IRON STATUS IN PATIENTS WITH CONGESTIVE HEART FAILURE AT KENYATTA NATIONAL HOSPITAL

A DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE.

BY:

DR. OMONDI KWAYE ERIC
RESIDENT, INTERNAL MEDICINE

UNIVERSITY OF NAIROBI, SCHOOL OF MEDICINE
KENYA.

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DECLARATION

I declare that this is my original work and has never been presented to any other university for any academic credit purpose.

Signed:……Date:……..

DR OMONDI KWAYE ERIC

MB.ChB (U.O.N)

DEDICATION

This work is dedicated to Chandler and Jazmine for the inspiration and faith they had in me in the process my thesis. They are the reason that gave me the motive and the zeal to complete this thesis, to you Chandler and Jazmine.

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PRINCIPAL INVESTIGATOR:

DR. OMONDI KWAYE ERIC

MB.ChB (U.O.N)

Resident

Department of Internal Medicine and Therapeutics

Signature …….

SUPERVISORS:

DR. KARARI E.

Lecturer Department of Internal Medicine and Therapeutics

Consultant Physician/Cardiologist

University of Nairobi

Signature……..

PROF. KAYIMA J.K.

Associate Professor of Medicine

Consultant Physician/Nephrologist

University of Nairobi

Signature …….

PROF. OGOLA E.

Associate Professor of Medicine

Consultant Physician/ Cardiologist

University of Nairobi

Signature……

LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
AIDS	Acquired immunodeficiency syndrome
BP	Blood pressure
CDC	Centre for disease control
CHF	Congestive heart failure
CRAS	Cardiorenal anaemia syndrome
Cyt	Cytochrome
DCM	Dilated cardiomyopathy
EF	Ejection fraction
Fe	Iron
HB	Haemoglobin
HIV	Human immunodeficiency virus
HTN	Hypertension
ID	Iron deficiency
IDA	Iron deficiency anaemia
IL	Interleukin
Iv	Intravenous
KNH	Kenyatta National Hospital
Kgs	Kilograms
L	Litre
MBChB	Bachelor of medicine and bachelor of surgery
ml	Millilitre
Mmed	Master of medicine
ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association
Sd	Standard deviation
SPSS	Statistical package for social sciences
TIBC	Total iron binding capacity
TSAT	Transferrin saturation
TNFa	Tumour necrosis factor alpha
U.O.N	University of Nairobi
µg	microgram
WHO	World health organization

TABLE OF CONTENTS

ABSTRACT

Congestive heart failure is associated with increased morbidity and mortality. It is common among the elderly and tends to co-exist with other co-morbid conditions; anaemia, diabetes and hypertension among others. It is also associated with nutritional deficiencies of micro-nutrients; minerals including iron and vitamins. The role of iron in anaemia and congestive heart failure has been studied extensively, with some reports demonstrating a negative relationship between low serum iron levels and congestive heart failure; functional classification, morbidity in terms of duration of hospital stay and anatomical changes associated with iron deficiency. Most published reports on the subject matter indicate increased morbidity associated with iron deficient state. However, there are no local studies to compare with. This study assessed serum iron levels and correlated it with the functional classification of heart failure using New York Heart Association (NYHA) classification of the patients.

Objective: To assess the iron status and prevalence of anaemia among patients with congestive heart failure at the Kenyatta National Hospital.

Methods: the study was a cross sectional descriptive study carried out at the out-patient cardiac clinic at the Kenyatta National Hospital over a 6 month period. Adults and minors over 13 years of age who had a confirmed diagnosis of heart failure were interviewed, patient records were perused and the information extracted, was recorded in the study proforma. Every participant was examined and blood samples taken for determination of serum iron and haemoglobin levels. Data analysis was then done using statistical package for social scientists (SPSS) version 24. Descriptive analysis was done to summarize serum ferritin, transferring saturation (TSAT), haemoglobin (HB), body mass index (BMI), sex, iron status, aetiology of congestive heart failure (CHF) and NYHA. Chi square test was used to determine associations between iron status, anaemia and NYHA. A two tailed chi square test was done at 95% confidence level.

Results: The study was conducted between January and July 2015 at the Kenyatta National Hospital out-patient cardiac clinic. A total of 1136 patients were on follow up at the clinic were screened to identify those with a diagnostic label of congestive heart failure. 360 patients with an age range of between 14-98 years and a mean age of 53.4 ($SD \pm 12.3$)were recruited into the study after meeting the inclusion criteria. There was a female preponderance of 53.1% and a high literacy level with 80% of them having some form of formal education. A majority of the patients, 66.6% were in NYHA class II and III. The prevalence of iron deficiency was 56.7%. Among patients with anaemia, the prevalence of ID was 86% and in non-anaemic patients, the prevalence was 43%. Functional iron deficiency was more common at 32.5%, compared to absolute iron deficiency which occurred in 24.4%.

Conclusion: In patients with congestive cardiac failure, iron deficiency is common and is associated with a poor functional status irrespective of the presence of anaemia.

1.0 LITERATURE REVIEW

1.1 Introduction

Cardiovascular diseases are a major and growing public health concern worldwide. On a global perspective these diseases account for about 31% of total deaths annually. In 2016, 17.9 million deaths were reported by WHO to have resulted from cardiovascular diseases. Out of these, over three quarters occurred in low and middle income countries[1].In Kenya, 25% of all hospital admissions are due to cardiovascular diseases and 13% of autopsies showed CVDs as the cause of death[2].

Heart failure is a common clinical syndrome representing the end-stage of a number of cardiac diseases. It results from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood [3].

In sub-Saharan Africa, the etio-pathogenesis of heart failure (HF) is largely attributable to non-ischemic causes, with hypertensive heart disease, rheumatic heart disease, dilated cardiomyopathy (DCM) and uncorrected congenital heart defects contributing the majority of cases [1]. Cardiac involvement ofHuman Immunodeficiency Virus(HIV), Cor Pulmonale and pericarditis reflects the continued impact of HIV and tuberculosis on heart disease in this region.The emerging lifestyle diseases of hypertension, type 2 diabetes and obesity, are increasingly contributing to the ischemic causes of heart failure.[4]

In Kenya, Oyoo and Ogola [5] found congestive heart failure prevalence of 3.3% in all medical admissions while evaluating the clinical and socio demographic aspects of heart failure at Kenyatta National Hospital Lodenyo, McLigeyo [6] in their prospective study evaluating cardiovascular disease among elderly patients admitted at Kenyatta National Hospital found that Congestive heart failure patients comprised 49% of all those with cardiovascular disease.

HF is a burden not only to the patient but also to the healthcare systems. The economic burden of HF is estimated at about 1-2% of the total healthcare expenditure with approximately two thirds being attributed to hospitalisations[7]. Locally, the cost of HF in the healthcare system is undetermined partly due to under reporting of non-communicable diseases.

Iron deficiency (ID) is one of the commonest nutritional deficiencies world-wide affecting about one third of the population[8]. ID is a common co-morbidity in patients with chronic inflammatory diseases including HF[9]. It is a common factor aggravating anaemia in HF, but it is also a distinct co-morbidity independent of anaemia. ID is more prevalent than Iron Deficiency Anaemia (IDA) in HF[10-13]. However, ID remains unrecognized in heart failure. Deficiency generally develops slowly and is not clinically apparent until iron stores are exhausted and iron supply to tissues becomes compromised. Deficiency has been found in some observational studies to be an important predictor of death and urgent heart transplantation[14, 15].

1.2 Physiological role of iron.

Iron is a metabolically active micronutrient with unique biochemical features that allows it to shuttle between two oxidative states, the bivalent ferrous and the trivalent ferric iron. Hence, it can be a cofactor for enzymes and the catalyst of biochemical reactions.

Iron plays a crucial role in oxygen transport through haemoglobin, and oxygen storage, through the myoglobin component. In addition to this, iron has a role in cardiac and skeletal muscle metabolism, via the oxidative enzymes and respiratory chain proteins. It equally plays a crucial role in the synthesis and degradation of proteins, lipids, ribonucleic acids as an enzyme component of the mitochondrial function.

Iron is required for optimal haematopoiesis. The majority being taken up by erythroblasts, and reticulocytes for haemoglobin synthesis. Iron deficiency thus results in resistance to hematopoietic growth factors and impairs the differentiation of all types of hematopoietic cells.

In addition to its unquestionable role for optimal haematopoiesis, iron is indispensable for the maintenance of cellular energy and metabolism of extra hematopoietic tissues such as cardiac and skeletal myocytes. This is important in HF, as abnormal energy generation and the utilization in the myocardium and peripheral tissues contribute to the HF pathophysiology.

Iron excess accumulates in cells and generates oxidative stress and triggers cardiomyocyte necrosis.

1.3 Regulation of iron balance

Total body iron content is approximately 4-5 g and exists mainly in the form of haemoglobin (2.5 g) ≈ 70%. The rest exists as iron containing proteins (≈ 400mg), bound iron on plasma transferrin (≈ 3-7 mg) and the remainder as storage iron in the form of ferritin and hemosiderin (≈ 1g) [16]. Adult females have less storage iron which is dependent on menses, pregnancies, deliveries, lactation and iron intake. Iron homeostasis is tightly regulated at the level of intestinal absorption and release from macrophages. The amount of iron absorbed is 1-2 mg per day of which a similar amount is lost in a day through desquamating surface and luminal epithelial cells and through sweat.

1.4 Diagnosis and classification of iron deficiency

Absolute iron deficiency-reflects depleted iron stores with intact iron homeostatic mechanisms and erythropoiesis[17].

Functional iron deficiency-reflects inadequate iron supply to meet the demand in the erythroid precursors and other tissues despite normal or abundant body iron stores. It is believed to be mainly caused by pro-inflammatory activation and hepcidin overproduction [18].

The gold standard for evaluating iron stores in target tissues is bone marrow biopsy. However, its invasive nature limits its use and as such it has been replaced by measurement of several blood markers:

Serum ferritin (SF)-reflects amount of storage iron but not necessarily severity of depletion as it progresses. Ferritin is an acute phase response protein and concentrations rise in inflammation, and as a result under such circumstances, it no longer reflects the size of body iron stores. Accepted cut off values are <30µg/L for absolute iron deficiency and <100µg/L in chronic inflammation. The sensitivity of SF alone ranges from 64.9 % to 82 % with a specificity of between 95 % and 96.1 %. In combination with TIBC the specificity rises to 100 % while the sensitivity drops to 55.9 % [19-21]

Transferrin saturation (TSAT) - is the percentage of transferrin that has iron bound to it [ratio of serum iron to Total iron binding capacity (TIBC) x100%]. A level <20 % is considered reduced with the normal values ranging between 20% and 50%. It is a

surrogate for iron available for metabolizing cells. Ferritin levels of 100µg/L - 300µg/L is common in chronic inflammatory states, however <20% TSAT under such circumstances can be used to diagnose functional ID. Transferrin saturation on its own has a sensitivity of 60.5 % and specificity of 48.1 %, however, in combination with SF the specificity rises to 100 % against a drop in the sensitivity to 31.4 %[21].

Soluble transferrin receptor- This is the single, most sensitive indicator of iron deficiency because it is the only iron status index unaffected by infection and inflammation, its sensitivity is about 90 %. Serum levels mirror levels on red blood cell progenitor cells in the bone marrow and can be used as a marker of severity of iron insufficiency when iron stores are exhausted. It however has the lowest specificity of about 37 % [22].

There are several other iron assessment indices including TIBC, MCV, MCH, MCHC, haematocrit, reticulocytes count, serum free iron and erythrocyte protoporphyrin that may be used in conjunction with iron status to give an indication of the severity of Iron Deficiency (ID). However, due to variable sensitivity, specificity and practical application, these may not be of clinical utility in routine set up. [21, 23]

1.5 Heart failure and iron deficiency

Iron is a micronutrient at the centre of cellular metabolism in several organs, and as such, is critical for the maintenance of normal homeostasis[24-26].

Attention in iron deficiency has been directed primarily to anaemia and symptoms in the iron deficient patient, conveniently ascribed to anaemia for several reasons. More specifically, and related to the fact that 80% of iron is found within the erythron, the recognition of iron deficiency begun with the determination of haemoglobin. Recently it has been shown that close to half of individuals who are iron deficient by chemical criteria have no demonstrable anaemia Anaemias [20] raising the question whether iron deficiency without anaemia represents any physiological liability.

The pathophysiology milieu in HF syndrome favours the development of both absolute and functional iron deficiency.

The presumed mechanisms involved in the development of iron deficiency in HF include: Insufficient dietary iron supply, poor gastro-intestinal (GI) absorption, and GI blood loss.

Heart Failure is a state characterized by generalized inflammation with augmented immune response and high circulating levels of pro inflammatory mediators. This inflammatory state is associated with increased levels of hepcidin that interferes with mobilization of iron from the enterocytes and bone marrow macrophages into circulation resulting in negative iron balance.

There is indisputable evidence that the inflammatory milieu orchestrated by elevated levels of TNFα, IL6 and IL 1 is maladaptive and leads to the development and progression of CHF by virtue of their toxic effects on the cardiac structure and peripheral vasculature. These negative effects includes ; the activation of foetal myocardial gene program, myocardial hypertrophy, apoptosis of myocardial cells, endothelial dysfunction, disturbance of myocardial structure and extracellular matrix, myocardial depression and systolic dysfunction[27-30]. This chronic inflammatory state is the basis for functional ID in Heart failure.

Finch CA et al evaluated the work performance of normal and iron deficient rats in a tread mill after removing anaemia as a variable by adjusting the haemoglobin of all animals to the same concentration and demonstrated, marked impairment of running ability in the iron deficient rats compared to the control animals[19].

Feng DONG et al while examining the mechanisms of action of iron deficiency induced cardiovascular damage demonstrated ultra-structural and biochemical alterations that together suggests iron deficiency induces cardiac hypertrophy characterized by aberrant mitochondrial and irregular sarcomere organization accompanied by increased reactive nitrogen species expression [31].

Experimental evidence suggest that iron supplementation in ID may activate molecular pathways that protect the heart and prevent myocardial remodelling [19, 31, 32].

Recent studies have shown that administration of intravenous iron in iron deficient heart failure patients was well tolerated and resulted in improved functional status, exercise capacity and quality of life[10, 11, 25, 33] In the FAIR-HF trial, Anker,

Comin Colet [33]demonstrated significant improvement in quality of life, functional capacity and improvement of heart failure symptoms in patients who had ID with or without anaemia following ferric carboxymaltose administration as assessed by self-reported patient global assessment and NYHA functional classification.

Silverberg, Wexler [34], in an interventional study of 26 patients with severe CHF and anaemia despite maximally tolerated CHF therapy, demonstrated improved cardiac and renal function when IV iron and subcutaneous erythropoietin were administered. The number of hospitalizations fell by 91.9%. The NYHA functional classification fell significantly as did doses of oral and IV furosemide. The left ventricular ejection fraction and mean Hb increased significantly.

Okonko, Grzeslo [35],in the FERRIC-HF study after 16 weeks of intravenous iron sucrose therapy in HF patients and ID with or without anaemia, demonstrated marked improvement of heart failure symptoms and exercise capacity, more significantly in the anaemic patients.

1.6 Cardio renal anaemia syndrome (CRAS)

Heart failure, anaemia and renal impairment frequently exacerbate each other in a vicious circle of clinical deterioration. Correction of anaemia has been shown to improve cardiac and renal functions[14, 15, 36]. However, in spite of the correction of anaemia, prognosis remains poor in this leading to the question, whether there are other factors contributing to the observed morbidity and mortality. The role of iron deficiency in anaemic and non-anaemic patients with heart failure as regards prognosis has been questioned and previous studies have shown that iron deficiency was playing a significant role in the progression of CHF[10, 15, 24].

This study aims to determine the prevalence of iron deficiency as a co-morbidity in patients with congestive heart failure at the Kenyatta National Hospital.

There is paucity of data regarding iron status in the general population in Kenya and none in patients with CHF[37] Renson in his MMED dissertation; Iron status in patients with end stage renal disease on haemodialysis at Kenyatta National Hospital renal unit found the prevalence of Iron Deficiency(ID) of 35.2%, functional ID-26.1%, normal iron status – 36.4%, iron overload-2.4% and Iron Deficiency Anaemia(IDA) of 34.5%.

NHANES II using the definition of SF < 12 µg/L as ID found the prevalence to be 30 %(30)

Jankowska, Rozentryt [24], in their prospective study of 546 chronic stable CHF patients demonstrated a 37±4% incidence of ID (SF <100 µg/L or SF 100 – 300 µg/L with TSAT < 20%)

2.0 STUDY JUSTIFICATION

Congestive heart failure is a common chronic medical condition of public health importance. It occurs, often with other co-morbidities which when not concurrently managed, worsens its prognosis.

Iron deficiency has been shown to be a common co-morbidity in CHF. It may coexist with or without anaemia. Management of ID as a co-morbidity in CHF has shown improvement in outcomes such as improved symptoms, increased ejection fraction and reduced diuretic dose.

As the prevalence of heart failure is expected to substantially rise in the Sub-Saharan Africa, epidemiological studies of the condition and subsequent interventions may help to decrease morbidity and mortality.

There is paucity of data in this subject, locally and regionally in Sub- Saharan Africa. Previous studies in Africa have revolved around anaemia and heart failure.

The data available is largely drawn from the west where the etio-pathogenic mechanisms leading to CHF as well as the age profiles are significantly different from our setting.

Major society guidelines such as the European Society of Cardiology currently recommend the supplementation of iron in patients with CHF and ID yet there is no data is available locally about iron status in this group of patients.

This study therefore aims to obtain data regarding iron status in patients with CHF at the KNH and associate the findings with the functional classification of the patients as well as the aetiologies of CHF.

These findings shall go a long way in determining whether or not our patients are iron deficient. It will also provide a basis of comparison of data from a low income

country with those from high income countries that have previously been published. Finally, the results of this study may influence policy making with regards to care of patients with CHF.

3.0 RESEARCH QUESTION

What is the iron status of patients with congestive heart failure at Kenyatta National Hospital?

4.0 OBJECTIVES

4.1 Broad objective

To assess the iron status and prevalence of anaemia among patients with congestive heart failure at Kenyatta national hospital.

4.2 Specific objectives

1. To determine the iron status of patients aged 13 years and above with clinical diagnosis of CHF attending KNH outpatient clinic.

2. To determine the prevalence of anaemia in patients aged 13 years and above with clinical diagnosis of CHF attending KNH outpatient clinic.

4.3 Secondary objective

1. To correlate iron status and NYHA functional classification of patients with CHF at KNH.

2. To correlate the NYHA functional classification and anaemia in patients with CHF at KNH.

5.0 MATERIALS AND METHODS

5.1 Study design

This was a cross-sectional descriptive study.

5.2 Study site

The study was carried out at Kenyatta National Hospital (KNH). Kenyatta National Hospital is a tertiary referral hospital located in the capital city of Kenya, Nairobi. It was established in 1900 and is the largest hospital in East and Central Africa. It has a capacity of 2000 beds. It serves as a teaching hospital for the University of Nairobi, College of Health Sciences, both for the undergraduate and graduate programs. It serves as a referral for Kenya and East Africa. It runs general and specialized clinics and in-patient services in surgical, medical, obstetrics and gynaecology, ophthalmology and paediatrics. The study was carried out in adult out-patient cardiac clinic which runs every Tuesday.

5.3 Study population

The study population consisted of patients aged 13 years and above with documented diagnosis of CHF by modified Framingham criteria on follow up at KNH cardiac outpatient clinic.

5.4 Case definition

Patients who had a file diagnosis of CHF during the study period, that satisfied the Framingham criteria which was applied retrospectively (with information obtained from the patient's medical records) to confirm the diagnosis of CHF.

The patient required documented evidence of at least two major or one major and two minor criteria that could not be attributed to another medical condition, to confirm the diagnosis of CHF.

i. Major Criteria

- Orthopnoea
- Pulmonary rales
- Pulmonaryoedema on Chest X Ray
- Third heart sound
- Elevated Jugular Venous Pressure

- Positive Hepatojugular reflux
- Cardiomegaly on Chest X Ray
- Paroxysmal Nocturnal Dyspnoea
- Weight loss > 4.5 kg in 5 days in response to treatment of presumed heart failure.

ii. Minor Criteria

- Bilateral leg oedema
- Nocturnal cough
- Dyspnoea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded.
- Tachycardia (>120 bpm)

When available, echocardiographic data shall be added to support diagnosis.

Outcome variables of ID, anaemia.

- Iron Deficiency as Serum Ferritin < 100 µg/L or Transferrin Saturation< 20 % if Serum Ferritin was 100-299 µg/L
- Absolute Iron Deficiency- Serum Ferritin< 100 µg/L
- Functional Iron Deficiency- Ferritin levels of 100µg/L - 299µg/L and Transferrin Saturation <20%.
- Normal Iron status- Serum Ferritin 100 – 500 µg/L and Transferrin Saturation 20-50%
- Iron overload- Serum Ferritin> 500 µg/L and Transferrin Saturation> 50%
- Anaemia- Hb < 12.0 g/dl (females) and Hb < 13.0 g/dl (males)

- Iron Deficiency Anaemia – Serum Ferritin < 100 µg/L, TSAT < 20%, Hb < 12.0 g/dl(Female) or Hb < 13 g/dl (Male and post-menopausal women) (33)
- NYHA classification (34) (appendix 3)

5.4.1 Inclusion criteria

a). Patients with an established diagnosis of CHF.

b) Patients aged 13 years and above.

c) Patients who gave informed consent/assent.

5.4.2 Exclusion criteria

a) Patients on Iron supplementation.

b) Patients who had undergone blood transfusion recently.

c) Patients with peptic ulcer disease

5.5 Sample size calculation

A sample size of **358** patients was calculated for the study based on the study by Jankowska, Rozentryt [24]that demonstrated the prevalence of ID to be 37± 4% in their study of 546 patients.

Using OpenEpi- Sample size for frequency in a population:

- Hypothesized frequency of ID, p - **37±5%**
- Confidence limits as % of 100(absolute)±%(d)- **5%**
- Sample size, n (95% confidence level) = **358**. This sample size was adequate to answer both first and second specific objectives.

$$\mathbf{N=1.96^2p(1-p)/d^2}$$

6. STUDY PROCEDURES

6.1 Recruitment and sampling

The cardiac clinic handles about 100 patients every Tuesday morning and all the files of the booked patients are availed to the clinic on the Monday afternoon preceding the clinic. The principal investigator visited the out-patient clinic records desk each Monday afternoon and perused through all the files of the patients booked for review at the cardiac clinic the following day. He screened on Monday afternoon, all the files presented to the clinic and sampled consecutively all the files that had a diagnosis of CHF until a figure of 50 had been attained or all the files had been perused. He then applied Framingham's criteria retrospectively in the patients with documented diagnosis of CHF using information obtained from the patient's medical records to determine eligibility for inclusion into the study. Most records of patient information were complete and adequate for the CHF diagnosis to be confirmed or rejected. Incomplete information was regarded as patient not meeting the criteria for CHF diagnosis .Consecutive sampling of the potential participants was conducted until the required sample size was achieved.

Every Tuesday (clinic days) during the study period the principal investigator visited the clinic with three research assistants, two final year medical students and a qualified nurse. The principal investigator briefed the potential study patients identified on the day before the clinic about the study and subsequently recruited those willing to participate in the study up on obtaining their informed consent. On average 15 patients were recruited per clinic day. A targeted history and physical exam was done by the principal investigator to establish the signs and symptoms of CHF, use of iron supplementation, history of recent transfusion and to functionally categorize the patient into a NYHA group on the study day, then blood samples were drawn. The study questionnaire was administered and the file documented aetiology of CHF was also recorded. The research assistants (two final year medical students and one qualified registered nurse) worked with the principal investigator to ensure that data was collected efficiently, on time and that it was recorded accurately. All recorded data were verified by the principal investigator, who also ensured that all relevant forms were completed. The supervisors offered guidance to the principal investigator throughout the process.

The participants signed a written informed consent form upon agreeing to participate in the study (see appendix 1-4). Social-demographic and health related information was gathered through direct questioning aided by the study questionnaire (see appendix 5).

6.2 Sample collection and analysis

Using a tourniquet, a suitable vein in the ante-cubital fossa was located and the venepuncture site disinfected. Using a sterile syringe and needle while observing universal safety precautions, 5mls of blood was drawn. 5mls of blood drawn was dispensed into a sterile plain labelled vacutainer for iron studies. The samples were immediately transferred to the laboratory (University of Nairobi, Clinical Chemistry and Endocrinology Department) where serum samples were frozen at – 20 ºC until the time of analysis. Serum ferritin, Serum iron and TIBC were measured by colourimetric assay using Selectra proS by Elitech chemistry analyzer. Transferrin saturation (TSAT) wasthen be calculated;

TSAT= serum iron/TIBC x 100 %

6.3 Quality assurance

The blood specimen collection was undertaken using standard instruments and aseptic techniques to minimise pre-analytical errors.

Standard operating procedures were followed in carrying out of laboratory investigations.

University of Nairobi Clinical Chemistry and Endocrinology Department as well as the Haematology laboratory performs both internal and external quality control to ensure precision of results and hence their reliability.All equipment was calibrated according to the manufactures specifications. Commercial control materials were used to validate the calibrations. These were included in all analytical runs. Results were only accepted if the control values were within the expected ranges.

6.4 Data storage

All the raw data in this study was filed in a suitable box file which was stored in a lockable drawer accessible only to the principal investigator. In addition, all the sheets were checked to confirm completeness before being filed.

All the study questionnaires were assigned a unique study number, linking the documents to the patient files. The study number was only accessible to the PI.

6.5 Data management and Analysis

Coded data was filled into the questionnaire and cleaned before being entered in to a predesigned pass word protected Microsoft Access data base. Analysis was undertaken using the STATA statistical software with the input of a statistician.

Continuous data; serum ferritin, TSAT, HB, BMI and age were summarized into means and standard deviations and presented in tables, bar charts and pie charts while categorical data, sex, iron status, aetiology of CHF and NYHA functional classification were summarized into proportions and presented as tables and pie charts.

Association between iron status and NYHA functional classification, as well as association between anaemia and NYHA was done using chi square test method. Prevalence of iron deficiency and anaemia were calculated as percentages within 95% confidence interval.

Statistical significance was defined as a two-tailed p-value of less than or equal to 0.05.

7.0 ETHICAL CONSIDERATIONS

The study was carried out following approval and permission from UON/KNH research and ethics committee.

Benefits of the study for example correction of anaemia and iron supplementation and the expected minimal pain on drawing the blood sample was fully explained to the patients.

Informed consent was sought in writing or finger printing for those who could not write. Those who did not consent were not discriminated against.

All patient data was treated with utmost confidentiality at all stages of the study

Only samples intended for the study were drawn.

The results of the study will be disseminated to relevant groups of our heath care and academic fraternity and may be used as a basis for designing possible interventional studies as may be relevant. All specimens were discarded according to standard procedures in the laboratory.

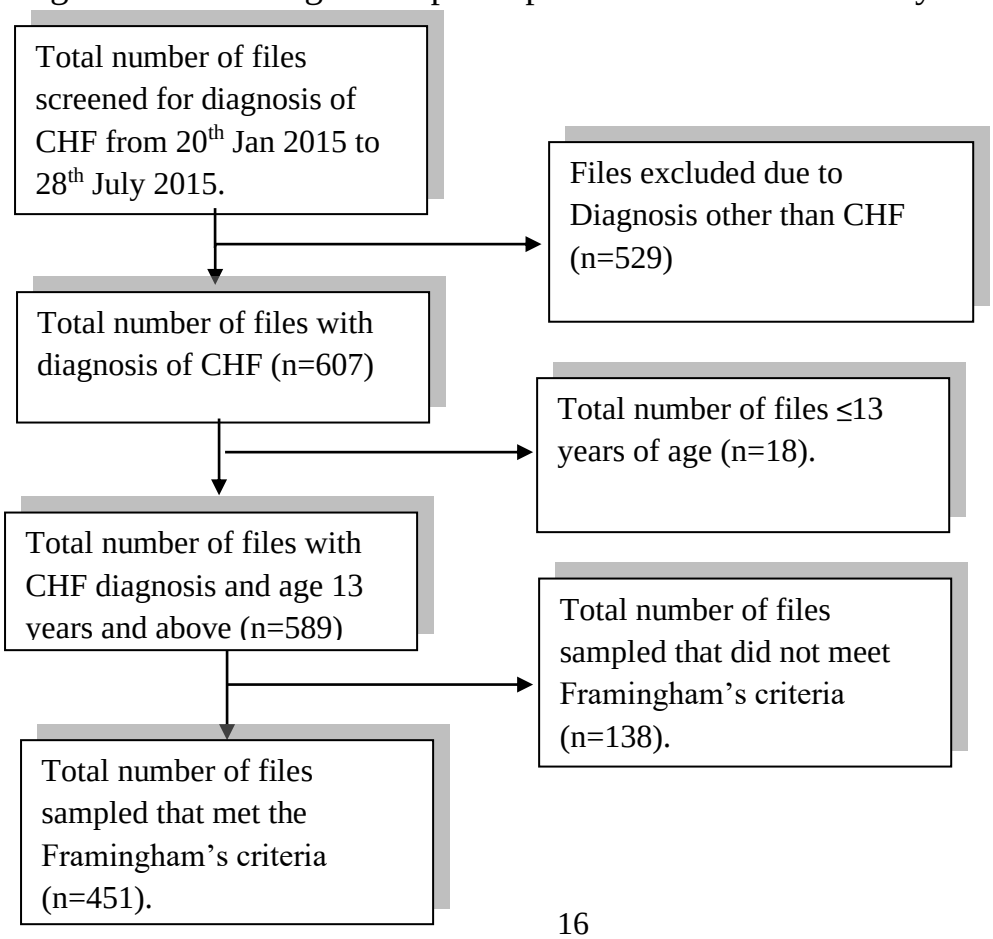
8.0 RESULTS

8.1 Participant recruitment

The study was carried out between January 20 and July 28 2015 at the Kenyatta National Hospital cardiac clinic. During this period, files of 1136 patients on follow up at the cardiac clinic were screened, out of which 516 patients were identified as being 13 years and above and having the diagnostic label of congestive heart failure. Out of the previously identified files, an average of 15 patients was picked consecutively for inclusion into the study after applying the inclusion/exclusion criteria on each clinic day for the 6 months period. Framingham criteria were applied retrospectively to confirm the diagnosis of CHF using patient records. 451 cases of heart failure were identified and of these

Figure 1 shows the study profile from initial screening of 1136 files of patients of heart failure and exclusions due to absence of CHF diagnosis or being outside target age (n = 620), not meeting Framingham criteria (n=65) ineligibility (n = 86) and difficulties in obtaining samples (n = 5). Among the 86 patients ineligible for the study, 38 patients had been receiving iron supplements, 13 had received recent transfusion and 9 had peptic ulcers, a known cause of iron deficiency.

Figure 1: Flow Diagram of participant enrolment in the study



8.2 Demographic profile

The mean age of the patients was 53.4 (SD ± 12.3) years, range 14-98 years and 46.9% were males (Table 1). 40.4% of patients had primary education and 75.7% of adult patients were married.

Table 1: Socio-Demographic profiles of study patients.

		Frequency (n)	Percent (%)
Age	13-25 years	24	6.7
	25-34 years	42	11.7
	35-44 years	49	13.6
	45-54 years	48	13.3
	55-64 years	40	11.1
	65-75 years	46	12.8
	75+ years	71	19.7
Sex	Male	169	46.9
	Female	191	53.1
Marital status	Single	81	22.5
	Married	249	69.2
	Widowed	18	5.0
	Divorced	12	3.3
Education	Primary	136	40.4
	Secondary	90	26.7
	Tertiary	44	13.1
	No formal education	67	19.9

8.3 NYHA functional classification and CHF aetiology

The most common severity classification for CHF was class II (38.3%), Table 2. Regarding CHF aetiology, dilated cardiomyopathy (37.8%) and hypertensive heart disease (32.2%) were the leading aetiologies.

Table 2: NYHA functional classification and CHF aetiology

	Frequency	Percentage	95%CI
Functional class			
I	85	23.6	19.3-28.3
II	138	38.3	33.3-43.6
III	102	28.3	23.7-33.3
IV	35	9.7	6.9-13.3
Aetiology			
Cardiomyopathy	136	37.8	32.7-43.0
Idiopathic	82	22.7	19.1-28.1
Alcoholic	30	8.3	5.7-11.7
Peripartum	20	5.6	3.4-8.4
Cytotoxic	4	1.1	0.6-3.6
Hypertensive Heart Disease	116	32.2	27.4-37.3
Rheumatic Heart Disease	48	13.3	10.0-17.3
Corpulmonale	35	9.7	6.9-13.3
Ischemic Heart Disease	17	4.7	2.8-7.5
Congenital Heart Disease	08	2.2	1.0-4.3

8.4 Iron status

A total of 205 patients were diagnosed with iron deficiency corresponding to an overall prevalence of 56.9% (95% CI 51.7-62.1%) among patients with CHF. The prevalence of specific types of iron deficiency is presented in Table 3.

Table 3: Prevalence of iron deficiency according to types in CHF patients

	Frequency	Percentage	95%CI
Iron status			
Normal	149	41.3	36.3-46.7
Absolute	88	24.4	20.0-28.9
Functional	117	32.5	27.7-37.6
Overload	6	1.7	0.6-3.6

8.5 Prevalence of anaemia

There were 114 out of 360 patients with anaemia defined using sex-specific haemoglobin cut-offs. This corresponds to a prevalence of 31.7% (95% CI 26.8-36.5%) for anaemia in CHF.

8.6 Proportion of ID without anaemia

A total of 205 patients had iron deficiency and 106(51.7%) out of the 205 did not have anaemia. Among the patients with anaemia, 99 had iron deficiency while 7 patients, had anaemia without iron deficiency.

8.7 Correlation of anaemia and NYHA functional classification

Anaemia was significantly associated with NYHA class IV (p=0.022) but not with class I, II and III (Table 4)

Table 4: Correlation between anaemic status and NHYA functional classification

	Anaemia	No anaemia	Chi (df)	P
NYHA class				
I	22(25.6%)	63(74.4%)	1.62(3)	0.204
II	39(28.7%)	98(71.3%)	0.93(1)	0.335
III	35(34.4%)	67(65.6%)	0.53(1)	0.466
IV	17(49.4%)	18(50.6%)	5.25(1)	0.022

In patients with CHF, prevalence of anaemia progressively increases with worsening NYHA functional class but statistical significance is only seen in stage 4 NYHA.

This shows that presence of anaemia was positively associated with s worsening cardiac function.

8.7.2 Correlation between ID and NYHA functional classification

There was a significant association between iron status and NYHA classification in CHF patients (Table 5). The NYHA class I/II was used as a reference class. The risk of absolute ID was two-fold higher in NYHA class III compared to class I/II and 3.9 times greater in NYHA class IV compared to class I/II.

Table 5: Correlation between iron status and NYHA functional classification

	Absolute	Normal Iron status	RR (95% CI)	P
NYHA class				
I/ II	36(24.1%)	113(75.9%)	Ref.	
III	32(47.8%)	35(52.2%)	2.0(1.4-2.9)	<0.001
IV	20(95.2%)	1(4.8%)	3.9(2.9-5.3)	<0.001

9.0 DISCUSSION

Iron deficiency is common in patients with heart failure affecting up to half of all patients attending ambulatory clinic at KNH. In this study, we report on the findings of a survey, to determine the burden of iron deficiency and anaemia in patients attending an out-patient clinic at the largest public, teaching and referral hospital in a low income country.

The overall prevalence of ID was 56.7%. Among patients with anaemia the prevalence of ID was 86% while non anaemic patients had an ID prevalence of 43%. A study carried out in Tanzania by Makubi, Hage [39]in 2015,estimated prevalence of iron deficiency in CHF to be 49%, 69% in subjects with anaemia and 21% in those without anaemia. Tanzania is an equally low income country within the same geographical region of Sub-Saharan Africa. The differences in the findings between this study and the Tanzanian study may be attributed to the methods used to determine ID, the Tanzanian study used MCV which has a sensitivity of 71%, while we used serum ferritin and TSAT. The prevalence of ID reported in this current study is slightly higher than the prevalence of 50% in an international pooled analysis based on data obtained from five cohorts in developed countries. Further the prevalence of ID among patients with anaemia is similarly higher than that reported by the same international pooled analysis, which stood at between 21-69% [41].The differences that exist between our reported figures in the prevalence of iron deficiency in the current analysis compared to other reports, could be explained by several factors including but not limited to: population characteristics such as racial and age differences, geographical and regional variations in micronutrient status, differences in case definitions of iron deficiency across studies, and disease case mix in study populations as well as possible role played by chronic infections in our subjects and finally by the differences in the pathophysiology of heart failure; in the high income countries, the setting of HF is largely in an ischaemic background, compared to non-ischaemic background locally.[39] whether or not this contributed to the observed differences is beyond the scope of this study and can only be speculative. In this study, hypertension and hypertensive heart disease contributed to 32.5 of the HF cases while in the high income countries hypertension contributed to 40% of the cases.

In a study carried out in 2011in Poland at two tertiary cardiology referral centres by Jankowska and Ponikowski [38],had a mean age of 55 years and 88% males. Makubi [39] in 2015 in Tanzania found an average age of 56 years with 49% males.
A majority of the patients, 66.6% were in NYHA functional classes II and III. This was during the study day and did not reflect the worse case ever and neither considered whether or not patients were compliant to their treatment. Further, the other causes of worsening cardiac function were not explored. In a Canadian study by Ezekowitz [36] in 2003 of anaemia in heart failure he had a finding of 80.4% of patients being in class II and III [36][35][34] while Makubi, Hage [39]had 68% of their patients to be in NYHA class II and III, closely resembling our findings .

Despite these differences and in common with existing estimates from both high and low income countries, the current study confirms that iron deficiency is widespread in patients with CHF. In addition, the current study is a significant addition to the regional literature that previously had limited information on iron deficiency in CHF within sub-Saharan Africa population.
In our sample functional iron deficiency was more prevalent (32.5%) than absolute iron deficiency (24.4%).The spectrum of iron deficiency in heart failure patients is variable and remains among the areas that require more detailed epidemiological analysis.
Iron deficiency is commonly linked to anaemia in most study reports, but while anaemia and iron deficiencies are common co-morbid conditions in CHF there is growing recognition of a latent burden of iron deficiency in non-anaemic patients. These cases represent a significant proportion of iron deficiencies and could benefit from specifically targeted screening and intervention to correct iron status.

It is important to note that poor functional status is a predictor of poor prognosis and outcomes which were not evaluated in the current analysis.

The epidemiology and pathophysiological consequences of Iron Deficiency on CHF are newly described phenomena and data on the same is scarce. Till recently ID was only considered in the context of anaemia thence the prevalence of ID has only been established in CHF patients with concomitant anaemia.

This study demonstrated that the prevalence of ID in patients with CHF was 56.9% with a significant difference between anaemic vs. non-anaemic patients 86% and 43%respectively.That while there is higher prevalence of ID in anaemic patients with HF, there is a significant number of non-anaemic patients with ID in HF of about 40%.

Patients with peptic ulcer disease, since there source of iron deficiency was known and together with patients who were receiving iron supplements as well as those who had received blood transfusion recently were excluded in order to avoid possible confounder.

10.0 STUDY LIMITATIONS

- Co-morbidities such as renal dysfunction in the patients may confound the association between NYHA classification and iron deficiency reported in the study.
- Other causes of iron deficiency were not looked for.
- Sampling method could have introduced a bias.

11.0 CONCLUSIONS

In patients with congestive cardiac failure, iron deficiency is common.

12.0 RECOMMENDATIONS

This study recommends that:

1. Patients with heart failure should routinely be screened for iron deficiency despite normal haemoglobin levels especially those in NYHA stage 4.

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APPENDICES

Appendix 1: CONSENT EXPLANATION
IRON STATUS IN PATIENTS WITH CHF AT KNH

Principal Investigator

Dr. Omondi Kwaye

Purpose of the study

This study aims to establish levels of iron in patients with the diagnosis of CHF attending outpatient Cardiac Clinic at KNH hence laying ground for further discussions on the impact of iron levels on disease progression.

Benefits for participating

The results of the study will help in enhancing the understanding of the possible role iron plays in heart failure in our setting.

Expected risks

No other risks are expected apart from a mild bearable pain during blood sampling

Confidentiality

Strict confidentiality will be maintained and data obtained will be kept and used for the purpose of this study only.

Conclusion

The participation in this study is voluntary. Patients are free to withdraw at any time during the course of the study period and whoever refuses to participate in the study, the quality of treatment will not be compromised. Apart from the above mentioned benefits, no financial compensation for participation shall be offered. In case of any questions concerning this study, contact the following:

DR. OMONDI KWAYE
P. O. Box 52093-00100
Nairobi.
Telephone: 0722325356
DR. EMMA KARARI
Lecturer and Consultant Cardiologist
Department of Clinical Medicine and Therapeutics
University of Nairobi
P. O. Box
Nairobi

Telephone: 0722847345

PROF. GUANTAI

Chairperson-Ethics Research Committee

Kenyatta National Hospital

P. O. Box 20723-00200

Nairobi.

Telephone: 02002726300 Ext.44355

E-mail; uonknh_erc@uonbi.ac.ke

Appendix 2: MAELEZO YA IDHINI

Mtafiti

Dr. Omondi Kwaye

Nia ya Utafiti

Utafiti huu unalenga kutambua na kuonyesha hadhi ya madini ya chuma kwa wagonjwa walio na shida ya moyo wanaohudhuria kliniki ya moyo katika hospitali kuu ya Kenyatta. Na kuwekeza misingi ya majadiliano zaidi juu ya athari za ngazi ya chuma kwa maendeleo ya ugonjwa wa moyo.

Faida za kushiriki

Matokeo ya utafiti huu yatasaidia kuimarisha ujuzi juu ya majukumu ya chuma katika ugonjwa wa moyo katika mazingira yetu.

Hatari zinazotarajiwa

Hakuna hatari zozote zinazotarajiwa ila kwa uchungu mdogo wakati damu inapochukuliwa.

Usiri

Majibu yoyote yatakayo tokana na utafiti huu yata hifadhiwa kwa siri na kutumiwa kwa asili ya utafiti huu peke yake.

Hitimisho

Kushiriki katika utafiti huu ni hiari. Mgonjwa yuko huru kujitoa kwenye utafiti wakati wowote na yeyote atakayekataa kushiriki katika utafiti huu, ubora wa matibabu yake hauta athirika. Mbali na manufaa hayo hapo juu, hakuna pesa utakayopewa ili kufidia au kushiriki kwako katika utafiti huu.

Kwa maelezo na maswali yoyote juu ya utafiti huu, unaweza kuuliza;

DR. OMONDI KWAYE
S.L.P 52093-00100
Nairobi.
Nambari ya Simu: 0722325356

DR. EMMA KARARI
Mhadhiri na daktari wa moyo
Idara ya magonjwa ya ndani
Chuo Kikuu Cha Nairobi
S.L.P
Nairobi
Nambari ya Simu: 0722847345

PROF. GUANTAI
Mwenyekiti-Kamati ya maadili ya utafiti
Hospitali Kuu ya Kenyatta
S.L.P 20723-00200
Nairobi.
Nambari ya Simu: 02002726300 Ext.44355
E-mail; uonknh_erc@uonbi.ac.ke

Appendix 3: CONSENT FORM

I…….

Do hereby agree voluntarily to participate in this research on **Iron status in patients with CHFat KNH.** The details of the study have been explained to me by the principal investigator, **Dr.Omondi Kwaye.**

Signed/Thumb print……. (Participant)

Next of kin

Name……..Relationship…….

Signature/ Thumb print……...

I confirm that I have explained to the patient in detail the content explanation form.
Signature ……(Researcher), Date…….

Appendix 4: KARATASI YA IDHINI YA USHIRIKI KATIKA UTAFITI

Mimi…….

Na kubali kushiriki kwa hiyari kwenye utafiti huu, Hadhi ya madini ya chuma kwa wagonjwa walio na shida za moyo wanaohudhuria kliniki ya moyo katika KNH baada ya kuelezewa yaliyopo na mtafiti mkuu Dk. Omondi Kwaye.

Sahihi/ Alama ya kidole gumba…… (Mshirirki) Tarehe….....

Ndugu Zangu

Jina …….Uhusiano……Sahihi……..

Ninathibitisha ya kwamba nimemweleza mgonjwa yaliyomo katika karatasi hiiya idhini ya ushiriki katika utafiti .

Sahihi…….. (Mtafiti) Tarehe…….

Appendix 5: QUESTIONNAIRE

IRON STATUS IN CHF PATIENTS AT KENYATTA NATIONAL HOSPITAL

Dear sir/madam,

Thank you for accepting to participate in this important study. By doing so, you have agreed to be part of a scientific process which will positively impact on follow up and management of patients with heart failure. Please answer a series of questions that I will read to you. Hopefully, you will do this to the best of your ability.

Thank you for accepting to spare this very valuable time.

Dr. Omondi Kwaye (principal investigator)

Questionnaire Design

File no. ……..

Patient's study no. …….

BIODATA

- Sex: 1.Male ☐. Female ☐
- Age ……..years
- Marital status: 1.Single 2.☐arried 3.C☐er ☐
- Level of education: 1. Primary 2.S☐ondary 3.Tertia☐ ☐

1. Date of CHF diagnosis; ECHO/clinical……

2. Date of review/specimen collection……

-Functional classification- NYHA…….

3. Known co-morbidities 1. Yes 2☐No ☐

If yes in 3 above specify……(Hypertension, diabetes, chronic renal failure and chronic obstructive pulmonary disease)

4. Weight…….Kg

5. Height……cm

6. BMI……

7. Aetiology of CHF……. (as documented in the file)

8. Serum ferritin.....µg/L

9. Transferrin Saturation……. %

10. Haemoglobin level……..g/dl

11. Iron deficiency

a). Yes ☐

b). No ☐

12. Iron status

a). Normal ☐

b).Absolute Iron deficiency ☐

c). Functional Iron deficiency ☐

d). Iron deficiency anaemia ☐

Appendix 3: NYHA FUNCTIONAL CLASSIFICATION (34)

NYHA class I

Cardiac disease but no symptoms and no limitation to ordinary physical activity egshortness of breath on walkingclimbing stairs**…**

NYHA class II

Mild symptoms (shortness of breath and or angina) and slight limitation during ordinary activity

NYHA class III

Marked limitation in activity due to symptoms,even during less than ordinary activity. Comfortable only at rest.

NYHA class IV

Severe limitations; experiences symptoms even while at rest.