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PREVALENCE OF THYROID DYSFUNCTION AMONG RHEUMATOID ARTHRITIS PATIENTS ATTENDING THE RHEUMATOLOGY CLINIC AT KENYATTA NATIONAL HOSPITAL

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

DECLARATION

I certify that this dissertation is my original work. It has not been presented for the award of a degree in any other institution. Where other people's work or my work has been used, this has been properly acknowledged and referenced as per the University of Nairobi's requirements.

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DEDICATION

I dedicate this work to my daughter Ella, my family, teachers, friends and fellow residents without whom it would not have been possible to complete my study.

LIST OF ABBREVIATIONS

ACR/EULAR: American College of Rheumatology/European League Against Rheumatism

AITD: Autoimmune Thyroid Disease

BMI: Basal Metabolic Index

CATCH: Canadian Early Arthritis Cohort

CDAI: Clinical disease activity index

CRP: C Reactive Protein

CVD: Cardiovascular Disease

DAS: Disease Activity Score

DAS 28: Disease Activity Score 28

DMARDS: Disease Modifying Anti Rheumatic Drugs

EDTA: Ethylenediamine Tetraacetic Acid

ESR: Erythrocyte Sedimentation Rate

FT3: Free Triiodothyronine

FT4: Free Tetraiodothyronine

HAQ: Health assessment questionnaire

HAQ-DI: Health assessment questionnaire- Disability Index

HLA: Human Leucocyte Antigen

KNH: Kenyatta National Hospital

MHC: Major Histocompatibility Complex

NHANES III: National Health and Nutrition Examination Survey III

PAD 14: Peptidyl Arginine Deaminase 14

PI: Principal Investigator

PTPN22: Protein Tyrosine Phosphatase Non-receptor type 22

RA: Rheumatoid Arthritis

SDAI; Simplified Disease Activity Index

SJC: Swollen Joint Count

STAT 4: Signal Transducer and Activator of Transcription 4

SPSS: Statistical Package for the Social Sciences

TGab: Thyroglobulin antibody

TJC: Tender Joint count

TPOab: Thyroid Peroxidase Antibody

TSH: Thyroid Stimulating Hormone

UON: University of Nairobi

VAS: Visual Analogue Scale

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic polyarthritis affecting 0.5-1% of the adult population. It also present with systemic manifestations that include; subcutaneous nodules, hematological changes, neuropathy, myopathy, scleritis, episcleritis, vasculitis, and renal disease. The cause of RA is unknown but knowledge of its pathogenesis is anchored on autoimmunity with recognition of self-antigens as foreign leading to chronic inflammation in the various tissues. A higher prevalence of thyroid dysfunction is observed in patients with RA compared to the general population. This increase has been attributed to the common pathogenetic mechanism of autoimmunity in RA and Autoimmune thyroid disease.

There is some overlap between the clinical manifestations of thyroid dysfunction and those of RA including arthritis, myopathy, neuropathy, and hematological changes. RA patients with concurrent thyroid dysfunction will have more symptoms and a worse functional status despite appropriate therapy. Further thyroid dysfunction and RA are both considered to be contributing factors to the development of cardiovascular disease.

Objectives: The objective of this study is to establish the prevalence of thyroid dysfunction among ambulatory RA patients at the Kenyatta National Hospital Rheumatology clinic. The secondary objective is to describe the association between thyroid dysfunction and the patients' demographic characteristics, level of disease activity, and their functional status.

Methodology: This was a cross-sectional descriptive study conducted at the Kenyatta National Hospital Rheumatology clinic. We included all consenting adult patients on follow up for RA and meeting the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA. Recruited patients underwent a face to face interview and their sociodemographic data and clinical details were obtained from their records. A thorough physical examination focusing on the musculoskeletal system was conducted. A venous blood sample was obtained and analyzed

for

Thyroid-stimulating hormone (TSH), free triidothyronine (fT3), and free tetraiodothyronine (fT4). The Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ) scores were computed from the examination findings, laboratory tests, and the questionnaires.

SPSS version 21.0 Chicago Illinois was used for data entry and analysis. Prevalence of thyroid dysfunction was calculated as a percentage. The various types of thyroid function abnormalities were presented as percentages. Odds ratio was used to test the association between the presence of thyroid function abnormalities and patient demographic characteristics, disease activity scores, and functional status. P-values and 95% confidence intervals (CIs) were calculated where applicable. P-value <0.05 was considered statistically significant.

Results: A total of 76 patients were recruited into the study. Sixty-one (61) participants were females while fifteen (15) were male; the male to female ratio was 1:4. The mean TSH level was 5.8Miu/L. The prevalence of thyroid dysfunction was 47.4%. Thirty-nine percent of participants had overt hypothyroidism, 6.6% had Sick euthyroid and 1.3% had subclinical hypothyroidism. The majority of patients, 59(77.6%) had low disease activity or were in remission. Forty-one (53.9%) participants had no disability as estimated by the HAQ. Correlations between thyroid dysfunction and advancing age, longer duration of disease, level of disease activity, and functional disability did not attain statistical significance.

Conclusion: We found a high prevalence of thyroid dysfunction among patients with RA. We observed no association between thyroid dysfunction and advancing age, longer duration of disease, increasing severity of disease, and functional disability.

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CHAPTER ONE

1.0 INTRODUCTION AND PROBLEM STATEMENT

1.1 INTRODUCTION

Rheumatoid arthritis (RA) refers to a symmetric polyarthritis caused by joint inflammation, coupled with a variety of systemic manifestations that include; subcutaneous nodules, hematological changes, neuropathy, scleritis, vasculitis, and renal disease. The estimated worldwide prevalence among the adult population is 0.5-1%(1).

The exact etiology of RA has not been elucidated; however current evidence in the understanding of the mechanism of disease have led to the development of targeted medical strategies that have reduced disease progression. Autoimmunity resulting in persistent uncontrolled inflammation that leads to erosive joint inflammation is central to the pathogenesis of RA. Despite therapy, many patients experience a chronic progressive fluctuating course of the disease that may result in severe joint destruction and deformities (2).

Thyroid dysfunction has been described in 1-10% of the adult population with wide variations depending on sex, age, demographic location and even testing modalities (3). The most common cause of dysfunction is deficiency of iodine commonly presenting with goiter formation and various degrees of hypothyroidism (4),5). Autoimmune associated thyroid disease is the other common cause of thyroid dysfunction (5).

1.2 PROBLEM STATEMENT

Thyroid dysfunction occurs more commonly in RA patients and those with autoimmune diseases in contrast to those without these conditions. Possible explanations for this include the observation that autoimmune conditions tend to overlap due to the common pathogenetic mechanism of loss of self-tolerance (6).

The clinical manifestations of RA also overlap significantly with musculoskeletal features of thyroid dysfunction that include myopathy and arthropathy, this may mask the diagnosis of thyroid disease. For this reason patients on management for RA who have concurrent thyroid dysfunction that remains

undiagnosed may remain symptomatic despite optimal RA management and these patients will also have worse physical functional status (7).

Both RA and thyroid hormone dysfunction are known risk factors for cardiovascular disease. Their co-occurrence has been found to confer additional risk for cardiovascular events above that caused by the conventional risk factors (6,7).

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 BACKGROUND

2.1.1 EPIDEMIOLOGY AND PATHOGENESIS OF RHEUMATOID ARTHRITIS

RA is a symmetric polyarthritis that affects 0.5-1 percent of the population worldwide (1). There is a female preponderance, with a 2-4-fold higher incidence in females than males; this has been attributed in part to the role played by hormones such as estrogen in the pathogenesis (8). In 1979 Bagg et al described 76 RA patients at KNH where he found that the male to female ratio was 1:2.8 congruent with the pattern in the West but in more recent local studies an even greater female preponderance has been demonstrated; Owino et al in 2007 conducted a study in KNH on the evaluation of clinical and quality of life of patients with RA and found that, 52 were female with male to female ratio of 1:6.5(9), (10). Similarly, Mbuthia B in a study on platelet counts in patients with RA found a male to female ratio of 1:6.4(11). Ndirangu et al in a study on disease activity measurement among RA patients at KNH described a higher ratio of male to female at 1:8.5(12).

The pathogenesis involves an interaction of various genetic factors and environmental triggers. Human Leucocyte Antigen DRB1 (HLA DRB1) alleles constitute the main genetic risk factor. The strongest susceptibility to RA has been linked to the HLA DRB1*0404 allele (13). Non-Major Histocompatibility Complex (MHC) genes linked to RA include Protein tyrosine phosphatase, non-receptor type (PTPN22), Peptidyl arginine deaminase 14 (PADI4), and signal transducer and activator of transcription (STAT) genes. These risk alleles however do not explain the entire role of genetics in RA disease causation, they only represent about 5% of the entire genetic burden (13).

Cigarette smoking and various infections have been found to trigger or alter the expression of RA.

Infectious agents are thought to act as triggers to the inflammation that is central to the pathogenesis of RA. *Epstein barr* virus, *Parvovirus* and *Escherichia spp* have been implicated. Molecular mimicry is the postlated process by which inflammation is triggered (13), (2).

Heavy cigarette smoking in males causes an increased risk of RA equal to the risk of RA in females. (14). Cigarette smoking relates to the pathogenesis of RA by aggravating oxidative stress, chronic inflammation, and formation of autoantibodies (1), (14).

Interactions between genetic factors and environmental exposures leading to break down of recognition of self-antigens are core in the mechanism of disease. Lymphocyte responses characterized by an orchestrated interplay of pro-inflammatory cytokines initiate and maintain a chronic inflammatory state and cause articular damage. Inflammation in various tissues leads to the other systemic manifestations of RA (1).

RA is linked to enhanced cardiovascular disease risk. The state of chronic systemic inflammation in RA causes atherogenesis with circulating cytokines postulated to cause pro-atherogenic changes in various tissues including adipocytes, the pancreas, and the liver. Cytokines also cause endothelial dysfunction and damage in areas distant from the inflamed joints triggering an acceleration of atherogenesis (15).

The severity of depression among RA patients was found to correlate with the level of inflammation measured by C-reactive protein (CRP) in recent studies (16).

2.1.2 Epidemiology and pathogenesis of Thyroid dysfunction

In the adult population the prevalence of thyroid dysfunction ranges from 1-10 percent (5). The majority of cases from community screening programs have subclinical thyroid dysfunction (3).

In the USA, the National Health and Nutrition Examination Survey (NHANES III) which included 13,444 disease free people above 12 of age, the prevalence of thyroid dysfunction was as follows; hypothyroidism was described in 4.6% of study subjects and majority had subclinical hypothyroidism (4.3%).

This study found that higher TSH levels were observed with advancing age and also occurred more frequently in female subjects (17).

The Colorado thyroid disease prevalence study of 24,337 participants who on average were 56 years old, found increased TSH levels in 9.5% of all the total study population, and 8.9% of those who had not been

on any form of thyroid hormone therapy previously. In this study high TSH levels were more frequent in females than in males; 16 percent of females aged 65-74 years vs. 11% in males of the same age cohort (18).

Iodine deficiency has been the commonest cause of thyroid dysfunction. This has however been attenuated by community iodization programs. Hypothyroidism occurs in 1-2% of adults and is 10% more frequent in females and with advancing age (5).

There scanty data on thyroid dysfunction in Africa and the exact prevalence is not known. A Study in Nigeria on thyroid disorders in sub-Saharan Africa in 2011 revealed that iodine deficiency was the commonest cause of thyroid dysfunction. The prevalence of AITD was 1.2 to 9.9 percent with Graves' disease manifesting as thyrotoxicosis being a common biochemical disorder (4).

Autoimmune diseases tend to overlap as a common consequence incited by loss of self-tolerance. There are shared genetic abnormalities in the HLA region that result in this co-occurrence of autoimmune disease (19). Consequently, RA patients tend to disproportionately have other autoimmune conditions including autoimmune thyroid disease (AITD) and insulin dependent Diabetes Mellitus. The pathogenesis of thyroid dysfunction among RA arthritis patients is thought to be due to autoimmunity resulting in chronic inflammation and this has been inferred from studies on the prevalence of thyroid antibodies and how they correlate with disease activity (20), (21).

Thyroid specific antibodies have been found in increasing frequency in patients on follow up for RA. In a study of 70 patients, twenty-six (37%) of RA patients had Thyroid peroxidase antibody (TPOab) and 16 (23%) had Thyroglobulin Antibody (TGab). Further a correlation was observed with the TGab and Erythrocyte sedimentation rate (ESR), which is a surrogate for RA disease activity, $p = 0.014$. There was also a correlation with the TGab and fT3 levels, $p= 0.037$. However, the association between thyroid-specific antibodies and surrogates for disease activity, was insignificant (20).

2.2 PREVALENCE AND PATTERN OF THYROID DYSFUNCTION AMONG RA PATIENTS.

The burden of thyroid dysfunction in the RA patient population ranges between 12-44% in various studies. The commonest abnormality is hypothyroidism [overt/subclinical].

In a study of 150 patients on follow up for RA in Egypt, 29.3% of participants had thyroid profile abnormalities. Hypothyroidism was the commonest disorder i.e. 24%, while 4% and 1.3% had subclinical hypothyroidism and subclinical hyperthyroidism respectively (22).

In Egypt Hala H. Mosli in a retrospective study on the prevalence of thyroid dysfunction in RA patients reviewed data collected on 151 patients and found as follows; subclinical hypothyroidism 19.2%, overt hypothyroidism 2.6%, and hyperthyroidism in 0.7% of participants (23). A positive correlation was described between presence clinical hypothyroidism and positive Rheumatoid factor, p=0.027.

One study in India by Nadeem and colleagues included 385 RA patients in 2017. They demonstrated a rate of 47% thyroid dysfunction most of the cases being Subclinical hypothyroidism (37.9%). The other significant observation was 3.6% overt hypothyroidism (24).

In a study in Montreal Canada, of the 91 RA patients studied, 30% had evidence of thyroid dysfunction with 18 patients having hypothyroidism, 6 subjects had confirmed Hashimoto's thyroiditis while 1 patient had Graves' disease (25). Table 1 provides a summary of studies on thyroid dysfunction, the geographical locations, study populations, and the prevalence observed.

Table 1: Summary of various studies on the prevalence of thyroid dysfunction in Rheumatoid arthritis

AUTHOR	NO. OF PTS	POPULATION	PREVALENCE OF DYSFUNCTION	TYPE OF THYROID DYSFUNCTION
Osama(26)	122[42 RA]	Jordan	Total 21.3% RA 14.3%	Subclinical hypo 7.1% Hypothyroid 4.7% Hyperthyroid 2.3 %
Nadeem(24)	[385]	India	47%	Subclinical hypo 37.9% Hypothyroid 3.6% Euthyroid 5.2%
Quian li(27)	[65]	China	32.3%	Hypothyroid 26.2% Hyperthyroid 6.2%
Jeffery (25)	91	Canada 30%	Hypothyroid 20%	Hashimoto's 6%
Prakash(28)	52	India	38.4%	Hypothyroid 38.4%
Hala Mosli(23)	151	Saudi Arabia	26.3%	Subclinical hypo 19% Hypothyroid 4% Subclinical hyperthyroid 2.6% Hyperthyroid 0.7%
Enas(22)	150	Egypt	29.3%	Subclinical hypo 4.1% Hypothyroid 24% Subclinical hyperthyroid 1.3%

2.3 THYROID DYSFUNCTION AND RA PATIENT DEMOGRAPHICS

RA has a female preponderance. Thyroid dysfunction among RA patients has also be found in higher frequency among female than male patients (22).

In one Canadian study, a controlled prospective survey, RA patients were evaluated for thyroid dysfunction alongside healthy controls. The occurrence of thyroid dysfunction was found to be 30% among female RA subjects and only 7% among the male RA subjects, compared to 11% among the female controls and none in the male controls (25). Comparing female subjects with RA to the female controls for the occurrence of thyroid disease, there was a significantly higher prevalence of thyroid dysfunction in RA (p>0001), odds ratio 3.5. In Contrast, another study in India by Prakesh Joshi and colleagues found no significant difference in the occurrence of thyroid dysfunction among women and men with RA, P value=0.591(28).

The duration a patient has had the diagnosis of RA may influence the occurrence of thyroid dysfunction. A positive correlation between a longer duration of disease and higher rates of thyroid dysfunction has been described in various studies (22).

In a study on RA patients in India, those having both hypothyroidism and RA for more years; 11 years+/-7.9 compared to those with RA but with no thyroid dysfunction; 7.2years+/-5.4. This observation was significant P-value 0.033(28). Similarly, in a study on RA patients in Egypt, a longer disease duration 9.8 years +/-4.3 was associated with more occurrence of thyroid dysfunction than a shorter duration of disease 3.2years+/-5.3, P-value <0.05(22). In contrast, a cross-sectional analytical Columbian study of 800 patients with RA for the occurrence of AITD found that there was no notable increase in the development of AITD in those who had RA for more than 10 years, AOR 0.27, P-value 0.058(21).

2.4 Effect of thyroid dysfunction on RA disease activity

2.4.1 Development and validity of RA Disease activity scores

In RA activity of disease cannot be determined using any one single variable. A variety of clinical, laboratory, radiological, and general patient assessment values are used to infer the burden of disease. Various composite scores have been developed among RA patients to quantify joint inflammation in daily clinical practice providing crucial information for treatment decision making. Scores that correlate well with actual joint inflammation are best able to predict long term outcomes (29),(30). Various scores have been developed such as Disease Activity Score involving 28 joint counts (DAS 28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI).

DAS28 is one of the widely used scores of disease activity. It utilizes assessment of swollen joints, Tender Joints (TJC), the level of acute phase markers; ESR or CRP, and a mark on patient's self-report of their general health which is subjected to a formula that gives one score that factors in the different weighting of each variable resulting in one measure of disease activity (30).

Disease Activity Score (four variables) =DAS28-4=0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*in(ESR) + 0.014*(General Health) (30).

The SDAI score was developed after the DAS28 score to eliminate the need for a calculator and the complex weighting of the variables that make up the composite score. It involves a tally and subsequent simple summation of 5 variables; TJC (0-28), SJC (0-28), CRP (0-10mg/dl), the patient's and provider's assessment of their disease activity on a visual analog scale (0-10cm). In the development of the SDAI, it was correlated with DAS 28 with a Pearson co-efficient of 0.9 at the beginning of the study and at the end of 6-12 months of follow up (31).

The CDAI score was further derived from the SDAI. It has greater utility in clinical practice as it excludes the use of acute phase reactants which in daily clinical practice might not be available at the time of evaluating a patient. This aids in quick decision making on patient management based on a spot assessment.

The 28 SJC and 28 TJC and The Patient Global Assessment and Provide Global Assessment are summed up. The level of disease activity is interpreted as follows

a) Remission <0- 2.8
b) Low activity 2.9- 10.0
c) Moderate activity 10.1- 22.0
d) High activity > 22.1- 76.0

CDAI was also found to correlate with both SDAI and DAS 28 at 0.87-0.90. The exclusion of CRP only left 5% of SDAI unexplained in the original CDAI study. Further, the ESR in DAS 28 only had a contribution of approximately 15% to the final score (31).

CDAI score is reliable, reproducible, and predictive of actual joint damage as it correlates with radiographic changes estimated using by Larsen scores (R 0.59, P=0.0001). The CDAI is endorsed by the ACR and European League against Rheumatism (EULAR) for RA disease activity measurement in patient monitoring. It is easy to use (32).

In KNH a study by Ndirangu et al sought to measure the congruence of these three Disease activity measurement tools among RA patients. The correlation coefficient between DAS28 and SDAI was 0.960 while that between DAS28 and CDAI was 0.892 both of which were statistically significant, P<0.001.
They found congruence of SDAI and CDAI with DAS28 for moderate and high disease activity categories. DAS28 was however found to over-classify patients as being in remission by redistributing them from the low disease activity category (12).

The CDAI score was be used to estimate disease severity in this study.

2.4.2 THYROID DYSFUNCTION AND RA DISEASE ACTIVITY

Thyroid dysfunction has been found to occur more frequently in RA patients with higher activity of disease. One study of 58 RA patients in India found an association between TSH levels and DAS 28 scores, P-value

=0.0033, similarly a correlation was demonstrated between elevated ESR and elevated TSH P-value =0.043(28).

A study on the prevalence hypothyroidism and its relation to disease activity among Egyptian patients enrolled 150 patients with RA and 50 suitable controls. Those who had RA and hypothyroidism had higher DAS 28 scores those who only had RA, P-value=0.05. Additionally, the participants with both RA and hypothyroidism had higher ESR levels than those with RA only, P-value=0.0005(22).

In Saudi Arabia, a retrospective survey of 151 RA patients found that 26.5% of patients had thyroid dysfunction with the majority having subclinical hypothyroidism. The correlation between TSH and CRP was significant, P-value=0.029. High CRP occurred with high TSH level, and hence likelihood of having hypothyroidism (23).

2.5 Effect of thyroid dysfunction on RA patients functional status

2.5.1 The health assessment questionnaire structure and validation

Originally developed in 1978, the Health Assessment Questionnaire (HAQ) is a self-reported tool used in determining the functional status of patients across many disease entities including arthritis. It describes patient outcomes in 5 main domains i.e. disability, discomfort, pain, drug side effects, and cost of health care (33), (34).

The short version of the HAQ assesses disability, discomfort, and pain. Disability is assessed in the following categories; Dressing, arising, eating, walking, personal hygiene, reach, grip, and usual activities.

Patient responses relate to the week before the interview and are scored from 0 to 3. Where 0 represents no difficulty in performing the activity while 3 represents complete inability to perform the activity. Dependence on physical aids such as a walking cane and assistance in performing tasks is also factored in; this increases the overall score in the category being tested. A horizontal Visual Analogue

Scale is used to score the patient's level of pain from 0 to 3. 0 represents no pain while 3 represents severe pain. An overall score from the 8 tasks is then computed (33).

The HAQ is frequently used to assess functional status in RA (33). It has been tested and validated as a dependable measure for the assessment of functional status across many population groups. The test and retest correlations to confirm the reproducibility of the scores have been found to range from 0.87 to 0.99. Further, the correlations between the questionnaire scores obtained and the actual ability to perform the tasks have been found to range from 0.75 to 0.99 indicating criterion for validity (33).

Originally developed for the United States in English, various translations and language modifications have been made but the original version remains copyrighted to guarantee validity. Translations are usually done at the interview level by the questionnaire administrator. Cultural adaptations to include common expressions and translated versions have been found to be reliable and valid (33).

The HAQ scores correlate with other health status measures including DAS and biochemical markers of disease burden. In a Canadian study of 1143 newly diagnosed RA patients, correlations between HAQ and the DAS 28 were done at 3 month intervals for the first year and then at 18 and 24 months of follow up. There was variable correlation throughout though the strongest correlation was found at the initial visit ($r=0.59$ $n=1143$) and then at 18months ($r=0.57$ $n=321$) and 24 months ($r=0.59$ $n=214$) (35).

In a study conducted on 95 Iraqi RA patients to assess the validity of HAQ, there was a correlation between HAQ scores and tender joint counts P-value=0.005. This correlation was found stronger in those with high activity of disease P-value=0.005 than those with moderate activity of disease P-value=0.109(36).

2.5.2 THYROID DYSFUNCTION AND RA PATIENT FUNCTIONAL STATUS

In a study on the prevalence hypothyroidism and its relation to disease activity among 150 RA patients and 50 controls in Egypt, patients who had both RA and hypothyroidism scored higher in the Modified Health Assessment Questionnaire (MHAQ), an average of 11.98 compared to those with RA with no thyroid dysfunction whose average score was 3.98. This correlation was statistically significant, P-value <0.05(22).

2.6 STUDY JUSTIFICATION

The thyroid profile of RA patients who are newly diagnosed or on follow up is seldom evaluated. As a result, there are no local studies on the burden of thyroid dysfunction in this particular patient population. This study will bridge this gap in knowledge.

There is considerable overlap in musculoskeletal symptoms of thyroid dysfunction and RA and co-occurrence of these conditions may explain some observed poor patient functional status despite being on otherwise adequate management for RA (7). This study will identify the specific characteristics of RA patients with thyroid dysfunction hence provide data on criteria for selection of patients for screening for thyroid dysfunction.

Both abnormal thyroid function and RA contribute to development of cardiovascular disease independent of the other well elucidated factors. Identifying thyroid dysfunction in RA is important since these patients are at additional risk and may require more intense modification of risk factors (8), (6), (18). This study will characterize these patients with increased cardiovascular risk who require intensive risk factor modification.

This study will identify the characteristics of RA patients that are at risk of having abnormal thyroid function and provide a guide on which subset of patients need screening for early diagnosis of thyroid dysfunction and timely intervention.

2.7 SCOPE OF THE STUDY

This study will access patients with established RA at the Kenyatta National Hospital rheumatology outpatient clinic. It will involve physical examination to establish disease activity among recruited patients. A blood sample will also be collected to determine the thyroid function of recruited patients. Further, the Health assessment questionnaire will be administered to determine these patients' functional status.

2.8 CONCEPTUAL FRAMEWORK

Narrative

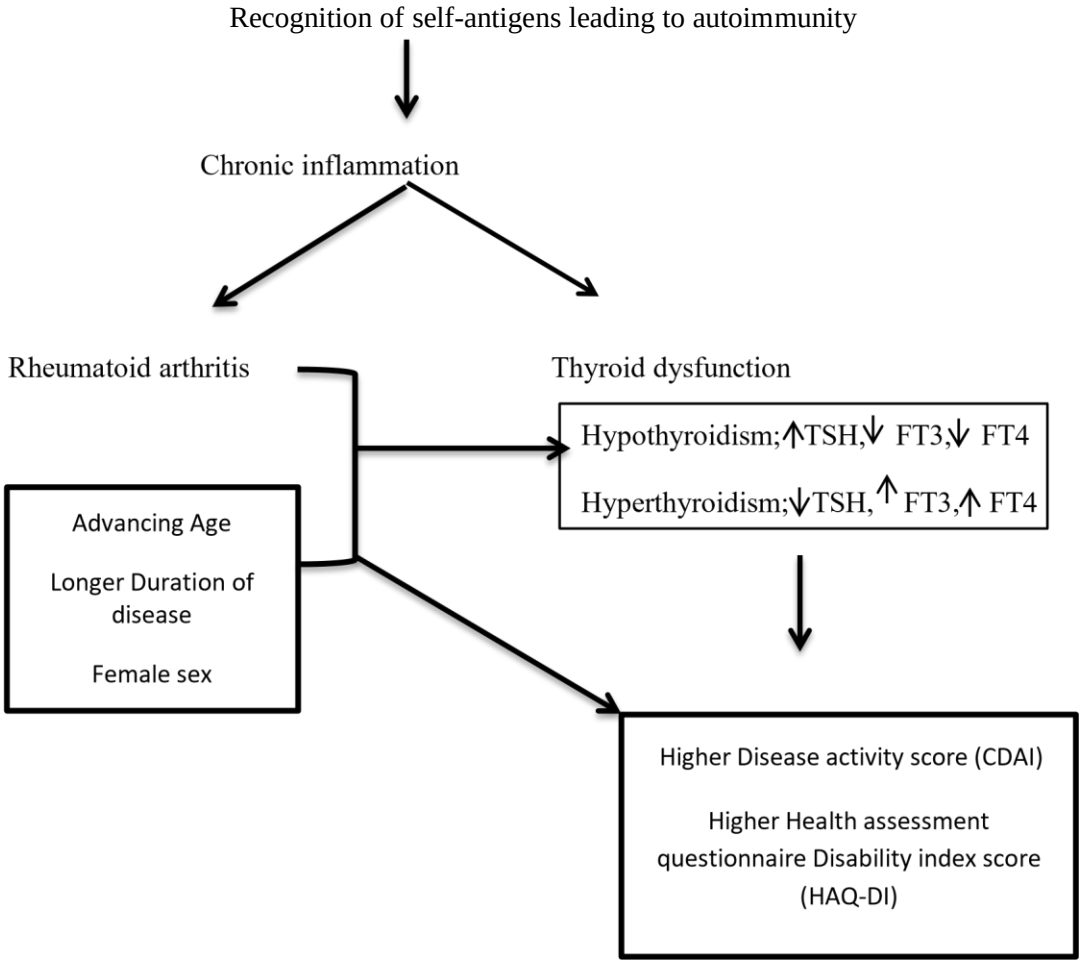
RA is a condition caused by chronic inflammation which is autoimmune in origin. There is often an overlap of autoimmune conditions with loss of self-tolerance and subsequent destructive chronic inflammation which is also implicated in causation of AITD. The result is thyroid dysfunction; thus RA patients are likely to have more thyroid dysfunction than those without RA. Thyroid dysfunction may manifest as hyperthyroidism or hypothyroidism.

Thyroid dysfunction among RA patients is more likely if they are female, older, and have a longer duration of disease.

Further concurrent thyroid dysfunction is linked to poorer functional status and their RA disease activity scores are higher indicating poor disease control.

Schematic

Figure 1: Relationship between Rheumatoid arthritis and thyroid dysfunction



2.9 RESEARCH QUESTIONS

What is the prevalence of thyroid hormone abnormalities among patients with RA?

2.10 BROAD OBJECTIVE

To determine the prevalence of thyroid dysfunction among RA patients on follow up at KNH rheumatology clinic.

2.11 SPECIFIC OBJECTIVES

2.11.1 PRIMARY OBJECTIVE

1. To assess the prevalence of thyroid dysfunction among patients on follow up for RA at the KNH rheumatology clinic

2.11.2 SECONDARY OBJECTIVES

1. To determine the association of the age, gender and disease duration of RA and thyroid dysfunction.
2. To determine the association of CDAI scores of RA patients and thyroid dysfunction.
3. To determine the association of the functional status of RA patients and thyroid dysfunction.

CHAPTER 3

3.0 METHODOLOGY

3.1 STUDY DESIGN

A hospital-based, cross-sectional, descriptive study.

3.2 STUDY SITE

The Rheumatology Clinic at KNH is conducted weekly on Thursday afternoon at medical outpatient clinic number 17 from 2 pm.

3.3 STUDY POPULATION

Adult males and females with a diagnosis of RA.

3.3.1 CASE DEFINITION

Patients aged18 years or older with a confirmed diagnosis of RA having met the 2010 ACR/EULAR classification criteria.

3.3.2 INCLUSION CRITERIA

a) Confirmed diagnosis of RA
b) Consenting patients

3.3.3 EXCLUSION CRITERIA

a) Any connective tissue disease other than RA.
b) Pregnancy
c) Pre-existing chronic liver disease or chronic kidney diseases.
d) All types of Diabetes Mellitus.

3.4 SAMPLE SIZE DETERMINATION

To calculate the minimum sample size required for the determination of the prevalence of thyroid dysfunction patients with RA, the Daniel formula (1999) was used for this finite population as described by Naing et al (37).

$$n = \frac{NZ^2\,P\,(1-P)}{d^2(N-1) + Z^2P\,(1-P)}$$

Where

n = sample size with finite a population

N=Population size

Z=1.96

P = the prevalence of thyroid dysfunction in RA patients ranges from 6% to 44% in various populations. P was considered as a prevalence of 14.3% from a study done by Osama Khataybeh and colleagues in Jordan (26). This was a single-center, hospital-based study similar to the study we conducted.

d = desired precision (0.05)

$$n = \frac{120(1.96\times1.96)0.14(1-0.14)}{0.05\times0.05\,(110-1) + (1.96\times1.96)0.14(1-0.14)}$$

Therefore, n=75

3.5 SAMPLING TECHNIQUE

Consecutive patients satisfying the inclusion criteria recruited into the study after giving informed consent. Since there is a finite number of patients with a diagnosis of RA at the KNH rheumatology clinic, this method of sampling allowed for enrollment of all subjects meeting the inclusion criteria and available on each clinic day. The sample size was hence achieved within the required duration of the study. This method also ensured ease of recruiting patients by the study research assistant since it is simple and has minimal chances of errors in sampling.

3.6 SCREENING AND RECRUITMENT

Consecutive sampling was used to recruit participants for the study. The principal investigator/research assistant perused the files of patients booked in the weekly Rheumatology clinic and identified those with a diagnosis of RA only. These patients were requested to participate in the study. Those who gave consent [appendix 5] and who met the eligibility criteria were recruited to participate in the study. Baseline characteristics and medical history was obtained from these patients using standardized questionnaires. These included age, gender, medical history, current management for RA, and the duration of time since RA diagnosis.

3.7 DISEASE ACTIVITY

Careful general and rheumatological examinations were conducted. CDAI was used to calculate disease activity. CDAI interpretation was done as follows;

a) Remission <0- 2.8
b) Low activity 2.9- 10.0
c) Moderate activity 10.1- 22.0
d) High activity > 22.1- 76.0

3.8 FUNCTIONAL STATUS ASSESSMENT

RA functional status was assessed by face to face interview using the HAQ [appendix 5].

HAQ score was interpreted as follows;

a) 0 (No disability)
b) <0.3 (Mild)
c) 0.3-1.8 (Moderate)
d) >1.8 (Severe)

3.9 ASSAY OF THYROID HORMONES

Four milliliters of venous blood was collected from each participant. The blood samples were then transferred to a plain vacutainer and clearly labeled with the participant's unique study number before transported to the laboratory.

I. The TSH was determined using Enzyme-Linked Immunosorbent Assay (ELISA). A test based on the principle of a sandwich ELISA which utilizes a unique monoclonal antibody directed against a specific antigenic determinant on the intact TSH molecule. The procedure results in color change which was measured spectrophotometrically to determine TSH concentration.

II. FT3 measurement was based on a competitive enzyme immunoassay with a step by step incubation. The kit method was utilized.

III. Free T4 (FT4) estimation was based on competitive binding between FT4 in test specimen and T4 peroxidase conjugate or a limited number of binding sites on anti T4 coated wells. The kit method was utilized.

3.10 QUALITY CONTROL

3.10.1 CLINICAL

The principal investigator recruited and trained a competent research assistant to ensure timely, efficient, and accurate data collection and recording. All the recorded data was verified against the study proforma by the Principal Investigator to ensure accuracy in the transfer of information.

3.10.2 LABORATORY

In order to eliminate pre-analytical errors, the Standard operating procedures were adhered to in the process of specimen collection and handling. Laboratory tests were carried out by a study dedicated technician. Controls for the various concentration ranges were run individually at least once every 24 hours when the test was in use, once per reagent kit, and following each calibration.

3.11 CLINICAL VARIABLES

3.11.1 DEPENDENT VARIABLES; SERUM TSH, FT4, FT3

TSH is recommended as the primary investigation for screening for thyroid disease by the American Endocrinologists Association. However, the TSH reference ranges vary from one population to another (38). There is no data on the normal reference ranges for thyroid function tests among Africans. The serum levels are affected by a population's iodine intake and are also assay specific (39). Tables 2 and 3 provide the manufacture's assay-specific ranges available in the kit utilized for TSH, fT3, and fT4 quantification in the study and the interpretation of the findings.

Table 2: Thyroid function reference ranges.

	Normal range
TSH	0.3-5.2 mIU/L
FT4	10-23.2pmol/l
FT3	2.5-7.5pmol/l

Table 3: Interpretation of thyroid hormone profile results

Diagnosis	**TSH**	**FT4**	**FT3**
Subclinical hypothyroidism	Increased	Normal	Normal
Overt hypothyroidism	Increased	Reduced	Reduced
Subclinical hyperthyroidism	Reduced	Normal	Normal
Overt hyperthyroidism	Reduced	Increased	Increased
Secondary hypothyroidism	Reduced	Reduced	Reduced
Secondary hyperthyroidism	Increased	Increased	Increased
Sick euthyroid	Normal	Normal	Reduced

3.11.2 INDEPENDENT VARIABLES

1. Age in years
2. Sex; male, or female determined by the phenotypically observed features of female and male secondary sexual characteristics.
3. Duration of disease in years. Determined from the earliest date the diagnosis of RA was documented to the date of the interview to the nearest years.
4. CDAI; the total number of tender joints and the total number swollen joints was obtained through physical examination. The patient's and provider's global assessment of function (PtGA and PrGA) was obtained to compute the CDAI using the formula 28SJC+28TJS+PrGA+PtGA (40).
5. HAQ score was computed using the 8 item Stanford school of medicine HAQ-DI questionnaires.

3.12 DATA MANAGEMENT AND ANALYSIS

3.12.1 DATA COLLECTION

A study proforma specifically designed for this study was administered by the

Principal Investigator. The participants' files were reviewed for any additional information not availed during the administration of the questionnaire.

3.12.2 DATA PRIVACY

Standards to protect personal data were followed. Data collection instruments only bare the study number. These are stored safely in a lockable cabinet by the Principal investigator.

3.12.3 DATA ENTRY AND ANALYSIS

SPSS version 21.0 was used to enter and analyze data. Upon completion of data entry, the hard copy forms were used to clean and verify the correctness of the entered data and then stored safely in the lockable cabinet. Continuous variables; age, CDAI scores, and HAQ scores were summarized as means, median, and interquartile ranges. Categorical data was analyzed using frequencies and proportions. The prevalence

of thyroid dysfunction was expressed as a proportion of the total study participants. The results were then group into those with thyroid dysfunction and those with normal thyroid function and odds ratios was used to test associations between the presence of thyroid dysfunction and demographic characteristics, CDAI scores, and HAQ scores. P values and 95% confidence intervals were computed and a P-value of <0.05 was considered significant.

3.13 ETHICAL CONSIDERATION

Approval was sought from the Department of Clinical Medicine and Therapeutics and the Kenyatta National Hospital/ The University of Nairobi (KNH/UON) Ethics and Research Committee before commencement of participant recruitment.

The participants were provided with adequate information on the objectives and purposes of the study. This was done in a language they were conversant with before inclusion into the study and only consenting patients were recruited. The patients who did not participate in the study were not victimized and those who were recruited were free to drop out at any time without victimization.

All data collected from the participants was kept confidential. Each participant was assigned a study number used as the only identifier on all materials uses in the study.

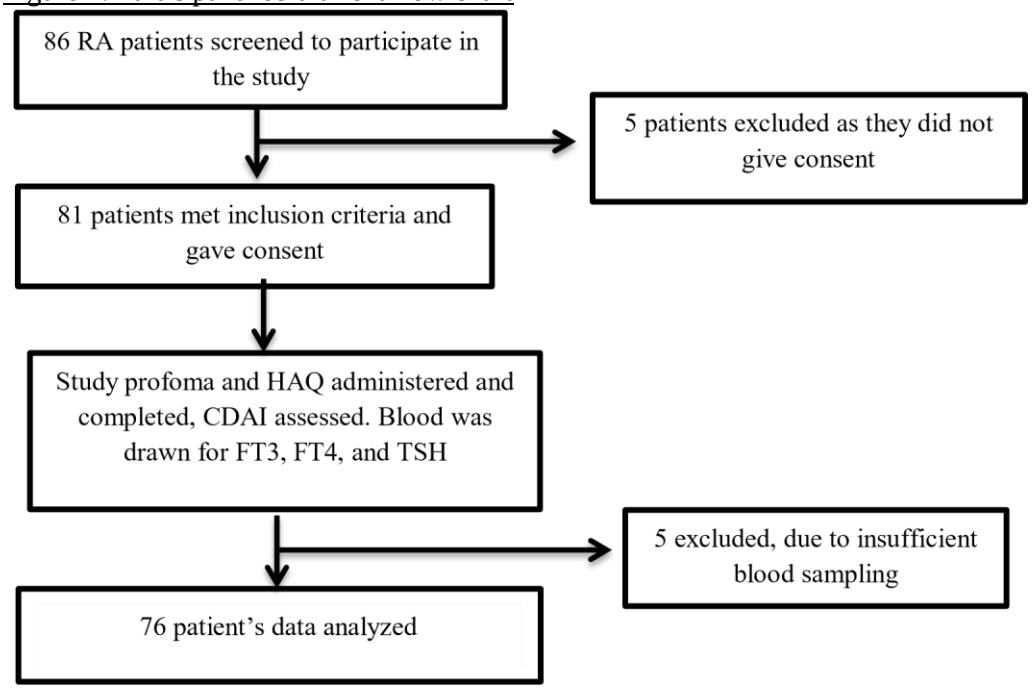
CHAPTER 4

4.0 RESULTS

4.1 RECRUITMENT OF STUDY PARTICIPANTS

Of the Eighty-six (86) patients aged 18 years and above screened between December 2019 and February 2020, Eighty-one (81) were recruited having provided consent. The final analysis included 76 participants as 5 study specimens were eliminated due to insufficient sampling as shown in figure 2.

Figure 2: Participant recruitment flow chart



4.2 SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

The study population was made up of relatively young participants. The mean age was of 41years (Range 18-78 years). Fifteen participants were male (19.7%) and 61(80.5%) participants were female. The male to female ratio was 1:4. Majority of participants (84.2%) had attained post-primary education and 73.7% were married.

Table 4 provides a summary of age and sex distribution as well as the education level and marital status of study participants.

Table 4: Demographic Characteristics of participants

Age (years)	**Frequency N (%)**
≤30	7(9.2)
31-40	15(19.7)
41-50	22(28.9)
51-60	17(22.4)
>60	15(19.7)
Gender	
Male	15(19.7)
Female	61(80.3)
Education	
None	3(3.9)
Primary	9(11.8)
Secondary	44(57.9)
Tertiary	20(26.3)
Marital status	
Married	56(73.7)
Single	15(19.7)
Widowed	5(6.6)

4.3 CLINICAL CHARACTERISTICS OF STUDY PARTICIPANTS

55.3% of the patients had the diagnosis of RA for 5 years or less. 36.8% of patients had RA for 6 to 10 years while 7.9% had had RA for more than 10 years as depicted in table 5.

All the study subjects were on DMARDS while 44.7% were on steroids. None of the study participants were on biological agents as illustrated in table 5.

Table 5: Clinical characteristics of study participants

Variable	**Frequency**	**Percentage**
Duration of disease		
>6 years	42	55.3
6-10 years	28	36.8
>10 years	6	7.9
Drugs	**Frequency**	**Percentage**
DMARDS	35	46.1
DMARDS + STEROIDS	34	44.7
DMARDS + Other	7	9.2
Biological Agents	0	0

4.4 THYROID FUNCTION TESTS

The median TSH levels were 5.8 (IQR 4.1-7.5), higher than the laboratory reference range provided.

The prevalence of thyroid dysfunction was 47.4%. The majority of the patients 39.5% had overt hypothyroidism with only 1% having subclinical hypothyroidism. Table 6 illustrates the median TSH levels and pattern of thyroid dysfunction.

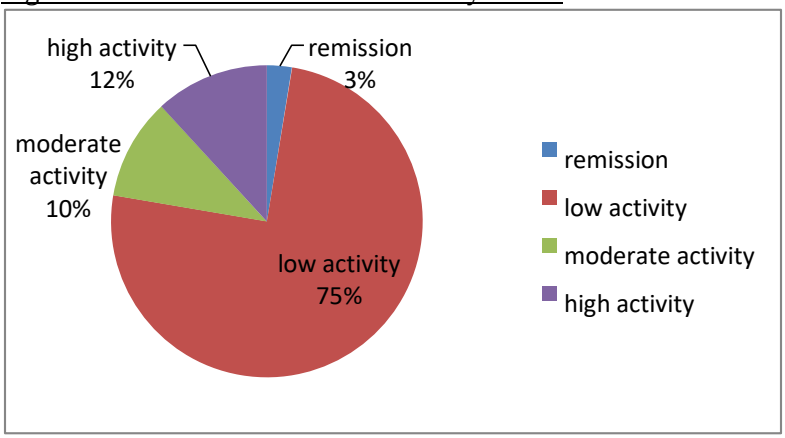
Table 6: Prevalence of thyroid dysfunction

Variable	
TSH Median 5.8 IQR 4.1-7.5	
Variable	n=76(%)
Thyroid function status	
Normal	40 (52.6)
Abnormal	36 (47.4)
• Subclinical hypothyroidism	1 (1.3)
• Overt hypothyroidism	30 (39.5)
• Sick euthyroid	5 (6.6)

4.5 DISEASE ACTIVITY IN THE STUDY POPULATION

The CDAI score was used to estimate the level of disease activity. The mean CDAI score was 11.6 (IQR 4-10). Low disease activity was the most prevalent at 75%. Only 2.6% were in remission. Almost twelve percent (11.8%) of the study population had high disease activity. This is illustrated in Figure 3.

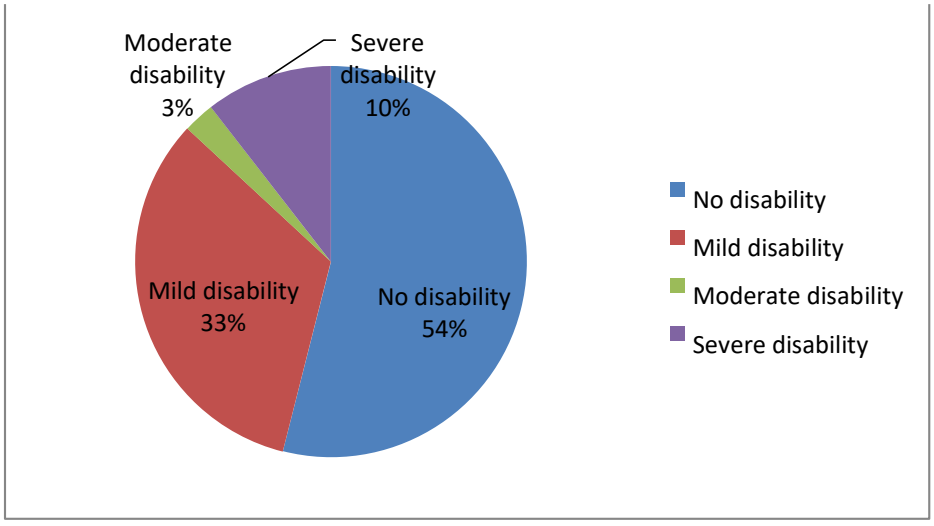
Figure 3: Distribution of Disease activity scores



4.6 FUNCTIONAL DISABILITY IN THE STUDY POPULATION

Functional disability was estimated by use of the HAQ DI questionnaire. HAQ score mean was 0.5 (IQR 0.0-0.8).86.3% of patients had mild to no disability while 8 participants (10.5%) were found to have high disease activity. This is illustrated in figure 4.

Figure 4: Frequency of disability



4.7 ASSOCIATION BETWEEN VARIABLES

Univariate analysis was done to interrogate the presence of correlations between thyroid dysfunction and various patient and disease characteristics: Age, sex, duration of disease, CDAI, and HAQ scores.

Participants that were less than 30 years old had three times the likelihood of having thyroid dysfunction compared to those above 60years. This observation was however not significant, P-value 0.297.

Male participants had a higher likelihood of having thyroid dysfunction compared to females OR 1.3; this observation was not significant, P-value 0.6. Participants with a duration of disease >6years were more likely to have thyroid dysfunction compared to those who had RA for less than 6 years OR 1.2 (P-value 0.6). The associations between thyroid dysfunction and patient demographics and clinical characteristics are as summarized in table 7.

Table 7: Association of thyroid dysfunction and patient and clinical characteristics

	Thyroid Hormone Abnormal				
	Yes	**No**	**Total**	**OR (95% CI)**	**p-value**
Age (years)					
≤30	4 (11.1)	3 (7.5)	7 (9.2)	2.67 (0.42-16.83)	0.297
31-40	6 (16.7)	9 (22.5)	15 (19.7)	1.33 (0.30-5.91)	0.705
41-50	11 (30.6)	11 (27.5)	22 (28.9)	2.00 (0.51-7.80)	0.318
51-60	10 (27.8)	7 (17.5)	17 (22.4)	2.86 (0.67-12.11)	0.154
>60	5 (13.9)	10 (25.0)	15 (19.7)		
Gender					
Male	8 (22.2)	7 (17.5)	15 (19.7)	1.35 (0.43 -4.18)	0.606
Female	28 (77.8)	33 (82.5)	61 (80.3)		
Duration of disease					
<6 years	19 (52.8)	23 (57.5)	42 (55.3)		
6-10 years	14 (38.9)	14 (35)	28 (36.8)	1.21 (0.46 -3.16)	0.696
>10 years	3 (8.3)	3 (7.5)	6 (7.9)	1.21 (0.22 -6.7)	0.827
Drugs					
DMARDS	14 (38.9)	21 (52.5)	35 (46.1)	0.27 (0.05 -1.57)	0.144
DMARDS + STEROIDS	17 (47.2)	17 (42.5)	34 (44.7)	0.40 (0.07 -2.35)	0.311
DMARDS + Other	5 (13.9)	2 (5)	7 (9.2)		

The participants with low disease activity were less likely to have thyroid dysfunction compared to those with high disease activity OR 0.72, this observation was not significant P-value=0.72. Participants with

severe disability had a marginally higher likelihood of having thyroid dysfunction compared to those with no disability; OR 1.2. This observation did not achieve statistical significance, P-value 0.75. These associations are summarized in table 8.

Table 8: Association of thyroid dysfunction with disease activity scores and functional disability scores

	Thyroid Hormone Abnormal				
CDAI	**Yes**	**No**	**Total**	**OR (95% CI)**	**p-value**
0.0-2.8 (Remission)	0 (0.0)	2 (5.0)	2 (2.6)	-	
2.9-10.0 (Low activity)	27 (75.0)	30 (75.0)	57 (75.0)	0.72 (0.18-2.96)	0.720
10.1-22.0 (Moderate activity)	4 (11.1)	4 (10.0)	8 (10.5)	0.80 (0.12-5.40)	0.800
22.1-76.0 (High activity)	5 (13.9)	4 (10.0)	9 (11.8)	Ref	
	Thyroid Hormone Abnormal				
HAQ	**Yes**	**No**	**Total**	**OR (95% CI)**	**p-value**
0 (No disability)	18 (50.0)	23 (57.5)	41 (53.9)	Ref	
<0.3 (Mild)	13 (36.1)	12 (30.0)	25 (32.9)	1.38 (0.51-3.76)	0.523
0.3-1.8 (Moderate)	1 (2.8)	1 (2.5)	2 (2.6)	1.28 (0.07-21.86)	0.866
>1.8 (Severe)	4 (11.1)	4 (10.0)	8 (10.5)	1.28 (0.28-5.82)	0.751

CHAPTER 5

5.0 DISCUSSION

5.1 DISCUSSION

The association between RA and thyroid dysfunction has been envisaged for a long time and several studies have been done to quantify the co-occurrence. This is the first study in Kenya describing the prevalence of thyroid dysfunction among RA patients.

This study investigated 76 RA who were attending the outpatient Rheumatology clinic at the KNH. The prevalence of thyroid dysfunction was 47.4%. The predominant pattern of thyroid dysfunction was overt hypothyroidism at 39.5%, while 1 participant (1.3%) had subclinical hypothyroidism.

A wide range of thyroid abnormalities has been observed in various studies around the world. Our prevalence was higher than most studies reviewed. The differences in prevalence across various populations has been attributed to: Differences in assay techniques, presence of other goitrogens that alter thyroid function and the influence of medications such as steroids. Persistent inflammation characterized by high disease activity also causes thyroid dysfunction (48).

Nadeem et al in India found that 42% of the patients studied had thyroid dysfunction. Unlike our observation, 37.9% of participants in Nadeem's study had subclinical hypothyroidism and only 3.6% had overt hypothyroidism (24).

In India, one study by Joshi et al looking at the prevalence of hypothyroidism in RA demonstrated a prevalence of 38.4% which is similar to the prevalence of overt hypothyroidism in our study (28).

A study in china in 2019 observed a prevalence of 32.3% thyroid dysfunction of which there was a predominance of overt hypothyroidism at 26.2% (27). Elattar et al in Egypt in their study also demonstrated a high rate of overt hypothyroidism among the proportion of participants who had thyroid dysfunction. The prevalence of thyroid dysfunction and overt hypothyroidism were 29.3% and 24% respectively (41). These

studies had lower prevalence demonstrated than our study but were similar in that the majority of cases had overt hypothyroidism. SCH has been shown advance to overt hypothyroidism at an estimated rate of 1-4% per year (42).

The lack of standard reference ranges for interpretation of thyroid function results provides a possible explanation for the variations in prevalence reported. Different studies used different assay and laboratoryspecific reference ranges. ELISA and chemiluminescence are second and third generation thyroid hormone assays respectively. At the lower ranges of TSH for the detection of hyperthyroidism, chemiluminescence has been shown to have higher precision than ELISA. At the upper ranges of euthyroidism, these two immunoassays have comparable precision. In one study comparing the sensitivity of ELISA and chemiluminescence in the estimation of TSH, in patients with hypothyroidism, ELISA had a sensitivity of 96% compared to 100% for chemiluminescence. The sensitivity of ELISA makes it suitable for the detection of thyroid hormone abnormalities at baseline. In our study, we employed the ELISA technique which is appropriate for initial assessment of thyroid disorders (43) (44).

Joshi and colleagues in India utilizing the ELISA method of thyroid hormone assay observed a high prevalence of 38% hypothyroidism. This is similar to the prevalence of overt hypothyroidism we demonstrated at 39.5%(28).

Amany and colleagues in a study on thyroid dysfunction in RA patients in Egypt utilized the ELISA method of thyroid hormone assay and observed a low prevalence of 8.3%(45). In another study by Osama in Jordan, thyroid dysfunction in a population of RA patients was determined by utilizing the ELISA method and a prevalence of 14.3% was observed (26). These findings were low compared to the prevalence we observed despite utilizing the same assay technique.

Among the studies that utilized the chemiluminescence method of thyroid hormone assay, they also observed a wide variation in the prevalence of thyroid dysfunction. Nadeem and colleagues demonstrated a high prevalence of thyroid dysfunction at 47% which was comparable to what we observed (24). In Italy

a study by Fabiola and colleagues utilizing this assay technique for thyroid hormones, observed a low prevalence of thyroid dysfunction at 7.1%(20).

These varied results demonstrated even with similar assay techniques utilized suggest caution should be used in drawing comparisons.

While the local rate co-occurrence of thyroid dysfunction in the RA patient population and at the community level in Kenya is not known, comparisons can be made to prevalence in select population groups. Ngugi and colleagues in a study on patients with type 2 diabetes at the KNH, determined the presence of thyroid dysfunction by utilizing ELISA to assay thyroid hormones. This study described a prevalence of 60% which was higher than what we observed in our study (46). These findings may indicate that thyroid dysfunction is prevalent in the general population and hence more pronounced in these patient groups with other factors contributing to dysfunction. The high prevalence observed in both studies is expected because, in addition to being in the same geographical location and having exposure to common possible goitrogens, some of the pathogenetic mechanisms underlying the development of thyroid dysfunction in these patient populations such as chronic inflammation are similar (47).

44.7% of our study participants were found to be on steroids at various doses. Glucocorticoids suppress thyroid hormone production leading to low FT4 and high TSH (48). This may explain the high prevalence of thyroid dysfunction which we observed to be predominantly hypothyroidism.

Thyroid dysfunction, especially hypothyroidism has been found to occur in chronic inflammation. Cytokines elaborated during inflammation such as IL1 and IL6 suppress the hypothalamic-pituitary and thyroid axis. TSH action on the thyroid gland and peripheral conversion of T3 to T4 is inhibited directly by IL1 and to a lesser degree IL6. These cytokines which are implicated in the mechanism of disease in RA explain the observed high prevalence of thyroid dysfunction. Further, they are targets for biological agents in RA disease control which results in improvement in thyroid function (47) ,(49). Thyroid dysfunction as a disease of chronic inflammation was also evident in a study by Amira et al on COPD patients in Egypt who exhibited high levels of TNF and IL6 which were related to low T3 and T4(50).

The concept of overlap of autoimmune diseases in this case, AITD and RA has been established in multiple studies. In one study Somers et al in a review of 54 studies quantifying the co-existence of autoimmune diseases within individuals and families. Prevalence of AITD was found to be 0.5-9.8% among RA patients compared to controls, all the studies reviewed also revealed an increased odds ratio for AITD in RA. Among AITD patients, the prevalence of RA was found to range between 1.417.6%(51). In one Italian study involving 71 active RA patients, 60% of the participants had antithyroid antibodies in circulation, 7.1% also had a high TSH (20). In a review of 6 prospective cohort studies of patients started on biologically active agents for RA a reduction in TPOab and TSH in hypothyroid participants was observed (52).

Iron, selenium, and iodine deficiency are also known goitrogens that are prevalent in our region and may explain the high prevalence observed.

Thyroid hormone synthesis is influenced by iron deficiency which has been shown to reduce the activity of the heme-dependent thyroid hormones especially thyroid peroxidase. This has been noted to blunt the effects of iodine supplementation in areas of low iodine like Kenya (53). The prevalence of iron deficiency in the national nutritional survey of 2011 which included 2851 participants was 18.4%. In this survey, the prevalence of iodine deficiency ranged from 19.1% among adult males to 30% among non-pregnant women. Salt is the main mode of supplementing iodine in Kenya it was hence significant to note that 48% of salt samples tested during this survey had lower than the recommended levels of iodine (54). In an Indian study that included 50 newly diagnosed hypothyroid patients and 50 appropriate controls, Kiran et al observed that levels of ferritin and serum Iron were low in those who were hypothyroid relative to the controls, P-value less than 0.005(55).

High concentrations of selenium are found in the thyroid gland where seleno-proteins are incorporated into iodinases in thyroid hormone synthesis (56). Selenium levels are dependent on diet and geographical areas. One study identified the risk of the inadequacy of dietary selenium at 22% across Africa (57). In Istanbul a 9-month selenium supplementation study in patients with AITD on therapy with thyroxine was conducted,

after the follow up period it was observed that there was the suppression of levels of TPOab by 26.2% to 30% P-value=<0.001(58). This indicates an association between selenium deficiency and thyroid function.

Our study did not demonstrate a significant relationship between advancing age and having RA for a longer duration with occurrence of thyroid dysfunction. Presence of high disease activity and increasing functional limitation did not correlate significantly with occurrence of thyroid dysfunction.

Previous studies have however made some associations. In one case-control study in Canada that recruited 119 RA patients and 108 appropriate controls, age and thyroid disease were not significantly correlated. There was a significant correlation between thyroid dysfunction and duration of disease, P value=0.03(25). Similarly, in India, a prospective study of 52 RA patients found no statistically significant relationship between advancing age and occurrence of thyroid function, P-value=0.99 but there was a correlation with duration of disease, P-value=0.33(28).

This study in India demonstrated an association between TSH levels and severity of RA, P-value=0.003. There was also a correlation between having hypothyroidism and having more severe RA disease activity P-value=0.007. In contrast, another prospective study involving 385 RA patients in India did not find a correlation between thyroid dysfunction and severity of RA. For those who had SCH the P-value was 0.075 and among those with overt hypothyroidism P-value was 0.28.

A case-control study in Egypt involving 200 participants found that high TSH levels were associated with higher Modified Health Assessment Questionnaire scores, P-value= 0.01. Similarly, high TSH was associated with high disease severity estimated using MDAS, P value=0.02. The varied results on associations between thyroid dysfunction and patient demographics, disease severity, and functional disability, delineate the need for more investigation to further explore these associations.

5.2 STUDY LIMITATIONS

1. The study sample is small and is powered to only focus on the prevalence of thyroid dysfunction among patients with RA, other factors associated with co-occurrence of thyroid dysfunction and RA were investigated but associations were not made conclusively.

2. This study provides data on a one-time estimate of thyroid function whereas changes in thyroid hormone levels occur from time to time. However, this study provides a baseline assessment that will inform decisions on the need for screening of RA patients for thyroid dysfunction and further follow up schedule for those with established thyroid dysfunction.

3. There is no population data on the prevalence of thyroid dysfunction from which comparisons with the prevalence in our population could be drawn

4. There are no standard population reference ranges for thyroid hormone profiles in Kenya.

CHAPTER 6

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

There is a high prevalence of thyroid dysfunction among RA patients. No significant associations were found between thyroid dysfunction and advancing age, having RA for a longer duration, increasing severity of disease, and functional disability.

6.2 RECOMMENDATIONS

1. All patients with rheumatoid arthritis should be screened for thyroid dysfunction.
2. A case-control among RA patients and healthy controls would be useful to investigate whether the occurrence of thyroid dysfunction is preferential higher among RA patients.
3. Due to lack of local reference ranges to compare with, a population-based study should be done to define population reference ranges for thyroid hormones and describe the patterns of thyroid dysfunction in the general population

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APPENDICES

APPENDIX 1: SCREENING PROFORMA

Study N°……..

Age …….

Date of birth……..

Gender:

Male:

Female, LMP..../…. /….

Year of Rheumatoid arthritis diagnosis ……..

Are you willing to participate in the **study prevalence of thyroid dysfunction among ambulant patients of follow up at KNH rheumatology clinic**?

1. YES ----
2. NO----

Tick where appropriate*:*

3. Have you been diagnosed with Diabetes mellitus, chronic kidney disease or chronic liver disease?

   YES--- NO----

APPENDIX 2: DATA ABSTRACTION TOOL

Study number ---------- Date: ----------

1. Age in years: ----------

2. Gender: Male------ Female --------

4. Level of education (circle one): Primary------ Secondary------ Tertiary----- None -----

5. Duration of Rheumatoid arthritis ----------

6. Type of medication used for Rheumatoid arthritis (check patients' current prescription)

---------- ---------- ----------

7. Other medication ----------

8. History of Diagnosis of Thyroid disease Yes ------- No --------

If yes, which type of thyroid dysfunction ----------?

Is the patient on medication for thyroid dysfunction Yes---------- No…….

Physical Examination

Temp.....C PR...../min RR...../min BP.....mm/Hg

Weight.....Kg Height..... m BMI.....Kg/m2

Musculoskeletal exam

No of tender joints------- No of swollen joints--------

APPENDIX 3; INFORMED CONSENT EXPLANATION FORM

I am Dr. Mary Nderitu a post graduate student at the University of Nairobi, School of Medicine, Department of internal medicine and therapeutics.

I would like to invite you to participate in a study I am conducting on the presence of thyroid hormone abnormalities among rheumatoid arthritis patients attending the KNH rheumatology clinic.

The thyroid gland is an organ that is located in the neck anteriorly. It produces thyroid hormones that are essential in maintaining body metabolic processes. Abnormalities in hormone production by this gland are found to be commoner in patients with Rheumatoid arthritis than the general population. Abnormal thyroid function may lead to symptoms such as cold or heat intolerance, unintended weight fluctuations, joint and muscle aches, mental changes and abnormal blood pressure and heart function. Most of these symptoms mimic symptoms of Rheumatoid arthritis hence the need to screen for concurrent thyroid dysfunction.

The aim of this study is to determine the prevalence of thyroid hormone abnormalities among Rheumatoid arthritis patients and to also correlate this with the level of disease activity and patient reported functional status.

Your participation in this study is voluntary and refusal to participate shall not impact the management you are receiving. If you accept to participate in the study you will undergo a face to face interview, Questions about your condition and function will be asked. A physical examination will be conducted focusing on your neck, the joints of your upper limbs and the knees. 6mls of venous blood will be drawn for analysis in the lab.

Abnormal results will be communicated to your attending doctor for appropriate management. All information collected from you including your lab results will be kept confidential and any publications of this study will not identify you in person.

If you have understood the information I have given you and you are willing to participate in this study, I will require you to sign a form indicating your willingness to participate.

For further information, you may contact any of the following:

1. Dr. Mary Nderitu

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

Telephone number: 0726525610

2. Professor Omondi Oyoo

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

Telephone number: 0722522359

3. Dr Marybeth Maritim

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

Telephone number: 0733729963

4. The Secretary KNH-UON Ethics and Review Committee.

Telephone number: 2726300 Ext 44102

Email: uonknh_erc@uonbi.ac.ke

APPENDIX 4: CONSENT FORM

I _____, do confirm that I have read/ been explained to the above study, understood the information presented to me and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw from this study at any time without giving reason. I confirm that I have agreed to have a physical examination done on me and blood drawn for analysis.

I agree to take part out of my own free will and no coercion or incentive has been offered.

Signature of participant_____ Date: _____

Signature of investigator _____ Date: _____

KIAMBATISHO CHA TANO; FOMU INAYOELEZA IDHINI

UTANGULIZI

Mimi ni Dkt. Mary Nderitu, kutoka Chuo Kikuu cha Nairobi. Kwa sasa nasomea uzamili katika Tiba ya Ndani.

Ninafanya uchunguzi kuhusu kazi ya tezi miongoni mwa wagonjwa wanaougua maumivu ya viungo, maarufu kama Rheumatoid arthritis, wanaofuatiliwa katika Hospitali Kuu ya Kenyatta.

Tezi ni kiungo kinachopatikana upande wa mbele wa shingo. Linahusika na kutoa homoni ambazo zina dhibiti jinsi viungo tofauti vya mwili vinavyo tenda kazi. Wagonjwa wanaougua maumivu ya viungo, maarufu kama Rheumatoid arthritis huwa katika hatari zaidi kuwa na viwango duni vya homoni za tezi kuliko wale wasio na magonjwa ya viungo

Lengo la utafiti huu ni kuchunguza kiwango cha wagonjwa wa Rheumatoid arthritis ambao wana viwango duni vya homoni za tezi Pia nitalinganisha viwango vya homoni na viwango vya maumivu ya viungo na hali ya maisha ya mgonjwa kwa jumla.

Tunakualika kukubali kushiriki katika utafiti ambapo, Ukikubali kwa hiari yako na baada ya maelezo haya, tutakuuliza maswali machahe kulingana na utafiti profoma. Baadaye tutakufanya uchunguzi wa kimwili ambao unahusisha uchunguzi wa tezi na uchunguzi wa viungo, kisha tutateka mililita tano ya damu na kutuma kwa maabara kupima kazi tezi homoni.

Ushiriki wako katika utafiti huu ni wa kujitolea. Hata ukichagua kushiriki au ukatae kushiriki haitaathiri matibabu yako. Una uhuru wa kujiondoa katika utafiti huu wakati wowote. Una uhuru wa kuuliza maswali kabla ya kutia sahihi katika fomu ya idhini na wakati wa utafiti. Maswala yote yatahifadhiwa
kwa siri wakati wote.

Mwishoni mwa utafiti huu, nitawasilisha matokeo ya utafiti katika idara ya Tiba ya Ndani katika Chuo Kikuu cha Nairobi. Matokeo tata yakipatikana pia yatawasilishwa kwa madaktari wako ili kusaidia katika

matibabu. Habari zozote muhimu zitakazotokana na utafiti na ambazo zitasaidia matibabu kuwa bora, madaktari wako watafahamishwa ili hatua mwafaka ichukuliwe.

Habari zote zitakazokusanywa wakati wa utafiti zitahifadhiwa kwa siri. Ni watafiti pekee ndio wanaoweza kufikia habari za kibinafsi. Habari zitakazokusanywa zitaandikwa na kuainishwa bila kutaja washiriki.

Kabla sijakuhusisha katika utafiti wangu, Naomba utie sahihi katika fomu ya idhini iliyopo hapo chini.

Ikiwa una swali lolote wakati wa utafiti, unaweza kuwasiliana na wafuatao:

1. Dr. Mary Nderitu

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

Telephone number: 0726525610

2. Professor Omondi Oyoo

Department of Internal Medicine. University of Nairobi. P.O BOX 19676.

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4. The Secretary KNH-UON Ethics and Review Committee.

Telephone number: 2726300 Ext 44102 Email: uonknh_erc@uonbi.ac.ke.

KIAMBATISHO CHA SITA; FOMU INAYOELEZA IDHINI

FOMU YA IDHINI /KUBALI- WAGONJWA

Mimi…….Nimesoma habari hapo juu na nimepata majibu ya maswali yoyote

Natoa idhini andishi na ninayoifahamu ili kuniruhusu kushiriki katika utafiti huu kuhusu kazi tezi miongoni mwa wanaougua maumivu ya viungo maarufu kama Rheumatoid arthritis, katika Hospitali Kuu ya Kenyatta. Ninafanya hivi kwa vile naelewa lengo kuu la utafiti huu na taratibu zitakazohusishwa kama vile kujibu maswali katika fomu ambayo nimepewa, kupimwa na kutolewa damu.

Ninaelewa kuwa haki zangu zitaheshimiwa, na suala la kuhifadhi utambuzi wangu utadumishwa wakati wote. Pia ninaelewa kuwa idhini ya kushiriki ni ya kujitolea, na nina uhuru wa kujiondoa katika utafiti huu bila malezi yangu kuathiriwa.

Sahihi ya Mgonjwa……Tarehe……..

Sahihi ya mchunguzi……Tarehe……..

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach
☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores