EVALUATING DIFFERENT TREATMENT METHODS FOR OSTEOPOROSIS USING FUZZY PROMETHEE

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By
SHARMAIN DUBE

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Biomedical Engineering

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name:

Signature:

Date

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Abstract

Osteoporosis is a progressive, degenerative skeletal disease mainly characterized by low bone mass, degeneration of bone tissue, and disruption of bone microarchitecture. It occurs when the body's bone turnover is very, meaning either the body is producing too little bone or losing too much bone (resorption), which can lead to weakened bones and an increased risk of fractures. Osteoporosis is a silent disease which usually shows no signs, and so the bone loss occurs gradually until the first fracture occurs. It affects people globally regardless of age, gender and ethnicity, although it is more common in Caucasians (white people), the elderly and women. There are two types of osteoporosis: primary and secondary. Primary osteoporosis, which includes postmenopausal (type 1) and senile (type 2) osteoporosis, is the most frequent form of the condition. Women between the ages of 50 and 70 are more likely to develop postmenopausal osteoporosis, which is linked to increased bone resorption caused by a gradual reduction of estrogen and androgen. Senile osteoporosis is characterized by the slow loss of bone due to the aging of stem-cell precursors. It affects both men and women over the age of 70, but it is twice as common in women. Secondary osteoporosis is defined as bone loss caused by certain medical conditions. Osteoporosis is a disorder that is not totally reversible, therefore a variety of treatment options are utilized to control it. In this study six alternative treatments were evaluated, that are used to treat osteoporosis including; bisphosphonates, fluoride, hormones, antibodies, calcitonin and hormonereplacement therapy. The Fuzzy PROMETHEE multi-criteria decision-making method was the tool utilized for the analysis ranking of the alternatives. From results of the analysis, it was found that bisphosphonates are the best alternative having the highest net flow of 0,0083,while hormone replacement therapy is the least preferred treatment option with the lost et flow of -0,0125. This ranking is based on the weights, criteria and parameters used for the analysis.

Keywords: Osteoporosis, treatment alternatives, Fuzzy PROMETHEE, MCDA

Ozet

Osteoporoz, esas olarak düşük kemik kütlesi, kemik dokusunun dejenerasyonu ve kemik mikro mimarisinin bozulması ile karakterize ilerleyici, dejeneratif bir iskelet hastalığıdır. Vücudun kemik döngüsü çok yüksek olduğunda ortaya çıkar, yani vücut çok az kemik üretiyor veya çok fazla kemik kaybediyor (rezorpsiyon), bu da kemiklerin zayıflamasına ve kırık riskinin artmasına neden olabilir. Osteoporoz genellikle hiçbir belirti göstermeyen sessiz bir hastalıktır ve bu nedenle ilk kırık oluşana kadar kemik kaybı kademeli olarak gerçekleşir. Kafkasyalılarda (beyaz insanlar), yaşlılarda ve kadınlarda daha yaygın olmasına rağmen, yaş, cinsiyet ve etnik kökene bakılmaksızın küresel olarak insanları etkiler. İki tip osteoporoz vardır: birincil ve ikincil. Postmenopozal (tip 1) ve senil (tip 2) osteoporozu içeren primer osteoporoz, durumun en sık görülen şeklidir. 50 ila 70 yaş arasındaki kadınların, östrojen ve androjenin kademeli olarak azalmasının neden olduğu artan kemik rezorpsiyonu ile bağlantılı olan postmenopozal osteoporoz geliştirme olasılığı daha yüksektir. Senil osteoporoz, kök hücre öncüllerinin yaşlanması nedeniyle yavaş kemik kaybı ile karakterizedir. 70 yaş üstü hem erkekleri hem de kadınları etkiler, ancak kadınlarda iki kat daha sık görülür. Sekonder osteoporoz, belirli tıbbi durumların neden olduğu kemik kaybı olarak tanımlanır. Osteoporoz, tamamen geri dönüşü olmayan bir hastalıktır, bu nedenle onu kontrol etmek için çeşitli tedavi seçenekleri kullanılmaktadır. Bu çalışmada osteoporoz tedavisinde kullanılan altı alternatif tedavi değerlendirildi; bifosfonatlar, florür, hormonlar, antikorlar, kalsitonin ve hormon replasman tedavisi. Bulanık PROMETHEE çok kriterli karar verme yöntemi, alternatiflerin analiz sıralamasında kullanılan araçtır. Analiz sonuçlarından, 0,0083 ile en yüksek net akışa sahip bifosfonatların en iyi alternatif olduğu, kayıp et akışı -0,0125 ile hormon replasman tedavisinin en az tercih edilen tedavi seçeneği olduğu bulundu. Bu sıralama, analiz için kullanılan ağırlıklara, kriterlere ve parametrelere dayanmaktadır.

Anahtar Kelimeler: Osteoporoz, tedavi alternatifleri, Fuzzy PROMETHEE, MCDA

CHAPTER 1

INTRODUCTION

1.0 Introduction

This serves as an introductory chapter to the research, providing insight into the whole study through background information, problem statement, research objectives and research questions, research justification and a snippet of a review of related literature as well as provision of the structure the thesis will follow.

1.1. Background of the Study

Osteoporosis is a disease that presents itself in fractures when patients fall due to the fragility of their bones furthermore the prevalence of osteoporosis is related to age though women suffer more bone loss as they age and are thus most affected. Citing it a silent disease due to the absence of symptoms before a fracture occurs, (Ferdous, Afasana, Qureshi, & Rouf, 2015) defines osteoporosis disease as "*a progressive systemic skeletal disease characterised by reduced bone mass/ or density and micro-architectural deterioration of bone tissue.*" It is thus a condition affecting bone tissue, making it deteriorate gradually as bone density reduces. Further description offered by (Allen, et al., 2017) , it is as a skeletal disorder resulting from deterioration of bone quality and compromised bone strength hence affecting mobility and resulting in mortalities.

In diagnosis, following a fracture, bone density, bone mass or bone fragility according to (Kaise Permanente, 2019) and (NICE, 2011) is measured using a T-score derived from standard deviation (SD) within a population measured including young and healthy participants, and for osteoporosis a Normal T- score is ≥ -1, while severe osteoporosis was indicated by a T-score 2.5SD or more below, plus a fracture.

(Allen, et al., 2017) state that osteoporosis consequently occurs as people experience bone loss as in adulthood there is no longer bone formation that happens in childhood and growth. They suggest that populations in vulnerable societies need to be regularly screened for osteoporosis through bone mineral density assessments before symptoms can surface, to facilitate prompt interventions, and additionally, prone populations need preventative interventions to curb the onset of the bone disorders which become costly to manage once fragility fractures are experienced. Screening serves as the best approach as it is more of a natural condition that everyone loses bone due to aging, and it occurs gradually and unnoticed with discomfort only experienced when the bone eventually breaks after degeneration into osteoporosis (American Academy of Orthopaedic Surgeons(AAOS), 2018). The two common types of osteoporosis are postmenopausal (type 1), and senile (type 2) osteoporosis. The important factor to note is that anyone can be affected by osteoporosis but the most at risk have been established as the Asian and Caucasian people (Ferdous, Afasana, Qureshi, & Rouf, 2015) and (American Academy of Orthopaedic Surgeons(AAOS), 2018).

It needs to be noted that other causes of osteoporosis are lifestyle related (American Academy of Orthopaedic Surgeons(AAOS), 2018) and (Ferdous, Afasana, Qureshi, & Rouf, 2015) and result from habits that weaken the bones, such as smoking, lack of exercise, excessive alcohol, among others. Some medications such as steroids are also indicated as risk factors, hence the important role that lifestyle management plays in preserving bone quality as people age. The (American Academy of Orthopaedic Surgeons(AAOS), 2018) states an alarming but important factor that has a reflection on the adversity of osteoporosis, the fact that the effects could not be reversed but rather intervention just served to prevent further loss or weakening of remaining bone tissue. Treatment had however various options with healthy lifestyles, exercise and diet management as key.

The background that osteoporosis is a silent diseases (asymptomatic), its treatment usually cannot be separated from investigations which according to (Ferdous, Afasana, Qureshi, & Rouf, 2015), include the bone mass measurement (DEXA scanning) for diagnosis or ultrasound bone measurement after a fragility fracture has occurred. Further (Ferdous, Afasana, Qureshi, & Rouf, 2015) referring to the recommendations of United Stated Report

on Osteoporosis (2004) cited a 3 level pyramidal approach in Figure 1.1. physicians had to adopt in treating osteoporosis.

At the base of the pyramid is a preventative stage citing fall prevention, which can be can be through exercises to build muscle and bearing weights regularly as physical therapy preventative of falls as well as osteoporosis. Since bone quality deterioration can be caused by lack of vitamin D and Calcium, daily doses of supplements is recommended over and above the diet(Kaise Permanente, 2019).

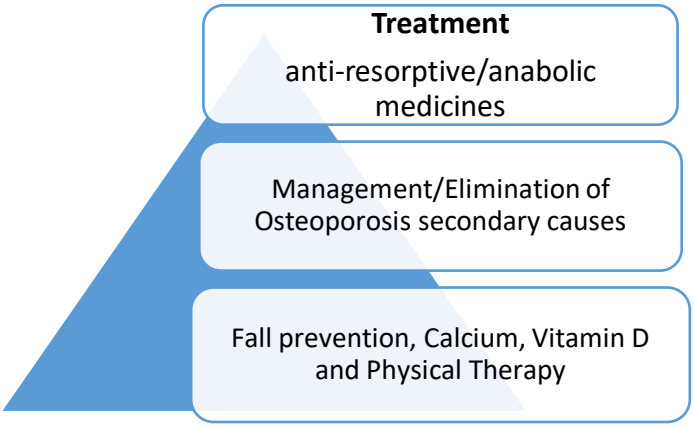

Figure 2.1 Osteoporosis Interventions (Ferdous et. al 2015)

Figure 1.1 shows the interventions or classes of treatments for osteoporosis.

As an extension, the second stage for the management and elimination of secondary cause of osteoporosis involves encouraging cessation of smoking in adults as well as limiting alcohol intake as well as maintaining a balanced diet. (Kaise Permanente, 2019) and (Ferdous et. al., 2015)

The treatment approach since the condition is not reversible , involves reducing the risk factors for preventing fractures through medication and lifestyle changes. However of

importance are considerations on the effects of the treatment options. Some treatments may have side effects hence requiring additional interventions to reduce the side effects or patient tolerance of the medications (Kaise Permanente, 2019). Of note is also the financial impact the various treatment or therapy interventions may have on the patients or their caregivers hence the need for an evaluation of the implications of the various treatment methods.

1.2. Statement of the Problem

The female gender is given by (Ferdous et. al., 2015) as the top risk factor for reduced bone mass density, among an array of other risk factors. Osteoporosis has affected women for many centuries, some of the proof being seen in Egyptian mummies from about 4000 years ago. With increasing risks and higher susceptibility to osteoporosis being on women there has been increased research in understanding the disease and treatment options to reduce or regulate the disease. Further to the concern is that the onset of fractures (osteoporotic fractures) due to bone fragility caused by osteoporosis significantly increases the chances of additional fractures hence call for serious interventions in treatment after onset, though prevention is ideally more critical. Awareness through an evaluation of treatment options is an area that is not adequately covered in research though facts on the causes, symptoms and treatments are vastly covered and well researched, hence the need for this evaluation thesis. Research provides information on a number of treatment that have been developed to manage osteoporosis which include; Change of lifestyle, taking supplement of calcium and vitamin D and harmacological treatments (bisphosphates, artificial hormones, antibodies or biologic drugs, hormone replacement therapy (HRT), calcitonin and sodium fluoride, etc..)

This thesis seeks to review the various treatment methods for osteoporosis available on the basis of the variables; dosage, cost, time, side effects, advantages and disadvantages.

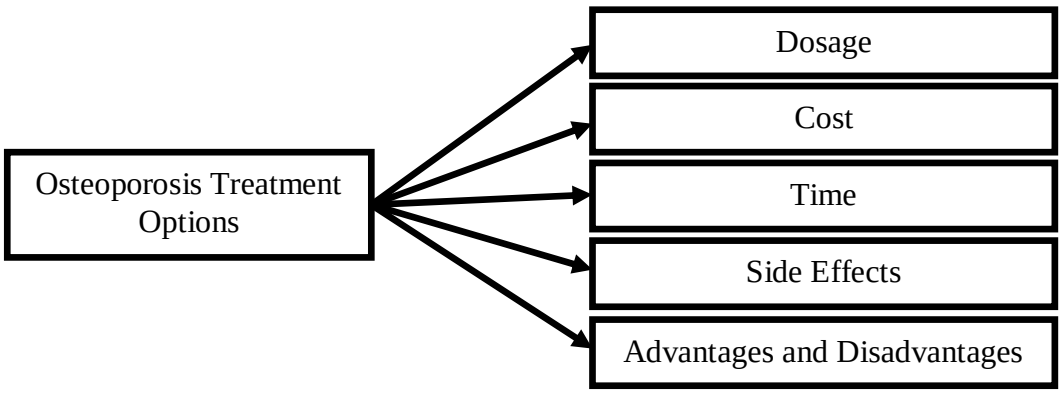

Figure 1.2 Criteria for osteoporosis treatment options

Figure 1.2 shows the criteria used to analyse and evaluate the osteoporosis treatment options. Dosage will refer to the quantity of medication to be administered, cost will refer to the cost of the drugs or medications prescribed, time will refer to the length of the treatment period, the side effects will refer to the adverse effects of the drugs on the patients, while the advantages and disadvantages will seek to weigh the positive and negative aspects of each medical choice to be able to select the best for a scenario.

Table 1.1 Treatment options for osteoporosis (Dobbs MB, et. a1., 999)

Classes of osteoporosis treatment	**Name of treatment**
Fluoride	Sodium fluoride
Bisphosphonates	Alendronate Risendronate Ibanndronate Zoledronic
Calcitonin	Calcitonin
Antibodies	Denosumab Romosozumab
Hormones	Raloxifene Teriparatide Abaloparatide
Hormone Replacement Therapy	Estrogen and Bazedoxifene)

Table 1.1 shows the osteoporosis treatment methods that will be put under evaluation are as well as examples of each option.

1.3. Research Objectives

The main aim of this study is to evaluate the different types of treatments for osteoporosis, with the sub objectives being:

1. To raise awareness about osteoporosis.
2. To evaluate the different types of treatments for osteoporosis by researching and competitively comparing the dosages, costs, usage, advantages and side effects of the treatment methods

1.4. Methodology

The study aims to evaluate the different types of treatments used for osteoporosis. To acquire the appropriate and necessary data, the use of different online databases/publications such as journals, articles, conferences and book chapters will be the main drive of the study. The data will then be inserted into excel which visibly gives an idea of how effective each treatment method is and it also shows the strengths and weaknesses of teach treatment by comparing factors such as cost, dosage, time, side effects and advantages. The analysis of the data is the last part of the research before reaching a conclusion. The data is first converted into numerical data comprising of fuzzy data on which the Fuzzy PROMETHEE method will be used to further evaluate the data from which to draw a conclusion. The Fuzzy PROMETHEE method will be used in the decision making and from there the evaluation can be concluded.

1.5. Significance of the Study

While contributing to literature, this thesis will save as an informative and awareness tool on the prevalent condition of osteoporosis as an initial basic outcome. Additionally, it will aid in bridging the research gap of treatment evaluation in the medical research arena for osteoporosis. The evaluation criteria or variables in treatment interventions are most critical

for the patient through the decision making of the physician hence the importance of the research to the medical fraternity in their prescription decisions for osteoporosis patients as it is of paramount importance to consider dosage, cost, time, side effects, advantages and disadvantages of treatment recommendations. Effective and cost-effective treatment will thus be administered by considering the thesis recommendations hence achievement of cost and lifesaving implications

1.6. Organisation of the Study

*The thesis consists **of 6 c**hapters with the first Chapter being the introduction. The consecutive Chapters will be structured as follows:*

Chapter 2 Literature Review

Previous studies have been conducted on the research area and this section will review literature with the aim of informing this research and providing information on previous findings and conclusions that are critical to consider and form a basis for the evaluation. Various research articles, Reports, Books among other secondary sources will form the guiding structure for the thesis.

Chapter 3 Research Methodology

For a research to be systematic hence valid, it has to follow a structured method of execution and this chapter will seek to outline the research methodology adopted for the research as well as justify the same through validity, reliability and ethical tests on the approaches , data collection and data analysis tools applied.

Chapter 4 Results and Data Analysis

This chapter will provide a presentation of results and analysis of the same against the study objectives to provide an overall picture of study findings on the evaluated osteoporosis treatment methods.

Chapter 5 Results Discussion

This chapter will evaluate the study findings based on research criteria or variables from the primary findings and analysis

Chapter 6 Conclusions and Recommendations

Conclusions will be derived from the results discussion and recommendations offered based on the assessment of these.

1.7. Conclusion

This chapter provided an introduction and background to the thesis. The chapter included the problem statement, the research objectives, the significance of the study, methodology and study structure. These sections gave an elaboration of highlight areas in the evaluation of osteoporosis treatment methods.

CHAPTER 2

LITERATURE REVIEW

2.0. Introduction

The first chapter was introductory to the research. This chapter presents a review of literature on the history of osteoporosis diagnosis and treatment and the present treatment methods available. A review of literature informs the research on background information and current developments on the topic under evaluation.

2.1. The History of Osteoporosis

Studies show gradual developments in the identification of osteoporosis, the subsequent diagnostic and treatment methods development. (Stride, Patel, & Kingston, 2013) state that the initial indications on the oestrogen levels effect on bone density were first discovered in pegion studies by Preston Kyes (1875-1945) and Potter 1934. These osteoporosis discoveries were advanced by Fuller Albright (1900-1969) who together with his colleagues studied weakened bone and established that it had osteoblasts deficiency and that weakened bones were more prevalent in postmenopausal women with susceptibility of those who had experienced early menopause. Stride et. al. (2013) states that the first treatment prescribed by Albright was oestrogen which worked by stopping further damage to the bone and that the causes of osteoporosis recognised at this stage, were mainly; use of proton pump inhibitors, gastric hypoacidity and Cushing's disease.

In 1955, Alexander Cooke (1899-1999) also noting lack of osteoblasts for replacing osteoclastic erosion, came up with a definition that osteoporosis was " *a disease of inadequate bone formation from lack of 'matrix'".* Cooke prescribed androgens, which was later eliminated because of adverse side effects leading to subsequent trials with calcitonin, fluoride, anabolic steroids which also proved to have side effects too. In the 1960s, discoveries by Hebert Andre Fleish (1933-2007) brought light to osteoporosis treatment as discovery of devices for bone loss detection started and bone mass density measuring and diagnosis machines started. These have developed to the current studies into intracellular biochemical pathophysiology and biological therapies(Stride et. al., 2013)

The Crisis of osteoporosis treatment over the years between 1996 and 2012 is depicted in a diagram figure 1 presented in (Lems & Raterman, 2017). Figure 2.1. shows the high prevalence captured in women compared to men. There was a sharp rise in osteoporosis from 1999 to 2008 and a decline thereon.

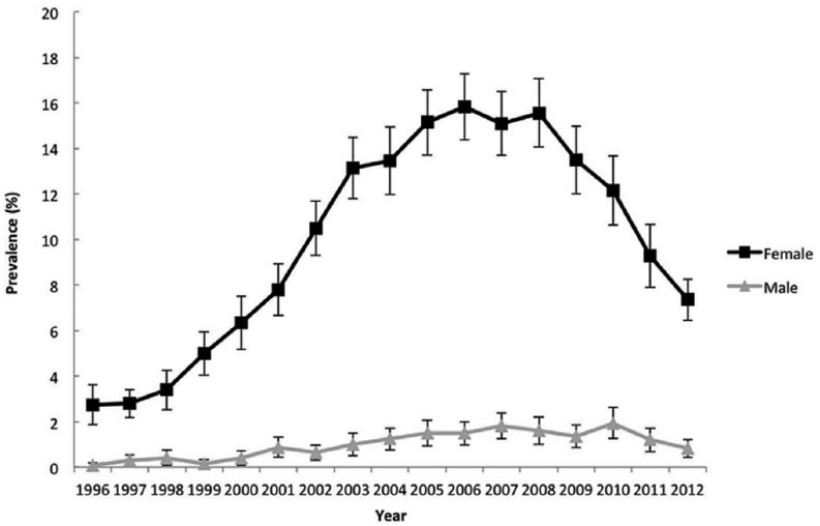

Figure 2.1. *Prevalence of Osteoporosis in Women Compared to Men (Lems & Raterman, 2017, p300)*

Figure 2.1 shows the prevalence of Osteoporosis in Women Compared to Men.

Lorentzon & Cummings (2015) in a rather peculiar perspective, explains the prevalence of osteoporosis in recent years as based on the commonness of people in advanced elderly ages resulting from the trend towards longevity translating in the increased population of older persons with disease conditions normally affected by osteoporosis. The major concern is that the increased hip and vertebral fractures consequence in morbidity and mortality as well as substantial healthcare costs.

While emphasising that what stood as a chief intervention was finding fracture preventative measures, (Lems & Raterman, 2017) cited that the period depicted on the Osteoporosis treatment crisis diagram was characterised by presence of; fracture lowering antiresorptive drugs (bisphosphonates and genosurnab), prevalence level 11-14; new bone building anabolic drugs (teripatide), level 15; and phase 3, level 16-19 involved the use of abaloparatide and monoclonal antibodies. The period of 2008-2009 was coupled with declining prescription of bisphosphonate (anti osteoporotic drugs) in the USA and United Kingdom.

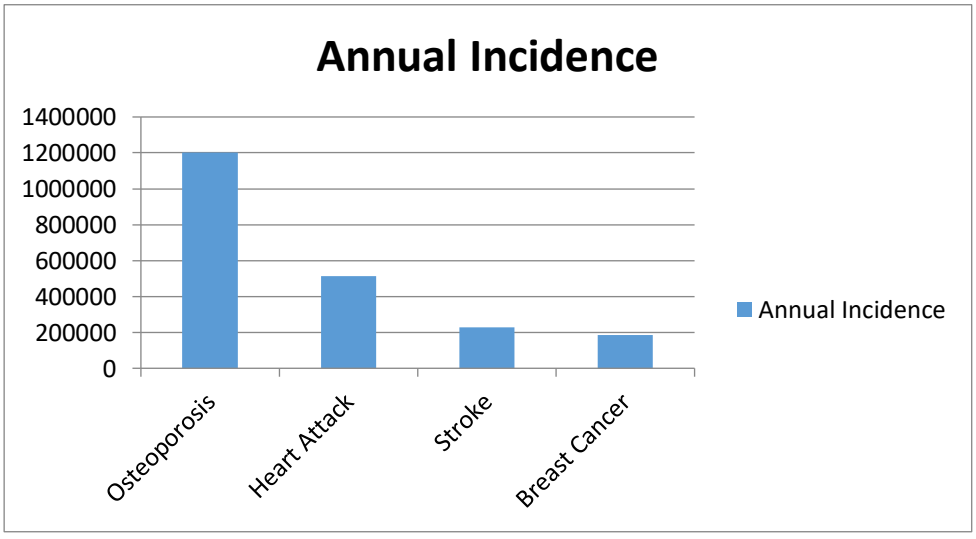

Figure 2.2. Comparison of Osteoporosis Fractures in Women with other Diseases (National Osteoporosis Foundation (2002) (South-Paul, 2014))

Figure 2.2 shows annual incidence of osteoporosis fractures compared to other diseases (heart attack, stroke and breast cancer)

The estimate of women who suffer from osteoporotic fractures in their lifetime is approximated at 50%, a case which has to be viewed with much concern in the health sector as fragility fractures result in reduction of quality of life, due to disability, frequent hospitalisation and mortality risks. This further carries with it financial burden in terms of treatment and lifestyle adjustments. To improve bon quality, there are anti osteoporotic drugs available for use, however the preventative measure is to ensure the build up of peak bone quality in young individual's and the use of bone imaging techniques such as dual energy X-ray absorptiomery (DXA) , vertebral fracture assessment (VFA) among other bone quality measuring techniques, as well as the use of nonmedical treatment options and surgical techniques of fracture healing. (Lems & Raterman, 2017)

2.2. Nature of Osteoporosis

Literature offers descriptions on the nature of osteoporosis and summarily, osteoporosis is a highly problematic disease because of its asymptomatic nature, it is a disease that affects the bones, and manifests as fractures normally affecting, the spine, the pelvis, wrists, hip with severity that necessitates hospitalisation (Ferdous, Afasana, Qureshi, & Rouf, 2015), (Kaise Permanente, 2019) and (Tu, et al., 2018) as most patients become bedridden. The bone structure weakens and gets prone to fracture due to various conditions on the bone itself (Tu, et al., 2018); impaired bone microarchitecture/mineralisation, low bone mineral density (BMD) or decrease of bone strength. The high prevalence of osteoporosis makes it a topical and concern rising phenomenon as a staggering 10-14 million people is the projected population at risk of contracting it by 2030 in the United States alone according to (Tu, et al., 2018). Concerning its dominance, (Kaise Permanente, 2019) cites a one in five diagnosis on men, a proposition that women accounted for the greater proportion affected by osteoporosis with prevalence mostly in the older population.

Despite the depressing nature of osteoporosis, as it presents itself in both fatal and nonfatal falls, while emphasising the importance of BMD screening and treatment, (Lim & Bolster, 2015) highlight the preventable nature of osteoporosis through diet management, lifestyle management and interventions for fall prevention.

The impact of osteoporosis stemmed from the fact that osteoporosis was an irreversible condition had adverse effects with impact in the form of loss of lives, descent of the quality of life, incessant economic burden emanating from treatment costs, further, upkeep costs and costs associated with managing the consequences of the disease (American Academy of Orthopaedic Surgeons(AAOS), 2018).

Christodoulou & Cooper (2003) highlighted that for elderly women who had hip fractures, mortality rate was 20% and mortality rate was worse in vertebral fractures, however mobility for survivors remained impaired for the majority. When patients experience multiple fractures on the vertebra, this results in effects in the form of chronic acute back aches, progressive height loss, physical activity limitation and progressive kyphosis, This further culminates into depression and low self esteem due to functional incapability, The fear and anxiety over further fractures as well as pain, induces limitation of physical activity which on its own has the impact of worsening the risk of further fractures as well as osteoporosis itself. (Christodoulou & Cooper, 2003).

2.2.1. The Bones (Pathophysiology)

Osteoporosis is a condition that affects the bones. The structure of the body is provided by bones, and they also provide protective structure for body organs (Tu, et al., 2018). Further, for development and stability, bones store minerals such as phosphorus and calcium. Bone development occurs from birth and reaches a peak at around 30 years of which, at which stage individual's acquired bone strength is dependent on various factors, genetics, lifestyle, nutrition, fitness, diseases or medication which impact on BMD (Dobbs, Buckwalter, et. Al)

(Tu, et al., 2018) state that during this development stage bones go through a process of maintenance and repair through osteoclasts and osteoblasts respectively, to build their mechanical strength, such that any imbalance of the two processes on bone resorption results in bone weakening seen as osteoporosis. Bone function and structure is also regulated by hormones, oestrogen and testosterone ((NICE) National Institute for Health and Clinical Excellence, 2011), which play the role of inhibiting bone breakdown. Further on, another important hormone for bone formation which supports by increasing osteoblasts, is

Parathyroid hormone (PHT), whose intervention is by regulating calcium homeostasis (Das & Crockett, 2013).

2.2.2. Causes of Osteoporosis (ETIOLOGY)

The causative factors of osteoporosis are categorised into primary and secondary (Tu, et al., 2018). This study specifically studied the women impact of osteoporosis, a cluster which primarily is affected by osteoporosis on the basis of age (resulting in the deterioration of the bone component called trabeculae) and sex hormone deficiency (bone loss resulting from the reduced production of oestrogen after menopause). These two are primary factors.

The secondary causes of osteoporosis are disease and medications and differed between genders. The medications related accelerators of bone loss are related to hormones imbalance as well as minerals imbalance (Calcium Na Vitamin D), for example rheumatoid arthritis, Cushing's syndrome, diseases requiring the administration of glucorticoid therapy that commonly induced and accelerated osteoporosis (NIH, 2015). The fast rate at which bone deterioration occurs after the glucorticoids calls for the need for treatment management and prevent the induction of osteoporosis through glucorticoids (Tu, et al., 2018). (Tannenbaum, Clark, & Schwartzman, 2002) cited in (Tu, et al., 2018) concurred with the prevalence of osteoporosis attributable to secondary causes (32.4%) and observed the notable glucocorticoid induced osteoporosis, adding that in women it was also attributable to, calcium malabsorption, hypercalcium, vitamin D deficiency, hyperparathyroidism, hyperthyroidism, hypocalciuric and hypercalcemia.

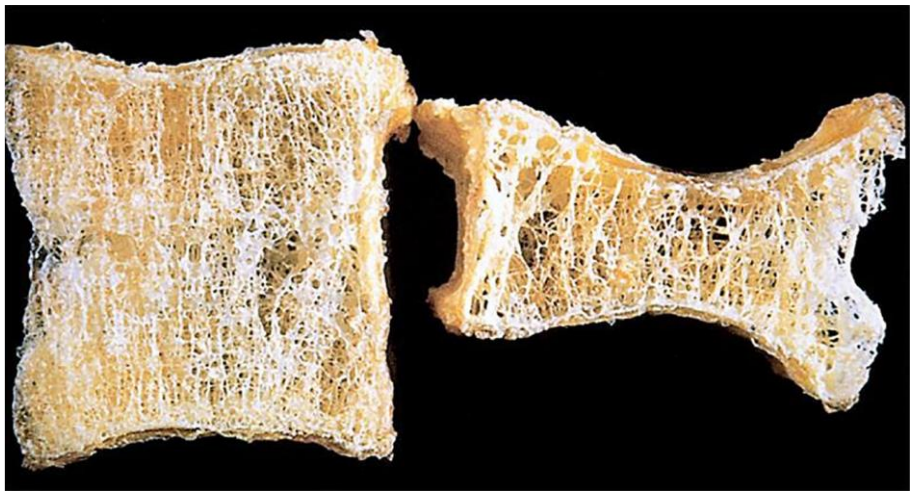

Figure 2.3 Compressed Osteoporotic Vertebra with reduced trabecular number, connectivity and density ((Lorentzon & Cummings, 2015)

Figure 2.3 shows a compressed osteoporotic vertebra (right), with reduced trabecular number, connectivity and density.

Since osteoporosis manifests in fractures, (Lems & Raterman, 2017) suggested risk factors for osteoporotic fracture as; low body weight, which inhibits development of peak bone mass, bone mineral density, alcohol consumption, cigarette smoking, nutrition deficiencies(calcium and vitamin D), sex hormone deficiency, and physical inactivity. Other osteoporosis causes (Christodoulou & Cooper, 2003) are given as;

- Malignant disease (e.g. myeloma and lymphoma)
- Endocrine Disorders (e.g. hypoparathyroidism, hypogonadism and Cushing's syndrome)
- Drugs/ medications (e.g. heparin and corticosteroids)
- Genetic factors (peak bone mass is dependent on genetic alignment hence hereditary,
- Diverse disorders (e.g. chronic renal failure and connective tissue diseases

2.2.3. Bone Affecting Physiological Events in Women Lives

The bone structure/ density is affected by oestrogen fluctuations which are prevalent in women more than in man because of physiological events such as menopause, menarche, pregnancy and lactation, events bring about hormonal changes that affect none density.

(Stride, Patel, & Kingston, 2013). These factors are opined to relate to the prevalence of osteoporosis, since women in historical times even women with elite backgrounds and capable of providing well balanced diet, those that did engage in bone strengthening physical work and those that were exposed to a fair amount of sunlight still were affected by osteoporosis.

Historical Evidence indicates teenage onset of productivity, which occurred before full BMD had been achieved hence weakening the bones coupled with that it was during the hormonal imbalance phase, short periods of breaks between pregnancies and lactation which did not provide a recovery phase for weakened bones until the peak bone development phase was reached hence the compromised bone quality of women leading to osteoporosis. This was then followed by the evidence of early menarche and menopause evidenced during historical times compare to current times where the normal onset was above 50 years of age. This explained the yester millennia prevalence of osteoporosis among women compared to current times. The effects of lactation and the reproductive span in women was an important consideration to explain osteoporosis and conclusions reached by (Stride et. al., 2013), (Tanenbaum et. al., 2002)

- Osteoporosis has been a common disease for at least five millennia in spite of reduced longevity and increased activity in the past, even in societies where food was abundant.
- Throughout recorded history post-menopausal women have always lost bone mass at a faster rate than age-matched males.
- Lactation reduces bone mass, but this is usually replaced on weaning. The effect of prolonged lactation for multiple pregnancies with only brief periods not lactating, as was more common in the past, along with the impact of low nutrition is unknown, but available evidence suggests this may cause lower bone mass.
- Increased parity up to five pregnancies in well-nourished contemporary women appears to increase bone density. Current evidence suggests that an initial pregnancy in adolescence, as was common in the past, leads to a persisting reduction of BMD. This appears to be a major factor in the causation of osteoporosis in past millennia.

- A shorter reproductive lifespan between menarche and menopause is associated with a reduced bone mass. In the past, menarche was later and menopause usually occurred earlier than today. This appears to be a second major factor responsible for osteoporosis in ancient female skeletons.

2.3. Osteoporosis Diagnosis

(Das & Crockett, 2013) stated the varying approaches among caregivers, some recommending screening as early as 50 years of age in women depending on the risk factors present, while some recommend screening at the age of 65 or older, to enable early detection and decrease fracture risk. After considering the risk factors applying on a patient, the health practitioner has to make a decision to conduct a DXA scan which through an X-ray measures BMD at the spine, hips and wrists, depending on the assessment results (Consumer ReportsL Best Buy Drugs, 2016). Only a T-Score that is extremely low -2.5 SD or less qualifies the BMD as severe and called Osteoporosis. Diagnosis for osteoporosis on the other hand involves the assessment of clinical risk factors and (Lash et. al., 2013) tabulated the risk categories concerned.

2.3.1. Categories of Osteoporosis and Osteoporosis Fracture Clinical Risk

Table 2.1 Osteoporosis Categories and Fracture Clinical Risks (Lash et. al., 2013)

Extremely High Risk	High Risk
Prior osteoporotic fracture Use of Glucorticosteroid for over 6 months Pre/ post Solid organ Transplant	Use of Glucorticosteroid for over 3 months Women above 65 years Postmenopausal women who have experienced at least one of the following; - Caucasian or Asian - Low impact fracture - Hip, spine and wrist fracture in family history - Smoker

	- Rheumatoid Arthritis - BMI < 20 - Falling risk factors (Poor sight, poor cognition, age, decreased strength etc.
Moderate Risk	
Hormonal Conditions - Hypogonadism - Late menarche (> 15years) - Early Menopause (< 45 years) - Premenopausal amenorrhoea - Cushing's syndrome - Hyperparathyroidism - Thyrotoxicosis Gastrointestinal and nutritional factors - Gastrectomy - Low Gastric acids - Impaired absorption Heavy use of alcohol Medications Family History of Osteoporosis	Other significant associations - Chronic Kidney Disease - Severe Liver disease - Type 1 Diabetes Mellitus - Multiple myeloma - Long term immobilisation - Prior smoking Other possible Associations - Addison's disease - Sarcoidosis - Nephrolithiasis - Depression - Multiple Sclerosis - Thalassemia - Amyloidosis

Table 2.1 shows the categories of fracture risks and the factors affecting those risks, such as age, pre-existing conditions, life style, gender as well as ethnicity.

Concerning osteoporosis medical investigations, (Christodoulou & Cooper, 2003) highlighted that women where the main targets as it was in women that as early as the 30s that bone loss began to occur in the femoral neck. Since the determinant of bone strength was bone mass, the widely used method for diagnosis of osteoporosis is indicated as the dual energy X Ray absorptiometry as well as some investigations for diagnosis that involved the assessment of bone mass though according to (Allen, et al., 2017) there were factors that affected the measurement of Bone Mass Density (BMD) in elderly patients, such as the presence of extra skeletal calcification, vertebral deformity, scoliosis and osteophytes.

2.3.2. Bone Mass Assessment Methods

- DXA Scan

It can assess bone mass at both axial and appendicular sites, high reproducibility and uses very low radiation doses

- Quantitative Computed Tomography

Allows the measurement of cortical and cancellous bone in the peripheral skeleton or spine though the equipment is expensive and uses relatively high radiation doses.

- Broadband Ultrasonic Velocity and attenuation of os calcis, tibia or patella

This method is radiation free and portable hence inexpensive, however, besides poor reproducibility, it fails to diagnose osteoporosis in the characteristics it is defined by the World Health Organisation.

(Allen, et al., 2017) gave emphasis with regards diagnosis, that at present , population based screening using DXA was not justifiable , as such patients with strong clinical risk factors only had to be assessed and also considering measuring only those patients for which the results would influence patient management. Moreover, bone densitometry had to be used only in patients with radiological evidence of osteopenia or vertebral deformity and those with a history of fragility fracture at the wrist, hip, or spine. Also, bone densitometry had to be used in the monitoring of therapy of osteoporosis, for example, in patients on bisphosphonates (Christodoulou & Cooper, 2003).

2.4. Osteoporosis Prevention

Factors that enhance peak bone mass optimisation to prevent fractures are the main components of prevention and treatment hence the need for an understanding of the components that influence peak bone mass during skeletal growth and body as it is critical for the later life as protection against fractures. Unfortunately, it is unclear what the optimal strategies are to build up a strong skeleton in the first decades of life, though genetic factors were established to play a great role in bone mass development as well as another nonmodifiable factor; sex, as males tend to have higher peak bone mass compared to females, Modifiable factors that influence peak bone mass include mechanical stress on the

bone, physical activity dietary intake of vitamin D and Calcium and body composition in terms of health status. (Lems & Raterman, 2017)

Before considering the treatment of osteoporosis, it is thus important to consider the means of preventing the disease as a first level management approach. At the base of the pyramid by (Kaise Permanente, 2019), is a preventative stage citing fall prevention, which can be through exercises to build muscle and bearing weights regularly as physical therapy preventative of falls. A lifelong preventative approach is most ideal (Kaise Permanente, 2019), through weight bearing exercises and intake of appropriate vitamin D and Calcium. Since bone quality deterioration can be caused by lack of vitamin D and Calcium, daily doses of supplements is recommended over and above the diet to prevent osteoporosis. In support of the preventative approach, (Consumer ReportsL Best Buy Drugs, 2016) vouches on the scarce evidence on the impact of medicine on pre-osteoporosis yet these drugs the brand names or generic drugs pose side effects and differ in diminishing the rate of repeat fractures. Instead lifestyle changes with the right amounts of vitamin D and calcium in the diet as well as weight bearing exercises as well as precautionary measures to prevent falls in the first place which are among the vast range of manageable risk factors.

There is a challenge in the treatments and supplements as they also have side effects. For example calcium is regarded for its usefulness in improving only the quality of only hip bone, yet its continuous intake may increase heart attack risk. Health interventions prevent the development of osteoporosis by helping preserve bone mass (American Academy of Orthopaedic Surgeons(AAOS), 2018) and (Kaise Permanente, 2019). (Tu, et al., 2018) identifies the osteoporosis management criteria below as nonpharmacological management.

2.4.1. Preventative Lifestyle Changes

Table 2.2 *Lifestyle Changes for Preventing Osteoporosis (Consumer ReportsL Best Buy Drugs, 2016,p7)*

	Lifestyle Change	Recommendations
1.	Taking a diet containing adequate Vitamin D and Calcium	• 1,000mg Calcium per day for ages 18-50 • 1.200mg Calcium a day for ages above 50 • 600 IU(International Units) Vitamin D up to 70 years of age • 800 IU a day for ages above 70
2.	Performing Weight Bearing Exercises	• Resistance exercises such as dancing, walking and strength training • Balance improving exercises
3.	Fall Prevention Precautions	• Checking of sight • Limiting or cessation of alcohol intake • Avoiding sleeping pills • Lighting walking pavements for visibility • Keeping spaces clutter free • Secure loose rugs • Installing Grab Bars and rubber mats
4.	Quit Smoking	• Bone loss is worsened by smoking

Table 2.2 shows lifestyle changes and recommendations for preventing osteoporosis.

It is important to take note of the side effects available even in non-pharmacological treatment as established by various studies. Cosman de Beur et. al. (2015) states in particular the risk of kidney stones that is associated with high calcium supplements intake in contrast with dietary calcium which protects against kidney stones, hence the recommended increased intake of dietary calcium before initiating the intake of calcium supplements. Vitamin D supplement intake also has adverse results as suggested by (Chung, Lee, & Terasawa, 2011) and affirmed by (Bischoff-Ferri et. al., 2016) as cited in (Tu, et al., 2018) who sight the prevalence of falls associated with increased intake of

vitamin D supplements, hence warranting lower vitamin doses, according to (Cosman et. al., 2015)

Bischoff-Ferrri, Dawson-Hughes, & Orav (2016) concurred with other presentations that both treatment and prevention efforts towards osteoporosis were meant to curb further fractures from occurring hence the major value in lifestyle changes and safety adjustments, but further added the value of supportive therapy over and above osteoporosis treatment. Complementary treatment was in the form of physiotherapy, analgesia, orthopaedic management and hydrotherapy.

2.5. Criteria for Osteoporosis Treatment Selection

An evaluation of the comparative effectiveness of osteoporosis drugs is essential to be able to consider especially safety issues and manage adverse side effects, There stands basic criteria for drug selection (Consumer ReportsL Best Buy Drugs, 2016) , first the drugs have to be (Food and Drug Administration (FDA) approved for osteoporosis treatment, bare record safety on patients above other medications options for osteoporosis and have an average price lower than the other fracture prevention medicines meeting the first two criteria (Cosman, de Beur, & LeBoff, 2015) and (Watts & Bilezikian, 2012) also provides the criteria for selecting the most effective treatment for osteoporosis. Further, on the importance of considering side effects, (Lems & Raterman, 2017) highlights vast range of these affecting people taking medications.

Sophie, Hervoue, Poiraudeau, Briot, & Roux (2016) in a study concluded that the concerns relating to the adverse effects of osteoporosis medications had diminished prescriptions of some drugs through negative publicity and adverse reviews on media platforms, yet also it was of importance to appreciate that the effectiveness of osteoporosis medication while heavily dependent on relevance of prescriptions, correct use by patients had significant impact on its effectiveness.

2.6. Nature of Osteoporosis treatment options Available

Interventions towards osteoporosis include Nonpharmacological Management discussed earlier and Pharmacological Treatment (Tu, et al., 2018). This section considers pharmacological treatment, therapy meant to reduce fracture risks and coming in the form of medications. These can be arranged into two categories:

Antiresorptive (reduces rate of bone resorption)

- Bisphosphonates
- Estrogen agonist; antagonists (EAAs)
- Estrogens
- Calcitonin
- Denosumab

Anabolic (increases the rate of bone formation more than the rate of bone resorption)

- Teriparatide

While treatment options are dependent on the patient characteristics in terms of gender, age and underlying conditions and medications, the recommended criteria for treatment choice is based on considering the risk assessment factors highlighted above. As a recommendation (Cosman, de Beur, & LeBoff, 2015) and (Watts & Bilezikian, 2012) provides that for most Post-menopausal osteoporosis (PMO) patients at high risk of fracture first line treatment includes alendronate, risedronate, zoledronic acid, and denosumab. For those who cannot use oral therapy and are at high risk of fracture, recommended is; teriparatide, denosumab, or zoledronic acid.

2.6.1. Pharmacological Doses for treating Osteoporosis

Table 2.3 *Osteoporosis Treatment Doses* (South-Paul, 2014)

Medication	Route	Dosage
Raloxifene	Oral	60mg per day

Alendronate	Oral (prevention)	5mg per day
	Oral (treatment)	10mg per day
Estradiol Patch	Topical	0.05mg q week
Conjugated Estrogens	Oral	0.625 – 1.25mg per day
Vitamin D	Oral	400IU per day
	Oral	800IU per day (in north)
Elemental Calcium	Oral	1000-1500mg per day
Calcitonin	IN	200IU per day
	SC/IM	50-100 IU per day

Table 2.3 shows the medication options, their route of administration as well as dosage requirement for the treatment of osteoporosis.

2.7. Evaluation of Osteoporosis Pharmacological Treatment

Table 2.4 Osteoporosis Treatment Evaluation

Class of osteoporosis treatment	Name of treatment	Advantages	Disadvantages
Fluoride	Sodium fluoride		
Bisphosphonates	Alendronate Risendronate Ibanndronate Zoledronic	Reduce risk of spine fractures, non-spine fractures and hip fractures No evidence for Ibandronate for nonspine and hip fractures	Diarrhoea, nausea, heartburn, vomiting, oesophageal irritation Low blood calcium levels Increased risk of thigh bone fracture Bone, joint and muscle pain Permanent jaw bone deterioration Zoledronic associated with kidney problems and kidney failure
Calcitonin	Calcitonin	Reduces pain of acute fracture	Risk of Renal failure

Antibodies	Denosumab Romosozumab	Denosumab reduces the risk of spine, hip and other fractures	DenosumabRisk of serious skin infection, abdomen, urinary tract, ear, jaw osteonecrosis and low blood calcium level
Hormones	Raloxifene Teriparatide Abaloparatide	Raloxifene reduces the risk of spine fractures and no other fractures Teriparatide reduces the risk of spine and other non-spine fractures but not hip fractures	Raloxifene Increases the risk of life threatening blood clots, hot flashes and muscle pain Teriparatide Causes headaches, high blood calcium levels and risk of bone cancer
Hormone Replacement Therapy	Estrogen and Bazedoxifene	No evidence of reduced risk of spine fractures, non-spine fractures of hip fractures	needs continuous intake for at least 8 years though posing the risk of breast cancer with prolonged use.

2.7.1. Implications of Osteoporosis Treatment Methods

Lerns et. al. (2017) provides factors that inform understanding of implications osteoporosis treatment methods had:

1. Bisphosphonates

   These are synthetic analogues of inorganic pyrophosphate that inhibit bone resorption. Regimens include cyclical etidronate/calcium, risedronate, and alendronate.

- Cyclical etidronate/calcium is given as 400 mg of etidronate daily for 14 days followed by a calcium supplement of 500 mg daily for 76 days.
- Alendronate is given as a daily dose of 10 mg or 70 mg once weekly
- Rrisedronate as a daily dose of 5 mg.

- Calcium supplements though not part of the bisphosphonates, are encouraged for women who take low calcium in their diets.

The evidence for the antifracture efficacy of alendronate and risedronate appears to be better for non-vertebral and hip fractures compared with cyclical etidronate. On the other hand, there is good evidence for the antifracture efficacy of alendronate, risedronate, and cyclical etidronate for spinal fractures.

2. Hormone Replacement Therapy (HRT)

- Oestrogens can prevent bone loss around the menopause as well as fractures of the radius, hip, and vertebrae. Combination of oestrogens with progestagens reduces the risk of endometrial cancer. They need continuity as stopping intake restarts bone loss and results in the diminishing of the previous positive therapy effects hence the need to be taken continuously for at least 8 years though posing the risk of breast cancer with extended use.

Good HRT compliance is achievable despite the extended period of treatment. A patient takes a daily bone dose of (oestradiol 2mg and conjugated equine oestrogen 0.625mg).

- Testosterone can be considered in hypogonadal men but Raloxifene is a non-steroidal benzothiophene. It has been classified as a selective oestrogen receptor modulator and it inhibits bone resorption. Over the long term, significant BMD increase of the lumber spine, hip and total body at daily doses of raloxifene at 30, 60 and 150mp in a long term, while for decrease in BMD is experienced with placebo.

  These raloxifene doses are indicated to notably reduce new vertebral fracture risk in women and compared to placebo, and further in relation to oestrogen, raloxifene did not increase the risk of breast cancer in postmenopausal women and neither did it seem to stimulate endometrial hyperplasia.

- Calcitonin a natural hormone restrain bone resorption, lessens osteoclast formation and decreases osteoclast attachment. In postmenopausal women with osteoporosis, salmon

calcitonin nasal spray at a dose of 200IU per day considerably diminished new vertebral fracture risk as well as increase lumber spine BMD as well as provided pain relief.

- Parathyroid hormone injections administered intermittently, restore bone strength through bone formation stimulation, cortices and skeletal trabecula thickening, as well as enhancing trabecular population and connectivity.

In a 19 month period study of postmenopausal women a daily subcutaneous dose of human parathyroid hormone 20g and 40g reduced occurrence of vertebral fractures by 53% and significantly increased spine and femoral neck BMD. Nausea and vomiting was however experienced with high parathyroid hormone doses hence the approval of just 20g per day for the treatment of osteoporosis.

3. Calcium Supplements are grated as appropriate for administration in conjunction with other treatments rather than independently as they have a positive effect on BMD both pre and post menopause though not in the perimenopausal period, and prevent vertebral fractures.

4. Vitamin D supplements are meant to correct vitamin D deficiency, repress secondary hyperparathyroidism and augment femoral neck BMD. A dose of 1200mg per day calcium and 800IU per day of Vitamin D3 decrease hip fracture occurrence and other peripheral fractures.

The active metabolite of Vitamin D, Calcitriol in daily doses taken twice a day of 0.25g condensed the rate of vertebral fracture in post-menopausal osteoporosis patients. However it needs regular monitoring as it bears adverse side effects including hypercalcaemia and hypercalciuria.

2.7.2. Treating glucocorticoid induced osteoporosis

Lems & Raterman (2017) states that over 200 000 take glucocorticoids in the UK yet the drug negatively affected bone quality without these patients receiving mitigating drugs that prevent bone loss to counter the glucocorticoids effect. It results in worrying complications, as the highest bone loss impact occurs during the initial months of taking the treatment hence resulting in fractures in 30-40% of patients taking corticosteroids over a long term.

Bone loss induced by corticosteroids occurs due to both increased bone resorption and decreased bone formation. Corticosteroids decrease the level of sex steroids, reduce the number and activity of osteoblasts, decrease intestinal calcium absorption, and increase the resorption activity of osteoclasts, increase urinary calcium excretion, and increase bone cellular responsiveness to parathyroid hormone. Treatment should be considered as well as lifestyle advice. The glucocorticoid doses should be kept to the minimum necessary for disease control and alternative routes of administration such as inhaled glucocorticoids (which have less effect on bone than oral preparations) should be considered where possible. Moreover, alternative glucocorticoids should be considered, such as deflazacort and budesonide, which affect the bone minimally.

Pharmacological measures that can be considered in both the primary and secondary prevention of glucocorticoid induced osteoporosis and treatment include the most commonly used bisphosphonates and HRT; and then calcitriol, calcitonin, and vitamin D and calcium (Allen, et al., 2017).

CHAPTER THREE

METHODOLOGY

This chapter discusses the research methodology and research approach applied for evaluating the various treatment methods for osteoporosis. The study followed Fuzzy Logic and the Multi Criteria Data Analysis (MCDA) and these will be discussed as they are applied in selection problems of Medicine and how they were applied for this study.

Osteoporosis a bone affecting disease is highly problematic because of its asymptomatic nature, manifesting as fractures and normally affecting, the spine, the pelvis, wrists, hip with seriousness that necessitates hospitalisation. (Ferdous, et. al., 2015), (Kaise Permanente, 2019) and (Tu, et al., 2018) as most patients become bedridden. The bone structure weakens and gets prone to fracture due to various conditions on the bone itself (Tu, et al., 2018); impaired bone microarchitecture/mineralisation, low bone mineral density (BMD) or decrease of bone strength. The high prevalence of osteoporosis makes it a topical and concern rising phenomenon as a staggering 10-14million people is the projected population at risk of contracting it by 2030 in the United States alone according to (Tu, et al., 2018). Concerning its dominance, (Kaise Permanente, 2019) cites a one in five diagnosis on men, meaning that women accounted for the greater proportion affected by osteoporosis with prevalence mostly in the older population. Osteoporosis is however preventable, according to (Lim & Bolster, 2015) through; diet management, lifestyle management and interventions for fall prevention. Various osteoporosis treatment methods were also available, the choice of which was influenced by a number of factors for which specific criteria had to be applied.

Fuzzy logic is a technique in soft-computing used to grade reasoning systems. It can be applied in developing knowledge based systems useful in the medicine fraternity for activities like diagnosis, medicine selection for treatment and seamless patient data monitoring. The possibility of these activities is through the various linear programming modelling approaches imbedded and combined with Fuzzy Logic such as geometric programming, non-linear programming, linear programming, dynamic programming and

integer programming. The functionality involves the creation of investigative conditions that offer flexibility to the decision maker. On the other hand, the use of MCDA in medicine is based on its efficiency and effectiveness in data manipulation where multiple, conflicting criteria is involved.

The aim of the study was to evaluate the various treatment methods for osteoporosis from a range of antiresorptive treatments that reduce rate of bone resorption to anabolic treatments that increase the rate of bone formation more than the rate of bone resorption; as these impacted patients differently and each bore both positive and negative effects in varying scales.

3.1. Fuzzy Logic

This is a technique of data analysis introduced by a Computer Science Professor Lotfi A. Zadeh (Zadeh, 1965), (Zadeh, L;, 1973) and (Zadeh, L;, 1968) which examines the reasoning behind expressions of truths and falsehoods and grades them accordingly, analysis of natural language vagueness and in various applications. It is tolerant to vagueness and sub-optimality, hence its value. Communicated data is categorised systematically based on characteristics such as yes or no, true or false, high or low etc. and these are defined mathematically in a manner that introduces human-like mindset or perspective in computer programming (Zadeh, L, 1984).

Essentially the contrast of fuzzy logic is based on ancient Greek though patterns, being the laws of thought and theories of logic as well as mathematics as postulated by Aristotle and other philosophers (Korner, 1967).

The law of Exclude the middle (Parmenides 400BC) expresses that each opinion can either be true or false, a law however protested by other philosophers like Plato and Heraclitus, who suggested instead that thing could just either be true or not true. Also philosophers such as Marx, Engels and Hegel object the Fuzzy logic is an extension of the Boolean logic based on the fuzzy sets mathematical theory.

Disadvantages of Fuzzy logic Systems (Guru99, 2019)

1. It can be applies broadly, both in business and practical fields
2. It is easy to understand as it is based on a simple structure
3. Only acceptable reasoning is presented
4. It doesn't need any specific input
5. It solves uncertainty problems in a broad spectrum of fields
6. Complex problems are solved
7. It is possible to amply changes and modifications

Disadvantages of Fuzzy Logic Systems (Guru99, 2019)

1. It presents subjectivity from use of assumptions and can carry system inaccuracies
2. Some tasks may be overly complex
3. Validation and verification of the system involves extensive hardware testing
4. Its functionality lacks capacity in comparison to machine learning

3.1.1. Fuzzy Logic Sets

3.1.1.1. Mathematical Definition

A fuzzy set Ã in *IR* is a set of ordered pairs:

$$\tilde{A} = \{(x, \mu_{\tilde{A}}(x)) | x \in IR\}$$

where $\mu_{\tilde{A}}: IR \rightarrow [0,1]$and $\mu_{\tilde{A}}(x)$ is called the membership function of the fuzzy set (Uzun & Krral, Application of markov chains-fuzzy states to gold price, 2017)

3.1.1.2. Representation

The description of fuzzy sets can be in the form of discrete and continuous cases:

- Case One

Where *"U"* is discrete and finite:

$$\tilde{A} = \left\{\frac{\mu_{\tilde{A}}(x_1)}{x_1} + \frac{\mu_{\tilde{A}}(x_2)}{x_2} + \frac{\mu_{\tilde{A}}(x_3)}{x_3} + \cdots\right\} = \sum_{i=1}^{n} \frac{\mu_{\tilde{A}}(x_i)}{x_i}$$

- Case Two

Where *"U"* is continuous and infinite:

$$\tilde{A} = \left\{ \int \frac{\mu_{\tilde{A}}(x)}{x} \right\}$$

The equations show that the collection of each element is represented by the summation of the symbol where *"U"* is the universe of information.

3.1.1.3. Basic Operations

The relations between the union, complement and intersection on fuzzy sets are expressed as follows:

A. Union

$$\mu_{\tilde{A} \cup \tilde{B}}(x) = \mu_{\tilde{A}} \vee \mu_{\tilde{B}}, \qquad \forall x \in U$$

Where ∨ = 'max' operation,

- Intersection

$$\mu_{\tilde{A} \cap \tilde{B}}(x) = \mu_{\tilde{A}} \wedge \mu_{\tilde{B}}, \forall x \in U$$

Where ∧ = 'min' operation

B. Complement:

$$\boldsymbol{\mu'_{(\widetilde{A})}(x) = 1 - \mu_{\tilde{A}}(x)}$$

Other Cases

$$\tilde{A} \cap \tilde{A}' \neq 0$$

3.1.2. Properties of Fuzzy Sets

Fuzzy sets main properties can be stated in various forms

a. Commutative: Let's assume A and B are two Fuzzy Sets

$$\tilde{A} \cup \tilde{B} = \tilde{B} \cup \tilde{A}$$

$$\tilde{A} \cap \tilde{B} = \tilde{B} \cap \tilde{A}$$

b. Associated : Let's assume A, B and C are three Fuzzy Sets

$$\tilde{A} \cup (\tilde{B} \cup \tilde{C}) = (\tilde{A} \cup \tilde{B}) \cup \tilde{C}$$

$$\tilde{A} \cap (\tilde{B} \cap \tilde{C}) = (\tilde{A} \cap \tilde{B}) \cap \tilde{C}$$

c. Distributive : Let's assume A, B and C are three Fuzzy Sets

$$\tilde{A} \cup \left(\tilde{B} \cap \tilde{C}\right) = \left(\tilde{A} \cup \tilde{B}\right) \cap \left(\tilde{A} \cup \tilde{C}\right)$$

$$\tilde{A} \cap (\tilde{B} \cup \tilde{C}) = (\tilde{A} \cap \tilde{B}) \cup (\tilde{A} \cap \tilde{C})$$

d. Idempondency: Having a prior fuzzy set $\tilde{A}$

$$\tilde{A} \cup \tilde{A} = \tilde{A}$$

$$\tilde{A} = \tilde{A} \cap \tilde{A}$$

e. Identity : For fuzzy set $\tilde{A}$ and a universal set U:

$$\tilde{A} = \tilde{A} \cup \emptyset$$

$$\emptyset = \tilde{A} \cap \emptyset$$

$$A = \tilde{A} \cap \mathrm{U}$$

$$\mathrm{U} = \tilde{A} \cup \mathrm{U}$$

f. Transitivity: The property used in cases of fuzzy sets $\tilde{A}$, $\tilde{B}$and $\tilde{C}$,

$$\text{If } \tilde{A} \subseteq \tilde{B} \text{ and } \tilde{B} \subseteq \tilde{C} \text{ then } \tilde{A} \subseteq \tilde{C}\text{t}$$

g. Involution Property: Provided there is Fuzzy set $\tilde{A}$

$$\tilde{\tilde{A}}=\tilde{A}$$

h. De Morgan's Law:

$$\overline{\tilde{A} \cup \tilde{B}} = \bar{\tilde{A}} \cap \bar{\tilde{B}}$$

$$\overline{\tilde{A} \cap \tilde{B}} = \bar{\tilde{A}} \cup \bar{\tilde{B}}$$

3.2. Multi Criteria Decision Analysis (MCDA)

MCDA is a systematic process for solving problems that involve decision making on the basis of different choices. The decision making being a discipline on its own involves other disciplines. It is important for individuals, groups, societies to note that in life decision making roles and responsibilities:

- Theories and decision models help people understand why they have to make decisions as well the motivation for making decisions
- Theories and models also provide designs and guidelines for decision making to ensure appropriate decisions are reached with no negative implications. Theories and models hence support positive and good decision making that enable goal achievement (Application of Multi-Criteria Decision Making Theories in Healthcare and Biomedical Engineering)

Multi Criteria Decision Analysis (MCDA) is one analysis method for decision making with advantages in that it does not limit decision making to one aspect. It is based on the reality that everything humans do involves making choices and rarely encounter challenges in individual decisions except for complications that arise in decisions involving others on decisions made on behalf of others for example, children and especially older people. Every decision is made for the purpose of satisfying a need successfully and without consequences hence the need for risk evaluation within decision making. Positions of authority and experts thus demand payment for their decision making roles for the success of organisations or activities (Application of Multi-criteria Decision Analysis in Environmental and Civil Engineering 2001).

In reality each and every decision has with it both negative and positive implications hence the need for expert decision making through critical thinking capabilities for the selection of

the most ideal decision with minimal or acceptable consequences either positive or adverse. MCDA hence comes as a tool for an expert to inform, analyse, justify and clarify variables for successful decision making.

The International Society of Multi Criteria Decision Making (MCDM) observe decision making as an extensive discipline such that they split the fields to clearly outline the implication of each term and concept within MCDM and Decision Analysis:

- **Multiple (multi)**

The word multiple is similar to words such as numerous, many and several, which means that there are diverse criteria.

- **Criteria**

It is the plural form of criterion, the standard or principle by which something is judged or assessed. For example, decision making on pharmaceuticals could involve criteria such as product quality, manufacturer, service and quantity in use.

- **Decision**

The Latin origin of the word decision literally means "to cut off". Making a decision is about "cutting off" choices, essentially cutting you off from another course of action. In fact, making a decision frees you from the shackles of endless choices so that individuals or groups can get to where they want to go. In summary, a decision is a conclusion or resolution reached after consideration.

- **Analysis**

Analysis is the process of breaking a complex topic or matter into smaller parts in order to gain a better understanding of it. According to the dictionary definition, it can be described as a detailed examination of the elements or structure of something.

- **Multi-Criteria Decision Making** (MCDM)

It is a discipline in its own right that deals with decisions involving the choice of a best alternative from several potential candidates subject to several criteria or attributes that may be concrete or vague.

- **Decision Analysis** (DA)

It is a systematic, quantitative and visual approach for addressing and evaluating important choices confronted by decision maker/s (it is the mobilization of resources or inputs being processed in view of acquiring desired objectives, goals or outputs geared towards profit maximization or solving societal problems). It can be used by individuals or groups attempting to make decisions related to risk management, capital investments and strategic business decisions.

3.2.1. Application of Multi Criteria Decision Making

There are various benefits presented by use of multi criteria approach in decision making when compared to other decision making tools that are not systematic criteria (Grosan, Abraham, & Tigan, 2008).

- MDCA allows the comparison of decisions from various agents hence associate the results
- Data from various sources or of various classes can be combined without affecting the quality of decision arrived at.
- It is a simple, clear and reliable method to use in decision making hence effective and friendly
- Decision making criteria can be adjusted as the decision is being made to balance the variables influencing the decision
- MDCA is applicable in various scenarios as well as in various fields of study
- The decision maker does not necessarily need an expect to make decisions for them but can use MCDA to make their decisions independently

3.2.2. The Functionality of the MCDA

3.2.2.1. Included Techniques

Multi Criteria Decision Analysis is accomplished through the following steps below:

1. **Problem Identification**

The problem has to be identified and clearly defined as a starting point, bearing in mind that understanding the exact nature of the problem is part of the solution. Where people lack understanding of the actual problem in a matter in any field, complexities arise in searching for a solution as the wrong matter is targeted or rather the constituency fails to understand the intensity of the problem to align with the nature of solution attached. MCDA hence seeks to foremost identify the problem.

2. **Defining the objectives**

The identification of the problem is followed by defining the objectives in finding a solution. Objectives give direction to solution finding in decision making and in experiments as well as determine the achievement of the goals. For example in making a purchase decision, the objectives are often cheap, good quality, size, and acccessibility.

3. **Criteria Definition**

Criteria selection is linked to objectives as another success measure. It is paramount to set meaningful criteria for problem solving, that aligns with the identified objectives/ The definition of criteria involves the means of measuring the achievement of objectives and therefore has to make sense.

4. **Develop Options**

This stage involves the development of a list of options to take as solutions as we progress towards the real solution. Having a clearly defined criteria does not suffice, there is need for alternatives that are presented as possible solutions for analysis. This is based on the availability of varying solutions to a problem which however have each differing implications to the case. Selection will then ideally follow the ranking as per crtiteria.

5. Evaluation of Options

Evaluation of alternatives, is based on a set criteria which is applied in ranking the alternatives available and also considering the consequences (cost benefit analysis). Articulate evaluation ensures the elimination of underlying risks attached and obtaining confidence on the applicability of the solution. Each option is analysed based on the criteria and also taking care not to sway from the goal or target. Each time we consider an option, we need to always remember the objective of the experiment, if the risks exceed what we could potentially gain, as well as how easy or difficult it is to achieve the objective. In production systems, it is important to evaluate the cost of inputs, the process and the outputs.

6. Calculation

This is the determination stage where all the data, criteria, target are used to select the closest to favoured solution based on the best score. This is an important step where also, results are obtained by taking the product of each criterion score and weight and summing them. The final score is derived from summing up all the other scores and choosing the option scoring best.

7. Documentation

Following obtaining the desired results, all that remains is to monitor the implementation and also preserve it for future use, just as models and theories are recorded in books for use in decision making and learning.

3.3. Preference Ranking Organisation Method for Enrichment Evaluatioins PROMETHEE

To make good decisions under Fuzzy conditions, the MCDA has in recent times been combined with fuzzy logic forming a hybrid that facilitates the evaluation of linguistic or bounded continuous data, this is termed PROMETHEE evaluation. MCDA, Multi Criteria Programming Model for medical diagnosis and treatment was proposed by (Grosan, Abraham, & Tigan, 2008). This MCDA is applied in diverse ways fused with fuzzy logic in the medical field; colon cancer analysis (Sani Musa & Uzun Ozsahin, 2019), leukaemia (Ozsahin, Nyakuwanikwa, Wallace, & Ozsahin, 2019), liver cancer, pancreatic cancer breast cancer and even HIV therapy alternatives (Uzun, Sarigul Yildirim, Sayan, Sanlidag, & Uzun Ozsahin, 2019).

The PROMETHEE technique has been used in assessing nuclear medicine imaging devices (Ozsahin D. , et al., 2017), algorithms of image reconstruction in nuclear medicine, (Ozsahin, Isa, Uzun, & Ozsahin, 2019), X Ray based nuclear medical imaging devices, sterilisation methods for medical devices, and solid-state detectors in medical imaging (Ozsahin, Sharif, Ozsahin, & Uzun).

3.3.1. Preference Ranking Organisation Method for Enrichment Evaluatioins (PROMETHEE)

It is a multicriteria technique for decision making that allows analysis and ranking of alternative solutions based on criteria for each alternative which are then weighted based on importance. PROMETHEE is regarded more highly in comparison with other decision making tools (Uzun et al) because:

- It can be used to handle qualitative and quantitative criteria simultaneously.
- It deals with fuzzy relations, vagueness and uncertainties.
- It is easy to handle and provides the user with maximum control over the weights of the criteria.

Only two types of information are required from the decision maker when using PROMETHEE:

- information regarding the weights of the selected criteria, and
- the preference function to be used in comparing the alternatives' contribution in regard to each criterion (Maisaini et. al., 2018)

The different available preference functions (P_j) on PROMETHEE make the model unique and offers the decision maker control over the definition of the preference value or level for the alternatives for each criteria. The discrepancy between two alternatives (a and a_t) in relation to a specific criterion and a preference degree ranging between 0 and 1 is referred to as the preference value.

The preference functions for practical purposes include: Gaussian function, V-shape function, linear function, usual function, level function, and U-shaped function. A detailed description of the preference functions used, their ranking and how to make a decision on which function best suits a scenario was discussed by (Brans, Vincke, & Mareschal, 1986).

Generally, type III (V-shape) and type V (linear) preference functions are mostly used for data with quantitative measures, while type I (usual shape) and type IV (level) preference functions are mostly used for qualitative data. The definitions of the parameters are as follows:

- q= threshold of indifference
- p= threshold of strict preference
- intermediate point between q and p

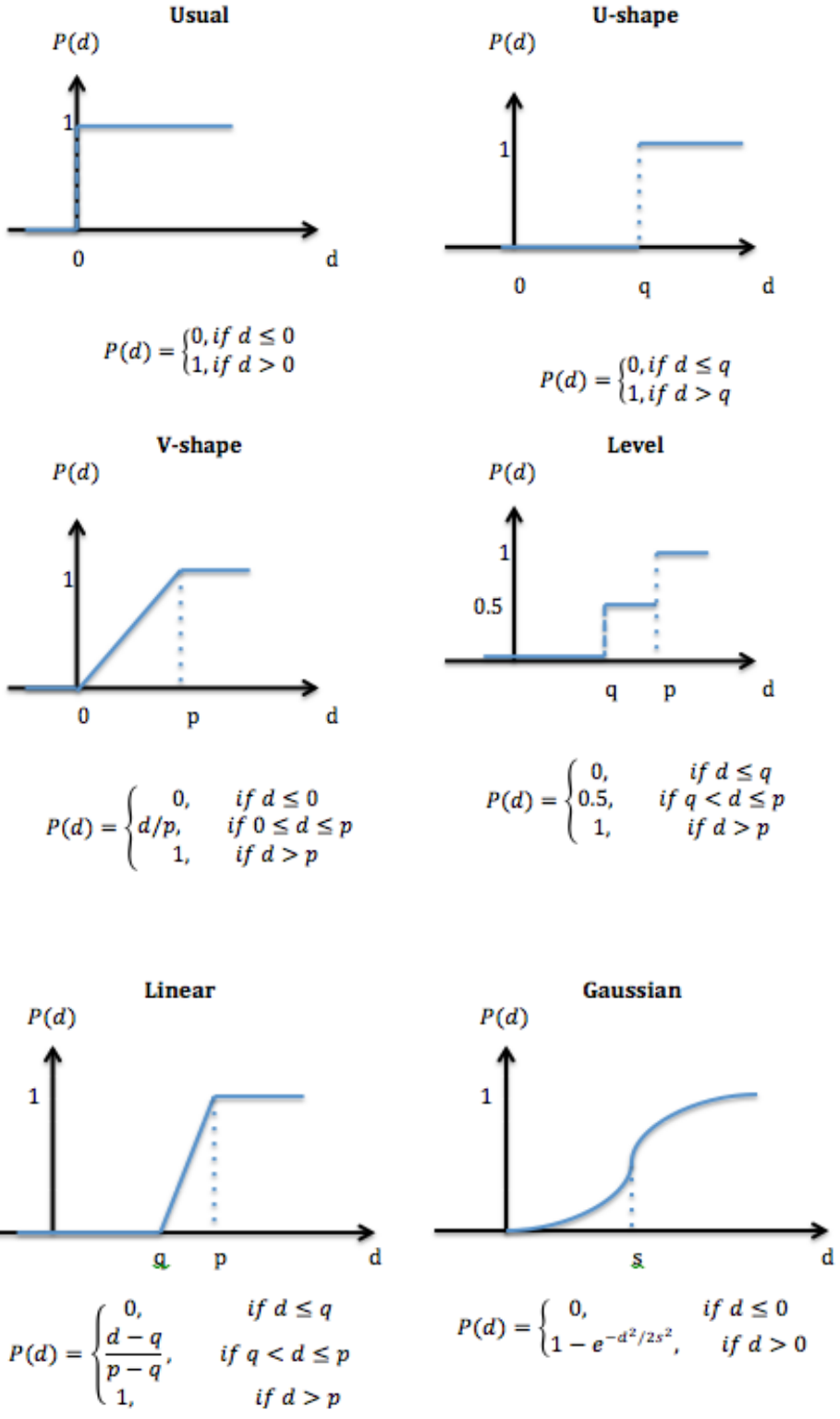

Figure 3.1. Types of the Preference Functions of the PROMETHEE Method (Brans, J; Mareschal, B;, 2019)

Figure 3.1 shows types of the Preference Functions of the PROMETHEE Method

Steps in PROMETHEE Method

a. Define a specific preference function *(d)* for each criteria *j*.
b. Determine each criterion's weight $w = (w_1, w_2, \dots, w_k)$.

Decision on weights normalization or weights equality is at the decision maker's discretion based on the application.

1. For each alternative, $a_t, a_{t'} \in A$, determine the outranking relation π.

$$\pi(a_t, a_{t'}) = \sum_{k=1}^{K} w_k . \left[p_k\left(f_k(a_t) - f_k(a_{t'})\right)\right], \qquad AXA \rightarrow [0,1]$$

2. Determine the positive and negative outranking flows

- Positive outranking flows for a_t: $\Phi^+(a_t) = \frac{1}{n-1}\sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_t, a_{t'})$

Where n = number of alternatives and every alternative is compared to an $n-1$)

This expression concerns how one alternative is better than the others meaning that the alternative scoring the higher positive outranking is the better alternative.

- Negative outranking Flows for a_t: $\Phi^-(a_t) = \frac{1}{n-1}\sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_{t'}, a_t)$

Where n = number of alternatives and every alternative is compared to an $n-1$)

This expression concerns how one alternative is beaten by the others meaning that the alternative scoring the lowest negative outranking is the better alternative.

3. Define the partial preorder for available alternatives of A a_t is desirable to $a_{t'}$ $(a_t P a_{t'})$ in PROMETHEE in any of the following scenarios.

$$\begin{cases} \Phi^+(a_t) > \Phi^+(a_{t'}) and \Phi^-(a_t) < \Phi^-(a_{t'}) \\ \Phi^+(a_t) > \Phi^+(a_{t'}) and \Phi^-(a_t) = \Phi^-(a_{t'}) \\ \Phi^+(a_t) = \Phi^+(a_{t'}) and \Phi^-(a_t) < \Phi^-(a_{t,} a_{t'}) \end{cases}$$

Where two alternatives are available (a_t and $a_{t'}$) with similar or equal leaving and entering flows

a_t is indifferent to $a_{t'}$ ($a_t I a_{t'}$) if:

$\Phi^+(a_t) = \Phi^+(a_{t'})\ and\ \Phi^-(a_t) = \Phi^-(a_{t'})$.

$a_t$is incomparable to $a_{t'}(a_t R a_{t'}$) if:

$$\begin{cases} \Phi^+(a_t) > \Phi^+(a_{t'})\ and\ \Phi^-(a_t) > \Phi^-(a_{t'}) \\ \Phi^+(a_t) < \Phi^+(a_{t'})\ and\ \Phi^-(a_t) < \Phi^-(a_{t'}) \end{cases}$$

4. Determine the net outranking flow for each alternative

$$\Phi^{net}(a_t) = \Phi^+(a_t) - \Phi^-(a_t)$$

A complete preorder could be derived from the net flow and given as:

$a_t$is preferred to $a_{t'}$ $(a_t P a_{t'})$ if $\Phi^{net}(a_t) > \Phi^{net}(a_{t'})$

a is indifferent to $a_{t'}$ ($a_t I a_{t'}$) if $\Phi^{net}(a_t) = \Phi^{net}(a_{t'})$.

Table 3.1 Data (classes of treatment and criteria)

Class of osteoporosis treatment	Name of treatment	Dosage	Cost	Time	Side effects	advantages	Disadvantages
Fluoride	Sodium fluoride	high	very low	Medium	medium	High	very low
Bisphosphonates	Alendronate Risendronate Ibanndronate Zoledronic	med	low	High	very low	very high	medium
Calcitonin	Calcitonin	very low	med	Medium	low	very low	High
Antibodies	Denosumab Romosozumab	low	high	Low	High	low	very high
Hormones	Raloxifene Teriparatide Abaloparatide	very high	very high	Medium	very high	very high	low
Hormone Replacement Therapy	Estrogen and Bazedoxifene)	very high	very high	very high	very high	medium	very high

Table 3.1 above shows the data that was collected for analysis which includes; classes of osteoporosis treatment also known as alternatives, names of the treatment and criteria. The criteria used included: dosage, cost, time, side effects, advantages and disadvantages.

Linguistic fuzzy scale has been used in this analysis as shown inn Table 3.2 .

Table3.2. Linguistic fuzzy scale using triangular fuzzy sets

Scale of evaluation	Fuzzy scale
Very High (VH)	(0.75, 1, 1)
High (H)	(0.50, 0.75, 1)
Medium (M)	(0.25, 0.50, 0.75)
Low (L)	(0, 0.25, 0.50)
Very Low (VL)	(0, 0, 0.25)

CHAPTER FOUR

RESULTS

The results of the analysis show that with the set dosage, cost, time, side effects, advantages and disadvantages, bisphosphonates are the most preferred treatment method for osteoporosis whereas hormone replacement therapy is the least preferred.

Table 4.1: Complete ranking of treatment methods of Osteoporosis

Complete Ranking	Alternative	Positive outranking flow	Negative outranking flow	Net flow
1	Bisphosphonates	0,0100	0,00017	0,0083
2	Fluoride	0,0102	0,0021	0,0082
3	Calcitonin	0,0073	0,0058	0,0015
4	Hormones	0,0051	0,0076	-0,0025
5	Antibodies	0,0041	0,0075	-0,0034
6	HRT	0,0004	0,0125	-0,0121

Table 5.1 shows the complete ranking of alternative treatment methods for osteoporosis, showing the positive, negative and net outranking flow values. Bisphosphonates are ranked first as they have the highest net flow of 0,0083. Fluoride is second with a net flow of 0,0082, then on third place is calcitonin with a net flow of 0,0015. The treatment option ranked fourth is hormones with a net flow of -0,0025. It is then followed by antibodies which are fifth in

the ranking and having a net flow of -0,0034. The alternative ranked sixth and also least preferred is hormone replacement therapy (HRT).

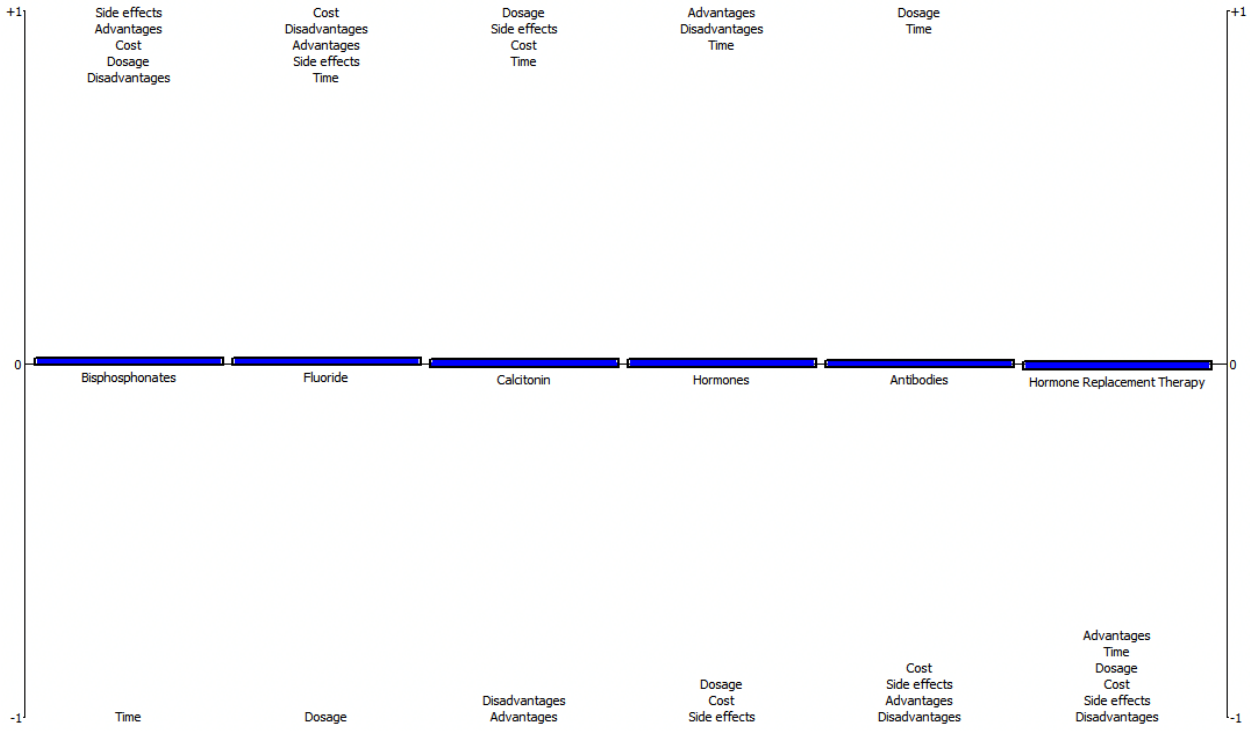

Figure 4.1: Ranking showing the criteria for each alternative treatment methods in their positive and negative outranking flows

Figure 4.1 above shows the ranking showing the criteria for each alternative treatment methods in their positive and negative outranking flows. The alternatives are listed from most preferred to least preferred (left to right).

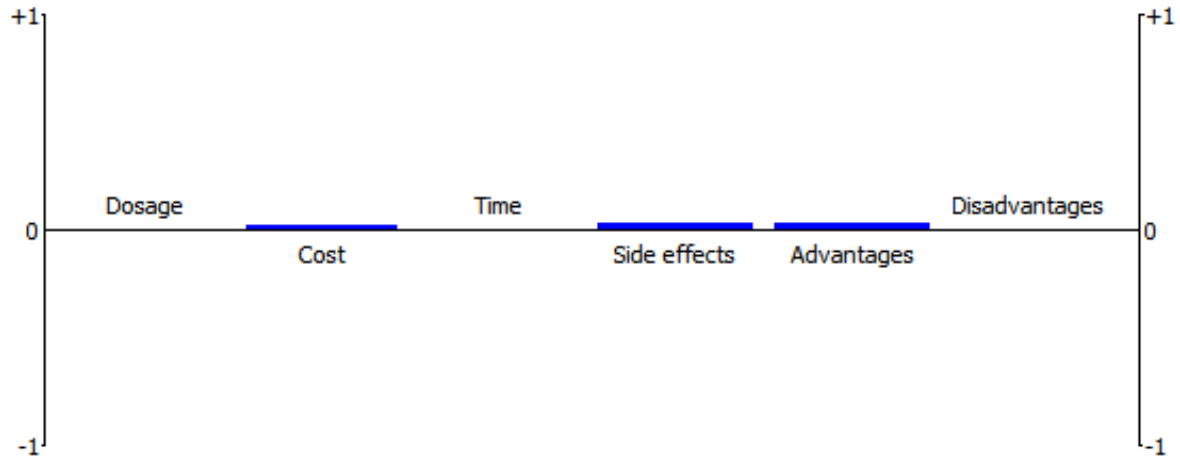

Figure 4.2: Action profile of Bisphosphonates

Figure 4.2 shows the action profile of bisphosphonates which shows strength in cost, side effects and advantages criteria.

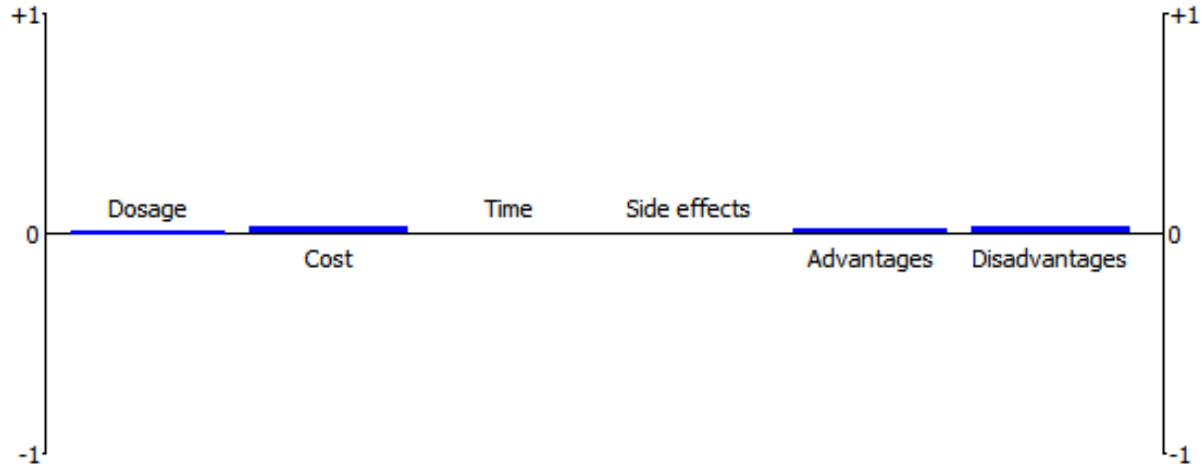

Figure 4.3: Action profile of Fluoride

Figure 4.3 shows positive ranking in cost, advantages, disadvantages and dosage in relation to fluoride as a method of treatment for osteoporosis.

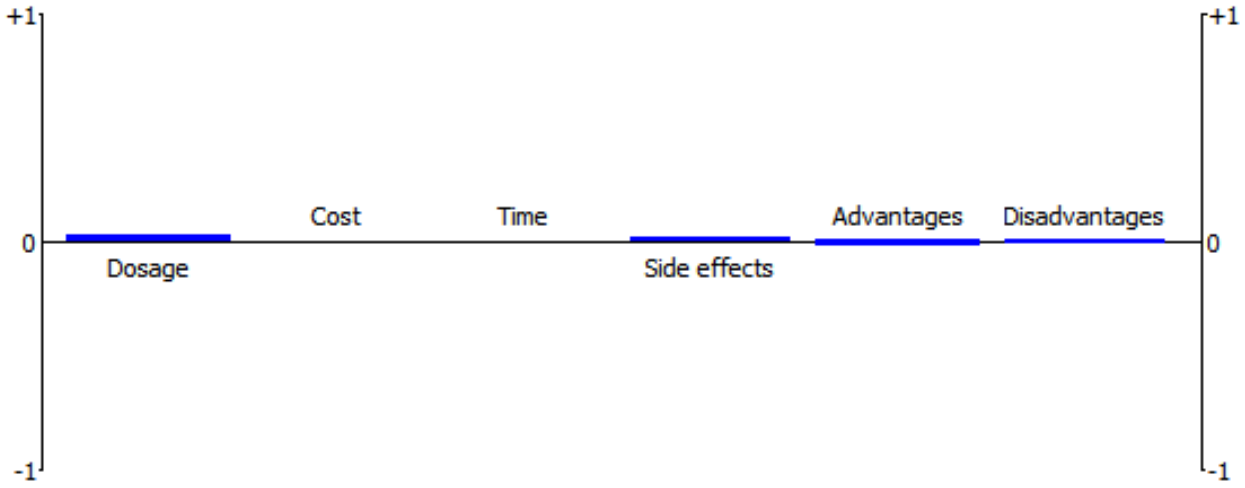

Figure 4.4: Action profile of Calcitonin

Figure 4.4 above shows strong points of Calcitonin which are shown by positive rankings in dosage, side effects as well as disadvantages, and neutral flow in advantages.

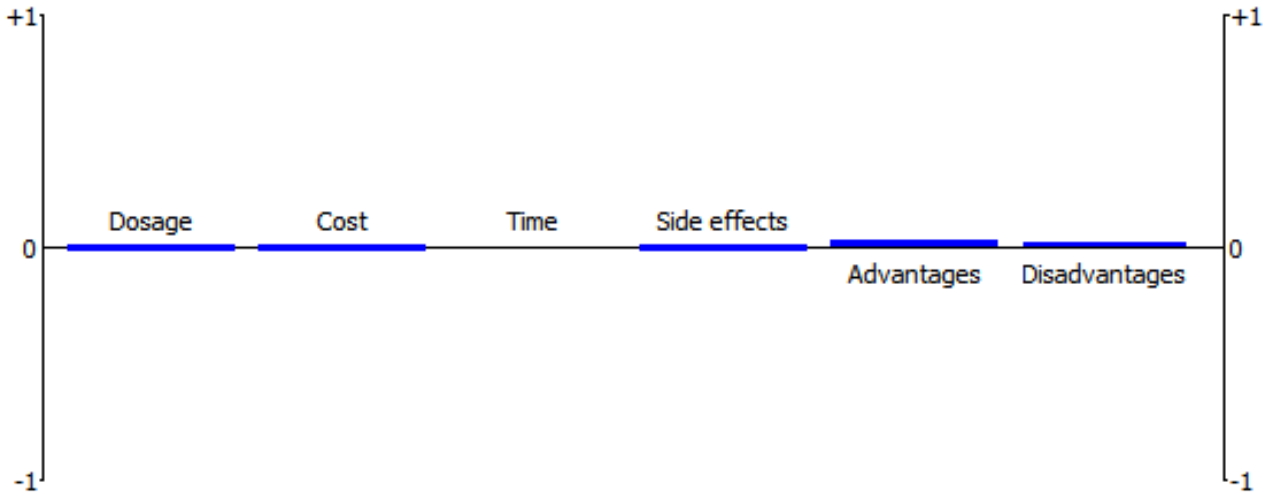

Figure 4.5: Action profile of Hormones

Figure 4.5 above shows the action profile of hormones, indicating positive rankings in advantages and disadvantages whereas the rest of the criteria including; dosage, cost and side effects are neutral.

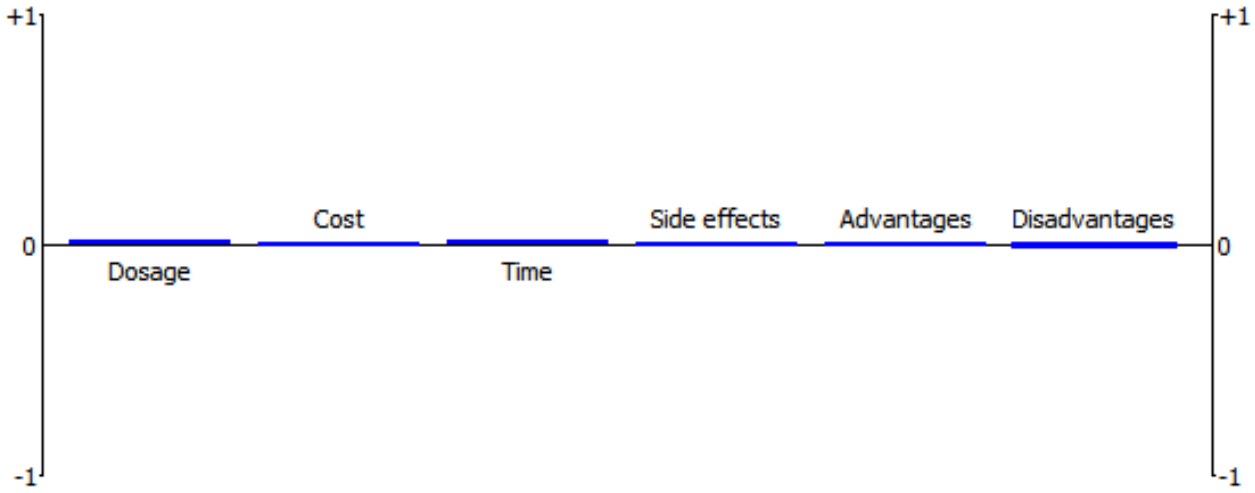

Figure 4.6: Action profile of Antibodies

Figure 4.6 above shows the action profile of antibodies showing positive ranking in dosage and time, negative ranking in disadvantages and neutral points in cost, side effects and advantages.

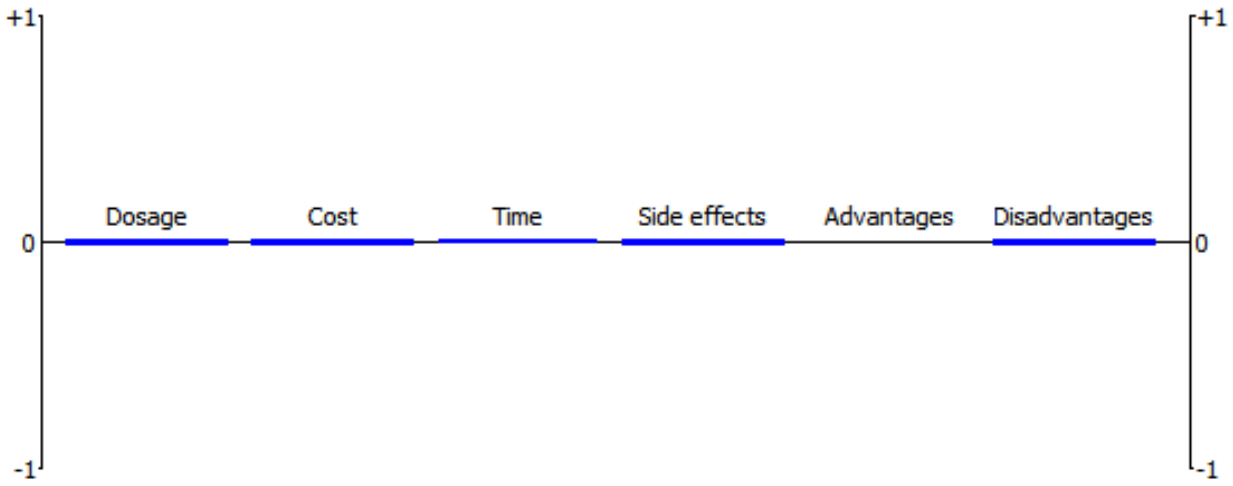

Figure 4.7: Action profile of Hormone Replacement Therapy

Figure 4.7 above shows the action profile of HRT having a positive outranking flow of 0.0004 and a negative outranking flow of 0.0125 which gives a net flow of -0.0121 which is why HRT is the least favorable method of treatment for osteoporosis.

CHAPTER FIVE

DISCUSSIONS, CONCLUSION AND RECOMMENDATIONS

5.1 Discussions

Although appropriate BMD (bone mineral density)screening based on age, gender, among other risk factors; and treatment with medication is important, osteoporosis is preventable with proper management of diet, lifestyle, and fall prevention interventions. It was established that fractures did occur, mainly in the elderly, however fear of severe side effects, lack of education in professionals and in the lay public, lack of osteoporosis medical prioritization, poor healthcare systems, coordination and diagnosis inadequacies resulted in low treatment compliance to anti osteoporotic drugs. Therefore, to facilitate effective treatment, the study established that BMD testing should be utilized as a teaching moment, hence the importance of health providers education concerning interfering factors such as the anxiety that BMD test results may cause in patients that are highly concerned about health to avoid a provider-level barrier to treatment.

Further, while non-pharmacological strategies such as caution and exercise were determined ideal for patients at high fractur risk. However, the absence of established targets to define current fracture care in terms of whether treatment prioritized fracture prevention or an increase in BMD posed problems for osteoporosis treatment. Bisphosphonates remained the first-line and most cost-effective treatment option for osteoporosis, though there was increasing concern over their long-term safety. One of the main reasons being that with bisphosphonates, normalization of BMD was usually not possible. However, with denosumab and with osteoanabolic drugs, substantially larger increases in BMD were an achievable treatment goal. It was established that, most likely, side effects stood side effects stood as a key treatment limitation than lack of efficacy thus, the lower use of bisphosphonates established to be related to skepticism over severe side effects than for the reoccurring (mild) side effects. The classification of side effects is :- relatively common, mild and reversible side effects, particularly dyspepsia, and severe, but infrequent side effects.

5.2 Conclusion

In this study six treatment option for osteoporosis were evaluated namely; bisphosphonates, fluoride, hormones, antibodies, calcitonin and hormone replacement therapy using Fuzzy PROMETHEE method. The alternatives were evaluated based on the criteria; dosage, time, cost, side effects, advantages and disadvantages using MCDA, PROMETHEE and fuzzy logic to process the data collected on the alternatives.

The aim of this research was to evaluate these alternatives and rank them from most favored to least favored. The result of the evaluation show that bisphosphonates are most favored treatment option, followed by fluoride, calcitonin, antibodies, hormones and the least favored alternative being hormone replacement therapy. Seeing as there are six criteria, we used in the study it is very important to know that ranking the alternatives does not necessarily mean they will work best on every individual in the controlling of the disease, but the point is to provide individuals with a general preference based on the six criteria that are mainly considered before starting osteoporosis treatment.

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