PREVALENCE OF FIBROMYALGIA SYNDROME IN DIABETICS WITH CHRONIC PAIN AT THE KENYATTA NATIONAL HOSPITAL

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STUDENT'S DECLARATION

This research protocol is my original work and has been presented as part of a prerequisite to my Masters degree at the department of Internal Medicine, University of Nairobi.

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DEDICATION

This is a dedication to all those persons who played a part in making me what I am so far. And for achieving this milestone.

My Mom and Dad, without you, I'd be born in a different family. I'd never want that.

My Wife, Neemat, the Reason to Smile. (Not to forget our unborn baby as part of you)

My loveliest nieces, Aaliya and Mehek.

My brothers, Hussein and Hassan. The pillars I can always rely on for support.

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LIST OF ABBREVIATIONS

ACR – American College of Rheumatology

ADL – Activities of Daily Living

CCC – Comprehensive Care Centre

CHS – College Of Health Sciences

CNS – Central Nervous System

CSS – Central Sensitization Syndrome

CO – Clinical Officer

CWP – Chronic Widespread Pain

DM – Diabetes Mellitus

DOPC – Diabetes Outpatient Clinic

DPP 4 - Dipeptidyl-peptidase 4

DPN – Diabetic Polyneuropathy

FIQR – Fibromyalgia Impact Questionnaire

FMS – Fibromyalgia Syndrome

HIV – Human Immunodeficiency Virus

HPA – Hypothalamic Pituitary Adrenal axis

IBS – Irritable Bowel Syndrome

ICD – International Classification of Disease

IL - interleukin

KDHS - Kenya Demographic Health Survey

KNH – Kenyatta National Hospital

MOPC – Medical Outpatient Clinic

MSC – Musculoskeletal Complaints

NE – Norepinephrine

NT – neurotransmitters

OGLA – Oral glucose lowering agents

OTC – over-the-counter (medications)

PI – Principal Investigator

QoL – Quality of Life

RA – Rheumatoid Arthritis

RTA – Road Traffic Accident

SIQR – Symptoms Impact Questionnaire

SPSS – Statistical Package for Social Scientists

SSRI – Selective Serotonin Receptor Inhibitors

TCA – tricyclic Antidepressants

TMJ – temporomandibular Joint

TNF α – Tumor Necrosis Factor - alpha

TP – tender points

UoN – University Of Nairobi

ABSTRACT

Background

Fibromyalgia Syndrome (FMS) an increasingly recognized medical condition characterized by chronic widespread pain (CWP) and a heightened response to pressure, for which no other cause is identified with variable aetiopathogenesis including metabolic factors. Diabetes mellitus (DM) is the most common metabolic disease. The spectrum of musculoskeletal disease in DM varies greatly. Musculoskeletal complaints of DM are very common endocrine arthropathies. In 2004, the National Health Survey revealed that 58% DM patients will have some form of functional disability. FMS is one disease process that contributes to CWP and chronic musculoskeletal complaints (MSC) in DM.

This study evaluated the prevalence and impact of FMS in diabetics with chronic MSC.

Objectives

We set out to establish the prevalence and disease burden of FMS in Diabetic outpatients presenting with CWP.

Methods

This was a cross-sectional study with random consecutive sampling carried out at The Diabetes Out-Patient Clinic (DOPC), KNH (April 2016 to June 2016). Prior consent was sought from the Ethics & Research Committee, KNH/UoN prior to commencement. Diabetic patients were interviewed for presence of chronic MSC and subsequently Fibromyalgia Syndrome diagnoses was done using the ACR 1990 criteria for diagnosis using tender point assessment. Those with Fibromyalgia, were given the FIQR questionnaire and those without, were given the SIQR. HBA1c levels for all patients to correlate the FMS disease activity with glycemic control was done. SPSS version 21.0 was utilized to process the available data. The study population was described using sociodemographic factors and a 95% Confidence Interval was used to express the prevalence of Fibromyalgia.

Results

A total of 1280 patients were interviewed of which 219 patients met all of the inclusion criteria. The prevalence of Fibromyalgia in this group of patients was n = 61 (27.9%) (95% CI 21.9-34.2). Mean age for patients with FMS was 59.9 years, significantly older than patients without FMS (55.6) (P=0.034). There was a higher female preponderance at 80% (n=49). The mean tender-point count for patients with FMS was estimated at 13.7 (SD 2.1). Majority of our study population were on follow-up for Type 2 DM (94.1%). Patients with FMS had a higher HBA1c value compared to those without although this was not statistically significant. (9.6% vs. 9.3%) (P=0.565). From our inferences, other factors such as marital status, nature of

employment, activities of daily living and type of medications used were not found to be statistically significant. (P>0.05)

Conclusion

Fibromyalgia syndrome is prevalent at 27.9% *(n=61)* of all diabetic patients presenting with chronic pain as seen at the DOPC, KNH during the study period with the majority of our patients had moderate disease activity based on the FIQR scoring system (51.9)

Early recognition and therapy is possible to alleviate the pain, suffering and frequent institutionalization for this group of patients with lifelong debilitation.

1.0 CHAPTER ONE: INTRODUCTION

Fibromyalgia, a medical condition characterized by chronic widespread pain and a heightened and painful response to pressure. Fibromyalgia is the preferred term for widespread pain accompanied by other symptoms for which no alternative cause can be identified. Other symptoms that form the spectrum of disease include feeling tired to a degree that normal activities are perturbed, sleep disturbances, joint stiffness, dysphagia, bladder and bowel abnormalities, paresthesia and cognitive decline.[1] The prevalence of this disorder is related to age and sex and more commonly affects older females and older individuals as compared to the younger age-groups. Most of this diagnoses is made during the middle ages with a linear increase in prevalence as age progresses. The pain and tenderness waxes and wanes in the course of this disease. Earlier, there was doubt regarding the organic basis for this disease, but today, there's irrefutable evidence from brain imaging that Fibromyalgia Syndrome (FMS) has strong biologic underpinnings, even though psychological, behavioral and social factors play a significant role.

Fibromyalgia, the term was first coined by Hench in 1976 with several modifications put in place thereafter. Muller and Lautenschlager in 1990, formulated the criteria for generalized tenomyopathy. The cause of this condition remains unknown but postulations as regards its pathogenesis and causal factors have been outlined since.

Viral infections such as Hepatitis C, parvovirus B19, Human Immunodeficiency Virus (HIV) and Lyme's disease have all been associated as likely triggers for Fibromyalgia. [2]

Large prospective population based studies have also shown that physical and emotional stressors at workplace and depressed mood are risk factors for development of FMS.

Diabetes mellitus (DM), the most common metabolic disorder has also been shown to have a causal effect in the development of this not so rare syndrome.

The diagnoses of FMS can be made with accurate clinical precision. This is based on the American College of Rheumatology (ACR) criteria which were developed back in 1990, and it requires the presence of Chronic Musculoskeletal Pain (> 3 months duration). Physical evaluation is then carried out to elicit tenderness at 11 or more specific tender points. This criteria has been widely utilized for research and clinical settings so as to make a diagnoses of FMS. [1] Fibromyalgia is a common frustrating disease that frustrates physicians due to the vagueness of complaints, lack of clear lab and imaging findings and the intransigence to

therapy. The attendant chronic Musculoskeletal pain together with other symptoms such as sleep disorder and mood changes can all negatively impact on the quality of life of these subset group of patients who are already condemned to this progressive debilitating life-long disorder i.e. Diabetes Mellitus. It also frustrates patients to a much greater degree due to the severity of suffering, lack of specific therapy and in many cases, the disbelief and skepticism handed out by the health care providers. It therefore makes it prudent to clearly identify this clinical entity with an intention of offering management to alleviate the added suffering that usually results from this symptomatology.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 Definition of Fibromyalgia

The ACR 1990 criteria defines FMS as chronic pain lasting more than 3 months in multiple parts of body i.e.

- Pain in the axial skeleton (cervical spine, thoracic spine, anterior chest and lumbar region)
- Pain in the right and left side of the body
- Pain above and below the waist
- Pain on palpation of at least 11/18 "tender points"

Chapter XIII of International Classification of Disease 10 (ICD 10), which is entitled "Diseases of Musculoskeletal System and Connective Tissues" contains a heading M79, which is entitled "other soft tissue disorders not elsewhere classified". FMS is under appendix M79.7. These guidelines also recommend classifying FMS as a functional somatic disorder. The nomenclature of Fibromyalgia has evolved with time. In 1904, a British Neurologist, Sir William Gowers, attributed its pathophysiology to inflammation of the fibrous tissues and termed it as "fibrositis". He also made close note of other associated symptoms present including fatigue and sleep disturbances. (3)

In 1970s, Smyth et al described FMS exclusively as a generalized pain syndrome, along with fatigue, poor sleep, morning stiffness with emotional distress as an aggravating factor and multiple tender points. His work formed the very basis for formulation of the ACR criteria in the 1990s. (4)

Fibromyalgia is considered as the 2nd most common Rheumatic disorder behind Osteoarthritis.

A newer diagnostic criteria published in 2010-2011, no longer requires performing a tender point count to make the diagnoses and instead entails asking about the constellation of Non-Pain Somatic Symptoms that are typically present in addition to the widespread pain. Nearly all individuals eventually diagnosed with FMS have several bouts of chronic pain in other regions of the body earlier on in their lives.

2.2 Epidemiology of FMS

The prevalence is related to both age and sex. A large study done in Wichita, Kansas, found the prevalence of FMS in the general population to be 2%. It also concluded that female gender was predominantly affected by this disease process. Patients above the age of 40 years are more likely affected. (5)

Prevalence in the general population varies between 2% to 8% in various studies.[49] [50]

In Europe, a large summary of about 10 studies done across 5 countries representing the general adult population in various countries, the prevalence of FMS ranging between 0.7% to 3.3% . The prevalence was between 1- 4.9% in females and 0 -1.6% in males. The female to male ratio varied greatly between 2:1 and 21:1. In women, the prevalence rises steadily from younger age groups of 18-30 years with a peak at 55-64 years. From there it is a progressive decline. [6]

Gender differences are also noted in some of the clinical manifestations whereby women tend to present with longer duration of chronic widespread pain and "tender point" count [7]

Dokwe et al, in 2011, did a study locally and estimated the prevalence of FMS in patients attending the Medical Outpatient Clinic (MOPC) and Rheumatology clinics in KNH at 11%. [8]

Mumo et al in 2013, studied HIV patients attending the Comprehensive Care Centre (CCC), KNH, the prevalence was estimated at 17.9% in this subset of population. The female preponderance was true with the males being at only 12% [9]

Of particular interest, a study done by Tishler et al, the prevalence of FMS in diabetes mellitus was at 17%, with a higher female preponderance. No differences were noted in the prevalence of FMS between Type I and Type II DM. He also noted that FMS in DM patients was associated with elevated levels of HbA1c than those without FMS. DM patients with FMS had significantly higher levels of HbA1c than those without FMS. ((9.2 ± 1.1%) vs. (6.4 ± 1.5%)). From his study, he also noted that patients with FMS had more tender points than those without FMS (12.8 ± 1.4 vs. 3.1 ± 2.2) and higher levels of pain (7.1±2.2 vs. 1.1±1.8 $P < 0.001$). The prevalence of sleep disturbance, fatigue and headaches were significantly higher among patients with both FMS and DM, while occurrence of peripheral neuropathy and Irritable Bowel Syndrome (IBS) did not differ significantly between the two groups. He concluded that the correlation between the number of "tender points" and HbA1c level was significant. (P = 0.027) [10]

Another recent study by Yanmaz et al, who found a prevalence of 18% in patients with Type II DM. They used a sample size of 93 patients. Again, not surprisingly, females predominated. **[11]**

2.3 Etiology, pathogenesis and pathophysiology

The exact cause of this condition remains unknown. Environmental factors such as infection, post-traumatic stress and certain genetic factors have all been found to play a role in the pathogenesis of FMS.

Central Nervous System (CNS) sensitization has been noted as a major pathophysiologic aspect of FMS. Current evidence and research points towards existence of a genetic basis of disease and to that effect a number of candidate genes that are implicated. The hallmark is understanding the altered pain processing pathway of FMS. [12]

Pain and tenderness are thus the defining features of FMS. This central features are currently attributed to an increase in central pain processing i.e. a disturbance in which the CNS and the spinal cortex handle and transmit the pain signals. Allodynia is frequently present. The severity of pain, and its frequency may have significant inter and intra-patient variability. Although pain is central, other associated symptoms are frequently present too. Sleep disturbances are almost universal and patients describe nocturnal awakening and non-refreshing sleep. [13] Symptoms of IBS may also be associated with FMS including intermittent diarrhea with constipation, bloatedness and abdominal pain.

Therefore the clinical features accompanying the Chronic widespread musculoskeletal pain (CWP) include disturbed sleep, chronic fatigue, IBS, headaches (including migraine), Temporo-Mandibular Joint (TMJ) disorders, non-cardiac chest pain, Raynaud's phenomenon, sicca syndrome, restless leg syndrome, irritable bladder, and premenstrual syndrome (PMS)

2.3.1 Physical findings in a patient with FMS

The TP are distributed symmetrically

- Over the occipital area
- Low cervical
- Trapezius
- Supraspinatus
- Second rib
- Lateral epicondyle
- Gluteus
- Greater trochanter
- Medial fat pad of the knee

Each point is palpated by the Thumb of the examiner using gradually increasing pressure until pain is elicited. A point is considered 'positive' if minimal pain elicits irrational amount of pain. Unless a concomitant pathology is pre-existent, the rest of the clinical exam is unremarkable.

2.3.2 Pathogenetic Theories

1) Infection and Vaccination

Viral agents such as Hepatitis C, hepatitis B, HIV and Lyme's disease, whereby these infectious agents are considered as possible triggers for development of FMS. Parvovirus B19, was previously thought of as an association but recent research has opted otherwise. [(2)]

2) Secondary Fibromyalgia Syndrome

This refers to a situation in which a localized painful condition e.g. tendinitis, herniated disk etc. causes pain which then becomes widespread. This evolves into FMS. There are increased rates of FMS in patients who suffer from C-spine whiplash injuries post Road Traffic Accidents(RTA)

3) Role of Biogenic Amines and Neurotransmitters (NT).

Rusell et al clearly demonstrated that both Serotonin and Norepinephrine (NE) were decreased in the cerebrospinal fluid (CSF) of patients diagnosed to have FMS. On the other hand, Substance P, known to correlate with pain, were found to be elevated. [(14)]

Although FMS is not considered as an inflammatory disease, complex interactions between the biology of pain and an inflammation has led to identification of alterations in various cytokines in patients with FMS. Levels of IL-1-RA and IL-6 have been shown to be increased in the peripheral macrophages of patients with FMS. IL-1-β, IL-6 and TNF-α levels have also been shown to be increased in the skin biopsies of patients with FMS. [(15)]

It is not clear whether the changes are primary or represent an epiphenomenon, but it is clear that the imbalance in the CNS of neurotransmitters has a role in the pathogenesis of disease.

4) Hormonal imbalance

Perturbations in Hypothalamic-pituitary-adrenal (HPA) axis are present and redemonstrated in FMS. Alterations in the functioning of Sympathetic Nervous System (SANS) involved in the response to stress. Despite the high female preponderance, sex hormones have not been shown to play an active role. [(16)(43)]

5) FMS and the concept of central sensitization.

A hallmark of these pain syndromes is that patients display diffuse hyperalgesia (increased pain to normally painful stimulus) and/or allodynia (increased pain to normally non-painful stimulus). This suggests that these individuals have a fundamental problem with augmented pain or sensory processing in the CNS.

Central sensitization constitutes a condition of general over-reactivity of the CNS to a wide spectrum of stimulation. Various areas in the brain are responsible for inhibiting the pain transmission impulses e.g. the locus ceruleus, corticoreticular system, brainstem nuclei, hypothalamus, and this is mediated through activity of inhibitory NT such as Serotonin, NE, Encephalin, Gamma Aminobutyric Acid (GABA) and Adenosine. A decrease in the pain inhibitory loop is central to the pathophysiology of FMS.

Functional Magnetic Resonance Imaging (fMRI) have been used to delineate this altered pathways and are now used as standard diagnostic tools in resourced settings.

The initial observation that individuals with FMS are diffusely tender led to subsequent functional, neurochemical and structural brain studies, all of which gave the best objective evidence that the pain in FMS is real. fMRI evidently showed that individuals with FMS have increased connectivity between brain regions involved in increased pain transmission and decreased connectivity to key anti-nociceptive regions.[44][45]

6) Role of AMPK activation [83]

In a recent study done by Alcocer et al (2015), they looked at Metformin and Caloric restriction in FM patients. Impaired AMPK is associated with a wide spectrum of clinico-pathologic conditions ranging from obesity, metabolic syndrome, inflammation, disturbed mitochondrial biogenesis and defective response to oxidative stress. FMS comprises all of the above pathophysiologic states. AMPK activation in fibroblasts from FMS patients was tested and it was noted that AMPK was not phosphorylated in fibroblasts from FMS patients. This was associated with decreased mitochondrial biogenesis, reduced oxygen consumption, decreased levels of antioxidant enzymes and resultant mitochondrial dysfunction. Interestingly, AMPK activation by metformin led to improved response to oxidative stressors and ameliorated mitochondrial metabolism in FM fibroblasts. These results suggest that AMPK plays an important role in FMS pathophysiology and could represent a novel therapeutic strategy in treating Fibromyalgia.

7) Other factors

FMS has been shown to be strongly aggregated in families. 1st degree relatives of patients with FMS are 8.5 fold more likely to have this condition compared to family members of controls. (17)

A higher preponderance was also noted in rural more than urban population in a large scale study done in Pakistan (18)

Other pathogenetic mechanisms implicated include sharing of environmental factors, learned patterns behavior and response to stress and anxiety.

Interestingly, shared intra-uterine factors are under study. (19)

Recently, expanding knowledge is present regarding a predisposing role of genetic factors leading to chronic pain states. (46) (47) (48)

8) Substance P in FMS

Substance P is an 11 amino acid neurokinin and has diverse actions in nociception. Substance P levels have been shown to be elevated in patients with FMS. (20)

The overall effect therefore is that these patients have a lower threshold of stimulation of neurons that perceive pain (21)

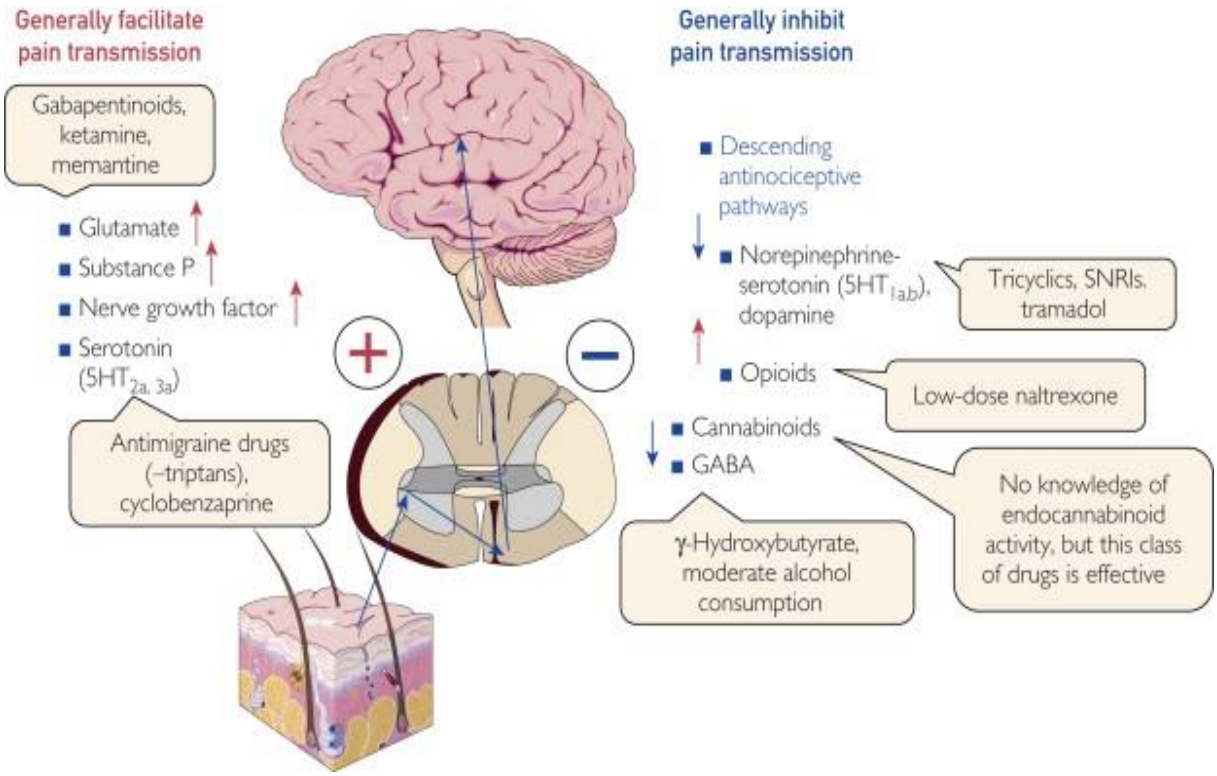


Figure 1: Different neurochemicals involved in pain transmission and modalities of intervention (35)

2.4 Diagnoses of FMS

Establishing the diagnoses of FMS is key to successful therapy. The specific signs and symptoms form the basis of the 1990 ACR diagnostic criteria for FMS and these include

i. Pain > 3 months
ii. Presence of 11 out of 18 specified tender points.

CWP means pain involving the four quadrants of the body, i.e. right and left and above and below the waist. The axial skeleton (i.e. cervical spine, anterior chest, thoracic spine, or lower back) are also included in the definition.

Tender points (TP) are elicited by applying 4Kg pressure on pre-specified areas. This amount of force would result in blanching of the examiners thumb capillaries. A tender point has to be painful on palpation not just tender. This is referred to as allodynia

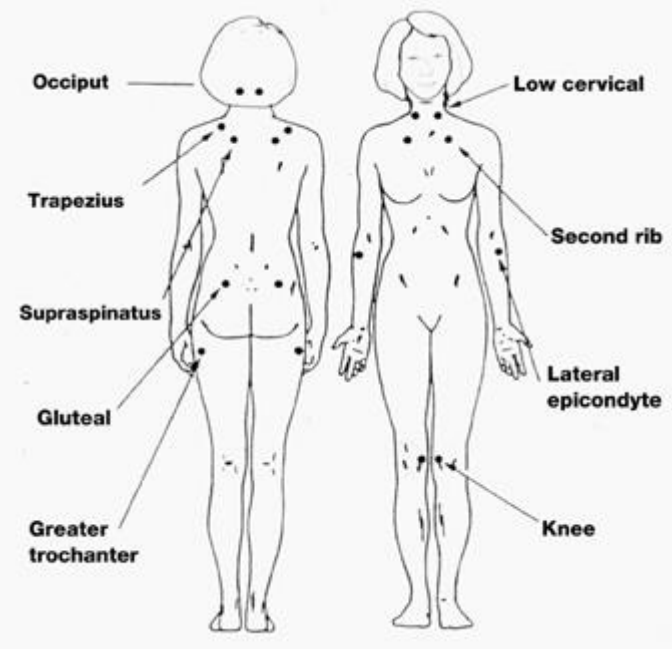


Figure 2: Tender points for evaluation

FMS may coexist with other medical conditions and terminologies such as secondary FMS are not widely used. Initially, this criteria was designed for research purposes but has now become a diagnostic tool in the clinical setting with a sensitivity of 88% and a specificity of 81.4%. There are no lab tests nor radiologic investigations that may diagnose FMS. [22]

The ACR diagnostic criteria 1990 does not capture other aspects of FMS including sleep, IBS, chronic fatigue and lack of balance or overall functionality.

2.4.1 The FIQR (Fibromyalgia Impact Questionnaire)

This tool, validated, can be used to assess some of the other coexistent symptoms. It has 3 domains and useful when it comes to assessing symptoms, functionality and overall impact of condition to each patient. [23]

2.4.2 The SIQR (Symptoms Impact Questionnaire)

Very similar to the FIQR, it stands for Symptoms Impact Questionnaire will be used to assess for similar symptoms in patients with chronic musculoskeletal pain that are not FMS.

2.4.3 Scoring System for the FIQR and SIQR

Step 1 – each of the three domains (function, overall and symptoms) are scored on a scale of 0 to 10. The 11 boxes represent the numbers 0 to 10 from left to right on the questionnaire.

Step 2 – a. The sum of the function domain (0-90) is divided by 3 (upper limit 30)

b. the sum of the overall impact domain (0-20) is divided by 1 (upper limit 20)

c. the sum of the symptom domain (0-100) is divided by 2 (upper limit 50)

Step 3 – add the resulting domain scores (a, b and c) to obtain the total score of the FIQR and SIQR. (Range 0 to 100)

Severity scores for FMS with 0-39, 40-59 and more than 60 denotes mild, moderate and severe disease respectively.

2.5 Impact of FMS

FMS has major socioeconomic impact on healthcare and non-healthcare resources. The individual and the society are both burdened by the nature of this disease. The number of clinical visits, prescriptions, OTC pain-medications increase tremendously in patients with FMS.

2.6 Diabetes and Chronic Musculoskeletal Complaints

DM, a metabolic disease characterized by absolute or relative deficiency of insulin, leading to hyperglycemia. It affects the connective tissue in various ways.

Musculoskeletal complications of Diabetes can be grouped into the following categories

a. Consequence of DM complications
b. Consequence of metabolic derangements inherent to Diabetes
c. Syndromes that share etiologic mechanisms with micro vascular disease

d. Probable associations e.g. Fibromyalgia Syndrome

Many rheumatic diseases have been associated with DM including DM-osteoarthropathy, stiff hands syndrome, osteoporosis, neuropathic joints and calcific peri-arthritis

It is estimated that more than 50% of diabetic patients will suffer from chronic disability [54]. Factors known to contribute include vascular complications and in addition, predisposing factors such as age, obesity, low physical activity also play a role. It is reported that patients with Type 2 DM had greater impairments in performing activities of Daily Living (ADL) than similarly aged Non diabetic persons. This translates to loss of independence and can be an important predictor of morbidity, recurrent hospitalizations, frequent institutionalization and subsequent death [55]

Very few studies have evaluated musculoskeletal pain and related complication in Diabetes. One study detected a prevalence of 38% in which, the researchers excluded patients with Osteoarthritis [56]. One study looked at a cohort of 80 patients, and this group reported a much higher prevalence of 58% of chronic musculoskeletal pain in patients with Diabetes [57]. Among the musculoskeletal complications related to DM, it was noted that Carpal Tunnel Syndrome [51] [58], adhesive capsulitis [51] [52], flexor tenosynovitis [51], and limited joint mobility [51] were more prevalent in DM. A Japanese cohort, of about 302 patients, demonstrated significant association between different types of Musculoskeletal complaints especially flexor tenosynovitis and limited joint mobility, in association with DM. [59]

Over the past few years, the most important predictor that predisposed to development of musculoskeletal complications is Blood glucose control. [52] [56] [60-64]

Vascular complications in DM are also known to be very important predictors of predisposition to chronic pain. From some studies, it has been noted that retinopathy is a significant predictor with patients having an 85% chance of developing chronic musculoskeletal complaints. [56]

Occupations such as manual labor increase the risk of hand complications [51] [61] [64]. The risk of flexor tenosynovitis and Carpal Tunnel Syndrome was noted to be much higher in patients with peripheral Neuropathy. This group often present late, due to masking of pain secondary to secondary denervation, when surgery becomes the only option for rehabilitation. [51]

2.7 Diabetes and Fibromyalgia

Prevalence of DM in all age groups worldwide was estimated at 2.8% worldwide and expected to rise to a staggering 4.4% by 2030. Prevalence of DM is higher in men than in women. The number of people is increasing due to increased population growth, aging, urbanization, prevalence of obesity and physical inactivity. [24]

The global prevalence of Non-Communicable Diseases (NCD), dominated by DM, have the greatest burden occurring in developing nations.[25] It is projected that by 2020, NCDs will surpass the communicable diseases as a leading cause of mortality. [26][27]

Diabetes is a huge and rapidly growing problem and the costs to the society are high and escalating. In 2013, an estimated 382 million people were estimated worldwide to have Diabetes. This numbers are expected to rise by a staggering 55% to about 592 million in 2035.

Africa is expected to have a rise of 109% (from 19.8 million to 41.4 million). Despite the urban impact of this epidemic, type 2 DM is fast becoming a major health concern in rural communities in low and middle income nations.

An estimated 80% of the total world population with Diabetes live in low and middle income nations. The greatest number of people with DM are between 40-59 years. [42]

Currently, the estimated prevalence of DM in Africa is 1-3% in rural areas and 5-6% in urban sub-Saharan populations.

The epidemiology of DM in Kenya has not been studied extensively, but the best estimate of DM is from an opportunity sample of an urban and rural population that reported a Non-age adjusted prevalence of 4.2% [28]. According to the IDF Atlas 2013, Kenya has approximately 750,000 diagnosed diabetics. An extra 562,000 are supposedly living undiagnosed. [42]

A study done by Ayah et al detecting the prevalence of diabetes and correlates in an urban-slum community in Kenya inferred an age-adjusted prevalence of 5.3% (95% CI 4.2-6.4), and this prevalence increased with age, peaking at 10.5% in the 45-54 year age category.[29]

The long term relatively specific effects of DM include development of retinopathy, nephropathy and Neuropathy. [40] Persons living with DM are also at an increased risk of developing cardiac, peripheral arterial and cerebrovascular disease [41]

The HUNT study, published in biomedcentral in 2008, outlined the association between DM, glucose and chronic musculoskeletal complaints in a large cohort of Norwegians. [30] This

study looked at 64,785 patients above 20years, of which 1940 were known DM. The results revealed that DM was associated with a high prevalence of chronic MSC, and in particular, chronic widespread MSC. In this study, chronic widespread MSC was defined as pain with or without stiffness for 3 months, during the past 1 year, with symptoms in all of the following regions (i.e. axial skeleton, pain above and below the waist.) Also noted in this large study, there was a high prevalence of FMS with a positive correlation between HbA1c levels and more tender points.

Musculoskeletal complaints of DM are very common endocrine arthropathies. These manifestations lead to chronic disability. FMS is one of those diseases that contributes directly to persistent Chronic Musculoskeletal pain and related complaints in this subset of patients. As the numbers of Diabetics rise, this functional disability will increase, posing a major public health concern.

Tender point count assessment is a simple and non-invasive examination finding that can augment information about disease severity in patients with FMS. A study on patients with primary FMS on the relationship between Tender Point counts and disease severity revealed that TP count (14.66 ± 2.5) was positively correlated with the mean total FIQR score (62.75 ± 15.57). The authors of this study found no correlation between TP count and age and duration of disease [(89)].

Attar et al, in a tertiary facility in Saudi Arabia, revealed that upto 17.9% of Diabetics suffer from chronic musculoskeletal manifestations, fibromyalgia being one of them.[(51)] Mohamed Yunus, in his review article, in 2011, noted that central sensitization syndromes (CSS) have an increased prevalence in patients with Diabetes Mellitus[(53)].

The study done in 2012, by Suzan Attar, revealed that Musculoskeletal Pain manifestation in DM were at 17.9%. She used a sample size of 252 patients. From her analysis, she noted that age, gender, obesity and low physical activity all strongly contributed to development of pain syndromes in the Diabetic population. The patients affected were all condemned to loss of independence, and this could predict strongly to future hospitalizations and institutionalization [(51)]

Ramchurn et al, studied a British Cohort with Diabetes. He noted that musculoskeletal manifestations have a strong association with poor glucose control. [(52)]

It cannot be over-emphasized that diabetes has significant polyneuropathic syndromes and patients present with pain.

A study done to differentiate Diabetic Polyneuropathy (DPN) and FMS revealed that DPN and FMS differ substantially in the pathogenetic factors and spatial distribution of pain [(31)]. Sensory perceptions in both conditions include paresthesia, prickling and allodynia. DPN is characterized as chronic neuropathic pain, caused by a metabolic damage of afferent neurons and the sensory abnormalities present mainly in the hands and feet. In contrast, FMS is a chronic painful condition characterized by chronic widespread pain mainly perceived in the deep somatic tissues i.e. tendons and muscle groups. FMS is also characterized by abnormal pain sensitivity and frequent additional comorbidities including sleep disturbances and affective disorders. In contrast to the classic neuropathic pain caused by DM, the general perception of FMS is that in this disease, nerve lesions are not demonstrable. Epidemiologically, DPN gender ratios are noted to be similar, whereas in FMS, a 10:1 ratio is noted with a high female preponderance. Patients with polyneuropathies secondary to DM, perceive their discomfort in both skin and deeper structures of hands and feet, contrary to patients with FMS who perceive their discomfort in deeper tissues, in particular, the muscle groups. Both groups may have perception of allodynia, which is a heightened response to otherwise non-painful stimulus, and is thought to be induced by activation of touch-sensitive Ab nerve fibers that synapse on 2nd order neurons in the CNS.[(32)]. Clinical experience also indicates that DPN suffer from heat hyperalgesia contrary to FMS who report that their pain is more enhanced when in contact with cold environmental temperature.[(33)(34)] Numbness is the only symptom that has overlap, but commoner in patients with DPN than in patients with FMS. It is a length dependent denervation and mainly affects hands and feet. Pressure induced pain i.e. deep somatic hyperalgesia, is the hallmark characteristic of FMS with the pathogenesis being linked to hyperactive nociceptive processing from sensitized nociceptors innervating deep somatic tissues. Jana et al clearly outlined that 58% of patients with FMS described the pain intensity to slight pressure as “strong” or “very strong” as compared to only 22% of patients with DPN perceiving pain on slight pressure. [(35)] In majority of patients with FMS, no clear nerve lesions were demonstrable, and the concept of central sensitization with loss of descending inhibitory control (as characterized by an increase in Substance P and decreases in Serotonin) making FMS different from DPN.

Diabetes may cause significant sensorimotor and autonomic neuropathy. Of interest here, is the sensory neuropathy, which is often a slow insidious process due to time related afferent

denervation. Sensory symptoms are classified as positive or negative. Negative sensory symptoms include feeling of numbness or deadness, which patients describe as being akin to wearing gloves or socks. Painless injuries due to loss of sensation are very common. Positive symptoms may be described as burning, prickling pain, tingling, electrical shock-like feelings, aching and tightness. These negative sensory symptoms may actually mask the pain caused by fibromyalgia syndrome, creating a necessity to identify persons with Fibromyalgia Syndrome in patients with Diabetes mellitus.[66]

2.8 Management of FMS

Clinicians often encounter such patients and label them as "somatizers" and that their disorder is "all in their head" and therefore, the key to management is a timely diagnoses.

A multidisciplinary approach is paramount due to the vast nature of differing symptoms. Management should also be individualized depending on the severity of pain, and the associated co-morbidity. Therapeutic modalities may be classified as pharmacologic and non-pharmacologic. Some of the drugs that have been recommended for use include analgesics (local and systemic). More recently, antidepressants e.g. TCA, SSRI and MAOI have all gained approval for use in this disease state. Non-pharmacologic interventions include use of physical therapy, exercise, patient education and dietary measures [36].

Once the phenomenon is recognized, it helps determine what types of treatments will work (i.e. centrally acting analgesics and non-drug therapies) and just as importantly, what will not (i.e. opioids and surgery)

Treatment of FMS results in an overall amelioration of pain scores and daily life functions. Use of certain medication e.g. Olanzapine has been associated with a significant improvement of pre-treatment pain scores [37]. In 2007, the FDA approved use of Pregabalin, Duloxetine and Milnacipran for treatment of FMS.

3.0 CHAPTER THREE: STUDY JUSTIFICATION

Diabetes mellitus is a major public health problem, and it is the greatest burden amongst all of the NCD. Its prevalence and incidence is continually rising with the maximum impact felt in the developing world. Current prevalence of DM in Kenya is estimated at 3.3% and projected to rise to 4.5% by 2025 if the trends are not in check, according to the Kenya National Diabetes Strategy. [38] Christensen et al concluded the prevalence at 4.2% [28] whereas Ayah quoted it at 5.3% in a subset of population [29] Rheumatologic conditions and indeed FMS are some of the comorbid conditions that affect these patients. DM is one of the NCD that has been linked with FMS. The ageing cohort and better health care facilities for all does not improve the prevalence of chronic musculoskeletal complaints, as age is a common predisposing factor for development of pain related disorders in the Diabetic subset.

FMS, a condition, with CWP is associated with significant morbidity which can be debilitating. The comorbid states of sleep deprivation, fatigue and IBS not only affect the quality of life but also impact on control of DM and the productivity of patients suffering. Musculoskeletal pain is the central symptom of FMS and this makes it important to identify it and manage it accordingly.

In our setting, there is paucity of data regarding the disease burden of FMS in Diabetics with chronic musculoskeletal pain. This is the first study, maybe on the continent, aimed at establishing the prevalence of FMS in a subset of population with Diabetes Mellitus. Other studies done by Mumo et al (2013) and Dokwe et al (2011) looked at prevalence of the same disease state in HIV infected individuals and the general medical and Rheumatology outpatient clinics respectively.

This study aimed to establish the prevalence of FMS and sensitize the clinicians on the disease condition. It is our hope, that patients with chronic musculoskeletal pain will henceforth be screened for FMS and duly managed with available modes of therapy, and this should be able to improve their quality of Life.

As at present, there are very well established guidelines which are aimed at detecting microvascular complications such as Retinopathy, Neuropathy and Nephropathy [65] However, none have been established to guide clinicians to follow up these patients for detection and follow up of chronic musculoskeletal complications.

From this study, it is also our hope that part of Diabetes Care will include asking patients about their pain related symptoms and other signs of CSS in their overall management.

3.1 Research Question

What is the magnitude of Fibromyalgia Syndrome in patients with Diabetes and chronic musculoskeletal pain at the Diabetic Out-Patient Clinic, Kenyatta National Hospital?

3.2 Objectives

3.2.1 Broad Objective

To determine the burden of FMS in Diabetic patients with chronic pain at the DOPC, KNH?

3.2.2 Specific Objectives

1) To determine the prevalence of FMS in diabetic patients with chronic pain
2) To determine the Tender point count in these study patients using the ACR 1990 criteria.
3) To determine the severity of FMS related symptoms using the FIQR tool.

3.2.3 Secondary Objective

To correlate FMS with sociodemographic characteristics and metabolic control of patients attending the DOPC presenting with chronic musculoskeletal pain.

3.3 Study Methodology

3.3.1 Study design

Descriptive cross-sectional study

3.3.2 Study site

The Kenyatta National Hospital is the largest referral facility in East and Central Africa. It runs numerous medical out-patient clinics from all fields of specialty. The Diabetes clinic is one of the largest, and arguably the busiest out-patient clinic with an estimated 6000 registered patients as per the records department, KNH. Numbers for newly diagnosed DM patients continue to rise every day. These patients are all on follow up at the DOPC.

These clinics, dedicated to the care of the Diabetic population, are both housed in the Medical Out-patient Clinic facility Number 17, a large clinic facility within KNH. The mini-clinic that runs daily from Monday to Thursday, serves an average of 30-40 patients per day and a major consultant clinic takes place every Friday, averaging approximately 90-120 patients per clinic day. This specialized clinic is attended by Consultant Physicians/Endocrinologists, residents in the Internal Medicine program, Diabetes Educators and Nutritionists. [39]

The consultant clinic and the mini-clinics are all run from the same premises i.e. Clinic 17, at the KNH.

Patients are booked in to these out-patient clinic facilities, and given appointments for clinical reviews. For patients with less severe glucose control, and fewer DM related complications, this group of patients are reviewed in the mini-clinic, which runs on a daily basis. For those with complications and multi-organ involvement secondary to Diabetes Mellitus, these patients are reviewed on a regular basis every Friday on pre-specified appointments.

3.3.3 Study population

All diabetic outpatients with chronic musculoskeletal pain. This is defined as pain more than 3 months duration with Bones, Joints, tendons and Muscle involvement. This study included patients on Insulin therapy, Oral Glucose Lowering agents (OGLA) or a combination of both.

3.3.4 Patient selection

3.3.4.1 Inclusion criteria

i. Patients with a file diagnoses of DM and on follow-up at the DOPC
ii. Patients above 16 years
iii. Patients with chronic musculoskeletal pain lasting more than 3 months
iv. Patients who give an informed written consent or assent for participation.

3.3.4.1 Exclusion criteria

i. Patients with significant CNS abnormalities who are unable to give a proper description of symptoms
ii. Patients with neuro-cognitive impairment including dementia and/or mental confusion

3.3.5 Sample size estimation

From previous studies, an average prevalence of 17% will be used with a Confidence Interval of 95%. The Fischers formula used will be as follows

$$n = \frac{z2\ P\ (1-P)}{d2}$$

Where n= minimum sample size

$Z^2 = 1.96^2 = 3.8416$

P = prevalence (17%) = (0.17)

Margin of error (d) = 5%

Therefore;

$$n = \frac{3.8416x\ 0.17\ (1-0.17)}{0.0025}$$

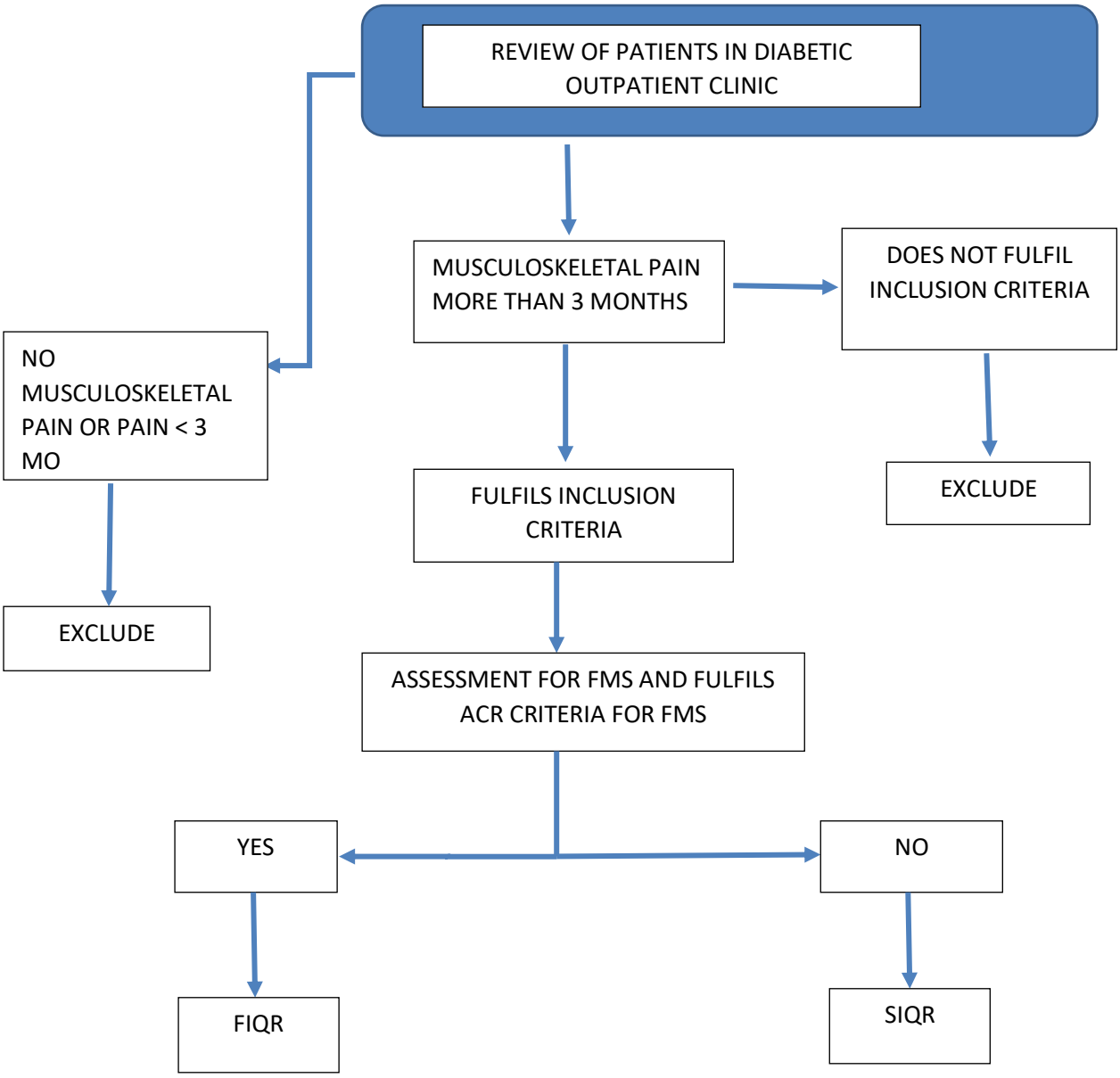
$$n = 216.8=217$$

The prevalence was derived from a study by Professor Tishler et al, published in Rheum Int (2003), [10] titled "Fibromyalgia in Diabetes", where the prevalence was estimated at 17%. This study was used as it is the only study available that directly outlines the prevalence of FMS in DM.

3.4 Sampling Procedure

Convenient sampling technique was used to select the patients into the study. Patients were recruited consecutively every clinic day until the desired sample size was attained. Recruitment took place in the main clinic and the mini-clinics that were operational on a daily basis. These patients were assessed for chronic musculoskeletal pain, which is defined as pain greater than 3 months affecting all the four quadrants and the axial skeleton. Patients with pain less than 3 months were excluded. An interviewer administered study proforma was administered and a Principal Investigator (PI) directed examination performed for Tender points (TP). Those with TP ≥11/18 were given the FIQR, and those with ≤11/18 TP on examination, were given the SIQR.

Figure 3: Flow chart for patient Recruitment


REVIEW OF PATIENTS IN DIABETIC OUTPATIENT CLINIC
MUSCULOSKELETAL PAIN MORE THAN 3 MONTHS
DOES NOT FULFIL INCLUSION CRITERIA
NO MUSCULOSKELETAL PAIN OR PAIN < 3 MO
FULFILS INCLUSION CRITERIA
EXCLUDE
EXCLUDE
ASSESSMENT FOR FMS AND FULFILS ACR CRITERIA FOR FMS
YES
NO
FIQR
SIQR

3.5 Data Collection and Clinical Methods

3.5.1 Data Collection Tools

1) The Fibromyalgia Impact Questionnaire (FIQR) – this was used to assess aspects of FMS like functionality, symptoms and the quality of life on those diagnosed to have FMS
2) The Symptoms Impact Questionnaire (SIQR) – this questionnaire was used to assess aspects of musculoskeletal symptoms e.g. functionality, other symptoms and the quality of Life in patients without FMS.

3.6 Data Collection Methods

Patients attending the DOPC during the study were assessed for chronic MSC. This involved interviewing them on presence of current pain involving any parts of the body including bones, joint, tendons and muscle groups. This pain had to be present for the past 3 months. Those who fulfilled the above pre-requisites and above 16 years of age were recruited into the study. Determination of DM was a file-diagnosis. Clinical data entailed type of Diabetes (i.e. type I or type II), main modes of therapy (Insulin versus OGLA or combination) and a most recent HbA1c level (taken at time of patient recruitment).

A targeted physical exam was performed by the PI to establish the number of “tender-points”. A total of 18 specified points will be examined for tenderness by digital palpation using the thumb of the examiner, whereby, a force of 4kg (which would cause blanching of the capillaries of the thumb).

The following tender points were examined:

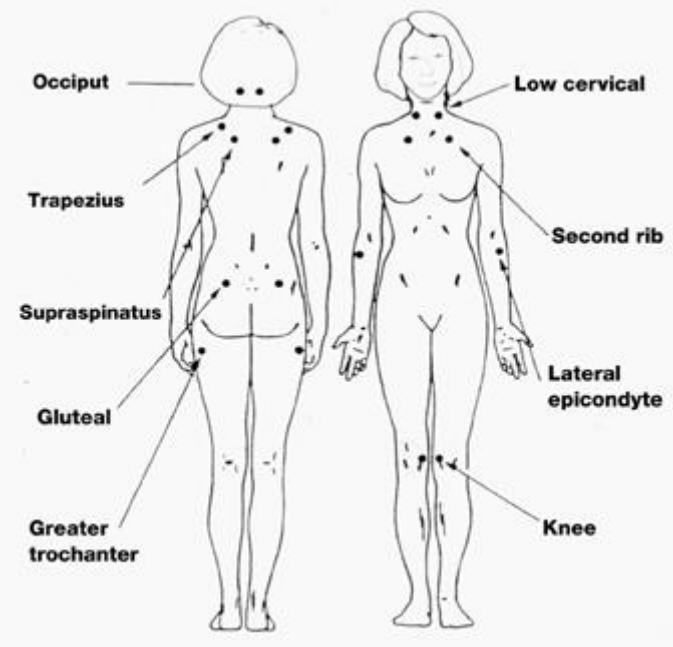


Figure 4: Tender points for evaluation

Those who satisfied the ACR 1990 criteria of CWP with ≥11/18 TP, were diagnosed to have FMS. Thereafter, the FIQR was administered to this group of patients to assess the frequency and severity of FMS.

Those with CWP more than 3 months, without Fibromyalgia, were given the SIQR to assess their overall functionality, impact and symptoms associated.

A sample of blood was drawn for assessment of the latest HbA1c levels for all patients recruited into the study.

The FIQR and SIQR have 3 domains each. The first domain has 9 questions whereby patients were asked about level of difficulty in performing ADL. The 2nd domain has 2 questions and this assessed the overall impact of patients' symptoms. The 3rd domain has 10 questions that assessed the specific symptoms and their severity on a scale of 0-10.

The scores for each domain will be added up and a 'normalization factor' will be applied thus dividing the 1st domain by three, the 2nd domain by one and the 3rd domain by 2. The total score of, between 0-100 was the sum of the 3 normalized domain scores.

3.7 Lab methods

Upto 3ml Blood was drawn from the antecubital fossa aseptically for all patients. This blood was put in an EDTA bottle (purple top) and taken to the lab for processing.

The machine used was a Cobas 111 (from Roche). It was an invitro test for HbA1c in whole blood and hemolysate prepared from whole blood. The principle used involves TTAB (Tetradecyletrimethylammonium Bromide) as the detergent in the hemolysing reagent to eliminate interference from leucocytes (TTAB does not hemolyse leucocytes). Sample pretreatment to remove labile HbA1c was not necessary. The HbA1c determination was based on turbimetric inhibition immunoassay for hemolysed whole blood.

3.8 Quality assurance.

The ACR 1990 criteria was adhered to when making the diagnosis of FMS and tender point examination was done by the PI, who is trained by a Consultant Rheumatologist. The consultant rheumatologist was also available for subject verification and independent assessment as data collection was taking place during the study period.

The Research assistants were qualified Clinical Officers who were trained and supervised to assist the PI to fill the questionnaires to ensure optimal standards. These are qualified personnel with a diploma in Clinical Medicine from renowned institutions.

Calibration of the HbA1c machines was done daily to ensure no errors in processing the sample.

Blood was drawn in aseptic techniques to ensure strict infection control measures.

3.9 Duties of Members of the Study Team

The Research assistants were trained and supervised on data collection methods prior to and during the study period. Recruitment and enrollment of patients was done by the PI and the Research assistants. The study proforma and the questionnaire was administered by these COs and the PI did the Tender point evaluation.

3.10 Data Management

3.10.1 Data handling

Data for questionnaires was collected during visits to the DOPC. Details about Diabetes, i.e. type and duration of disease and current medications was retrieved from the file. For adequate

standardization of the HbA1c results, a central lab was used to get these samples analyzed. Completed questionnaires were stored under lock and key by the PI.

3.10.2 Data Analysis and presentation

Questionnaires were coded, entered and managed in Microsoft Access 2013 database. Statistical analysis was done in SPSS version 21.0. The study population was described using their sociodemographic and clinical characteristics. Continuous data was summarized into means and standard deviations or medians and interquartile ranges for data with skewed distributions. Categorical variables was summarized into percentages. Prevalence of FMS was analyzed and presented as a percentage of all DM patients with chronic musculoskeletal pain and a 95% confidence interval (CI) of the prevalence was presented.

$$^{x}/_{n}\ x\ 100\%$$

Where x = Number of patients with Fibromyalgia

n = minimum sample size i.e. 217 *(Fischers 1999)*

Severity of FMS was assessed using validated questionnaires i.e. the FIQR and the SIQR, results for these were also presented as percentages based on the mild, moderate and severe categorization system.

FMS was correlated with age, sex, marital status, occupation, type of medication, duration of disease and the HbA1c. Comparison of means or medians between patients with FMS and those with no FMS was done using Student's t test or Mann Whitney U test respectively. FMS was also associated with categorical variables using Chi square test. Odds ratios were calculated to estimate the relative risk of FMS associated with the different independent variables. Multivariate analysis using logistic regression was used to determine factors independently associated with FMS. Findings were presented in tables and graphs.

3.11 Study Variables

The independent variables included demographic characteristics, like age, gender, marital status, nature of occupation, type of medication used and type of Diabetes (Type I or Type II). The HbA1c was listed as an independent variable. The dependent variable was the prevalence of Fibromyalgia.

3.12 Ethical consideration

This study was carried out after a written approval by the Department of clinical Medicine & Therapeutics, UoN, and the KNH / UoN Ethics and Review committee based at the Kenyatta National Hospital.

Prior authorization from the administration offices at the Kenyatta National Hospital was sought before commencement of this study.

All patients recruited into the study were clearly informed on the objectives of this study and patients were free to choose enrollment. Only patients who approved their participation in the form of a written consent (or assent) were recruited. Patients who were unwilling, were allowed to withdraw from this study at their discrimination. Information gathered from this study was kept in high confidentiality by the PI.

All patients who are found to have FMS were informed and educated of their diagnoses and duly referred to the Rheumatology Clinic for further management.

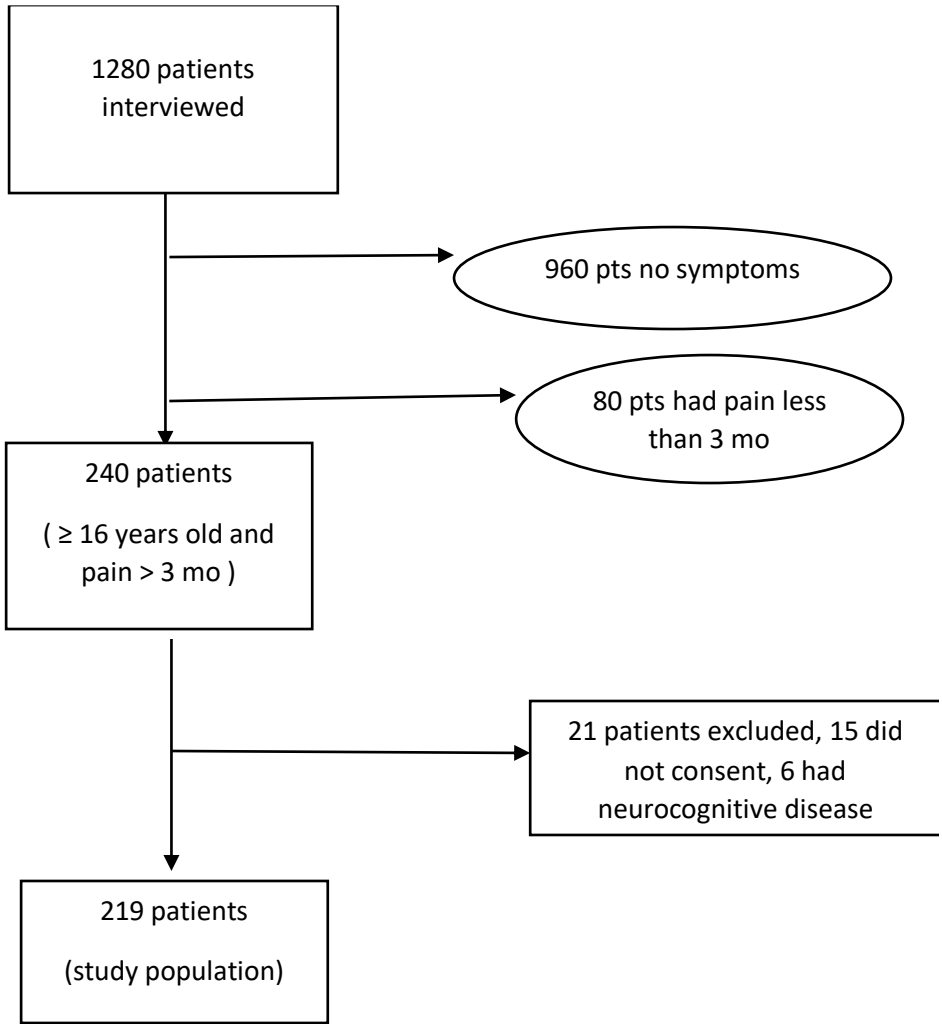
4 .0 CHAPTER FOUR: RESULTS

4.1 Patient recruitment

A total of 1280 Diabetic patients attending the DOPC were evaluated for chronic musculoskeletal pain between April 2016 and June 2016. This was done by direct interview of patients for presence of Bone, Joint and Muscle complaints. Of these, 960 did not have any symptoms, while 80 reported to have had pain lasting less than 3 months. We remained with 240 patients, of which, 21 of them were excluded as they did not meet the inclusion criteria. 15 patients did not consent to participate in the study and 6 had neurocognitive impairment.

We enrolled 219 patients into the study. All patients were greater than 18 years of age.

Figure 5: Patient Flow chart



4.2 Demographic Characteristics of Sample population

The mean age of the patients was at 56.8 years (SD 13.6). Majority, 155 (70.8%) were of the female gender giving a male to female ratio of 1:2.4. One hundred forty eight (148) (67.6%) were married, 45 (20.5%) were widowed, 13 (5.9%) were separated from their spouses and an equal number i.e. 13(5.9%) were single at time of recruitment.

About 114 patients (52.1%) reported that they were involved in activities that did not require any manual form of labor. 64 (29.2%) reported to be engaging in manual activities during their daily activities and 41 (18.7%) worked in an office setting.

Ninety patients (41.1%) were unemployed at time of study and 52 (23.7%) reported to be staying a retired lifestyle. The rest (i.e. 35%) were employed.

Table 1: Sociodemographic characteristics of study population

Variable	**Frequency (%)**
Mean age (SD)	56.8 (13.6)
Gender	
Male	64 (29.2)
Female	155 (70.8)
Marital status	
Single	13 (5.9)
Married	148 (67.6)
Separated	13 (5.9)
Widowed	45 (20.5)
Daily activities	
Manual labor	64 (29.2)
Office job	41 (18.7)
Non manual	114 (52.1)
Occupation	
Employed	77 (35.2)
Unemployed	90 (41.1)
Retired	52 (23.7)

4.3 Clinical characteristics of the sample population

Table 2 summarized the clinical characteristics of the Diabetic population with chronic musculoskeletal pain.

206 (94.1%) were Type 2 DM on follow up, and only 13 (5.9%) were on follow up for Type 1 DM. The worldwide prevalence rates for Type I DM currently at 5-10%.

Majority, 104 (47%) of these patients were on Oral Glucose lowering agents (OGLA), followed by Combination Therapy with 78 (35.6%) (i.e. both OGLA and Insulin). 38 patients (17.6%) were on Insulin based regime as monotherapy for glycemic control.

Biguanides i.e. Metformin and Sulfonylureas (Insulin secretagogues) were predominantly used for Glycemic control for these group of patients at 146 and 99 respectively. A significant number of the sample population were on Biguanide – Sulfonylurea dual therapy. DPP 4 inhibitors and Glitazones were not as widely used. None was on Meglitinides.

Premixed Insulin (i.e. Mixtard 30/70) was the only insulin based regime of choice for all the patients on Insulin Therapy (both as monotherapy and Combination regime). Short acting insulin and Basal Bolus insulins were at 0%.

Table 2: Clinical characteristics of study population

Variable	**Frequency (%)**
Type of diabetes	
Type I	13 (5.9)
Type II	206 (94.1)
Medications use	
Insulin based regime	38 (17.4)
OGLA	104 (47.0)
Combination	78 (35.6)
OGLA (n=182)	
Sulfonylureas	99 (45.2)
Biguanides	146 (80.2)
DPP 4 inhibitors	7 (3.8)
Glitazones	2 (1.1)
Insulin	
Pre mixed	38 (100.0)

The mean HBA1c levels for the study subjects was at 9.4% (SD 2.6). Seventy seven (35%) of these patients had an HBA1c at greater than 10% and conversely, only 37 patients (16.9%) had an optimum HBA1c at less than 7%

This information is clearly depicted on the table as follows.

Table 3: Mean HBA 1c levels for the Study Population

Variable	Frequency (%)
HbA1c	
Mean (SD)	9.4 (2.6)
Category, n (%)	
<7	37 (16.9)
7-7.9	39 (17.8)
8-8.9	35 (16.0)
9-9.9	28 (12.8)
>=10	77 (35.2)
Missing	3 (1.4)

4.4 Prevalence of Fibromyalgia Syndrome in Diabetic patients with Chronic Musculoskeletal Pain

Of the 219 patients studied, 61 patients satisfied the ACR 1990 criteria for Fibromyalgia Syndrome. We thus found a prevalence of 27.9% (95% CI 21.9 – 34.2)

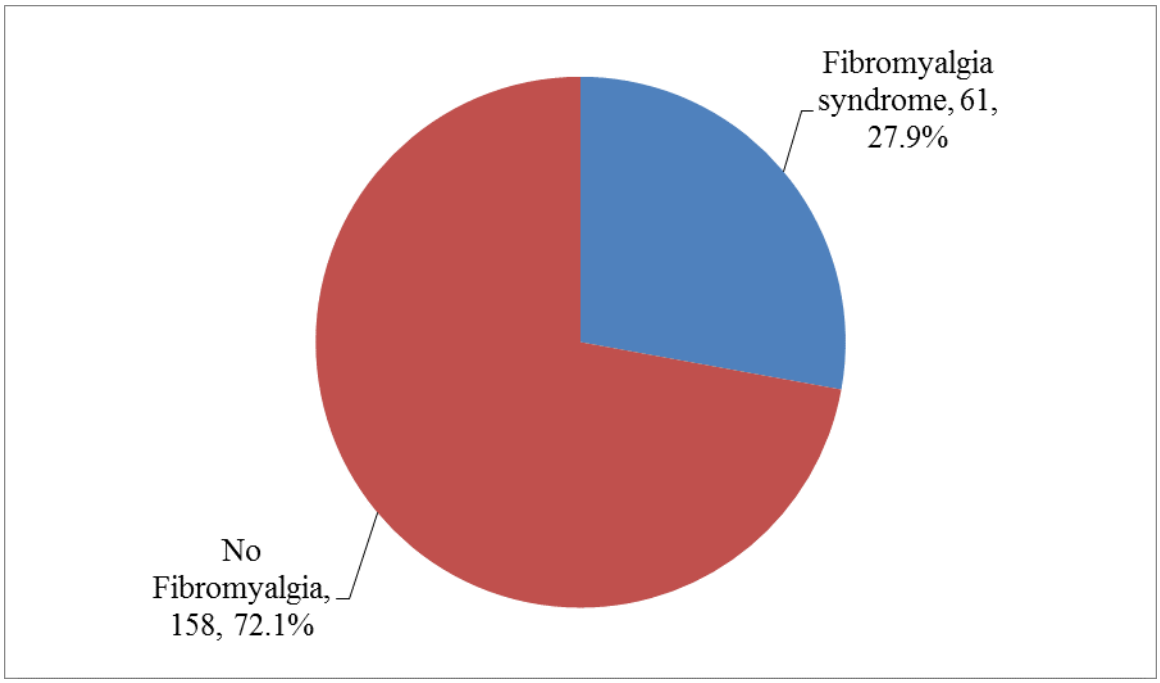


Figure 6: Prevalence of Fibromyalgia syndrome in diabetic patients

4.5 Severity of Fibromyalgia Syndrome

FMS was diagnosed in 61 (27.9%) (95% CI 21.9-34.2) patients with Diabetes presenting with chronic musculoskeletal pain.

To assess the severity, the FIQR scores were rated as follows: 0-39, 40-59 and more than 60, classified as having mild, moderate and severe disease respectively. The mean FIQR score for the 61 patients was 51.9 (SD 18.4). This denotes them as having moderate disease.

From our study, 24.6% had mild disease, 42.6% moderate disease and 32.8% had severe disease.

We also further classified these scores based on 3 domains. We looked at the level of function, overall impact of disease and symptoms. The mean overall scores for these 3 domains were as follows: the function score was at 13.6 (SD 7.1), overall impact was at 11.0 (SD 5.8) and symptom score was at 27.3 (SD 8.0)

Table 4: The FIQR domain scores

Variable	**Frequency (%)/ mean (SD)**	**95% CI**
FMS, n (%)		
Yes	61 (27.9)	21.9-34.2
No	158 (72.1)	65.8-78.1
FIQR score (n=61)		
Mean (SD)	51.9 (18.4)	
Severity		
Mild	15 (24.6)	13.1-36.1
Moderate	26 (42.6)	29.5-54.1
Severe	20 (32.8)	21.3-45.9
SIQR score (n=158)		
Mean (SD)	25.4 (12.2)	
Severity		
Mild	139 (88.0)	82.9-92.4
Moderate	14 (8.9)	5.1-13.3
Severe	5 (3.2)	0.6-5.7

4.6 Factors associated with FMS in Diabetic patients with Chronic Musculoskeletal Pain

Patients with FMS were significantly older (59.9 years) compared to those without FMS (55.6 years) P value = 0.034.

Gender, though not statistically significant (P value = 0.053) showed a trend in which a female preponderance was notable (31.6%) compared to male counterparts (18.8%). The Odds Ratio was calculated at 2.0 (95% CI 1.0-4.1)

All other sociodemographic factors were not significantly associated with FMS (P value >0.05). Those carrying out activities involved with manual labor were 50% more likely to develop FMS (OR 0.5)

The mean HBA1c for patients with FMS was 9.6% (SD 2.9) compared to 9.3% (SD 2.5). This was however not statistically significant. (P value = 0.565)

Type of Diabetes (i.e. Type I or Type II) and medications used were not significantly associated with FMS. (P value > 0.05)

Table 5: Factors associated with FMS

	FMS		OR (95% CL)	P value
	Yes (%)	**No (%)**		
Mean age (SD)	59.9 (15.0)	55.6 (12.8)	-	0.034
Gender				
Male	12 (18.8)	52 (81.2)	1.0	
Female	49 (31.6)	106 (68.4)	2.0 (1.0-4.1)	0.053
Marital status				
Single	6 (46.2)	7 (53.8)	1.4 (0.4-4.9)	0.587
Separated/Widowed	22 (37.9)	36 (62.1)	1.0 (0.3-3.7)	0.964
Married	33 (22.3)	115 (77.7)	1.0	
Daily activities				
Manual labor	13 (20.3)	51 (79.7)	0.5 (0.3-1.1)	0.068
Office job	10 (24.4)	31 (75.6)	0.7 (0.3-1.5)	0.290
Non manual	38 (33.3)	76 (66.7)	1.0	
Occupation				
Employed	18 (23.4)	59 (76.6)	1.0	
Unemployed	27 (30.0)	63 (70.0)	1.4 (0.7-2.8)	0.337
Retired	16 (30.8)	36 (69.2)	1.5 (0.7-3.2)	0.351
HbA1c, mean (SD)	9.6 (2.9)	9.3 (2.5)	-	0.565
Type of diabetes				
Type I	5 (38.5)	8 (61.5)	1.7 (0.5-5.3)	0.383
Type II	56 (27.2)	150 (72.8)	1.0	

Medications use				
Insulin based regime	14 (36.8)	24 (63.2)	1.2 (0.5-2.6)	0.709
OGLA	21 (20.4)	82 (79.6)	0.5 (0.3-1.0)	0.051
Combination	26 (33.3)	52 (66.7)	1.0	

4.7 Frequency and severity of FMS related symptoms in Diabetic patients with Chronic Musculoskeletal pain

Table 6 showed a depiction on the frequency and severity of symptoms using questions in the 3rd domain of the FIQR

100% had pain over the past 7 days, 100% reported reduced levels of energy, 100% had stiffness experienced, 98% reported disturbances in sleep patterns and reported to have had unrefreshed sleep, depression was present in 95%, memory problems in 93%, anxiety was reported in 91%. 100% reported to have tenderness to touch, balance problems were present in 98% and increased sensitivity to loud noises was reported in 98%

Table 6: Frequency and severity of FMS related symptoms in study population

Symptoms	**Severity of symptoms (n=61)**			
	0(%)	**1-3(%)**	**4-6(%)**	**7-10(%)**
Pain	0	13 (21.3)	18 (29.5)	30 (49.2)
Energy	0	12 (19.7)	21 (34.4)	28 (45.9)
Stiffness	0	10 (16.4)	21 (34.4)	30 (49.2)
Sleep quality	1 (1.6)	8 (13.1)	12 (19.7)	40 (65.6)
Depression	3 (4.9)	16 (26.2)	28 (45.9)	14 (23.0)
Memory	4 (6.6)	17 (27.9)	29 (47.5)	11 (18.0)
Anxiety	5 (8.2)	19 (31.1)	26 (42.6)	11 (18.0)
Tenderness	0	15 (24.6)	29 (47.5)	17 (27.9)
Balance	1 (1.6)	23 (37.7)	21 (34.4)	16 (26.2)
Sensitivity	1 (1.6)	9 (14.8)	17 (27.9)	34 (55.7)

4.8 Assessment of Tender point counts in patients with FMS

From our study, we noted that patients with FMS had a mean Tender Point count of 13.7 (SD 2.0) on evaluation. The overall mean for the study population, with and without Fibromyalgia Syndrome was 8.2 (SD 4.0)

From the 61 patients with FMS, 50.8% had tender point counts of 11-13, 41.0% had tender point counts of 14-16 and 8.2% had tender point counts of 17-18.

Further there was no significant difference in glycemic control among patients in different categories of tender point counts (p=0.941). As shown in table 7, patients with tender point counts of 11-13 had mean HBA1c of 9.7%, those with 14-16 tender point counts had mean HBA1c of 9.5% and at tender point counts of 17-18, the mean HBA1c was at 9.2%.

Table 7: FMS, Tender-point counts and Glycemic Index

Variable	**Tender point counts**		**HbA1c**
	Categories	Mean (SD)/ n (%)	Mean (SD)
Overall (n=219)	-	8.2 (4.0)	9.4 (2.6)
FMS patients (n=61)	-	13.7 (2.1)	9.6 (2.9)
	11-13	31 (50.8%)	9.7 (2.5)
	14-16	25 (41.0%)	9.5 (3.2)
	17-18	5 (8.2%)	9.2 (3.6)

4.9 Comparison of Mean Scores of patients with and without Fibromyalgia Syndrome using FIQR and SIQR

The average FIQR score was 51.9 (SD 18.4) for patients with Fibromyalgia Syndrome. When compared with the SIQR, the mean score for the SIQR, for patients without FMS, this was at 25.4 (SD 12.2)

This difference was statistically significant, P value <0.001

The subtotals for the 3 domains were also assessed and it was of note, that these scores were higher in patients with Fibromyalgia compared to those without Fibromyalgia Syndrome

Table 8: Comparison of Mean scores for FIQR and SIQR

Variable	**FIQR (SD)**	**SIQR (SD)**	**P value**
Function score	13.6 (7.1)	7.0 (4.4)	<0.001
Overall impact score	11.0 (5.8)	3.9 (3.6)	<0.001
Symptom score	27.3 (8.0)	14.5 (5.9)	<0.001
Total score	51.9 (18.4)	25.4 (12.2)	<0.001

5.0 CHAPTER FIVE: DISCUSSION

5 .1 Study Population

The DOPC is a daily outpatient clinic facility, run on a daily basis at the KNH. We sampled 219 patients with chronic musculoskeletal pain who consented to participate in this study. 70.8% were of the female gender, with a 1:2.4 ratio of male to females. 94.1% were on follow up for Type 2 Diabetes. This is in concordance to the most recent WHO global report on Diabetes where being female and a high proportion of body fat were the strongest risk factor for Type 2 Diabetes [(67)]

Also of note is that musculoskeletal complaints are more commonly seen in females [(68)]

Our population was predominantly urban and suburban, as the Kenyatta National Hospital, is central to these areas, and serves its environs. From the 2008 Kenya Demographic Health Survey (KDHS), it was noted that 60.3% of women and 19.5% of men in urban areas, compared to 22.6% women and 10% men in rural areas were shown to have rising levels of obesity and overweight problems [(85)]

This point also reflects the higher female preponderance in our study.

In comparison in two other landmark studies in the same area of research, by Tishler and Yanmaz et al, both of which concluded the higher female to male ratios in patients with Diabetes having chronic musculoskeletal complaints [(10)] [(11)]

5.2 Prevalence of Fibromyalgia Syndrome in Diabetic patients with chronic musculoskeletal pain.

Sixty one patients of the 219 sample size were noted to have Fibromyalgia, this gives a prevalence rate 27.9% (95% CI 21.9 – 34.2).

This only confirms with great certainty that FMS is indeed a reality in this group of patients. This is also in concordance to findings by Moshe Tishler and Yanmaz et al, done in a different ethnic population outside of Africa. [(10)] [(11)]

Tishler found a prevalence of 17% whereas Yanmaz found a prevalence of 18%.

The difference in prevalence rates can be explained by a relatively smaller study sample size by these preceding studies, where n was 100 patients in the former and 83 in the latter. The population under study was largely Caucasian in these two preceding studies, with both studies reporting a higher female preponderance.

We acknowledge the large variation in the prevalence rates compared to other studies and we attributed this to poorer glycemic control (mean HBA1c 9.6%), involvement in manual labor (30%), an ageing population (mean age 59.9 years) and most importantly, different ethnicities of the study group (largely black).

This possibly corresponds to a study done to evaluate ethnic differences in pain tolerance, Edwards et al noted that African-American subjects reported higher levels of clinical pain as well as greater pain related disabilities. [86]

A much older, much cited Harvard affiliated study done in 1943, also concluded black people to be more sensitive to pain when compared to European, Jewish or Mediterranean races. [87]

A population based prevalence study on fibromyalgia done in South Africa of a predominantly black ethnicity revealed a prevalence of 3.2%. This appeared to be much higher than in any Western European country. [88]

We selected the Diabetic population as it is a very well-known fact that DM patients tend to have more musculoskeletal complaints than healthy counterparts. This is with regard to a prospective cohort study done in Taiwan (from 2001 to 2010) over 10 year period. This study showed that people in the Diabetic group had a much higher 10 year cumulative incidence and a higher mean number of doctor visits for musculoskeletal pain than Non diabetic population, $P < 0.05$. [69]

There is increasing evidence to suggest that there are mechanistic links between metabolic diseases, low grade systemic inflammation and musculoskeletal complaints all of which lead to prominent musculoskeletal symptoms, Fibromyalgia being a key presentation. [70] [71] [72] [73]

Local studies done in KNH, by Mumo et al and Dokwe et al, looked at FMS in the HIV population and the Rheumatology Clinic, and estimated its prevalence at 17.9% and 11% respectively [9][8]

The above results reiterate the fact that musculoskeletal pain secondary to Fibromyalgia syndrome is common in the Diabetic population [74], and the prevalence being as high as 27.9% only confirms the increased need to have greater awareness of this syndrome as a clinical entity worth looking for in the daily Diabetes Care practice.

5.3 Assessment of Tender Point Counts in patients with Diabetes Mellitus

We found a mean Tender point count of 13.7 (SD 2.0) for patients with FMS in Diabetes.

This mirrored the findings inferred by a pioneer study by Tishler et al, who found patients with FMS had more Tender point counts than those without FMS. (12.8 ± 1.4 vs. 3.1 ± 2.2) [10]

We compared the tender point counts to controls in our study without FMS, and it was of note that the Tender point counts for patients without FMS was estimated at 6.0, statistically significant with $P < 0.05$. The mean tender point count for our study population (n=219) was estimated at 8.2 (SD 4.0)

From the 61 patients with FMS, 50.8% had tender point counts of 11-13, 41.0% had tender point counts of 14-16 and 8.2% had tender point counts of 17-18.

The largest ever study conducted in a European cohort, the HUNT study, which looked at 1940 cases of DM, and this group was followed up over a 10 year period. They concluded that patients with DM are more likely to develop chronic widespread pain (involving all 4 quadrants and the axial skeleton) with more tender points on examination than those without DM. This study however did not attest to the use of the classic ACR 1990 criteria for FMS. [30]

These findings also correspond to results authored by Ali Salli et al, who concluded in their study that TP count was positively correlated with disease activity in primary FMS [89].

A local study done by Dokwe et al in the Rheumatology clinic at the KNH, revealed the mean Tender point count at 11.0.[8] Mumo et al carried out a similar study on the HIV population, but did not document the tender point counts on these patients.[9]

The difference in tender point counts with higher levels in our study can be explained by the fact that DM, a metabolic disease, affects connective tissues in many ways, causing alterations in periarticular and skeletal systems. It also is associated with a great variety of musculoskeletal manifestations, many of which remain subclinical and correlate well with disease duration and its inadequate control. [75].These complications profoundly compromise the quality of life [76]

5.4: Severity of FMS related symptoms using the FIQR

Analysis was done using the 3rd domain of the FIQR questionnaire that assessed the intensity of fibromyalgia symptoms over the past seven days prior to recruitment. Of note was that pain, lack of energy, stiffness and level of tenderness were all present in 100% of all those

diagnosed to have FMS. The severity for each of these symptoms varied, however, upto 49.2% reported presence of pain on a scale of 7-10 (severe disease).

Pain is central to both the diagnostic criteria, and the FIQR and our findings were in proportion. The concept of Central sensitization is important to note as pain in FMS is thought to be due to hyper-excitability of neurons and more importantly, loss of the normal inhibitory pathways to pain[44][45]. More recent advances show increased levels of pain mediators e.g. Substance P in the CSF of patients thought to have FMS [20]. Dokwe et al studied prevalence of FMS in the Rheumatology clinic and there seemed to be a meticulous overlap between other rheumatic diseases and FMS [8]. This point explains presence of stiffness. The concept of hyperalgesia and Allodynia, both of which are key in the diagnoses of Central sensitization syndromes would best explain the high incidence of tenderness to touch [21].

Other components of this domain in the FIQR questionnaire looked at incidence of sleep disturbances, depression and anxiety, loss of balance and increased sensitivity to otherwise non-noxious stimuli (visual, auditory or olfaction) and this study concluded that patients with FMS are affected to a great deal in these activities of daily living. Gregg and Gupta in two previous studies reported that patients with chronic pain in Diabetes had much greater impairments in mobility, and more difficulty in performing ADLs than similarly aged Diabetic populations without pain [77][78]

All these findings mirror the premier research done by Tishler et al who inferred that pain scores, sleep disturbances (unrefreshed sleep), fatigue and headaches were commoner in patients with FMS in Diabetes as compared to controls. [10]

When we assessed the data on functionality (1st domain) and overall impact (2nd domain), the summative score for all the three domains was 51.9 for our study group. This concludes that majority of our patients had moderate disease. When compared with the SIQR, the mean score for the SIQR, for patients without FMS, this was at 25.4 (SD 12.2)

This difference was statistically significant, P value <0.001

5.5 Sociodemographic characteristics and Metabolic control of patients with FMS

From this study, we concluded that patients with FMS were significantly older (59.9 years) compared to those without FMS (55.6 years) P value = 0.034. A fact that cannot be over-emphasized that chronic musculoskeletal pain is more prevalent in the aging and the aged

population. Diabetes is a degenerative metabolic disease affecting connective tissues in more than one way. It is well known that the prevalence of FMS rises from 18-29 years and peaks at about 55-64 years. Our study is a true reflection of that fact.

Gender, though not statistically significant (P value = 0.053) showed a trend in which a female preponderance was notable (31.6%) compared to male counterparts at 18.8%. The Odds Ratio was calculated at 2.0 (95% CI 1.0-4.1). Tishler[10], Yanmaz[11], Mumo[9] and Dokwe[8] all inferred in their respective studies that the female gender was more prone to developing fibromyalgia. The first two evaluated patients with chronic pain in DM, in a different ethnic population outside of Africa whereas studies done locally looked at FMS in HIV and the Rheumatology clinic. Females commonly experience Rheumatic complication and the exact aetiopathogenesis remains obscure, however, it has been postulated that Estrogen could play a significant role in pain perception. [79]

Of note, women with chronic pain from fibromyalgia are at an augmented risk for metabolic syndrome, which may have association with relatively increased NE levels in conjunction with reduced epinephrine and cortisol release [84]

The mean HBA1c for patients with FMS was 9.6% (SD 2.9) compared to 9.3% (SD 2.5). This was however not statistically significant. (P value = 0.565). This clearly outlines that rheumatic disorders in DM are closely associated with disease duration, degree of metabolic control and presence of end-organ damage.[80][81][82] In his study, Tishler also showed a positive correlation between increased prevalence of FMS in patients with suboptimal glycemic control.(9.2±1.1% vs. 6.4±1.5%, $P<0.05$)[10]

Type of Diabetes (i.e. Type I or Type II) and medications used were not significantly associated with FMS. (P value > 0.05). Wolak et al did a study on Prevalence of Fibromyalgia in Type 2 DM and inferred that diabetic men had more pain and tender points than men in the control group, who were nondiabetic. Diabetic women, had a significantly higher prevalence of fibromyalgia than women in the control group: 23.3% versus 10.6% respectively (P = 0.043).[74]

An analysis of the medications used for treatment of patients diagnosed to have FMS comprised OGLA (21%), combination therapy (43%) and Insulin based regime (23%). Majority of our study group were on Metformin (alone or as combination) (80% of the study population). From the study by Alcocer, it was shown that a novel approach to therapy for FMS includes activation of AMPK by metformin, which leads to improved mitochondrial

function [83]. This was however not clearly reciprocated from our study findings, meaning that there are other factors leading to a high prevalence rate of FMS in our population. Compliance to medication was however not evaluated.

Other factors such as the marital status, nature of occupation and ADLs were not statistically significant ($P > 0.05$) Negative life stressors such as unemployment, or demise of spouse have been shown to increase one's risk of developing FMS. Patients with FMS are more likely to opt for early retirement due to the severity of this disabling disease. This was not clearly elucidated from our study.

5.6 Conclusion

Fibromyalgia is a pertinent problem in Diabetic patients presenting with musculoskeletal pain with a prevalence rate of 27.9%. Majority of these patients are Type 2 DM. Patients with FMS have a higher FIQR score at 51.9 compared to 25.4 for those with chronic musculoskeletal pain not having FMS. Sleep disturbance, pain, tenderness to touch were present in 100% of the patients with FMS using the FIQR questionnaire. Patients with FMS also had a higher Tender point count at 13.7. There was no association between FMS and marital status, nature of occupation and ADLs when related to the disease.

5.7 Study limitations

This was a single center study, largely recruiting patients from urban and suburban residences attending the DOPC at the KNH. Self-reporting on the severity of symptoms can be biased as patients may be highly subjective. Recall bias may be a key factor to consider as patients were meant to respond to queries that had occurred over the previous 7 days.

5.8 Recommendation

Elderly people are a growing segment in our population and Diabetes Mellitus is an age related metabolic endocrinopathy with an exponential rise expected in numbers suffering from this chronic debilitating disease. Musculoskeletal manifestations need to be evaluated and Fibromyalgia, as a clinical entity must be sought for. Consultants, senior house officers and other clinicians need to be familiar with the disease entity, tender point counts, the FIQR & SIQR, and the scoring system for Fibromyalgia syndrome. This will impact on the quality of life of patients frequently referred to as "attention seekers" or commonly termed as in local language "Hapa na Hapa"

Therapy does exist, and a careful diagnosis is essential to direct these patients in the most appropriate fashion. Rheumatologists, diabetologists, physiotherapist and psychotherapists need to be aware of this disease for effective amelioration of symptoms.

The need for larger, multicenter population based studies cannot be over-emphasized.

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BUDGET

Stationary – 10,000 Ksh

Printing – 15,000 Ksh

Research Assistants – 30,000 Ksh

Statistician – 30,000 Ksh

HbA1c – 220,000 Ksh

Total Cost – 305, 000 Ksh

APPENDICES

Appendix I: Informed Consent Form

PATIENT STUDY NUMBER -_____

Introduction

My name is Dr. Umar Abdul Jin, a finalist resident Masters in Medicine, Internal Medicine program. I am conducting a study on:

Prevalence of Fibromyalgia Syndrome in patients with Diabetes and chronic musculoskeletal pain at the Kenyatta National Hospital.

I would like to invite you to participate in this study.

Type of Research Intervention

This study entails looking at the prevalence of Fibromyalgia in patients chronic musculoskeletal with Diabetes at the KNH.

After enrollment into this study, information about your condition including the type of Diabetes, your weight, your age, your gender, the medications you are currently on and a most recent HbA1c level will be noted and filled up in this questionnaire. You will then be asked about your pain and a physical examination for pain assessment will be performed by myself. You will also be asked about other symptoms associated and how this disease affects your life in general including your activities of daily living. If found to have this condition, you will be advised on the way forward, which will include referral to a consultant Rheumatologist for further treatment.

Participation in this study

Participation in this study is voluntary and you can withdraw your participation at any time. Refusal to participate in this study will not result in any penalty or loss of rights. I assure you that the information collected will remain confidential. You can ask any other questions appertaining to assessment and treatment and this will be availed to you at any time.

Purpose of Study

We want to find the prevalence of Fibromyalgia Syndrome in Diabetics on follow up. This study will help us manage Chronic Musculoskeletal Pain better. From this study, we will also be able to make recommendations for better control of your pain symptoms.

The results of this study will be published as a book (theses) or in a Medical Journal. It will also serve as information for teaching purposes. Results will be made available to the community for better understanding of this illness.

We will inform you on the results and make these available to the healthcare giver at the Diabetes Outpatient Clinic for better follow up. We assure you that we will NOT use your name anywhere in the presentation of these results.

Cost

No added costs will be incurred to the patient.

Duration of participation

Every participant will be enrolled only once but the study will take place over a 3 month period at the Diabetic Out-patient clinic.

Risks and Benefits

While participating in this study, you will not be exposed to any risks and you will not incur any losses. Blood will be drawn from you for an HbA1c sample only. A mildly unpleasant sensation may be felt during collection of a blood sample (for a few seconds).

Participants Declaration

Just as an indication that you have agreed to participate in this study, kindly sign below,

I, _____ hereby agree to participate in this study being carried out by DR UMAR ABDUL JIN, the nature of which has been explained to me. I have understood the purpose of this study and my questions have been answered satisfactorily by Dr Umar Abdul S Jin.

Signed (Patient): _____

Signed (PI): _____

Date: _____

Whom to Contact:

If you have any queries about this study, please feel free to contact the persons underlisted now or at any time.

Dr. Umar Abdul Jin 0738 074850

Prof. Omondi Oyoo 0722 522359

Prof. C. F. Otieno 0722 752558

Dr. Marybeth Maritim 0733 729963

Dr. Nancy Ngugi 0722 788533

The Secretary

KNH/UoN Ethics and Review Committee

Tel: 2726300, Ext 44102

Appendix II: Informed Consent Form (Swahili version)

PATIENT STUDY NUMBER -_____

KUHUSU IDHINI

Mimi ni Daktari Umar Jin, na ni mwanafunzi katika Chuo Kikuu cha Nairobi. Ninatarajia kutekeleza utafiti kuhusu ugonjwa unaodhuru misuli, mifupa na viungo kwa wale wanaoathirika kwa ugonjwa wa Sukari (Diabetes)

Sababu za Kufanya Utafiti

Utafiti huo utasaidia kujua idadi ya watu ambao wameathirika na ugonjwa huo mbali na ile ya Ugonjwa wa Sukari na jinsi tutaeza kuwasaidia.

Matukio ya Utafiti itaweza kuwaelimisha wale wanaopatia huduma katika Kiliniki ya Wagonjwa wa Sukari. Hayo yataweza kuwasaidia kupata madawa ambazo zitaweza kuboresha afya na kupunguza uchungu unaosababishwa na huu ugonjwa wa misuli na mifupa.

Manufaa Ya Kuhusika

Manufaa ya huo utafiti ni kuwaelezea watu vile ugonjwa huwaathiri na kuwapa elimu wenye wanatibu hao wagonjwa katika cliniki. Mapendekezo ya utafiti huo yatasaidia kuboresha huduma wanazozipata wagonjwa hawa hasa watakapogunduliwa kuwa na uchungu au maumivu katika viungo mbali vitakavyochunguzwa.

Mbali na hayo, tutachukua kipimo cha damu, itakayotuonyesha wastani wa kiwango cha sukari kwa miezi mitatu ilopita.

Madhara Ya Kuhusika

Hakuna madhara yoyote yatakayotokana na kuhusika katika utafiti huo. Unaeza kuhisi uchungu kidogo kutokana na sindano wakati wa kutolewa damu. Uchungu huu ni sawa na ule unaosikika wakati unapotolewa damu kwa vipimo vingine. Kiwango cha damu ni mililita tatu pekee. Huo uchunguzi wa damu ni ubwete kwako wewe.

Gharama

Hakuna gharama yoyote ya ziada kwa wewe ambaye umekubali kupatiana idhini.

Idhini ya kuhusika

Kuhusika kwako katika utafiti huu ni kwa hiari yako, na unaeza kujiondoa kabla au baada ya huo utafiti. Matibabu yanayostahili yatapewa kwa watu wote wahusika na wanaokataa, hawatabaguliwa kwa njia yoyote ile.

Sahihi (Mhusika)_____ **Sahihi (Mtafiti)_____**

Tarehe _____ **Tarehe _____**

Mawasiliano:

Ijapo uko na maswali ama mapendekezo, kuwa huru na utuelezee kwa namba hizo zilizoandikwa.

Dr Umar Abdul Jin 0738 074850

Professor Omondi Oyoo

Professor C. F. Otieno

Dr Marybeth Maritim

Dr Nancy Ngugi

The Secretary

KNH/UoN Ethics and Review Committee

Tel: 2726300, Ext 44102

Appendix III: Assent Form (16-18yrs)

PATIENT STUDY NUMBER -_____

Introduction

My name is Dr. Umar Abdul Jin, a finalist resident Masters in Medicine, Internal Medicine program. I am conducting a study on:

Prevalence of Fibromyalgia Syndrome in patients with Diabetes and chronic musculoskeletal pain at the Kenyatta National Hospital.

I would like to invite you to participate in this study.

Type of Research Intervention

This study entails looking at the prevalence of Fibromyalgia in patients chronic musculoskeletal with Diabetes at the KNH.

After enrollment into this study, information about your condition including the type of Diabetes, your weight, your age, your gender, the medications you are currently on and a most recent HbA1c level will be noted and filled up in this questionnaire. You will then be asked about your pain and a physical examination for pain assessment will be performed by myself. You will also be asked about other symptoms associated and how this disease affects your life in general including your activities of daily living. If found to have this condition, you will be advised on the way forward, which will include referral to a consultant Rheumatologist for further treatment.

Participation in this study

Participation in this study is voluntary and you can withdraw your participation at any time. Refusal to participate in this study will not result in any penalty or loss of rights. I assure you that the information collected will remain confidential. You can ask any other questions appertaining to assessment and treatment and this will be availed to you at any time.

Purpose of Study

We want to find the prevalence of Fibromyalgia Syndrome in Diabetics on follow up. This study will help us manage Chronic Musculoskeletal Pain better. From this study, we will also be able to make recommendations for better control of your pain symptoms.

The results of this study will be published as a book (Theses) and in a Medical Journal. It will also serve as information for teaching purposes. Results will be made available to the community for better understanding of this illness. We will inform you on the results and make these available to the healthcare giver at the Diabetes Outpatient Clinic for better follow up.

Cost

No added costs will be incurred to the patient.

Duration of participation

Every participant will be enrolled only once but the study will take place over a 3 month period at the Diabetic Out-patient clinic.

Risks and Benefits

While participating in this study, you will not be exposed to any risks and you will not incur any losses. Blood will be drawn from you for an HbA1c sample only. A mildly unpleasant sensation may be felt during collection of a blood sample.

Voluntary participation

You do not have to be in the study if you don't wish to be. After we begin our study and you do not want to take part in it any further, it is fine. We have informed your parents/guardian about this study.

Participants Declaration

Just as an indication that you have agreed to participate in this study, kindly sign below,

I, _____ hereby agree to participate in this study being carried out by DR UMAR ABDUL JIN, the nature of which has been explained to me. I have understood the purpose of this study and my questions have been answered satisfactorily by Dr Umar Abdul S Jin.

Signed (Patient): _____

Signed (Parent/Guardian) _____ Signed (PI): _____

Date: _____ Date: _____

Whom to Contact:

If you have any queries about this study, please feel free to contact the persons underlisted now or at any time.

Dr. Umar Abdul Jin 0738 074850

Prof. Omondi Oyoo 0722 522359

Prof. C. F. Otieno 0722 752558

Dr. Marybeth Maritim 0733 729963

Dr. Nancy Ngugi 0722 788533

The Secretary

KNH/UoN Ethics and Review Committee

Tel: 2726300, Ext 44102

Appendix IV: Assent Form (16-18yrs) (Swahili Version)

PATIENT STUDY NUMBER -_____

KUHUSU IDHINI (kwa walio kati ya miaka 16 hadi 18)

Mimi ni Daktari Umar Jin, na ni mwanafunzi katika Chuo Kikuu cha Nairobi. Ninatarajia kutekeleza utafiti kuhusu ugonjwa unaodhuru misuli, mifupa na viungo kwa wale wanaoathirika kwa ugonjwa wa Sukari (Diabetes)

Sababu za Kufanya Utafiti

Utafiti huo utasaidia kujua idadi ya watu ambao wameathirika na ugonjwa huo mbali na ile ya Ugonjwa wa Sukari na jinsi tutaeza kuwasaidia.

Matukio ya Utafiti itaweza kuwaelimisha wale wanaopatia huduma katika Kiliniki ya Wagonjwa wa Sukari. Hayo yataweza kuwasaidia kupata madawa ambazo zitaweza kuboresha afya na kupunguza uchungu unaosababishwa na huu ugonjwa wa misuli na mifupa.

Manufaa Ya Kuhusika

Manufaa ya huo utafiti ni kuwaelezea watu vile ugonjwa huwaathiri na kuwapa elimu wenye wanatibu hao wagonjwa katika cliniki. Mapendekezo ya utafiti huo yatasaidia kuboresha huduma wanazozipata wagonjwa hawa hasa watakapogunduliwa kuwa na uchungu au maumivu katika viungo mbali vitakavyochunguzwa.

Mbali na hayo, tutachukua kipimo cha damu, itakayotuonyesha wastani wa kiwango cha sukari kwa miezi mitatu ilopita.

Madhara Ya Kuhusika

Hakuna madhara yoyote yatakayotokana na kuhusika katika utafiti huo. Unaeza kuhisi uchungu kidogo kutokana na sindano wakati wa kutolewa damu. Uchungu huu ni sawa na ule unaosikika wakati unapotolewa damu kwa vipimo vingine. Kiwango cha damu ni mililita tatu pekee. Huo uchunguzi wa damu ni ubwete kwako wewe.

Gharama

Hakuna gharama yoyote ya ziada kwa wewe ambaye umekubali kupatiana idhini.

Idhini ya kuhusika

Kuhusika kwako katika utafiti huu ni kwa hiari yako, na unaeza kujiondoa kabla au baada ya huo utafiti. Matibabu yanayostahili yatapewa kwa watu wote wahusika na wanaokataa, hawatabaguliwa kwa njia yoyote ile.

Tumeongea na wazazi wako juu ya huo utafiti kwa ukamilifu.

Kama uko na tashwishi wowote, ama unataka kutohusika na huo utafiti, basi ni hiari yako. Hakuna shida yoyote ambayo itatokea kama haukuhusika na huo utafiti, na tutaendelea na matibabu yako kama kawaida.

Sahihi (Mhusika) _____

Sahihi (Mzazi /Mlezi) _____ **Sahihi (Mtafiti) _____**

Tarehe _____ **tarehe _____**

Mawasiliano:

Ijapo uko na maswali ama mapendekezo, kuwa huru na utuelezee kwa namba hizo zilizoandikwa.

Dr Umar Abdul Jin 0738 074850

Professor Omondi Oyoo

Professor C. F. Otieno

Dr Marybeth Maritim

Dr Nancy Ngugi

The Secretary

KNH/UoN Ethics and Review Committee

Tel: 2726300, Ext 44102

Appendix V: Investigator's statement

Investigator's statement

I, the investigator have educated the research participant on the intention and applications of this study.

Signed: _____ date: _____

For further inquiries during the course of this study, contact the following:

Principal Investigator

Dr Umar Abdul S Jin

Mobile: +254 738 074850

Supervisors

Prof. Omondi Oyoo 0722 522359

Prof. C. F. Otieno 0722 752558

Dr. Marybeth Maritim 0733 729963

Dr. Nancy Ngugi 0722 788533

The Secretary

KNH/UoN Ethics and Review Committee

Tel: 2726300, Ext 44102

Appendix VI: Case Definitions

Chronic Musculoskeletal Pain – pain affecting muscles, bones, joints and tendon insertion points lasting 3 months or more.

Fibromyalgia – as defined by the ACR 1990 criteria, this is presence of chronic widespread pain, lasting for at least 3 months, involving all 4 quadrants of the body and the axial skeleton. This is coupled with tenderness at 11 (or more) out of 18 pre-specified tender points.

Chronic widespread pain – pain in the axial skeleton, above and below the waist, the right and left side of the body.

Chronic pain – pain persistent for more than 3 months in duration.

Fibromyalgia related symptoms – fatigue, morning stiffness, depression, memory problems, irritable bowel syndrome, non-cardiac chest pain, balance problems, sleep disturbances and increased abnormal sensitivity to the environment.

Fatigue – decreased energy or increased need for rest that is disproportionate to a recent change in activity.

Insomnia – the lack of refreshing sleep, easily arousable and difficulty in falling asleep associated with daytime somnolence, at least 3 times per week for the past three months.

Morning stiffness – stiffness of joints lasting more than an hour in the morning.

Depression – persistent sadness and/or low mood with marked loss of interest in usual daily activities.

Anxiety – excessive disproportionate worry about a number of events or activities, and this worry is pervasive and often difficult to control.

Diabetes Mellitus – an endocrine disorder characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and/or protein metabolism resulting from defects in Insulin secretion, Insulin Action or both. Has two main types, i.e. Type I and Type II.

Oral Glucose Lowering Agents – medication in tablet form that help to maintain Euglycemia in Diabetic patients. These tablets work mainly as insulin sensitizers or act as secretagogues. They include drugs such as biguanides, Meglitinides and Sulfonylureas. Newer agents include the DPP-4 inhibitors.

HbA1c – glycated hemoglobin. A diagnostic test approved by WHO and IDA for diagnosis and follow-up of patients with Diabetes. It gives an average of 8 to 12 weeks of glycemic control, independent of current physiologic state. This test can be done at any time of the day and does not require fasting.

Appendix VII: Study Proforma

PATIENTS STUDY NUMBER - _____

(a) Biodata

1. Age _____ (in years at last birthday)

2. Gender i. Male ii. Female

3. Marital status i. Single ii. Married iii. Separated iv. Widowed

4. Daily activities i. Manual labour ii. Office job iii. Non manual

5. Occupation i. Employed ii. Unemployed iii. Retired

(b) Clinical History

6. Type of Diabetes i. Type I ii. Type II iii. Other

7. HbA1c Level _____

8. Medications use
   i. insulin based regime
   ii. OGLA
   iii. Combination

9. If on OGLA, state type
   i. sulfonylureas eg Glibenclamide, glimepriride, glipizide, gliclazide
   ii. Biguanides eg metformin
   iii. Meglitinides eg Repaglinide
   iv. DPP IV inhibitors eg Saxagliptin, Sitagliptin, Vildagliptin
   v. Glitazones eg Pioglitazone

10. If on Insulin

i. Rapid-acting e.g. Lispro, Aspart
ii. Short acting e.g Regular insulin
iii. Intermediate acting e.g NPH
iv. Long Acting e.g Lantus (Glargine), Levemir (Detemir)
v. Pre-mixed e.g. Humulin 70/30, Mixtard 30, Humalog mix 25

11. Presence of Musculoskeletal Pain i. Yes ii. No

12. If Yes, duration of illness i. <3 months ii. >3 months

Is the pain present in the following quadrants of the body

i. Right upper
ii. Right lower
iii. left upper
iv. left lower
v. Axial skeleton

Satisfies the criteria for Chronic Widespread Pain i. YES ii. NO

13. Is tenderness present on the following areas (tick where appropriate)

a. Occiput at sub-occipital muscle insertion
   i. Right ii. Left

b. Low cervical, at the anterior aspect of intertransverse spaces of C5-C7
   i. Right ii. Left

c. Trapezius, at midpoint of upper border
   i. Right ii. Left

d. Supraspinatous at the origins above the scapula, spine, near medial border
   i. Right ii. Left

e. Second rib at the 2nd costochondral junction

i. Right ii. Left

f. Lateral epicondyle, 2cm distal to the epicondyles

i. Right ii. Left

g. Gluteal, upper outer quadrant of buttocks in anterior fold of muscle

i. Right ii. Left

h. Greater trochanter, posterior to the trochanteric prominence

i. Right ii. Left

i. Knee, at the medial fat pad proximal to the joint line

i. Right ii. Left

Total number of Tender Points - _____

15. Fits criteria for FMS

a. Yes, then proceeds to FIQR
b. NO, then proceeds to SIQR

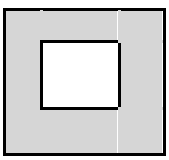
Appendix VIII: Revised Fibromyalgia Impact Questionnaire (FIQR)

PATIENT STUDY NUMBER - _____

Last Name: **First Name:** **Age:**

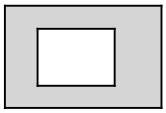
Directions: For each question, place an "**X**" in the box that best indicates how much your fibromyalgia made it difficult to do each of the following activities during the past 7 days

Brush or comb your Hair	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Walk continuously for 20 minutes	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Prepare a homemade Meal	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Vacuum, scrub or sweep floors	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Lift and carry a bag full of groceries	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Climb one flight of Stairs	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Change bed sheets	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Sit in a chair for 45 Minutes	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Go shopping for Groceries	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**

Function sub-total 

Directions: For each question, check the one box that best describes the overall impact of your fibromyalgia over the last 7 days:

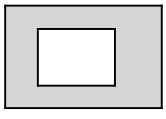
Fibromyalgia prevented me from accomplishing goals for the week	**Never** ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Always**
I was completely overwhelmed by my fibromyalgia symptoms	**Never** ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Always**



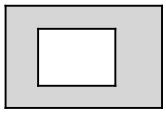
Overall Impact sub-total

Directions: For each of the following 10 questions, select the one circle that best indicates the intensity of your fibromyalgia symptoms over the past 7 days

Please rate your level of Pain	**No pain**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Unbearable pain**
Please rate your level of Energy	**Lots of energy**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**No energy**
Please rate your level of Stiffness	**No stiffness**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Severe stiffness**
Please rate the quality of your sleep	**Awoke well rested**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Awoke very tired**
Please rate your level of Depression	**No depression**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very depressed**
Please rate your level of memory problems	**Good memory**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very poor memory**
Please rate your level of Anxiety	**Not anxious**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very anxious**
Please rate your level of tenderness to touch	**No tenderness**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very tender**
Please rate your level of balance problems	**No imbalance**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Severe imbalance**
Please rate your level of sensitivity to loud noises, bright lights, odors and cold	**No sensitivity**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Extreme sensitivity**



Symptom sub-total



FIQR TOTAL SCORE

Appendix IX: Symptom Impact Questionnaire (SIQR)

PATIENT STUDY NUMBER - _____

Last Name: **First Name:** **Age:**

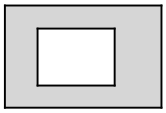
Directions: For each question, place an "**X**" in the box that best indicates how much difficulty you have experienced in doing the following activities during the past 7 days.

Brush or comb your Hair	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Walk continuously for 20 minutes	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Prepare a homemade Meal	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Vacuum, scrub or sweep floors	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Lift and carry a bag full of groceries	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Climb one flight of Stairs	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Change bed sheets	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Sit in a chair for 45 Minutes	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**
Go shopping for Groceries	**No difficulty**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very difficult**

Function Sub-total ☐

Directions: For each question, check the one box that best describes the overall impact of any medical problems over the past 7 days:

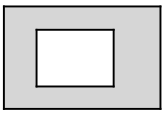
My medical problems prevented me accomplishing goals for week	**Never** ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Always**
I was completely overwhelmed by my medical problems	**Never** ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ **Always**



Sub-total

Directions: For each of the following 10 questions, select the one box that best indicates the intensity, over the past 7 days, of the following common symptoms.

Please rate your level of Pain	**No pain**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Unbearable pain**
Please rate your level of Energy	**Lots of energy**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**No energy**
Please rate your level of Stiffness	**No stiffness**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Severe stiffness**
Please rate the quality of your sleep	**Awoke well rested**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Awoke very tired**
Please rate your level of Depression	**No depression**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very depressed**
Please rate your level of memory problems	**Good memory**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very poor memory**
Please rate your level of Anxiety	**Not anxious**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very anxious**
Please rate your level of tenderness to touch	**No tenderness**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Very tender**
Please rate your level of balance problems	**No imbalance**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Severe imbalance**
Please rate your level of sensitivity to loud noises, bright lights, odors and cold	**No sensitivity**	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	**Extreme sensitivity**

Sub-total 

SIQR TOTAL