Treatment Pattern of Osteoporosis in Bangladesh

A dissertation submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

Submitted by

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DECLARATION BY THE CANDIDATE

I, Md. Sayed, hereby declare that the dissertation entitled **"Treatment Pattern of Osteoporosis in Bangladesh"** submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy is a record of original research work carried out by me under the supervision and guidance of Naifsa Tanjia, Lecturer, Department of Pharmacy, East West University and the thesis has not formed the basis for the award of any other degree/diploma/fellowship or other similar title to any candidate of any university.

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Last but not the least, I would like to thank my family and friends for their care and encouragement during my research work.

DEDICATION

This research paper is dedicated to

My beloved parents

Abstract

Epidemiological studies have projected a vast increase in osteoporotic fractures in Bangladesh. Awareness of osteoporosis among medical professionals and the pattern of management in Bangladesh have not been explored. In the year, 2005; 147 doctors who were involved in treating osteoporosis, 69% doctors were specialists and 9% were consultants, to whom the questionnaire was distributed at this meeting, 115 questionnaires were returned with a response rate of 78%. Eight surveys were excluded because of incomplete biographical information, resulting in a total of 107 completed questionnaires that for analysis. 84% attended any specialized osteoporosis program but only 24% had subscription in any medical journal or website**.** Bangladeshi doctors' awareness of WHO criteria about T-score is 75% but 11% doctors were not aware**.** Approximately 59% doctors follow guideline and 22% do not follow any guideline but only 15% were able to write specific guideline name, 86% were unable to write the name of the following guideline. DXA was suggested by 25% doctors, 23% suggested plain radiography, 17% used CT skin imaging, 5% QUS, 10% MRI, 18% X-ray for diagnosis of osteoporosis. Plain radiography is useful for fracture prediction thought by 70% doctors, 51% of them selected CT scan as most sensitive diagnostic tool and CT scan is used by 31% doctors because of lower cost vs. DXA**.** 38% of them thought that DXA does not measure BMD directly, 36% used to predict fractures on postmenopausal women**.** For the prevention of osteoporosis, physical exercise was preferred by 19% doctors, 20% ticked on calcium rich diet, 15% on hormone replacement, 17% on calcium supplementation, and 17% on vitamin D supplementation**.** For the treatment purpose, most of the doctors; 15% used bisphosphonates, 12% calcium supplement, 11% estrogen, 10% estrogen agonist/ antagonist and very few doctors; 0.5% on vitamin C, 5% on chondroitin sulfate, 3% on sodium fluoride, 0.3% on others, 0.1% on combination, 6% on calcitonin, 6% on glucosamine, 7% ticked on strontium ranelate, 8% on parathyroid hormone, 8% on calcitriol, 8% on tibolone. 27% doctors prescribed bisphosphonates, 22% calcitonin, and 26% estrogen for prevention of osteoporosis. This study showed that physicians in Bangladesh were moderately aware of osteoporosis, though the disease was still under-diagnosed due to inaccessibility and high cost of the diagnostic tools and therapeutic agents. So government and doctors should take initiative to increase the awareness of osteoporosis among the physicians in Bangladesh.

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List of abbreviation

AI- Aromatase Inhibitors

ARI- Absolute Risk Increase

BMC- Bone Mineral Content

BMD- Bone Mineral Density

BMI- Body Mass Index

BMDm- Bone Mineral Density measurement

BUA- Broadband Ultrasound Attenuation

CR- Canadian Rheumatologists

CYP- Cytochrome P450

DMPA- Depot Medroxyprogesterone Acetate

DXA- Dual energy X-ray Absorptiometry

FDA- Food and Drug Administration

FEA- Finite Element Analysis

FSH- Follicle Stimulating Hormone

GC- Glucocorticoids

GIOP- Glucocorticoid Induced Osteoporosis

GnRH- Gonadotropin Releasing Hormone

GP- General Practitioner

H2RA- Histamine 2 Receptor Antagonist

HRCT- High Resolution Quantitative Computed Tomography

HRMRI- High Resolution Magnetic Resonance Imaging

HRT- Hormone

HSA- Hip Structure Analysis

IU- International Unit

LH- Luteinizing Hormone

Micro-CT- Micro Computed Tomography

Micro- MRI- Micro Magnetic Resonance Imaging

NaF- Sodium Fluoride

O&G- Obstetricians and Gyencologists

OP- Osteoporosis

PCP- Primary Care Physician

PoM- Post menopausal

PPI- Proton Pump Inhibitor

PrM- Pre menopausal

PTH- Para Thyroid Hormone

QCT- Quantitative Computed Tomography

QUS- Quantitative Ultrasound

RANKL- Receptor Activator of Nuclear factor Kappa B Ligand

RA- Rheumatoid Arthritis

Replacement Therapy

ROI- Region of Interest

SERM- Selective Estrogen Reuptake Modulators

SHO- Senior House Officer

SOS- Speed of Sound

SSRI- Selective Serotonin Receptor Inibitor

TCA- Tricyclic Antidepressant

TSH- Thyroid Stimulating Hormone

UCR- Ultrasound Critical angle Reflectometry

UK- United Kingdom

USA- United States of America

VFA- Vertebral Fracture Assessment

VQCT- Volumetric Quantitative Computed Tomography

WHO- World Health Organization

1. INTRODUCTION

1.1 Overview

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., micro fractures) and mineralization. A fracture occurs when a failure-inducing force (e.g., trauma) is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

It is important to acknowledge a common misperception that osteoporosis is always the result of bone loss. Bone loss commonly occurs as men and women age; however, an individual who does not reach optimal (i.e., peak) bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence sub-optimal bone growth in childhood and adolescence is as important as bone loss to the development of osteoporosis.

Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70 percent of bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 standard deviations below the mean for young white adult women. It is not clear how to apply this diagnostic criterion to men, children, and across ethnic groups. Because of the difficulty in accurate measurement and standardization between instruments and sites, controversy exists among experts regarding the continued use of this diagnostic criterion (NIH, 2000).

The consequences of osteoporosis include the financial, physical, and psychosocial, which significantly affect the individual as well as the family and community. An osteoporotic fracture is a tragic outcome of a traumatic event in the presence of compromised bone strength, and its incidence is increased by various other risk factors. Traumatic events can range from high-impact falls to normal lifting and bending. The incidence of fracture is high in individuals with osteoporosis and increases with age. The probability that a 50-year-old will have a hip fracture during his or her lifetime is 14

percent for a white female and 5 to 6 percent for a white male. The risk for African Americans is much lower at 6 percent and 3 percent for 50-year-old women and men, respectively. Osteoporotic fractures, particularly vertebral fractures, can be associated with chronic disabling pain. Nearly one-third of patients with hip fractures are discharged to nursing homes within the year following a fracture. Notably, one in five patients is no longer living 1 year after sustaining an osteoporotic hip fracture. Hip and vertebral fractures are a problem for women in their late 70s and 80s, wrist fractures are a problem in the late 50s to early 70s, and all other fractures (e.g., pelvic and rib) are a problem throughout postmenopausal years. The impact of osteoporosis on other body systems, such as gastrointestinal, respiratory, genitourinary, and craniofacial, is acknowledged, but reliable prevalence rates are unknown.

Hip fracture has a profound impact on quality of life, as evidenced by findings that 80 percent of women older than 75 years preferred death to a bad hip fracture resulting in nursing home placement. However, little data exist on the relationship between fractures and psychological and social well-being. Other quality-of-life issues include adverse effects on physical health (impact of skeletal deformity) and financial resources. An osteoporotic fracture is associated with increased difficulty in activities of daily life, as only one-third of fracture patients regain pre-fracture level of function and one-third require nursing home placement. Fear, anxiety, and depression are frequently reported in women with established osteoporosis and such consequences are likely under-addressed when considering the overall impact of this condition (NIH, 2000).

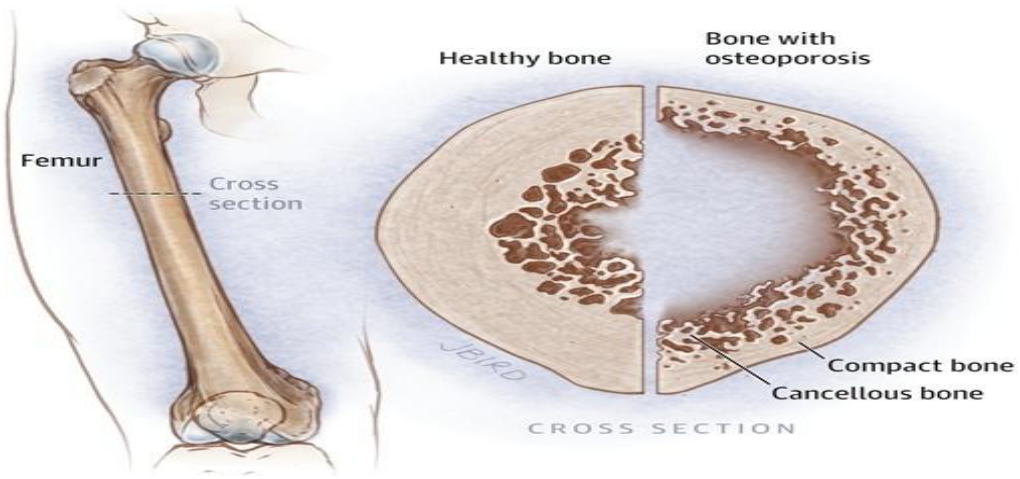


Figure 1.1: Bone structure cross section (Deborah, 2014)

1.2 Types of osteoporosis

Osteoporosis is traditionally divided into primary and secondary osteoporosis. Both types can occur simultaneously in the same person. The cause of primary osteoporosis is not fully understood. Primary osteoporosis is divided into postmenopausal (type I) and senile (type II) osteoporosis. Secondary osteoporosis is less common and defined as bone loss occurring as a result of other diseases, such as Cushing's syndrome or malignancy.

1.2.1 Type I - Accelerated or postmenopausal osteoporosis

Bone loss is accelerated in women for five to ten years after menopause due to reduced production of the female sex hormone, estrogen. Ten or more years after menopause, accelerated bone loss slows down and approaches the rate of decline observed in older men. In five to ten percent of postmenopausal women, bone loss is severe and leads to fractures before age 75. Postmenopausal osteoporosis most often results in collapsed vertebrae, which may lead to the dowager's hump. Other bones, such as wrist bones, are also affected. Type I bone loss occurs in women over six times as frequently as men.

1.2.2 Type II - Age-related osteoporosis (due to +75)

Age-related osteoporosis occurs in both sexes in women over age 70 and men over age 80.There is very good evidence that the incidence of fractures increases with the lowering of bone mineral density. Type II bone loss typically results in hip fractures, although fractures occur in other types of bone as well. Elderly men are very susceptible to bone loss, but women get hip fractures about twice as often. It is not clear whether the bone loss is simply an expression of old age which affects some people to a larger extent than others. An underlying disease, a hormonal imbalance or nutrient deficiency may accelerate age-related bone loss.

In general, women have less dense bones than men (usually 30 percent less), and they suffer more bone loss after menopause. This puts women at a disadvantage when age-related bone loss occurs. Women live longer than men, and thus may be more likely to develop fractures. Osteoporosis is rare in young adults and middle-aged men (Heinz, 2000).

1.2.3 Secondary osteoporosis (independent of age due to medication)

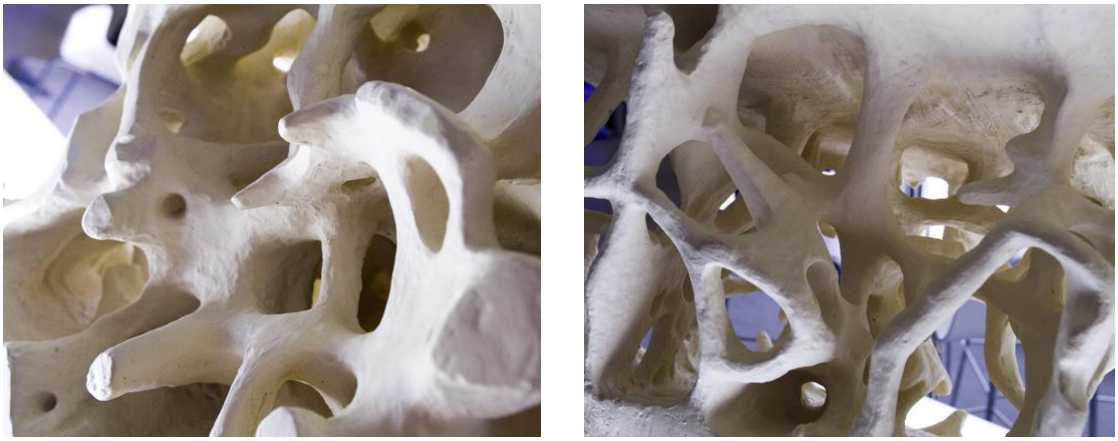
In some instances, osteoporosis is a side-effect of another health condition. For example, overproduction of cortisone, as in Cushing Syndrome, can lead to osteoporosis. Abnormally low production of sex hormones, as in hypogonadism, castration or "total hysterectomy" can lead to bone loss; certain malignancies, particularly myeloma (a bone marrow cancer), hyperthyroidism and hyperparathyroidism can also result in bone loss. Digestive, kidney, or liver disorders may lead to bone loss.

Osteoporosis is a form of osteopenia. Osteopenia literally means "little bone". In osteoporosis bone mass is lost. However, the composition of the remaining bone is similar to healthy bone, although not as dense. To diagnose osteoporosis correctly, other bone disorders should be excluded. In osteomalacia, bone tissue is not adequately mineralized, and bone quality is softer than healthy bone. Osteomalacia is primarily due to severe vitamin D deficiency and is an adult form of rickets (Heinz, 2000).

1.3 Pathophysiology

Bone mass in older adults equals the peak bone mass achieved by age 18-25 years minus the amount of bone subsequently lost. Peak bone mass is determined largely by genetic factors, with contributions from nutrition, endocrine status, physical activity and health during growth. The process of bone remodeling that maintains a healthy skeleton may be considered a preventive maintenance program, continually removing older bone and replacing it with new bone. Bone loss occurs when this balance is altered, resulting in greater bone removal than replacement. The imbalance occurs with menopause and advancing age. With the onset of menopause, the rate of bone remodeling increases, magnifying the impact of the remodeling imbalance. The loss of bone tissue leads to disordered skeletal architecture and an increase in fracture risk.

Figure 2 shows the changes within cancellous bone as a consequence of bone loss. Individual trabecular plates of bone are lost, leaving an architecturally weakened structure with significantly reduced mass. Increasing evidence suggests that rapid bone remodeling (as measured by biochemical markers of bone resorption or formation) increases bone fragility and fracture risk.



Normal bone Osteoporotic bone

Figure 1.2: Micrographs of Normal vs. Osteoporotic Bone (Dawson-Hughes, *et. al.*, 2013)

Bone loss leads to an increased risk of fracture that is magnified by other aging-associated declines in functioning. Figure 3 shows the factors associated with an increased risk of osteoporosis-related fractures. These include general factors that relate to aging and sex steroid deficiency, as well as specific risk factors, such as use of glucocorticoids, which cause bone loss, reduced bone quality and disruption of micro architectural integrity. Fractures result when weakened bone is overloaded, often by falls or certain activities of daily living (National Osteoporosis Foundation, 2010).

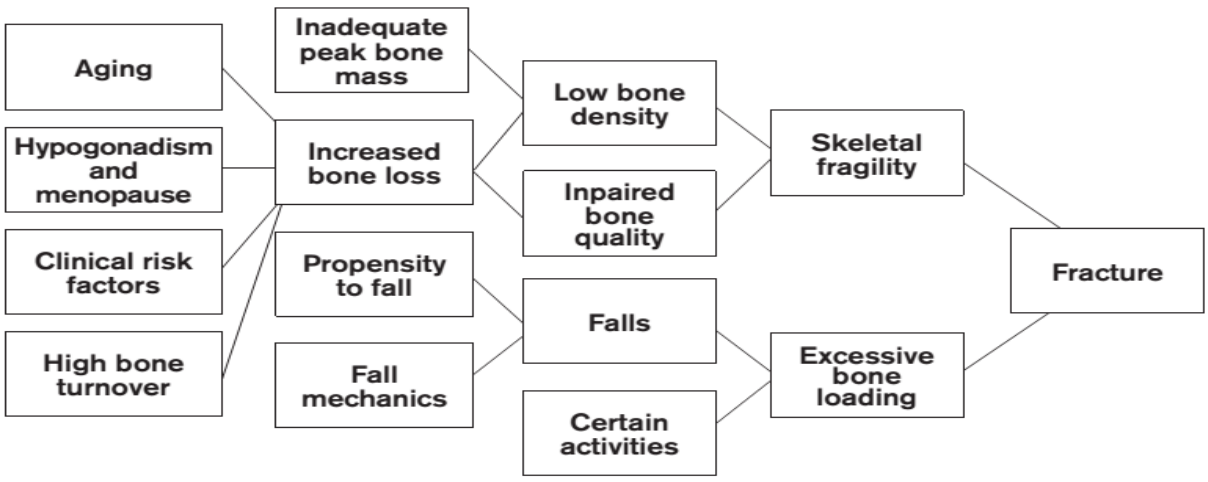


Figure 1.3: Pathogenesis of osteoporosis-related fractures (National Osteoporosis Foundation, 2010).

1.4 Risk factor of osteoporosis:

1.4.1 Age

Osteoporosis affects mostly older individuals. For unknown reasons, osteoclasts gradually begin to outperform osteoblasts. Thus, more bone is lost than rebuilt. In the elderly, osteoblasts are probably not as efficiently produced as in younger people. Bone turnover has either slowed down or come to a standstill. Hormone balance changes with age. Women produce much less estrogen after menopause. Men gradually produce less androgen with age. PTH concentrations are often slightly increased, probably to compensate for low vitamin D or low calcium concentrations, common in older people. The elderly are usually less efficient in synthesizing vitamin D. The kidney may become less efficient in converting vitamin D into its active form or the intestine may be less responsive to vitamin D. These disturbances can result in a vicious cycle less functional vitamin D results in less calcium uptake. This leads to low blood calcium, which in turn causes PTH to be released, which causes bone resorption. These processes may be a natural part of aging, but they may also be accelerated by other mechanisms. As people age, they often tend to change their lifestyle. Many become less mobile and eat less varied diets, which may ultimately lead to weakened bones (Heinz, 2000).

1.4.2 Estrogen deficiency

Postmenopausal women tend to be in negative calcium balance. The main reason for this is estrogen deficiency. Calcium requirements appear to rise with decreasing estrogen concentrations. Thus, postmenopausal women may need more than the usual amounts of calcium. Sex hormone deficiency increases bone resorption. Natural menopause or premature loss of ovarian function causes a sudden reduction of estrogen resulting in significant loss of both cortical (the predominant constituent of the long bones or the arms and legs) and cancellous bone (very porous, spongy bone which predominates in the vertebrae, ribs, hips, wrists and the interior of long bones), especially cancellous bone located in the spine. Bone loss is substantially accelerated for five to ten years after menopause. Thereafter, the rate of bone loss returns to that observed in normal aging. Estrogen replacement therapy can significantly slow down this accelerated bone loss if started early enough. Postmenopausal women may also have slightly reduced PTH blood concentrations, which also lead to less production of active vitamin D .Less vitamin D results in less calcium absorption in the intestine. Without estrogen, the bones are more

sensitive to PTH and more bone will be destroyed in spite of lower concentrations of PTH. This leads to calcium loss in the urine. Estrogen may also interfere with the formation of local bone destroying factors. Even before menopause, women gradually produce less estrogen and progesterone. Thus, bone can also be lost before menopause. Female athletes who exercise to the point where menstruation ceases (amenorrhea), as a result of less estrogen, also increase their risk for osteoporosis. More recent evidence suggests that other disturbances in the menstrual cycle (shortened luteal phase, cycles in which ovulation does not occur, or excess production of the hormone prolactin) can lead to bone loss even in relatively young women, often as severe as that observed in older women. The culprit is assumed to be progesterone deficiency (Heinz, 2000).

1.4.3 Diet

The extent to which diet influences bone loss is not known. However, an inadequate diet can lead to nutrient deficiencies. Insufficient calcium intake throughout life can contribute to osteoporosis. An intake of excess dietary protein may increase urinary calcium secretion by causing urine to be acidic. However, dietary phosphate reduces calcium excretion. Thus, foods high in protein and phosphate such as meat, fish and dairy products result in little or no increase in calcium excretion. Insufficient dietary protein is also detrimental because some protein is needed for calcium absorption. Protein is also necessary for bone production. Excess caffeine intake is associated with reduced calcium absorption or excess excretion. Moderate caffeine consumption is not considered to endanger calcium balance in women who consume sufficient calcium. Similarly, excess sodium may reduce absorption of calcium to some degree. Adequate calcium intake is necessary to achieve peak bone mass, and lifelong calcium deficiency is a recognized risk factor for osteoporosis. Older people may need more calcium to stay in calcium balance. However, sex hormones appear to play a more important role in maintaining a positive calcium balance than dietary calcium. Middle-aged women appear to consume less calcium than most other people. Older people, particularly those in extended care facilities, may not be receiving sufficient vitamin D through sunlight or through their diet. While severe vitamin D deficiency leads to osteomalacia, mild vitamin D deficiency may contribute to osteoporosis. When blood calcium concentrations are low due to mild deficiency of vitamin D, PTH is released to raise blood calcium concentrations. Mild vitamin D deficiency may lead to a modest rise in PTH, which results in increasing in bone resorption. Phosphate supplies in our food are usually more than sufficient. There is

some concern that we are consuming too much phosphate in our food. However, high dietary phosphate intake appears to help build bones rather than the reverse. People who consume high levels of aluminum antacids may be prone to phosphate deficiency, and thus to osteomalacia, which can contribute to osteoporosis. Malabsorption syndromes can also lead to insufficient calcium uptake. Deficiencies of other micronutrients such as vitamins A, C, and K and minerals, copper, boron, zinc, manganese, fluoride and magnesium may also negatively affect bone density. Their role in osteoporosis is currently being investigated (Heinz, 2000).

1.4.4 Alcohol

Chronic alcohol consumption decreases bone mass and strength, increases the risk of falling. Alcohol is directly toxic to bone cells. It decreases osteoblast proliferation and activity, and significantly lowers serum osteocalcin. Bone histology is usually characterized by a reduction in bone formation, but may also show signs of impaired mineralization if vitamin D insufficiency is present. Chronic alcohol consumption may result in hypogonadism, metabolic acidosis, malnutrition, liver disease and hypovitaminosis D, as well as pseudo-Cushing's syndrome with hypercortisolaemia. Alcohol use is often associated with lifestyle factors, like smoking or lack of exercise, known to adversely influence bone health.

1.4.5 Smoking

Smoking is a risk factor that is, in part, dependent on BMD. Smoking increases the metabolism of endogenous and exogenous estrogen to inactive derivatives and is also associated with early menopause and lower body weight. The decrease in fat mass reduces peripheral conversion of androgens to estrogen, decreases mechanical loading of bone and diminishes resistance to falls. Smoking also lowers the intestinal absorption of calcium and is often associated with alcohol use and a sedentary lifestyle (Houge *et. al.*, 2010).

1.4.6 Low body weight

Reduced body weight is a risk factor for osteoporosis. Thin and petite women are more susceptible than obese women. Weight increases the load on bones and thus increases bone density. Anorexics have reduced body weight and are also at higher risk. Anorexics may also be at risk because they are nutritionally deficient, often to the point of becoming amenorrheic. Obese women are less prone to osteoporosis, possibly because their bones

carry more weight or possibly because their fat cells convert the steroid hormone androgen into estrogen.

1.4.7 Lack of weight-bearing exercise

Immobilized limbs in casts lose bone, as do invalids and people who spend much time in bed. Astronauts lose bone mass during their travel into gravity-free space. Exercise increases the load on the skeleton and promotes greater bone density. Exercise may also affect hormone concentrations that favor bone strength. Similar to muscle tissue, disuse of bone tissue can lead to bone loss. Weight-bearing exercise such as tennis is more effective than swimming. Apparently, antigravity muscles must be involved to maximize the benefits of exercise. Exercise is most effective if calcium intake is adequate (Heinz, 2000).

1.4.8 Rheumatoid arthritis

Sufferers of rheumatoid arthritis (RA) have lower BMD and are at increased risk of fracture. RA is the only secondary cause of osteoporosis in the FRAX® algorithm that is considered a predictor of fracture independent of bone density. The degree of bone loss observed in RA is correlated with the severity of disease activity. Proinflammatory cytokines released into the circulation from the inflamed synovium are thought to cause the bone loss.

1.4.9 Early menopause

Premature menopause (before age 40 years) and early menopause (between ages 40 and 45 years) are associated with osteoporosis and a range of other health concerns. The earlier the menopause occurs, the lower the bone density will be later in life. Women who undergo oophorectomy (surgical removal of the ovaries) before age 45 years are at increased risk of developing osteoporosis (Dawson-Hughes *et. al.*, 2013).

1.4.10 Excessive leanness

A low body mass index (BMI) is a well-documented risk factor for fracture that is only partially independent of BMD. The effect of body weight appears to be contributed to by both fat and lean mass and is probably mediated by a number of mechanisms, including skeletal loading, secretion of hormones from pancreatic beta cells (e.g. insulin, amylin), secretion of bone-active hormones from adipocytes, as well as hormones related to nutrition. Excessive leanness was an important risk factor, particularly for hip fracture, in both men and women.

1.4.11 Hypogonadal status

Estrogen deficiency is associated with a decreased BMD, as well as micro architectural deterioration of bone. A premature menopause/ovarian failure and other causes of hypogonadism are recognized risk factors for osteoporotic fractures.Hypogonadism resulting from athletic amenorrhoea, delayed puberty or the prolonged use of the depot progestin contraception, which is so popular in this country, is also a risk factor for osteoporosis in younger individuals. Hypogonadism, often asymptomatic, is an important risk factor for osteoporosis in men (Houge *et. al.,* 2010).

1.4.12 Family history of osteoporosis and fracture

Genetics have considerable influence upon the peak bone mass attained by an individual and, in the case of postmenopausal women, the rate of bone loss in the early years after menopause. Heritability is evident as long as bone metabolism is primarily determined by physiological factors, such as hormonal levels and the activity of bone forming osteoblast cells. With advancing age, the impact of co morbid conditions, immobility, nutrition and absorption issues, and neurodegenerative disorders becomes dominant. A parental history of fracture is associated with an increased risk of fracture that is independent of bone mineral density.

1.4.13 Previous fragility fracture

Osteoporosis is a chronic disease which is manifested in the form of fragility fractures defined as fractures which occur as a result of low trauma, and usually result from a fall from standing height. Fragility fractures are very common. 1 in 3 postmenopausal women will suffer at least one during their remaining lifetime. Several studies have evaluated future fracture risk associated with suffering fractures at various skeletal sites (Dawson-Hughes *et. al.,* 2013).

1.4.14 Gender and ethnicity

Osteoporosis occurs more frequently in women than in men. This difference is partly due to a greater bone size and thus, higher areal BMD in men, but also involves a less abrupt decline in gonadal function with ageing (with its accompanying micro architectural deterioration) larger muscle mass and shorter life expectancy. The incidences of osteoporosis and fractures vary markedly between different races and populations. The significantly lower incidence of osteoporosis in black, compared with white.

1.4.15 Fall

More than 90% of hip fractures occur after a fall. The pathogenesis of falls is complex, and various extrinsic (e.g. environment) and intrinsic factors are involved (Houge *et. al.*, 2010).

Table 1.1: That Increase Risk of Falling and Fracture

Environmental risk factors	
Lack of assistive devices in bathrooms	Obstacles in the walking path
Loose throw rugs	Slippery conditions
Low level lighting	
Medical risk factors	
Age	Medications causing sedation (narcotic analgesics, anticonvulsants, psychotropics
Anxiety and agitation	Orthostatic hypotension
Arrhythmias	Poor vision
Dehydration	Previous falls or fear of falling
Depression	Reduced problem solving or mental acuity and diminished cognitive skills
Vitamin D insufficiency	Urgent urinary incontinence
Malnutrition	
Neurological and musculoskeletal risk factors	
Kyphosis	Reduced proprioception
Poor balance	Weak muscles/sarcopenia
Impaired transfer and mobility	Deconditioning

(Dawson-Hughes *et. al.*, 2014)

Low bone mass is not the only contributor to risk for fractures. The general mental and physiological state of the individual is also important since neurological and

cardiovascular disorders can increase the likelihood of accidents and resulting fractures. Similarly, certain medications, such as antihistamines and tranquilizers, reduce coordination and alertness (Heinz, 2000).

1.5 Drug induced osteoporosis

1.5.1 Bone Mineral Density Loss and Fractures Associated with Oral Glucocorticoid Use Long-term administration of GCs induces a rapid loss of bone mass of between 5 and 15% annually. Histomorphometric as well as densitometric studies have shown that GC-induced bone loss is most pronounced during the first 3–12 months of therapy, but continues as long as treatment is maintained. The demineralization is more pronounced in trabecular than in cortical bone compartments and not all regions of the skeleton are affected alike. In a study, after 20 weeks of treatment with prednisone (mean daily dose of 7.5 mg) the average loss of bone density in the lumbar spine was 8% in heart transplant patients. In a longitudinal histomorphometric study of the treatment with prednisone (10–25 mg) over 5–7 months resulted in a reduction of 27% of the trabecular bone volume in the crista iliaca. Not all patients treated with GCs are similarly affected. Differences are possibly genetically determined and could be related to variants of the steroid receptor and individual pharmacokinetic differences.

The response of bone formation markers to GCs can be predicted by the urinary measure of this enzyme, a recent finding which may contribute to the identification of individuals at highest risk of developing GIOP. Total bone mineral loss correlates directly with the cumulatively given steroid dose. Although 7.5 mg of prednisone equivalent a day was considered to be the threshold dose for skeletal side effects, recently published data have shown that lower doses and even inhaled GCs may induce skeletal side effects. In children under low-dose inhaled steroids even impaired growth has been demonstrated. In adults under high-dose inhaled GCs, a dose dependent reduction of bone density has been observed and the cumulative dose of inhaled corticosteroids in adult asthmatics was shown to correlate negatively with bone density (Albrecht *et. al.,* 2006).

1.5.2 Bone Mineral Density Loss Associated with Inhaled Glucocorticoids

Inhaled high-potency glucocorticoids used to treat asthma and chronic obstructive airways disease have been shown to cause bone loss when used over an extended time period. A cross-sectional study showed that cumulative exposure to 5,000 mg of beclomethasone (2,000 mcg/day for seven years) was associated with enough loss of bone

mineral density to double fracture risk. One three-year longitudinal study of inhaled triamcinolone therapy in chronic obstructive pulmonary disease showed significant bone loss compared to those treated with a placebo inhaler. No studies documenting or suggesting increased rates of fracture attributable to inhaled or nasal glucocorticoids have been done (Florence *et. al.*, 2013).

Mechanisms of Bone Loss:

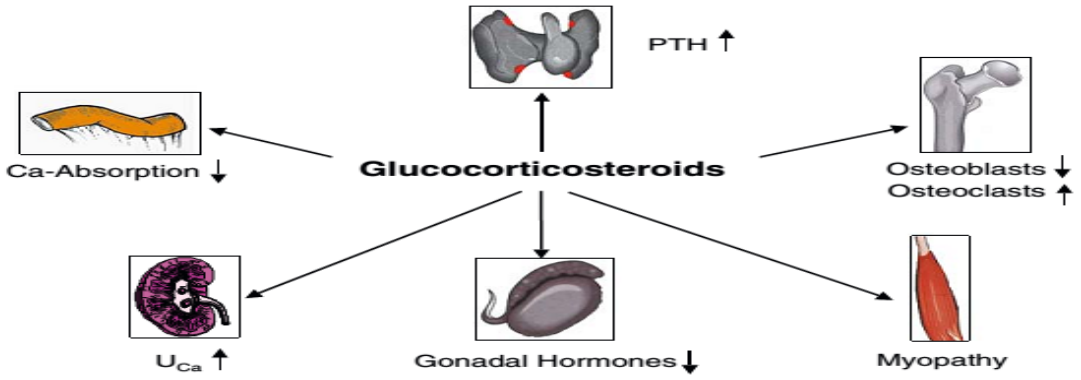


Figure 1.4: Pathophysiology of glucocorticosteroid-induced osteoporosis.

Glucocorticosteroids exert direct deleterious effects on bone leading to decreased formation and increased resorption. In addition, bone loss may be indirectly promoted by reduced gonadal hormone levels and by myopathy as well as by decreased calcium absorption from the gut and increased renal calcium excretion. However, secondary hyperparathyroidism is an inconstant finding (Albrecht *et. al.*, 2006).

1.5.3 Hormonal Therapies

Estrogen and testosterone are important regulators of the bone remodeling process, so it is not surprising that osteoporosis is associated with a decline in hormonal concentrations after menopause. Similarly, testosterone deficiency is the most common cause of osteoporosis in men, although the role of testosterone is not as straight forward as once thought. Drugs inhibiting secretion or altering the metabolism of sex hormones have the potential to induce osteoporosis. These drugs include the aromatase inhibitors (AIs) and gonadotropin releasing hormone (GnRH) agonists used in the treatment of breast and prostate cancers, as well as the contraceptive depot medroxyprogesterone acetate (DMPA). Thyroid hormones also affect bone metabolism, with increased bone resorption observed in hyperthyroidism. The bone effects result from both endogenous and exogenous causes of hyperthyroidism.

1.5.4 Aromatase Inhibitors

The use of AIs as adjuvant treatment for breast cancer has been shown to improve disease free survival and decrease the occurrence of metastatic disease in post- menopausal women with estrogen receptor–positive disease. However, the pharmacologic activity of these agents also affects BMD and fracture risk. After menopause, estrogen is produced in the peripheral tissues by the conversion of adrenal androgens to estrogen. The AIs inhibit the aromatase enzyme, responsible for this conversion, and result in decreased estrogen concentrations. Because many postmenopausal women have several underlying risk factors for osteoporosis, further estrogen loss from treatment with AIs might be expected to cause bone loss and increased fracture risk (Susann *et. al.,* 2010).

1.5.5 GnRH Agonists

These agents are sometimes used in combination with AIs or tamoxifen. The GnRH agonists down-regulate the secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH), resulting in suppression of ovarian function and a corresponding decline in estrogen production. Suppression of ovarian function by GnRH agonists is a treatment strategy also employed in the management of endometriosis. Regardless of the indication for ovarian suppression, bone metabolism is likely to be affected and result in bone loss.

1.5.6 Depot Medroxyprogesterone Acetate

Current drug use patterns indicate that DMPA is the contraceptive of choice for more than 2 million women, including some 400,000 adolescents. This agent prevents pregnancy by inhibiting LH and FSH, causing an ovulation and a corresponding decrease in estrogen production. The potential loss of bone owing to DMPA-related estrogen deprivation is of particular concern for teenage girls and women younger than 30, a time when BMD normally increases. Prolonged use could potentially decrease the peak bone mass and increase the risk of fragility fractures in 20–30 years.

1.5.7 Thyroid Replacement Therapy

Hyperthyroidism and thyroid replacement therapy are both associated with bone loss. Thyroid-stimulating hormone (TSH) receptors have been identified on osteoclastic and osteoblastic precursor cells with accelerated bone resorption occurring during hyperthyroid states when TSH concentrations are suppressed. Over supplementation of thyroid replacement hormone causes an exogenous hyperthyroidism, suppressing TSH concentration, with direct effects on bone remodeling that result in bone loss (Susann *et. al.,* 2010).

1.5.8 Central Nervous System Agents

Several classes of central nervous system agents have been associated with an increased risk of fracture. These include anticonvulsants, antidepressants, and antipsychotics.

1.5.8.1 Anticonvulsants

There are several mechanisms by which anticonvulsants might affect bone metabolism. Initially, it was thought that the anticonvulsants that are potent inducers of cytochrome P450 (CYP) (i.e., carbamazepine, phenobarbital, and phenytoin) might increase the metabolism of vitamin D, leading to a reduction in calcium absorption, subsequent elevation in parathyroid hormone, and increased bone turnover. It has also been suggested that CYP induction leads to lower circulating concentrations of estrogen and testosterone, resulting in bone loss. However, many anticonvulsants that do not affect CYP metabolism are associated with bone loss, indicating that other mechanisms are likely responsible. However, these other mechanisms are poorly understood. Early data in animals suggested that anticonvulsants directly inhibit intestinal calcium absorption. More recently, in vitro studies suggested that anticonvulsants directly inhibit osteoblasts, resulting in decreased bone formation.

1.5.8.2 Antidepressants

The serotoninergic system appears to play an important role in bone physiology, which has implications for the effect of selective serotonin reuptake inhibitors (SSRIs) and serotoninergic tricyclic antidepressants (TCAs) on bone health. Specifically, serotonin appears to modulate skeletal response to parathyroid hormone, possibly through receptors and transporters found on osteoblasts and osteocytes. Several studies have shown bone loss among SSRI users, suggesting a clinical effect on bone metabolism.The association between antidepressant use and fractures is well established; however, recent evidence suggests that depression itself is associated with decreased BMD and increased fracture risk. In addition to drugs, behavioral and biologic factors can interact in an individual to negatively affect bone health.

1.5.8.3 Antipsychotic Agents

Similar to antidepressants, a well-established relationship exists between antipsychotic agents and falls and fracture. The postulated biologic mechanism by which antipsychotic agents affect bone physiology is related to their effect on prolactin concentrations. Conventional antipsychotics, in particular, are known to cause a rise in prolactin

concentration; this in turn lowers estrogen and testosterone concentrations, potentially leading to bone loss. As with depression, other mental illnesses might also represent an independent risk factor for osteoporosis. Schizophrenia and other psychotic disorders were associated with higher rates of osteoporosis and fragility fractures (Susann *et. al.*, 2010).

1.5.9 Gastric Acid–Reducing Agents

1.5.9.1 Proton Pump Inhibitors

Interest in the association between proton pump inhibitor (PPI) use and hip fracture arose from studies that showed decreased calcium absorption in patients taking PPIs. Less potent gastric acid agents, the H2-receptor antagonists (H2RAs), were not observed to have the same effect. However, the studies varied in method and may not have used correct testing to document these potential drug-drug or drug-food interactions. Other data suggest that PPIs have a direct effect on bone metabolism. Proton pumps have been identified on osteoclasts and appear to be used during the excretion of hydrogen ions for bone resorption. Inhibition of these proton pumps may interfere with the resorption process, resulting in decreased bone density with time.

Proton pump inhibitors appear to affect BMD in men; a small but significant difference in hip BMD was observed among male PPI users compared with non-users. However, similar observations were not found in women, suggesting that men are at somewhat increased risk compared with women.

1.5.10 H2-Receptor Antagonists

In contrast to PPIs, data on H2RA use were equivocal; one study found these agents to have a protective effect on BMD, whereas another showed a significant association between hip fracture and H2RA use, although this association was not as strong as that observed with PPIs. Although epidemiologic data alone are insufficient to prove a causal relationship between gastric acid–reducing agents (particularly PPIs) and an increase in osteoporotic fracture, gastric acid reducers may contribute to overall risk when assessing bone health in patients using these agents.

1.5.11 Thiazolidinediones

The risk of fracture appears to be increased in individuals with type 2 diabetes, with some suggestion that good glucose control reduces the association between the disease and fracture risk. However, there is an apparent increased risk of fracture associated with the

thiazolidinediones rosiglitazone and pioglitazone; this was first identified in randomized controlled trials examining the efficacy of these agents in the management of type 2 diabetes.

However, when stratified by sex, the ARI was significantly increased for women at 2.8% compared with no difference in risk for men. In fact, men using thiazolidinedione experienced fewer fractures than the control group of either metformin or sulfonylurea users. Most fractures were observed in the periphery rather than the hip or spine, but this may simply be a reflection of the younger patient sample in the randomized controlled trials (average age 50–60 years) (Susann *et. al.*, 2010).

1.6 Diagnosis of osteoporosis

Symptoms seldom announce the presence of osteoporosis before the first fractures occur. By this time bone loss has already reached a significant stage. The earliest symptom is pain, typically back pain following a vertebral fracture. Some fractures may be so minute that they are not noticed immediately. However, they can add up and lead to bone weakening. More severe fractures may cause intense pain. It is difficult to detect osteoporosis in its early stages. Bone mass measurement techniques have not yet reached a stage where they can be applied for mass screening, although they are rapidly increasing in sophistication. Currently available tests submit the patient to low-level radiation, are time-consuming and can be costly. These procedures measure the current density of the bones, but one measurement is usually not sufficient to accurately determine whether the patient is losing bone rapidly. The measurements need to be performed at intervals of one to three years to determine a trend in changing bone mass. At present, these techniques may be useful in supporting the diagnosis in persons considered to be at high risk, to follow the success of treatment in patients and to test new experimental treatment in clinical studies (Heinz, 2000).

1.6.1 Diagnostic techniques

A variety of techniques are available to measure bone mass, to detect osteoporotic fractures, and/or to assess bone strength and fracture risk. These include:

- Conventional skeletal radiology.
- Dual energy X-ray absorptiometry (DXA): vertebral fracture assessment (VFA) and hip structure analysis (HSA).

- Quantitative computed tomography (QCT) and high resolution CT (HRCT).
- Quantitative ultrasound (QUS).
- Other specialised techniques to assess bone density and/or structure.

1.6.2 Conventional skeletal radiology

Conventional radiography is employed to detect the presence of vertebral and appendicular fractures. Conventional radiology of the spine, proximal hip and appendicular skeleton have also been used to detect low bone mass, but this is notoriously unreliable, since 30-40% of skeletal mass must be lost before osteopenia can be detected on routine radiographs. Moreover, some 25% of patients with apparent radiographic osteopenia (technical faults) or vertebral fracture (juvenile epiphysitis, trauma or even normal variations in vertebral body shape) have a normal BMD and may not be at increased risk of subsequent fractures (Houge *et. al.*, 2010).

1.6.3 Dual energy X-ray absorptiometry

1.6.3.1 Use of DXA to measure BMD

DXA measures the attenuation of X-rays of two different photon energies that are passed through the body, allowing for the measurement of bone and soft tissue mass. The machine computes the bone mineral content (BMC in g) and areal bone mineral density for a given region of interest (ROI). DXA is capable of measuring the bone mass of the lumbar vertebrae, various hip areas and the distal radius, as well as the total body, very accurately (4-8% error), precisely (1-3%) and safely, with negligible radiation exposure. The WHO diagnostic criteria are based on the use of central DXA, and numerous studies have underscored its value in assessing fracture risk. Its ease of use and short measurement times are further advantages.

1.6.3.2 Use of DXA to assess bone structure (HSA)

HSA software is now provided by several DXA manufacturers, and can be used to assess hip geometry and mechanical properties. This modality has yielded novel information on how fracture risk is affected by exercise and various bone-active drugs (Houge *et. al.*, 2010).

1.6.4 Quantitative computed tomography

Use of QCT to measure BMD

QCT measures true volumetric density (g/cm3), rather than areal density (g/cm^2), of the spine, which is independent of bone size. It can also discriminate between the

metabolically more active trabecular and less active cortical bone of the spine, which suggests that this technique may be more accurate in assessing early bone loss.

1.6.5 Quantitative ultrasound

A number of ultrasound variables have been employed to assess bone density (± structure) and include (i) velocity (e.g. speed of sound, SOS), (ii) attenuation (e.g. broadband ultrasound attenuation, BUA), and (iii) reflection (e.g. ultrasound critical angle reflectometry, UCR). QUS can be performed at the heel, tibia, patella and other peripheral skeletal sites. The ISCD only recommends measurements at the heel.

These variables, either alone or in combination, have been shown to predict fracture risk in both cross-sectional and longitudinal studies. Ultrasound is less expensive than densitometry, measuring time is short, and the device is portable and uses no radiation source.

1.6.6 Other specialized techniques to assess bone structure

A number of new techniques, including three-dimensional volumetric quantitative CT (vQCT), micro-CT (μCT), high resolution magnetic resonance imaging (HRMRI), micro-MRI (μMRI), and QCT-based finite element analysis (FEA), are currently being tested to assess structural bone properties, but are not yet available for clinical use (Houge *et. al.*, 2010).

1.7 Prevention of osteoporosis

1.7.1Exercise

Studies have shown that individuals with a sedentary lifestyle are more likely to have a hip fracture than those who are more active. For example, women who sit for more than nine hours a day are 43% more likely to have a hip fracture than those who sit for less than six hours a day. Exercise has been shown in randomized controlled trials to lead to small but statistically significant increases in bone mineral density (BMD) of the order of 1-2%. The main benefit of exercise appears to be the associated reduction in risk of falling (Dawson-Hughes et. al., 2013).

1.7.2 Exercises to build strong bones

1.7.2.1 For healthy postmenopausal women who do not have osteoporosis

Besides maintaining bone strength, the main goal of exercise therapy in postmenopausal women is to increase muscle mass in order to improve parameters of muscle function such as balance and strength, which are both important risk factors for falls and independent of bone density risk factors for fractures. Overall, most people should aim to exercise for 30 to 40 minutes three to four times each week, with some weight-bearing and resistance exercises in the program.

Examples of weight-bearing exercises include:

- Dancing
- High-impact aerobics
- Hiking
- Jogging/running
- Jumping rope
- Stair climbing
- Tennis

Examples of muscle-strengthening exercises include:

- Lifting weights
- Using elastic exercise bands
- Using weight machines
- Lifting your own body weight
- Standing and rising on your toes

1.7.3 Protein

Body composition changes after middle age, including increases in fat mass and decreases in lean mass (i.e. muscle). Dietary protein is responsible for bone loss in older people. Both lower protein intake and lower animal protein intake were associated with loss of BMD at the hip and spine. Another study highlighted the need for individuals to achieve an adequate calcium intake in order for the beneficial effect of protein on BMD to be realized.Lower protein intake is associated with loss of bone mineral density at the hip and spine. Diets rich in fruits and vegetables have been shown to be associated with higher bone mineral density.

1.7.4 Acid-base balance of the diet

The impact of acid-base balance on bone is a comparatively new area of research. Investigation of the effect of aging on blood acid-base composition suggests that reduced renal function in older people diminishes the kidney's ability to excrete hydrogen ions in response to changes in blood pH. Accordingly, healthy adults manifest a low-grade diet-dependent metabolic acidosis which increases with age. Diet can contribute to acidosis when alkali-producing fruits and vegetables are consumed in insufficient amounts to balance the intake of acid producing foods such as cereal grains and protein. The organic acids in fruits and vegetables are metabolized to alkaline bicarbonate; cereal grains contribute phytic and other acids and protein adds acid in proportion to its content of sulphur containing amino acids (which are metabolized to sulphuric acid). An acidic environment has negative effects on preservation of bone in that it can impair bone forming cells, activate bone resorption, as well as exert a direct chemical effect on bone (Dawson-Hughes *et. al.,* 2013).

1.7.5 Maintaining a healthy weight

Leanness defined as a body mass index (BMI) <20 kg/m2 regardless of age, sex and weight loss, is associated with greater bone loss and increased risk of fracture. People with a BMI of 20 kg/m2 have a two-fold increased risk of fracture compared to people with a BMI of 25 kg/m2. Whilst anorexia is primarily of concern in younger women, the associated malnutrition, thinness and accompanying loss of oestrogen is devastating to bone health. The elderly are particularly vulnerable to malnutrition and it is important that seniors, or their caregivers, ensure sufficient caloric intake. As they age, individuals may be less capable of making the effort to prepare balanced meals, have less appetite, or suffer from chronic diseases and use medications that may impair appetite

1.7.6Alcohol

Alcohol taken in moderation up to two glasses (2 x 120 ml) of wine per day - does not negatively impact on bone health. A Finnish study reported that mild to moderate alcohol intake was actually associated with greater bone mass amongst postmenopausal women. A recent study suggests that the inhibitory effect of alcohol on bone turnover attenuates excessive bone turnover associated with menopause. However, long-term heavy alcohol use has been shown to increase fracture risk in women and men. The mechanisms by which alcohol may adversely affect fracture risk include:

- Alcohol has direct effects on osteoblasts (bone-forming cells)
- Alcohol increases the endogenous secretion of calcitonin, a hormone which suppresses resorption of bone by inhibiting the activity of osteoclasts. Calcitonin also inhibits reabsorption of calcium and phosphorus in the kidney, leading to increased rates of their loss in urine.
- Heavy drinkers may have poor nutrition with respect to calcium, vitamin D, or protein.
- Alcohol increases the risk of falls or interferes with the protective response to injury (Dawson-Hughes *et. al.,* 2013)

1.7.7 Caffeine

Patients should be advised to limit their caffeine intake to less than 1 to 2 servings (8 to 12 ounces in each serving) of caffeinated drinks per day. Several observational studies have shown an association between consumption of caffeinated beverages and fractures. Caffeine intake leads to a slight decrease in intestinal calcium absorption and an increase in urinary calcium excretion, suggesting that a moderate intake of caffeine would not be harmful to bone health. The most important effect of caffeinated beverages is that, by replacing milk in the diet, they contribute to overall inadequate calcium intake in the United States

1.7.8 Smoking

Cigarette smoking is a risk factor that has been validated by multiple studies to increase osteoporotic fracture risk and thus should be avoided. The exact mechanism is unclear but may be related to increased metabolism of endogenous estrogen or direct effects of cadmium on bone metabolism. No prospective studies have been done to determine whether smoking cessation reduces fracture risk, but a meta-analysis showed a higher risk of fractures in current smokers than in previous smokers. Smokers should be advised on smoking cessation.

1.7.9 Prevention of fall

Falls is the precipitating cause of the majority of osteoporotic fractures, and an effective osteoporosis treatment regimen must include a program for fall prevention. All patients should be counseled on fall prevention. Some measures that can be taken to avoid falls at home are outlined below. Particularly predisposed are persons who are older, are frail,

have had a stroke, or are taking medications that decrease mental alertness. Although several interventions have been shown to reduce the risk of falling, none has been shown to reduce the risk of fractures, although it is logical that they would. Hip protectors do not reduce the risk of falling. Intuitively, hip protectors should reduce the risk of fracture. Positive results have been seen in some trials, but not in all, and compliance is poor. Hip protectors may be considered for patients who have sustained a prior hip fracture, for slender or frail patients who have fallen in the past, and for patients who have major risk factors for falling because of postural hypotension or difficulty with balance, whether they have osteoporosis or not (Nelson *et. al.,* 2010).

1.7.10 Adequate intake of calcium and vitamin D

Providing adequate daily calcium and vitamin D is a safe and inexpensive way to help reduce fracture risk. Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of fracture. Now briefly review the effects of calcium/vitamin D on (i) peak bone mass attainment, (ii) age-related bone loss, (iii) fracture risk.

1.7.10.1 Peak bone mass attainment

Retrospective epidemiological studies of calcium nutrition in populations aiming to explain differences in the prevalence of osteoporosis and fracture, have generally produced conflicting results, which is not surprising, given the fact that calcium intake is difficult to assess. Nonetheless, observational studies have suggested that the largely genetically determined peak bone mass is augmented by a high calcium intake. calcium supplementation increases the gain in bone mass, although the magnitude of the effect appears to vary depending on dose, baseline calcium intake, skeletal sites examined, pubertal maturation and genetic factors, including vitamin D receptor polymorphism. Calcium supplementation resulted in a small, but significant, increase in total body bone mineral content.

1.7.10.2 Age-related bone loss

Calcium deficiency has a more pronounced effect on age-related bone loss and intervention later in life appears to be more beneficial. Calcium slowed or stopped bone loss. Supplemented calcium significantly reduced both trabecular and cortical bone loss in older women but, in women less than 5 years postmenopausal, it had no effect on trabecular bone loss. The beneficial effect of calcium supplementation was largely

confined to subjects with a low dietary calcium intake (< 400 mg per day). Employing larger doses of supplemented calcium showed that bone loss could be arrested, irrespective of dietary intake.

Severe prolonged vitamin D deficiency induces osteomalacia, but less marked deficiency causes secondary hyperparathyroidism, an increase in bone turnover and osteoporosis. Vitamin D is obtained from two sources: dietary intake and cutaneous production. The ability of the intestine to absorb vitamin D decreases with as much as 40% with age. Exposure to sunlight, as well as the synthetic capacity of the skin, also decreases with age.

1.7.10.3 Fracture risk

Calcium and vitamin D supplementation significantly reduced the risk of non-vertebral or hip fracture. Supplementation with 1 g of calcium, plus vitamin D 800 IU per day, was associated with a 20–25% reduction in hip fracture. A number of recent publications have, however, challenged the anti-fracture efficacy of calcium and vitamin D. Many of these studies did not target individuals at high fracture risk, often a low dose of vitamin D (≤ 400 IU per day) was administered and, frequently, compliance was poor (Houge *et. al.*, 2010).

Table 1.2: Recommended daily calcium intake for several countries

Country	Age range	Calcium intake(mg)	Organization
Australia	51-70 years	1300	National Health and Medical Research Council
	> 70 years	1300	
Canada	≥ 50 years	1200	Osteoporosis Canada
Korea	≥50 years	700	Korean Nutrition Society
UK	≥50 years	700	Department of Health
Country	Age range	Calcium intake(mg)	Organization
USA	51-70 years	1200	Institute of Medicine
	≥71 years	1200	
WHO/FAO	Postmenopausal women	1300	WHO/FAO 2002

(Dawson-Hughes *et. al.*, 2013)

1.7.11 Hormone replacement therapy

Estrogen deficiency is the most frequent risk factor for osteoporosis. Although randomized trials provide strong evidence that bone loss can effectively be prevented even with rather small doses of hormone replacement therapy (HRT) and that fracture risk can be reduced with conventional doses, even in postmenopausal women who do not suffer from osteoporosis, the consensus has changed now after several studies. HRT is no longer recommended as a first-line therapy for osteoporosis. Because prolonged use of HRT especially in elderly women pertains an increased risk of breast cancer, thromboembolic disease, and cerebrovascular accidents, confirming that the presence of a history of one of these affections should be considered as an absolute contraindication to HRT prescription and that the presence of important risk factors of breast cancer, thromboembolic disease, and cerebrovascular accidents should be viewed as relative contraindications (Body *et. al.,* 2010).

1.7.12 Avoid bone-toxic drugs

A number of drugs, other than alcohol and smoking, predispose to fracture, either by reducing bone strength or by predisposing to a fall. That drug like the anticonvulsants which promote the catabolism of 250HD may cause not only osteoporosis but also osteomelacia (Houge *et. al.,* 2010).

1.8 Treatment of osteoporosis

1.8.1 Goals of Treatment

The therapeutic goals in patients with osteoporosis are as follows:

• To prevent fractures by improving bone strength and reducing the risk of falling and injury

• To relieve symptoms of fractures and skeletal deformity

• To maximize physical function

Achieving these goals depends on commitment to therapy from the patient and the health-care provider and the potential for the chosen therapy to yield results(Nelson *et. al.,* 2010)

1.8.2 Calcium and vitamin D

Calcium absorption decreases with advancing age and also the renal excretion of calcium increases. Intra and extra cellular levels of calcium are tightly controlled.Since bone is a major reservoir for calcium, bone mass may be sacrificed to maintain the necessary intra

and extra cellular concentrations. Calcium (as calcium carbonate for example) is best given with food, because the acid load of the meal provides better absorption. Recommended Dietary Allowances for calcium summarizes in Table 1.3.

Table 1.3: Recommended Dietary Allowances for calcium

Life-stage Group	Estimated Adequate daily calcium intake
Infant (birth to 6 month) and (6 to 12 month)	210 mg/d and 270 mg/d
Young children (1 to 3 years)	500 mg/d
Older children (4 to 8 years)	800 mg/d
Adolescents (9 to 18 years)	1300 mg/d
Men and women (19 to 50 years)	100mg/d
Men and women (51 and older)	1200mg/d

(Irene Hamrick *et. al.*, 2015)

If more than 500 mg/d is used, the dosage should be split to increase absorption.

As to vitamin D, cholecalciferol is preferred to ergocalciferol. The active metabolite 25 cholecalciferol (calcidiol) is available as is also the most active metabolitecalcitriol (1,25-dihydroxycholecalciferol). They are prescribed under certain conditions (in cases when the metabolism of cholecalciferol is impaired in liver and/or kidneys. They are not routinely used for the treatment of osteoporosis. The recommended dose of vitamin D is 400 to 800 IU/d (Jaroslav 2007).

Although vitamin D is stored in the adipose tissue, blood levels drop below baseline in 2 weeks after a 50,000 IU dose of vitamin D2 and remain above baseline after 30 days of a dose of vitamin D3. Infrequent high dosing showed increased fractures and falls in a study of elderly given 500,000 IU of vitamin D3 once a year. The IOM recommends 600 IU daily for 70-year olds and 800 IU for > 70-year olds with 4000 IU upper level intake for adults. The National Osteoporosis Foundation of the USA and the American Geriatrics Society recommend 1000 IU daily. Replacement of vitamin D deficiency is usually done with weekly 50,000 IU for 3 months, but a small study of 163 women over age 57 showed that 800 IU daily increased serum levels to 50 mmol/l in 97.5 % (Irene *et al.*, 2015).

1.8.3Bisphosphonates

Bisphosphonates are structural analogs of pyrophosphates. They have a pharmacologic activity specific for bone, due to the strong chemical affinity of bisphosphonates for hydroxyapatite, a major inorganic component of bone. The general chemical structure of bisphosphonates is shown in Figure 6. Substitution of different side chains for hydrogen at locations R l and R2 changes the in vitro potency and side effect profile of the compound. Alkyl side chains (eg, etidronate) characterize first-generation bisphosphonates. Second-generation bisphosphonates include aminobisphosphonates with an amino-terminal group (eg, alendronate and pamidronate). Third-generation bisphosphonates have cyclic side chains (eg, risedronate).

Table 1.4: Generations of bisphosphonates

Chemical modification	Generic Name	Antiresorptive potency
First generation		
Short alkyl	etidronate	1
Halide side chain	Clodronate	10
Second generation		
Amino-terminal	Tiludronate	10
	Pamidronate	100
	Aledronate	100-1000
Third generation		
Cyclic side chain	Risedronate	1000-10000
	Ibandronate	1000-10000
	Zoledronate	10000+

(Jaroslav, 2007)

The antiresorptive properties of bisphosphonates increase approximately ten-fold between drug generations. Bisphosphonates reduce the rate of bone turnover and are potent inhibitors of osteoclasts. They reduce the rate at which new bone remodelling units are formed; reduce the depth of resorption; and produce a positive bone balance at individual remodelling units, resulting in an increase in bone mass over time. As a pharmacologic class, bisphosphonates are poorly absorbed, and thus must be taken on an empty stomach. Alendronate, risedronate and ibandronate are mostextensively used for the treatment of

osteoporosis. Bisphosphonates increase bone mineral density and decrease fracture incidence in postmenopausal women with osteoporosis.

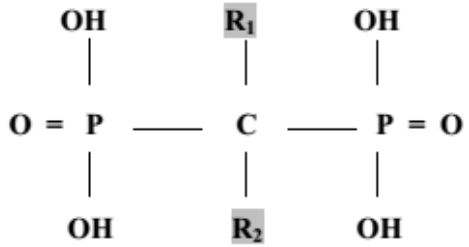


Figure 1.5: General structure of bisphosphonates Side chains can be modified to alter the potency and the side-effect profile (Jaroslav, 2007)

1.8.4Alendronate

Alendronate, taken orally, has been approved for the prevention of osteoporosis at a daily dose of 5 mg and for the treatment of osteoporosis at a daily dose of 10 mg or a weekly dose of 70 mg. Alendronate reduces the risk of vertebral fractures in postmenopausal woman with and without previous vertebral fractures. Alendronate use reduces bone resorption and improves BMD.

1.8.5 Risedronate

Risedronate maintains bone mass and preserves bone microarchitecture and it reduces the risk of vertebral and nonvertebral fractures. In the Vertebral Efficacy with Risedronate Therapy trials 5 mg of risedronate daily reduced the incidence of new fractures within 6 months of the start of therapy and significantly lowered the risk of new vertebral fractures within 1 year. The reduction in risk was maintained for up to 7 years of treatment. Elderly women at high risk, risedronate reduced the risk of nonvertebral fractures after 3 years of treatment and also reduced the risk of hip fractures. Studies involving early-postmenopausal women demonstrated that 5 mg of risedronate daily increased the BMD at the lumbar spine by more than 5% during 2 years of treatment as compared with both baseline and placebo (Aliya *et. al.,* 2014).

1.8.6 Calcitonin

Calcitonin is an endogenous peptide that binds to osteoclasts and impedes bone resorption. Calcitonin is present in many different species, but salmon calcitonin is used therapeutically in humans because it binds strongly to human calcitonin receptors.

Calcitonin is available to be used via intranasal, subcutaneous, and intramuscular routes. Intranasal calcitonin has the fewest side effects and is used most of the time. Calcitonin is approved for treatment of osteoporosis in women who are at least 5 years beyond menopause. Its antiresorptive effects are less potent than other medications, which is why it is used as a second-line treatment. It is very effective for treating bone pain after an osteoporotic vertebral compression fracture.

1.8.7 Selective estrogen reuptake modulators

Selective estrogen reuptake modulators (SERMs) are compounds that lack the steroid structure of estrogen, but bind to estrogen receptors throughout the body with varying agonist and antagonist effects. Raloxifene is Food and Drug Administration (FDA) approved for prevention and treatment of osteoporosis in the USA. Although tamoxifen was the first SERM developed, its agonist activity on the endometrium which may lead to endometrial hyperplasia and cancer limits its usefulness in osteoporosis prevention.

1.8.8 Recombinant human parathyroid hormone analog

PTH regulates calcium and phosphate in the kidneys as well as bone metabolism and facilitates calcium resorption from bone. However, PTH given intermittently stimulates osteoblasts, the bone building cells, whereas continuous administration stimulates osteoclasts. Teriparatide is recombinant human PTH analog. Teriparatide increases trabecular and cortical bone turn over by increasing osteoblast activity over osteoclast activity. Teriparatide is indicated by the FDA for treatment of postmenopausal osteoporosis, glucocorticoid induced osteoporosis in both men and women, and bone loss in men with primary or hypogonadal osteoporosis at high risk for fracture. Avoid using PTH in patients with bone metastases, history of skeletal malignancies, or hypercalcemic disorders. Teriparatide shows benefit over placebo in reduction of fracture and increase in BMD at all sites.

1.8.9 Antibody against receptor activator of nuclear factor kappa-B ligand

Denosumab is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL. It binds to RANKL, a transmembrane on osteoclasts, decreasing bone resorption and reducing bone turnover. Bone mass as well as strength in cortical, subcortical, and trabecular bone increase. Denosumab is FDA approved for treatment of osteoporosis in postmenopausal women and men, including those on androgen-

deprivation therapy for prostate cancer and aromatase inhibitor therapy for breast cancer (Irene et. al., 2015).

1.8.10 Raloxifene

A tissue selective oestrogen receptor modulator (SERM) that is used for the prevention and treatment of osteoporosis. Raloxifene reduces the risk of vertebral fractures, but not hip fractures, and has the added advantage of reducing the risk of breast cancer, without any adverse effect on the endometrium. It does not seem to affect the risk of cardiovascular disorders, but, similar to HRT, increases the risk of venous thromboembolism. It provides a good therapeutic option in late postmenopausal women at high risk for vertebral but not hip fractures and with concerns regarding breast cancer risk (Dawson-Hughes *et. al.*, 2013)

1.8.11 Fluoride

It is still not clear whether treatment with sodium fluoride (NaF) is beneficial. It increases cancellous bone mass dramatically when combined with adequate calcium and vitamin D. theoretically, it may be useful in preventing vertebral crushing. However, it was not shown to reduce spinal fractures and it may actually increase fractures of the hip. Fluoride supplementation, in amounts above those in fluoridated water, contributes to higher bone density, but possibly of a lesser quality. It is currently not recommended as treatment and is still under investigation.

1.8.12 Thiazides

In some people or in some conditions, excess calcium is lost in the urine. Calcium-sparing diuretics are given to prevent this loss. Whether thiazide therapy has a role in osteoporosis has not been determined (Heinz, 2000).

1.8.13 Non-FDA-Approved Drugs for Osteoporosis

These drugs are listed for information only. These non-approved agents include:

1.8.13.1 Calcitriol

This synthetic vitamin D analogue, which promotes calcium absorption, has been approved by the FDA for managing hypocalcemia and metabolic bone disease in renal dialysis patients. It is also approved for use in hypoparathyroidism, both surgical and idiopathic, and pseudohypoparathyroidism. No reliable data demonstrate a reduction of risk for osteoporotic fracture.

1.8.13.2 Strontium ranelate

This medication is approved for the treatment of osteoporosis in some countries in Europe. Strontium ranelate reduces the risk of both spine and non-vertebral fractures, but the mechanism is unclear. Incorporation of strontium into the crystal structure replacing calcium may be part of its mechanism of effect.

1.8.13.3 Tibolone

Tibolone is a tissue-specific, estrogen-like agent that may prevent bone loss and reduce menopausal symptoms but it does not stimulate breast or uterine tissue. It is indicated in Europe for the treatment of vasomotor symptoms of menopause and for prevention of osteoporosis, but it is not approved for use in the US (National Osteoporosis Foundation, 2010).

1.8.14 Future trends in the treatment and prevention of osteoporosis and fractures

1.8.14.1Nitrates

Nitric oxide (NO) is produced by NO synthetases in all bone cells. NO mediates effects of strain (physical activity) and estrogen on bone and arteries. Clinically available nitrates (such as nitroglycerine) prevent bone loss in ovariectomized and corticosteroid treated mice.

1.8.14.2 Beta-blockers

Beta-blockers increase osteoblast activity in experimental animals. Mice treated with propranolol have increased bone mass. However, the clinical use of beta-blockers in osteoporosis is uncertain.

1.8.15 Kathepsin K inhibitors

Kathepsin K produces H+ thus acidifying the area under the osteoclast leading to an increase in dissolving bone mineral exposing the matrix for degradation by proteinase. The inhibitors of kathepsin K reduce the resorption of bone and enable the activity of osteoblasts (Jaroslav Blaho, 2007).

2. Literature review

2.1 Multinational survey of osteoporotic fracture management

Anderson *et. al.,* (2005) performed a survey on 3,422 orthopedic surgeons in France, Germany, Italy, Spain, the United Kingdom, and New Zealand. The majority of the respondents in all countries had the opinion that the orthopedic surgeon should identify and initiate the assessment of osteoporosis in patients with fragility fractures. Heterogeneous practice pattern exist in different countries; however, identification and treatment of the osteoporotic patient seems to be insufficient in many areas: half of the orthopedic surgeons surveyed received little or no training in osteoporosis. Only approximately one in four orthopedic surgeons in France, the UK and New Zealand regarded themselves as knowledgeable about treatment modalities. Less than one-fifth of the orthopedic surgeons arranged for a surgically treated patient with a fragility fracture to have a bone mineral density (BMD) test. Twenty percent said that they never refer a patient after a fragility fracture for BMD. Only half of the orthopedic surgeons in southern Europe know about the importance of some external risk factors for hip fractures (cataracts, poor lighting, pathway obstacles, poor balance). In summary, this survey clearly indicates that many orthopedic surgeons still neglect to identify, assess and treat patients with fragility fractures for osteoporosis. More educational opportunities need to be offered to orthopedic surgeons through articles, web-based learning and educational seminars. Development of a simple clinical pathway from evidence-based guidelines is an important step to ensure that optimal care is provided for patients with fragility fractures (Anderson *et. al.,* 2005).

2.2 Awareness of osteoporosis among physicians in China

Cindy, L.K. *et. al.,* (2004) Epidemiological studies have projected a vast increase in osteoporotic fractures in Asia, with the majority occurring in China. Awareness of osteoporosis among medical professionals and the pattern of management in Asia have not been explored. A total of 504 doctors in Hong Kong, China with their self-reported practice likely to receive clients with or at risk of osteoporosis were invited to complete a postal questionnaire on the diagnosis and management of their osteoporotic patients. In all, 204 questionnaires were returned, with a response rate of 41%. Only 76% of the respondents reported treating osteoporosis patients in their practice. Ninety-one percent believed that osteoporosis was under-diagnosed. The asymptomatic nature of the disease

(66%), inaccessibility (45%) and high cost (54%) of the diagnostic tools were considered major reasons for under-diagnosis. DXA was employed for diagnosis by only 53% of the doctors. Peripheral machines such as ultrasound and quantitative computed tomography were used by 35% of the responders as the only diagnostic tool, especially among clinic-based doctors (clinic-based physicians 47%, hospital-based physicians 17%; $P<0.001$). Thirty-three percent of the surveyed doctors were unaware of published guidelines for bone mineral density (BMD) measurements. Concerning treatment goals, 82% considered prevention of future fractures and 66% believed improvement in the quality of life of patients as critical or highly important, whereas only about half of the doctors thought that increase in BMD was important. On the other hand, 60% of the doctors considered the cost of therapy a critical or highly important element in the management of osteoporosis. This study showed that physicians in Hong Kong were aware of osteoporosis, though the disease was still under-diagnosed due to inaccessibility and high cost of the diagnostic tools and therapeutic agents. These findings stress the importance of expanding efforts to increase knowledge and awareness among health care providers and also provide future directions for developing strategies for managing osteoporosis in developing Asian regions (Cindy *et. al.,* 2004).

2.3 Osteoporosis management in long-term care

McKercher H.G. *et. al.,* (2000) conducted a survey physician in Ontario regarding their approach to diagnosis and treatment of osteoporosis among residents of long-term care facilities. Respondents returned 275 of 490 questionnaires, for a response rate of 56.1%. Most respondents (92.4%) were family physicians; 28.7% were caring for more than 100 patients in long-term care. Most (85.8%) saw from one to 10 hip fractures yearly in their practices. Although 49.6% of respondents estimated the prevalence of osteoporosis to be 40% to 80% among their long-term care patients, 45.5% said that they did not routinely assess their patients for the disease, and 26.8% do not routinely treat it. Half (50.9%) of physicians would treat patients at high risk based on clinical history; 47.9% if patients had a vertebral compression fracture on plain x-ray examination; 43.8% if patients were highly functional; 42.0% if osteoporosis were confirmed with bone mineral densitometry; and 30.0% if patients had a recent fracture. Perceived barriers to initiating treatment included cost of therapy, patient or family reluctance to accept therapy, and time or cost of diagnosis (McKercher *et. al.,* 2000).

2.4 Hormone replacement therapy in general practice: a survey of doctors in the MRC's general practice research framework

Wilkes H C *et. al.,* (1991) performed a survey current prescribing practice for hormone replacement therapy among general practitioners and to elicit their views on the role of hormone replacement therapy in the prevention of osteoporosis in UK. Design postal questionnaires to general practitioners throughout the United Kingdom. Participated 1268 general practitioners in the Medical Research Council's general practice research framework.1081 (85%) doctors in 220 (95%) practices responded. The doctors were currently prescribing hormone replacement therapy to an estimated 9% of their female patients aged 40 to 64, and 55% of doctors were prescribing opposed hormone replacement therapy (oestrogen plus progestogen) to more patients than a year previously. Over half the doctors would consider prescribing hormone replacement therapy for prevention of osteoporosis (670, 62%). Overall, 79% of the doctors (851) would definitely or probably consider entering women who have had a hysterectomy into a randomized controlled trial comparing unopposed (oestrogen only) hormone replacement therapy with opposed hormone replacement therapy; 49% (524) would enter patients with a uterus into such a trial. Among a subsample, 85% (180/210) would consider entering patients without menopausal symptoms into a trial comparing hormone replacement therapy with no treatment (unopposed in patients who have had a hysterectomy, opposed in those with a uterus) (Wilkes *et. al.,* 1991).

2.5 Use of bisphosphonates and dual-energy X-ray absorptiometry scans in the prevention and treatment of glucocorticoid-induced osteoporosis in rheumatology

Wall E *et. al.,* (2008), conducted a survey in UK by physician on the Patients treated with steroids are at risk of glucocorticoid-induced osteoporosis. Appropriate investigations and therapeutic agents can decrease rate of bone loss and fracture according to current UK guidelines. Participated 519 patients attended rheumatology outpatient clinics, amongst which 104 were current glucocorticoid users. Most patients had been taking oral steroids for over 12 months (n = 79, 76%). The majority had also received steroids by at least one other route (n = 67, 64.4%). According to the guidelines, 51 patients, at relatively low risk of osteoporosis (<65 years, no previous fragility fracture) should have been referred for bone density assessment; of these, 27 (53%) had received a DEXA scan. In total, 58 subjects fulfilled criteria for bisphosphonates (>65 years, fragility fracture, T-score <-1.5)

and, of these, 51 (87.9%) were appropriately treated. In 21 cases, a DEXA scan had been performed when guidelines recommended that treatment could commence without further assessment (Wall *et. al.*, 2008).

2.6 Survey of spine surgeons on attitudes regarding osteoporosis and osteomalacia screening and treatment for fractures, fusion surgery, and pseudoarthrosis

Dipaola Christian P. *et. al.*, (2009) performed a survey when spine surgeons attending the "Disorders of the Spine" conference (January 2007, Whistler, British Columbia, Canada). A ten-question survey was administered to orthopedic surgeons and neurosurgeons that treated spine fractures and degenerative spine conditions in their practice. The survey was given to those who were attending a continuing medical education spinal disorders conference. The survey asked about treatment patterns with respect to osteoporosis and osteomalacia workup and treatment for patients with low-energy spine fractures, pseudoarthrosis, and those undergoing spinal arthrodesis. Of the 133 surgeons to whom the questionnaire was distributed at this meeting, 114 questionnaires were returned that corresponds to a response rate of 86%. Twenty-one surveys were excluded because of incomplete biographical information, resulting in a total of 93 completed questionnaires that were available for analysis. When treating patients with low-energy spine fractures, 60% checked dual-energy X-ray absorptiometry (DEXA) and 39% checked metabolic laboratories (of those who did not order laboratories and DEXA about 63% refer for treatment). Before instrumented fusion, 44% of those queried checked DEXA and 12% checked metabolic laboratories (vitamin D, parathyroid hormone [PTH], and calcium [Ca]). Before no instrumented fusion, 22% checked DEXA and 11% checked metabolic laboratories. Before addressing pseudoarthrosis, 19% checked DEXA and 20% checked metabolic laboratories (Dipaola *et. al.*, 2009).

2.7 Recognition of Osteoporosis by Primary Care Physicians

Gehlbach Stephen H. *et. al.*, (2002) explored the recognition and treatment of osteoporosis and vertebral fracture among older women by primary care physicians. Data from the National Ambulatory Medical Care Survey from 1993 to 1997 were examined for evidence of diagnosis and treatment of osteoporosis or vertebral fracture during visits by White women 60 years and older to primary care physicians. Fewer than 2% of the women received diagnoses of osteoporosis or vertebral fracture, although expected prevalence is 20% to 30%. Appropriate drug treatment, including antiresorptive agents

and calcium and vitamin D, was offered to only 36% of the diagnosed patients (Gehlbach *et. al.*, 2002).

2.8 A Canadian survey on the management of corticosteroid induced osteoporosis by rheumatologists

Soucy E. *et al.*, (2000) conducted a survey on the practice pattern of Canadian rheumatologists (CR) on their management of corticosteroid induced osteoporosis in their premenopausal (PrM) and postmenopausal (PoM) female patients. Most CR investigated and treated osteoporosis themselves, 13% referred to other specialists for investigation, and 22% referred for treatment. Eighty-two percent of CR used dual energy x-ray absorptiometry (DEXA) to confirm a diagnosis of osteoporosis. Most CR initiated investigation for osteoporosis at the start or within the first year of starting longterm systemic corticosteroid therapy: PrM 87% and PoM 93%. The most frequently used initial strategy for the prevention of osteoporosis was as follows. PrM: calcium and vitamin D3 (53%); PoM: hormone replacement therapy (HRT) and calcium (29%). The most common initial choice for treatment of established osteoporosis was as follows: PrM: etidronate (53%); PoM: bisphosphonates +/- HRT (53%). Ninety-six percent of CR used only bone mineral density (BMD) measurement to monitor therapy for corticosteroid induced osteoporosis. Most CR monitored BMD every 12 to 24 months for PrM (81%) and PoM (84%). The BMD parameter(s) (T and Z scores as measured by DEXA) used to initiate therapy for corticosteroid induced osteoporosis was variable (Soucy *et. al.*, 2000).

2.9 Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: a systematic review

Elliot-Gibson V. *et. al*., (2004) lead a literature search in Medline, Healthstar, CINAHL, EMBASE, PreMedline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews identified 37 studies on OP diagnosis, treatment, and interventions. The studies varied in design methodology, study facilities, types of fractures, and pharmacological treatments. Some studies revealed that no patients with fragility fractures received investigation or treatment for underlying OP. Investigation of OP by bone mineral density was low: 14 of 16 studies reported investigation of less than 32% of patients. Investigation by bone mineral density resulted in high rates of OP diagnosis (35–100%), but only moderate use of calcium and vitamin

D (8–62%, median 18%) and bisphosphoates (0.5–38%) in patients investigated postfracture. Studies on barriers to OP identification and treatment focused on various groups of health practitioners. Barriers included the cost of therapies, time and cost of resources for diagnosis, concerns about medications, and the lack of clarity regarding the responsibility to undertake this care (Elliot-Gibson *et. al.,* 2004).

2.10 Knowledge and Opinions of Orthopaedic Surgeons Concerning Medical Evaluation and Treatment of Patients with Osteoporotic Fracture

John G. Skedros *et. al.,* (2006) 'performed a survey that consisting of twenty-two questions was administered to 171 orthopedic surgeons in Utah, Idaho, and Wyoming. Of the 171 surveys that were mailed, 107 usable surveys were returned (a 63% response rate). A majority of the orthopedic surgeons thought that it was appropriate to expand their orthopedic practice to include prescribing pharmacological treatments for osteoporosis (68% agreed or strongly agreed with that statement). However, 47% were concerned enough about adverse events related to some conventional pharmacological treatments that they would rather avoid prescribing them. Of the surgeons who were willing to prescribe these treatments, 74% felt most comfortable prescribing bisphosphonates and >77% felt most comfortable prescribing calcium and vitamin-D supplements. Fifty-one percent considered an apparent osteoporotic fracture and several other clinical risk factors for osteoporosis as sufficient evidence for initiating pharmacological treatments, whereas 72% thought that a bone-density scan should be made before initiating treatment. Although 32% thought that all nonoperative treatment should be the responsibility of a primary care provider, 63% thought that the orthopedic surgeon should initiate a workup to look for secondary causes of the osteoporosis and should begin medical treatment of patients with an osteoporotic fracture before referring them (John *et. al.,* 2006).

2.11 Attitudes and Beliefs of Family Physicians and Gynecologists in Relation to the Prevention and Treatment of Osteoporosis

Suarez-Almazor *et. al.,* (1997) completed a survey by mailed to a random sample of primary care physicians (PCPs) and to all obstetricians/gynecologists (O&Gs) registered in the province of Alberta (Canada). The survey evaluated their practice patterns using closed-ended questions; Likert scaled items, and two case studies. Cases 1 and 2 were 52-year-old and 62-year-old healthy postmenopausal women, respectively, with no known

risks for OP. Neither had received hormone replacement therapy (HRT). One hundred fifty-seven PCPs and 57 O&Gs participated in the study. Thirty-eight percent of the PCPs and 32% of the O&Gs stated that they never requested bone mineral density measurements (BMDm) in early postmenopausal women. Most would request BMDm only in the presence of risk factors. The most important criteria to request BMDm were chronic glucocorticoid use and recent fractures. For case 1, 7% of the PCPs and 11% of the O&Gs would request BMDm; 76% of the PCPs and 80% of the O&Gs would recommend HRT. For case 2, 29% of the PCPs and 47% of the O&Gs would request BMDm (p 5 0.01); 43% of the PCPs and 49% of the O&Gs would prescribe HRT. In general, O&Gs were more inclined to intervene in relation to BMDm and HRT. O&Gs were also more likely to be influenced by clinical trials than PCPs ($p < 0.001$). Our findings show variations in the patterns of practice of physicians in relation to the prevention of OP. In general, use of densitometry appears to be low. The results of the case studies suggest that individual physician perceptions may be more influential than patient characteristics when requesting BMDm and prescribing HRT, particularly in older postmenopausal women. This group of healthy older women has approximately equal odds of being offered versus not being offered BMDm and HRT according to the physician they consult (Suarez-Almazor *et. al.*, 1997).

2.12 Physicians' Attitudes to Contemporary Issues on Osteoporosis Management in Korea

Ha Yong-Chan *et al.,* (2014) conducted a survey. One hundred participants answered the questionnaire. The questionnaire included the questions about the physicians' attitude to current issues and the barriers to osteoporosis treatment in Korea. Most physicians used bone densitometry devices (99%) and, central DXA was the most accessible device (95%). Eighty-eight percent were aware of FRAX®, but among them, only 19.3% used it. The main reason for not using FRAX® was the lack of time in their proactive (76%). Screening for vitamin D status and secondary osteoporosis was performed by 59% and 52% of the respondents, respectively. The lack of awareness among patients and high costs of medication were perceived as the most important barriers to osteoporosis management in Korea (Yong-Chan *et. al.,* 2014).

2.13 The aims and objectives of the study were

- To know the current situation in the treatment of osteoporosis.
- To know the doctor's knowledge and attitude towards osteoporosis.

3. Method

3.1 Study area

This cross-sectional descriptive study was carried out at 8 different hospitals and medical colleges of Bangladesh situated in 2 different districts. The government hospitals and medical colleges are

- Dhaka Medical College, Dhaka
- Sir Salimullah Medical College, Dhaka.
- Comilla Medical College, Comilla.

The private hospitals and medical colleges are

- United Hospital
- Eastern Medical College and Hospital
- Moon Hospital
- Health & Doctors
- CD path hospital

The questioner was distributed to all doctors in hospital, diagnostic center and personal chamber

3.2 Study population

The survey was performed on 107 doctors who are treating osteoporosis.

3.3 Inclusion criteria

Doctors who are involved in treating osteoporosis both male and female doctors. Example: General practitioner, Orthopedic Surgeon, Neuro Surgeon, Neuro Medicine.

3.4 Exclusion criteria

The Doctors who are not willing to participate

3.4 Statistical analysis

The data were coded, entered, and analyzed using the Microsoft Excel 2007. Descriptive results were expressed as percentage and plotted with pie and bar diagrams. The variables of the study are government and non-government institution, age, gender and year of study.

4. Result

4.1 Socio-demographic data

Variables		n (%)
Sex	Male	58 (54%)
	Female	49 (46%)
Age	24-35	54(50%)
	36-45	45(43%)
	>45	8(7%)
Years of experience	One to ten years	76 (71%)
	Eleven to twenty years	28 (26%)
	Twenty to thirty one years	3 (3%)
Income per year	1-4 lac	74 (69%)
	5-9 lac	31 (29%)
	10 to above	2 (2%)
Professional qualification	GP	18(17%)
	Medicine	35(33%)
	Neuro medicine	7(6%)
	Neuro surgeon	1(1%)
	Orthopedic surgeon	20(19%)
	gynecologist	22(20%)
	SHO, pediatric, oncologist and CCM	4(4%)
Professional grade	Specialist	74 (69%)
	Consultant	10 (9%)
	No response	23 (22%)
Attendance on OP program	Yes	90 (84%)
	No	15 (14%)
	No response	2 (2%)

Internet access at work place	Yes	96 (90%)
	No	9 (8%)
	No response	2 (2%)
Following guidelines	Yes	63 (59%)
	No	24 (22%)
	No response	20 (19%)
Guidelines followed	Nice	3(3%)
	Guideline of England	2(2%)
	Textbook	8(7%)
	WHO	2(2%)
	No response	92(86%)
Journal or website subscription	Yes	68 (64%)
	No	24 (22%)
	Blank	15 (14%)
Knowledge about WHO T score criteria	Yes	80 (75%)
	No	12 (11%)
	No response	15 (14%)
Major types of osteoporosis	1 type	9 (9%)
	2 types	53 (54%)
	3 types	26 (27%)
	Blank	9 (9%)
	4 types	1 (1%)
Identification of types of osteoporosis	Primary type 1 (after menopause)	44%
	Primary type 2 (due to 75 years)	30%
	Secondary type (independent of age due to medication)	24%
	Not known	2%

4.2 Signs and symptoms of osteoporosis

From 107 doctors, the total number of response was 235 (100%). 97 (41%) of them ticked on bone pain, 49 (21%) of them on kyphosi, 47 (20%) of them on loss of weight, 34 (14%) of them on fatigue and 8 (3%) of them ticked on others.

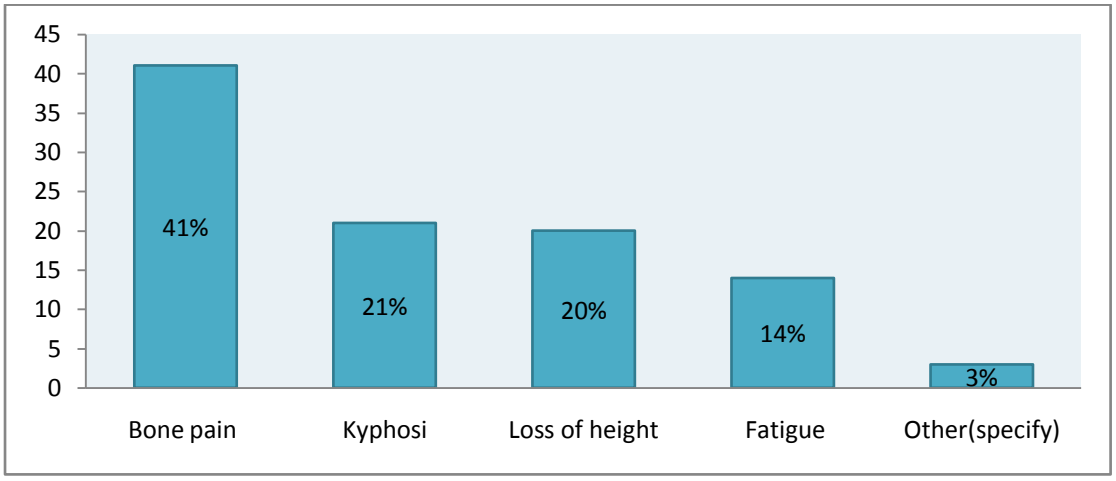


Figure 4.1: Signs and symptoms of osteoporosis

4.3 Main factors that influence bone density

Among 107 doctors, 63 (39%) of them ticked on calcium intake during childhood, 69 (42%) of them ticked on calcium intake during adolescence, 17 (10%) of them ticked on calcium intake during early adulthood and 14 (9%) of them ticked on others. The total numbers of responses were 163 (100%) because some doctors gave multiple answers.

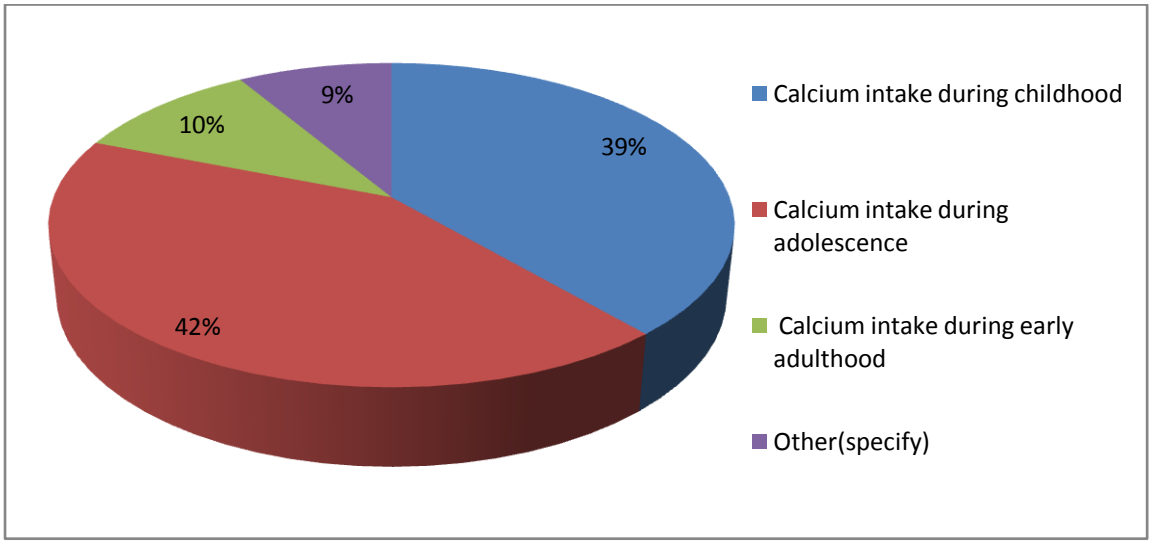


Figure 4.2: Main factors that influence bone density

4.4 Uncontrollable risk factors of osteoporosis

The total number of responses from the 107 doctors were 742 (100%).97(13%) of them on age,58(8%) on family history, 33(4%) low body weight,99(13%) on menopause, 41(6%) on hysterectomy, 41(6%) on rheumatoid arthritis, 94(13%) on female gender, 44 (6%) on previous fracture, 44 (6%) of them ticked on ethnicity, 75 (10%) of them on estrogen deficiency, 82 (11%) of them on long term glucocrorticoid therapy, 34 (5%) of them ticked on primary/secondary hypogonadism in men.

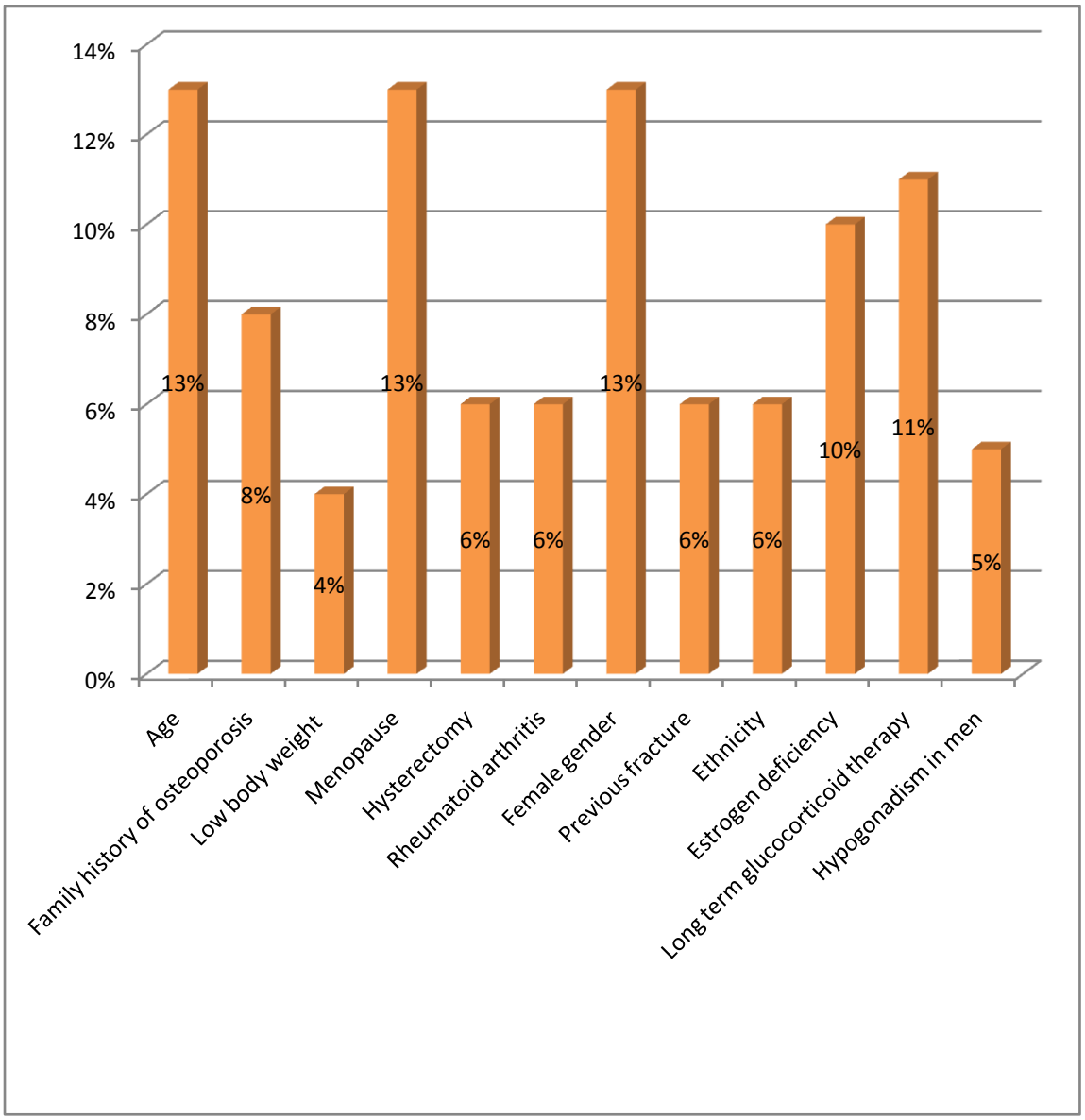


Figure 4.3: Uncontrollable risk factors of osteoporosis

4.5 Disorders that affect the skeleton

The number of total responses was 525 (100%) from 107 doctors because there were multiple answers. 63 (12%) of them ticked on asthma, 62 (12%) of them on nutritional/gastrointestinal problems, 74 (14%) of them on rheumatoid arthritis, 40 (8%) of them on malignancy, 44 (8%) of them on some inherited diseases, 89 (17%) of them on hypogonadal states, 80 (15%) of them on endocrine disorders and 73 (14%) of them ticked on immobility.

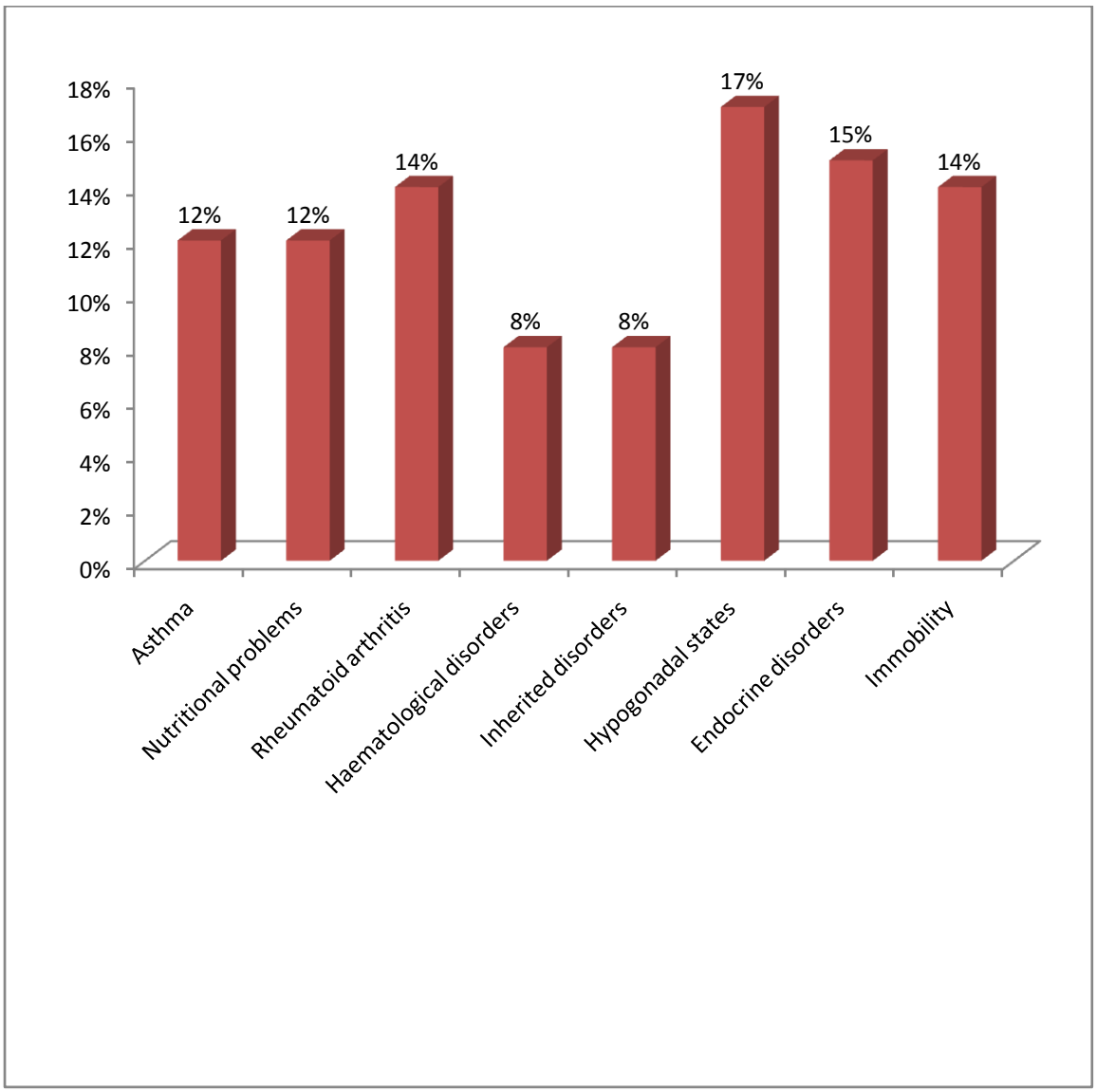


Figure 4.4: Disorders that affect the skeleton

4.6 Medical treatments that affect bone health

The total number of responses was 583 (100%) from 107 doctors because there were multiple answers. 106 (18%) of them ticked on glucocorticoids, 69 (12%) of them on certain immunodepressants, 48 (8%) of them on thyroid hormone treatment, 59 (10%) of them on certain steroid hormones, 22 (4%) of them on aromatase inhibitors, 16 (3%) of them on certain antipsycotics, 19 (3%) of them on antacids, 25 (4%) of them on certain anticonvulsants, 57 (10%) of them on previous fracture, 17 (3%) of them on certain antiepileptic drugs, 43 (7%) of them on lithium, 63 (11%) of them on methotrexates and 39 (7%) of them ticked on proton pump inhibitors.

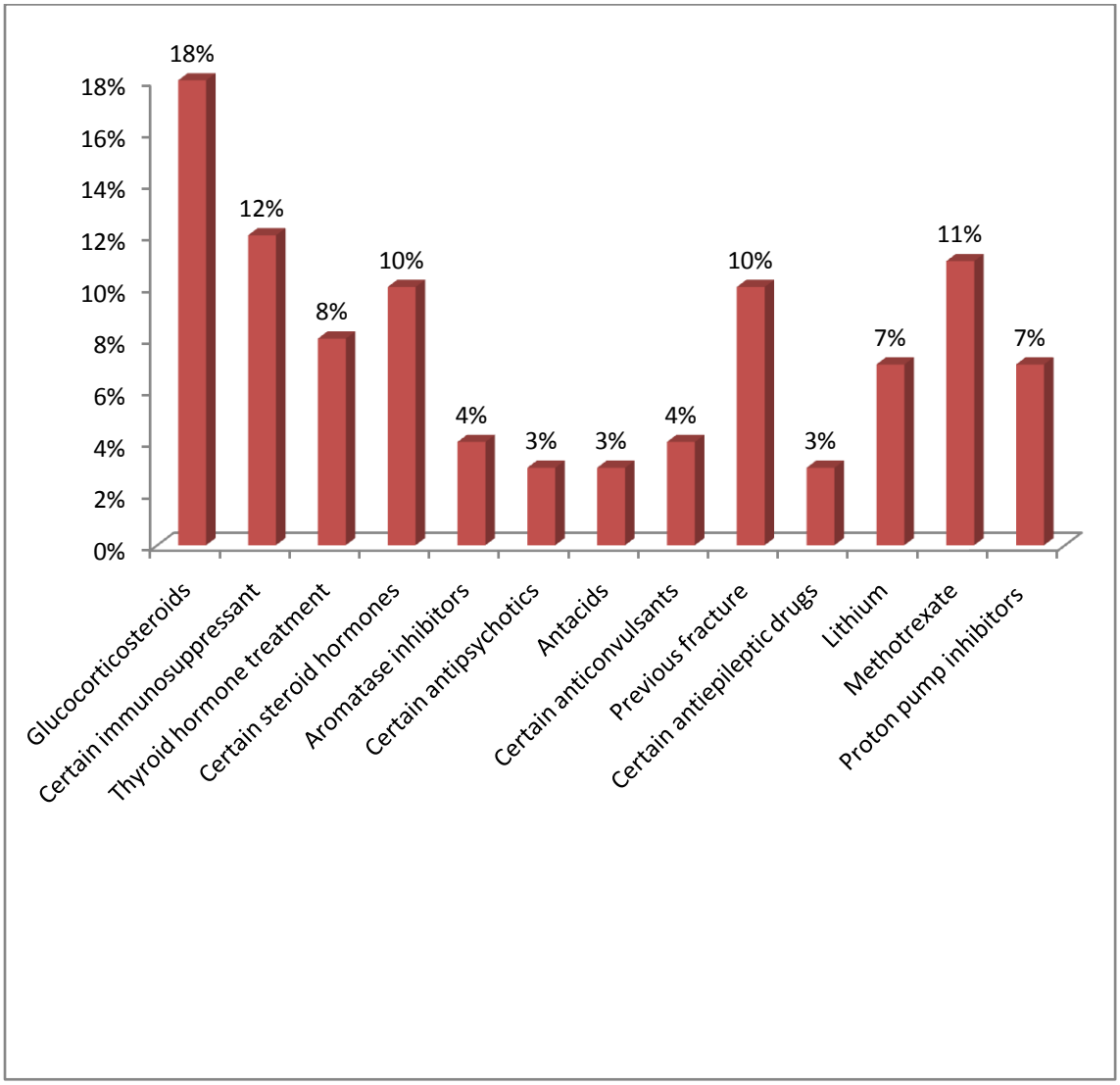


Figure 4.5: Medical treatments that affect bone health

4.7 Controllable risk factors of osteoporosis

The number of total responses was 840 (100%) from 107 doctors.9% of them on alcohol,10% poor nutrition,7% caffeine,6% on sunlight and beverage, 10%vitamin D deficiency, 11% on smoking,4% on smoking passively and low body mass,3% on lack of protein, 7% of them ticked on eating disorder, 67 (8%) of them on insufficient exercise, 71 (8%) of them on low dietary calcium intake, 17 (2%) of them on low salt intake and 41 (5%) of them ticked on frequent falls.

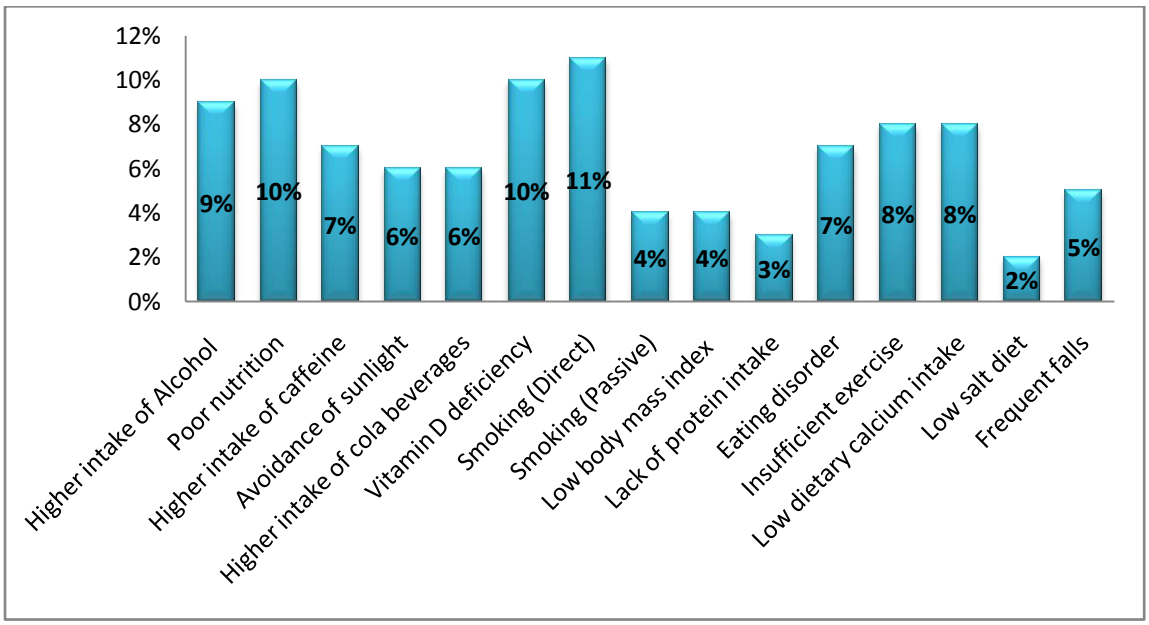


Figure 4.6: Controllable risk factors of osteoporosis

4.8 Complications of osteoporosis

The total number of responses was 186 (100%) from 107 doctors. 103 (55%) of them ticked on bone fractures, 71 (38%) of them on slouched body posture, 12 (6%) of them on others and 1 of them did not respond.

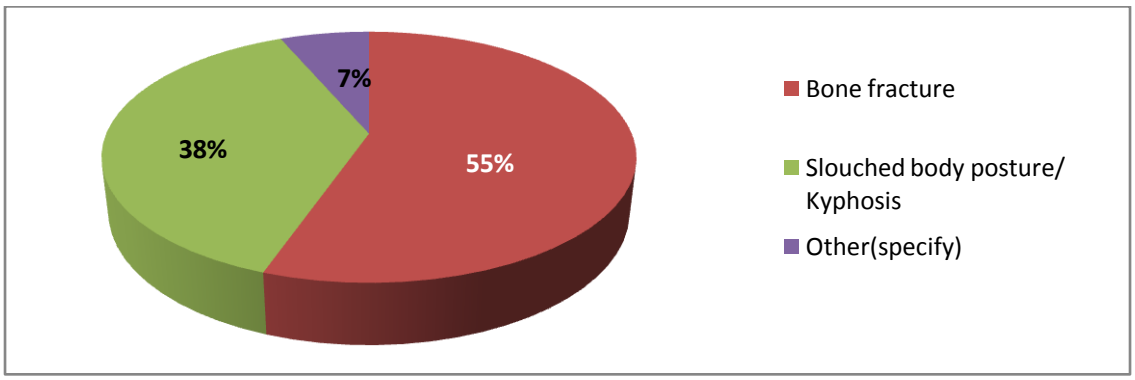


Figure 4.7: Complications of osteoporosis

4.9 Knowledge about clinical evaluation of osteoporosis

The total number of responses was 208 (100%) from 107 doctors. 104 (50%) of them ticked on BMD, 63 (30%) of them on serum calcium, 32 (15%) of them on creatinine and 9 (4%) of them ticked on others.

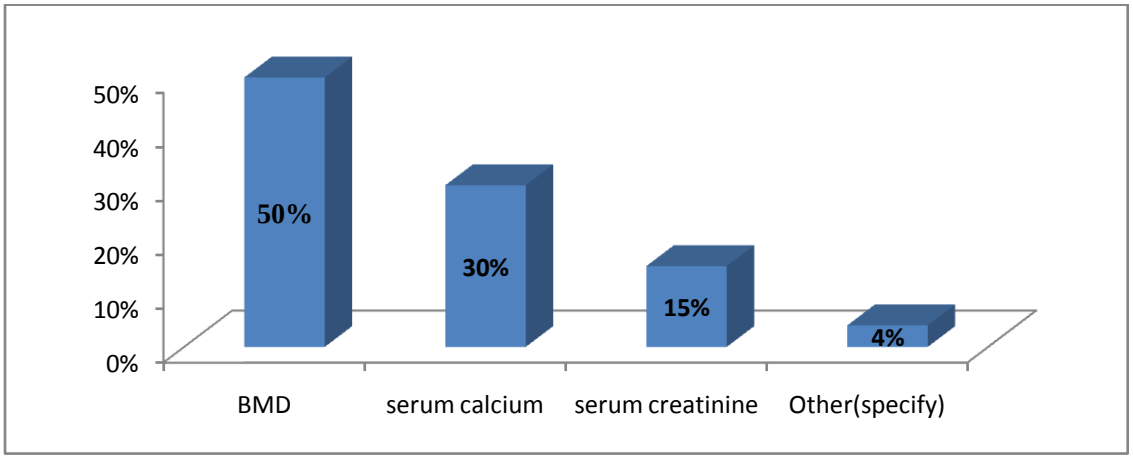


Figure 4.8: Knowledge about clinical evaluation of osteoporosis

4.10 Knowledge about diagnosis of osteoporosis

The total number of responses was 350 (100%) from 107 doctors due to multiple answers. 89 (25%) of them ticked on DXA, 81 (23%) of them on plain radiography, 61 (17%) of them on CT skin imaging, 19 (5%) of them on QUS, 36 (10%) of them on MRI, 63 (18%) of them on X-ray and 1 (0.03%) of them ticked on others.

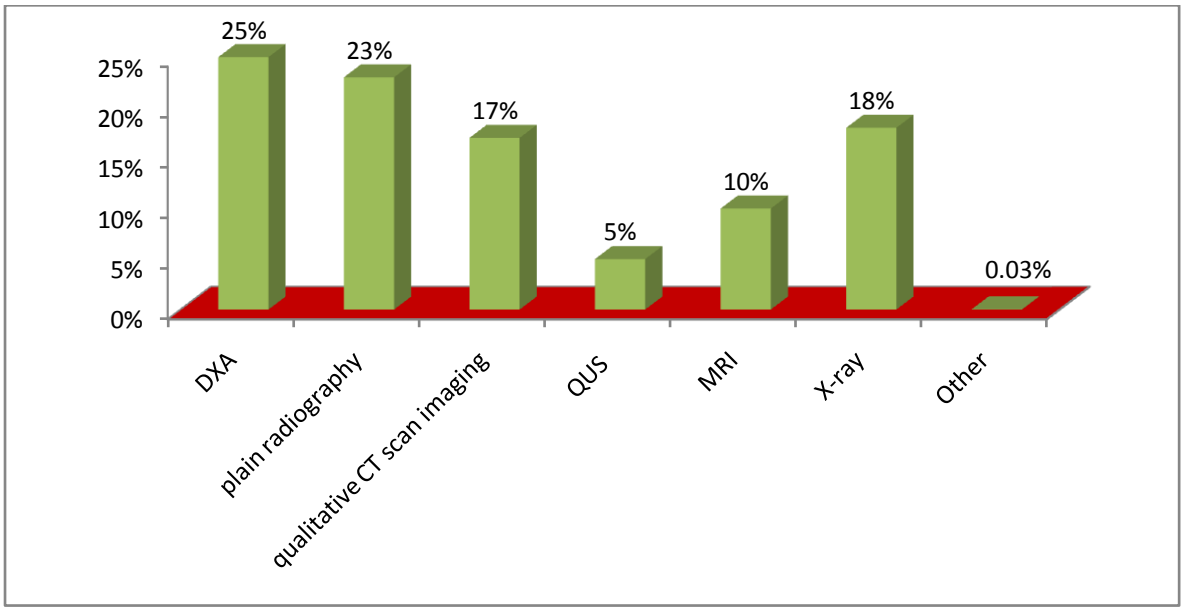


Figure 4.9: Knowledge about Diagnosis of osteoporosis

4.11 Knowledge about Plain radiography

The total number of responses was 140 (100%) because of multiple answers. 98 (70%) of them ticked on useful for fracture prediction, 31 (22%) of them on useful for determining BMD, 11 (8%) of them on others.

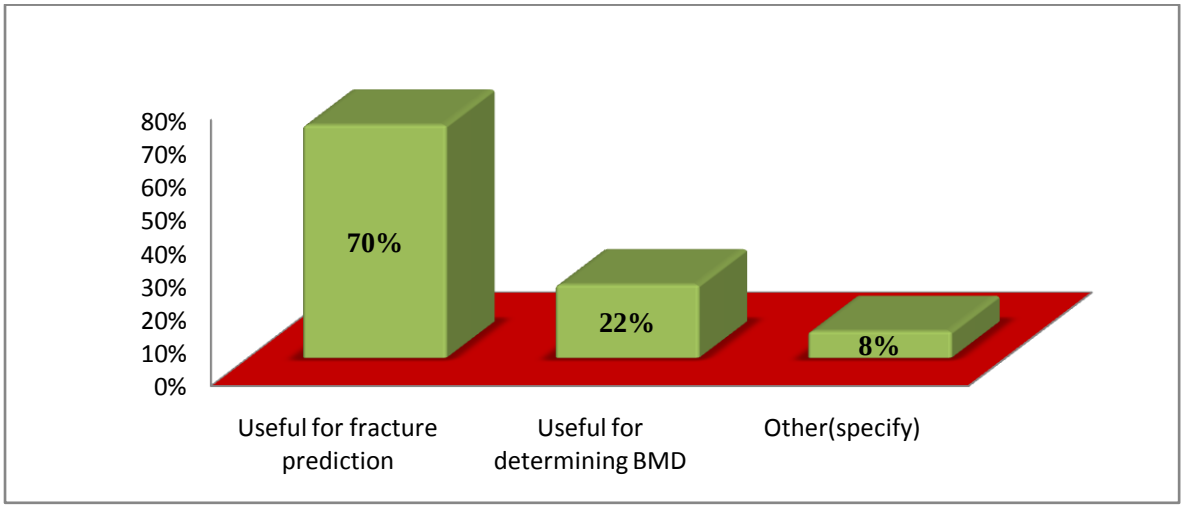


Figure 4.10: Knowledge about plain radiography tests of osteoporosis

4.12 Knowledge about Qualitative CT skin imaging

In 100% of all the responses, 51% of them ticked on most sensitive diagnostic tool, 31% on lower cost vs. DXA, 9% on higher sensitivity vs. DXA, 8% on others. The total number of responses was 132 because of multiple answers but 13 of the doctors did not give any response.

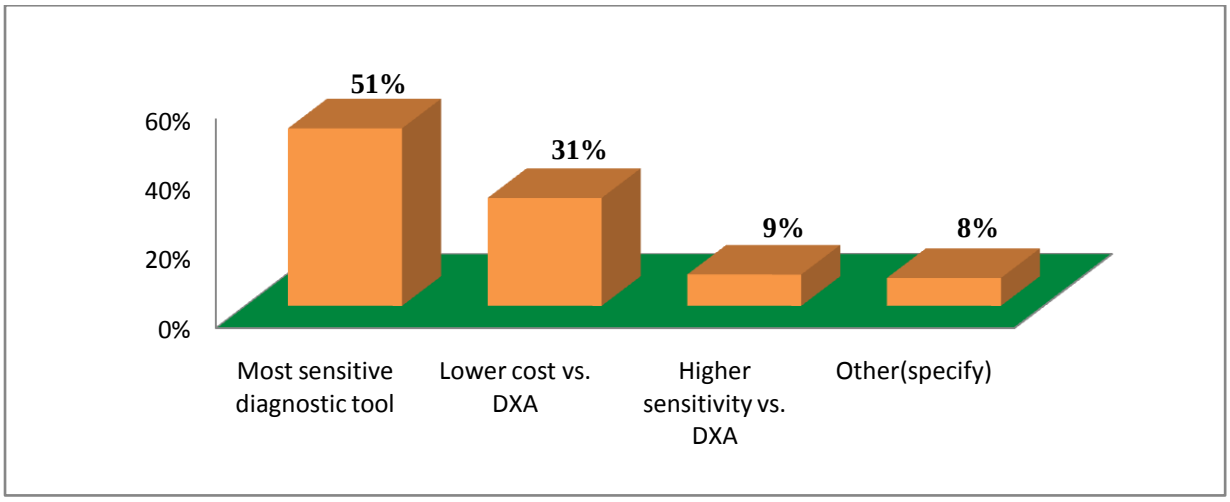


Figure 4.11: Knowledge about qualitative CT skin imaging

4.13 Knowledge about DXA

The total number of responses was 249 from 107 doctors where 16 of them did not respond to the question and others gave multiple answers. 22% of them ticked on confirm a diagnosis of osteoporosis, 18% on predict future risk of fractures, 24% on monitor BMD, 16% on best diagnostic tool, 10% on need long time, 6% on lower radiation vs. CT and 5% ticked on others.

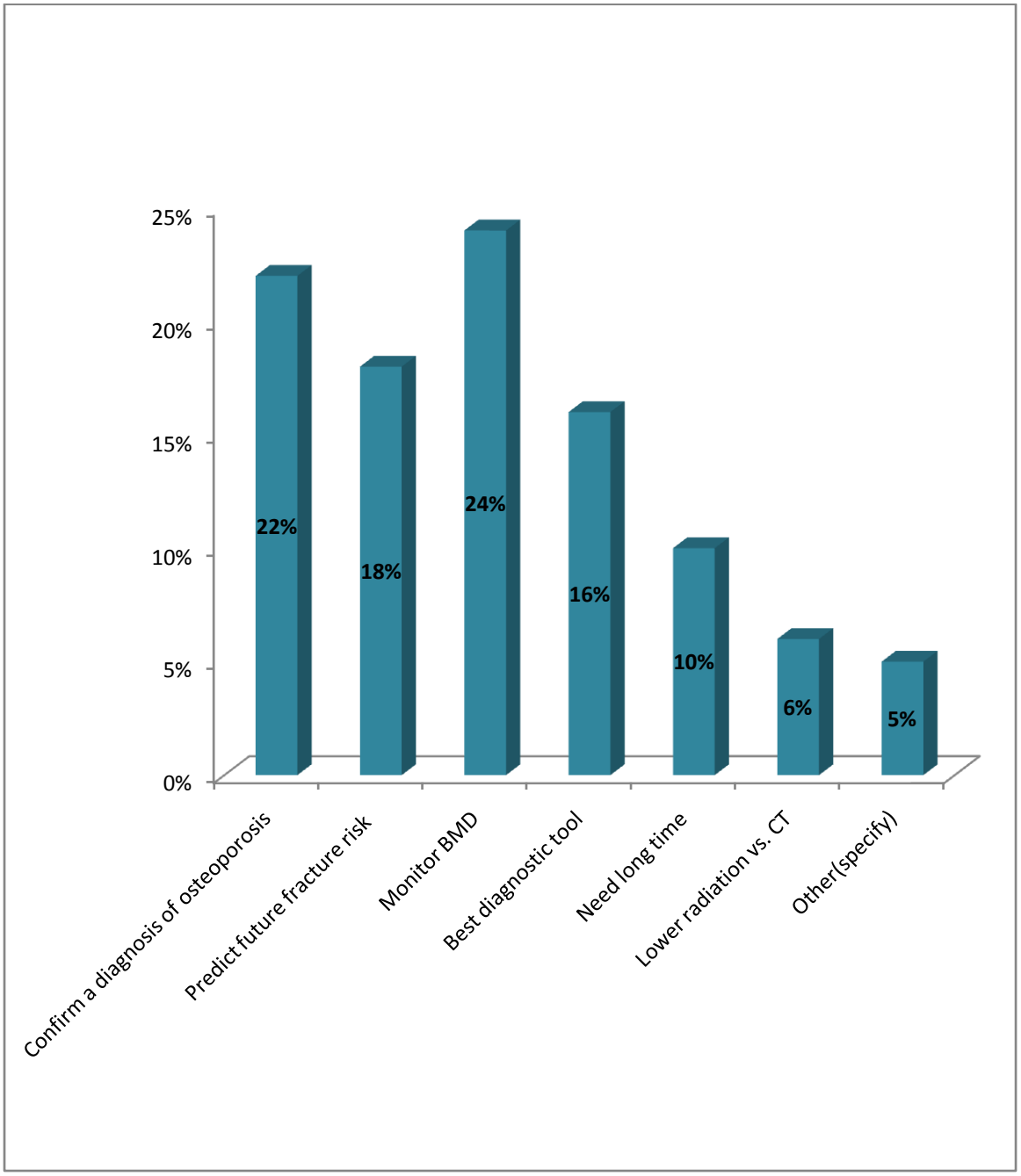


Figure 4.12: Knowledge about DXA

4.14 Knowledge about QUS for osteoporosis diagnosis

The total number of responses was 77 from 107 doctors where 42 of them did not respond to the question and others gave multiple answers. 38% of them ticked on does not measure BMD directly, 36% on predict fractures on postmenopausal women, 20% on not associated with radiation exposure and 5% ticked on others.

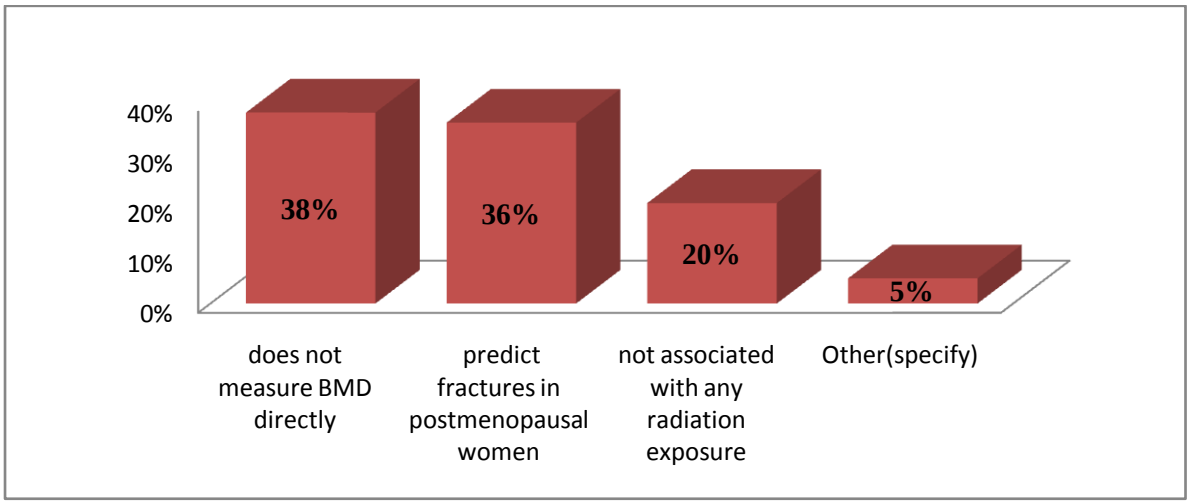


Figure 4.13: Knowledge about QUS for osteoporosis diagnosis

4.15 Ratio of the prevention of osteoporosis

From 107 doctors, 60 (61%) of them responded affirmatively, 38 (39%) of them responded negatively and the rest 9 of them did not respond on their opinion of the prevention of osteoporosis

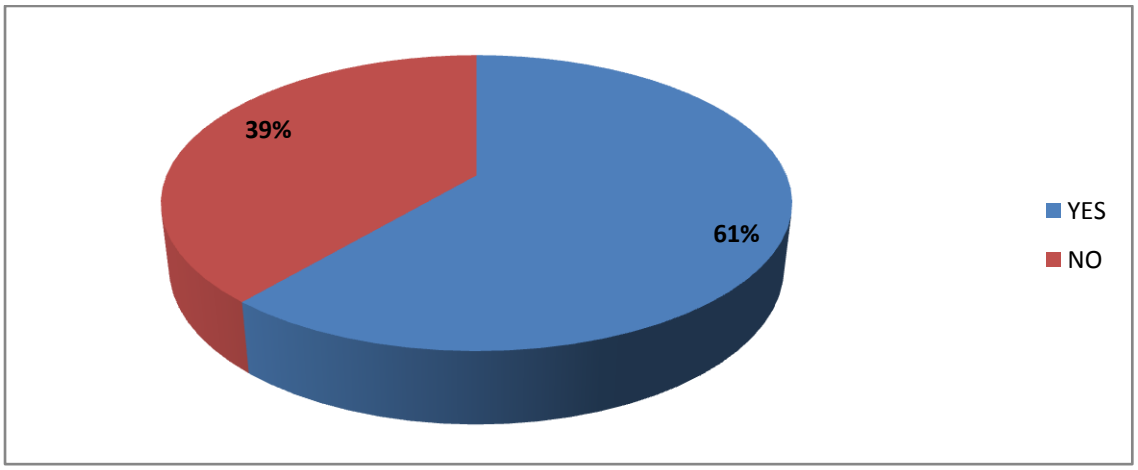


Figure 4.14: Ratio of the prevention of osteoporosis

4.16 Accessibility of biology marking test

From 107 doctors, 57 (57%) of them responded affirmatively, 43 (43%) of them responded negatively and the rest 7 of them did not respond.

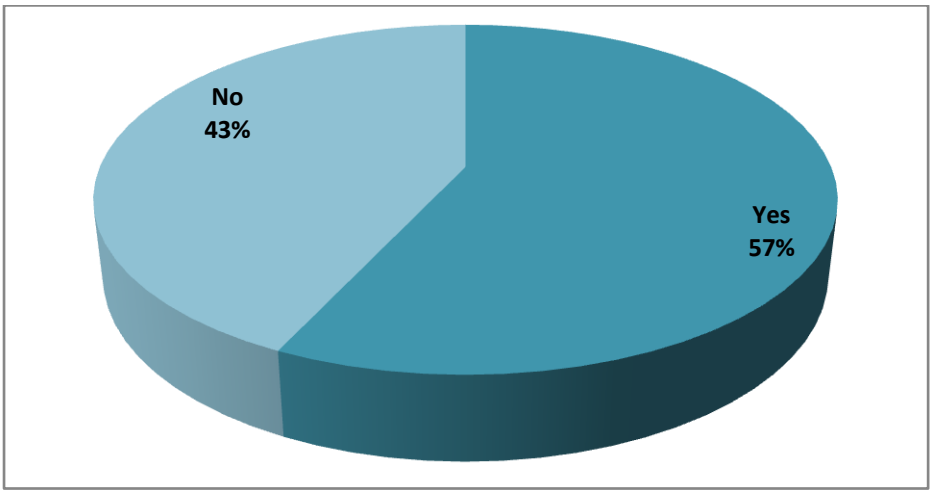


Figure 4.15: Accessibility of biology marking test

4.17 Accessibility to perform bone mineral density test

From 107 doctors, 63 (61%) of them responded affirmatively, 41 (39%) of them responded negatively and the rest 3 of them did not respond.

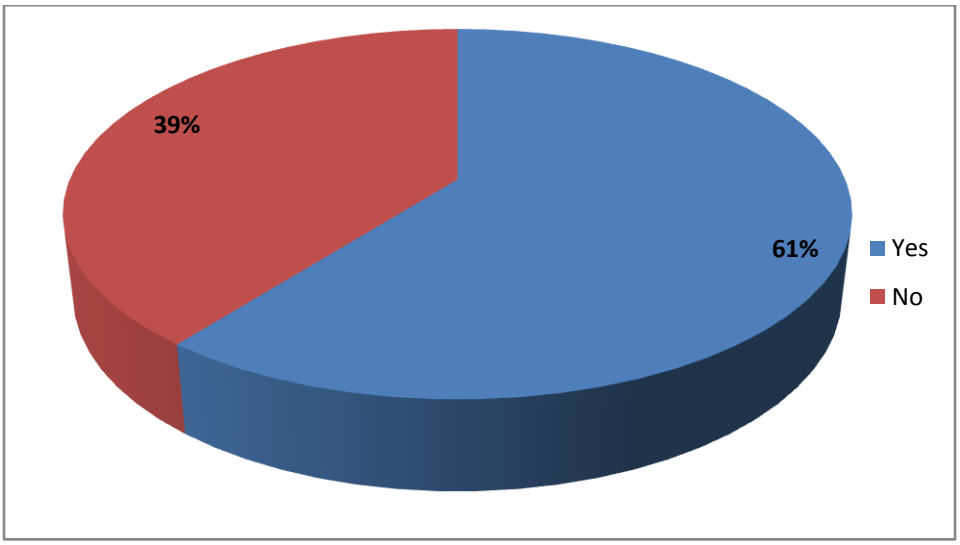


Figure 4.16: Accessibility to perform bone mineral density test

4.18 Examination of osteoporosis

The total number of responses was 940 from 106 doctors. 1 doctor did not answer the question. 9% ticked on kyphosis, 7% on loss of weight, 5% on low body weight, 10% on back pain, 8% on history of fracture, 5% on family history of osteoporosis, 5% on daily calcium intake in diet, 10% on age, 8% on medical treatment currently taken by the patient, 9% on estrogen deficiency, 10% on postmenopausal women, 4% on other disorders of the patient, 10% on the lifestyle of the patient and 0.32% ticked on others.

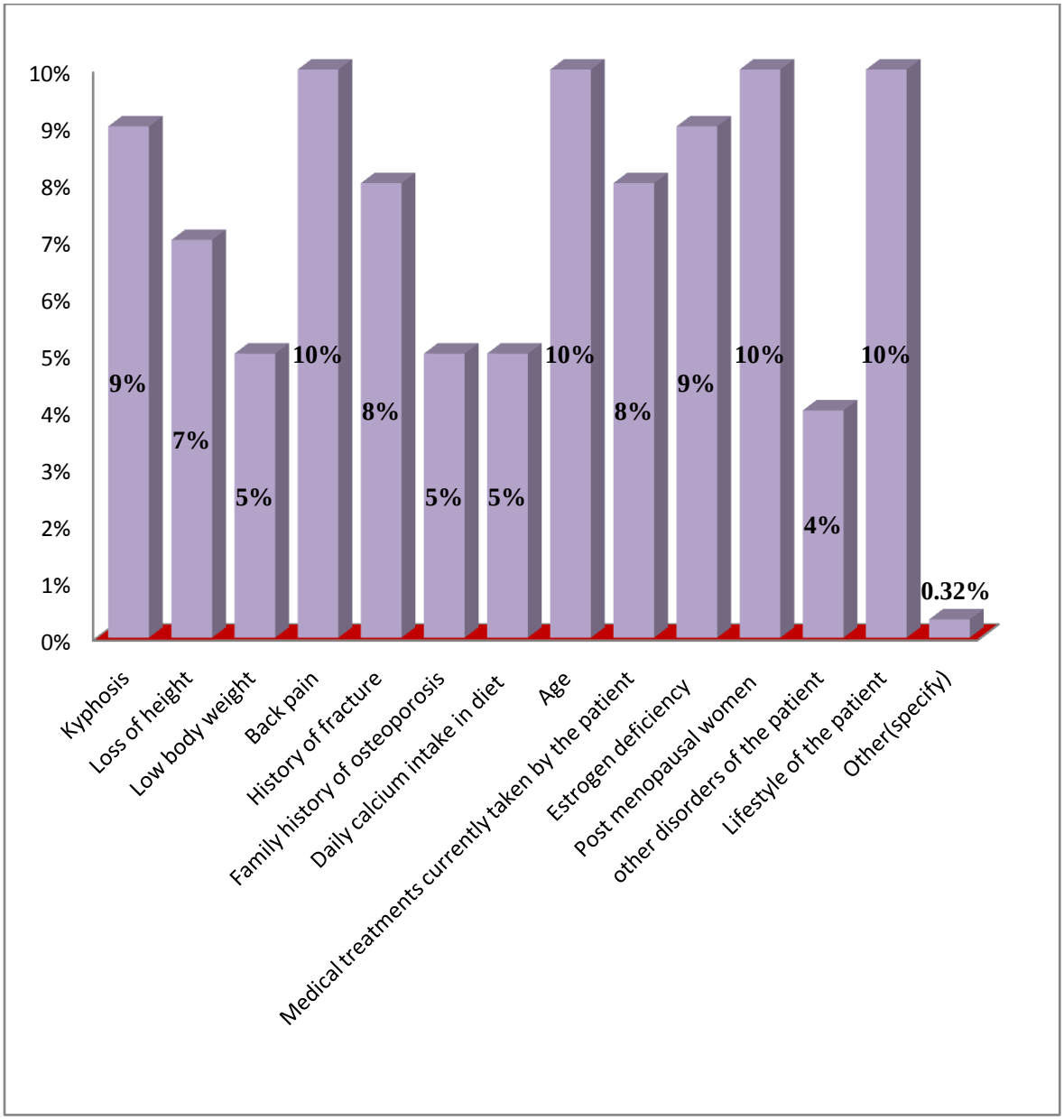


Figure 4.17: Examination of osteoporosis

4.19 Patient's awareness of osteoporosis

From 107 doctors, 17 (17%) of them responded affirmatively, 81 (83%) of them responded negatively and the rest 9 of them did not respond regarding the question.

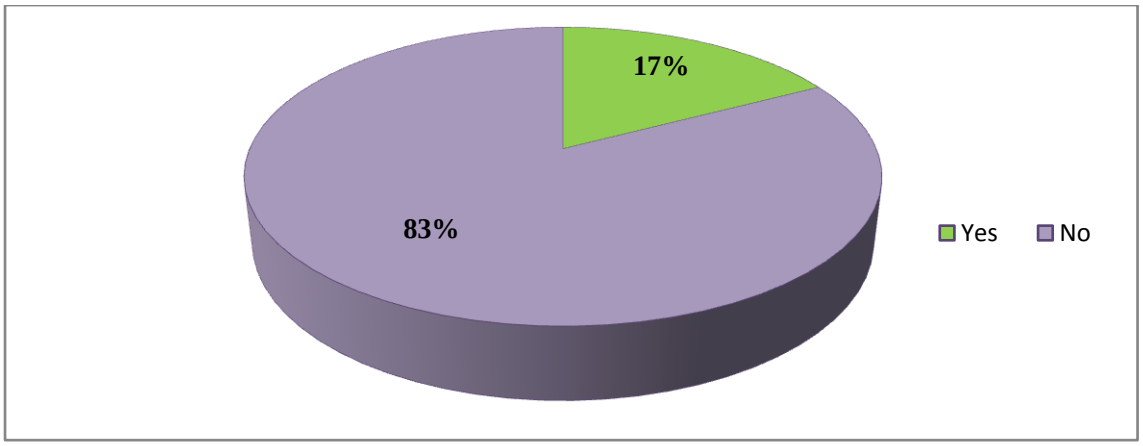


Figure 4.18: Patient's awareness of osteoporosis

4.20 Tools used to prevent osteoporosis

The total number of responses was 525 from 107 doctors. 19% ticked on physical exercise, 20% on calcium rich diet, 15% on hormone replacement, 17% on calcium supplementation, 17% on vitamin D supplementation, 5% on vitamin C supplementation, 2% on appropriate protein intake, 4% on avoiding underweight and 0% ticked on others.

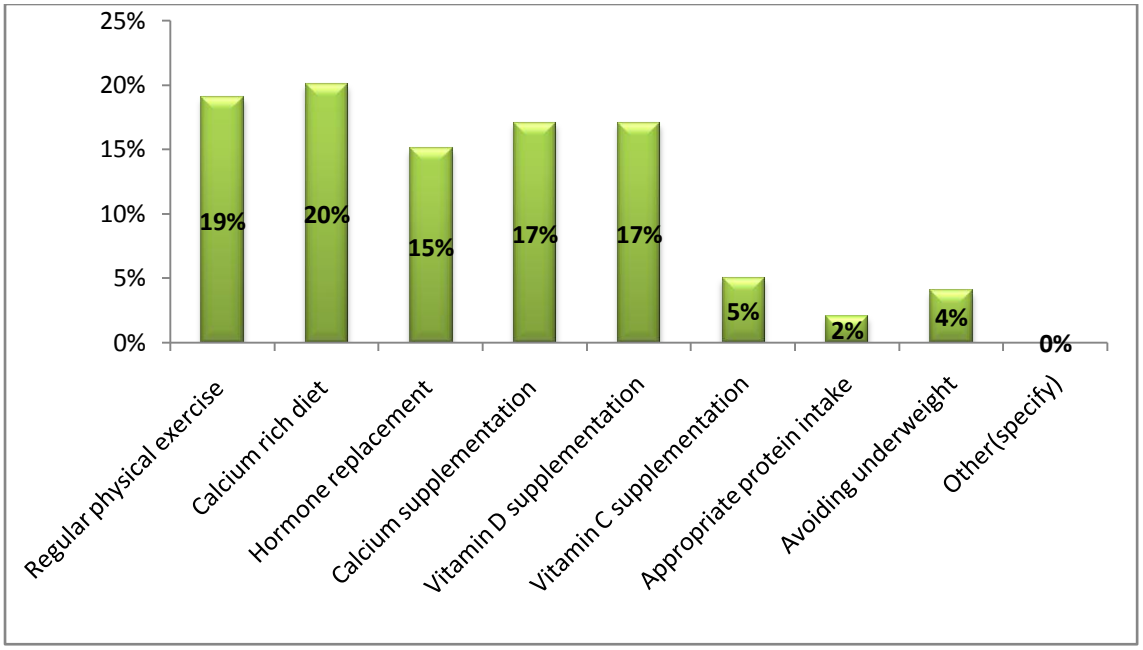


Figure 4.19: Tools used to prevent osteoporosis

4.21 Impact of the diseases

The total number of responses was 271 from 91 doctors because of multiple answers. 21% ticked on coronary heart disease, 21% on Diabetes mellitus, and 21% on cerebrovascular disease, 18% on osteoarthritis, 19% on osteoporosis and 0% ticked on others. 16 (14%) of the doctors did not respond.

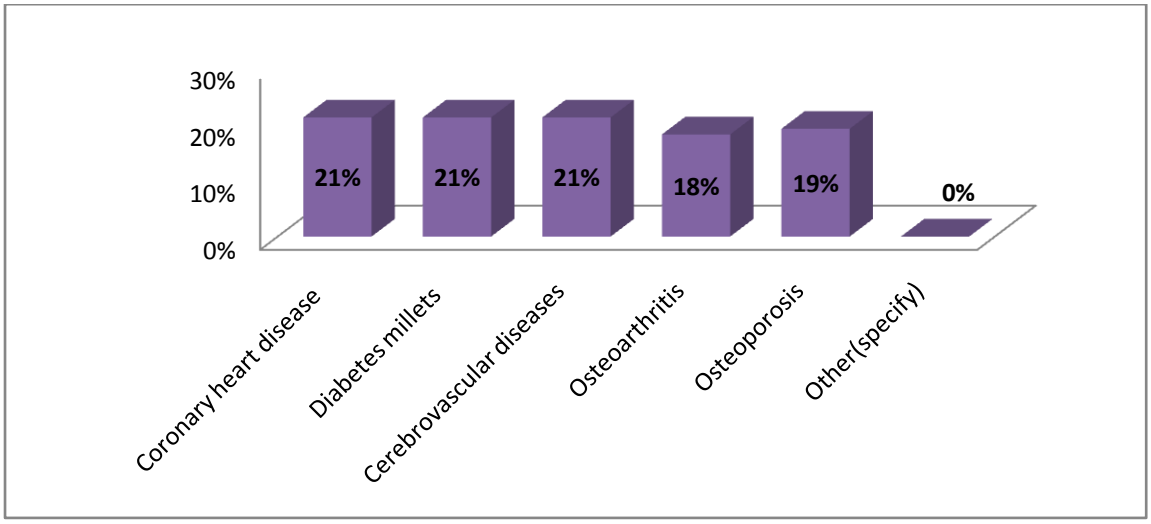


Figure 4.20: Impact of the diseases

4.22 Drugs for prevention of osteoporosis

The total number of responses was 286 (100%) from 101 doctors. 6 (6%) of them did not respond. 27% ticked on bisphosphonates, 22% on calcitonin, 26% on estrogen, 16% on estrogen agonist/antagonist, 9% on parathyroid hormone and 1% ticked on others.

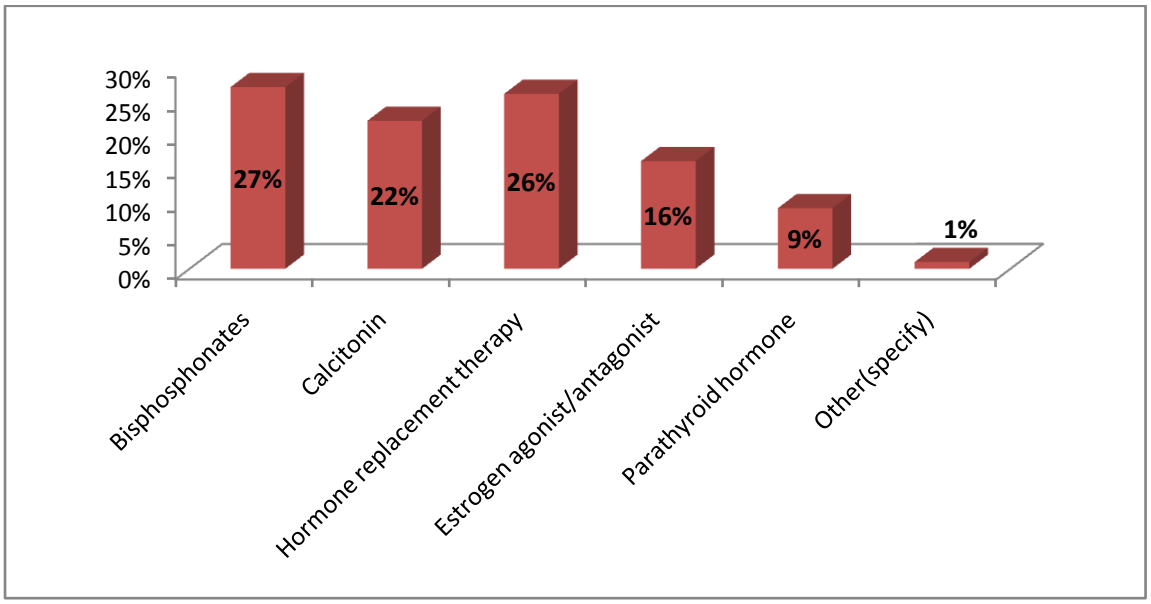


Figure 4.21: Drugs for prevention of osteoporosis

4.23 Drugs for osteoporosis

The total number of responses was 669 from 107 doctors due to multiple answers. 15% ticked on bisphosphonates, 11% on estrogen, 8% on parathyroid hormone, 0.5% on vitamin C, 5% on chondroitin sulfate, 3% on sodium fluoride, 8% on tibolone, 0.3% on others, 0.1% on combination, 6% on calcitonin, 10% on estrogen agonist/antagonist, 12% on calcium supplement, 6% on glucosamine, 8% on calcitriol and 7% ticked on strontium ranelate.

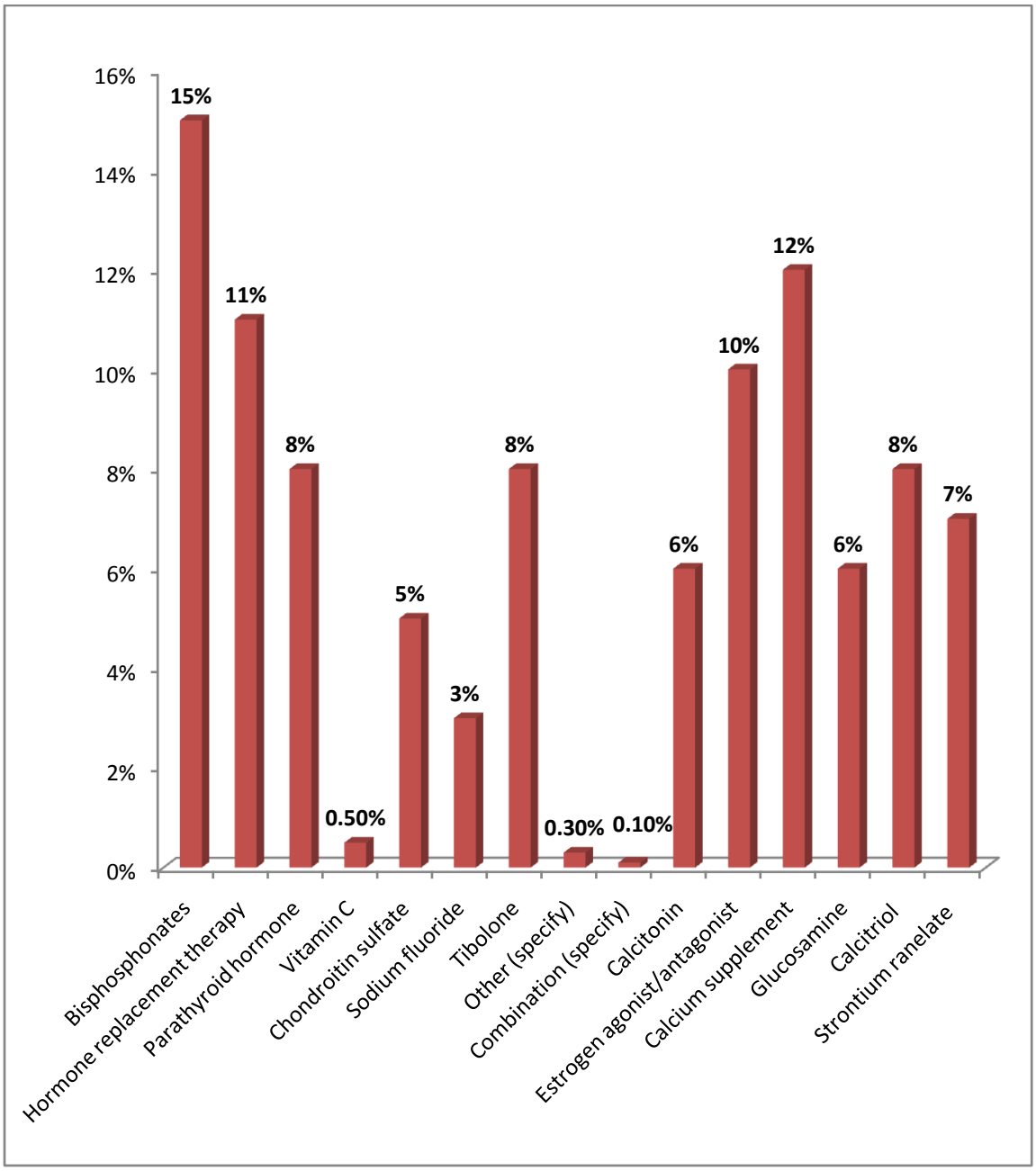


Figure 4.22: Drugs for osteoporosis

5. Discussion

From the demographic data, most of our respondents doctors are aged between, 24-45 (93%),and male respondents, 58(54%), are more than the female respondents 49 (46%). Most of the participated doctors, 76 (71%), are one to ten years experienced and their income range varied with the place. Most of the doctors 74 (69%) income range between one to four lac. In this study, qualification of the participated doctors, 35(33%), were of medicine, of 22(20%) gynecologist, of 20(19%) Orthopedic surgeon, 18(17%) of GP and very few number were of Neuro medicine 7(6%), SHO, pediatric, oncologist and CCM 4(4%), Neuro surgeon 1(1%).74 (69%) doctors are specialist and 10 (9%) are consultant.

Anderson, M. *et. al.*, (2005) performed a survey on 3,422 orthopedic surgeons in France, Germany, Italy, Spain, the United Kingdom, and New Zealand. 50% of the orthopedic surgeons surveyed received little or no training in osteoporosis. Only approximately one in four orthopedic surgeons in France, The UK and New Zealand regarded themselves as knowledgeable about treatment modalities.

Cindy, L.K. *et. al.*, (2004) conducted a survey on 204 doctors in Hong Kong, China. 33% of the surveyed doctors were unaware of published guidelines for bone mineral density (BMD) measurements. Half of the doctors thought that increase in BMD was important. Ninety-one percent believed that osteoporosis was under-diagnosed.

In this survey participated 107 doctors 90 (84%) were attended any specialized osteoporosis program, 96 (90%) had internet access at work place but only 68 (24%) had subscription in any medical journal or website, so all are not utilizing their facility to know or get updated about new researches of osteoporosis. 80 (75%) Bangladeshi doctors are aware of published guideline and WHO criteria about T-score but 12 (11%) doctors were not aware and 15 (14%) were not responded on this questions. 63 (59%) doctors were followed guideline, 24 (22%) were not followed any guideline but 15% were able to wrote specific guideline name, 92(86%) ignored this question. So that indicates a huge lacking and threat to osteoporosis treatment in our country. In this country 61% thought osteoporosis is preventable but other 39% did not thought like that.

Cindy, L.K. *et. al.*, (2004) conducted a survey on 204 doctors in Hong Kong, China. DXA was employed for diagnosis by only 53% of the doctors and ultrasound and quantitative computed tomography were used by 35%.

Soucy, E. *et. al.,* (2000) conducted a survey on the practice pattern of Canadian rheumatologists (CR) on their management of corticosteroid induced osteoporosis in their premenopausal (PrM) and postmenopausal (PoM) female patients. Eighty-two percent of CR used dual energy x-ray absorptiometry (DEXA) to confirm a diagnosis of osteoporosis. Prevention of osteoporosis was as follows. PrM: calcium and vitamin D3 (53%); PoM: hormone replacement therapy (HRT) and calcium (29%). The most common initial choice for treatment of established osteoporosis was as follows: PrM: etidronate (53%); PoM: bisphosphonates +/- HRT (53%). Ninety-six percent of CR used only bone mineral density. The BMD parameter(s) (T and Z scores as measured by DEXA) used to initiate therapy for corticosteroid induced osteoporosis was variable.

Wilkes, H. C. *et. al.,* (1991) performed a survey current prescribing practice for hormone replacement therapy among general practitioners in UK. 1081 (85%) doctors in 220 (95%) practices responded. The doctors were currently prescribing hormone replacement therapy to an estimated 9% of their female patients aged 40 to 64, and 55% of doctors were prescribing opposed hormone replacement therapy (oestrogen plus progestogen) to more patients than a year previously. Over half the doctors would consider prescribing hormone replacement therapy for prevention of osteoporosis (670, 62%).

John, G. S, *et. al.,* (2006) 'performed a survey that consisting of twenty-two questions was administered to 171 orthopedic surgeons in Utah, Idaho, and Wyoming. A majority of the orthopedic surgeons thought that it was appropriate to expand their orthopedic practice to include prescribing pharmacological treatments for osteoporosis (68% agreed or strongly agreed with that statement). However, 47% were concerned enough about adverse events related to some conventional pharmacological treatments that they would rather avoid prescribing them. Of the surgeons who were willing to prescribe these treatments, 74% felt most comfortable prescribing bisphosphonates and >77% felt most comfortable prescribing calcium and vitamin-D supplements. Fifty-one percent considered an apparent osteoporotic fracture and several other clinical risk factors for osteoporosis as sufficient evidence for initiating pharmacological treatments, whereas 72% thought that a bone-density scan should be made before initiating treatment.

Dipaola, C. P. *et. al.,* (2009) performed a survey on 144 doctors when spine surgeons attending the "Disorders of the Spine" conference. 60% checked dual-energy X-ray absorptiometry (DEXA) and 39% checked metabolic laboratories (of those who did not order laboratories and DEXA about 63% refer for treatment).

From Performed study found that 25% doctors were suggested DXA, 23% plain radiography, 17% CT skin imaging, 5% QUS, 10% MRI, 18% X-ray for diagnosis . 98 (70%) doctors thought plain radiography is useful for fracture prediction, 22% selected for determining BMD and 8% selected on others. 51% of them selected CT scan as most sensitive diagnostic tool, 31% selected on lower cost vs. DXA, 9% selected on higher sensitivity vs. About DXA, 8% on others. 38% of them ticked on does not measure BMD directly, 36% on predict fractures on postmenopausal women, 20% on not associated with radiation exposure and 5% ticked on others.

Physical exercise preferred 19% doctors, 20% on calcium rich diet, 15% on hormone replacement, 17% on calcium supplementation, 17% on vitamin D supplementation, 5% on vitamin C supplementation, 2% on appropriate protein intake, 4% on avoiding underweight as the prevention tools. For the treatment purpose most of the doctors 15% ticked on bisphosphonates, 12% on calcium supplement, 11% on estrogen, 10% on estrogen agonist/antagonist and very few doctors 0.5% on vitamin C, 5% on chondroitin sulfate, 3% on sodium fluoride, 0.3% on others, 0.1% on combination, 6% on calcitonin , 6% on glucosamine, 7% ticked on strontium ranelate , 8% on parathyroid hormone, 8% on calcitriol, 8% on tibolone. 27% doctors prescribed bisphosphonates, 22% calcitonin, and 26% estrogen for prevention of osteoporosis.

Doctors were chosen uncontrollable risk factor mainly 13% of them on age, menopause and female gender.10% of them on estrogen deficiency, 11% of them on long term glucocrorticoid therapy, 8% on family history, 6% on previous fracture, 6% of them ticked on ethnicity 4% low body weight, 6% on hysterectomy, 6% on rheumatoid arthritis, 5% of them ticked on primary/secondary hypogonadism in men. 42% of them thought that calcium intake during adolescence, 39% of them ticked on calcium intake during childhood were main factor that influence bone density. 41% of them chosen bone pain, 21% of them on kyphosi, 20% of them on loss of weight, 14% of them on fatigue and 8 (3%) of them on others as osteoporosis sign and symptoms. 63 (12%) of them selected on asthma, 62 (12%) on nutritional, 14% on rheumatoid arthritis, 40 (8%) of them on malignancy, 44 (8%) of them on some inherited diseases, 89 (17%) of them on hypogonadal states, 80 (15%) of them on endocrine disorders and 73 (14%) of them ticked on immobility as that effect the skeleton.

Medical treatment also affected the bone health 18% doctors ticked on glucocorticoids, 12% of them on certain immunodepressants and main controllable risk factors chosen by

doctors were smoking (direct or passive), high intake of alcohol, poor nutrition and vitamin D deficiency. Most of the doctors thought that osteoporosis is not a preventable disease and there are not aware about osteoporosis.

6. Conclusion

Osteoporosis is a long term disorder that causes several harmful consequences. It's a rapidly growing disorder the world. Mainly women and old aged people are affected by osteoporosis. Treatment completely depends on doctor's knowledge and treatment attitude. On the basis this study was conducted on 107 doctors who treat osteoporosis in Bangladesh to know the recent doctors knowledge, their treatment standard and diagnosis that use in our country. From our study it is found that doctors have some skills and knowledge limitation and also lack of training facilities. So they provide traditional treatment because they are not updated with new science. One threatening fact is that they are not actually following a fixed guideline for osteoporosis treatment. In spite of that Government should take proper and powerful steps to minimize the lack of knowledge and increase the standard of osteoporosis treatment by creating awareness among osteoporosis practitioner.

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