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DEPARTMENT OF CLINICAL MEDICINE AND THERAPEUTICS

CAROTID ATHEROSCLEROSIS AND CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH RHEUMATOID ARTHRITIS AT KENYATTA NATIONAL HOSPITAL

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF DEGREE OF MASTERS OF MEDICINE IN INTERNAL MEDICINE

DECLARATION

I solemnly declare that this dissertation is my original work and to the best of my knowledge has not been submitted elsewhere for examination.

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LIST OF ABBREVIATIONS

ACR/EURLA	American College of Rheumatology/ European League Against Rheumatism
BP	Blood pressure
CIMT	Carotid Intimal Media Thickness
COX-2	Cyclooxygenase-2
CVD	Cardiovascular disease
DM	Diabetes Mellitus
HDL-C	High Density Lipoprotein Cholesterol
IMT	Intima Medial Thickness
IBM SPSS	International Business Machines Statistical Products and Service Solutions (Formerly statistical package for scientists)
ILs	Interleukins
IL1-β	Interleukin 1 Beta
KNH	Kenyatta National Hospital
LDL-C	Low Density Lipoprotein Cholesterol
MCT	Mixed Connective Tissue
RA	Rheumatoid Arthritis
TC	Total Cholesterol.
TNF-α	Tumour Necrosis Factor-alpha

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with increased cardiovascular disease. The purpose of my study was to determine the prevalence of carotid atherosclerosis and selected cardiovascular risk factors namely: hypertension, diabetes, obesity, dyslipidaemia and smoking among patients with RA at the Outpatient Rheumatoid clinic in Kenyatta National Hospital.

Methodology: This was a cross-sectional descriptive study with a comparative arm, undertaken at the Kenyatta National Hospital, Rheumatology clinic. Study subjects with RA were patients who satisfied the ACR/EULAR 2010 criteria and above the age of 18 years. Comparative arm comprised of age and sex matched individuals without RA. History of medications used, diabetes, hypertension and cigarette smoking were obtained. Bilateral carotid Doppler ultrasounds, blood pressure, weight and height were recorded. Drawing of blood was done from each participant to measure the non-fasting total cholesterol and blood sugar level. The outcomes of interest were prevalence of carotid atherosclerosis as defined as Carotid intima-medial thickness, CIMT, of more than 0.9 mm or carotid plaque, CIMT of more than 1.5 mm and the prevalence of cardiovascular risk factors. Data was analysed by use of SPSS version 21, p value <0.05 considered as significant.

Results: 78 RA subjects were randomly selected of which 8 were excluded. 73 controls were recruited, giving a total of 143 participants. Of all the study participants, not even one had a previous history of cardiovascular event. The prevalence of subclinical carotid atherosclerosis among RA patients was 28.6% Vs 13.7% in those with no RA (p = 0.029). The prevalence of hypertension was 30% in RA Vs 35.6% in those with no RA (p=0.475), Diabetes 4.3% in RA Vs 11.0% in those with no RA (p=0.134). Prevalence of dyslipidaemia was 21.4% among those with RA and 13.7% among those with no RA

(p=0.224). The prevalence of abnormal BMI (>25) was 58.6% among those with RA and 75.3% among those with no RA (p=0.033).

Conclusion: Almost one in every three RA patients had subclinical atherosclerosis. RA patients were more prone to dyslipidaemia than those with no RA.

Recommendation: Subclinical atherosclerosis and dyslipidaemia is common in RA and the clinicians should be alert and intervene early to prevent cardiovascular diseases.

CHAPTER ONE

1.0 Introduction

Rheumatoid arthritis (RA) is a chronic disease that is debilitating. It is associated with cardiovascular risks (1), that cause 50% of the premature deaths in these patients (2). RA predominantly presents with articular features and systemic manifestations have been described. Though joint involvement causes immense pain and disability in this population, the extra-articular manifestations especially cardiac disease is responsible for the biggest clinical impact in both morbidity and mortality in patients with RA(3).

Rheumatoid arthritis has a female preponderance with a four to five fold increase in prevalence below the age of 50. This prevalence changes with age such that in the 7^{th} and 8^{th} decade the male to female ratio is estimated to be 2:1. (4). Cigarette smoking predisposes one to RA, which could also predispose these patients to cardiovascular diseases.

In a recent study by Sheila Jacobs, the effect of various risk factors in the establishment of CVD was evaluated from thirteen rheumatology centres. It was evident that traditional cardiovascular risk factors such as smoking, hypertension and higher total cholesterol levels contributed to CVD. In addition to this, a sizeable percentage of CVD events were attributed to RA characteristics such as disease activity and severity. A total of 70% of CVD events were attributable to all CVD risk factors and RA characteristics combined (separately 49% CVD risk factors and 30% RA characteristics). Among the traditional risk factors, smoking and hypertension had the highest population attributable risk overall among both sexes, followed by total cholesterol. The population attributable risk for disease activity score and seropositivity were comparable in magnitude to that of lipids (5).

Recent studies have shown that reducing the inflammation and thus reducing the disease

activity in RA reduces cardiovascular risk in these patients (6). A study carried out from 2000 to 2007, set out to assess the trend in mortality due to cardiovascular disease in RA patients, compared to decades before 2000, showed an improved overall CV mortality in the recent years. This was hypothesized to be due to better management of the disease activity (7).

A study done in Kenya by Kirui et al in 2009 at KNH found that the prevalence of hypertension was 41.3% in RA patients and 22.5% in the control group. Other risk factors such as dyslipidaemia and cigarette smoking between those with RA and those with no RA showed no statistical difference (8). However, there was an increased prevalence of Type 2 Diabetes in individuals with RA as compared to healthy controls (9).

All these traditional risk factors lead to endothelial dysfunction in RA which contributes to the development of atherosclerosis, but this cannot fully explain the extent of cardiovascular diseases seen in these patients. It is thus postulated that the chronic inflammation largely contributes to the increased cardiovascular risk.

Carotid ultrasonography has been used to investigate the prevalence of atherosclerosis by assessing the presence or absence of plaques and the thickness of the carotid intima and media layers. This helps to identify those with a higher cardiovascular risk and to monitor follow-up.

CIMT predicts future cardiovascular and ischemic stroke incidence (10). Whether treatment of inflammation can cause changes in CIMT is still a discussion point under investigation (11). However, one study has shown reduction in progression but not regression of the CIMT measurement (12).

Our study mainly sought to find out the prevalence of atherosclerosis in subjects with RA in comparison to those with no RA. This was achieved by measuring CIMT and determining whether or not the study participants had plaques in the carotid artery. We also wanted to establish the prevalence of some of the selected cardiovascular risk factors for instance dyslipidaemia, hypertension, cigarette smoking and diabetes. These traditional cardiovascular risk factors were chosen because they were found to be significant in other studies (8, 9)

CHAPTER 2
LITERATURE REVIEW

2.0 Definition

Rheumatoid arthritis (RA) is an autoimmune condition associated with chronic inflammation leading to articular and extra-articular manifestations (13).

2.1 Epidemiology

RA affects people of all ethnic groups with a female preponderance with an increasing prevalence with age. The worldwide prevalence is estimated at 1% (14). There is paucity of data in Africa but the prevalence was estimated to be 0.36% in 1990 and projected that it will be at 0.42% by 2010 (15). However, no studies have been published since then to determine the current prevalence. In Kenya, the prevalence of RA has not been established though a few non prevalence studies have been done, showing characteristics of patients with RA. There was a study done to characterize the patients with Rheumatoid arthritis by Bagg et al, in 1979 (16). Another study done in 1979 by Houba et al looked at the sera of individuals with RA, testing for the occurrence of rheumatoid factor using different methods (17).

RA is associated with a higher incidence of cardiovascular disease (CVD) and especially coronary artery disease (CAD). Though management in RA has improved, morbidity and mortality owing to CVD is still high. CVD contributes to an estimate of 50% of premature deaths in RA(2). Individuals with RA are twice prone to CAD than those without RA (18), similar in extent as that caused by diabetes mellitus (19). At the time of diagnosis, RA patients are over thrice more probable to have suffered a previous myocardial infarction than subjects without RA (18). This is not fully because of diabetes, smoking and

hypertension. Having RA contributes majorly to this, as it is now considered an independent CVD risk factor because of inflammation (20). Propagation of atherosclerosis is faster in RA subjects and these lesions are more susceptible to rupture in comparison to the general populace. These subjects not only have a higher occurrence of CVD events but also have more frequent recurrent ischemic events after acute coronary syndrome (20).CVD does not only impact mortality, but has associated morbidity and poor quality of life. Cytokines and aberrantly stimulated cells of the immune system play a role in the commencement, propagation and exacerbation of atherosclerosis (21).

Atherosclerosis refers to plaque formation mainly in the intima of large and medium sized arteries. Though atherosclerosis was considered to be due to deposition of lipids in the arterial walls, it is now considered a continuous inflammatory process involving both innate and adaptive immunity. Clinical presentation of atherosclerosis arises from atherosclerotic plaque rupture, with thrombosis causing vessel occlusion. Inflammation is key in the balance between plaque erosion and stability. Anti-inflammatory agents used in the management of RA might, theoretically, play a role in secondary prevention of coronary artery disease (CAD).Several coronary risk factors such as hypercholesterolemia, hypertension and diabetes cause damage to the endothelium leading to endothelial dysfunction that trigger atherosclerotic process. However, even young subjects with RA who have a low disease activity and no CVD risk factors have been reported to have endothelial dysfunction (22).

Endothelial dysfunction leads to excessive production of endothelin 1 and decrease in nitric oxide levels. This alters hemostasis, causing more expression of adhesion molecules that promote thrombogenicity. In RA, several studies have shown that the chronic inflammatory

state of the disease predisposes the patient to more endothelial dysfunction, therefore, more prone to atherosclerosis. One study showed that increased amounts of monocyte chemotactic protein-1 induced protein found in RA correlated negatively with levels of nitric oxide and demonstrated increased levels of endothelial dysfunction (23). Another study delivered new insight in the mechanism of endothelial dysfunction in RA. It showed that at the onset of RA, there is enhanced activity of endothelial nitric oxide synthase (NOs) as a compensatory response to endothelial dysfunction. As the disease progresses, there is normalization of NOs activity, leading to an imbalance between NOs and COX-2 pathway and increased plasma levels of IL1-β and TNFα. At this point, endothelial dysfunction is apparent (24).

With endothelial dysfunction, inflammatory cells especially monocytes bind to adhesion molecules on the endothelium, migrating into the subendothelium where they differentiate to become macrophages. These macrophages then phagocytose LDL in the subendothelium, and transform to become foam cells. This contributes to the formation of fatty streaks. Cytokines and chemoattractant molecules such as monocyte chemoattractant protein 1, TNF alpha and ILs) are released by activated macrophages which in turn recruit more macrophages and smooth muscle cells into the plaque. Smooth muscles synthesise extracellular matrix components. Macrophages secrete matrix metalloproteinase enzymes responsible for the digestion of extracellular matrix and cause disruption of the plaque.

The integrity of the plaque and its tendency to rupture is determined by the balance between macrophages and smooth muscle cells. The progression is variable.

2.2 Factors determining plaque integrity

Plaques with a big lipid core, thin cap and have calcification are more likely to rupture. It is also now known that, increased production of matrix metalloproteinases leads to degradation of collagen, making the plaque more prone to rupture. Increased new vessel formation within the plaques and intraplaque hemorrhage is also another reason for a plaque to rupture.

A prospective study done in England showed that RA patients have a plaque phenotype that ruptures more readily as opposed to those in the general population. The plaques also had elevated calcium content and increased inflammation compared to controls (25).

2.3 Link between inflammation and atherosclerosis in RA

Current evidence shows that inflammation correlates directly with rapid progression of atherosclerosis and even death. Baseline CRP levels in recently diagnosed polyarthritis were found to be an independent determinant of CVD-related death in this group of individuals (26). It was found that in the two years preceding formal diagnosis of RA, incidence of myocardial infarction increased (15). This therefore means, before joint involvement in RA, systemic inflammation may result in increased atherosclerosis. Conversely, CVD events increased with the duration of the disease. This was thought to be because of accelerated plaque formation in the carotid artery, thus suggesting need for early therapeutic intervention in these patients.

TNF alpha and IL6 are released into systemic circulation and are independent predictors of subsequent CVD events in these patients (27).

Inflammation may also cause atherosclerosis by increasing LDL oxidation and by alteration

of HDL constituents, causing loss of their capacity to extract cholesterol from atherosclerotic lesions, hence, a reduction in its antioxidant activity. This is thought to be due to reduced paraoxonase (PON) activity. PON activity has been shown to be reduced in RA patients (28).

2.4 Risk factors for atherosclerosis and RA

Smoking predisposes to RA and CVD. Abdominal obesity was found to be more common in RA patients and this is also a risk factor for CVD development. In RA the degree of muscle breakdown is higher than that of fat tissue since it is a catabolic condition. This explains the increased adipose tissue in patients with RA despite the low BMI in these patients. This is important since adipose tissue secretes adipokines which are associated with the propagation of RA and atherosclerosis (29).

2.5 Effect of RA Therapy on Cardiovascular disease risks.

The main goal in treatment of RA is to reduce inflammation. Glucocorticoid use in RA to reduce inflammation and thus control pain has been shown to increase cardiovascular risks. The use of steroid is linked to increased formation of carotid plaques and stiffening of arteries, hypertension, insulin resistance and dyslipidemia. Nonsteroidal anti-inflammatory drugs (NSAIDs) use in pain management confer a CV risk (30).

Methotrexate which is a first-line treatment for RA lowers CV risk. Recent study showed that the use of methotrexate depicted positive correlation with fewer CV events (31). Methotrexate has no effect on lipid profile, hypertension, insulin resistance or increase atherosclerosis (32) Hydroxychloroquine, cornerstone drug used in the management of RA prevents the propagation of atherosclerosis by targeting cytokine production, T cell and

monocyte activation, toll-like receptor signaling, endothelial dysfunction and oxidative stress (33). Tumor Necrosis Factor (TNF) inhibitors have been shown to reduce cardiovascular risk by decreasing inflammation, increasing HDL cholesterol and improved insulin sensitivity(34).

2.6 Subclinical atherosclerosis

Atherosclerosis is a progressive inflammatory condition that causes occlusion of the major vessels. It is a disease of the intima causing plaque formation and narrowing of the vascular lumen. Occlusive lesions of the coronary, cerebral and peripheral arteries can cause deleterious effects such as ischemic heart disease, ischemic strokes and limb ischemia respectively. Subclinical atherosclerosis is vaso-occlusive disease that is not severe enough to cause readily observable symptoms. The incidence and extent of atherosclerosis increases with age. Risk of cardiovascular events can be predicted from measurement of subclinical atherosclerosis.(35).

Because atherosclerosis is a systemic disease, assessment of the carotid for intima medial thickness and presence of plaque formation provides a robust and direct measurement of systemic atherosclerosis.

2.7 Diagnosis of carotid atherosclerosis

Measurement of carotid atherosclerosis involves different invasive and non-invasive techniques. Measurement of the luminal diameter, intima-media thickness and luminal stenosis can be assessed. Presence of a plaque together with its size and volume can also be measured (36).

2.7.1 Intima Medial Thickness

Intima medial thickness (IMT) measurements of the carotid artery with B-mode ultrasound reflects arterial wall alterations which occur due to atherosclerosis. IMT measurements is an acceptable and valid surrogate for atherosclerosis and vascular disease risk. Serial IMT measurements can also provide data on the efficacy of therapy such as lipid lowering agents (37).

2.7.2 Carotid intima medial thickness in detection of subclinical atherosclerosis

Carotid intima-medial thickness (CIMT) is a simple, reproducible, non-invasive and economical tool to access the incremental effect of atherosclerotic risk factors. It is also an independent predictor of future cardiovascular risk and can also identify vulnerable patients who would profit from aggressive interventions to prevent CVD events (38) .

CIMT is a measure of the thickness of the intima and media layer of the carotid artery most commonly assessed by the brightness mode (B-Mode) ultrasound to detect early atherosclerosis. The use of B-mode ultrasound at frequency range of 5-15 MHz can be used to visualize the large superficial arteries like the carotids. Longitudinal images are obtained from the near and far walls of the right and left distal common carotid arteries, the carotid bifurcation and the proximal internal carotid arterial segments. Using standardized ultrasound equipment, protocols and dedicated software for image analysis, the inter-scan, inter-observer and intra-observer reproducibility of CIMT is excellent, an interclass correlation coefficient >0.9 (39).

CIMT measurement is, therefore, indicated in screening for atherosclerosis, risk stratification for future CVD events and suggested as a way of assessing drug efficacy such

as statins and antihypertensive medication (40).

2.8 Increased CIMT and CVD risk

CVD events such as acute coronary syndromes and strokes are common manifestations of atherosclerotic vascular disease. Thus, it is prudent to accurately identify individuals at risk and promptly intervene before such events occur.

An increased CIMT is regarded as atherosclerosis and, therefore, an increased cardiovascular risk. Studies among the general population have shown a gradual graded increase in CVD risk with increased CIMT (41-43).

There are other methods that can be used in detection of atherosclerosis such as measurement of coronary calcium scoring by using computed tomography (CT) scan, high resolution MRI, ankle-brachial index and invasive techniques such as coronary angiography and intravascular ultrasound.

There are several pros and cons in each of the modalities mentioned above. Ankle-brachial index though non-invasive and relatively easy to perform, has the challenge of reproducibility. Coronary calcium score though an established marker of coronary atherosclerosis, exposes patients to a large dose of radiation. Some atherosclerotic lesions which occur without calcification go undetected. The sensitivity of ultrasound, CT and MRI imaging is 94%, 83% and 100% and the specificity is 93%, 73% and 89% (44) Considering the above factors, carotid IMT by ultrasonography was thus chosen as the ideal for this study.

2.9 Study justification

Rheumatoid arthritis is associated with morbidity and mortality. This is mainly because of accelerated atherosclerosis in these patients when contrasted to those with no RA. Studies have shown that cardiovascular events occur almost ten years before in these patients. In addition, these patients are predisposed to other traditional cardiovascular risk factors that cumulatively lead to faster progression of atherosclerosis.

There is, therefore, an increasing need to prevent cardiovascular diseases in people living with RA. Though there was a study done in 2009 that looked at the burden of traditional cardiovascular risk factors in patients with RA at Kenyatta National Hospital, this was ten years ago and a lot has changed in the treatment of RA. There is a greater use of DMARDs in the management of RA and this has helped with reducing cardiovascular risk factors among this population. In addition, this study did not have a comparative arm and no study has been done to assess CVD risk using CIMT measurement in RA which is addressed in this study.

Lastly, this study will compare the prevalence of atherosclerosis in those with rheumatoid arthritis against those without, giving information of the true burden of atherosclerosis in RA patients in our population.

2.10 Research question

What is the prevalence of carotid atherosclerosis as measured by CIMT and some selected cardiovascular risk factors among patients with rheumatoid arthritis on follow-up at Kenyatta National Hospital?

2.11 Study objectives

2.11.1 Primary objectives

1. To determine the prevalence of atherosclerosis as measured by increased CIMT in RA patients compared to healthy non-RA individuals.
2. To compare the prevalence of selected cardiovascular risk factors in patients with RA comparing with those with no RA.
    i. Obesity
    ii. Cigarette smoking
    iii. Diabetes
    iv. Hypertension.
    v. Dyslipidemia

CHAPTER 3
METHODOLOGY

3.0 Study design

Cross-sectional analytical survey that studied patients going to the Rheumatology clinic at KNH. The controls were age and sex matched in a ratio of 1:1

3.1 Selection and recruitment

Cases were those who fulfilled ACR /EURLA 2010 criteria for RA.

The comparative arm constituted of randomly selected age and sex matched healthy individuals-nurses, medical students and support staff working in KNH without RA. Matching by age was done within a five year bracket.

3.1.1 Inclusion criteria

1. Those who were 18 years and above.

2. Those who agreed to sign an informed consent.

3.1.2 Exclusion criteria

1. Those who could not move the neck for reasons such as cervical spine injury or severe muscle pain.

2. Those with impaired mental status making them unable to cooperate.

3.2 Study variables

Independent variable	Dependent variable
1. Obesity	ATHEROSCLEROSIS
2. Hypertension	
3. Cigarette smoking	
4. Diabetes	
5. Dyslipidemia	

3.2.1 Definition of Study Variables

Carotid atherosclerosis

An abnormal carotid IMT or the presence of a plaque on carotid ultrasonography (45)

Abnormal CIMT

A value greater than 0.9mm.(45)

Carotid Plaque

This was designated as CIMT greater than 1.5mm (45).

Hypertension Status

History of patient being on anti-hypertensive medication or systolic BP ≥140 mmHg or Diastolic BP ≥ 90 mmHg was considered as hypertension (46).

Diabetes

Random blood sugar ≥11.1mmol/l or history of the patient being on oral hypoglycemic or

history of using prescribed insulin (47).

Obesity

Obesity was as per WHO guidelines which is BMI≥30.

Cardiovascular event

History or documentation of any of the following: myocardial infarction, stroke, transient ischemic attack, limb ischemia or angina. This was viewed as having had a clinical atherosclerosis.

Dyslipidemia

Total cholesterol: Less than 5.17mmol/l is desirable; 5.17-6.18mmol/l- borderline high; More than 6.19 mmol/l is high (48) .

3.3 Sample size determination

This was calculated using the formula with finite population correction

$n = (Z_{\alpha/2}+Z_{\beta})^2 * (f_1*p_1 (1-p_1) + f2*p_2 (1-p_2)) / (p_1-p_2)^2$

Where $f_1 = (N_1-n)/ (N_1-1)$ and $f_2 = (N_2-n)/ (N_2-1)$

Therefore, $n = X*A / (1 + X*B)$,

Where,

$X = (Z_{\alpha/2}+Z_{\beta})^2 / (p_1-p_2)^2$,

$A = (N_1/ (N_1-1)*(p_1*(1-p_1) + (N_2/ (N_2-1)*(p_2*(1-p_2)$, and

$B = (1/ (N_1-1)*(p_1*(1-p_1) + (1/ (N_2-1)*(p_2*(1-p_2)$

$Z_{\propto/2}$= standard normal deviate for two-tailed test corresponding to 95% CI i.e. 0.05

Z_β= standard normal deviate corresponding to power level of 80% i.e. 0.842

p_1 = proportion of RA patients with atherosclerosis 0.323(49)

p_2= proportion of general population with atherosclerosis 0.260 (50)

N_1 and N_2 = population size (number of 100 followed up at KNH, 61 the staff working at KNH).

X = $(1.96+0.842)^2 / (0.323-0.260)^2$ = 1978,
A = (100/ (100-1))*(0.323*(1-0.323)) + (61/ (61-1))*(0.260*(1-0.260)) = 0.416, and
B = (1/ (100-1))*(0.323*(1-0.323)) + (1/ (61-1))*(0.260*(1-0.260)) = 0.004

Therefore, *n* = 1978*0.416/ (1 + 1978*0.004) = 70.34
Therefore the cases will be 70 and the controls will be 70, in a ratio of 1:1

3.4 Sampling Technique

Consecutive sampling technique was applied to recruit 70 participants with RA.70 age and sex matched controls were conveniently sampled. The principal investigator and the research assistant went to the rheumatology clinic and perused through patient files booked for the clinic and identified those with a diagnosis of RA. They then confirmed the diagnosis based on previous information in the file to determine whether the patient had RA as per ACR/EULAR 2010 criteria. They approached each patient who satisfied this criteria in order of their arrival time to the clinic and invited them to take part in the study. Confirmation of the eligibility of participants was done through assessing the information filled in the eligibility questionnaire. Those who were eligible and agreed to sign the consent form were recruited into the study.

Patients who gave an informed consent and met the inclusion criteria were recruited. Similar procedure was repeated on each recruitment day until the desired sample size was attained. The controls were also conveniently selected from nurses and other workers within KNH.

3.4.1 Recruitment Procedure

Recruited RA patients who had come for their routine follow-up at the KNH rheumatology clinic had blood taken for measurement of non-fasting blood sugar and non-fasting total cholesterol. They also had ultrasound imaging of their carotids done to obtain the CIMT measurement.

Recruited participants in the comparative arm, who were randomly selected age and sex matched individuals working in KNH, had similar tests done, that is non-fasting blood sugar, non-fasting total cholesterol and carotid ultrasonography for the measurement of CIMT.

3.5 Data collection

Relevant medical history to assess CVD risk i.e known history of diabetes, hypertension and smoking was obtained for both the RA patients and those in the comparative arm. History of previous cardiovascular event to establish clinical atherosclerosis was also taken. Blood was taken and blood sugar and total cholesterol measured. Further clinical assessment of their BPs, weight and height were also be documented.

Both the RA patients and those in the comparative arm underwent measurement of CIMT using B mode Doppler.

Blood pressure

Blood pressure was measured as per American Heart Association guideline recommendations, using a standard adult blood pressure cuff and a manual sphygmomanometer with the subject sitting upright with the back and arm supported (51).

Weight

Measurement of each participant was done with the participant being barefoot and wearing very light garments, standing straight on a lever balance. The weight was rounded off to the nearest 100 grams.

Height

Subjects will be measured while barefoot, standing against a wall. They should be looking forward with the set square on their scalp. The measurement will be done to the nearest 0.5 cm.

CIMT measurement

All RA patients who fulfilled the inclusion criteria underwent CIMT measurement as per standard procedure. Both carotids were imaged by an experienced consultant radiologist in the department of Radiology at KNH using a linear array transducer of 6-13 Mhz. Images of the far wall of the common carotid artery (1 cm distal) was documented as per the guideline recommendation (52) Proper positioning of the neck to obtain horizontal position of the vessel with focus and gain adjustments was employed to increase accuracy of the CIMT measurement. CIMT testing was done with patient lying facing upwards and head slightly elevated with a pillow at 45 degrees. The neck was positioned such that it was slightly hyper-extended and rotated. This position was adjusted for optimization of images

(52).

Twelve values of mean CIMT (six on each side) were taken and an average calculated to obtain the mean CIMT. CIMT values above 0.9 mm were considered significant and were associated with an increased absolute risk of cardiovascular disease (45).

3.6 Laboratory procedures

The study participants had blood drawn from the ante-cubital fossa for random blood sugar and total cholesterol. 2mls of blood was drawn from each patient and put in a plain vacutainer bottle. This was then taken to the laboratory where it was handled by qualified laboratory personnel. The sample was then centrifuged and the serum subjected to analysis.

3.7 Quality assurance protocol

Standard operating procedures (SOPs) of Lancet Kenya Laboratories were used for specimen collection, preparation and storage to minimize pre-analytical errors. Machines used were properly calibrated using standard calibration methods and materials and tests assayed against controls.

All carotid ultrasound scans were performed using a single machine, the General Electric Vivid IQ ultrasound machine. The orientation included utilization of the machine and acquisition of images for interpretation and analysis. One radiologist with experience in vascular imaging obtained all the ultrasound scans to reduce on errors. CIMT measurements was obtained electronically using automated software.

3.8 Data analysis

Data was collected, organized, cleaned, coded and evaluated for accurateness in preparation

for analysis using International Business Machines Statistical Products and Service Solutions IBM SPSS version 21 (formerly Statistical Package for Social Sciences).

Descriptive statistics was done by calculating proportions, percentages, measures of central tendency, dispersion and performing cross tabulations, to compute demographic and clinical characteristics. Inferential statistics was done using chi-square to assess significant associations between dependent and independent variables.

3.9 Ethical considerations

Before starting any data collection, the UoN/KNH Ethics and Research Committee granted permission to start the study. Participants were recruited on a voluntary basis. Only participants who agreed to sign an informed consent participated in the study. No coercion, monetary or otherwise was used to make the subjects join or remain in the study.

All the information obtained from the subjects remained confidential. This was achieved by assigning a study number to the participants at enrolment and that number was used to identify participants for all matters related to data analysis. Data collection forms were stored in a lockable cabinet accessible only to the principal investigator. All the data obtained from this study was used solely for the purpose of meeting the objectives stated in this proposal.

CHAPTER FOUR
STUDY RESULTS

Between the months of June to August 2019, the clinic booked 113 RA patients. We consecutively sampled 78 patients. None of the subject participants had a wrong diagnosis of RA as all had certified the ACR/EULAR 2010 criteria for RA. We excluded 6 of them who had Mixed Connective Tissue (MCT) disorder with RA and 2 cases who were below the age of 18. We therefore had a total of 70 cases and recruited 73 age and sex matched controls. None of the study participants in both arms, had a previous history suggestive of a cardiovascular event. The next figure shows the recruitment process.

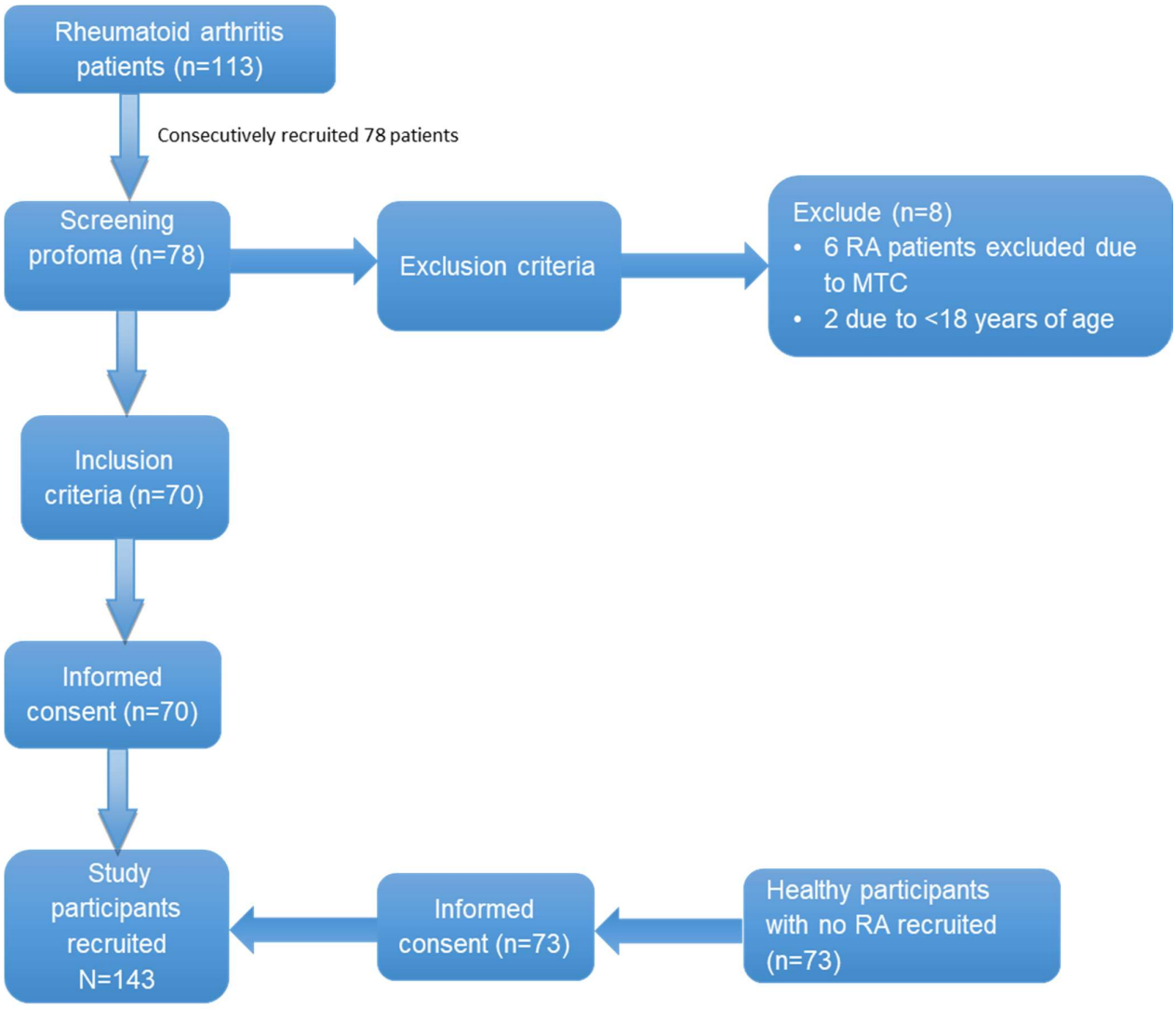

Figure 1: Flow chart of the process of screening and recruitment of the participants in the study.

4.1 Socio-demographic characteristics of study participants

The mean age of RA patients was 47.0 (SD 15.2) while the mean age in the comparative arm was 47.0 (SD 14.9). The median age was 48.5 among those with RA and 51.0 among the comparative arm. The participants were mainly females 134(93.7%), 94.2% among those with RA and 93.2% among the comparative arm. Majority, 79.02 were married, 74.3% among those with RA and 83.6% among the healthy individuals with no RA. 69% had attained tertiary level of education 42 (42.4%) in the RA group and 57 (57.6%) in the comparative group. The next table depicts this.

Table 1: Socio-demographic characteristics

VARIABLE	RA PATIENTS n=70(%)	CONTROLS n=73(%)
Age –years		
Mean(SD)	47.0(SD=15.2)	47.0 (SD=14.9)
Median(IQR)	48.5 (IQR=22)	51.0 (IQR=22)
Sex		
Female	66(94.3)	68(93.2)
Female:male ratio	16.5:1	13.6:1
Marital status		
Single	13 (18.6)	8 (11.0)
Married	52 (74.3)	61 (83.6)
Divorced	2 (2.9)	0
Widowed	3 (4.3)	4 (5.5)
Education		
Primary	4 (5.7)	5 (6.8)
Secondary	24 (34.3)	11 (15.1)
Tertiary	42 (60.0)	57 (78.1)

4.2 Prevalence of Carotid Artherosclerosis

The prevalence of carotid atherosclerosis was 28.6% in those with RA as compared to 13.7% in those with no RA (OR 2.5, p value of 0.029). Of the 20 RA patients with

subclinical atherosclerosis, 8 had plaques while in the comparative arm, 1 out of the 10 with subclinical atherosclerosis had a plaque. 16 (80%) of the RA patients who had subclinical atherosclerosis had other traditional risk factors such as dyslipidemia, obesity, hypertension and DM.

The results of the prevalence of subclinical carotid atherosclerosis are as shown in the table in the next page.

Table 2: Prevalence of subclinical atherosclerosis

Clinical charactaristics	N	Subclinical atherosclerosis		p-value	OR (95% CI)
		SA	No SA		
RA	70 (48.9)	20 (28.6)	50 (71.4)	0.029	2.5 (1.1-5.9)
No RA	73 (51.1)	10 (13.7)	63 (86.3)	REF	

n - Sample size; **P -** P value (level of significance <0.05); **OR** - Odds ratio; **CI** - Confidence interval; **REF** -Reference/Base

4.3 The prevalence of traditional risk factors among those with RA and those with no RA.

The prevalence of hypertension among those with RA was 30% while that among the comparative arm was 35.6%, though this was statistically insignificant (p=0.475). None of the participants with RA were diagnosed to have hypertension during data collection by the principle investigator. However, 2 (0.029%) were newly diagnosed to have hypertension during data collection. The prevalence of diabetes among those with RA was 4.3% while that among the comparative arm was 11% (OR 0.4, 95% CI p=0.134). Prevalence of abnormal BMI (>25) was 58.6% among those with RA and 75.3% among those with no

RA. The p value was 0.033 which was of statistical significance. Prevalence of dyslipidemia was 21.4% among the study subjects with RA as compared to 13.7% among those with no RA (p=0.224).

The prevalence of the traditional risk factors is as shown in the table in the next page.

Table 3: Prevalence of traditional risk factors

Variables	Cases n(%)	Controls n(%)	P
Hypertension			
Yes	21 (30.0)	26 (35.6)	0.475
No	49 (70.0)	47 (64.4)	
Diabetes			
Yes	3 (4.3)	8 (11.0)	0.134
No	67 (95.7)	65 (89.0)	
Cholestrol			
<5.17 (Desirable)	55 (78.6)	63 (86.3)	0.224
5.17-6.18 (Dyslipidemia)	15 (21.4)	10 (13.7)	
BMI			
Normal (18.5-24.9)	29 (41.4)	18 (24.7)	0.033
Abnormal (>25)	41(58.6)	55(75.3)	

CHAPTER FIVE
DISCUSSION, LIMITATION AND RECOMMENDATION

5.1 Discussion

This study set out to find out the prevalence of carotid atherosclerosis as measured by CIMT, among patients with Rheumatoid arthritis compared to healthy individuals without RA. We also compared the prevalence of other risk factors for atherosclerosis such as diabetes, obesity, hypertension and dyslipidemia between those with RA and those with no RA.

When we compared the prevalence of atherosclerosis in the two groups, there was more atherosclerosis in the RA group than in those with no RA. The prevalence of atherosclerosis in RA group was 28.6%. The prevalence in the comparative arm was about half that in the RA group at 13.7% (p=0.029). These results were in agreement with what is found in majority of literature as we expect more atherosclerosis in the RA group (48,51) This is because the chronic inflammation in RA, is in itself an independent CVD risk factor (18). In comparison to other studies, our prevalence was comparable to that found by Christophe et al, in Kinshasa in 2015 (32%). He also used a CIMT cut off of 0.9mm similar to that used in our study. We think their prevalence was slightly higher because his study population was relatively older (mean age of 47 in our study Vs. 51.8 in his study) which increased their risk of developing atherosclerosis (53).

Our second objective was to determine the prevalence of selected cardiovascular risk factors in patients with RA as compared to those with no RA. The traditional CVD risk factors assessed were hypertension, diabetes, obesity, dyslipidaemia and cigarette smoking. Obesity is expected to be less in RA patients because it is a catabolic state. On the other

hand, the other cardiovascular risks are often more prevalent in RA patients because of endothelial damage. Our findings were variable.

The prevalence of hypertension was lower among those with RA as compared to those with no RA. This difference was not significant statistically. The prevalence of diabetes was also lower among those with RA than among the comparative arm. The difference was not statistically significant. These findings could have been spurious and require further evaluation.

Expectedly the prevalence of obesity was lower among the cases (32.4%) as compared to the controls (67.6%). This is because, theoretically, chronic inflammation in RA increases the catabolic rate with loss of muscle bulk (54).

Though more RA patients had a normal BMI as compared to those with no RA, they had more dyslipidaemia at 21.4% compared to 13.7% among the controls. This is in keeping with the physiologic explanation of increased inflammation causing impaired lipid metabolism in RA. Uzma et al in Pakistan found more than double (53.3%) rates of dyslipidaemia in their RA cases compared to our study (55). This could be explained by the fact that we used total cholesterol in our analysis of dyslipidaemia as opposed to the entire lipid profile used in Pakistan. Total cholesterol alone can underestimate derangements in the different lipid parameters. Asians are also ethnically predisposed to dyslipidaemia and this could contribute to higher prevalence seen in this study. Total cholesterol has a modest increase than the alterations seen with HDL cholesterol(56).In addition to this, paradoxically, active RA is associated with reduced levels of Low density lipoprotein and total cholesterol.

In the prevalence of smoking, only one participant in the cases had history of smoking while only two controls were smokers. The low prevalence could be because the population

was composed of female participants and smoking is less prevalent in women as compared to men. The other reason could be that the participants shied away from giving this information.

5.2 Conclusion

Carotid atherosclerosis in our study was significantly higher among those with RA as compared to those with no RA. Almost one in every three RA patients has carotid atherosclerosis. RA patients were found to have lower rates of obesity though they had a higher burden of dyslipidaemia.

5.3 Recommendations

This study has shown that there is a higher prevalence of carotid atherosclerosis and dyslipidaemia in those with RA as compared to those with no RA. The following are therefore recommended:

1. To continuously screen for cardiovascular risk factors in these patients as this may impact cardiovascular disease outcomes.
2. There is a significant increase in dyslipidaemia in those with RA. It would therefore be prudent to recognize this early enough and treat, as this may impact atherosclerosis.
3. It is better to screen for dyslipidaemia using the complete lipid profile than using one component only.
4. A larger cohort study should be undertaken to review the effect of modifying the traditional risk factors on CIMT, whether it will retard the progression or cause regression of atherosclerosis.
5. To conduct a longitudinal study to see the effect of DMARDs on atherosclerosis and other traditional risk factors.
6. There is need for public sensitization on regular blood pressure and blood sugar

monitoring in the general population.

7. Due to the high prevalence of obesity in the general population, there is an urgent need on nutritional advice to the population on the complications related to overweight and obesity.

5.4 Study limitations

1. Blood pressure monitoring on the spot is not a true reflection of patient's blood pressure and this might have influenced the prevalence of hypertension both in the cases and controls.
2. Due to lack of funds, a whole lipid profile could not be done. It would have been good to see the values of other variables such as triglycerides, HDL and LDL.

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APPENDICES

Appendix 1: Screening Proforma

Study number……..

Age……..

Date of birth……..

Contact: Telephone number…….

Number of Next of Kin……

Demographics

Gender: Male

Female

Occupation……

Residence……

Eligibility

1. Are you willing to participate in the study: CAROTID ATHEROSCLEROSIS IN PATIENTS WITH RHEUMATOID ARTHRITIS AT KNH?

   Yes

   No

2. When were you diagnosed with Rheumatoid arthritis?
3. Which medication have you been using for the management of Rheumatoid arthritis?
4. Which of the following tests have you done recently in the last 4 months?

   Random Blood Sugar

   Lipid Profile

   HbA1c

5. (a)Do you suffer from diabetes?

   Yes

   No

   (b) Which drugs are you currently using for Diabetes?

6. (a) Do you suffer from hypertension?

   Yes

   No

   (b) Which drugs are you currently on for the management of hypertension?

7. Have you ever suffered from or told by the doctor that you have any of the following-Tick where appropriate

   Stroke

   Transient ischemic attack

   Heart attack

   Angina Pectoris (chest pain that is caused by poor blood supply to the heart)

   Blockage of arteries supplying the legs

   Had any procedure done on the heart because of blocked arteries

8. (a)Do you smoke cigarettes?

   Yes

   No

   (b) For how long have you been smoking cigarettes?

Kiambatisho 1:

Numbari kwa uchunguzi _____

Miaka _____

Tarehe ya kuzaliwa _____

Numbari yako ya simu _____

Numbari ya familia _____

Takwimu za umma: _____

Jinsia- mwanamume _____

Mwanamke _____

Kazi unayofanya _____

Unakoishi _____

Uhakiki

1. Ungependa kushiriki katika uchunguzi wa kukusanyika kwa mafuta katika mishipa ya damu ya shingo yaani carotid miongoni mwa walioathiriwa na ugonjwa wa viungo, kwa kimombo Rheumatoid Arthritis?
   Ndio
   Hapana

2. Uligunduliwa lini kuwa na ugonjwa wa viungo,yaani Rheumatoid Arthritis?
3. Umekuwa ukitumia madawa yapi kwa minajili ya matibabu ya ugonjwa huu?
4. Baadhi ya vipimo hivi, ni kipi ulichofanya katika muda ya miezi nne iliyopita?
   Kipimo cha sukari kinachofahamika kama Random Blood Sugar?
   Kipimo cha mafuta mwilini
   Kipimo cha sukari ,kwa kimombo HbA1c
5. Unao ugonjwa wa sukari?
   `
   Hapana
   Unatumia madawa gani kwa ugonjwa wa sukari?
6. Unao ugonjwa wa damu kupanda (Shinikizo la damu) kwa kimombo hypertension?

Ndio
Hapana
Ni madawa gani unayoyatumia kwa ugonjwa huu wa shinikizo la damu?

7. Umewai athiriwa au kuelezwa kuwa uko na vifuatayo
   Kiharusi?
   Mshtuko wa moyo
8. Unavuta sigara?
   Ndio
   Hapana
   Iwapo jibu lako ni ndio, umevuta kwa muda upi?

Appendix 2: Consent explanation form

Research Topic:

Carotid Atherosclerosis in patients with Rheumatoid Arthritis seen at KNH

Principal investigator and institution affiliation: Dr. Robina Oyaro, University of Nairobi, Health Sciences.

Co-Investigators and Institutional affiliation:

Professor E. Ogola, University of Nairobi,

Professor Omondi Oyoo, University of Nairobi,

Professor Munyao, University of Nairobi,

Dr. A Aywak, University of Nairobi.

Brief introduction

My name is Dr. Robina Oyaro currently doing master degree in Internal Medicine. I am conducting a study on carotid atherosclerosis and cardiovascular risk factors in patients with rheumatoid arthritis. The purpose of this consent form is to give you the information you will need to decide whether or not you will a participant of this study. Feel free to ask any questions about the purpose of the research, what happens if you participate in the study, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear.

Once you understand and agree to be in the study, I will request you to sign your name in this form. You should understand the following: your decision to participate is entirely voluntary, you may withdraw from the study at any time without necessarily giving a reason for your withdrawal and refusal to participate in the research will not affect the services you are entitled to in this health facility.

This study has approval by the Kenyatta National Hospital- University of Nairobi Ethics

and Research Committee protocol number_____

What the study entails

Rheumatoid arthritis is a condition that is associated with complications such as heart attack, stroke and reduced blood supply to the limbs all due to blockage of the major arteries. Majority of the medication given to manage rheumatoid arthritis also helps to prevent these complications. We do not have recent studies showing the complications that can occur in the blood vessels in our local setup. This study aims at investigating these complications and with these answers, aims at providing better management to the patients.

What will happen if you decide to be in the research study?

If you agree to participate in the study, you shall be asked a few questions about yourself and the disease progress. Then a medical officer will take a few measurements such as weight, height, and draw blood for a few tests. You shall also have a carotid Doppler scan of your neck.

Are there any risks associated with this study?

There are no foreseeable risks associated with this study. Information obtained will be kept confidential as much as possible. You may, however, experience some discomfort when drawing blood for total cholesterol and blood sugar.

Will being in the study cost you anything?

All these shall be at no fee.

We will ask for your telephone number by which we can contact you if necessary.

How will you benefit from the project?

It will enable the patient to know the status of their vessels. If there are any problems noted, the patient will be advised on what to do next to prevent a CVD event.

Confidentiality

Taking part in the study is voluntary and you are free to withdraw from the study if you so wish. Information obtained from this study will be kept confidential and will only be assessed by persons authorized to do so.

What if you have questions in the future?

If you have further questions or concerns about participating in this study, please call or send a text message to the study staff at the number provided at the bottom of this page.

For more information about your rights as a research participant, you may contact the secretary/ chairperson, Kenyatta National Hospital- University of Nairobi Ethics and Research Committee Telephone number 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke

KIAMBATISHO 2

FOMU YA MAELEZO KUHUSU UTAFITI HUU

MADA: Ugonjwa unaosababisha kukusanyika mafuta katika mishipa ya damu ya shingo (carotid) kwa wagonjwa walioathiriwa na ugonjwa wa viungo(Rheumatoid arthritis)

Mtafiti mkuu: Dr. Robina Oyarokutoka chuo kuu cha Nairobi

Watafiti wengine:

Profesa E. Ogola kutoka chuo kuu cha Nairobi

Profesa Omondi Oyoo- chuo kuu cha Nairobi

Profesa Munyao- chuo kuu cha Nairobi

Dr. Aywak- chuo kuu cha Nairobi

Utangulizi

Jina langu ni Daktari Robina Oyaro, ninasomea shahada ya juu katika matibabu ya watu wazima katika chuo kikuu cha Nairobi. Ninafanya utafiti kutathmini ugonjwa wa kukusanyika mafuta katika mishipa ya shingo baadhi ya walio na ugonjwa wa Rheumatoid arthritis. Madhumuni ya fomu hii ni kukupa maelezo unayohitaji kutoa uamuzi iwapo utapenda kujiunga na utafiti huu. Uko na uhuru wa kuuliza swali lolote kuhusu utafiti huu, kitachofanyika iwapo utajiunga na utafiti huu, faida na hatari za utafiti huu na swala lolote lisiloeleweka katika fomu hii.

Utakapo elewa na kukubali kugiunga katika utafiti huu, utahitajika kutia sahihi katika fomu hii.

Ningependa uelewe yafuatayo:kuwa uwamuzi wa kushiriki katika utafiti huu ni kwa hiari yako, uko huru kujiondoa wakati wowote bila kupeana sababu yoyote na kuwa iwapo utaondoka, hakutakuwa na adhabu yoyote wala maafa na utapewa huduma unayoitaji

katika hospitali hii bila ubaguzi wowote.

Utafiti huu umepewa kibali na kamiti ya Chuo kuu cha Nairobi pamoja na Hospitali kuu ya Kenyatta , numbari _____

Utafiti wenyewe

Kwa ajili ya mkusanyiko wa mafuta kwa mishipa mwilini hasa kwa wagonjwa wa RA, baadhi yao hupatwa na magonjwa mbali mbali kama kiharusi (stroke), mshtuko wa moyo yaani heart attack. Utafiti huu unatafuta sababu ya haya kutokea na njia ya kujua kuwa mtu aliye na RA ana uwezekano wa kupata madhara haya.

Ukijiunga na utafiti huu

Iwapo utakubali kujiunga na utafiti huu, utaulizwa maswali kadhaa, kupimwa mwili kikamilifu na kupigwa picha ya shingo ili kuona iwapo pana shida yoyote. Damu pia itatolewa kupima kiwango cha mafuta mwilini na kiwango cha sukari mwilini.

Je,utalipa chochote?

Vipimo hivi vyote vitagharamiwa na mtafiti mkuu wala hautahitajika kulipa chochote.

Manufaa ya kujiunga na utafiti huu

Utaweza kujua iwapo una mafuta mengi kwa mishipa ya shingo na iwapo mafuta iko, utaelezwwa jinsi ya kujikinga na matokeo kama kiharusi.

Swala la kuhifadhi rekodi kwa siri

Rekodi zote za matibabu na matokeo yatawekwa siri na kuangaliwa na watafiti walioidhinishwa pekee.

Ikiwa utakuwa na maswali mengine baadaye:

Tafadhali piga au tuma ujumbe mfupi katika simu kwa numbari iliyoandikwa katika fomu hii.

Kwa ujumbe Zaidi, piga nambari 2726300 Ext. 44102 au tuma barua pepe kwa uonknh

erc@uonbi.ac.ke.

Asante sana kwa kuchukua muda wako kusoma maelezo haya.

Appendix 3: Patient consent form for participation in the study.

I, …….consent that I have read and understood the explanation given regarding this project. All my questions have been addressed fully. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study.

Participant's name…….. Signature ……

Date……

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly given his/her consent.

Researcher's name _____ Date _____

Signature _____

For further information you may contact

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Kenyatta National Hospital- University of Nairobi Ethics and Research Committee

Telephone number 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke

KIAMBATISHO 3

Mimi _____ natia sahihi kuwa nimesoma na kuelewa maelezo yote nimepewa kuhusu utafiti huu. Maswali yangu yote yamejibiwa kikamilifu.Faida na hatari ya utafiti huu yameelezwa kikamilifu. Ninaelewa kuwa kujiunga na utafiti huu ni kwa hiari yangu na kuwa ninao uhuru wa kujiondoa wakati wowote.

Jina la mshiriki _____ Tarehe _____

Sahihi ya mshiriki _____

Kauli ya mtafiti

Ninatia sahihi kuwa nimemwelezea mshiriki maswala yote na ninaamini kuwa ameelewa na kukubali kushiriki bila shinikizo lolote.

Jina la Mtafiti _____ Tarehe _____

Sahihi _____

Kwa maelezo Zaidi

Wasiliana na

Dr. Robina Oyaro

Sanduku la Posta 2542-40100

Numbari ya simu 0728451559

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