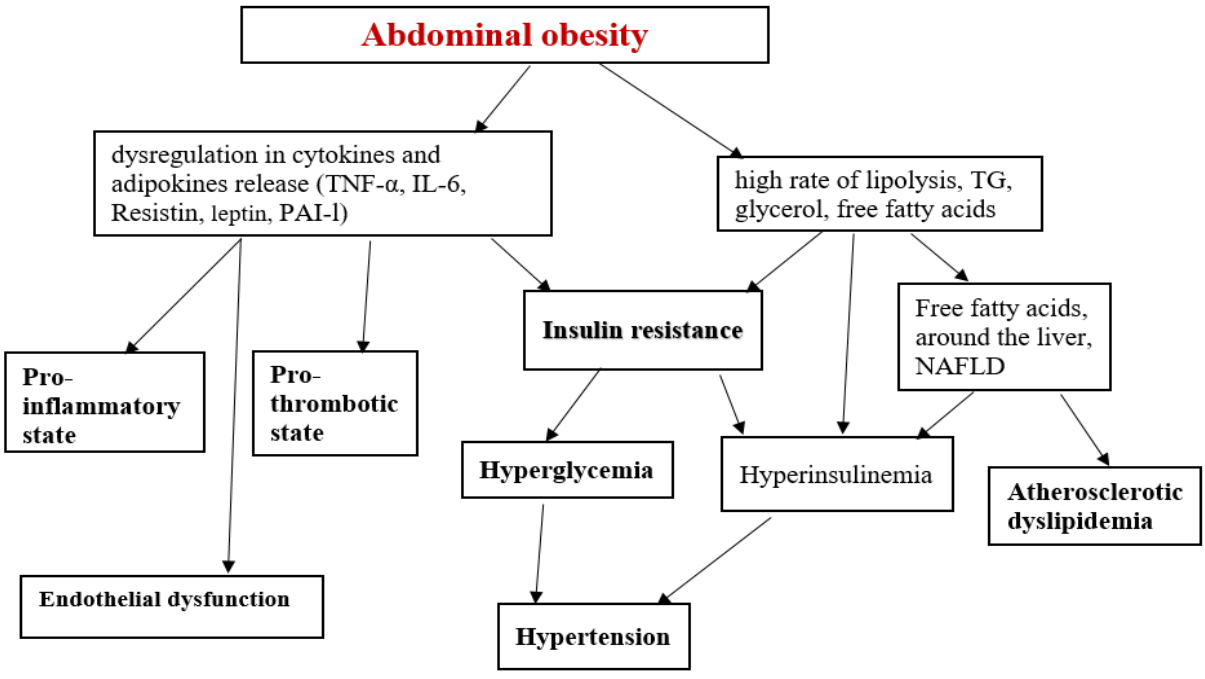

Figure 1.2: Illustration indicating central obesity as the critical factor in developing cardiometabolic syndrome, an adaptation from Chatterjee et al. [3].

Central obesity is a critical risk factor for almost all non-communicable diseases, including atherosclerotic heart disease, stroke, type two diabetes, and cancers [20]. The current pieces of evidence indicate that central obesity is prevailing higher in women of reproductive age than in men of the same age. This high prevalence of central obesity in women was observed globally and locally, where the global prevalence was estimated to be 41.5%; it was approximately 47.6% in women and 30.4% in men [21]. In sub-Saharan Africa, Ethiopia reported a prevalence of 53% in women and 15% in men [22], Tanzania reported 35% in women and 6% in men [23], and Kenya reported 63% in women and 17% in men [24]. In Rwanda, the prevalence is still unknown.

This elevated prevalence of central obesity in women highlights an increased risk of cardiometabolic disease in this population as it masks the cardio-protective effect of the high oestrogen level suggested by the literature in childbearing age [25]. Factors associated with the high prevalence of central obesity in women of reproductive age are still debatable, and most of those reported are common in both men and women. The common factors associated with central obesity in both groups include alcohol intake, overeating fat and carbohydrate-containing foods, physical inactivity, and age [26, 27]. However, these factors are insufficient to justify the high difference in the prevalence of central obesity between men and women. Additional factors unique to women, such as hormonal contraceptive use, need to be evaluated.

Hormonal contraceptives are synthetic hormones resembling natural female hormones. They are all made of synthetic steroid hormones or derivatives, except that they come in different designs, doses, and compositions. The most prevalent hormonal contraceptives include oral contraceptives (pills), injectables, and implants. There are two main types of injectable contraceptives: Progestogen-only Injectables (POI) containing synthetic progesterone only and Combined Injectables Contraceptives (CIC) containing oestrogen (usually Ethinyl estradiol) and progesterone. Progestogen-only injectables include a three-month injection, Depot Medroxyprogesterone Acetate (DMPA), also called Depo Provera, used to treat endometriosis and prevent pregnancy [28].

DMPA injectable contraceptive is one of the reversible and effective hormonal contraceptive methods currently used by a large number of women on the globe. The World Family Planning Report (2022) indicated that 966 million women of reproductive age use methods of contraception, and 72 million of them (7.5%) use injectable contraceptives. The report also

indicated that 33% of contraceptive methods users in Sub-Saharan Africa utilise injectable contraceptives [29]. Furthermore, it was observed that the most used injectable contraceptive in this region and more so in East Africa is the DMPA injection [30]. Data in 2014-2015 demographic health surveys (DHS) of East African countries showed that the majority of users of family planning prefer DMPA injection. The prevalence of DMPA use among users of any method of contraception was 48.5 % in Rwanda, 47.5% in Uganda, 47.9% in Kenya, and 30.6% in Tanzania [31, 32, 33, 34].

Despite the high prevalence of DMPA use in the East African region, the discontinuation rate for this method has also increased primarily due to side effects/health issues [35]. The most reported side effects of DMPA include weight gain, disruption of periods, headache, acne, and mood change, among others [36]. The WHO guidelines on the side effects of contraceptives recommend that users report any embarrassing experiences and persistent intolerable side effects to the health practitioner, who may decide to shift one method to another until the user finds a method that works better for her health [37].

However, there are quiet side effects that the user cannot easily feel, nor can they be easily noticed by the health providers, yet they adversely affect the body's functioning. The reported asymptomatic side effects of hormonal contraceptives include those related to their influence on cardiometabolic risk factors. DMPA was reported to influence blood glucose metabolism, as indicated in a controlled trial where users showed a significant increase in blood glucose compared to other types of injectables [38]. Moreover, a twelve-month follow-up study found that DMPA impacted lipid and lipoprotein metabolism. The study revealed that DMPA was linked with increased triglycerides, total cholesterol, and LDL (often called "bad cholesterol"). At the same time, it was correlated with a decrease in HDL (often called "good cholesterol") [39, 40].

The literature suggests that the use of DMPA predisposes users to the risk of CMD through risk factors such as dyslipidemia [41], body fat deposition [42], high calcium levels [43], and increased body weight [42]. However, there is insufficient data to conclude the effect of DMPA on cardiometabolic health. Several studies in this area focused only on dyslipidemia, hypertension, and weight gain, leaving other factors under-investigated. Additional factors to be considered include chronic inflammation, central obesity, and glycated haemoglobin (HbA1C) levels, as these are potential cardiometabolic risk factors [44, 45, 46].

1.2. Problem statement

The available guidelines on the use of DMPA insist on its use with precaution for women with multiple cardiometabolic risk factors to reduce the risk of cardiovascular disease. The WHO guideline does not recommend DMPA use for users with numerous cardiovascular risk factors, as doing so worsens the risk of cardiovascular diseases [28]. Furthermore, the New Zealand guideline recommends that DMPA should not be used for women with hypertension and with caution for women with metabolic risk factors of cardiovascular disease like obesity, dyslipidemia, and diabetes [47]. Moreover, the updated Family Health International 2015 checklist recommends a prior evaluation before initiating DMPA for users with health conditions that could increase the risk of heart attack or strokes, such as obesity, smoking, high blood pressure, and high blood sugar [48].

According to the guidelines, checking cardiometabolic risk factors is essential before initiating DMPA. However, in most African countries, including Rwanda, women are only screened for blood pressure and weight and then allowed to begin DMPA regardless of other cardiometabolic risk factors. Furthermore, there is no follow-up to check for any cardiometabolic health risk that could arise from the method. The concern is that checking all cardiometabolic risk factors might be expensive and inconvenient in under-resourced settings, indicating the need for an effective and cost-friendly mechanism to check cardiometabolic risk.

The evidence that injectable contraceptives expose users to the risk of CMD suggests the necessity to follow up with them routinely. The lack of follow-up with women users of contraceptives might be associated with a shortage of knowledge on the possible development of cardiometabolic risk factors and associated outcomes. However, before establishing this follow-up, much needs to be done, among them identifying other potential cardiometabolic risk factors that the use of DMPA could influence. The knowledge of additional factors such as glycated haemoglobin, visceral fat deposition, and systemic inflammation will help to have a clear picture of the influence of DMPA on cardiometabolic health. This study aimed to examine the cardio-metabolic risk factors among users of DMPA injectable contraceptives, specifically dyslipidemia, hypertension, visceral fat deposition, hyperglycemia, and chronic or systemic inflammation. The aim was to ensure the safety of users and, if required, to establish a routine follow-up to guarantee their well-being.

1.3. Aim and objectives

1.3.1. Aim

To evaluate the effect of DMPA injectable contraceptive on cardiometabolic risk factors to document whether there is a need for routine follow-up to track any side effect that could lead to cardiometabolic disease.

1.3.2. Objectives

Main objective: To evaluate the effect of DMPA injection on cardiometabolic risk profile among women of reproductive age (15-49 years) in Kigali, Rwanda.

Specific objectives:

1. To determine the prevalence of central obesity and its association with other cardiometabolic risk factors among women of reproductive age wishing to adhere to DMPA injection in Kigali, Rwanda.
2. To assess the effect of DMPA injection on lipid profile, blood pressure, glycated haemoglobin, waist circumference, and inflammatory markers in women living in Kigali, Rwanda.
3. To evaluate the changes in cardiometabolic risk markers in abdominally obese women during the use of DMPA injection in Kigali, Rwanda

1.4. Significance of the study

There is a research concern highlighting the coincidence of the increased incidence of cardiometabolic disease in young women, which goes in hand with the growing use of hormonal contraceptives in Africa. This study intends to contribute to the existing knowledge on the effect of hormonal contraceptive use on cardiometabolic health. It evaluated the effects of DMPA on cardiometabolic risk factors. Its findings provide basic information on the need for routine health check-ups of biochemical changes among DMPA to control the potential development of cardiovascular diseases. It will also contribute to the knowledge of whether it is needed or not to check for cardiometabolic risk factors before initiating injectable contraceptives.

The study was in line with Sustainable Development Goal 3, which focuses on the better health and well-being of the population by preventing premature deaths from non-communicable diseases. Further, Rwanda targets to lessen the reproductive population rate through modern

contraceptive use by 2050 and aims to address non-communicable diseases. Therefore, with the global increase of users of hormonal contraceptives in the future and the need to address non-communicable diseases, a study investigating the association between hormonal contraceptives and cardiovascular diseases is essential.

1.5. Methodology

Three studies with various designs were performed to evaluate the effect of DMPA injectable contraceptives on cardiometabolic risk factors to document whether there is a need for routine follow-up to track any side effects that could lead to cardiometabolic disease. The first study was cross-sectional by design (sample size: 138 women of reproductive age) and determined the prevalence of central obesity and its association with other cardiometabolic risk factors in women of reproductive age in Rwanda. Data from the first study served to choose a study group (45 participants without any risk factor of interest whose choice of contraception was DMPA) for the second study, which was a prospective cohort study that assessed the effects of DMPA on lipid profile, waist circumference, blood pressure, glycated hemoglobin, and inflammatory markers among women of reproductive age in Rwanda. The control group for the second study (45 participants without any risk factor of interest whose choice of contraception was non-hormonal methods) was chosen from the general community. The third study was a pre-post study that evaluated the changes in cardiometabolic risk markers among abdominally obese women (65 participants identified in the first study) of reproductive age during the use of DMPA in Rwanda. Studies one and two were published in peer-reviewed journals, while study three is under review as indicated on the publication list (Appendix F).

1.6. Ethical approval

The study was approved by the College of Medicine and Health Sciences Institutional Review Board, University of Rwanda (reference: 042/CMHS IRB/2020); Appendix A. Permission was granted by the Rwanda Biomedical Center (reference: 417/RBC/2020); appendix C and the Rwanda Ministry of Health (ref: NHR/2020/PROT/030); appendix B. The consent form (Appendix E) indicating the study's purpose, importance, and involvement was prepared in Kinyarwanda, the local language, and given to participants to read and sign to show that they willingly accepted to be part of the study. All the records were kept confidential.

1.7. Thesis organization

This study purposed to assess the effect of DMPA injectable contraceptives on cardiometabolic risk profile in women of reproductive age, with the ultimate goal to advocate for a routine follow-up with them while using this method. The study focused on the influence of DMPA on the most common cardiometabolic risk parameters, such as high blood pressure, dyslipidemia, visceral obesity, high glycated haemoglobin level, and systemic inflammation. In order to achieve this purpose, the study was organized into six chapters.

The first chapter is the general introduction; it overviews the study's importance and describes its problem statement, goal, objectives, methodology, and significance. The second chapter provides the details of the literature review, where cardiometabolic diseases are described, and their prevalence and burden between genders are discussed. Also, cardiometabolic risk parameters (dyslipidemia, central obesity, systemic inflammation, hyperglycemia, and high blood pressure) and their relationship with hormonal contraceptive use are discussed in detail, and the research gap is widely documented. Chapter three is about the prevalence of central obesity and its association with other cardiometabolic risk factors in women of reproductive age who wish to start DMPA injection.

Chapter four is about the effect of DMPA on cardiometabolic risk factors. It discusses the influence of DMPA on lipid profile, visceral fat deposition, blood pressure, glycated haemoglobin, and inflammatory markers. Chapter five describes the changes in cardiometabolic markers in abdominally obese women using DMPA. Chapter Sis talks about the general discussion, conclusions, and recommendations. It summarizes the study's overall findings, indicating the direction for further research, and provides recommendations to health policymakers and providers. On the last pages, some appendices include the CMHS IRB ethical clearance approval (Appendix A), approval by the Ministry of Health (MoH); Appendix B, the collaboration note from Rwanda Biomedical Centre (RBC); Appendix C, data collection tool (appendix D), the informed consent form (appendix E) in English and Kinyarwanda, and the list of publications (appendix F) which include three related to the thesis and five published with others in the field.

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Chapter Two: Literature Review

2.0. Introduction

This chapter is made of 4 sections. The first section overviews cardiometabolic diseases such as hypertensive heart disease, coronary artery disease, stroke, periphery artery disease, venous thromboembolism, and type two diabetes mellitus. The second section explores the cardiometabolic risk parameters, emphasizing dyslipidemia, central obesity, glycated haemoglobin, high blood pressure, and systemic inflammation. The third section discusses the types of contraceptive methods, describing two classes: non-hormonal and hormonal contraceptive methods. The fourth section discusses the associations between hormonal contraceptive use, specifically DMPA, and cardiometabolic disease risk.

In this literature review, the examined data focused on the existing evidence on the effect of DMPA on cardiometabolic risk. The reviewed literature was used to compare and contrast the findings of this study with other studies in the historical context of the research and to show the originality of the study and its importance. The search of literature targeted online books and research articles through PubMed, BioMed, Web of Sciences, and Cochrane Library using predefined keywords in this exercise. The literature included all articles published in English from 2000 to date.

The review consists of primary research studies, such as original experimental and observational investigations, including case-control, cohort, cross-sectional designs, and systematic reviews. All articles were organized into a literature review matrix to facilitate easy access to information. This matrix is essentially a table that presents key details about each study, such as its purpose, research gap, conceptual framework, and primary findings. It was instrumental in identifying the research gap and defining the research questions to guide the analysis.

2.1. Cardiometabolic disease

Cardiometabolic disease (CMD) is a range of conditions involving endocrine, nutritional, and metabolic disruptions. These conditions primarily include hypertensive heart disease, atherosclerotic heart disease (commonly known as CAD), stroke (either ischemic or hemorrhagic), peripheral arterial disease, deep venous thrombosis (DVT), and pulmonary embolism. Additionally, metabolic diseases such as type two diabetes mellitus (T2DM) are considered a part of the cardiometabolic disease spectrum [1, 2]. Cardiometabolic disease has

no early signs or symptoms; the only way to cope with its burden is to identify its risk factors early and initiate an intervention as soon as possible when the condition is still reversible.

2.1.1. Hypertensive heart disease

Hypertensive heart disease refers to a collection of conditions that arise due to long-standing hypertension. It can induce structural changes in the heart, including myocardial thickening and enlargement of the heart chambers, impairing its ability to pump blood efficiently. The thickening of the blood vessel walls increases the risk of clot formation and end up with other heart diseases such as coronary artery disease and stroke [3]. Hypertensive heart disease can cause various symptoms, including shortness of breath, fatigue, chest pain, and palpitations. In some cases, hypertensive heart disease can lead to complications such as heart failure, arrhythmias, and sudden cardiac death [4].

Hypertensive heart disease is a significant health burden in Sub-Saharan Africa, where non-communicable diseases are increasingly prevalent. Studies have shown that the prevalence of hypertension in Sub-Saharan Africa is high, ranging from 15% to 30% [5]. The prevalence is higher in urban areas and among women [6]. Chronic hypertension is most prevalent in females, and the risk of hypertensive heart disease increases in women with lower blood pressure than men [7].

Prevention and management of hypertensive heart disease in Sub-Saharan Africa require a comprehensive approach. That includes increasing awareness of hypertension and its complications, improving access to healthcare, and implementing effective prevention and control programs. Strategies should include community-based interventions, strengthening primary healthcare systems, and improving the availability and affordability of essential medicines [6].

2.1.2. Coronary artery disease

Coronary artery disease occurs due to the narrowing of coronary arteries supplying the heart with oxygenated blood. The leading cause of this narrowing is plaque build-up in the vessel's walls (atherosclerosis or hardening of arteries) [8]. The plaque comprises lipids (fats, cholesterol, and waxy), calcium, and other blood components [9]. As the plaque grows over time, it causes a decline in the blood reaching the heart muscle. It can rupture inside the vessel, generating clots that can completely stop the blood supply to the heart and end with sudden

death due to heart attack or myocardial infarction [2]. Coronary artery disease has no early signs or symptoms; however, it increases the risk of angina (chest pain), heart attack, heart failure, and cardiac arrhythmias [10].

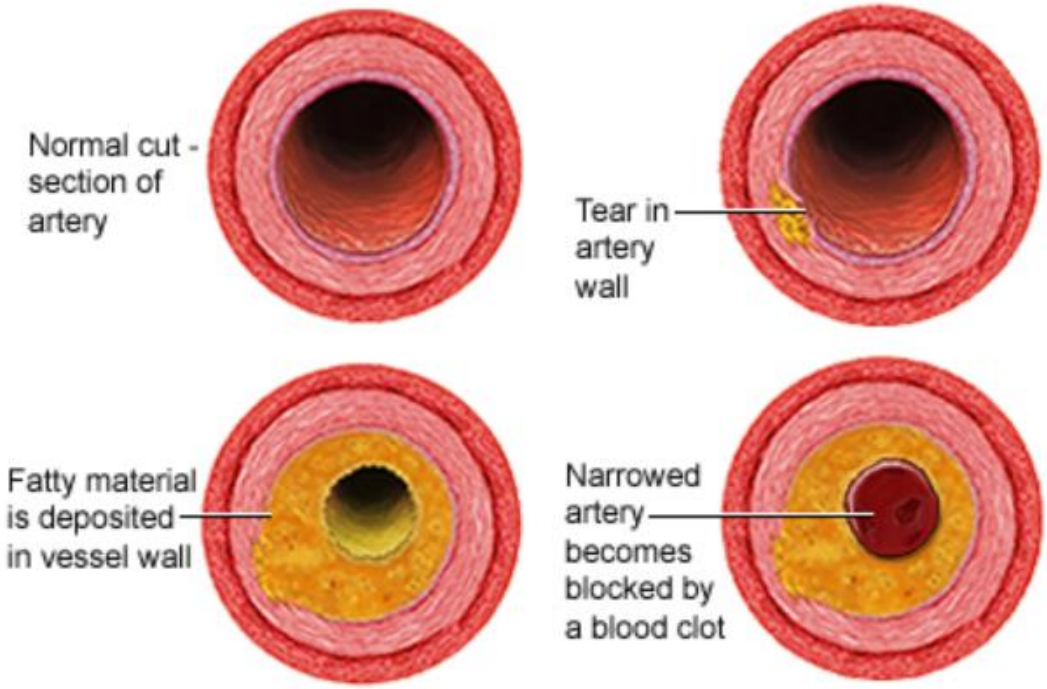

Figure 2.1: Atherosclerosis process [8].

The last decade's evidence indicated that men experience the symptoms of CAD ten years earlier than women, and both genders equalize at sixty years. However, older women (60-80 years) showed an accelerated incidence of CAD characterized by poor prognosis and linked with a high mortality rate compared to men of the same age. This high mortality rate in older women correlates with a high incidence of hyperlipidaemia, hypertension, central adiposity, and diabetes compared to men in this age category [11, 12].

Premenopausal women are considered to have a low risk of CAD due to the high oestrogen level, which is known to stimulate insulin production and enhance insulin sensitivity [13]. However, the presence of potential risk factors such as hypertension, smoking, diabetes, alcohol use, and central obesity, among others, outweighs this protection and potentiates the CAD risk [14]. Evidence shows that young men and women have an equal risk of CMD if exposed to the same risk factors [15]. Women of reproductive age have an additional risk associated with the

use of hormonal contraceptives, which is also reported to influence some of the potential risk factors.

2.1.3. Stroke

Strokes, also known as cerebrovascular accidents (CVAs), occur when there is a disruption in the blood supply to the brain, leading to brain cell damage or death. There are mainly two types of strokes: ischemic and hemorrhagic stroke. Ischemic stroke occurs due to blood flow blockage to the brain, a condition called a brain attack, central nervous system ischemia, or cerebrovascular disease. Two subtypes of ischemic stroke include thrombotic stroke, occurring when a blood clot (thrombus) forms within one of the brain's arteries, and embolic stroke, occurring when a blood clot or other debris forms elsewhere in the body (e.g., the heart) and travels through the bloodstream to block a brain artery. Hemorrhagic strokes occur when a blood vessel in the brain ruptures or leaks, causing bleeding within (intracerebral hemorrhage) or around the brain (subarachnoid hemorrhage) [16, 17]. Any cause of blood prevention to the brain induces the brain cells' death due to the lack of oxygen. Depending on the specific area of the brain affected, stroke can cause permanent neurological dysfunction or death if quick intervention is not provided [2]. Ischemic strokes are the most prevalent; they account for 85% of all cases while hemorrhagic strokes account for 15% of all stroke cases [16].

The proportion of stroke between genders varies across regions and populations. A study conducted in Asia reported a greater incidence of stroke in men than women, with a higher percentage of hypertension, smoking, and alcohol consumption among men [18, 19]. Similarly, studies from Europe and North America have reported a higher incidence and prevalence of stroke in men, with men having a more significant burden of risk factors such as hypertension, hyperlipidaemia, and diabetes [9, 18]. African studies also reported a higher proportion of stroke in men, with a higher burden of risk factors such as hypertension, obesity, and diabetes [20, 21].

Stroke is a major cause of long-duration illness and death worldwide, and Africa is no exception. The World Health Organization (WHO) identifies stroke as one of the prominent contributors to both death and disability in Africa, responsible for approximately 10% of all deaths in the region [22, 23]. Women tend to have worse outcomes after stroke compared to men, including higher rates of disability, cognitive impairment, and depression [24].

Several factors may contribute to these gender differences in stroke outcomes. Firstly, women may have different risk factors for stroke compared to men. For example, women have a higher prevalence of obesity, hypertension, migraine with aura, and atrial fibrillation, all of which increase the risk of stroke [17, 24]. Additionally, hormonal factors such as pregnancy, menopause, and oral contraceptives may also increase the risk of stroke in women [25, 26]. Secondly, there may be differences in how stroke is diagnosed and treated in women compared to men. Women may face challenges receiving timely and appropriate stroke care, potentially resulting in poorer outcomes [18].

2.1.4. Peripheral arterial disease

Peripheral arterial disease (PAD) mainly occurs concomitantly with other vascular diseases, especially coronary artery disease, and is caused by the deposition of fatty materials in the vessel's walls [27]. The condition occurs when arteries supplying the oxygenated blood to the arms and legs are narrowed or blocked. When the vessel's lumen is narrowed enough, it causes blood stasis in that area and increases the risk of clot formation that can block the passage of blood to the lower limbs [2]. Ischemia in the lower limbs generally manifests in two forms: leg pain upon walking, relief upon rest (Claudication), and leg pain without movement. The leg rest pain may be associated with gangrene or ulceration and occasionally lead to amputation (surgical removal of the body part) [28].

Several studies have investigated the prevalence of PAD and associated risk factors in different populations. In the United States, the prevalence of PAD varies depending on the population studied. The National Health and Nutrition Examination Survey (NHANES) estimated that the prevalence of PAD in adults over 40 years was 8.5%, with a higher prevalence in certain subgroups, such as individuals with diabetes, smokers, and those with a history of cardiovascular disease [29]. A systematic review in sub-Saharan Africa reported a PAD prevalence ranging from 1.9% to 39.5%, with an overall prevalence of 13.3%. The study also found that smoking, hypertension, diabetes, and hyperlipidemia were significant risk factors for PAD in the region [30].

Earlier studies have suggested the possibility of gender disparities in the correlation between PAD and certain risk factors. One study reported that hypertension was a more potent risk factor for PAD in women than men [30]. Another study found that the association between diabetes and PAD was stronger in women than men [31]. Recent studies have reported that women

exhibit a higher likelihood of having diabetes, a significant risk factor for PAD, than men [32]. Women are also more prone to autoimmune diseases, which can further elevate the risk of PAD [33]. Also, women who smoke are found to have a greater susceptibility to developing PAD compared to male smokers, possibly due to differences in how nicotine is metabolized in women compared to men [32].

2.1.5. Venous thromboembolism

Venous thromboembolism (VTE) involves clot formation in the deep veins of legs, hips, pelvis, arms, neck, and chest and/or migration of the clot in the lung. A clot formed in the deep vein is called Deep Vein Thrombosis (DVT), and its migration into the lungs is called Pulmonary Embolism (PE). The contributing factors to thrombus formation include blood stasis in deep veins, hypercoagulability disorders, and vessel wall damage [34].

Venous thromboembolism (VTE) is a prevalent and potentially serious condition that exhibits variability among different populations. In a large population-based study in the United States, the overall incidence of VTE was 247.89 per 100,000 person-year [35]. Another African study reported an incidence of VTE varying between 380 and 448 deaths per year in pregnant and postpartum women [36]. The incidence of VTE is also higher in specific subpopulations, such as hospitalized patients and those undergoing surgery [37].

Age is an associated risk factor for VTE, and the incidence of VTE increases with age. This evidence was indicated in a systematic review and meta-analysis study, where the risk of VTE increased by approximately 3-fold for each decade of age [38]. Gender is another important risk factor, with a higher incidence of VTE in women than men [36]. Several other risk factors have been identified for VTE, including immobility, surgery, pregnancy, cancer, and inherited thrombophilia. Immobility and surgery increase the risk of VTE by causing venous stasis and endothelial damage [39]. Pregnancy and the postpartum period are also associated with an increased risk of VTE, likely due to hormonal changes and increased venous stasis [40]. Cancer and chemotherapy increase the risk of VTE by causing hypercoagulability [41]. Inherited thrombophilia, such as factor V Leiden and prothrombin gene mutations, also increase the risk of VTE [42].

2.1.6. Type two diabetes

Type two diabetes is a multifaceted condition influenced by genetic, environmental, and lifestyle factors. While it is more prevalent in individuals above 40, it can develop at any stage of life. Approximately 90-95 percent of diagnosed diabetes cases are attributed to type 2 diabetes, with a significant proportion of affected individuals being overweight or obese [43]. In this form of diabetes, the liver and skeletal muscle exhibit insulin resistance, leading to increased glucose production in the liver and excessive release of free fatty acids by fat cells. Additionally, there is a relative deficiency of insulin. As the condition progresses, insulin secretion gradually decreases due to beta-cell failure [44]. The manifestation of clinical symptoms often coincides with the occurrence of insulin resistance or relative insulin deficiency [45].

Many individuals with type 2 diabetes remain oblivious to their condition for an extended period, as symptoms may take years to manifest or be acknowledged. Unfortunately, this prolonged period of unawareness allows excess blood glucose to inflict damage on the body. [45] Persistent metabolic dysfunction often gives rise to enduring and irreversible alterations in the cellular functions and structures of the body, particularly affecting the vascular system. These changes play a crucial role in the emergence of distinct clinical conditions referred to as the complications of diabetes mellitus [46].

Untreated or inadequately controlled, type 2 diabetes can give rise to numerous complications. Among the well-recognized complications is diabetic retinopathy, which, if not promptly addressed, can result in vision impairment and blindness [47], and diabetic nephropathy, a primary contributor to end-stage renal disease [48]. Other complications encompass diabetic neuropathy, which can induce nerve impairment, resulting in numbness, tingling, or discomfort in the extremities, such as the feet and hands [49]. Type 2 diabetes has a close association with cardiovascular disease [49] and is a contributor to foot ulcer development. These complications can be challenging to manage and, in severe cases, may necessitate amputation as a treatment measure [50]. Additionally, type 2 diabetes patients are more susceptible to infections, including bacterial and fungal infections, due to the compromised immune system associated with diabetes [51].

Type two diabetic women are at a higher risk of developing and dying of vascular disease than men due to polycystic ovary syndrome (PCOS), hormonal changes, and pregnancy-related

complications unique to women. Women with PCOS are at higher risk of developing diabetes and cardiovascular disease due to insulin resistance, obesity, and high levels of androgens [50, 51]. Women experience hormonal changes throughout their lifetime, affecting their blood sugar control and increasing their risk of vascular disease. For example, during menopause, women may experience changes in their cholesterol levels and blood pressure, amplifying the risk of heart disease and stroke [52]. Additionally, Women who have experienced gestational diabetes or preeclampsia during pregnancy are at an increased risk of developing type 2 diabetes and cardiovascular disease in the future [53].

2.1.7. The burden of cardiometabolic disease

Cardiometabolic disease has emerged as a prominent global cause of death and disability, with prevalence rising over the past few decades [54]. According to the World Health Organization, NCDs country profiles 2018, CVD is responsible for approximately 17.9 million deaths worldwide yearly [55]. In addition, the International Diabetes Federation (IDF reported that the global diabetic population currently stands at approximately 537 million individuals, and this figure is predicted to surge to 793 million by 2045. Currently, more than 76 million people in the Middle East and North Africa have diabetes, and this is predicted to be 136 million in 2045 [56]. These statistics highlight the alarming global burden of CMD and the urgent need for prevention and management strategies.

In the United States, CMD is a significant health concern and a major cause of morbidity and mortality. The National Academies of Sciences, Engineering, and Medicine report 2019 indicated that around 5 million US working-age adults (25-64) died of CMD between 1990 and 2017 [57]. Subsequently, the American Heart Association (AHA) report indicated CVD as the main cause of death in the US, accounting for 874,613 deaths in 2019 [58].

The African continent is experiencing a rapid epidemiological transition, shifting from infectious to non-communicable diseases (NCDs), including CMD [59]. The World Heart Association reported that in 2019, one million Sub-Saharan Africans died of cardiovascular disease (CVD). That number represents 5.4 % of all CVD-related deaths in the Whole of Africa and 13% globally [60]. Epidemiological studies in Africa revealed that CVD is the leading cause of mortality and morbidity, especially in the Sub-Saharan region, where it represents a substantial health burden that claims much of the economy for its management [61]. In Rwanda,

around 45% of the deaths in 2017 came from non-communicable diseases, and cardiovascular diseases alone claimed one-third [55].

Recent literature suggests there are still disparities in cardiovascular disease (CVD) incidence between genders, with men having a higher incidence than women [11]. The reported high incidence in men compared to women remains questionable due to the lack of research interest in CVD in women following the traditional suggestion that CVD is a men's issue [14]. In addition, it was indicated that symptoms of CVD in women are different from those in men, where women tend to present with atypical symptoms or not show signs at all [11]. It was also reported that about 64% of women dying of coronary heart disease had no previous known symptoms [62].

The European Cardiology Society revealed that around 35% of deaths in women annually come from CVD, and more women than men die of CDV, and women killed by CVD are more than twice those killed by breast cancer [63]. There is evidence that women with CMD may experience more severe complications, such as heart failure and stroke, and have a higher risk of CMD-related mortality than men [11]. Additionally, women are more likely to have non-obstructive coronary artery disease, which can be challenging to diagnose and treat [12].

Multiple factors contribute to differences in outcomes, including differences in biological, behavioural, and social determinants of health [64]. Women may experience different risk factors, such as gestational diabetes and preeclampsia during pregnancy, which increase their risk of developing CVD later in life [65]. Women also have a higher proportion of risk factors, such as hypertension, diabetes, and obesity, which can increase their risk for CVD [11]. Furthermore, differences in access to care, social support, and health literacy may affect women's engagement with preventive care and their ability to manage CVD risk factors [66].

2.2. Cardiometabolic risk parameters.

2.2.1. Obesity

General obesity is a health measure that indicates an individual's high weight disproportionately to their height. It is defined by the magnitude of the body mass index (BMI), which is estimated by taking the weight (in kilograms) of an individual and dividing the square of his or her height (in meters); it is expressed as kg/m^2. According to WHO, a BMI under 18.5 kg/m^2 indicates an individual is underweight, and a BMI between 18.5 and 24.9 kg/m^2 indicates a normal-weight

individual. In contrast, a BMI between 25-29.9 defines overweight, while a BMI greater or equal to 30 kg/m^2 shows obesity [67].

Body mass index correlates with the degree of body fat deposition where the value of BMI greater or equal to 30 appears to relate to high body fat composition [68]. Metabolically, obesity indicates an imbalance in energy intake and expenditure. In other words, it occurs when an individual ingests a lot of fats and carbohydrates and remains inactive. In that case, the body uses little food ingested, and the remaining energy gets stored in the adipose tissue [69]. However, the literature suggested the role of an individual's genetic makeup and environmental factors in increasing susceptibility to obesity [70].

Excessive deposition of fats in the visceral part of the body defines central obesity, and it was repeatedly reported to be associated with high morbidity and mortality worldwide [70, 71]. It is a pivotal determinant of metabolic syndrome, a condition defined by the concomitant presence of glucose intolerance, high blood levels of insulin, and dyslipidemia [72]. It is further linked to chronic systemic inflammation and an increased risk of various metabolic disorders such as diabetes, hypertension, microalbuminuria, atherosclerosis, arthritis, and certain types of cancer [70].

The pathophysiology of central obesity is based on the metabolic behaviour of the adipose tissue. Adipocytes in the visceral region are highly metabolically active, with a high rate of lipolysis, increasing the issue of triglycerides, glycerol, and free fatty acids in the bloodstream [73]. With their endocrine function, adipocytes release hormones like leptin, adiponectin, and other cytokines important in metabolism regulation [70]. They also release inflammatory mediators, which, together with free fatty acids, enter the portal vein and directly reach the liver, increasing the risk of fatty liver disease [74]. The inflammatory mediators, especially C-reactive protein, are markers of atherogenic diseases and a predictor of cardiovascular disease [75]. The high free fatty acid levels in the blood lead to the accumulation of fats in other tissues and are linked to insulin resistance and increase the risk of diabetes [72].

Body mass index has been used to judge an individual's health risks and was found to be associated with cardiovascular disease and high morbidity and mortality. However, the situation worsened in individuals with normal BMIs [72]. Even though high BMI was associated with a high degree of body fat deposition, it is not always related to central obesity, and central obesity is not always associated with abnormal BMI [76]. This controversy is known as the obesity

paradox and is partially explained by the limitation of BMI to provide enough information concerning abdominal fat distribution [71].

Waist circumference (WC) and waist-to-hip ratio (WHR) are ideal for assessing body fat deposition and diagnosing central obesity [71]. Central obesity is defined by waist circumference (WC) greater than 102 cm in men and greater than 88 cm in women or WHR greater than 0.90 in men and 0.85 in women [77]. It was reported as an independent determinant of metabolic syndrome and a key risk factor for cardiovascular disease, regardless of normal weight measured by BMI [76]. Previous studies combined WC and WHR to estimate the risk associated with central obesity; however, recent studies indicated that measuring WC alone provides a reliable estimate of central obesity [72, 76].

2.2.2. Dyslipidemia

Lipid is a general term representing naturally occurring organic molecules insoluble in water but soluble in organic solvents. They broadly include fats, phospholipids, wax, and sterols and are found in animals and plants. They serve several key biological functions, including acting as energy reservoirs, integral structural components of biological membranes, and playing crucial roles signalling molecules, such as prostaglandins. As insoluble substances, lipids are transported through the blood, bound on proteins called "apoproteins" to form particles called "lipoproteins."

a) Classes of lipoprotein and their function

Lipoproteins are classified according to their densities, which depend on lipids and protein contents. Five main classes are starting from the least dense to the highest: chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Chylomicrons transport dietary lipids from the gut to the liver, rich in triglycerides with very little cholesterol and proteins. Very low-density lipoprotein cholesterol, IDL, and LDL are related particles rich in cholesterol that transport endogenously synthesized lipids by the liver to peripheral tissues for energy production or storage. High-density lipoprotein cholesterol, the densest particle, transports excess cholesterol from peripheral tissues to the liver for further metabolism and, ultimately, for elimination. In the liver, cholesterol can be used in the biosynthesis of steroid hormones and

forming bile pigments. This pathway is the only way the body can get rid of excess cholesterol, as the body cannot use the latter for energy production.

Like any other physiological process, lipid metabolism is regulated, and any deviation leads to health problems. When tracing metabolic issues related to lipid metabolism, laboratory investigations include the lipid profile, which tests the concentration of triglycerides: TG, low-density lipoprotein cholesterol: LDL, high-density lipoprotein cholesterol: HDL and total cholesterol, which counts the sum of both LDL and HDL. Thus, dyslipidemia represents any alteration (increase or decrease) in blood concentration of one or more lipid profile components [78]. Researchers identified two types of dyslipidemia: primary dyslipidemia if it is of genetic origin and secondary if influenced by other factors. Secondary dyslipidemia is the most common and is mainly associated with uncontrolled diabetes, alcohol consumption, hypothyroidism, and albuminuria [79].

b) Dyslipidemia and cardiovascular diseases

Dyslipidemia is named based on the lipid profile component that is affected. Dyslipidaemias of health concerns include hypercholesterolemia, diagnosed when total cholesterol levels are above acceptable, and LDL-hypercholesterolemia, when LDL levers exceed the reference value. Other types of dyslipidaemias include hypertriglyceridemia, indicated when triglycerides level is high, and HDL-hypocholesterolaemia, defined by low HDL levels. Most reported dyslipidemia to be negatively associated with cardiovascular diseases is the high level of LDL-cholesterol as it favours the deposition of cholesterol in extrahepatic tissues, including blood vessels; they are called bad cholesterol. High LDL was found independently associated with atherosclerosis even at the normal level and in individuals without known cardiometabolic risk factors [80].

A high HDL level (over 60 mg/dl) is considered protective against cardiovascular diseases. In comparison, a low concentration of HDL- C (generally below 40 mg/dl) represents an increased risk factor for atherosclerotic disease. HDL removes the surplus cholesterol from peripheral tissues and transports it to the liver for excretion via bile; they are considered good cholesterol [81]. Recent studies indicate hypertriglyceridemia is associated with pancreatitis and cardiovascular diseases such as ischemic heart disease [82].

Dyslipidemia and cardiovascular diseases, in general, are associated with quiet health conditions that manifest at an advanced level, which cannot be reversed [83]. Treating dyslipidemia has

been proven effective in reducing cardiovascular disease incidence in high-risk individuals [84]. Individuals with dyslipidemia remain unaware until they show signs of cardiovascular disease complications such as angina and heart failure [78]. The only way to recognize dyslipidemia is through routine health checkups, as screening for all healthy adults with no evidence of heart disease is recommended to reduce the risk of cardiovascular diseases [85].

c) Measuring lipid profile

Generally, lipid profile measurement means measuring the concentration of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), and total cholesterol (TC) [86]. All components should be tested in a fasting state. The test is recommended to be performed every five years in an individual with no known risk factor and aged 21 and above and regularly for an individual with other risk factors to estimate the risk of developing cardiovascular diseases [85]. In available research articles, there is a slight difference in the reference values as each lab has to establish its reference values as they are influenced by age, sex, and ethnicity. In general, TC in individuals aged 21 and older, the reference values vary from 100-199 mg/dL. That of HDL is 40-60 mg/dL, LDL < 130 mg/dL, and TG < 150 mg/dL[87].

Scientists use lipid profiles to estimate the risk of cardiovascular diseases in asymptomatic individuals to initiate an intervention at an early stage to prevent complications and premature deaths. The risk is calculated and named Castelli index I = TC/HDL, Castelli index II = LDL/HDL, and TG/HDL ratio. The high risk is defined when Castelli index I >3.5 and Castelli index II > 2.5. For the TG/HDL ratio, a value less than two is ideal, while a value greater than two is associated with increased risk [87, 88]. A study in nondiabetic Koreans concluded that the TG/HDH ratio had been identified as the most effective predictor of ischemic heart disease, especially in women [89].

2.1.1. Glycated hemoglobin and hyperglycemia

Hyperglycemia represents a blood glucose level above the reference value (4.0- 5.4 mmol/L; 72 to 99 mg/dL when fasting, and 7.8 mmol/L (140 mg/dL) 2 hours after eating) [90]. It is a consequence of impaired carbohydrate and lipid metabolism manifested by insulin resistance, insulin insufficiency, or a combination of both [91]. Persistent hyperglycemia is an alarm that an individual is tending to diabetes and is associated with cardiovascular disease [92].

However, previous studies indicate that some individuals are genetically predisposed to hyperglycemia, which does not necessarily lead to diabetes [93]. Besides, the evidence in the literature suggests hyperglycemia is an independent risk factor for cardiovascular diseases, even in nondiabetic individuals [94]. According to the American Diabetes Association, fasting blood sugar above 7mmol/l (126 ml/dl) or above or random blood sugar of 11mmol/l (200ml/dl) or above is a criterion for a diabetes diagnosis. Individuals whose blood sugar level is above the reference range but below the diabetes value are considered prediabetes and have an increased risk of developing cardiovascular diseases [95].

However, blood glucose provides an instant estimate of blood sugar that cannot give information on variation in a given period. Glycosylated haemoglobin is ideal for providing a clear picture of blood sugar in two to three months, as it is not influenced by diet or physical status. Glycosylated haemoglobin is formed when the protein called haemoglobin found in red blood cells is exposed to higher blood sugar levels for a prolonged period. The attachment of glucose to haemoglobin is a non-enzymatic process that occurs only when the blood sugar is high. It is mainly tested to monitor diabetic patients and is more applicable where fasting is difficult to control.

Prediabetes and diabetes values are associated with an increased risk of cardiovascular diseases [96]. Even though not a gold standard test, the HbA1C is an accepted test to diagnose diabetes as it helps to know about the blood sugar levels in at least the previous three months for newly diagnosed patients where the time for the disease onset is uncertain. It is also recommended to be used as an estimator of the risk of coronary artery disease and stroke in nondiabetic individuals [97]. For nondiabetic individuals, HbA1C of 4.5 to a value less than 5.7% indicates a normal level. Values between 5.7 and 6.4% indicate prediabetes, while values greater or equal to 6.5% indicate diabetes [98].

Biochemical changes linking high blood glucose and cardiovascular diseases reside in its effect on endothelial dysfunction. In its function, endothelium produces substances (vasodilators and vasoconstrictors) responsible for regulating blood flow, and therefore, any imbalance in these two kinds of blood flow regulators leads to health problems [99]. Persistent high blood glucose level increases the rate of glucose auto-oxidation and leads to the high production of mitochondrial superoxide in all body cells, including the myocardium [100]. This oxidative stress impairs endothelial function by creating an imbalance between vasodilators and

vasoconstrictors and ultimately increases the risk of cardiovascular diseases, for instance, stroke and heart attack [101].

2.1.2. High blood pressure

Blood pressure is defined as the force used by the heart to pump blood against the blood vessel walls. It is reported into two numbers, the one representing the blood pressure when the heart relaxes (diastolic blood pressure: DBP), and the other representing the blood pressure during a heartbeat (systolic blood pressure: SBP). These two parameters are used to define, classify, and diagnose hypertension. According to the American Heart Association, individuals are classified as normotensive if they are not on antihypertensive medication and have an SBP of <120 mmHg and a DBP of <80 mmHg. The individual with elevated blood pressure is the one who is not taking antihypertensive medication and whose SBP ranges between 120– 139 mmHg and DBP ranges between 80–89 mmHg. A hypertensive patient is on antihypertensive medication or has SBP ≥140 mmHg and DBP ≥90 mmHg [102].

Hypertension is primarily a result of the dysregulation of standard homeostatic mechanisms responsible for maintaining blood pressure in the absence of identifiable secondary causes. The research showed that 95% of hypertension cases fall in this category. In comparison, only 5% of patients are secondary to underlying conditions such as renal disorders, endocrine disorders, high cardiac output, pregnancy, acute stress, surgery, and increased intravascular volume [103]. Whatever the origin of hypertension, it is a severe health condition that kills many people worldwide; it is secondary to dyslipidemia, increasing the risk of cardiovascular diseases [104]. High blood pressure is considered the "silent killer" because it typically manifests without noticeable warning signs or symptoms, leading many individuals to be unaware of their condition [105].

2.1.3. Systemic inflammation

Inflammation is a biological process triggered by the immune system when the body is distressed either by pathogens or any other foreign substance (toxins, some nutrients, metabolite) or action that causes injury to the affected tissues [106]. The literature has distinguished two kinds of inflammation: classic or acute inflammation and low-grade systemic inflammation, also called chronic or metabolic inflammation. Classical inflammation results from infection, irradiation, or tissue injury, and it is cleared by the immune system, restoring

the homeostatic state. If the body fails to regain homeostasis, when the inflammation trigger is not successfully eliminated, or the source of the trigger persists, the inflammation becomes chronic and leads to local tissue remodelling [107]. However, several chronic inflammations with an undefined origin do not involve infection or tissue damage and are primarily associated with inflammatory-related diseases such as diabetes, cancer, atherosclerosis, and obesity [75].

When the body struggles to restore the homeostatic condition, it releases some biological markers into the bloodstream called inflammatory markers. The most detected markers include C-reactive protein (CRP), whose secretion is triggered by pro-inflammatory cytokines such as interleukin-6 (IL-6) and tissue necrosis factor (TNF) [108]. Systemic inflammation is characterized by the persistent low levels of CRP that cannot be detected by the standard CRP test. These CRP low levels are detected by a specialized test called high sensitivity CRP (hs-CRP) that detects CRP in the range from 0.5 to 10 mg/L, while the standard CRP test detects CRP levels ranging from 10 to 1000 mg/ L. It was reported as an early risk marker of cardiovascular disease as it appears in the blood at the early stages of atherogenesis [109]. Measuring serum hs-CRP is an accepted tool to estimate the risk of cardiovascular diseases [110]]. A value less than 1mg/L is considered low risk, 1 to 3 mg/L is considered moderate risk, and a value greater than three mg/L is considered high risk [111].

2.2. Contraceptives

Contraception, often referred to as birth control, is the deliberate and voluntary use of various methods or devices to prevent pregnancy. Contraceptives are substances, devices, or methods used to avoid conception by inhibiting fertilization or implantation of the fertilised egg. Contraceptive methods broadly fit into two categories: traditional methods and modern methods. Traditional methods are based on biological changes determining the period a woman can get pregnant, while modern methods denote a product or medical practice restricting reproduction. Modern contraceptives are grouped into two categories: hormone-based and non-hormonal contraceptives.

2.2.1. Non-hormonal contraceptives

Non-hormonal contraceptive methods are designed to impede the union of sperm and egg through the use of physical barriers or by disrupting the fertilization process. These methods encompass various options, including barrier methods and copper intrauterine devices (IUDs).

Barrier methods include male and female condoms, diaphragms, cervical caps, spermicides, and contraceptive sponges, and they function by creating a physical obstruction to stop sperm from fertilizing the egg. On the other hand, copper IUDs are small T-shaped devices inserted into the uterus to prevent pregnancy efficiently. The copper ions released by the IUD create a toxic environment for sperm, thereby stopping fertilization. Copper IUDs provide long-term contraception for up to 10 or more years, depending on the specific type. Other methods in this category include withdrawal, fertility awareness, lactational amenorrhea, surgical sterilization, and abstinence [112].

2.2.2. Hormonal contraceptives.

Hormonal methods of contraception involve synthetic hormones, such as oestrogen and progestin or progestin alone, to regulate the reproductive system and prevent pregnancy. These methods include birth control pills, contraceptive patches, contraceptive injections (like depot medroxyprogesterone acetate or DMPA), intrauterine hormonal devices (IUDs), and contraceptive implants. Hormonal methods work by inhibiting ovulation, thickening cervical mucus to block sperm, or thinning the uterine lining to hinder implantation. Currently, three main types of hormonal contraceptives: oral contraceptives (pills), injectables, and implants are the most used methods worldwide [113], so the rest of this section discusses only these three hormonal contraceptives.

a. Oral contraceptives

Oral contraceptives, commonly called "the pill," are hormonal contraceptives taken daily to prevent pregnancy. They contain synthetic hormones, typically a combination of oestrogen, progestin, or progestin alone. They function by inhibiting ovulation, thickening cervical mucus to obstruct sperm mobility, and thinning the uterine lining, thereby reducing the chance of implantation. Various types of oestrogens and progestin exist, and different oral contraceptive pills feature different combinations of these hormones. Despite the variations, they all operate in a similar manner [114].

Combined oral contraceptives (COCs) contain both oestrogen and progestin hormones. They are usually taken for 21 consecutive days, followed by a 7-day hormone-free interval, during which withdrawal bleeding is similar to a menstrual period. Combination pills are available in different formulations, including monophasic pills (same hormone dose throughout the cycle),

biphasic pills (two different hormone doses), and triphasic pills (three different hormone doses). Progestin-Only Pills (Mini-pills) do not contain oestrogen. They are taken daily without a hormone-free interval and are particularly suitable for individuals who cannot or prefer not to use combination pills due to health considerations or personal preferences. Progestin-only pills must be taken consistently at the same time each day to maintain effectiveness [114].

b. Subdermal Implants

A subdermal contraceptive implant is a small and flexible rod that is inserted beneath the skin, typically in the upper arm. It releases a progestin hormone, etonogestrel, which effectively prevents pregnancy. The hormone inhibits ovulation by thickening the cervical mucus to impede the contact of sperm and egg and also modifies the uterine lining to reduce the likelihood of implantation. Once inserted, the contraceptive implant offers effective contraception for a specific duration, which can vary depending on the brand. For example, Jadelle is designed to offer protection for five years, Sino-implant (II) remains active for four years, and Implanon and Nexplanon remain working for three years [115].

c. Injectable contraceptives

Injectable contraceptives are synthetic hormonal preparations resembling natural female sex hormones administered to prevent pregnancy. They function by preventing the release of eggs from the ovaries and thickening the cervical mucus, creating a barrier that hampers the penetration of sperm into the upper reproductive tract, and thinning of endometrial lining to make it unfavourable for implantation of the fertilized ovum. They can be given through an intramuscular or subcutaneous route, and when issued, the hormone is slowly released into the bloodstream for 1-3 months [116]. There are two main types of injectable contraceptives: Progestogen-only Injectables (POI) containing synthetic progesterone only and Combined Injectable Contraceptive (CIC) containing synthetic estrogen (usually Ethinyl estradiol) and progesterone.

i. Progestin-only injectable contraceptives

Progestin-only injectables are of two types: a three-month injection of depot medroxyprogesterone acetate and a two-month injection of Norethindrone enanthate (NET-EN) or Noristerat. DMPA exists in two forms: DMPA 150mg, sold under the brand name DEPO-PROVERA® 150 mg/mL Injection (depot) given intramuscularly, and DMPA 104 mg, also

sold under the brand name Depot Sub-Q Provera, given subcutaneously. Noristerat is made of 200 mg NET-EN and given intramuscularly [117]; it is newer and, hence, less available on the market. DMPA is the most used method compared to other injectables due to its efficacy and long-acting [118]. DMPA 150 mg is considered the standard injection for contraception as it was the first to be designed and is highly available worldwide.

2.3. DMPA injectable contraceptives and cardiometabolic parameters.

2.3.1. DMPA and dyslipidemia

Dyslipidemia is the leading risk factor for atherosclerotic cardiovascular diseases such as coronary artery disease, stroke, and peripheral vascular diseases [84]. It represents a general term for any alteration in blood concentration of one or more lipid profile components. Available data on which type of lipid profile component is altered in DMPA injectable contraceptive users are controversial.

Several studies consistently reported the same effect of DMPA on lipid profile components. It is an example of the case-control study conducted in Pakistan, which reported a substantial increase in serum total cholesterol, low-density lipoprotein cholesterol, triglyceride, and a decrease in high-density lipoprotein level in DMPA users compared to controls [119]. Likewise, the prospective cohort study in India indicated a significant increase in LDL, TG, and TC and a decrease in HDL [120]. Another cross-sectional study in Nepal compared the lipid profile changes after two years of DMPA use and reported a significant increase in TC, LDL, and TG but a decrease in HDL [121].

Various studies consistently indicated some conflicting results. For instance, the prospective study in Iraq reported no association between DMPA use, higher total cholesterol and triglycerides, and association with increased LDL and decreased HDL [122]. This finding agrees with the other three-year prospective study done in Texas, where it was indicated that DMPA users experienced a significant decrease in HDL and an increase in LDL but not in TC and Triglycerides levels [123]. The same, in Egypt, a cross-sectional study comparing the effect of DMPA on lipid oxidative stress and lipid profile according to the duration of use (from one year to four years) reported a gradual increase in LDL and a decrease in HDL as the duration of use increase, however, concluded no significant effect on TC and TG [124].

Wildly opposing findings were observed in two cross-sectional studies done in different settings in Ethiopia. One study indicated that DMPA users experienced an increase in TC and LDL, a decrease in HDL compared to the control group, and no significant difference in triglyceride levels [125]. Another study reported that DMPA users significantly indicated higher mean TC and TG than non-hormonal users, with no difference in mean HDL and LDL [126]. This controversy raises a new understanding that contextual factors might contribute to these findings that need further investigation.

2.3.2. DMPA and hypertension

A few available studies investigating the relationship of hormonal contraceptives with blood pressure show controversy in their findings. A one-year follow-up study conducted in Ghana reported a highly significant increase (p=0.001) in DBP in injectable users when compared to results at baseline (72.70±3.47 mmHg) and results after one year (88.22±4.32). The same study also reported a significant increase (p=003) in SBP, which was 115.39±5.03 mmHg at baseline and 130.52±5.56mmHg after a year [127]. The study conducted in Pakistan women reported a difference where both SBP and DBP were significantly higher in injectable users (SBP: 118.33 ± 9.85 mmHg; DBP: 80.83 ± 10.91 mmHg) compared to controls (SBP: 112.0 ± 7.61 mmHg; DBP: 77.0 ± 5.50 mmHg) [128].

However, certain studies have reported no association between the use of DMPA (depot medroxyprogesterone acetate) and blood pressure. For example, a Kenya survey by Wanyoike et al. did not find a significant difference in blood pressure between DMPA users and non-users [129]. Also, the study by Zerihun et al. in Ethiopia reported no difference in both SBP and DBP between injectable users (108.4±12.47 mmHg; 70.7±7.82 mmHg, and controls (108.2±11.00 mmHg; 72.8±7.83 mmHg) [125]. The mixed findings about the association between DMPA use and blood pressure indicate the need for further research to understand this potential association better and determine whether it has clinical significance. Such study in the Rwandan setting is very important for properly managing side effects related to injectable contraceptives.

2.3.3. DMPA and obesity

Among hormonal contraceptives, DMPA is consistently reported to be associated with weight gain, with a big trend in users who start the methods already being obese based on high BMI. It is the example of the study done in the adolescent population in a prospective study of an 18-

month follow-up where the mean increase in weight at 18 months was 9.4 in obese users and 3.5 in non-obese users [125]. The same was reported in Indian postpartum women, where the six-month follow-up study indicated a significant progressive increase in weight [120]. In a cross-sectional study conducted in Ethiopia, there was a significant increase in individual body weight from 1-14 kg and a mean increase of $5kg/m^2$ in BMI regardless of the duration of use [125]. An increase in body weight is not enough to estimate the risk of cardiovascular diseases; instead, the waist circumference measure provides a good estimate of the risk of CDV [73].

2.3.4. DMPA and hyperglycemia

There is a controversy in available studies regarding the effect of hormonal contraceptives on blood glucose. A cross-sectional study indicated that continued use of hormonal contraceptives during childbearing age increases the risk of diabetes in postmenopausal [130]. In a cross-sectional study conducted in childbearing-aged women (20-49) in Indonesia, it was shown that users of hormonal contraceptives had a significantly higher average blood glucose of 26mg/dl above that of non-users [131]. The same in the study conducted in Nigeria, where two groups, hormonal contraceptive users combined and nonusers, were compared and showed a significant increase (5.2±2.2 mg/dl) in users [132]. Contrary to that conducted in young American women, white and black combined (19-30), where hormonal contraceptives reduced the blood glucose level, promising a protective effect on diabetes in users [133].

Another study on African Americans observed a deviation from this finding, where hormonal contraceptive users showed higher insulin resistance and glucose intolerance than nonusers [133]. This controversy in results could be due to contextual aspects that hormonal contraceptives affect users differently, which makes it essential to study in the Rwandan context where there is no available data regarding the effect of hormonal contraceptives on blood glucose regulation.

2.3.5. DMPA and systemic inflammation

Several published studies reported the association of combined hormonal contraceptives, primarily oral contraceptives, with the development of low-grade inflammation. For instance, the Williams et al. study reported a ratio change in CRP of 1.52 with a confidence interval of 1.27 and 1.82 CRP in young women using oral contraceptives compared to non-users [134]. In a randomized control trial with six months follow up, the hormone replacement therapy in

postmenopausal women reported an 84% increase in CRP in the study group compared to the group users of a placebo, a finding suggesting that hormonal contraceptives affect CRP increase independently of age [130].

Surprisingly, the literature provides evidence that oral contraceptives influence CRP production by hepatocytes differently than the usual inflammatory processes [135]. The suggestion that this effect is because combined oral contraceptives pass through digestive pathways and reach the liver seems unclear, as the same scenario happened in users of vaginal combined hormonal contraceptives [136]. These findings bring a hypothesis that the problem is not the mode of administration but the issue of combined hormonal formulations. Therefore, one can think that injectables, which are progesterone-only contraceptives, are ideal in not affecting CRP production; otherwise, there could be interfering factors that need further investigation.

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Chapter Three: Prevalence of Central Obesity and its Association with Cardiovascular Risk Factors Among Women of Reproductive Age in Kigali, Rwanda.

Abstract

Background: Central obesity is prevalent in women of reproductive age in Sub-Saharan Africa and has been a major risk factor for metabolic syndrome and cardiovascular diseases. However, few studies have analysed its association with cardiovascular risk factors among those women. This study seeks to assess the magnitude of central obesity and its association with cardiovascular risk factors among women of reproductive age in Rwanda.

Material and methods: the study used a cross-sectional design involving 138 women aged between 15 and 49 years attending selected family planning centres in Kigali. Central obesity was measured through the size of the waist circumference. The adjusted logistic regression analysis with 95% confidence intervals was used to determine the correlates of central obesity. A statistical significance was defined at a p-value <0.05.

Results: Participants mean age was 29.14 ± 6.72, ranging between 18 and 45 years old. The prevalence of central obesity was 48.5%, and it was significantly associated with age (OR=2, 95% CI: 1.24-3.35), alcohol use (OR=5.8, 95% CI: 2.08-16.08), meat consumption (OR=5.3, 95% CI: 1.94-14.63), hypertriglyceridemia (OR= 3.87, 1.02-14.76), and elevated diastolic blood pressure (OR=6.1, 95% CI: 2.80-17.92).

Conclusion and Recommendation: The prevalence of central obesity is relatively high among women of reproductive age, and it is associated with older age, elevated diastolic blood pressure, high triglyceride levels, and meat and alcohol consumption. The study recommends an intensive awareness of health risks associated with central obesity and its associated factors to address the rising risk of cardiovascular diseases in this population.

3.1.Introduction

There is a generalized misconception in the literature that premenopausal women are safe from cardiovascular diseases, thus ignoring the presence of potential cardiovascular risk factors. This delusion results from the existing literature arguing that the high level of oestrogen during reproductive age protects against cardiovascular risk [1, 2]. Consequently, almost all cardiovascular risk assessment studies focused mainly on men and postmenopausal women [3, 4]. However, some research indicates that potential risk factors like smoking habits, high blood pressure, dyslipidemia, diabetes, and central obesity reduce estrogen protection in young women [5, 6]. More recent evidence has revealed an equal risk for men and women as long as they are exposed to the same risk factors [2, 7].

Risk factors for cardiovascular diseases can fall into two categories. The first is lifestyle-related factors, including tobacco use, alcohol consumption, physical inactivity, and an unhealthy diet rich in fats and carbohydrates [8]. The second is the metabolic factors, including abdominal obesity, high blood pressure, abnormal blood lipids, systemic inflammation, microalbuminuria, and diabetes mellitus [9]. Central obesity, defined as excessive abdominal fat deposition, is a critical determinant of a metabolic syndrome characterized by a constellation of glucose intolerance, hyperinsulinemia, and dyslipidemia [10]. It is an associated factor of cardiovascular diseases, and many other metabolic diseases like diabetes, hypertension, microalbuminuria, atherosclerosis, arthritis, and cancers [11].

Reports by the World Health Organisation (WHO) have consistently indicated obesity as a global epidemic due to its increase at an accelerated rate in both developed and developing countries [12]. It is highly associated with the nutrition transition, accelerated urbanization, and technological advances encouraging sedentary lifestyles [13]. It prevails in both young and adults, affecting both males and females. There is evidence in various studies in African countries that central obesity is highly prevalent in women compared to men of the same age. For instance, a study conducted in Kenya reported the prevalence of central obesity as 68.3% in women and 21.1% in men [14]. In Tanzania, a study indicated a prevalence of 35.14% in women and 6.89% in men [15]. Also, a study conducted in Togo reported a prevalence of 53.6% in women and 8.4 % in men [16]. This high prevalence of central obesity in women calls for special attention as it represents this population's increased risk of cardiovascular diseases (CVD). Similarly, reports from developed countries reveal that CVD ranks top in causing high mortality and morbidity in women compared to men of the same age [17].

The findings show the need for more studies about cardiovascular risk factors in women to inform efforts to address this rising health threat in this population. We argue that central obesity needs attention, among other factors, because it remains central to developing CVDs. Awareness about the extent to which central obesity exists is critical in managing and preventing CVDs. However, there is a dearth of studies about the prevalence of central obesity and its association with cardiovascular risk factors among women of reproductive age in developing countries and Rwanda. Therefore, this study contributes to bridging that gap, using a sample selected among women of reproductive age in Rwanda.

3.2.Material and methods

3.2.1. Study setting and design

The study used a cross-sectional study design, and the data were collected from September to November 2020 among women of reproductive age recruited from two family planning centres in Kigali, Rwanda. The centres were selected because they were among the centres we expected to have enough women of reproductive age. The selected centres are among the few publicly managed centres mainly segregated to offer free-of-charge family planning services in Kigali city. Each of the selected centres receives approximately 30 to 40 women of reproductive age daily.

3.2.2. Sample size and sampling procedure

The study involved 138 women of reproductive age estimated using the formula designed for cross-sectional studies [18]. The sample was calculated referring to the prevalence of central obesity (35%) previously reported in women living in Dodoma, Tanzania [15], assuming 95% as a significance level with a precision of 8%. A convenient sampling procedure was used; participants were recruited as they arrived at the centre (provided that they had signed the consent form) until the required number was reached. At the centre, the research team had time to talk to potential participants, explaining the purpose and importance of the study, and they were given time to ask questions where they might need clarification. Those who fulfilled the earlier indicated requirements and were willing to participate were recruited. Based on participants' self-report, the study included only non-pregnant physically healthy women without a history of chronic diseases like diabetes, heart diseases, kidney diseases, pronounced hypertension, and HIV, as these diseases are more likely to be associated with heart diseases.

3.2.3. Data collection process and measurements

We used interviews to collect data on the bio-demographic characteristics of the study participants, including age, parity, breastfeeding status, education level, physical activity, dietary intake, smoking habit, and alcohol consumption, and we recorded data on their blood pressure and waist circumference. Also, we drew blood samples to test lipid profile, glycated haemoglobin, and inflammatory markers.

Data on the variable "age" was recorded in years, referring to the last birthday, while the data on breastfeeding status, smoking habit, alcohol, and coffee consumption were recorded as binary (Yes/No). For the variable "parity," the study participants were asked about the number of live births they have ever had and were grouped into three categories: primiparous for those with one live birth, multiparous for those with two to four live births, and grand multiparous for those with five and more live births. None of the participants reported to be nulliparous (no live births). For the variable "education level," study participants were asked what level of education they have completed regarding the education system in Rwanda. The variable was later analysed as "less than secondary, and secondary or tertiary."

The data on physical activity was collected by asking the study participants to describe their daily activities, whether they spend much time sitting, like working in an office, shop, or workshop, whether they have time for sports, or whether their daily occupation makes them move and spend energy. Then, we used the information to classify them as "sedentary and non-sedentary." Sedentary individuals were those who reported spending much of their time sitting, such as those working in the office, boutique, sewing/handcraft workshops, and housewives, while non-sedentary were those practicing farming activities, doing mobile business carrying things by head or hands, working at construction sites and those in security agencies.

Finally, for the data on dietary intake, the study participants were requested to report the frequency of taking milk, fruits, meat, and vegetables per week in reference to an average of the previous four weeks. The frequencies of taking milk, fruits, and meat were relatively low, so the variables were analysed as "No at all and once per week or more." However, for vegetables, the frequency was relatively high, and the variable was analysed as "three times or bellow, versus four times or higher."

Blood pressure was measured according to the International Society of Hypertension guidelines. [19] using a digital blood pressure monitor. Measurement was taken after 10 minutes of rest upon the participant's arrival and repeated twice at 5-minute intervals while the individual's pressure was defined as the average of two readings. Participants were classified as having normal blood pressure for SBP ≤ 130mmHg and DBP ≤ 85mmHg and elevated blood pressure for SBP > 130 and DBP > 85 mmHg [19].

Waist circumference measurements were done with a tape measure at the level of the narrowest point between the lowest rib and the iliac crest. The measurement was taken on the skin with arms relaxed at the sides and the end of a normal exhalation. Central obesity was defined according to the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) classification, which defines central obesity as a waist circumference ≥ 88 cm [20].

Fasting blood samples were drawn for lipid profile (Triglycerides: TG, low-density lipoprotein cholesterol: LDL-c, high-density lipoprotein cholesterol: HDL-c, and total cholesterol: TC), inflammatory markers (high sensitivity-C reactive protein: hs-CRP), and blood sugar (glycated haemoglobin) determination. Blood samples were analysed using the Abbott ARCHITECT ci4100 analyser (Abbott Diagnostics Inc., Lake Forest, IL, USA). After laboratory analysis, lipid ratios TC/HDL and LDL/HDL were calculated.

The reference values for lipid profile components were ≤5.2 mmol/L for total cholesterol, ≤ 3.4 mmol/L for LDL, HDL ≥1.03 mmol/L, and TG ≤ 1.7 mmol/L. The TC/HDL ratio > 3.5 indicates a high risk of cardiovascular disease, while a value below 3.5 indicates a low risk. The same LDL/HDL ratio > 2.5 indicates high risk, while a value below 2.5 indicates low risk [21]. Blood sugar was classified into two categories: HbA1C > 5.7% indicates normal sugar, while a value ≥ 5.7 % indicates elevated sugar [22]. For hs-CRP, a value ≤ 3 mg/L indicated low risk, and a value greater than three mg/L indicated a high risk of cardiovascular disease [23].

3.2.4. Statistical analysis

Central obesity was considered the dependent variable, while lipid profile components, lipid ratios, blood pressure, blood sugar, age, dietary intake, parity, breastfeeding status, alcohol consumption, education, and physical activity were independent variables. Data were described as mean ± standard deviation and percentages and presented in tables. The chi-square test was

used to assess whether there is an association between central obesity and baseline characteristics. The variables that showed a significant association were used in the adjusted logistic regression model, with 95% confidence intervals, to determine the correlates of central obesity.

3.3.Results

Table 3.1 shows the baseline characteristics of the study participants. The mean age was 29.1 ± 6.7, with ages ranging between 18 and 45 years old, and 29.7% had attained secondary or tertiary education. Over half (55.8%) of participants were multiparous, and 66.7% were breastfeeding. Concerning diet, few took alcohol (29.0%) and coffee (21.0%), 71.0% reported they eat meat at least once a week, 39.13% said they eat vegetables less than four times a week, and 73.2 % reported they eat fruit at least once a week, while those taking milk at least once per week were 71.6%. The assessment of the physical activity indicated that 75.4 % of participants were living a sedentary lifestyle. None of the participants reported a smoking habit.

Table 3.1: Basic characteristics of the study participants

Variable	Frequency (N=138)	Percentage/mean ± SD
Age	138 (Min. 18; Max. 45)	29.1 ± 6.7
Education attainment		
Less than secondary	97	70.3
Secondary or Tertiary	41	29.7
Parity (number of live births)		
1	52	37.7
2-4	77	55.8
≥5	9	6.5
Breastfeeding		
No	46	33.3
Yes	92	66.7
Physical activity		
Sedentary	104	75.4
Non-sedentary	34	24.6
Taking alcohol		
No	98	71.0
Yes	40	29.0
Taking coffee		
No	109	79.0
Yes	29	21.0
Eating meat		
Not at all	40	29.0
≥ 1 time per week	98	71.0
Eating vegetables		
< 4 times per week	54	39.2
≥4 times per week	84	60.8

Eating fruits		
Not at all	37	26.8
≥ 1 time per week	101	73.2
Taking milk		
Not at all	39	28.4
≥ 1 time per week	99	71.6

Table 3.2 shows the prevalence of central obesity according to all variables. 67 out of 138 (48.5%) participants had central obesity. The prevalence was significantly high in participants aged 30 years (66.7%, p= 0.001), participants with high (>3 mg/dl) hs-CRP (71.8%, p=0.001), individuals with elevated SPB (74.1%, p=0.003), and those with elevated DBP (75%, p<0.001). The prevalence was also significantly high among alcohol consumers (77.5%, p<0.001), participants who do not use coffee (56; p=0.001), participants who eat meat at least once a week (59.18%, p <0.001), those with elevated cholesterol (68%, p=0.032, those with elevated triglyceride levels (76.2%, p=0.006), and those with a high LDL/HDL ratio (60.4%, p=0.028).

Table 3.2: Chi-square test indicating the prevalence of central obesity according to other cardiometabolic risk factors

Variable	**Total sample (N=138) n(%)**	**Non-obese (N=71) n(%)**	**Obese (N=67) n(%)**	**p-value**
Age in years				
≤24	41(29.7)	27(65.8)	14(34.1)	0.001*
25-29	37(26.8)	24(64.9)	13(35.1)	
≥30	60(43.5)	20(33.3)	40(66.7)	
hs-CRP in mg/L				
≤3	99(71.7)	60(60.6)	39(39.4)	0.001*
>3	39(28.3)	11(28.2)	28(71.8)	
SBP in mmHg				
≤130	111(80.4)	64(57.7)	47(42.3)	0.003*
>130	27(19.6)	7(25.9)	20(74.1)	
DBP in mmHg				
≤ 85	102(73.9)	62(60.8)	40(39.2)	<0.001*
>85	36(26.1	9(25.0)	27(75.0)	
HbA1C in %				
<5.7	117 (84.7)	61(52.1)	56(47.9)	0.703
≥5.7	21 (15.2)	10(47.6)	11(52.4)	
TC in mmol/L				
< 5.2	113 (81.9)	63(55.7)	50(44.2)	0.032*
≥5.2	25 (18.1)	8(32.0)	17(68.0)	
LDL in mmol/L				
< 3.4	112(81.2)	62(55.4)	50(44.6)	0.057
≥ 3.4	26 (18.8)	9(34.6)	17(65.4)	

HDL in mmol/L				
≥ 1.03	98 (71.0)	50(51.0)	48(49.0)	0.875
< 1.03	40 (29.0)	21(52.5)	19(47.5)	
TG in mmol/L				
< 1.7	117 (84.8)	66(56.4)	51(43.6)	0.006*
≥1.7	21(15.2)	5(23.8)	16(76.2)	
TC/HDL				
< 3.5	58 (42.0)	35(60.3)	23(39.7)	0.075
≥ 3.5	80 (58.0)	36(45.0)	44(55.0)	
LDL/HDL				0.028*
< 2.5	85(61.6)	50(58.8)	37(41.2)	
≥2.5	53 (38.4)	21(39.6)	30(60.4)	
Eating meat				
No	40(29.0)	31(77.5)	9(22.5)	<0.001*
Yes	98(71.0)	40(40.8)	58(59.2)	
Alcohol use				
No	98(71.0)	62(63.3)	36(36.7)	<0.001*
Yes	40(29.0)	9(22.5)	31(77.5)	
Taking milk				
No	39(28.3)	24(61.5)	15(38.5)	0.137
Yes	99(71.7)	47(47.5)	52(52.5)	
Using coffee				
No	109(79.0)	48(44.0)	61(56.0)	0.001*
Yes	29(21.0)	23(79.3)	6(20.3)	
Eating fruit				
Not at all	37(26.8)	18(48.6)	19(51.3)	0.690
≥ 1 time per week	101(73.2)	53(52.5)	48(47.5)	
Eating vegetables				
< 4 times per week	54(39.1)	25(46.3)	29(53.7)	0.331
≥ 4 times per week	84(60.9)	46(54.8)	38(45.2)	
Parity (number of live births)				
Primiparous (1 birth)	52(37.7)	31(59.6)	21(40.4)	0.101
Multiparous (2-4 births)	77(55.8)	38(49.4)	39(50.6)	
Grand multiparous (≥ 5births)	9(6.5)	2(22.2)	7(77.8)	
Breastfeeding				
No	46(33.3)	22(47.8)	24(52.2)	0.547
Yes	92(66.7)	49(53.3)	43(46.7)	
Physical activity				
Sedentary	104(75.4)	55(52.9)	49(47.1)	0.555
Non-sedentary	34(24.6)	16(47.1)	18(52.9)	
Education level				
Less than secondary	97(70.3)	54(55.7)	43(44.3)	0.127
Secondary or tertiary	41(29.7)	17(41.5)	24(58.5)	

Note: *means statistically significant.

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; HbA1C, glycated hemoglobin

Similarly, the prevalence was high among individuals with a high TC/HDL ratio (55%; p=0.075) and LDL levels (65.4%; p<0.057; however, it did not reach statistical significance. Moreover,

the prevalence was high in participants who did not drink coffee (56.9%, p= 0.001). Also, Table 2 shows that eating fruits and vegetables, taking milk, parity, and breastfeeding were not associated with obesity. Similarly, physical activity and education level were not associated with obesity.

Table 3.3 indicates the results from logistic regression analysis stratified by obesity categories and adjusted for age, total cholesterol, low-density lipoprotein cholesterol, lipids ratios, triglycerides, hs-CRP, SBP, DBP, eating meat, coffee, and alcohol use. The results show that the odds of being obese in participants aged 30 years and above is three times (95% CI: 1.11-9.48) that of participants below 25 years. The odds of obesity were greater than four times (95% CI: 1.47-16.13) higher in individuals with elevated DBP than those with normal DBP. Eating meat is associated with obesity four times (95% CI: 1.49-12.59) higher than those who do not eat meat. The risk of obesity for those who use alcohol is more than five times (95% CI: 1.91-16.20) higher than that of those who do not consume alcohol. The odds of being obese for individuals with hypertriglyceridemia are four times (1.02-14.76) higher than those with normal blood triglyceride levels.

Table 3.3: Results of the logistic regression analysis of the association between central obesity and other cardiometabolic risk factors

	Unadjusted model			**Adjusted model**		
Variable	**Odds ratio**	**95% CI**	**P-value**	**Odds ratio**	**95% CI**	**P-value**
Age (in years)						
≤24	1	-	-	1	-	-
25-29	1.04	0.41-2.66	0.802	1.56	0.47-5.22	0.469
≥30	3.85	1.66-8.93	0.002*	3.25	1.11-9.48	0.031
SBP(mmHg)						
≤130	1	-	-	1	-	-
>130	3.89	1.52-9.95	0.005*	1.78	0.47-6.72	0.392
DBP (mmHg)						
≤85	1	-	-	1	-	-
> 85	4.65	1.98-10.91	0.001*	4.87	1.47-16.13	0.010*
TC in mmol/L						
<5.2	1	-	-	1	-	-
≥5.2	2.68	1.07-6.71	0.036	0.84	0.08-8.77	0.885
TG in mmol/L						
< 1.7	1	-	-	1	-	-
≥ 1.7	4.14	1.42-12.06	0.009*	4.12	1.02-14.76	0.047*
LDL in mol/L						
<3.4	1	-	-	1	-	-
≥3.4	2.34	0.96-5.70	0.061	0.77	0.7-7.8	0.831

TC/HDL						
≤ 3.5	1	-	-	1	-	-
> 3.5	1.86	0.94-3.69	0.076	0.75	0.21-2.70	0.756
LDL/HDL						
≤ 2.5	1	-	-	1	-	-
> 2.5	2.18	1.08-4.38	0.028*	2.12	0.51-8.20	0.301
Hs-CRP in mg/L						
≤3	1	-	-	1	-	-
>3	3.92	1.75-8.76	0.001*	2.33	0.79-6.87	0.123
Eating meat						
No	1	-	-	1	-	-
Yes	4.99	2.15-11.62	0.000*	4.34	1.49-12.59	0.007*
Alcohol						
No	1	-	-	1	-	-
Yes	5.93	2.54-13.85	0.001*	5.57	1.91-16.2	0.002*
Using coffee						
No	1	-	-	1	-	-
Yes	0.21	0.08-0.54	0.001	0.44	0.13-1.51	0.193

Note: * means statistically significant.
Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; CI, confidence interval.

3.4.Discussion

This study assessed the magnitude of central obesity and its association with other cardiovascular risk factors in women of reproductive age in Kigali, Rwanda. The results inform the health policymakers, practitioners, and individuals of the need to address the increase of central obesity among women of reproductive age to address the high prevalence of maternal cardiovascular diseases and death.

The findings reveal that the prevalence of central obesity among women of reproductive age was 48.5%, and it was associated with older age, frequent consumption of meat and alcohol, high diastolic blood pressure, and higher blood triglycerides levels. This prevalence is relatively high compared to that of 35% reported in Munyogwa et al. study conducted in Tanzania [15]; however, below that reported in the Mohamed et al. study (68.3%) done in Kenya [14] and by Yayehd et al. study (53.6%) in Togo [16]. The difference could be explained on the one hand by the different cut-off values in defining central obesity. In our study, and the Munyogwa et al. study, central obesity was defined according to NIH guidelines [24] as a waist circumference greater or equal to 88 cm, while Mohamed et al. and Yayehd et al. studies defined it according to the WHO guidelines [25] as a waist circumference greater or equal to 80 cm. On the other hand, it could be due to the differences in each study's settings and the sampled women's

associated lifestyle. Our study shares the high prevalence of central obesity with the studies conducted in Kenya and Togo [14, 16]. The studies were conducted in similar urban settings where most participants were housewives or did passive work such as working in the office, boutique, and sewing/handicraft workshops where they spent much of their time sitting in a condition that pushed them to have a sedentary lifestyle.

Central obesity has been reported in many previous studies to be associated with low physical activity [21, 25]. In contrast, our data showed no association between physical activity and central obesity. The difference could be due to different criteria used in defining the categories of physical activity as we based our criteria on the types of occupation, which we used to classify the participants as sedentary versus non-sedentary instead of counting the times an individual is engaged in an organized physical exercise as some studies did. This approach could be possible because none of the respondents reported engaging in organized sports. Our approach to considering the occupation types was equally adequate since it was clear whether a given activity was energy-demanding. Activities such as working on construction sites or doing hawking activities were classified as non-sedentary, and non-energy demanding, such as working in a kiosk or in-house activities, were classified as sedentary.

Central obesity was consistently associated with lifestyle factors, including fats-containing foods [26] and not eating vegetables regularly [27]. In part, this is consistent with our findings that central obesity is associated with regular consumption of meat and inconsistent with regularly eating vegetables. Our findings reveal a high prevalence of central obesity in alcohol consumers compared to non-consumers, which agrees with findings from other studies [28, 29, 30].

Previous studies have revealed that central obesity is associated with many metabolic diseases, such as dyslipidemia, hypertension, diabetes, and albuminuria [31], and this association becomes more substantial as individuals age [16]. Even though our participants were relatively young (18-45), the results indicated a statistically significant association between central obesity and an individual's age. This finding is consistent with various prior studies. [26, 32]

For women of childbearing age, we hypothesized that breastfeeding would be a factor associated with central obesity. We based our hypothesis on the fact that women need to eat more during breastfeeding to get enough milk for their babies. However, the results indicated no association between breastfeeding and central obesity, and this is similar to other previous studies [27, 28].

This implies that the quality of food ingested may play more of a role in inducing central obesity than breastfeeding.

The literature has documented the association of central obesity with markers of cardiovascular risks such as hypertension [33], consistent with our findings. The odds of obesity were more than four times higher in individuals with elevated diastolic blood pressure than those with normal diastolic blood pressure. The literature also indicated the association of central obesity with dyslipidemia, a potential risk factor for coronary heart disease [34]. It agrees with our findings as our data indicated a significant association between central obesity and hypertriglyceridemia, as reported in different studies [31, 35].

This study is among the pioneering research in Rwanda and sub-Saharan Africa that assessed the prevalence of central obesity and examined its association with cardiovascular risk factors in women of reproductive age. We hypothesize that Africa, which is undergoing rapid epidemiologic and nutritional transition [36], needs more studies in this area to inform the public health efforts that address the rise of NCDs and cardiovascular diseases in particular. The strength of this study lies in combining variables like dietary intake, metabolic, and lifestyle factors to discuss the prevalence of central obesity. However, the study has some limitations, including the fact that it was conducted in urban and peri-urban settings, limiting the generalization to the whole population. Another limitation may lay in the study's design as it was cross-sectional and did not allow the examination of causal relationships. Thus, further studies with a prospective approach will be helpful in the investigation of a causal relationship.

3.5. Conclusion

It is pretty established from the literature that cardiovascular diseases are currently the significant causes of morbidity and mortality in sub-Saharan Africa and Rwanda in particular. The study concludes that central obesity exists and is relatively high in young women in Kigali, and it is associated with older age, elevated blood triglycerides levels, elevated diastolic blood pressure, regular consumption of meat, and alcohol use. Therefore, the study recommends that health policymakers and public health officials establish strategies to manage modifiable risk factors like high blood pressure, alcohol use, physical exercise, and eating habits to reduce the risk of cardiovascular diseases in young women. Personal lifestyle change such as limiting alcohol consumption, reducing consumption of sugary beverages, processed foods, and foods

high in saturated and trans fats, and regular monitoring of waist circumference and blood pressure is also recommended.

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Chapter Four: Effect of Depot Medroxyprogesterone Acetate (DMPA) Injectable Contraceptive on Cardiometabolic Risk Factors Among Women of Reproductive Age in Kigali, Rwanda.

Abstract

Background: Depo medroxyprogesterone acetate (DMPA) injectable contraceptive is a widely used hormonal method that offers reversible and effective birth control for women worldwide. However, various studies have raised concerns regarding its potential association with increased cardiovascular disease risk, attributed to its influence on cardiometabolic risk factors. While previous studies have primarily focused on lipid profile, weight gain, blood pressure, and blood glucose, important aspects such as central obesity, glycated hemoglobin, and systemic inflammation have remained under-investigated. Thus, this study aimed to explore the influence of DMPA injectable contraceptives on lipid panel, glycated hemoglobin, visceral fat deposition, blood pressure, and inflammatory markers among women of childbearing age in Rwanda.

Material and methods: The study was a prospective cohort and recruited an equal number of DMPA users (45) as the study group and users of non-hormonal (NH) contraceptives (45) as the control group. We recruited participants from two selected family planning centers in Kigali and collected data at baseline, six months, and 12 months. We measured the waist circumference, blood pressure, lipids profile (HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, TC: Total cholesterol, and TG: triglycerides), glycated hemoglobin, and hs-CRP (high sensitivity C-reactive protein). We run the Mann-Whitney to compare the median change between DMPA and NH users. Data were presented as median (interquartile range), with a significance level of 5%.

Results: After a follow-up of twelve months, DMPA users experienced a significant increase in waist circumference, TG, LDL, TC, hs-CRP, and glycated hemoglobin ($p<0.05$), whereas they experienced a significant decrease in HDL than controls ($p<0.05$). However, our data did not indicate a significant difference in blood pressure changes between DMPA and NH users ($p> 0.05$).

Conclusion: The effect of DMPA injectable on cardiometabolic parameters was minimal in the first six months of use; however, it manifested statistically significant at 12 months of follow-up. It is recommended to initiate a follow-up with users at least 12 months of use and repeat every six months to check the status of cardiometabolic markers and intervene where necessary.

4.1. Introduction

DMPA is a widely used hormonal contraceptive method preferred by many women worldwide, especially in Sub-Saharan Africa and more so in East Africa, including Rwanda [1, 2]. However, previous studies highlighted the concerns about its potential impact on cardiometabolic risk factors that contribute significantly to the development of cardiovascular disease (CVD) [3, 4, 5], the main cause of long-duration illness and death globally [6].

DMPA significantly affects cardiometabolic risk factors that mostly lead to cardiometabolic disease. It was reported to be associated with body weight increase and body fat deposition, especially abdominal fat [7], a major risk factor for cardiovascular disease [8]. Abdominal fat deposition is highly associated with cardiovascular events like heart failure, coronary heart diseases, and atrial fibrillation [9]. DMPA was also reported to be associated with high calcium levels [10], a factor that reduces bone density and is associated with a high risk of vascular diseases and death [11]. Furthermore, it is associated with dyslipidemia [12, 13], also documented to be a major risk factor and predictor of atherosclerotic cardiovascular diseases such as coronary artery disease, stroke, and peripheral vascular diseases [14]. Also, various studies have consistently reported an association between DMPA and an elevated risk of venous thromboembolism [15, 16].

Traditionally, cardiovascular disease (CVD) was a men's issue, and available documentation about the disease's characteristics and treatment mainly focused on men [17]. Though the incidence of CVD is still high in men, there is a concern that it is also increasing in young women and appears to be the leading cause of death in this group globally, particularly in developing countries [18]. Recent evidence indicates an equal risk of cardiovascular disease for men and women, given that they have the same risk factors [19, 20]. However, women who take hormonal contraceptives, mainly DMPA injections, have additional risks associated with their close association with these potential cardiometabolic risk factors.

The evidence that DMPA injectable greatly affects major cardiometabolic risk factors that put users at high risk of CVD suggests the necessity of follow-up for users. However, further research is needed to fully characterize this effect as previous studies focused on lipid profile, weight gain, blood pressure, and blood glucose, leaving central obesity, glycated haemoglobin, and systemic inflammation under-investigated. At the same time, these are potential

cardiometabolic risk factors [9, 21, 22]. Further research considering these additional factors sounds crucial to widely characterize this effect to guide the decision to establish this follow-up.

Therefore, the purpose of this study was to evaluate the effect of Depot Medroxyprogesterone Acetate (DMPA) compared to non-hormonal methods on cardiometabolic risk parameters among childbearing-age women in Rwanda over one year. Specifically, we assessed changes in waist circumference, lipid profile, blood pressure, glycated hemoglobin, and systemic inflammation in DMPA users compared to NH users. By examining the impact of DMPA on cardiometabolic health in a Rwandan context, this study would contribute to the existing knowledge base and provide appreciated insights for healthcare providers and policymakers in making informed decisions regarding routine follow-up with users to ensure their better health and well-being.

4.2. Material and methods

4.2.1. Study design and setting

The study was a prospective cohort study. We collected data from each participant (women of reproductive age (15-49 years) at baseline, six months, and 12 months later. The design helped to compare the effect of hormonal contraceptive use over a prolonged period. The data were collected in selected family planning centers in Kigali. The chosen centers were among the limited number of public facilities that provide cost-free family planning services within Kigali city. Each center serves 30 to 40 women on average seeking family planning services.

4.2.2. Sample size and sampling procedure

The study estimated the sample size based on the following formula:

$$\mathbf{N= \{2x[}z(1-a/2) + z(1-b)\mathbf{]^2 x \sigma^2\} / \mu_d^2}$$

Where:

N is the number of individuals needed in each group

z(1-a/2) = value of the standard normal distribution corresponding to a significance level of 0.05 (1.96 for a 2-sided test at the 0.0 5 levels)

z(1-b) = value of the standard normal distribution corresponding to the desired level of power (1.28 for the power of 90%)

$\sigma = \sqrt{[(SD1)^2 + (SD2)^2 / 2]}$ is the standard deviation for both populations

$\sigma = \sqrt{[(0.91)^2 + (0.62)^2 / 2]} = 0.78$ mmol/L

μ_d = is the difference in the mean of the two groups

This formula is used to compare means between two groups [23], and for this study, the aim was to compare means between two groups of people with dyslipidemia as the primary variable. We used the reference results of a study conducted in Ghana, which estimated the mean total cholesterol of 3.35±0.62 mmol/L in non-hormonal contraceptive users and 4.07±0.91mmol/dl in hormonal contraceptive users. The study was used as a reference because it is the most recent study and used a sample with characteristics similar to the Rwandan context. Using this procedure, we estimated a sample of 25 individuals in each group (hormonal and non-hormonal contraceptive users). Considering four confounding factors (alcohol, physical inactivity, diet, and education level), the sample became 32 participants for each group. The sample size was 45 participants for each group, assuming a non-response rate of 20%.

The sample included two groups of participants, as earlier indicated. These were women wishing to initiate injectable hormonal contraceptives as a study group and non-hormonal users as a control group. We identified participants from family planning programs of two health centres in Kigali. Conveniently, all available participants who met inclusion criteria and consented to participate were consecutively recruited until the study reached the required sample.

4.2.3. Inclusion criteria

Participants in the study group had to be healthy, non-pregnant women whose choice of contraceptive method was injectable (DMPA) and without any other hormonal contraceptive method within six months before baseline. To be a control participant, a woman had to be physically healthy without pregnancy, whose choice of contraception was the non-hormonal (NH) method, and without a history of hormonal contraceptive use within six months before the baseline.

4.2.4. Exclusion criteria

Based on personal and family history, participants with chronic conditions like HIV, chronic liver diseases, cancer, diabetes, hypertension, chronic renal failure, and heart diseases were excluded from the study as these conditions were reported to be associated with heart diseases**.** Baseline data allowed us to exclude individuals with dyslipidemia, abdominal obesity, systemic inflammation, hyperglycemia, and high blood pressure. The study also excluded smokers; however, none of the respondents reported a smoking habit.

4.2.5. Data collection

Data were collected three times: at baseline, at six months, and after twelve months. Baseline data were corrected from September to November 2020, the second from April to May 2021, and the third from November to October 2021. A structured questionnaire (Appendix D) was used to record participants' waist circumference, blood pressure, and bio-demographic characteristics of study participants, such as age, education attainment, alcohol use, parity, breastfeeding, and diet (the consumption frequency of meat, milk, fruits, and vegetables).

The age variable was counted in years and categorized as 24 years or less, 25-29 years, and 30 years or more, while education attainment was categorized as primary or less and secondary or tertiary. We recorded data about breastfeeding and the use of alcohol in binary format, indicating a simple "Yes" or "No" response. To record data on parity, we asked participants to disclose the total number of live births they had ever had and were grouped into three categories: primiparous (one live birth), multiparous (two to four live births), and grand multiparous (five and more live births).

We measured blood pressure following the International Society of Hypertension guidelines [24]. Upon the participant's arrival, measurements were recorded following 10 minutes of rest. These measurements were repeated twice, with a 5-minute interval between each measurement. The individual's blood pressure was then determined by calculating the average of the two recorded readings. In addition, waist circumference was measured using a tape measure, specifically at the narrowest width between the lowest rib and the iliac crest. This measurement was taken on the bare skin, with the participant's arms resting naturally at their sides and at the end of a normal exhalation.

In addition, participants were provided fasting blood samples to assess their lipid profile components, including TG, LDL, HDL, and TC. Furthermore, the blood samples were tested for hs-CRP and glycated hemoglobin (HbA1C) levels. The blood samples were analyzed using the clinical chemistry analyzer named Abbott ARCHITECTci4100. This clinical chemistry analyzer is an automated machine that detects lipids using enzymatic and colorimetric methods and expresses the results in mmol/L. It detects hs-CRP by immunoassay method and expresses it in mg/L, while it detects the HbA1C by enzymatic method and expresses it in %. For both the study group and controls, we took their phone contacts for regular calls to remind them about the study.

Table 4.1: Reference values for cardiometabolic risk parameters [25, 26**,** 27]**.**

variable	**Risk associated**
WC (in cm)	
≤88	Low risk
>88	High risk
HDL (in mmol/L)	
≥1.04	Low risk
<1.04	High risk
hs-CRP (in mg/dL)	
<1	Low risk
1-3	Moderate risk
>3	High risk
TG (in mmol/L)	
< 1.7	Low risk
≥1.7	High risk
HbA1C (in %)	
<5.7	Low risk
≥5.7	Increased risk

4.2.6. Statistical analysis

We analyze data using Statistical Package for the Social Sciences (SPSS version 21). Data distribution analysis for all studied variables in all conditions indicated that none respected normal distribution following the Shapiro-Wilk Test. Accordingly, non-parametric statistical

tests were used to compare the data at each time point. To analyze the within-group changes, we ran the Wilcoxon signed-rank test, and the between-group changes were analyzed using the Mann-Whitney for continuous variables and the Chi-square for categorical variables. Data were presented as percentages or median (IQR), and the significance level was 5%.

4.3. Results

The study started with 45 participants in each group. At six months, one DMPA user got pregnant due to poor adherence; another claimed bleeding problems and quit the method. At 12 months, the other three DMPA users left the study for an unknown reason. Only 40 DMPA users completed 12 months of follow-up. Out of 45 controls, only 39 completed 12 months of follow-up; at six months, all controls were reported, while at 12 months, three controls desired to get pregnant, and 3 changed the method and adhered to hormonal methods.

Table 4.2 displays the results of the bio-demographic characteristics of the study participants. The results indicate no difference in age; P=0.246, breastfeeding; P=0.057, parity; P=0.082, alcohol use; P= 0.054, meat; P= 0.063 and fruit consumption; P=0.624 categories between DMPA and NH methods users. The results, however, indicated that 74% of all participants did not reach secondary school, with a high percentage (85%) of DMPA users than in the control group (62.5%); p=0.015. Also, 62% of all participants reported eating vegetables more or equal to four times a week, with a higher percentage in NH users (75.6%) than in DMPA users (48.9); P=0.009. Subsequently, 74% of all participants reported they took milk at least once per week, with a higher percentage in NH users (84%) than in the DMPA group (64%); P=0.030.

Table 4.2: Bio-demographic characteristics of study participants

Parameters	Categories	DMPA group N=45 n(%)	NH users N=45 n(%)	P-value
Age (in years)	≤24	17(37.8)	10(22.2)	0.246
	25-29	12(26.7)	13(28.9)	
	≥30	16(35.6)	22(48.9)	
Education attainment	Less than secondary	40(85.11)	27(62.49)	0.015*
	Secondary or tertiary	7(14.89)	16(37.21)	
Breastfeeding	Yes	37(82.2)	29(64.4)	0.057
	No	8(17.8)	16(35.6)	
Parity	primiparous	20 (44.4)	15(33.3)	0.082
	Multiparous	24(53.3)	23(51.1)	
	Grant multiparous	1(2.2)	7(15.6)	
Alcohol use	Yes	16(34.04)	7(30.43)	0.054
	No	31(65.96)	36(53.73)	
Eating meat	Not at all	17(37.8)	9(20)	0.063
	At least once a week	29(62.2)	36(80)	
Eating vegetables	< 4 times a week	23(51.1)	11(24.4)	0.009*
	≥ 4 times a week	22(48.9)	34(75.6)	
Eating fruits	Not at all	12(26.7)	10(22.2)	0.624
	At least once a week	33(73.3)	35(77.8)	
Taking milk	Not at all	16(35.6)	7(15.6)	0.030*
	At least once a week	29(64.4)	38(84.4)	

*Means that the difference is statistically significant at 5%.
Abbreviations: DMPA-Depot medroxyprogesterone acetate; NH-non-hormonal

Table 4.3. indicates the Wilcoxon signed rank test results comparing changes in cardiometabolic risk parameters within DMPA users. From baseline to six months, the results indicated the statistically significant median change in some parameters such as waist circumference, HDL, LDL, TG, and HbA1C; P<0.05. Except for HDL, which shows a clinically significant decrease in the median, other parameters indicated a non-clinically significant increase in the median. Comparing the sixth and twelve months' results, all parameters except glycated hemoglobin indicated statistically significant median changes, P<0.05, with HDL continuing to decrease while other parameters increased. There were statistically and clinically significant alterations in HDL, hs-CRP, and WC, while other parameters (TC, LDL, and TG) were statistically significant but not clinically significant. The same, from baseline to twelve months, HDL indicated both statistically and clinically significant decrease; P<0.05, whereas WC and hs-CRP indicated an increase. Other parameters (TC, TG, LDL, HbA1C, SBP, and DBP indicated a statistically significant but not clinically significant.

Table 4.3: The results of the Wilcoxon signed-rank test comparing changes in cardiometabolic risk parameters within DMPA users.

Variable	Baseline MD(IQR)	Six Months MD(IQR)	sig	Six Months MD(IQR)	Twelve Months MD(IQR)	sig	Baseline MD(IQR	Twelve Months MD(IQR)	sig
WC	82 (7)	89 (14)	<0.001	89(14)	93(10)	<0.001	82(7)	93(10)	<0.001
TC	4.01(2.43)	3.79(1.30)	0.699	3.79(1.30)	4.53(1.47)	<0.001	4.01(2.43)	4.53(1.47)	<0.001
HDL	1.26(0.42)	0.66(0.50)	<0.001	0.66(0.50)	0.89(0.41)	0.003	1.26(0.42)	0.89(0.41)	0.001
LDL	2.49(0.94)	2.89(1.30)	0.007	2.89(1.30)	3.55(1.18)	<0.001	2.49(0.94)	3.55(1.18)	<0.001
TG	0.98(0.49)	1.12(0.41)	0.009	1.12(0.41)	1.36(0.77)	0.008	0.98(0.49)	1.36(0.77)	0.003
hs-CRP	0.56(1.53)	0.95(2.42)	0.201	0.95(2.42)	3.78(3.71)	<0.001	0.56(1.53)	3.78(3.71)	<0.001
HbA1C	4.70(0.50)	5.61(0.78)	<0.001	5.61(0.78)	5.50(0.73)	0.127	4.70(0.50)	5.50(0.73)	<0.001
SBP	118(15)	119(19)	0.553	119(19)	126(20)	<0.001	118(15)	126(20)	0.001
DBP	77(11)	76(15)	0.428	76(15)	86(11)	<0.001	77(11)	86(11)	<0.001

Abbreviations: DMPA-Depot medroxyprogesterone acetate; MD-median; IQR-interquartile range; WC-waist circumference (in cm); DBP-diastolic blood pressure (in mmHg); HDL-high-density lipoprotein cholesterol (in mmol/L); LDL-low-density lipoprotein cholesterol (in mmol/L); SBP-systolic blood pressure (in mmHg); TC-total cholesterol (in mmol/L); TG- triglyceride (in mmol/L); HbA1C-glycated hemoglobin (in %); hs-CRP-high sensitivity C-reactive protein (in mg/L).

Table 4.4 shows the Wilcoxon signed rank test results comparing changes in cardiometabolic risk parameters within non-hormonal users. Baseline and six-month results did not indicate the difference in TC, SBP, and DBP; P>0.05. WC, LDL, and HbA1C increased significantly, while HDL, TG, and hs-CRP decreased significantly. From six to twelve months, there was a significant median increase in HDL, LDL, and DBP, while other parameters remained unchanged. The baseline results were compared to twelve months, where WC, HDL, hs-CRP, DBP, and HbA1C increased significantly; however, the increase was not clinically significant. On the contrary, triglycerides indicated a significant decrease.

Table 4.4: The results of the Wilcoxon signed-rank test comparing changes in cardiometabolic risk parameters within Non-hormonal users.

Variable	Baseline	Six Months	sig	Six months	Twelve months	sig	Baseline	Twelve months	sig
	MD(IQR)	MD(IQR)		MD(IQR)	MD(IQR)		MD(IQR)	MD(IQR)	
WC	83 (9)	86 (11)	<0.00	86 (11)	88(11)	0.337	83 (9)	88(11)	<0.001
TC	3.79(2.65)	3.96(1.28)	0.509	3.96(1.28)	4.09(1.30)	0.439	3.79(2.65)	4.09(1.30)	0.097
HDL	1.08(0.26)	0.99(0.22)	0.002	0.99(0.22)	1.19(0.58)	0.001	1.08(0.26)	1.19(0.58)	0.016
LDL	2.63(0.82)	2.89(0.94)	0.006	2.89(0.94)	2.96(1.00)	0.015	2.63(0.82)	2.96(1.00)	0.660
TG	0.99(0.78)	0.82(0.62)	<0.00	0.82(0.62)	0.79(0.79)	0.754	0.99(0.78)	0.79(0.79)	0.002
hs-CRP	1.18(1.67)	1.00(3.09)	0.006	1.00(3.09)	1.77(2.39)	0.426	1.18(1.67)	1.77(2.39)	0.003
HbA1C	4.70(0.45)	4.89(0.98)	<0.00	4.89(0.98	4.92(0.92)	0.872	4.70(0.45)	4.92(0.92)	0.004
SBP	118(15)	119(19)	0.459	119(19)	126(20)	0.780	118(15)	126(20)	0.310
DBP	79(12)	83(10)	0.428	83(10)	87(6)	<0.001	77(11)	87(6)	0.007

Abbreviations: NH-non-hormonal; MD-median; IQR-interquartile range; WC-waist circumference (in cm); DBP-diastolic blood pressure (in mmHg); HDL-high-density lipoprotein cholesterol (in mmol/L); LDL-low-density lipoprotein cholesterol (in mmol/L); SBP-systolic blood pressure (in mmHg); TC-total cholesterol (in mmol/L); TG- triglyceride (in mmol/L); HbA1C-glycated hemoglobin (in %); hs-CRP-high sensitivity C-reactive protein (in mg/L).

The observation of the results in Table 4.5 shows that at baseline, participants were not different in many cardiometabolic markers such as waist circumference (p=0.792), total cholesterol (p=0.735), LDL, (p=0.135), TG (p=0.208), HbA1C (p=0.100), SBP (p=0.184), DBP (p=0.129), and hs-CRP (0.100). However, HDL was significantly greater in DMPA starters 1.26(0.42) than in the control group 1.08(0.26); p=0.008. Also, after six months of follow-up, no difference in WC, hs-CRP, TC, LDL, and SBP changes, p>0.05, were detected between the two groups. However, the changes in HbA1C and TG were more significant in the DMPA than in the NH users, with p<0.05 different from changes in HDL, which were significantly lower in the DMPA users than in NH users, p<0.05. The comparison between the sixth and twelve months' results indicates that DMPA users experienced a significant increase in levels of almost all studied cardiometabolic parameters compared to the NH users. The raised parameters included WC, hs-CRP, TC, LDL, HbA1C, and TG; p<0.05. Differently, HDL indicated a significant decrease in the DMPA users than in the NH users; p<0.05.

Table 4.5: Mann-Whitney analysis to compare changes in cardiometabolic parameters between DMPA and NH over twelve months of follow-up.

Variable	Baseline			After six months			After 12 months		
	DMPA users MD(IQR)	**NH users MD(IQR)**	**Sig**	**DMPA users MD(IQR)**	**NH users MD(IQR)**	**Sig**	**DMPA users MD(IQR)**	**NH users MD(IQR)**	**Sig**
WC	82(7)	83(9)	0.792	89(14)	86(11)	0.216	93(10)	88(11)	<0.001
hs-CRP	0.56(1.56)	1.18(1.67)	0.100	0.95(2.42)	1.0(3.09)	0.386	3.78(3.71)	1.77(2.39)	0.002
HbA1C	4.70 (0.70)	4.70(0.45)	0.100	5.61(0.78)	4.89(0.89)	<0.001	5.50(0.73)	4.92(0.92)	<0.001
TC	4.01(2.43)	3.94(2.65)	0.735	3.79(1.30	3.96(1.28)	0.204	4.53(1.47)	4.09(1.30)	0.006
HDL	1.76(0.42)	1.08(0.26)	0.008	0.66(0.50)	0.99(0.22)	<0.001	0.89(0.41)	1.19(0.58)	<0.001
LDL	2.49(0.94)	2.63(0.82)	0.135	2.89(1.30)	2.89(0.94)	0.913	3.55(1.18)	2.76(1.00)	<0.001
TG	0.98(0.49)	0.99(0.78)	0.208	1.12(0.41)	0.82(0.62)	<0.001	1.36(0.77)	0.79(0.79)	<0.001
SBP	118(15)	122(16)	0.184	119(19)	122(20)	0.279	126(19)	124(14)	0.181
DBP	77(11)	79(12)	0.129	76(15)	83(10)	0.036	86(11)	87(6)	0.590

Abbreviations: DMPA-Depot medroxyprogesterone acetate; NH-non-hormonal; MD-median; IQR-interquartile range; WC-waist circumference (in cm); DBP-diastolic blood pressure (in mmHg); HDL-high-density lipoprotein cholesterol (in mmol/L); LDL-low-density lipoprotein cholesterol (in mmol/L); SBP-systolic blood pressure (in mmHg); TC-total cholesterol (in mmol/L); TG- triglyceride (in mmol/L); HbA1C-glycated hemoglobin (in %); hs-CRP-high sensitivity C-reactive protein (in mg/L).

The results in Table 4.6 compare the proportions of participants with abnormalities in cardiometabolic risk factors during the follow-up period. All participants (DMPA and NH users were free of abnormalities in studied parameters at baseline. After six months of follow-up, there was a significantly higher proportion (76%) of DMPA users than that (56%) of NH users who indicated lower HDL levels, p=0.036. The same was observed for glycated hemoglobin, where the proportion (42%) of DMPA users with higher HbA1c levels was significantly higher than that (6%) of NH users. p<0.001. After twelve months of follow-up, DMPA users indicated a significantly higher proportion of individuals with abnormality in WC (75% in DMPA vs. 46% in NH users), hs-CRP (52% in DMPA vs. 25% in NH users), TC (35% in DMPA vs. 15% in NH users), HDL (67% in DMPA vs. 36% in NH users), LDL (52% in DMPA vs. 18% in NH users), TG (30% in DMPA vs. 5% in NH users), and HbA1c (40% in DMPA vs. 10% in NH users), p<0.05.

Table 4.6: Comparison of proportions of participants with abnormalities in cardiometabolic risk factors during the follow-up

Variables	Baseline DMPA (N=45) n(%)	NH, N=45 n(%)	Six months DMPA N=43	NH N=45	p-value	Twelve months DMPA N=40	NH N=39	p-value
WC								
<88	45(100)	45 (100)	20(46.5)	29 (64.4)	0.090	10(25)	21(53.8)	0.009*
≥88	0	0	23(53.5)	16(35.6)		30(75)	18(46.2)	
hs-CRP								
≤3	45(100)	45(100)	35(81.4)	30(66.7)	0.116	19(47.5)	29(74.4)	0.015*
>3	0	0	8(18.6)	15(33.3)		21(52.5)	10(25.6)	
TC								
< 5.2	45(100)	45(100)	37(86)	38(86.4)	0.966	26(65)	33(84.6)	0.045*
≥ 5.2	0	0	6(14)	6(13.6)		14(35)	6(15.4)	
HDL								
≥ 1.03	45(100)	45(100)	10(23.3	20(44.4)	0.036*	13(32.5)	25(64.1)	0.005*
<1.03	0	0	33(76.7)	25(55.6)		27(67.5)	14(35.9)	
LDL								
<3.4	45(100)	45(100)	32(74.4)	35(77.8)	0.712	19(47.5)	32(82)	0.001*
≥ 3.4	0	0	11(25.6)	10(22.2)		21(52.25)	7(18)	
TG								
<1,7	45(100)	45(100)	40(93)	45(100)	0.071	28(70)	37(95)	0.004*
≥1.7	0	0	3(7)	0(0)		12(30)	2(5)	
HbA1c								
<5.7%	45(100)	45(100)	25(58)	42(93.3)	<0.001*	24(60)	35(89.7)	0.002*
≥5.7%	0	0	18(42)	3(6.7)		16(40)	4(10.3)	

4.4. Discussion

The study used a prospective approach to explore the effect of DMPA on cardiometabolic risk parameters in women of reproductive age in Rwanda to document the need for routine follow-up. The findings indicated a significant effect of DMPA on waist circumference, LDL, TC, triglycerides, HDL-c, hs-CRP, and glycated hemoglobin. Generally, the first six months' changes were not statistically significant for many of the studied parameters; however, at 12 months, the results indicated a statistically significant increase in WC, hs-CRP, HbA1C, TC, LDL, and TG in the DMPA group compared to NH users. Moreover, DMPA users experienced a significant decrease in HDL compared to NH users. Our findings did not indicate any influence of DMPA on blood pressure.

Various studies investigating the effect of DMPA on lipid profiles indicated an inconsistency in their findings. Our findings indicated a progressive increase in TG, TC, and LDL and a decrease

in HDL. It is consistent with the six-month follow-up study done in Indian postpartum women, which also indicated a significant progressive increase in triglycerides, LDL-C, TC and a decrease in HDL-C in DMPA users [28]. It differs from the two-year follow-up study conducted on Nepalese women, which reported a significant increase in TC and LDL-C with no significant changes in TG and HDL-C [5]. Again, the study on Nigerian women reported a significant increase in LDL-C and HDL-C with no change in TG and TC [29]. On the contrary, the study on Egyptian women concluded that injectables do not affect lipid metabolism in any way [30]. This inconsistency may be attributable to socio-cultural and lifestyle factors influencing the lipid profile differently in different communities.

Our study did not show the difference in median blood pressure between the DMPA group and NH group, and it agrees with the study done in Ethiopia, which also reported no difference in both SBP and DBP between injectable users and controls· [31]. Other studies reported statistically significant differences; for instance, a one-year follow-up study conducted in Ghana reported a significant increase in DBP in injectable users when compared results at baseline (72.70±3.47 mmHg) and results after one year (88.22±4.32), however, it was not clinically significant. The same study also reported a significant increase in SBP, where it was 115.39±5.03 mmHg at baseline and 130.52±5.56mmHg after a year; also, the difference was not clinically significant [32]. Another example is the study conducted in Pakistan women, which reported a difference where both SBP and DBP were significantly high in injectable users (SBP: 118.33 ± 9.85 mmHg; DBP: 80.83 ± 10.91 mmHg) compared to controls (SBP: 112.0 ± 7.61 mmHg; DBP: 77.0 ± 5.50 mmHg), again this difference is not clinically significant [33].

Among the objectives of this study was to evaluate the influence of DMPA on abdominal fat deposition as an independent risk factor associated with a high risk of CVD [34]. The results of this study indicated both statistical and clinically significant differences between DMPA users and controls at 12 months of use, where DMPA users indicated a higher median waist circumference than controls. Even though there is limited data on these findings, related findings indicate a direct relationship between DMPA and weight gain. These include the study done on the adolescent population in a prospective study of 18 months follow-up where the mean increase in weight at 18 months was 9.4 in obese users and 3.5 in non-obese users [31]. The same was reported in Indian postpartum women, where the six-month follow-up study indicated a significant progressive increase in weight [28]. In a cross-sectional study conducted in Ethiopia, there was a significant increase in individual body weight from 1-14 kg and a mean

increase of 5kg/m^2 in BMI regardless of the duration of use [31]. An increase in body weight is not enough to estimate the risk of cardiovascular diseases; instead, the waist circumference measure provides a reasonable estimate of the risk of CDV [35].

There is evidence that combined hormonal contraceptives, specifically oral contraceptives [36] and vaginal combined hormonal contraceptives [37], induce chronic CRP production in the liver independently of age and in a different manner than the usual inflammatory processes [38]. This evidence has raised a concern about whether DMPA, a progesterone-only contraceptive, can induce CRP production. In our study, the observed change was minimal and not different between DMPA users and controls until six months. However, at 12 months, a clinically significant increase was observed in DMPA users but not in controls. Regardless of the mode of administration, hormonal contraceptives induce chronic inflammation that needs further evaluation to elucidate the cardiovascular consequences.

Various studies that investigated the effect of hormonal contraceptives on blood sugar have either considered all methods together or put their focus on oral contraceptives and ended with controversial findings. A cross-sectional study conducted on childbearing-aged women (20-49) in Indonesia indicated a higher average blood glucose of 26 mg/dl above that of non-users [39]. The same study conducted in Nigeria showed a significant increase (5.2±2.2 mg/dl) in users compared to non-users [40]. Contrary to that conducted in young American women, oral contraceptives reduced blood glucose levels, promising a protective effect on diabetes in users [41]. Our study intended to determine the effect of DMPA on glycated hemoglobin as a measure of average blood glucose within 3-4 months. Our findings indicated a higher mean in DMPA users than in controls. Even though we used different measures, our findings are comparable to the three-month follow-up study, which indicated a significantly elevated blood glucose in DMPA users than non-hormonal users [4].

Strengths and limitations of the study

This study is the first to investigate the effect of hormonal contraceptives on cardiometabolic risk factors in Rwanda; it provides baseline information that potentially informs further studies in this area to characterize this effect and decide on the need for routine follow-up for users. The study used a prospective approach, which allows for investigating the cause-effect relationship. However, the study encountered some limitations, among them the self-report on the use of hormonal contraceptives and the duration of the previous use, which could introduce some bias

in the results**.** Another limitation is the failure to control participants' lifestyles during the follow-up period, which could influence some of the factors investigated in the study. Further study that considers all those factors, includes all types of hormonal contraceptives used in Rwanda, and extends the follow-up period would be appreciated.

4.5. Conclusion and recommendations

The study concludes that DMPA affects cardiometabolic parameters in users. The effect was minimal within the first six months of use but manifested significantly at 12 months of follow-up. The most affected parameters included waist circumference, lipid ratios, triglycerides, HDL, hs-CRP, and glycated hemoglobin, and these are currently identified as potential cardiometabolic indicators of the high risk of cardiovascular disease. We recommend a follow-up to users, which is to be initiated at least 12 months of use and repeated every six months to check the status of cardiometabolic markers and intervene where necessary. Checking lipid profiles, blood sugar, and waist circumference would provide helpful information to health providers for a decision on an individual user.

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Chapter Five: Changes in Cardiometabolic Risk Markers in Women with Central Obesity During Depot Medroxyprogesterone Acetate Injectable Contraceptive Use.

Abstract

Background: The use of hormonal contraceptives has been repeatedly reported to increase the risk of cardiometabolic disease due to its influence on cardiometabolic risk factors, and the risk worsens for obese users who are already at high risk. This study determines how depo medroxyprogesterone acetate (DMPA) injectable contraceptive affects blood lipids, glycated haemoglobin, blood pressure, and inflammatory markers among abdominally obese women of reproductive age.

Methods: The study used a prospective design and involved 65 abdominally obese women of reproductive age (15-49 years) using DMPA. Participants were recruited from two selected family planning centres in Kigali city (Rwanda); the data were collected at baseline, midline (after six months), and endline (after 12 months). Blood pressure, lipids profile (HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TC: Total cholesterol, and TG: triglycerides), glycated haemoglobin, and inflammatory markers (hs-CRP: high sensitivity C-reactive protein) were measured. Data were presented as median with minimum and maximum, and the Wilcoxon signed-rank test was used to compare data. A statistical significance was defined at a p-value <0.05.

Results: At six months of DMPA use, users indicated a significant increase in waist circumference, TC, LDL, TG, and lipids ratios (TC/HDL-c and LDL-c/HDL-c), and a decrease in HDL, while other parameters indicated no change. However, after twelve months, all parameters showed significant changes; there was a gradual decrease in HDL and an increase in lipid ratios, TG, LDL, TC, hs-CRP, waist circumference, SBP, DBP, and glycated haemoglobin ($p= <0.05$).

Conclusion: The use of DMPA contributes significantly to the alteration of lipid profile, blood sugar, blood pressure, and inflammatory markers, and the changes increase the risk of cardiometabolic disease in abdominally obese users. Checking central obesity before initiating DMPA and a cardiovascular risk assessment every six months is recommended as a cardiovascular disease prevention measure.

5.1. Introduction

The use of hormonal contraceptives has been repeatedly reported to increase the risk of cardiometabolic disease due to its influence on cardiometabolic risk factors [1, 2], and the risk worsens for abdominally obese users who are already at high risk. Cardiometabolic risk is a clustering of metabolic factors that increase the risk of cardiovascular disease (CVD) and/or type 2 diabetes mellitus [3]. The top five metabolic factors indicating cardiometabolic risk include abdominal obesity, atherogenic dyslipidemia manifested by high triglycerides (TG) level and/or low high-density lipoprotein cholesterol (HDL), high blood pressure, insulin resistance, and pro-inflammatory state primarily manifested by an abnormal level of high sensitivity C-reactive protein (hs-CRP) [4, 5]. An individual is diagnosed with a cardiometabolic syndrome (CMS) when he/she happens to have central obesity plus any other two of the factors [6]. The CMS is a strong risk factor for type 2 diabetes and many forms of CVD, including coronary artery disease, peripheral vascular diseases, myocardial infarction, ischemic heart disease, and stroke [7].

Studies have indicated that women with CMS have a higher CVD mortality rate than men [8] and an increased risk of developing acute ischemic heart disease than men [9]. The difference between men and women may be associated with the high prevalence of central obesity among women compared to men, which, in women, is highly associated with multiple cardiometabolic risk factors such as dyslipidemia, hypertension, and impaired fasting blood glucose [10]. Literature highlights central obesity as an estimator of cardiometabolic risk than the body mass index (BMI) [11, 12], which generally concerns height and weight but does not provide information regarding body fat distribution. It was indicated that central obesity is not always associated with higher BMI, as very recent studies reported that the prevalence of normal-weight central obesity in Africa varies between 27 and 39% [13, 14].

Unfortunately, central obesity remains a global concern in women of reproductive age (15-49 years), the same age category as the predominant users of contraceptives. For instance, in Rwanda, the Demographic Health Survey 2020 (DHS) shows that obesity/overweight among women aged 15 to 49 years has gradually increased over the years: it was 12% in 2005, 16% in 2010, 21% in 2015, and 26% in 2020. The survey also indicates a higher prevalence in urban (42%) than in rural (22%), with a high prevalence in Kigali city (43%) [15]. Central obesity was consistently reported to be higher in women than in men; for instance, the Mohamed et al. study in Nairobi-Kenya reported a prevalence of 75.6% among women and 24.4% among men

[14], that of Yayehd et al. in Togo reported a prevalence of 56.1% in women and 9.2% in men [16], and that done by Yohannes Tekalegn et al. in Ethiopia reported a prevalence of 53% in women and 15% in men [17]. The increased levels of obesity among women compared to men may be associated with hormonal contraceptives, mainly Depo Medroxy Progesterone Acetate (DMPA) injection, also called Depo Provera [10]. This injection is typically administered on a three-month basis and is used to treat endometriosis and prevent pregnancy [18].

Generally, the injection has been consistently reported to be associated with weight gain, with a big trend in users who started the methods already being obese. This was reported in a study conducted among adolescent girls in a prospective study of 18 months follow-up, where the mean increase in weight at 18 months was 9.4 kg in obese users and 3.5 kg in non-obese [19]. The same was reported in Indian postpartum women, where the six-month follow-up study indicated a significant progressive increase in weight [20]. In a cross-sectional study conducted in Ethiopia, there was a significant increase in individual body weight from 1-14 kg and a mean increase of $5kg/m^2$ in BMI regardless of the duration of use [21].

The available guidelines insist on using DMPA with precaution for women with multiple cardiometabolic risk factors. Checking metabolic risk factors is recommended before initiating DMPA to minimize risks for CVDs. For instance, the New Zealand guideline recommends that DMPA should not be used for women with hypertension and be used with caution for women with metabolic risk factors of cardiovascular disease like obesity, dyslipidemia, and diabetes [22]. Further, the WHO guideline recommends stopping the use of DMPA for women with multiple cardiovascular risk factors and when a woman contracts hypertension or shows rapid weight gain [18]. Moreover, the updated Family Health International 2015 checklist recommends a prior evaluation before initiating DMPA for users with obesity, smoking, high blood pressure, and high blood sugar, as these can increase the risk of heart attack or strokes [23].

However, in most African countries, including Rwanda, women are only screened for blood pressure and allowed to initiate DMPA regardless of the presence or absence of other cardiometabolic risk factors. Furthermore, there is no follow-up to check for any cardiometabolic health risk that could arise from the method. The concern is that checking all cardiometabolic risk factors might be expensive and inconvenient in under-resourced settings, indicating the need for an effective and cost-friendly mechanism to check cardiometabolic risk.

This study attempts to bridge the gap by assessing how informative the measures of central obesity before initiating DMPA and routine follow-up with obese users can be to reduce the risks of CVDs. It determines how much DMPA affects blood lipids, glycated haemoglobin, blood pressure, and inflammatory markers among abdominally obese women of reproductive age in Rwanda.

5.2. Materials and methods

5.2.1. Study setting and design

The study used an observational design with a prospective approach. We recruited participants from 2 selected family planning centres in Kigali, Gahanga, and Gikondo, chosen because they are among the centers that receive many women as they offer free family planning services. Data were collected thrice a year: at baseline, after six months, and after 12 months.

5.2.2. Participant's selection and sampling procedures

The potential participants were non-pregnant, abdominally obese, and physically healthy women (those who, at that moment, did not have any known disease or look sick) aged between 15 and 49 years. Participants also had to be free of hormonal contraceptive use in the last six months and wished to start or restart DMPA. The study specifically enrolled participants who self-reported having no history of chronic diseases such as diabetes, heart disease, kidney disease, severe hypertension, or HIV. This selection criterion aimed to exclude individuals with conditions commonly associated with heart diseases. To ensure a focused sample, we intentionally recruited 65 women with abdominal obesity, defined as having a waist circumference of ≥ 88 cm [8].

5.2.3. Data collection and measurements

A structured questionnaire (Appendix D) was used to record participants' data about age, parity, education level, physical activity, alcohol intake, diet, and blood pressure. The follow-up data concerned waist circumference, blood pressure, lipid profile, glycated hemoglobin, and inflammatory markers. Consented participants also provided blood specimens for determining lipid profile, glycated hemoglobin, and inflammatory markers.

The age was counted in years based on the date of birth, while educational level had two categories: less than secondary and secondary or tertiary education. The education level was kept to only two categories for analysis purposes, as many categories indicated a few participants. Physical activity was described as a sedentary and non-sedentary lifestyle based

on daily activity, as none of the participants reported doing planned physical exercise. The sedentary style was defined by occupations that do not require much energy, such as housekeeping, sewing and handcrafting, and boutique and office activities. Non-sedentary style included activities that allow energy expenditure, such as farming, mobile business, and building activities. Blood pressure was measured based on the International Association of Hypertension, where a systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg is considered elevated, while blood pressure below these values is considered normal [24]. Alcohol intake was measured as a binary variable (yes or no), and a diet focused on the self-report about the number of times they take meat, milk, and vegetables per week, considering the last four weeks before baseline.

Lipid profiles included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides (TG). Elevated results were defined for TC ≥ 5.2 mmol/L, LDL ≥ 3.4 mmol/L, HDL ≤ 1.04 mmol/L, and TG ≥ 1.7 mmol/L [25]. An elevated glycated hemoglobin (HbA1C) value was defined for HbA1C ≥ 5.7 %, while a value below 5.7 % was considered normal [26]. We measured high-sensitivity C-reactive protein (hs-CRP) for inflammatory markers, a measure of low-grade chronic or systemic inflammation. The hs-CRP method detects the concentration of C-reactive protein that cannot be detected by the routine method; hs-CRP detects CRP in the range of 0- 10 mg/L, while the routine method detects CRP from 10-1000 mg/L. The hs-CRP level is used to categorize the risk of CVD where hs-CRP < 1 mg/L indicates low risk, 1 ≤ hs-CRP < 3 mg/L indicates moderate risk, while hs-CRP ≥ 3 mg/L indicates a high risk [27].

5.2.4. Data management and analysis

After data collection, data were entered, cleared, processed, and analyzed using SPSS version 20. Data were presented in tables and expressed as percentages or median (minimum, maximum). A normality test was performed to decide on the appropriate statistical test and indicated that none of the variables respected normal distribution. Consequently, the non-parametric statistical test, the Wilcoxon signed-rank test, was used to compare two paired groups (before and after a given period of DMPA use) at each time point. The level of significance was fixed at 5%.

5.3. Results

Bio-demographic characteristics

Table 5.1 shows the bio-demographic characteristics of the study participants. The ages ranged between 20 and 45 years, with a median of 26. Also, a large number (70%) of participants had less than a secondary school education level, and most were sedentary (73.8%).

Table 5.1:Bio-demographic characteristics of study participants

Parameters	**Categories**	**Median age (Range)**	**Frequency (%)**
Age (in years)		26 (20- 45)	
Education attainment	Less than secondary		46 (70.8)
	Secondary or tertiary		19 (29.2)
Physical activity	Sedentary		48 (73.8)
	Non-sedentary		17 (26.1)
Breastfeeding	Yes		38 (58.5)
	No		27 (41.5)
Parity	primiparous		27 (41.5)
	multiparous		35(53.8)
	Grand multiparous		3(4.6)
Alcohol use	Yes		30 (46.2)
	No		35 (53.8)
Eating meat	Not at all		20 (30.8)
	At least once a week		45 (69.2)
Eating vegetables	< 4 times a week		28 (43.1)
	≥ 4 times a week		37 (56.9)
Eating fruits	Not at all		14 (21.5)
	At least once a week		51 (78.5)
Taking milk	Not at all		22 (33.8)
	At least once a week		43 (66.3)

Further, Table 1 shows that 58.5% were breastfeeding, and 53.8% multiparous at the time of data collection. Concerning diet, 46.2% take alcohol, 69.2% reported they eat meat at least once a week, 56% eat vegetables, 78% eat fruits, and 66% take milk at least once a week.

Changes in cardiometabolic parameters

Table 2 shows the data on the changes in cardiometabolic parameters, comparing the data before initiating the DMPA and that of six months of use and comparing the data after six months and those after 12 months of follow-up. The waist circumference changed significantly from the median of 96 (88 -129) to 98 (86 -129; P<0.001) in six months and 99.50 (87 - 131)

in twelve months. Similarly, the total cholesterol changed from the median of 3.93 (2.51- 6.47) to 4.27 (2.51- 6.79) in six months and 5.06 (2.74 - 7.85; P<0.016) in twelve months.
The median LDL changed from 2.90 (1.83- 5.01) to 3.26 (1.72- 5.18; P<0.001) in six months and 3.96 (1.83 - 6.48) in 12 months, while the median HDL decreased from 1.08 (0.46 - 2.01) to 0.94 (0.45, 1.45) after six months, and to 0.90 (0.44 - 1.43; P< 0.001) after twelve months.

Table 5.2:Changes in cardiometabolic markers between baseline and six months and between six months and 12 months of follow-up among abnormally obese women using DMPA

Variable	Baseline		At six months			At 12 months		
	Median	***Min, Max***	***Median***	***Min, Max***	***P-Value***	***Median***	***Min, Max***	***P-Value***
WC	96	88 - 129	98	86 - 129	0.001	99.50	87 - 131	0.001
TC	3.93	2.51 - 6.47	4.27	2.51 - 6.79	0.016	5.06	2.74 - 7.85	0.001
LDL	2.90	1.83 - 5.01	3.26	1.72 - 5.18	0.019	3.96	1.83 - 6.48	0.001
HDL	1.08	0.46 - 2.01	0.94	0.45 - 1.45	0.001	0.90	0.44 - 1.43	0.005
TG	1.15	0.45 - 2.86	1.27	0.53 - 3.83	0.007	1.57	0.47 - 4.10	0.038
TC/HDL	3.54	1.89 - 7.80	4.65	2.93 - 9.49	0.001	5.99	2.58 - 11.17	0.001
LDL/HDL	2.63	1.31 - 6.11	3.47	1.87 - 7.99	0.001	4.68	1.73 - 9.11	0.001
SBP	121	93 - 136	122	91 - 144	0.390	127	100 - 151	0.001
DBP	79	62 - 99	79	58 - 99	0.727	84	54 - 101	0.013
HbA1C	5.0	3.80 - 6.82	5.23	3.60 - 6.67	0.752	5.48	4.06 - 7.17	0.001
hs-CRP	1.05	0.10 - 9.76	1.21	0.10 - 9.16	0.926	3.16	0.10 - 9.85	0.001

Abbreviations: DMPA-Depot medroxyprogesterone acetate; Min-minimum; Max-maximum; WC-waist circumference (in cm); DBP-diastolic blood pressure (in mmHg); HDL-high-density lipoprotein cholesterol (in mmol/L); LDL-low-density lipoprotein cholesterol (in mmol/L); SBP-systolic blood pressure (in mmHg); TC-total cholesterol (in mmol/L); TG- triglyceride (in mmol/L); HbA1C-glycated hemoglobin (in %); hs-CRP-high sensitivity C-reactive protein (in mg/L).

Also, the data in Table 2 shows a median TG change from 1.15 (0.45,2.86) to 1.27 (0.53,3.83; P<0.007) in six months and 1.57 (0.47 - 4.10) in twelve months. The ratio TC/HDL changed from 3.54 (1.89,7.80) to 4.65 (2.93,9.49; P<0.001) in six months and 5.99 (2.58 - 11.17) in twelve months, while the LDL/HDL ratio changed from 2.63 (1.31,6.11) to 3.47 (1.87, 7.99; P< 0.001) in six months, and 4.68 (1.73 - 9.11) in twelve months.

Further, measures of systolic blood pressure (SBP) and diastolic blood pressure (DBP) changed as well. After six months of follow-up, the SBP shifted from 121 (93 - 136) to 122 (91,144) and to 127 (100,151), P<0.001 in twelve months, while the DBP shifted from 79 (93 - 136) to 79 (58,99), and to 84 (54, 101, P< 0.013) in twelve months. Similarly, the HbA1C increased from 5.0 (3.80 - 6.82) to 5.23 (3.60,6.67) in six months, and 5.48 (4.06,7.17; P= 0.001 in twelve

months, while the hs-CRP changed from 1.05 (0.10 - 9.76) to 1.21 (0.10,9.16) in six months and to 3.16 (0.10,9.85; P=0.001) in twelve months.

5.4. Discussion

This study aimed to determine how much DMPA injection affects cardiometabolic risk markers among abdominally obese women of reproductive age in Rwanda. The aim was to inform health professionals providing hormonal contraceptives of the need to check the levels of central obesity before the initiation of DMPA and conduct routine follow-ups with obese users to reduce the risks of CVDs. Evidently, in this twelve-month prospective study, participants experienced significant alterations in lipid profile components and lipid ratios with no change in glycated hemoglobin, blood pressure, and inflammatory markers in six months follow-up, and, within the second six months of use, they experienced a significant increase in total cholesterol, triglycerides, low-density lipoprotein cholesterol, lipid ratios, systolic and diastolic blood pressure, glycated hemoglobin, and high-sensitivity c-reactive protein. This confirms the hypothesis that obese women using DMPA would experience a worsened cardiometabolic risk than the study anticipated following the common cardiometabolic effect of obesity and DMPA.

Elffers et al. reported similar findings where the study observed the mean central fat deposition increasing significantly among DMPA users [10]. The study argues that visceral fat deposition in DMPA users increases gradually with time. This gradual increase in abdominal fat deposition bears potential health risks if the changes are not reversed upon DMPA discontinuation. Moreover, additional studies have reported a significant association between central obesity and chronic systemic inflammation and an increased risk of cardiovascular diseases and various metabolic disorders such as diabetes, hypertension, microalbuminuria, atherosclerosis, arthritis, and certain types of cancers [28].

Furthermore, the study confirms that within 12 months of follow-up, DMPA users experience a gradual increase in triglycerides, LDL, and TC and a decrease in HDL levels. This agrees with a similar prospective study conducted in India among postpartum women, indicating a progressive increase in triglycerides, LDL, TC, and HDL-C in DMPA users [20]. However, there are some disagreements with a study conducted in Iraq, which reported an increase in LDL and a decrease in HDL with no change in TC and TG when comparing the pre-injection results and the results after three months of DMPA use [29]. Similarly, a study conducted among Nepalese women indicated that after two years of DMPA use, there was a highly significant

increase in TC and LDL, and no significant changes were observed in TG and HDL [1]. The disagreements could be attributed to contextual factors such as diet and physical activities, as it was earlier discussed that diet and physical activities can influence the potential effects of DMPA in the user's body [30].

The study further reveals that using DMPA influences blood glucose variations along the usage period, as the data shows that the median of glycated haemoglobin increased significantly over 12 months of follow-up. The significant increase in blood glucose found in this study is not far from what was reported by an experimental study done in Indonesia [31]. These changes in blood glucose during DMPA use could be explained by the implication of progesterone in hepatic glucose production and insulin resistance [32, 33]. However, due to the effect of these hormones on insulin production and sensitivity, it was shown that estrogen functions by increasing production and enhancing insulin sensitivity [34]. Progesterone and estrogen effects are balanced to maintain homeostasis, but this typically happens during the pre-menopausal period. Therefore, hormonal contraceptives create an imbalance of sex hormones due to the addition of excessive hormones that could impact metabolism.

Strengths and limitations of the study

This study is among the few studies that evaluated the changes in cardiometabolic risk markers among abdominally obese women using DMPA. Therefore, it provides essential information that potentially guides scientists to expand studies in this area to fully understand the necessity of prior screening for potential cardiometabolic risk parameters before initiating the method and routine follow-up for users at risk of cardiometabolic disease. This was a pre-post study with a prospective approach where data were collected three times and compared at each time point. However, the lack of a group of abdominally obese women using non-hormonal contraception as a control group limits the study to conclude the synergic effect of DMPA and central obesity on cardiometabolic health.

5.5. Conclusion and recommendations

This study concludes that there is a significant effect of DMPA use on alterations of cardiometabolic parameters in abdominally obese women, particularly HDL-c, TG, blood pressure, blood sugar, and systemic inflammation, the known contributors of CVD and type two diabetes. Therefore, it is essential to screen for central obesity before initiating DMPA, even in those with normal weight, as it was indicated that normal-weight central obesity is common, especially in African countries. Health professionals are recommended to conduct

consistent follow-ups with DMPA users to diagnose the potential cardiometabolic risk markers as early as possible and counter any possible development of the cardiometabolic disease.

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Chapter Six: General Discussion, Conclusions, and Recommendations

6.1. General Discussion

6.1.1. Main findings

This study was designed to investigate the effect of DMPA on the cardiometabolic risk profile, emphasizing the importance of assessing cardiometabolic risk factors before initiating this method. The study focused on several critical factors, including central obesity, dyslipidemia, hyperglycemia, high blood pressure, high blood sugar, and systemic inflammation. The initial step was identifying these risk factors in participants preparing to start DMPA and analyzing their interrelationships. To do this, we considered central obesity the main factor due to its close association with other cardiometabolic risk factors. The second step focused on evaluating the changes in lipid profile, glycated hemoglobin, waist circumference, blood pressure, and inflammatory markers for users free of any abnormality in these parameters before starting DMPA. Lastly, we evaluated how these cardiometabolic parameters changed in women who began the method and were already abdominally obese.

a. First study

This study examined the prevalence of central obesity and its associated factors using a cross-sectional design. The results revealed that the overall prevalence of central obesity was 48.5%. This prevalence was comparable to that reported in various studies performed in the same context [1, 2]. Several factors were significantly associated with central obesity, including age, alcohol use, meat consumption, hypertriglyceridemia, and elevated diastolic blood pressure.

The association between age and central obesity was notable, with the odds ratio (OR) indicating that individuals were twice as likely to have central obesity as they aged. This finding suggests that advancing age may contribute to an increased risk of central obesity, similar to the findings of Tekalegn et al. and Agyemang et al. studies [2, 3]. Alcohol use was also strongly associated with central obesity, with individuals who reported alcohol consumption being nearly six times more likely to have central obesity than those who did not consume alcohol. This association highlights the potential influence of alcohol consumption on the development of central obesity, as reported in various studies [4]. Meat consumption emerged as another significant factor associated with central obesity. The results showed that individuals who reported higher meat consumption had 5.3 times higher odds of having central obesity than those with lower meat consumption. This finding suggests a potential link between meat intake and central obesity, as

the diet was also indicated as the main factor contributing to the development of central obesity [5].

Hypertriglyceridemia, a condition characterized by elevated levels of triglycerides in the blood, was identified as an associated factor of central obesity [6, 7]. The results indicated that individuals with hypertriglyceridemia had 3.87 times higher odds of having central obesity compared to those without this condition. Elevated diastolic blood pressure was also significantly associated with central obesity. Individuals with increased diastolic blood pressure had 6.1 times higher odds of having central obesity compared to those with normal diastolic blood pressure. This finding emphasizes the relationship between central obesity and cardiovascular health, as elevated blood pressure is a risk factor for cardiovascular diseases.

b. Second study

The study utilized a one-year prospective design to assess the effects of Depot Medroxyprogesterone Acetate (DMPA) on cardiometabolic risk profiles. The study focused on women without abnormalities in selected parameters who wished to start DMPA and were compared with women whose choice of contraception was non-hormonal methods. The findings revealed several significant changes in various parameters, including waist circumference, lipid profile, inflammatory markers, glycated hemoglobin, and high-density lipoprotein (HDL) levels, among DMPA users compared to the control group. This finding suggests that DMPA use may be associated with adverse metabolic changes that could contribute to an increased risk of cardiovascular disease.

One noteworthy finding was the significant increase in waist circumference observed in DMPA users compared to the control group. This finding suggests that DMPA use may be associated with increased abdominal fat deposition. Abdominal obesity is strongly associated with an increased risk of cardiometabolic disorders such as insulin resistance, metabolic syndrome, and cardiovascular diseases [8, 9]. Also, the study reported a significant elevation in high-sensitivity C-reactive protein (hs-CRP) levels among DMPA users. It indicates an association between DMPA use and increased systemic inflammation. Elevated levels of hs-CRP are considered a marker of chronic inflammation and have been implicated in the pathogenesis of atherosclerosis and other cardiovascular disorders [10].

The study also identified adverse alterations in the lipid profile of DMPA users. Increases in triglyceride (TG), low-density lipoprotein (LDL), and total cholesterol (TC) levels were

observed in these individuals, and the same findings were observed in various studies [11, 12]. Elevated levels of these lipid parameters are commonly associated with an increased risk of cardiovascular diseases. Furthermore, the study found that DMPA users had significantly lower high-density lipoprotein (HDL) levels than the control group. The reduced HDL levels among DMPA users may indicate a potential negative impact on cardiovascular health as the lower HDL levels are associated with an increased risk of developing cardiovascular complications [13].

Another finding of concern was the significant increase in glycated hemoglobin (HbA1c) levels among DMPA users. The increase in HbA1c suggests a potential adverse effect of DMPA on glucose metabolism, which may increase the risk of developing type two diabetes. It was also reported to be associated with an increased risk of cardiovascular disease in pre-diabetic individuals and non-diabetes patients [14]. Contrary to other studies [15, 16], the study did not observe any significant difference in blood pressure changes between DMPA users and the control group.

c. Third study

This study explored the changes in cardiometabolic risk markers in abdominally obese women during the use of DMPA to highlight the need to check central obesity before initiating the method. The hypothesis was that for an abdominally obese woman with an increased risk of cardiometabolic disease [17], the risk would potentiate when she uses DMPA injection, which is also reported to influence cardiometabolic risk parameters [18].

The findings demonstrated significant changes in multiple cardiometabolic parameters after twelve months of DMPA use, including alterations in lipid profile, inflammation markers, glycated haemoglobin, and waist circumference continued to rise as well. Additionally, the study found a significant increase in systolic and diastolic blood pressure after twelve months of DMPA use. Elevated blood pressure is a leading risk factor for cardiovascular diseases, including hypertensive heart disease and stroke [19]. The observed changes in blood pressure emphasize the need for careful monitoring and management of cardiovascular risk factors in abdominally obese women using DMPA.

6.1.2. Strength and Limitations

This study is the first to investigate the effect of hormonal contraceptives on the cardiometabolic risk profile in Rwanda using a prospective approach that allows for exploring the cause-effect relationship. It responds to a dearth of studies that evaluated changes in cardiometabolic risk markers among abdominally obese women using DMPA in Rwanda and a similar socioeconomic context. Specifically, the study pioneered the assessment of the prevalence of central obesity and examined its association with cardiometabolic risk factors among women of reproductive age.

Subsequently, the results provide critical information that guides scientists to expand studies in this area to fully document the necessity of prior screening for potential cardiometabolic risk parameters before initiating the method and routine follow-up for users at risk of cardiometabolic disease. The hypothesis was that Africa, currently experiencing a swift epidemiologic and nutritional transition, requires additional research in this field to guide public health initiatives targeting the increasing occurrence of non-communicable diseases (NCDs) and, specifically, cardiovascular diseases. Furthermore, the strength of this study lies in its incorporation of variables such as dietary intake, metabolic factors, and lifestyle factors, allowing for a comprehensive examination of the prevalence of central obesity.

However, the study encountered some limitations. The first limitation was that it was conducted in an urban setting, which limited its generalizability to the whole population. The second limitation was that we could not collect complete records of the respondents' dietary intake, meaning that if the study could consider the complete dietary profile, the findings could have revealed other potential types of diet that could influence central obesity and other cardiometabolic risk factors as well. The third limitation was the lack of a group of abdominally obese women using non-hormonal contraception as a control group, which limited the study to conclude the synergic effect of DMPA and central obesity on cardiometabolic health. Despite all these limitations, we remain confident that the findings of this study provide valuable information to health providers and policymakers on improving health education about the alarming risk of cardiometabolic diseases associated with the high prevalence of central obesity in women of reproductive age. The findings also highlighted the need to consider the cardiometabolic risk associated with DMPA injectable contraceptives and plan an early intervention to reduce the risk of cardiometabolic disease.

6.1.3. Future perspectives

This thesis studied the effects of DMPA on cardiometabolic risk profile using a prospective approach where 45 DMPA users and 45 non-hormonal users were followed for 12 months. Measurements were taken at a six-month month-interval where controlling lifestyle behaviour and health issues seemed challenging. A short follow-up pattern, such as three month-interval, would reduce the respondents' recall bias about lifestyle behaviour and health issues when taking measurements. Again, considering a large cohort would help cope with the loss of follow-up issues associated with this kind of study.

Most of the available studies that investigated the effect of hormonal contraceptives on cardiovascular health, including DMPA, were setting-based; ours also focused on participants in urban settings. The study comparing urban and rural areas would provide an expansive view of this effect. Also, for tracking changes in cardiometabolic risk markers for abdominally obese users, further studies incorporating a control group of abdominally obese women choosing a non-hormonal method would be appreciated.

6.2. Conclusions

To conclude, central obesity is common among women of reproductive age and is associated with increased age, alcohol use, frequent meat consumption, higher triglyceride levels, and diastolic blood pressure. This association indicates the need to increase awareness about cardiovascular risks associated with central obesity in young women who are typically considered safe from CVD following the literature.

The study highlights several critical cardiometabolic changes associated with DMPA use for women free of abnormalities in investigated cardiometabolic risk parameters. The observed increase in waist circumference, alterations in lipid profile, elevated inflammation markers, and impaired glycemic control suggest potential risks for cardiovascular health among DMPA users. These findings emphasize the importance of regular monitoring and comprehensive cardiovascular risk assessments for individuals using DMPA and intervention where necessary to reduce the risk of cardiometabolic disease.

For women with central obesity, the study indicated that after 12 months of follow-up, users experience a gradual increase in waist circumference, lipids ratios, lipid profile components (except HDL, which showed a gradual decrease), glycated haemoglobin, hs-CRP, SBP, and DBP. This finding suggests the importance of checking central obesity before offering the

method to the clients and planning a follow-up for those obese users who may experience worsening changes that potentiate the risk of cardiometabolic disease.

6.3. Recommendations

Considering the compelling evidence from the literature indicating that cardiometabolic diseases are currently major contributors to morbidity and mortality in sub-Saharan Africa, including Rwanda, this study strongly recommends that health policymakers and public health officials implement effective strategies to address modifiable risk factors. These risk factors include high blood pressure, alcohol consumption, physical activity, and dietary habits. Targeting these factors, particularly in young women, aims to mitigate the risk of cardiovascular diseases and improve overall health outcomes.

Following the effect of DMPA on waist circumference, lipid profile, glycated hemoglobin, and hs-CRP, the study recommends a follow-up to users, which is to be initiated at least 12 months of use and repeated every six months to check the status of cardiometabolic markers and intervene where necessary. Checking lipid profiles, blood sugar, and waist circumference would provide helpful information to health providers for a decision on an individual user.

With the suggested synergic effect of central obesity and DMPA use on cardiometabolic risk markers, it sounds essential to screen for central obesity before initiating DMPA, even in those with normal weight, as it was indicated that normal-weight central obesity is common, especially in African countries. Also, in the course of assisting obese women to control birth, health professionals need to consider the individual users' health risks and help them choose a suitable and safe method for contraception. Moreover, if DMPA is the choice, a follow-up every six months is recommended to screen for potential cardiometabolic risk markers to avoid any cardiometabolic disease involvement.

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Appendices

A. Ethical clearance

UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 18th/ March /2020

KANTARAMA Evelyne
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 042/CMHS IRB/2020

Your Project Title ***"Cardiometabolic Risk Factors Among Childbearing Aged Women Using Injectable Hormonal Contraceptives in Rwanda"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS			X
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 12th March 2020, **Approval has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 18th March 2020

Expiration date: The 18th March 2021

Professor GAHUTU Jean Bosco
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:

- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR

B. Approval of the Ministry of Health

Republic of Rwanda

MINISTRY OF HEALTH

National Health Research Committee
Ref: NHRC/2020/PROT/030

To: **Mrs. KANTARAMA Evelyne**
Principal Investigator

Scientific Review Approval Notice

With reference to your request for approval of the Research Protocol entitled; **"Cardiometabolic risk factors among childbearing aged women using injectable hormonal contraceptives in Rwanda";**

We are pleased to inform you that, following a thorough review and critical analysis of your proposal (**NHRC/2020/PROT/030**), National Health Research Committee has approved your Research Protocol.

However,

1) Changes amendments on approach and methodology must be submitted to the NHRC for review and approval to validate the changes.
2) Submission to NHRC of final results is mandatory
3) Failure to fulfill the above requirements will result in termination of study

Once again National Health Research Committee appreciates your interest in research.

Your final approval reference number is **NHRC/2020/PROT/030.**

Sincerely,

Dr. Parfait UWALIRAYE
Chairperson of NHRC

Date:.....02/09/2020

C. Collaboration noted by Rwanda Biomedical Centre

Rwanda Biomedical Centre
Healthy People, Wealthy Nation

Kigali, 28 AUG 2020
Ref: No 417/RBC/2020
Office of Director General

Evelyne Kantarama
University of Rwanda
Tel: +250788651907
Email: kantever11@gmail.com

Re: Research collaboration on the study **"Cardiometabolic risk factors among childbearing aged women using injectable hormonal contraceptive in Rwanda".**

Dear Principal Investigator,

Reference is made to your request for research collaboration to conduct the above-mentioned study;

Recognizing the importance of this study in terms of generating insight on cardiometabolic risk factors among users of injectable hormonal contraceptives and to determine the need for judicious follow up;

Rwanda Biomedical Centre is pleased to confirm its collaboration for effective implementation of this study. This collaboration includes technical support and guidance throughout study implementation. You are required to comply with the National Health Research Committee and Rwanda National Ethics Committee requirements; and the privacy and confidentiality standards including the Good Clinical Practices. You shall also share the findings with RBC before any dissemination and publication processes.

For more details or support, please liaise with Medical Research Centre (MRC) via email: info.mrc@rbc.gov.rw.

Sincerely,

RWANDA BIOMEDICAL CENTER

Dr. Sabin NSANZIMANA
Director General

D. Data collection tool

Title: ***Cardiometabolic risk factors among childbearing aged women using injectable contraceptives in Rwanda***

Specific objectives:

- To identify cardiometabolic risk factors present in women wishing to start injectable contraceptives to document the need or not for routine assessment for cardiometabolic risk factors before initiating injectables.
- To assess the effect of injectable contraceptives on lipid profile, blood pressure, blood sugar, waist circumference, and inflammatory markers in Rwandan women.
- To explore whether starting injectable hormonal contraceptives already having one or more cardiometabolic risk factors could aggravate their risk of cardiovascular diseases.

1. Serial number …… Date of attendance ……/……/…….

2. Name of participant……

3. Type of participation: study participant…… or Control……

4. Code given to participant ……

5. Bio-demographic information

a. Age……

b. have delivered: yes……..or not…… if yes, by which way? caesarian…… or normal delivery…….

c. Lactating: yes…… Or not……. If yes, for how long?.....

e. Alcohol use: yes……. or not……

f. Smoking: yes……. or not……

6. Clinical examination

a. waist circumference …….cm

b. Systolic blood pressure……mmHg

c. Diastolic blood pressure……mmHg

7. Diet

a. how many times do you eat meat in a week?.....

b. how many times do you eat vegetables in a week?.....

c. how many times do you eat fruits in a week?.....

d. how many times do you take milk in a week?.....

e. Do you take coffee? yes ……. or not …….

8. Physical activity related to occupation

a. Spending much of time sitting: office……. shop or boutique……, sewing workshop……, handcraft workshop…….

Do you have time for sport? Yes…….. or no……, If yes, how many times in a week?.....

b. Daily activity allows you to use physical energy: teaching in primary and secondary schools……., doing mobile business carrying things by head or hands……, housemaid……, construction helper……, farming activities……

9. Laboratory Results

a. Hs-CRP ……mg/L

b. CRP grades: Mild risk ……., Moderate risk ……., High risk…….

c. Total cholesterol…….mg/dl

d. HDL-cholesterol…….mg/dl

e. LDL-cholesterol…….mg/dl

f. Triglycerides……...mg/dl

g. Blood sugar…….mg/L

E. Informed consent form

Informed consent form in English

Researcher: Evelyne Kantarama, a Ph.D. candidate at the University of Rwanda College of Medicine and Health Sciences.

Protocol Title: Cardiometabolic risk factors among childbearing aged women using injectable contraceptives in Rwanda.

Dear participant,

We are contacting you to tell you about the research planned for childbearing-aged women wishing to start injectable contraceptives. Before accepting to participate in the study, you need to read and understand all the information related to this study. You have the right to ask all explanations for a better understanding of the study. Participation in this study is entirely by voluntary. If you choose not to participate in this study, you will continue receiving all the services usually provided in this hospital.

1. The Goal of the Study

This study aims to evaluate the effect of injectable hormonal contraceptives on cardiometabolic risk factors among women of reproductive age (15-49 years) in Rwanda. The study will involve approximately 90 participants, and participation will last 12 months.

2. Context of the Study

The study will involve two groups: 45 women committed to starting injectable contraceptives and 45 women users of non-hormonal contraceptive methods. The researcher will not assign nor recommend any contraceptive methods to participants.

3. The Study Procedure

To know if you are eligible to participate in the study, you will be interviewed for information regarding your medical history and hormonal contraceptive use within six months before the study. Explanations will be provided to participants not satisfying the inclusion criteria.

If you meet the inclusion criteria and accept to participate in this study, you will provide the information regarding age, parity, mode of delivery, lactation status, diet, physical activity, alcohol use, and smoking habit. You will be requested to attend the hospital every three months for the researcher to know about you. Your waist circumference and blood pressure will be

recorded every three months of your attendance at the hospital. You will be requested to give a venous blood specimen (approximately 10ml) for laboratory investigations. Blood samples will be drawn thrice yearly: at baseline, six months, and 12 months.

4. **What are the potential risks or inconveniences of being in the study?**

There are no risks involved in this study except for minor discomfort while drawing a blood specimen.

5. **What are the possible benefits of participating in the study?**

Your participation greatly contributes to the entire community, especially your fellow women, as the study's findings will inform health practitioners of the need for routine health check-ups of cardiometabolic risk factors before and after initiating the method to control the potential development of cardiovascular diseases. Besides, if you choose to participate in this study, you will benefit by knowing the status of your body, and for sure, in the case of any severe health condition, you will be notified and advised to find a doctor for treatment.

6. **Confidentiality**

Information on your health status will be kept confidential; all records will be kept away from the public except the health practitioner if you present a condition that needs medical intervention.

7. **Payment, expenses, and costs**

Your participation in the study is free; you will not be paid nor given any money from your pocket. The researcher will pay the cost related to the laboratory test.

8. **Persons to Contact**

If you have any questions regarding this study, please contact **Evelyne Kantarama at 0788651907**. If you have questions about your rights as a participant, you may contact the **Chairperson of the CMHS IRB 0783 340 040**

9. Statement of consent

By signing the above, I acknowledge that:

- I have read the information sheet and consent form, the Kinyarwanda version for this study,

- I had the opportunity to ask questions, and the answers were satisfactory.

- I took time to discuss this information with others and to decide whether to take part or not,

- I will receive a dated and signed copy of the consent form,

- I agree to take part in this study.

Name of the subject (in capital letters)

....

Date and signature of the subject

.....

Name of the researcher (in capital letters)

....

Date and signature of the Researcher

.....

Name of the witness (in capital letters)

....

Signature of the witness Date

Informed consent form in Kinyarwanda

URUHARE MU BUSHAKASHATSI BWIGA KU IHURIRO RY'INSHINGE ZIKORESHWA MU KUBONEZA URUBYARO N'INDWARA Z'MUTIMA, KU BAGORE BARI MU MYAKA YO KUBYARA.

Ikigamijwe: Gusaba ko mwagira uruhare mu bushakashatsi

Nitwa Evelyne Kantarama; ndi umwalimu n'umushakashatsi muri Koreji y'ubuzima Muri Kaminuza y'u Rwanda. Ndimo ndakora ubushakashatsi bugamije kureba ihuriro ryaba riri hagati y'inshinge zikoreshwa mu kuboneza urubyaro n'indwara z'umutima mu bagore bazikoresha. Ku impamvu yubwo bushakashatsi, ndabasaba ko mwanyemerera mukajya mumpa amakuru mbasabye ajyanye n'ubwo bushakashatsi kandi ndabizeza ko amakuru yose mumpa azabikwa mu ibanga rikomeye. Ntamuntu numwe uzamenya ibijyanye n'amakuru muzampa.

Icyo bisobanuye kwemera kugira uruhare muri ubu bushakashatsi:

1. Niba wemeye kugira uruhare muri ubu bushakashatsi, ndagusaba kumpa amakuru yerekeranye n'ubuzima bwawe ku bigendanye n'indwara zidakira cg z'akarande zaba ziri mu muryango wawe, imyaka yawe y'amavuko, imbyaro ugize, niba warabyaye ubazwe cg mu nzira zisanzwe, niba wonsa, ibigendanye n'imirire yawe, imirimo ukora n'ingufu igusaba, niba unywa inzoga cg itabi.
2. Muri ubu bushakashatsi uzapimwa umubyibuho n'umuvuduko w'amaraso.
3. Uzatanga ibizami by'amaraso azakorerwaho ubushakashatsi muri laboratwari harebwa ingano y'isukari n'ibinure mu maraso.
4. Ibi bizamini ndetse n'aya makuru bizakwa inshuro eshatu: iyambere ni none kuko aribwo dutangiye; iyakabili ni nyuma y'amezi atandatu, naho iya gatatu ni nyuma y'umwaka.

5. Nta kiguzi na kimwe uzakwa kubw'ibi bizamini tuzakora, ariko kandi nta nigihembo gitangwa kubwo gutanga aya makuru cyangwa ibi bizamini.
6. Mu gihe cyose uhamagawe kuza kwa muganga kubw'inyungu z'ubushakashatsi, amafaranga y'urugendo uzajya uyasubizwa.

Uburyo amakuru uzatanga azabungwabungwa: amakuru yose arebana n'ubuzima bwawe umushakashatsi azayagira ibanga, keretse mu gihe bigaragayeko ufite ikibazo gisabako abaganga bagukurikirana. Icyo gihe amakuru ajyanye n'ubuzima bwawe azamenyeshwa muganga ugukurikirana wenyine gusa.

Ingaruka wagirira muri ubu bushakashatsi: nta ngaruka n'imwe ku buzima bwawe uzagirira muri ubu bushakashatsi keretseko kugufata amaraso mu mutsi bizakubabaza gahoro.

Uburenganzira bwo kuva mu bushakashatsi: Ufite uburenganzira busesuye bwo kuba muri ubu bushakashatsi cg kutabubamo. Nutabujyamo nta ngaruka n'imwe bizakugiraho; uzakomeza guhabwa serivisi z'ubuvuzi zose wahabwaga hano ku bitaro nk'uko bisanzwe

Inyungu yo kuba muri ubu bushakashatsi: kuba muri ubu bushakashatsi, ku mwanya wa mbere bifiye inyungu abagore muri rusange kuko ibizavamo bizafasha inzego z'úbuzima kumenya neza isano yaba iri hagati y'imiti yo kuboneza urubyaro n'indwara z'umutima. Kuba muri ubu bushakashatsi kandi bigufitiye inyungu z'uko uzamenya uko ubuzima bwawe buhagaze ku bigendanye n' indwara z'umutima, kandi bigaragayeko hari ikibazo cy'ubuzima waba ufite wahuzwa na muganga akagufasha.

Uwo wabaza uramutse ugiriye ikibazo muri ubu bushakashatsi: ugize ikibazo kirebana n'ubu bushakashatsi wahamagara **Evelyne Kantarama kuri nomero ikurikira: 0788651907**. Niba ari ikibazo kirebana n'uburenganzira bwawe muri ubu bushakashatsi wahamagara Umuyobozi mukuru ushinzwe gukurikirana uburenganzira bw'abantu bakorerwaho

ubushakashatsi muri Coleji y'ubuganga muri Kaminuza y'u Rwanda kuri telefone igendanwa nomero: **0783340040**.

Wumvise neza icyo bisobanuye kugira uruhare muri ubu bushakashatsi? Yego …. Oya……

Wemeye kugira uruhare muri ubu bushakashatsi? Yego……. Oya……

Izina n'umukono byawe ko wemeye kugira uruhare muri ubu bushakashatsi

…….

Italiki: ……

Izina n'umukono by'umushakashatsi

…….

Itariki: ……..

Izina n'umkono by'umuhamya wabibonye

…….

Itariki: ……

F. List of Publications

1. **Kantarama E**, Uwizeye D, Uwineza A, Muvunyi CM. Prevalence of Central Obesity and its Association with Cardiovascular Risk Factors among Women of Reproductive Age in Rwanda. *Afr J Biomed Res. 2023;26(1):37–43.* https://doi.org/10.4314/ajbr.v26i1.5
2. **Kantarama E**, Uwizeye D, Uwineza A, Muvunyi CM. Effect of Depot Medroxyprogesterone Acetate on Cardiometabolic Risk Factors Among Women of Reproductive Age in Kigali, Rwanda. *Indian Journal of Medical Sciences. (In Production)- Manuscript #(IJMS_205_2022) Accepted for Publication*
3. **Kantarama E**, Uwizeye D, Uwineza A, Muvunyi CM. Changes in Cardiometabolic Risk Markers in Women with Central Obesity During Depot Medroxyprogesterone Acetate Injectable Contraceptive Use. *Heliyon. under review- Submission number: HELIYON-D-23-05431*
4. **Kantarama E**, Uwizeye D, Mselle T. Prevalence and Correlates of Microalbuminuria among Type 2 Diabetes Patients at Muhimbili National Hospital, Dar es Salaam, Tanzania. *Rwanda J Med Heal Sci. 2021;4(1):84–97.*
5. Uwizeye D, Muhayiteto R, **Kantarama E**, Wiehler S, Murangwa Y. Prevalence of teenage pregnancy and the associated contextual correlates in Rwanda. *Heliyon [Internet].2020;6(10): e05037.*
6. Bosco MJ, Jonas B, **Kantarama E**, Pauline K. Urinary tract infection and antimicrobial resistance profile in patients attending Nemba District Hospital in Rwanda. *Asian J Med Sci. 2020;11(6):101–5.*
7. Kabanyana P, Munyemana JB, **Kantarama E**, Muvunyi CM. Asthma Severity and Self-care Practices Among Asthma Patients. *Innovare J Med Sci. 2021;9(4):27–30.*
8. Martin O, Sankarapandian V, Kemunto MJ, Muchiri N, Albert O, Onkoba K, **Kantarama E** et al. Impact of Intervention Practices on Recurrence of Parasitemia among Artemether-Lumefantrine (Al) Treated Patients in Bushenyi District, Uganda. *J Biomed Clin Sci. 2023;8(1):67–80.*