II. REVIEW OF LITERATURE

The review of literature pertaining to the study titled "**Bone Health and Risk Assessment of Menopausal Women for Osteoporosis and Strategic Diet Care Practices using Calcite Enriched Recipes**" is discussed under the following headings.

A. Physiological nature and nutrient composition of bone
B. Osteoporosis, its causes and management
C. Calcium supplementation and its significance in the maintenance of bone health.
D. Role of egg shell powder in the management of bone health

A. PHYSIOLOGICAL NATURE AND NUTRITION STATE OF BONE

a. Bone Physiology:

Bone is a compact living connective tissue, which is well vascularized. It plays a vital role in calcium and phosphate homeostasis in addition to its other important functions.

i. Bone Structure:

Bone or osseous tissue is a specialized rigid connective tissue that forms the skeleton and most bones have a well-organized thick outer shell known as the cortex, which is made up of the osteons. It consists of special type of cells and tough intercellular matrix of ground substance. The matrix is formed by organic substances like collagen and it is strengthened by the deposition of mineral salts like calcium phosphate and calcium carbonate. Throughout the life, bone is renewed by the process of bone formation and bone resorption (Cowan and Kahai, 2021; Sembulingam, 2012).

According to Pal (2017) bone consists of two parts: the outer cortex and the inner trabeculae. The cortical bone, also called compact bone, constitutes 80 percent total bone mass of the body. It consists of dense concentric outer layers of the long bones and a thinner outer layer of the flat bones. The trabecular bone, also called spongy bone constitutes 20 percent of the bone mass. It consists of bone spicules that make up the inner part of the axial skeletons and the smaller interior of the long bones.

ii. Bone formation:

Osteoblasts synthesize collagen and extrude it into the adjacent extracellular space. The collagen fibrils form the organic matrix of the bone, which is called as osteoid. In the osteoid, calcium-phosphate is deposited which is called as mineralization of bone. Thereafter, to the organic matrix, hydroxides and bicarbonates are added to form the hydroxyapatite crystals (the complete mineralization). As the process of mineralization of matrix continues, the osteoblasts decrease their synthetic activity and become osteocytes (Pal, 2017).

This growth of bone produced by osteoblasts within the periosteum, a connective tissue sheath that covers the outer bone. As osteoblast activity deposits new bone on the external surface, other cells within the bone, the osteoclasts, dissolve the bony tissue on the inner surface next to the marrow cavity. In this way, the marrow cavity enlarges to keep pace with the increased circumference of the bone shaft (Sherwood, 2015).

b. Importance of Bone Health:

The skeleton is one of the largest organs in the human body. In addition to its conventional functions such as support, movement and protection, the skeleton also contributes to whole body homeostasis and maintenance of multiple important non-bone organs/systems (extra skeletal functions). Both conventional and extra skeletal functions of the skeleton are defined as bone function. Bone-derived factors (BDFs) are key players regulating bone function (Su, 2019).

There are several major functions of bones. Bone form the skeletal framework of the body, which is crucial for changing and maintaining various body postures. By providing stable postural background, bones allow movements to occur. Bone play important role in metabolism of various minerals, especially, contribute to calcium, phosphate and magnesium homeostasis. They also protect important structures and viscera in the thoracic and pelvic cavities and in the skull. Bone (bone marrow) is the primary site of hemopoiesis. They produce and supply formed elements of blood (Pal, 2017).

Protective function: Protects soft tissues and vital organs of the body, Mechanical function: Supports the body and brings out various movements of the

body by their attachment to the muscles and tendons, Metabolic function: Plays an important role in the metabolism homeostasis of calcium and phosphate in the body. Hemopoietic function: Red bone marrow in the bones is the site of production of blood cells. Recently, many studies have revealed that the skeleton contributes to whole body homeostasis and the maintenance of multiple important organs/systems such as hematopoiesis, immune activity, energy metabolism and brain function. These functions affecting non-bone tissues are called extra skeletal functions (Asada *et al.,* 2015 and Han *et al.,* 2018).

c. Nutrients and Bone Health:

Bone health and food supplementations:

Recent research demonstrated substantial increases in tibial and femoral mass in female rats following 8 weeks of 1g per kg body weight honey intake mixed with 40 jumps per day for 5 days per week jumping exercise. The findings suggest that combining jumping exercise with honey supplementation can improve bone health and minimise the negative effects of high-intensity exercise (Mosavat *et al.,* 2014).

Honey feeding has a beneficial effect on tibial bone density in ovariectomized rats, according to Zaid *et al*., (2010). Many researches have been conducted in recent years to study the influence of honey on bone health. Ariefdjohan *et al.,* (2008) investigated the effects of honey and its carbohydrate components, such as fructose, raffinose and glucose, on calcium absorption in rats during acute and chronic feeding. Acute ingestion of honey and its carbohydrate components improved calcium absorption, resulting in skeletal advantages, according to their findings.

Soybean is made up of isoflavones, which have a structure similar to oestrogen and have estrogenic properties. They can attach to oestrogen receptors and impact bone health. Furthermore, they have significant non-hormonal characteristics. Soy foods include phytoestrogens, which have estrogen-like effects and may help to prevent bone loss (Lewis *et al.,* 2008).

Calcium and Bone Health

Calcium as a nutrient is most commonly associated with the formation and metabolism of bone. Over 99 percent of total body calcium is found as calcium

hydroxyapatite in bones and teeth, where it provides hard tissue with its strength (Ross *et al.,* 2011).

Calcium is an essential element that plays numerous biological functions in the human body, of which one of the most important is skeleton mineralization. Bone is a mineralized connective tissue in which calcium represents the major component, conferring bone strength and structure. Proper dietary calcium intake is important for bone development and metabolism and its requirement can vary throughout life. The mineral composition of drinking water is becoming relevant in the modulation of calcium homeostasis. In fact, calcium present in mineral drinking waters is an important quantitative source of calcium intake. This, together with its excellent bioavailability, contributes to the maintenance of the bone health (Vannucci *et al.,* 2018).

The finding from Sharma *et al.,* (2022) conveys that circulating concentrations of CTX in overweight or obese postmenopausal women are similarly responsive to dietary calcium intake compared with non obese women has important implications for bone metabolism. Most forms of bone loss reflect increased bone resorption relative to bone formation, especially in postmenopausal women, who are susceptible to bone loss due to the decrease in estrogen after menopause.

The adult human body contains around 1 kg calcium on average, more than 99 percent of which exists in bone and teeth. In bone, calcium exists in mineral form as hydroxyapatite Calcium influences bone strength through its effect on bone mass. Calcium plays a role in preventing bone loss and osteoporotic fractures in later life. Meta-analyses report that calcium supplementation reduce bone loss by 0.5-1.2 percent and the risk of fracture of all types by at least 10 percent in older people. Low calcium intake is a widespread problem across countries and age groups (Zhu *et al.,* 2012).

Vitamin D and Bone Health

The most common symptom of vitamin D insufficiency is osteomalacia in adults and rickets in children, both of which are linked to an increased risk when plasma 25-hydroxyvitamin D (25(OH)D concentrations fall below 20-25 nmol/L, according to the (Scientific Advisory Committee on Nutrition , 2016).

According to the IOM Report (2012), there was sufficient evidence from observational studies to indicate a link between plasma 25(OH) D concentrations and BMD or changes in BMD at the femoral neck, but not at other locations. The IOM, on the other hand, found that most vitamin D supplementation Randomised Controlled Trails (RCT) had no effect on BMD. A meta-analysis of 23 RCTs of vitamin D supplementation indicated a slight improvement in femoral neck BMD but no impact on spine or total hip BMD (Reid *et al.,* 2014).

The meta-analysis of RCTs supports the use of calcium plus vitamin D supplements as an intervention for fracture risk reduction in both community-dwelling and institutionalized middle-aged to older adults (Weaver *et al.,* 2016), while the other revealed that vitamin D supplementation reduced hip bone loss considerably (Macdonald *et al.,* 2013). Another research recently demonstrated that vitamin D 1,000 IU per day improved BMD only in people with a baseline 25(OH)D concentration below 30 nmol/L (Macdonald *et al.,* 2018).

The IOM (2012) report indicated that while vitamin D supplementation alone did not lower the incidence of fractures in institutionalized older persons, combination therapy with vitamin D and calcium did. The data from three meta-analyses of vitamin D supplementation for fracture prevention was equivocal, but overall revealed that there was no reduction in fracture risk. A Cochrane Review found that vitamin D supplementation alone had no effect on fracture risk. Vitamin D and calcium decreased the incidence of hip fractures by a little amount, although the advantage appeared to be limited to those under institutional care (Avenell *et al.,* 2014).

When plasma 25(OH)D concentrations were in the 90-120 nmol/L range three months after dosage, there was an elevated risk of falls and fractures. Bischoff *et al*., (2016) found that 60,000 IU intermittent dosage increased the risk of fracture.

Protein and Bone Health

Dietary protein intake might have a role in bone health across both of these phases via pleiotropic mechanistic pathways. A high-protein intake may lead to an acidic residue that must be neutralised through the leaching of calcium and other minerals from the bone, subsequently leading to demineralisation and bone

weakening. Conversely and as described in the 'Against: mechanisms through which protein may negatively impact bone' section. The net effect of these contrasting pathways is described in the 'For: mechanisms through which protein may positively impact bone' section. Sometimes higher than recommended protein intakes are advised, e.g. during the earlier and later phases of the lifespan or during reduced energy availability (Dolan and Sale, 2019).

Bone mineral density, microstructure-estimated bone strength and trabecular and cortical microstructure are positively associated with total protein intake. Several studies indicate that fracture risk might be lower with a higher dietary protein intake, provided that the calcium supply is sufficient (Rizzoli *et al.,* 2021).

Dietary protein is associated positively with bone health through its ability to increase the secretion of insulin-like growth factor 1 (IGF-1), a mediator of tissue anabolism that stimulates the growth of multiple cells. Dietary protein sources rich in l-arginine were found to be effective at increasing growth hormone release, thereby increasing IGF-1. The growth hormone IGF-1 is known to stimulate osteoblasts, thereby improving bone mass through an upregulation of bone formation; however, further investigations are warranted (Bihuniak *et al.,* 2015).

Phosphorus and Bone Health

Phosphorus is a macroelement involved in many biological processes. Due to its mobility, it is a key human intracellular anion, which participates in maintaining the acid-base balance in the body, creating buffer systems in blood and urine (Soetan *et al.,* 2010). Phosphorus is involved in the conduction of nerve stimuli. Hydroxyapatites and phosphoproteins are bone building materials, while pyrophosphates play a regulatory role in the processes of osteogenesis and osteolysis (Penido *et al.,* 2012). Phosphorus is the second, next to Calcium, basic component of bone tissue. In the human body, it is present in the amount of 550-770 g, almost 85 percent of which is stored in bones and teeth in the form of phosphoproteins and hydroxyapatite crystals (Butusov *et al.,* 2013)

Inorganic phosphate (P_i) plays a critical function in many tissues of the body: for example, as part of the hydroxyapatite in the skeleton and as a substrate for Adenosine Tri Phisphate synthesis. P_i is the main source of dietary phosphorus.

Reduced bioavailability of P_i or excessive losses in the urine causes rickets and osteomalacia. While critical for health in normal amounts, dietary phosphorus is plentiful in the Western diet and is often added to foods as a preservative. This abundance of phosphorus may reduce longevity due to metabolic changes and tissue calcifications (Serna and Bergwitz, 2020).

B. OSTEOPOROSIS ITS CAUSES AND MANAGEMENT

a. Osteoporosis and its Classification:

The word osteoporosis is derived from the Greek language; 'osteo' meaning bone, and 'poros' meaning porous. The terminology itself gives an instant impression of the disorder and allows one to envisage its implications (Zhao *et al.,* 2011). Osteoporosis is a very common disease all over the world, in which a reduction in bone density can lead to an increased risk of fractures and a diminished physical height. Osteoporosis is also associated with acute and chronic pain, which especially occurs in the back and can significantly reduce the quality of life (Paolucci *et al.,* 2016).

Osteoporosis is a skeletal condition marked by a loss of bone mass and micro architectural degradation of bone tissue, resulting in lower bone tension and strength and an increased risk of fragility fractures. Usually after age of 40, bone mass decreases (Bouillon *et al.,* 2001; Kanis *et al.,* 2004 and Pal, 2017).

Osteoporosis is a very common disease all over the world, in which a reduction in bone density can lead to an increased risk of fractures and a diminished physical height. Osteoporosis is also associated with acute and chronic pain, which especially occurs in the back and can significantly reduce the quality of life (Paolucci *et al.,* 2016).

The most prevalent bone disease in humans, osteoporosis, is a huge public health issue. Caucasians, women and the elderly are more likely to have it. Just as hypertension is a risk factor for stroke, osteoporosis is a risk factor for fracture. Osteoporosis affects a large number of people of all races and genders and its incidence is expected to rise as the population ages. It's a quiet condition until it develops fractures, which can lead to serious secondary health issues and even death (Cosman *et al.,* 2014).

Individual trabecular bone plates are removed, leaving an aesthetically compromised structure with dramatically reduced mass; this increases the risk of fracture, which is exacerbated by other aging-related functional reductions. Rapid bone remodelling (as indicated by biochemical indicators of bone resorption or creation) is thought to enhance bone fragility and fracture risk (Wright *et al.,* 2014).

Osteoporosis can be classified into two main groups by considering the factors affecting bone metabolism as Primary osteoporosis and Secondary osteoporosis. Primary osteoporosis is further classified into two types as Type I - Involutional Osteoporosis which was also known as postmenopausal osteoporosis, and it's caused by a lack of oestrogen, mostly harming the trabecular bone. As a result, women are more prone to osteoporosis than males, as seen by a 4/5.7 men/women ratio (Cosman *et al.,* 2014). Secondary Osteoporosiscan be caused by a variety of disorders, drugs, and lifestyle changes (Compston *et al.,* 2013).

b. Prevalence of Osteoporosis

Global Scenario

An estimated 200 million individuals worldwide suffer from osteoporosis. In the United States, Europe, and Japan, an estimated 75 million individuals are afflicted. Every year, more than 8.9 million people worldwide suffer from osteoporosis-related fractures. In wealthy nations, the lifetime risk of an osteoporotic fracture is 30-40 percent, which is comparable to the risk of coronary heart disease. It causes 2.8 million Disability-Adjusted Life Years (DALYs) every year in America and Europe, accounting for around 1 percent of the DALYs caused by non-communicable illnesses (WHO, 2004).

According to Paruk *et al.,* (2020) the prevalence of osteoporosis in the world was 18.3 percent, which was computed based on reports of osteoporosis prevalence from 86 studies spanning five continents. Despite the fact, there are few epidemiological research on osteoporosis in Africa, recent investigations have found that osteoporosis and associated fractures are on the rise across the continent. As a consequence of the findings of this study, it was shown that the prevalence of osteoporosis in Africa is significantly higher than in other continents.

According to a comprehensive and meta-analysis research conducted in China between 2003 and October 2015, the prevalence of osteoporosis was 15.33 percent in males and 25.41 percent in women. According to the findings, the total prevalence of osteoporosis was 20 percent (Chen *et al.,* 2016).

The prevalence of osteoporosis was studied in people aged 50 and up in several industrialised countries (the United States, Canada, five European countries, Australia, and Japan). The following countries had the highest rates of osteoporosis in the spine or hip: 26.3 percent in Japan, 21 percent in the United States, 14.3 percent in Germany, 9.9 percent in France, 9.7 percent in Italy, 7.8 percent in the United Kingdom, 6.3 percent in Spain, 2.6 percent in Canada, and 2 percent in Australia. The total number of persons suffering from osteoporosis is estimated to be 49 million (Wade *et al.,* 2014).

In 2018, researchers in the eastern Mediterranean conducted a systematic review and meta-analysis based on World Health Organization (WHO) diagnostic criteria: the study was conducted without language restrictions between 2000 and 2017; the prevalence of osteoporosis is 24.4 percent in women and 20.5 percent in men (Zamani *et al.,* 2018).

An osteoporotic fracture is expected to affect one in every three women and one in every five men worldwide. By 2050, the incidence of hip fracture will have increased by 310 percent in males and 240 percent in women. Many Asian nations have seen a 2-3 times rise in the frequency of hip fractures over the last three decades, proving the fallacy that osteopenia and osteoporosis are illnesses of the West. By 2050, Asia is predicted to account for more than half of all osteoporotic hip fractures.

Indian Scenario

According to several research in India, the incidence of osteoporosis among women ranges from 8 to 62 percent (Khadilkar *et al.,* 2015). This reveals a broad range of prevalence in India. Furthermore, women have a higher risk of osteoporosis than males and the elderly have a larger risk than young ones. In accordance with this, a recent study from North India found that women (36.4 percent of women aged 30 to 39 years and >70 years, respectively) have a greater prevalence of osteoporosis than

males (0 and 5.6 percent for the two age categories). Furthermore, the prevalence of osteopenia was found to be greater in women (40.3 percent) than in men (29.9 percent) (Kaushal *et al.,* 2018).

According to reports, 61 million Indians suffer from osteoporosis, with 80 percent of them being women (Krishna *et al.,* 2000). In India, the peak incidence of osteoporosis occurs 10-20 years before it does in Western nations, putting a strain on both health and economic resources (Khajuria *et al.,* 2011).

Modagan *et al.,* (2018) reported that the incidence of osteoporosis was found to be 24.7 percent in a research of 773 Indian men and women aged 30 to 90 years. The prevalence in women was reported to be 1 percent with 10.3 percent of postmenopausal women and 4.7 percent of premenopausal women affected. According to Kaushal *et al.,* (2018), the frequency in men was reported to be 9.7 percent. The prevalence of osteoporosis was estimated to be 6.9 percent in a sample of 524 Indian persons aged 20 to 85, with 11.1 percent of women and 3.9 percent of males.

c. Risk Factors of Osteoporosis

An imbalance between bone resorption and production causes osteoporosis. A variety of modifiable risk factors for osteoporosis, such as nutrition and lifestyle variables, have been identified in research studies, whereas others are non-modifiable (Zaidi *et al.,* 2007).

i. Modifiable Risk Factors

The modifiable risk factors of osteoporosis include nutritional factors: calcium and vitamin D intake, the two main nutrients involved in bone health, plays a major role in influencing the risk of osteoporosis.

Calcium

The hardness of bone is determined by calcium deposited in the form of hydroxyapatite crystals in the bone matrix. Calcium is derived from both dairy and non-dairy sources in the diet. Calcium from dairy sources has a substantially greater bioavailability than calcium from non-dairy sources. Several studies have found that Indian diets do not fulfil the Indian Council of Medical Research's recommended

dietary requirements of 600 mg of calcium per day for adult women. One of the reasons for this may be lack of dairy intake (Mithal *et al.,* 2014).

Vitamin-D

When exposed to sunshine, the human skin produces vitamin D. Despite the abundance of sunlight in India, some researches claim that Indians are vitamin D deficient. Low sun exposure, traditional attire (saris, salwarkameezes), insufficient nutritional intake, poor vitamin D fortification of food and highly pigmented skin are all possible causes of vitamin D insufficiency in Indians (Tandon *et al.,* 2014).

Ineffective calcium absorption from the intestines is caused by vitamin D insufficiency, which inhibits bone mineralization. Vupputuri *et al.,* (2006) found that "functionally significant insufficiency of vitamin D impacting BMD at hip" was common among urban Asian Indians. The DeVOS data imply that participants who used calcium and vitamin D supplements had a decreased risk of osteoporotic fractures (Marwaha *et al.,* 2011).

Nutritional Status

Nutritional deficiency is also a significant risk factor for osteoporosis. Women with a body weight of 60 kg and a height of 155 cm are more likely to develop osteoporosis (Keramat *et al.,* 2008). A multitude of routes connect bone with fat, resulting in the development of a skeleton with adequate BMD to sustain the load it must bear. The key determinant of BMD is body weight, particularly adipose tissue. A favourable association between BMI and BMD has been found in several research (Aggarwal *et al.,* 2011 and Kumar *et al.,* 2010).

Body Mass Index (BMI)

Lee *et al.,* (2020) found that BMI of 23.0 to 24.9 kg/m^2 is the optimal range for minimizing the risk of osteoporosis. As BMI increases by 1 kg/m^2, the risk of osteoporosis in men and women appears to be reduced by 28 percent and 13 percent, respectively. Increased weight level was association with low risk of osteoporosis (Zhang *et al.,* 2019). Body mass index (BMI) is inconsistently associated with the progression of low bone mass-related fractures. Higher BMI may affect the risk of osteoporotic fractures regardless of the gender (Xiang *et al.,* 2017).

Influence of Lifestyle on Osteoporosis Risk

Sedentary lifestyles, less sun exposure and decreased physical exercise have all been linked to poor bone health as a result of urbanisation (Mithal *et al.,* 2014). Despite being a key risk factor for osteoporosis, cigarette smoking has been determined to be too low among Indian women to significantly enhance their risk (Keramat *et al.,* 2008). According to the DeVOS, neither cigarette smoking nor alcohol intake was found to be substantially linked with prevalent fractures in the research participants (Marwaha *et al.,* 2012).

Varied civilizations have different levels of health knowledge and awareness. According to a survey on osteoporosis knowledge and health attitudes in a sample of 262 males aged 36-55 years, osteoporosis awareness and perceived susceptibility were low. The rising frequency of osteoporosis-related fractures in males necessitates the development of measures to raise awareness and understanding (Babatunde *et al.,* 2017).

Physical Activity

Physical activity, particularly weight-bearing exercise, aids in the improvement and maintenance of muscle and bone strength as well as bodily balance (Meeta *et al.,* 2013). In Indian women, lack of exercise has been observed to be connected with reduced BMD (Aggarwal *et al.,* 2011; 2013).

The data reported indicates beneficial affect of exercise especially weighted and aerobic, in terms of improving bone formation biomarkers such as Alkaline phosphatase ALP and Bone-specific alkaline phosphatase (BALP) and decreasing bone resorption biomarkers such as NTX in the osteoporotic population (Marini *et al.,* 2020).

Walking, among other physical activities, is ineffective in preventing osteoporosis because it only adds a little amount of strain to the skeleton above gravity (Zhu *et al.,* 2017). Exercise intervention can help menopausal women enhance muscular strength and physical activity levels, lowering their risk of osteoporosis and sarcopenia (Yang *et al.,* 2017).

Sun Exposure

Sunlight exposure for ≥ 5 h a day was significantly associated with a decreased risk of fracture in older Korean adults with osteoporosis. This association was also significant in patients with vitamin D insufficiency (Lee *et al.,* 2021). Study by Jakobsen *et al.,* (2013) also revealed that one among the important factors that are associated with an increased risk of osteoporosis was limited sun exposure. Bess (2022) stated that adults who have limited sun exposure are at increased risk of vitamin D deficiency, especially if they have dark skin people, since people who have darker skin need more sun exposure to produce adequate amounts of vitamin D.

Previous History of Fractures

While some studies have found that a history of prior fractures in the past 5 years is a substantial risk factor (Keramat *et al.,* 2008; Marwaha *et al.,* 2012) found that a history of previous fractures did not significantly enhance the risk of vertebral fractures.

Maternal Nutrition

During pregnancy, diet has shown to be associated with epigenetic changes altering postnatal transcriptional activity of genes that affect childhood body composition (Godfrey *et al.,* 2011). In cohort study by Ganpule *et al.,* (2006) from India, it has been shown that children born to mothers who were dependent on higher uptake of calcium-rich foods during pregnancy had higher total and spine bone mineral content and BMD independent of parental size and DXA measurements. Offspring of pregnant rats fed with low-protein subsequently develop functional impairement in adulthood, including hypertension, progressive deterioration of renal function, cardiovascular disease, impaired immune response and altered lifespan .

ii. Non-Modifiable Risk factors

The non modifiable factors include age, gender, genetic factors, late menarche and early menopause.

Age

Age plays a significant influence in bone thinning and the development of poor bone density, since the BMD decreases with age. Pouresmaeili *et al.,* (2018) states that there is a significant association of ageing with bone mineral density.

It has been reported that age is one of the most important factors related to osteoporosis or osteopenia (Jilka *et al.,* 2016). The BMD of the spine and hip decreases significantly as men age, according to a research of south Indian males aged 41 and up (Elizabeth *et al.,* 2009).

Gender

Women start losing bone at an earlier age and at a faster rate than men. Women ≥ 50 years of age have a four times higher rate of osteoporosis and a two times higher rate of osteopenia, and they tend to have fractures 5 - 10 years earlier compared with men. Men usually have fractures at a higher bone density, especially at the lumbar spine and they tend to have a higher mortality risk after the hip fracture. Men are under-screened for osteoporosis and they are also undertreated even when they have fractures (Alswat, 2017).

Late Menarche and Early Menopause

Menopause is characterized by the loss of estrogen production by the ovaries. This may occur by natural means or by the surgical removal of both ovaries. This loss of estrogens accelerates bone loss for a period ranging from 5 to 8 years. In terms of bone remodeling (explained in detail on a previous page) the lack of estrogen enhances the ability of osteoclasts to absorb bone. Since the osteoblasts (the cells which produce bone) are not encouraged to lay down more bone, the osteoclasts win and more bone is lost than is produced (James, 2016). Postmenopausal women are susceptible to primary osteoporosis since osteoporosis is closely related to estrogen deficiency. During the menopausal transition period, the drop of estrogen leads to more bone resorption than formation, resulting in osteoporosis (Ji and Qi, 2015).

Genetic Factor

Genome-wide association studies have also identified common genetic variants of small effect size that contribute to regulation of BMD and fracture risk in the general population. Although there has been extensive progress in identifying the genes and loci that contribute to the regulation of BMD and fracture over the past 15 years, most of the genetic variants that regulate these phenotypes remain to be discovered (Ralston and Uitterlinden, 2010).

According to the study by Collet *et al.,* (2018*)* the clinical phenotype of patients carrying causal gene variants was indistinguishable. In conclusion, molecular screening of young osteoporotic adults revealed several variants and could be useful to characterize susceptibility genes for personalizing treatment, in particular for the new anabolic drugs.

Hsu *et al.,* (2020) found that a gene variant, SOX6 rs297325 was not significantly associated with osteoporosis but might have modulated the association between menopause and osteoporosis. The risk of osteoporosis was higher in menopausal women with the TC + CC genotype but lower in premenopausal women with the TC + CC genotype.

d. Other Risk Factors

Osteoporosis and Diabetes Mellitus

Around eight percent of young people in the United States have diabetes, with the number of diabetics expected to climb from 11 million in 2000 to 29 million in 2050 (Boyle *et al.,* 2010).

The current incidence of diabetes mellitus in Saudi Arabia is about 17 percent, with projections of 20 percent by 2030. Reduced BMD in Saudi women with type 2 diabetes is associated with advanced age, oral hypoglycemic medications, and vitamin D insufficiency (Al Homood *et al.,* 2017). Changes in insulin and IGF levels, hypercalciuria linked with glycosuria, decreased renal function, obesity, greater levels of Advanced Glycation End Products (AGEs)in collagen, angiopathies, neuropathies, and inflammation are all possible causes of skeletal problems in diabetes. (Inzerilla *et al.,* 2004; Raska *et al.,* 2005 and Wongdee *et al.,* 2011).

When BMD readings from type 1 and type 2 diabetic patients of similar ages were compared, it was shown that Type 1 Diabetes Mellitus (T1DM) is linked to a decrease in BMD. Increased BMD can, however, be linked to Type 2 Diabetic Mellitus (T2DM) (Tuominen *et al.,* 2009). It's possible that T1DM and T2DM are linked to an increased risk of fracture (Isidro *et al.,* 2010). In a study of osteoporotic fractures, Schwartz *et al.,* (2001) found that women with T2DM have a greater risk of hip, humerus and foot fractures than non-diabetic women.

Osteoporosis was more frequent in females than in males and was increased with ageing. Osteoporosis prevalence was higher in less developed areas than in developed areas (41.0% vs. 32.7%) and almost the same between the southern and northern regions (37.6% vs. 38.2%). The prevalence rate between 2010 and 2017 decreased compared with the period between 2001 and 2009 (42.3% vs. 35.6%). Additionally, the meta-regression suggested that gender and age could significantly influence the estimation of prevalence rates respectively (Yuhao *et al.,* 2019).

Diabetic Mellitus slows the pace of angiogenesis essential for bone regeneration by lowering the expression of endothelial progenitor cells produced from bone (Menegazzo *et al.,* 2012). Amylin and preptin are also produced by pancreatic cells. Amylin is known to promote bone growth and inhibit bone resorption. Preptin promotes osteoblast development and mineralization while reducing apoptosis. Diabetic Mellitus inhibits the formation of osteoclast cells, which has a favourable effect on osteogenesis (Hamann *et al.,* 2012).

However, Neumann *et al.,* (2016) found that the trabecular bone score was lower in T1DM patients with frequent fractures compared to healthy controls, indicating a change in bone strength in this cohort.

BMI is favourably related with BMD, according to Walsh and Vilaca (2017), and the causes of this connection in vivo may include greater loading, adipokines like leptin, and higher aromatase activity. Some fat depots, however, may have a deleterious impact on bone; T2DM is linked to better BMD, but also increased overall and hip fracture risk. Although there are some parallels between bone in obesity and T2DM, T2DM appears to have extra negative consequences, with glycation of collagen being a key component.

In obesity and T2DM, increased BMD but higher fracture risk complicates fracture prediction. Treatment for osteoporosis appears to minimise the incidence of fracture in obese and T2DM individuals with typically similar efficacy to that seen in other patients (Walsh and Vilaca, 2017) A recent meta-analysis found a substantial link between T2DM and an increased risk of overall fracture. These findings highlight the need of fracture prevention methods in diabetic individuals (Moayeri *et al.,* 2017).

Osteoporosis and Chronic Obstructive Pulmonary Disease (COPD):

Osteoporosis is prevalent in individuals with COPD and the prevalence seems to be high and similar in many countries. Patients with COPD should be screened for osteoporosis and contributing risk factors. The presence of COPD increased the likelihood of having osteoporosis (OR, 2.83). Other significant risk factors for osteoporosis in COPD patients were BMI < 18.5 kg/m^2 (OR, 4.26) and the presence of sarcopenia (OR, 3.65) (Chen *et al.,* 2019).

Inflammatory Bowel Diseases (IBDs) encompassing Crohn's disease and ulcerative colitis are known to be associated with decreased bone mineral density (BMD) (Larsen *et al.,* 2010 and Levine *et al.,* 2011).

Evidence has shown that osteoporosis is relatively common in Ankylosing Spondylitis (AS) patients; the major pathophysiological mechanisms appear to be systemic inflammation and low BMD resulting from decreased daily physical activities caused by pain, stiffness, and ankyloses (Vander *et al.,* 2011). In addition, numerous studies have demonstrated that, in AS patients, a low BMD and bone loss are observed within the first 10 years of disease (Ghozlani *et al.,* 2009; Vander *et al.,* 2012 and Briot *et al.,* 2015).

Patients with systemic lupus erythematosus have an increased risk of developing reduced bone mineral density (BMD) (Gracanin *et al.,* 2015). A study has shown that low volumetric bone mineral density (BMD) is present in 58% of all subjects with COPD, and is even more frequent in those with worse COPD, and has a prevalence of 84% among subjects with very severe COPD (Jaramillo *et al.,* 2015). A meta-analysis that contained the total number of patients with COPD from all studies is 3815, has shown the prevalence of osteoporosis among COPD is higher than that among healthy subjects (osteoporosis, 14%–66% and osteopenia, 18%–65%) (Bitar *et al.,* 2019).

Osteoporosis and Rheumatoid Arthritis (RA)

In an aging population, comorbidities such as cardio vascular disease and osteoporosis occur more frequently. These comorbidities develop even more often in patients with inflammatory rheumatic diseases such as Rheumatoid Arthritis (RA) (Lems *et al.,* 1998 and Szekanecz *et al.,* 2016, 2019).

Rheumatoid Arthritis (RA) patients have a high prevalence of osteoporosis. Older age, female sex, lower BMI and higher activity and severity of RA are closely related with osteoporosis (Tong *et al.,* 2020).

Bone loss in Rheumatoid Arthritis (RA) was significantly associated with age, low Body Mass Index (BMI), longer disease duration, rheumatoid factor, SvdH, atlantoaxial subluxation and corticosteroids use. Menopause, low calcium intake and erythrocyte sedimentation rate were risk factors for reduced BMD. Bone loss and fragility fracture are frequent in Rheumatoid Arthritis (RA) and related to disease severity, function impairment and corticosteroids use (Wafa *et al.,* 2019).

Osteoporosis and Cancer

Treatment-induced osteoporosis, on the other hand, can arise as a result of glucocorticoid medication, chemotherapy-induced ovarian failure and oestrogen deprivation therapy (Rizzoli *et al.,* 2014). As a therapy for metastatic prostate cancer, raises the risk of osteoporosis in men with the disease, which is linked to a steady decrease in hip BMD (Lau *et al.,* 2009).

Radiation therapy for prostate cancer causes bone damage by reducing blood flow and oxygenation in bone tissue, as well as reducing bone-forming cells and causing bone atrophy (Handforth *et al.,* 2018). Dickman *et al.,* (2004) found that in males exposed to Androgen Deprivation Therapy (ADT) within 6 months of diagnosis, the incidence of hip fracture from diagnosis to death was 1.6 times higher than in control men in a Swedish community. Because oestrogen and testosterone have been demonstrated to play a significant role in bone health in both men and women, breast and prostate cancer therapies that produce hypogonadism disturb the normal bone remodelling process (Reid *et al.,* 2006).

Osteoporosis and Dementia

Evatt *et al.,* (2008) discovered a high prevalence of vitamin D insufficiency in Parkinson's disease patients when compared to AD patients and controls. Parkinson's disease may lead patients to have fewer activity levels and less exposure to sunshine, according to some theories.

Hip fracture, the most prevalent kind of fracture, was consistently greater in individuals with AD (17.4 per 1,000 person-years) than in patients without

AD (6.6 per 1,000 person-years). The risk of hip fracture was the same in men and women with Alzheimer's disease. Around one-third (32.4 percent) of AD patients and 18.8 percent of non-AD patients did not survive a year following a hip fracture (Baker *et al.,* 2011), which is similar with another research by Haasum *et al.,* (2012) which found that hip fractures occurred in 16 percent of persons with dementia and 3 percent of those without dementia.

H_2O_2 and peroxides are powerful osteoclastogenesis inducers (Julus *et al.,* 2012). Receptor Activator of Nuclear Factor Kappa B Ligand is a critical component found in osteoblasts and stromal cells that encourages preosteoclast development into osteoclasts by activating nuclear factor and inducing Nuclear Factor of Activated T cells (NFAT) via Reactive Oxygen Species (ROS)-mediated mechanism (Kim *et al.,* 2010).

Osteoporosis and Hyperparathyroidism

Thyroid hormones are essential for normal skeletal development and normal bone metabolism in adults but can have detrimental effects on bone structures in states of thyroid dysfunction. Untreated severe hyperthyroidism influences the degree of bone mass and increases the probability of high bone turnover osteoporosis. Subclinical hyperthyroidism, defined as low thyrotropin and free hormones within the reference range, is a subtler disease, often asymptomatic and the diagnosis is incidentally made during screening exams. However, more recent data suggest that this clinical condition may affect bone metabolism resulting in decreased Bone Mineral Density (BMD) and increased risk of fracture, particularly in postmenopausal women (Delitala *et al.,* 2020).

Osteoporosis was principally associated with factors related to PHPT like higher age, lower BMI, and lower creatinine level, presumably reflecting lower muscle mass and frailty. Older individuals with slightly lower calcium and PTH levels were more likely to have undergone a DXA scan; this may have resulted in a slight overestimate of osteoporosis prevalence with respect to the total cohort, as age is the dominant determinant of osteoporosis risk (Reid *et al.,* 2015).

Medication

Hormone Replacement Therapy (HRT) at different doses rapidly normalizes turnover, preserves Bone Mineral Density (BMD) at all skeletal sites, leading to a significant, reduction in vertebral and non-vertebral fractures. Tibolone, a Selective Tissue Estrogenic Activity Regulator (STEAR), is effective in the treatment of vasomotor symptoms, vaginal atrophy and prevention/treatment of osteoporosis with a clinical efficacy similar to that of conventional Hormone Replacement Therapy (HRT) (Gambacciani and Levancini, 2014). Long-term glucocorticoid usage by the elderly has also been linked to an increase in the prevalence of osteoporosis in the senior Indian population (Mithal *et al.,* 2014).

According to Soydal *et al.,* (2019) Postmenopausal women, men and patients with a family history who receive TSH-suppression treatment have a tendency to develop osteoporosis. Another interesting finding of our analysis was that male patients who received TSH suppression therapy were found to have a 20-fold increase in developing osteoporosis as compared to premenopausal women. Synthetic glucocorticoids are used to treat autoimmune, pulmonary and gastrointestinal illnesses, as well as patients undergoing organ transplantation and those suffering from cancer.

Effect of co-morbidities on osteoporosis risk

Hypertension, heart disease, asthma, Chronic Obstructive Pulmonary Disease (COPD), arthritis, stroke, inflammatory bowel disease, Parkinson's disease, multiple sclerosis and type I diabetes were all linked to an increased fracture risk in a study involving participants from the Global Longitudinal Study of Osteoporosis in Women (GLOW) (Dennison *et al.,* 2012).

Furthermore, a recent research in Germany including just fewer than 20,000 individuals found that 95 percent of persons with osteoporosis had at least one concomitant condition and that adults with osteoporosis had a higher risk of arthrosis, arthritis, chronic low back pain, depression, and chronic heart failure (Puth *et al.,* 2018).

The cause for the increased risk of osteoporosis in those who have co-morbid conditions is likely multifaceted. Inflammatory disorders such as Rheumatoid

Arthritis (RA) and Crohn's disease are comorbidities, and studies have linked pro-inflammatory cytokines including TNF, IL-1 and IL-6 to bone resorption (Nakamura *et al.,* 2011).

In addition, some epidemiological studies have discovered negative relationships between BMD and C - Reactive Protein (CRP), a marker of active inflammation. Furthermore, the deterioration in functional ability and lack of activity associated with illnesses including Rheumatoid Arthritis (RA), osteoarthritis, stroke and multiple sclerosis contribute to bone loss (Cauley *et al.,* 2016).

e. Complications

The clinical consequences of osteoporosis are fractures and associated comorbidities. Until a patient has a fracture, osteoporosis is a quiet condition. A recent fracture at any major skeletal site in an adult older than 50 years with or without trauma, such as the vertebrae (spine), proximal femur (hip), distal forearm (wrist) or shoulder, should suggest that the diagnosis of osteoporosis requires further urgent assessment, diagnosis and treatment (Compston *et al.,* 2020).

A research of diverse populations found that African American women have greater BMD than white women at all body weight levels, which is consistent with their reduced fracture rates. In Asia, both lifestyle-related metabolic diseases and osteoporosis are becoming more common. In Asian males, metabolic syndrome is linked to bone loss, while atherosclerosis is linked to higher fractures (Sugimoto *et al.,* 2016).

f. Diagnosis of Osteoporosis

BMD (70 percent) and bone quality can be used to determine bone strength (20 percent). BMD is simple to assess, however bone quality is not currently detectable in clinical settings. BMD measurement, the incidence of a fragility fracture of the hip or vertebra or the lack of substantial trauma are all used to diagnose osteoporosis (e.g., motor vehicle accident or fall from multiple stories). There were no secondary causes of osteoporosis found in laboratory tests (Kanis *et al.,* 2013).

Osteoporosis is diagnosed when BMD falls 2.5 SD or more below the typical value for young healthy women (a T-score of 2.5 SD), according to the World Health Organization (WHO). A second, higher criterion assigns a T-score between 1 and

2.5 SD to "poor bone mass" or osteopenia. The term "severe" or "established" osteoporosis refers to the condition of having one or more verified fragility fractures. Bone mineral density can be easily tested to identify bone density, but the degree of bone tissue deterioration cannot be detected in clinical settings, with the exception of bone tissue biochemical indicators (Schousboe *et al.,* 2013).

The tests commonly used in clinical practice are,

DEXA (Dual Energy X-ray Absorptiometry)

An upgraded kind of x-ray technology called Dual Energy X-Ray Absorptiometry (DEXA), also known as bone densitometry or bone density scanning, is used to evaluate bone density. It is the most precise way of measuring BMD of all the methods available. It uses X-ray beams to determine the density of the hip and spine bones. X-ray photons easily penetrate through weak, less thick bones. Bones that are thick and strong enable less X-rays to pass through them. The amount of X-rays inhibited by bone and soft tissue is compared to one another. DEXA can detect as low as 2 percent bone density decrease over the course of a year (Sorenson *et al.,* 2008).

The DEXA test findings are divided into two categories:

T score - The T score value gives the amount of bone a person has compared to a young adult of the same gender with peak bone mass. This score can be used to estimate the risk of developing a fracture.

Z score - The Z score value reflects the amount of bone a person has compared with other people of the same age group and gender. If this score is unusually low, it indicates the need for further medical tests (Chatterton *et al.,* 2012).

QUS (Quantitative Ultrasound)

DEXA, a rather expensive and time-consuming treatment, has only been used for osteoporosis screening. However, a tiny and portable ultrasound device, the Quantitative Ultra Sound (QUS) machine created specifically for bone density assessment, may now be used to detect bone density. The calcaneal bone density is measured by QUS. The DEXA's hip and spine density values are equivalent to the QUS's heel readings. The QUS uses high-frequency sound waves to assess sound speed and broadband ultrasonic attenuation. As a result, it measures both how quickly

travels through the bone sound and how much of that sound reaches the other side to determine bone density. The QUS results are also expressed as a T-score and are interpreted similarly to the DEXA T- score results (Roux *et al.,* 1996).

Quantitative Computed Tomography (QCT)

Quantitative Computed Tomography (QCT) may only be performed in certain laboratories and must adhere to rigorous protocols. A QCT scan analyses the density of the spine's bones. A kind of QCT called peripheral quantitative computed tomography examines the density of bones in the arms or legs, most often the wrist. Because QCT measures decline more quickly than DEXA measurements, the T scores derived from QCT are lower (Eugene *et al.,* 2009).

Dual Photon Absorptiometry (DPA)

Dual Photon Absorptiometry (DPA) measures bone density using a radioactive material. It is capable of determining BMD in the spine and hip. It employs extremely low radiation doses as well, but scans considerably more slowly than the other approaches. The 153Gd is a common radionuclide that produces photons with dual energy peaks of 44 and 100 keV, which are measured independently using scintillation detectors. Inhomogeneity of soft affects the accuracy of photon absorptiometry (Lee *et al.,* 2008).

Vertebral Imaging (Vertebral Fracture Assessment)

Asymptomatic vertebral fractures are prevalent in older individuals, requiring vertebral imaging, which may be done with a lateral thoracic and lumbar spine X-ray or the lateral Vertebral Fracture Assessment (VFA) available on most DXA machines; this can be done at the same time as the BMD assessment. When the T-score is -1.0 at the spine, total hip, femoral neck and other locations, lateral spine imaging with conventional radiography or densitometry VFA is recommended (Cosman *et al.,* 2014).

Fracture Risk Assessment Tool Model (FRAX)

Fractures are the most serious health consequence of osteoporosis. Recently, algorithms that include substantial indicators of fracture risk in addition to BMD have been created to predict the risk of fracture in people. Algorithms that incorporate the weight of clinical risk fractures for fracture risk with or without information on the

BMD have been developed to estimate the 10-year risk of a significant osteoporotic fracture (i.e., fracture of the hip, vertebra (clinical), forearm, or proximal humerus). They can be used to calculate the chances of a hip fracture or a significant osteoporotic fracture in the next ten years (clinical spine, hip, forearm, or humerus) (Kanis *et al.,* 2007).

Biochemical Bone Turnover Marker (BTM)

Bone remodelling (or turnover) happens all the time to repair fatigue damage and micro fractures in the bone, as well as to maintain mineral homeostasis. Resorption markers, such as serum C-terminal telopeptide type I collagen (s-CTX) and urinary N-telopeptide (NTX), as well as formation markers, such as serum Procollagen type I N-Terminal Propeptide (s-PINP), may provide information on fracture risk independent of BMD and predict the rapidity of bone loss in untreated patients. As a result, their incorporation in evaluation algorithms may improve fracture risk prediction (Vasikaran *et al.,* 2011).

Other Diagnosis

An initial screening laboratory profile should be performed for patients diagnosed with osteoporosis using one of the preceding approaches. Individualized treatment for secondary causes of osteoporosis is required. The following tests are advised for those who have been diagnosed with osteoporosis.

25 hydroxy Vitamin D Level

To inhibit parathyroid hormone release to the greatest extent possible, blood levels of 25 hydroxyl vitamin D should be below 30 ng/mL. It is critical to have it assessed before to starting any pharmacologic treatment for osteoporosis to confirm that vitamin D reserves are adequate before starting medication (Eugene, 2009).

Serum Calcium

The existence of hypocalcemia (malabsorption/vitamin D deficiency) or hypercalcemia can be ruled out by blood calcium measurements (hyperpara-thyroidism). This is required to rectify hypocalcemia before beginning pharmacologic treatment for osteoporosis (Lee *et al.,* 2013).

24-hour Urine Calcium Excretion

This allows for the detection of malabsorption (e.g. celiac sprue) and vitamin D insufficiency in cases when the vitamin's value is low. Hypercalciuria, a treatable cause of bone loss, is high (Amicosante *et al.,* 2009).

Serum Creatinine

To determine 24-hour urine calcium excretion and guarantee the safety of newer pharmacologic osteoporosis therapy, serum Creatinine should be collected (Clowes *et al.,* 2006).

Approach to a Patient with Osteoporosis

To determine an individual patient's fracture risk, a complete history and physical examination are combined with BMD testing, vertebral imaging to identify vertebral fractures (where applicable) and the WHO-defined 10-year estimated fracture probability test. To assess the necessity for BMD testing and/or vertebral imaging, all postmenopausal women and men aged 50 and above should be screened for osteoporosis risk. The higher the chance of fracture, the more risk factors there are. Osteoporosis may be prevented and treated, but because there are no warning signals before a fracture, many patients are not identified early enough to undergo effective treatment (Kanis *et al.,* 2008).

g. Treatment of Osteoporosis

a. Pharmacological treatment

i. Bisphosphonates

When pharmacological treatment is started, bisphosphonates are frequently the first medications administered. Most bisphosphonates, such as alendronate daily, risedronate weekly, ibandronate monthly, and zoledronic acid annually, are accessible and widely used in India (Mithal *et al.,* 2014 and Tandon *et al.,* 2014).

In individuals who have had a previous vertebral fracture, alendronate and rise-dronate lower the risk of fractures in the spine and hip by 40 percent -50 percent over 3 years. Rise dronate has been linked to a 49 percent decrease in new vertebral fractures in women who had had previous vertebral fractures. Ibandronate lowers the risk of vertebral fracture by 62 percent, whereas zoledronic acid, administered once a year by intravenous infusion, lowers the risk of vertebral fracture by 70 percent (Cosman *et al.,* 2014).

In an Indian examination of osteoporosis treatment algorithms, the majority of clinicians said bisphosphonates were the first-line therapy in practically all patients with the disease (Lakhotia *et al.,* 2012). Nitrogen-containing (amino) bisphosphonates and nitrogen containing bisphosphonates (etidronate, tiludronate and clodronate) which are essential for osteoclast function and survival (Das and Crockett, 2013).

According to Duhan *et al.,* (2012), the impact of isosorbide mononitrate and alendronate in the treatment of postmenopausal osteoporosis in Indian postmenopausal women discovered that after 9 months of therapy with alendronate, the mean BMD at the lumbar spine increased by about 12 percent.

Tandon *et al.,* (2014) found that monthly regimens had a 56 percent adherence rate, weekly regimens had a 36 percent adherence rate and daily regimens had a 32 percent adherence rate in a study that aimed to evaluate the adherence and compliance of postmenopausal osteoporotic women for different regimens of bisphosphonates in Indian postmenopausal women. As a result, the authors found that overall treatment compliance was low, and that significant pre and post-treatment counselling and follow-up were required.

Nausea, epigastric discomfort, and heartburn are the most prevalent side effects related with alendronate. Long-term bisphosphonate medication, on the other hand, may increase the risk of atypical femoral fractures and extend bone remodelling suppression. Other uncommon consequences include post-dental treatment osteonecrosis of the jaw, atrial fibrillation and esophageal cancer, according to reports (Bhadada *et al.,* 2014).

Selective Estrogen Receptor Modulators (SERMs)

Selective Estrogen Receptor Modulators (SERMs) are the synthetic compound that acts as estrogen agonists on bone and estrogen antagonists on breast and brain tissue. Raloxifene is the only approved second generation SERMs for the prevention and treatment of osteoporosis in postmenopausal women. It acts as an estrogen receptor modulator which competes with estrogens for binding to the estrogen receptor. It functions as estrogen agonist at bone and liver by maintaining BMD and lowers LDL cholesterol levels as well an estrogen antagonist in breast and endometrial tissue (Provinciali *et al.,* 2016). Bazodoxifene and

Lasofoxifene are the 3rd generation SERMs that are approved by the European Union for the treatment of osteoporosis in postmenopausal women at increased risk of fracture (Gallaghera and Tella, 2013).

Hormone Replacement Therapy (HRT)

The rate of bone turnover accelerates after menopause due to a lack of estrogens, resulting in increased bone loss. According to Indian recommendations for the treatment of postmenopausal osteoporosis, oestrogen medication can be used to prevent and cure osteoporosis in symptomatic women in the early postmenopausal period. Over a three-year period, oestrogen or oestrogen plus progesterone therapy is thought to reduce osteoporotic fractures and raise lumbar spine and femoral neck BMD. Despite the lack of statistics on Hormone Replacement Therapy (HRT) use in India, research implies that Asian women are substantially less aware of and utilise HRT than their Caucasian counterparts (Gupta *et al.,* 2013).

Drugs are currently the first treatment choice with great effect on the treatment of osteoporosis; however, the target organs are diverse, and thus the adverse reactions caused by poor targeting are increased. Specifically, one of the most representative drugs is 17β-estradiol. Reducing the non-specific enrichment of hormone drugs in non-target tissues and improving their bone-targeting ability is extremely important for broadening the clinical applications of 17β-estradiol. Recently, nanomaterials emerged as ideal drug carriers for reducing the exposure of hormone drugs to non-target tissues and improving their therapeutic efficacy (Barry *et al.,* 2016 and Morabito *et al.,* 2002)

Data on current attitudes and methods for managing osteoporosis patients in India were collected for a research aimed at stepping up efforts to optimise the therapy of osteoporotic patients in India. The majority of osteoporosis clinicians agreed that, despite being aware of the potential risks of cancer and cardiovascular disease from oestrogen intake, HRT was still used in perimenopausal osteoporosis because it helped to alleviate menopausal symptoms until patients were switched to bisphosphonates (Meeta *et al.,* 2013).

Progestins with oestrogen are required for women who have not undergone a hysterectomy to preserve the uterine lining. During the 5 years of treatment with

conjugated equine oestrogen and medroxyprogesterone, while oestrogen with progestin reduced the risk of vertebral and hip fractures, it also increased the risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein phlebitis. There was no increase in breast cancer incidence in the estrogen-only group after 7.1 years of therapy (Brown *et al.,* 2014).

As a result of the hazards, it is suggested that HRT be administered at the smallest effective dosages for the shortest time possible to achieve therapeutic goals. However, during an extended follow-up to investigate the impact of oestrogen usage on longer-term breast cancer incidence, investigators discovered that oestrogen use for a median of 5.9 years was related with a decreased incidence of invasive breast cancer after a median follow-up of 11.8 years. Breast cancer risk was also reduced with oestrogen usage in women without benign breast illness or a family history of breast cancer, according to subgroup analyses (Gupta *et al.,* 2013).

Furthermore, initiating hormone replacement therapy with oestrogen alone in postmenopausal women 10 years after their last menstrual cycle appears to have a lower risk. According to reports, HRT administered to postmenopausal women 60 years of age may be more useful for symptom control, bone loss prevention and metabolic profile improvement (Mcclung *et al.,* 2013).

Estrogen Agonists

Raloxifene hydrochloride is a selective oestrogen receptor modulator that is used to prevent and treat postmenopausal osteoporosis at a dose of 60 mg/d. 7,705 postmenopausal women with osteoporosis were treated with raloxifene at a dose of 60-120 mg/d or with a placebo for three years in the Multiple Outcomes of Raloxifene Evaluation (MORE) research, which was a major experiment investigating the usage of raloxifene. The study found that raloxifene 60 mg/d reduced the incidence of new clinical vertebral fractures by 68 percent in the total study group and by 60 percent in women with prevalent vertebral fractures, who are at a higher risk of additional fractures, after one year when compared to placebo (Srividhya *et al.,* 2015).

The authors found no significant improvement in BMD over the 6-month treatment period in a study conducted in New Delhi to determine the effect of raloxifene on bone loss by quantitative ultrasound and bone turnover markers

(bone-specific alkaline phosphatase) in postmenopausal women with osteopenia/ osteoporosis. Raloxifene, on the other hand, had a beneficial effect on bone turnover, as seen by a substantial decrease in blood bone-specific alkaline phosphatase (Lakhotia *et al.,* 2012).

Calcitonin

Calcitonin has been proven to lower the risk of vertebral fractures by 30 percent in women who have previously had them, but it has not been demonstrated to reduce the risk of non-vertebral fractures (Rossouw *et al.,* 2002).

Compliance is anticipated to be higher because it is given as a once-daily intranasal spray. With calcitonin, calcium and vitamin D supplementation is required. Although calcitonin is an anti-resorptive agent, it is thought to have a lower effect than the other anti-resorptive substances (North American Menopause Society, 2010).

The efficacy and safety of calcitonin nasal spray in the treatment of osteoporotic back pain in postmenopausal women were investigated in an open-label, prospective, multi-centric, single-arm post-marketing monitoring research. There was a considerable reduction in pain and an increase in quality of life. Following therapy with calcitonin nasal spray, the usage of analgesics was dramatically reduced. As a result, the authors found that calcitonin nasal spray therapy was related with a significant improvement in back pain and quality of life in postmenopausal Indian osteoporotic women (Anderson *et al.,* 2012).

Combination therapy with calcitonin have also been described in studies. In postmenopausal Asian women with osteoporosis, the effects of teriparatide with salmon calcitonin therapy on changes in BMD, biochemical bone markers and safety were investigated. Both medications were well tolerated, but teriparatide was linked to larger increases in lumbar spine BMD and bone formation indicators, suggesting the treatment's distinct mechanism of action and safety in Asian women (Gurney *et al.,* 2014).

Anti-resorptive medications such as HRTs, bisphosphonates, calcitonin and oestrogen agonists enhance bone mass by inhibiting bone resorption; nevertheless, individuals with osteoporosis have lost more than 25 percent of their normal skeletal mass. As a result, even after therapy with these medications, many patients' BMDs

remain in the osteoporotic range and many are still at risk of fracture. As a result, medications that increase the function of osteoblasts, often known as bone anabolic treatments, are required to replace or repair damaged bone (Spencer *et al.,* 2009).

Denosumab

Denosumab is a fully humanised monoclonal antibody that specifically binds to receptor activator of nuclear factor kappa B ligand and prevents to Receptor Activator of nuclear factor kappa B ligand from binding to receptor activator of nuclear factor kappa, thereby inhibiting osteoclastogenesis and osteoclast survival. The U.S FDA has approved denosumab 60mg, given subcutaneously at 6-monthly intervals for the treatment of osteoporosis in postmenopausal women and men, and bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (Langdahl *et al.,* 2015).

Parathyroid Hormone

`The effectiveness of teriparatide in enhancing BMD in postmenopausal Indian women with osteoporosis was investigated in a research. The research involved 82 postmenopausal women in a randomised, prospective, multicenter, open-label, controlled trial. Both oral and injectable medications had great compliance (Sethi *et al.,* 2008).

Teriparatide, a recombinant human PTH, was well tolerated by patients, and there were no major side effects. When comparing the teriparatide group to the control group, the percentage increase in lumbar spine BMD was considerably larger in the teriparatide group (6.6 percentvs 1.06 percent). Teriparatide therapy resulted in a considerable rise in bone biomarkers as well. Healing was achieved with the use of recombinant PTH in a case report on a 62-year-old postmenopausal Indian lady who had a tensile type of fracture neck femur and had impeded fracture healing (Malhotra *et al.,* 2013).

Osteoporosis Treatment Gap

Despite the fact that osteoporosis treatment options have been proved to be extremely successful, research suggests that only a small percentage of osteoporosis patients undergo therapy, and hence the personal and societal cost of fragility fractures remains high (Hernlund *et al.,* 2013). According to a recent research from

the US National Osteoporosis Foundation, 2 million Americans had 2.3 million osteoporotic fractures in 2015, with only 9 percent having bone mineral density testing within six months of the fracture. A second fracture occurred in 307 000 of these people in the first 2-3 years after the fracture, costing more than $63 billion (Compston, 2020).

The 'Osteoporosis Treatment Gap' is a term used to describe the untreated population of people with osteoporosis and recent researches have attempted to close it. Fracture risk assessment methods (such as FRAX), for example, have been created to aid doctors in identifying 'at risk' persons by utilising clinical characteristics to produce a measure of fracture risk. However, there is a 1000-fold difference in the usage of fracture diagnostic tools throughout the world, which might be due to a lack of consistency in local rules or difficulties accessing the evaluation tools online or in print format (Curtis *et al.,* 2017).

Despite the development of fracture risk assessment techniques, the number of 'at risk' patients receiving osteoporosis medication has decreased in certain industrialised nations, notably the United Kingdom and the United States (Solomon *et al.,* 2014). This tendency might be due to a disproportionate focus in the lay media on uncommon adverse effects linked to bisphosphonate treatment, such as jaw osteonecrosis and atypical femoral fractures (Adler *et al.,* 2016). However, there is minimal evidence that the risk of these side effects is considerably higher in people who have been taking bisphosphonates for ten years compared to age-matched controls (LeBlanc *et al.,* 2017).

Prevention of Osteoporosis

Osteoporosis is a condition that goes unnoticed. Fractures, on the other hand, cause agony and disablement, as well as being a significant financial burden. As a result, in this disorder, prevention is crucial. BMD testing is based on the risk profile in postmenopausal women, while measurement of BMD is indicated in women over 65. It is good to measure your height once a year (for vertebral fractures). A calcium-rich diet (up to 1,000-1,200 mg/d) and sun exposure to create or vitamin D supplementation to attain 800-1,000 IU/d are suggested lifestyle adjustments. Weight-bearing and muscle-strengthening activities should be done on a regular basis.

Furthermore, it is critical to avoid activities that harm bone health, such as smoking, and to avoid falls in order to avoid fragility fractures (Tang *et al.,* 2007).

Calcium and vitamin D

Other studies, however, have not shown similar findings, and instead of calcium and vitamin D supplementation, variables such as increased oxalate consumption and reduced liquid intake have been indicated as risk factors in the production of renal stones (Sunyecz *et al.,* 2008). There are few data on calcium and vitamin D intake in Indian women for the prevention of osteoporosis; however, Indian government programs only give calcium supplements (500 mg/d) during pregnancy and lactation (Government of India: Ministry of Women and Child Development, 2009).

A study comparing the effects of two different doses of oral vitamin D3 (cholecalciferol) on serum 25-hydroxy vitamin D [25(OH)-d] concentrations in healthy postmenopausal Indian women concluded that higher doses of vitamin D (1,000 IU) with calcium carbonate were required to achieve optimum serum 25(OH)- d concentrations (>30 ng/mL) (Agarwal *et al.,* 2013).

In the case of osteoporosis or an elevated fracture risk, calcium and vitamin D supplementation is insufficient, necessitating pharmaceutical intervention in the form of anti-resorptive or anabolic medicines. According to the Indian Menopausal Society's guidelines for the management of osteoporosis, pharmacological treatment should be started in women who have fragility fractures, asymptomatic vertebral fractures, osteoporosis at the hip or spine (ie, T score of 2.5), and women who have secondary causes for osteoporosis are at high risk of fractures (Meeta *et al.,* 2013).

However, the National Osteoporosis Foundation (USA) guidelines also suggest that pharmacologic therapy is indicated in postmenopausal women with low bone mass (T score between 1.0 and 2.5, ie, osteopenia) at the femoral neck, total hip, or lumbar spine by DXA and a 10-year hip fracture probability >3 percent or a 10-year major osteoporosis-related fracture probability >20 percent based on the fracture risk model (Cosman *et al.,* 2014).

Protein

The spatial distribution of bone mass (as cortical and trabecular bone) and the intrinsic material qualities of bone are also important factors in determining skeletal fragility (Bouxsein and Seeman, 2009). The best technique to directly quantify bone strength in people is to measure BMD, or Bone Mineral Content (BMC). The majority of observational studies find a link between protein and bone density or between protein and BMD change (Dawson- Hughes and Harris, 2002 and Vatanparast *et al.,* 2007).

Investigations on premenopausal women, on the other hand, found no link between protein consumption and BMD (Beasley *et al.,* 2010). According to one study, bone mineral content has a negative correlation (Metz *et al.,* 1993). Finally, a case-control research compared 134 osteoporotic women to 137 controls and found total protein consumption to be an osteoporosis risk factor. When examining through observation studies, Darling and colleagues conclude that there is no evidence of a detrimental effect of protein consumption on bone; in fact, there is probably a minor favourable effect of protein on bone (Darling *et al.,* 2009).

Here are just a few interventional trials that compare high protein consumption to low protein intake. One of them looked at the effects of an amino acid and carbohydrate supplement on 13 men while they were on bed rest. The authors found a decline in bone mineral content in supplemented participants after 28 days, while bone mineral content in control subjects remained steady (Zwart *et al.,* 2005).

It should be mentioned that the energy intake of the two groups differed due to the presence of an energy-free placebo. Another trial gave 20.4 grams to hospitalised elderly men and women for 38 days. The authors found a reduction in BMD loss with the protein supplement, in addition to other favourable outcomes (reduced complication rate, shorter hospital stay) (Tkatch *et al.,* 1992). Finally, a year-long investigation of 62 postmenopausal women supplemented with 25 grams of soy protein found no effect on total hip BMD or BMC (Arjmandi *et al.,* 2005).

When it comes to bone, fracture risk is the most important clinical outcome. When protein consumption was increased, the relative risk of hip fracture was lower in a longitudinal trial of 32 050 postmenopausal women (Munger *et al.,* 2009).

In 1865 perimenopausal women, another study found that the frequency of high protein meal consumption is positively related with a lower risk of wrist fracture (Thorpe *et al.,* 2008).

The protein supplement raised IGF-1 after a hip fracture, reducing bone loss at 6 months and decreasing hospital stay (Schurch *et al.,*2006). The amount of IGF-1 produced is unaffected by the kind of protein consumed (casein, whey protein, or whey protein with amino acids) (Chevalley *et al.,* 2009). Protein's therapeutic impact is most likely due to a rise in IGF-1 levels as well as a repair of the patient's nutritional status.

Physical Activity

Exercise or physical training can prevent osteoporosis in the elderly as a non-drug preventive strategy. The interaction of mechanical loading, hormones or cytokines, and signaling pathways induced by exercise increased bone formation and reduced bone resorption, leading to the maintenance of healthy skeleton. Dysregulation of bone angiogenesis is associated with many bone diseases including osteoporosis, and exercise improves angiogenesis in bone via the regulation of key angiogenic mediators. Further understanding the mechanisms of angiogenesis, signaling pathways, and key regulators induced by exercise will lay the foundation for the prevention of osteoporosis in the aging population (Tong *et al.,* 2019).

Pharmaceuticals have no effect on improving other key fracture risk factors, including low muscle strength, power and functional capacity, all of which are associated with an increased risk for falls and fracture, independent of BMD. Targeted exercise training is the only strategy that can simultaneously improve multiple skeletal and fall-related risk factors, but it must be appropriately prescribed and tailored to the desired outcome(s) and the specified target group (Daly *et al.,* 2019).

The skeletal advantages of physical exercise during adolescence extend throughout young adulthood, according to cross-sectional and longitudinal research, and activity-associated bone loading during early adulthood boosts BMD in middle-age and later adults. Bone loading throughout adulthood enhances bone growth, cortical area, and strength, as well as lowering the chance of hip fracture later in life (Daly *et al.,* 2006).

However, no clinical trials have been conducted to show that these suggestions are effective in reducing fracture incidence, and the effects of exercise-based therapies on BMD are equivocal. As a result, the best exercise prescription for bone health (i.e., exercise mode, intensity, duration and frequency) has yet to be discovered. The processes by which exercise affects bone and the mechanical loading characteristics that result in the greatest improvements in bone strength should be the foundation of exercise prescriptions for bone health (Turner *et al.,* 2005 and Robling *et al.,* 2006).

C. CALCIUM SUPPLEMENTATION AND ITS SIGNIFICANCE IN THE MAINTENANCE OF BONE HEALTH

Calcium (Ca) is the most prevalent mineral in the human body and it is necessary for strong bones and a variety of physiological processes. Calcium is almost entirely deposited in bones and teeth, where it helps to maintain their structure and hardness. Calcium is also found in nerve cells, body tissues, blood and other bodily fluids (Pravina *et al.,* 2013).

Calcium is a vital component in muscle action, acting as a switch to turn on and off muscular activity. An increase in Ca concentration initiates an energy-intensive chain reaction that leads myofilaments to shrink and alter form. The contraction of muscles is caused by the shortening of thousands of myofilaments (Chung *et al.,* 2016).

Calcium in diets and supplements along with vitamin D play critical roles in calcium homeostasis. Low calcium intake or low vitamin D level can also result in bone diseases. High calcium intake can reduce the risk of breast cancer and contribute to the reduced rate of bone loss and fracture incidence in elders (Pu *et al.,* 2016).

Adequate intake of calcium is essential but when it is not achieved properly intake of calcium supplements should be considered in postmenopausal women and men older than 50 years (Kim *et al.,* 2012). The supplementation of calcium with vitamin D have a considerable effect on spinal and femoral bone mineral density in healthy males (Silk *et al.,* 2015). The supplementation of calcium supplements have a positive effects on BMD (Kanis *et al.,* 2007*).*

Though in most of the individuals the dietary calcium intake is adequate it is also evidenced that inadequate calcium and vitamin D intake in individuals, so it is important to supplement which is useful in preventing the osteoporosis and related fragility fractures (Rozenberg *et al.,* 2016). Calcium intake is very different among the various populations in the world and therefore the calcium supplementation is necessary to maintain the good bone health (Cano *et al.,* 2018).

Peak bone mass during adolescent and to prevent osteoporotic fractures at old age proper dietary calcium intake and calcium supplementation is required. Calcium supplementation directly or indirectly affects important functions such as control of blood pressure, plasma glucose, body weight, lipid profile and endothelial function in the body (Lima *et al.,* 2016).

Dietary calcium intake has not been associated with the adverse effects associated with supplements, probably because calcium is provided in smaller boluses, which are absorbed more slowly since they come together with quantities of protein and fat, resulting in a slower gastric transit time. These findings suggest that calcium supplements have little role to play in the modern therapeutics of osteoporosis, which is based around the targeting of safe and effective anti-resorptive drugs to individuals demonstrated to be at increased risk of future fractures (Reid *et al.,* 2014).

There is significant result existing between the drug taken, calcium and Vitamin D supplementation patients. The effect of drug in improvement of bone mineral density is not same when the drugs are given along with the calcium and Vitamin D supplement in everyday practices. This helps in better understanding of benefit of calcium and vitamin D supplement (Paschalis *et al.,* 2017).

Sources

Plant and animal foods both contain calcium. Dairy products (milk, yoghurt, and cheese) are the best sources of calcium in animal meals, whereas green leafy vegetables like amaranth, fenugreek leaves and broccoli are the best sources in plant foods. Calcium is found in foods such as ragi, almonds, pistachios and sesame seeds, as well as fish such as salmon and sardines (Ross *et al.,* 2011).

Milk is the best source of calcium. For infants, mother's milk has a high calcium content. Calcium is abundant in cow, buffalo, and goat milk. Milk contains a good amount of calcium and a good amount of phosphorus, thus it is properly utilised by the body. Calcium is found in milk products such as curd, paneer and mava. The calcium content of millet ragi and seasame seeds is high. Green leafy vegetables are a good source of calcium, albeit only a small portion of it is absorbed by the body (DVO, 2015).

Fresh and dried fish, especially fresh fish, supply significant amounts of calcium in the diet if the bones are also consumed. Aside from these, other spices, such as cumin seeds (jeera) and coriander seeds (dhaniya), have enough calcium to contribute to the diet if consumed frequently and in appropriate quantities (Kanis *et al.,* 2013).

Recommended Dietary Allowances of calcium for Indians

Indian Council of Medical Research (ICMR) recommends more calcium is important for children and teenagers who are growing up. Despite the fact that recommended calcium dietary allowances are around 600-800 mg/day, it is preferable to provide higher amounts of calcium to teenagers in order to reach high peak bone mass. A healthy adult male and female needs 600 mg per day. For pregnant and breastfeeding mothers, the RDA for calcium rises to 1200 mg/d (ICMR, 2011).

Supplemental sources of calcium and its types:

Individual attainment of peak bone mass is influenced by calcium intake during childhood and adolescence (Ross *et al.,* 2011). Calcium intake has a considerable impact on the degree of age-related bone loss in adults and postmenopausal women (Tang *et al.,* 2007). As a result, ensuring adequate calcium intake is a critical component in osteoporosis prevention and therapy (NOF, 2014). Furthermore, calcium has been shown to have beneficial effects on blood pressure (Rizzoli *et al.,* 2014), lipid profile (Reid, 2004) and body composition. Furthermore, increasing calcium intake appears to lower the incidence of stroke (Larsson *et al.,* 2013) and colorectal cancers (Huncharek *et al.,* 2009). As a result, individuals, particularly older men and women, regularly take calcium supplements.

There are numerous calcium sources available for the treatment of calcium insufficiency. Milk contains calcium phosphate minerals, as well as organic salts such as tricalcium citrate, calcium lactate, calcium lactate gluconate and calcium gluconate, as well as inorganic salts such as calcium chloride, calcium carbonate, and calcium phosphate. The selection of an acceptable calcium source for a particular application is usually based on a number of factors connected with the product, such as solubility, calcium content, taste and bioavailability. Economic concerns play a significant role as well (Reinwald *et al.,* 2008).

Calcium supplements can be given for those children and adolescents who are unable to acquire adequate calcium from dietary sources, including fortified foods, due to a medical condition. For the prevention and treatment of osteoporosis, calcium supplementation is routinely utilised. On the global market, there are a variety of calcium salts and formulations. Many calcium supplement formulations include vitamins K and magnesium as well as calcium (Deborah, 2007).

Calcium carbonate and calcium citrate are the two most frequent calcium types. Lactate, gluconate and hydroxyapatite are some of the other calcium types. Calcium supplements come in a variety of forms, including capsules, tablets, chewables, powders and liquids (Reid *et al.,* 2010).

Calcium Carbonate

In maintaining the calcium level in End-Stage Renal Disease (ESRD) patients, the commonly used supplements is calcium carbonate which requires intact hydrochloric acid production from gastric parietal mucosa, to enable effective glycemic index absorption and intestinal calcium based chelation processes, but calcium citrate supplementation is less appreciated for these patients (Afshan *et al.,* 2017).

In patients with achlorhydria, a frequent ailment among the elderly, calcium citrate should be the supplement of choice. The disadvantage of using calcium citrate supplements is that you have to take more pills or capsules to get the same amount as calcium carbonate. Compliance may be harmed if more tablets are required (Sharon, 2010).

When calcium carbonate is taken with a meal, it is well absorbed and tolerated by the majority of people. Calcium carbonate supplements provide more elemental calcium and hence require fewer tablets than other calcium supplements. In people who have achlorhydria, inflammatory bowel illness, or absorption problems, calcium citrate should be utilised. Supplementing with calcium citrate is also indicated for people using H2 blockers or proton pump inhibitors. Calcium citrate, which can be taken with or without food, is also a good option for busy people who find it difficult to supplement at meals (Kanis *et al.,* 2013).

Calcium carbonate are given to the patients with Chronic Kidney Disease (CKD) to bind dietary phosphorus, reduce phosphorus retention, and prevent negative calcium balance. A study was done with eight patients with stage 3 or 4 CKD in which the patients received a controlled diet with or without a calcium carbonate supplement. At the end feces ,blood, urine samples were collected and tested, patient on the calcium carbonate supplementation were found to be in positive calcium balance and did not affect the phosphorus balance, where as the other group was in neutral calcium balance (Hill *et al.,* 2013).

A longitudinal study was conducted between 8 to 12 years Gambian boys and girls supplementing with calcium carbonate supplement 1000 mg per day and 5 days a week till they reach 21 to 25 years. Finally by collecting anthropometric measurements, pubertal status and menarche data was collected, tested and proved that calcium supplementation for boys in later childhood advanced the age of peak height velocity but in low calcium intake population the adult stature was shorter and delayed puberty was common (Prentice *et al.,* 2012).

Calcium Citrate

Calcium citrate-malate is a compound made up of the calcium salts of citric and malic acids. Calcium citrate-malate contains around 26 percent elemental calcium, has a bioavailability of up to 42 percent, and has the highest bioavailability (consistently over 35 percent) in human tests. It is one of the most extensively researched forms of calcium in the field of bone health and is often regarded as the most efficient vegetarian calcium source (Shea *et al.,* 2002).

Because of its water solubility and mechanism of dissolution, calcium citrate-malate has a high bioavailability. It releases calcium ions and a calcium-citrate complex when dissolved. Calcium citrate malate's unique structure makes it 6 to 9 times easier to dissolve in the stomach than regular calcium citrate, with absorption rates of 36-37 percent in tablets and capsules and even greater when dissolved in orange juice. When taken with or without food, calcium citrate malate is effectively absorbed (Lorieau *et al.,* 2018).

Coral Calcium

Calcium supplements made from natural sources including coral, dolomite (a form of limestone) and oyster shell are available. Coral calcium (calcium carbonate matrix) comes from the exoskeletons of corals. It is mostly composed of calcium carbonate (20 percent) and magnesium (10 percent). None of these assertions, however, have been proven. It has not been established that calcium obtained from coral is superior than calcium obtained from other sources. There's also the possibility that some coral calcium products contain too much lead. Supplements containing dolomite may also contain dangerous levels of lead and other heavy metals (Trailokya *et al.,* 2017).

Calcium Lactate and Calcium Gluconate

Calcium lactate and calcium gluconate are calcium salts that are less concentrated. Calcium lactate contains 13 percent elemental calcium, but calcium gluconate contains just nine percent; thus, these forms are not suitable for therapeutic use. Due to low concentration of elemental calcium in calcium lactate and calcium gluconate, numerous tablets are required to get desired dosages (Reid *et al.,* 2005).

Calcium lactate and calcium gluconate are less concentrated calcium formulas that are not suitable for oral supplementation. Because research on hydroxyapatite as a calcium source is limited, this type of calcium is not advised (Papaiannou *et al.,* 2010).

There are also calcium products that incorporate magnesium and vitamin K. Vitamin K is becoming better recognised as having a role in bone health. It's supposed to help with bone growth and calcium absorption. Low vitamin K levels

have been linked to a higher risk of fractures, according to preliminary research by Maresz (2015).

A maximum of 500 mg of elemental calcium should be taken at a time. The dose of calcium should not exceed 500 mg at one time in clinical practise to get optimal clinical outcomes related to calcium supplementation. To reduce Para Thyroid Hormones (PTH) levels and bone resorption, supplementing in small dosages four times a day may be useful. Calcium absorption is best when given in doses of 500 mg or less (Straub, 2007).

Calcium Interaction with Other Medicinal Products

Iron, zinc, and strontium ranelate absorption may be hampered by calcium salts. As a result, iron, zinc, or strontium ranelate should be taken two hours before or after calcium carbonate. Quinolone and tetracycline antibiotics' absorption ion may be hampered if calcium is given at the same time. Antibiotics containing quinolones should be given two hours before or after calcium intake. If the patient is taking a bisphosphonate, this prescription should be given at least three hours before taking oral calcium, as gastrointestinal absorption may be affected. Calcium excretion in the urine is reduced by thiazide diuretics. Because of the increased risk of hypercalcemia when using thiazide diuretics, serum calcium should be checked on a frequent basis (Lorieau *et al.,* 2018).

Benefits of Calcium Supplementation

Osteoporosis

Osteoporosis is a skeletal condition that is linked with age and is defined by decreased bone strength due to decreased bone quantity and quality, resulting in increased bone fragility and predisposing a person to fractures, particularly in the vertebrae, hip and forearm. Vitamin D and calcium supplementation, whether in the form of calcium supplements or dietary calcium, appears to be beneficial in the prevention of osteoporosis in persons of all ages and genders. Calcium supplementation protects bone health by increasing BMD and lowering the risk of osteoporosis and osteoporotic fractures in women and men of all ages (Straub, 2007).

Postmenopausal Women

In the peri-menopausal and post-menopausal periods, bone remodelling is accelerated, characterised by a drop in oestrogen production and an increase in calcium resorption from bone, resulting in a significant loss in bone density. Calcium supplementation may be recommended in postmenopausal women with a history of osteoporotic fractures, a diagnosis of osteoporosis, vitamin D deficiency, or a high risk of osteoporosis (eg, primary ovarian insufficiency) (Islam *et al.,* 2010), but there is no evidence that it is beneficial in the primary prevention of fractures in community-dwelling asymptomatic premenopausal women (Grossman, 2018).

Pregnant and Lactating Women

Calcium supplementation for the skeletal health of the foetus and mother in pregnant or breastfeeding women is of dubious value. Calcium supplementation resulted in considerably decreased bone mineral content at the hip throughout 12-month breastfeeding in pregnant women in Gambia, West Africa, with poor calcium intakes. During breastfeeding, the women experienced larger losses in bone mineral at the lumbar spine and distal radius, as well as biochemical alterations associated with increased bone mineral mobilisation (Jarjou *et al.,* 2010).

Children

Bone modelling (i.e., creation over resorption) is the most common skeletal activity that necessitates mineralization in growing children; as a result, calcium requirements rise, especially during neonatal and pubertal growth spurts. Routine calcium supplementation is not recommended for healthy children; however, children with a high risk of osteoporosis (e.g., celiac disease, inflammatory bowel disease, or congenital bone problem) or insufficient calcium intake may benefit from it. Calcium supplementation resulted in greater bone mineral content and BMD in rural Gambian children who were exposed to a low-calcium diet (Prentice *et al.,* 2012).

Cardiovascular System

Dietary calcium consumption might lower the risk of mortality from all causes and cardiovascular illnesses, according to a research done among an older Chinese population (Chan *et al.,* 2013). Another research of postmenopausal women found that a high intake of food and supplementary calcium was linked to a lower risk of ischemic heart disease mortality (Bostick *et al.,* 2009).

Difference between Dietary Calcium and Supplementary Calcium

Variations in corresponding changes in serum calcium concentration might explain the difference between dietary calcium and calcium intake from supplements. Dietary calcium consumption does not raise blood calcium levels as much as supplementation does (Bolland *et al.,* 2010). Furthermore, dietary calcium consumption includes all other components of calcium-containing foods as well as considerably lower calcium concentrations than calcium supplements (Hotchkiss *et al.,* 2009).

D. EGG SHELL POWDER IN THE MANAGEMENT OF BONE HEALTH

Calcium supplements, which are given by doctors for impoverished individuals to heal ailments or satisfy dietary needs, are expensive (Silva and Nabavi, 2019). Chicken eggshell powder is an alternate source of calcium for human consumption, according to Ray *et al*., (2017).

a. Global production of eggs

Asia is the leading producer of hen eggs with North and South America, Europe and Africa following closely after Asia. Overall, hen egg output has grown from from 50 million tonnes in 2000 to around 74-78 million tonnes in 2018. China produces about 35 percent of the world's eggs with the United States, India, Mexico, Brazil, and Japan contributing eight percent, seven percent, four percent, four percent, and 3v of the world's eggs, respectively (FAO, 2018).

As eggs have been accepted as a high-protein food item, there has been an increasing trend in egg consumption, with emerging nations leading the way. As a result of the growing demand, output has grown as well (Waheed *et al*., 2020). In the previous three decades, global egg production has increased by over 1.5 times (FAO, 2020).

Global production of egg shells

Food manufacturers and egg-based product enterprises, chicken farms, hatcheries and restaurants generate a tonne of eggshell trash causing environmental difficulties (Amu *et al.,* 2005; Phil and Zhihong, 2009). The shell membrane and eggshell are non-edible by-products that also serve as a source of beneficial substances (Abdulrahman *et al.,* 2014).

The food processing sector generates roughly 250000 tonnes of eggshell waste each year due to the use of egg as a component in a variety of products (Verma *et al.,* 2012). Only the United States produces 150000 tonnes of garbage each year (Abdullah *et al.,* 2018).

The problem of eggshell waste is ranked as the 15th significant food-based pollution source by the Environmental Protection Agency. They can create a variety of environmental issues, including fungal growth and other issues (Ajala *et al*., 2018). Eggshell waste is a major contributor to the environment, and industries that use eggs in various products create a lot of it (Murakami *et al*., 2007).

The majority of the eggshell waste generated after consumption is thrown away. Hatcheries provide eggshell trash as well. As a result, eggshells constitute a significant pollutant (Kingori 2011). Most of this trash is disposed of in landfills, which are already overburdened. Eggshell trash is often high in protein, thus landfill owners are wary of allowing it since it attracts rats and other pests (Waheed *et al.,* 2020). China reported about 25 billion kilogrammes of eggshell trash, with projections of 35 million metric tonnes by 2020.

Eggshell Membrane Powder Market analysis by Future Market Analysis (2021) shows that the global eggshell market captured a market size of USD 125 Million in the year 2021 and is expected to grow at a CAGR of 10.5percent by 2032. The Eggshell Membrane Powder Market is also expected to capture a market size of USD 200 Million during the forecasted period 2022-2032.

b. Eggshell Composition

Eggs are separated into three components, according to Dri *et al*., (2011) eggshells (9.5 percent), egg white (63 percent) and egg yolk (10 percent) (27.5 percent). Eggshell contains 0.8 percent magnesium carbonate, 0.8 percent tricalcium phosphate and 98.4 percent calcium carbonate, according to the study. The eggshell is made up of 98 percent dry matter and 2percent moisture, with ash accounting for 93 percent of the dry matter and protein accounting for 5 percent. Calcium is the most abundant mineral in this ash, with low amounts of boron, copper, iron, magnesium, molybdenum, sulphur, silicon and zinc (Schaafsma *et al.,* 2000).

According to Dupoirieux *et al.,* (1995) the protein content of eggshell varies according to the structure of eggshell, which is composed of protein polysaccharide, with 70 percent protein and 11 percent polysaccharides (1955). Hydroxyproline, an amino acid, is found in cartilage-protein-polysaccharides (Baker and Balch, 1962), and both chondroitin sulphates A and B are present in the matrix, accounting for 35 percent of total polysaccharides.

Other proteoglycans and proteins found in eggshell include Osteopontin (OPN), ovalbumin, ovotransferrin, ovocleidin-17, ovocalyxin-32, and lysozyme, some of which assist eggshell calcite crystal shape and precipitation rate modulation (Pines *et al.,* 1995 and Panheleux *et al.,* 1999). The antibacterial action of the eggshell protein protects the egg content while also regulating mineralization (Rose and Hincke, 2009). In comparison to shell membrane, it also contains larger concentrations of other organic materials such as glycein, alanine, sialicacid and uronic acid (Nakano *et al.,* 2008).

c. Calcium extraction from eggshell

Calcium extraction can be accomplished by soaking, neutralisation, or calcination at extremely high temperatures. Garnjanagoonchorn and Changpuak (2007) describe a straightforward technique for extracting calcium from eggshell using hydrochloric acids, which involves incubating clean eggshell powder with acid for 3 hours until no gas bubbles appear. After every 30 minutes, the mixture is stirred. Furthermore, supernatant was collected using centrifugation and the supernatant was heated at 110-120^{0}C until dry calcium chloride crystals were formed.

Pulse Electric Field Treatment (PEF) assisted extraction

For calcium malate extraction and in vitro calcium absorption, Lin *et al*., (2012) employed Pulse Electric Field therapy (PEF). PEF is a method that is environmentally benign, energy efficient and effective. This eggshell powder was treated with malic acid at a flow rate of 25 ml/min, with a frequency of 1000-3000 Hz and an electric field strength of 15 kV/cm, which was then centrifuged. The chemical process has several drawbacks, including severe pollution, high energy consumption, and a difficult operation with a poor extraction rate.

Ultrasound assisted extraction of calcium from eggshell

Liew *et al*., (2015) used ultrasound processing (horn-type ultrasonic generator) to extract calcium from chicken and duck eggshells, resulting in biobased calcium carbonate (CaCO3) nano particles. Dried eggshell was immersed it in a solution of acetone and dichloromethane, which was then filtered. This aids in the removal of contaminants from eggshell powder. In addition, ultrasonication was used to irradiate eggshell powder in distilled water for 5 to 20 minutes in order to extract calcium effectively.

d. Application of eggshell as nonedible and edible

Edible application

Bread

Bread is a morning cereal product that may be fortified with good nutrients such as calcium, omega oil and other nutrients to help overcome numerous deficiencies (Marpalle *et al.,* 2014). Bread's fundamental nutrients include fat, protein, carbs and minerals (Ameh *et al.,* 2013). Multiple deficiency, which is caused by a lack of calcium, may be avoided by fortifying bread with calcium, which helps to maintain a healthy calcium balance in the body (Das *et al.,* 2013).

The calcium in eggshell enhances the negative charge proteins seen in dough production, allowing for the creation of a three-dimensional network between negatively charged proteins. These result in a more uniform matrix, and the calcium-induced rearrangement of the gluten network leads in stiffness (Daengprok *et al.,* 2003). The nutritional features of bread with calcium fortification are favourably influenced, while sensory attributes are adversely influenced (Alsuhaibani, 2018).

Cakes

Cakes, a popular flour-based bakery product, appeal to a wide range of customers due to its variety, flavour and low cost. Due to increased demand for nutritious foods and fierce competition, efforts are being undertaken to improve the nutritional value and composition of cakes. As a result, eggshell can be used to fortify or enhance cakes with calcium. Ray *et al*., (2017) use three percent, six percent, and nine percent eggshell powder as calcium fortification.

Biscuits

A biscuit is a popular snack that is sweet or salty, tiny, and flat, and is under the category of baked goods. Biscuits are made with soft wheat as the main component. Because of the local bakery, extended shelf life, texture, low cost, and variety in taste, demand for baked foods rises as cities grow. In their biscuit formulation, Wesley and Renitta (2018) employed 0.8 percent (optimised) eggshell powder, which had a higher sensory rating than the control in terms of colour, texture, scent, appearance, and overall acceptability. Increased calcium concentration also increases nutritional quality.

Preservation of fruits and vegetables

Fresh cut fruit such as musk melon, guava and papaya benefit from calcium chloride derived from eggshells as a firming agent. Calcium chloride aids in the preservation of fruit firmness by stabilising the membrane system and forming capectates, resulting in improved fresh product firmness. Because calcium is detrimental to the enzymes generated by fungal infections, it slows down the ageing of fruits (Thakur *et al.,* 2019).

The cross-connected polymer network and pectic chemicals that modulate physiological qualities and postpone senescence are responsible for the firmness retention in fresh cut fruits and vegetables (Poovaiah, 1986). The osmo regulatory mechanism in bacteria is triggered by calcium chloride, which suppresses germs and extends the shelf life of fruits and vegetables (Yaganza *et al.,* 2009).

Egg shell powder in the management of osteoporosis

According to Sakai *et al.,* (2016) the bone mass was nearly at the osteoporosis level but after 12 months of the eggshell calcium intake it increased nearly to the normal level, more than that of the calcium carbonate group, from which it is clear that the eggshell id usefull for the treatment of osteoporosis .

Study performed by Bose *et al.,* (2020) showed that positive effect on bone density in animal models of postmenopausal osteoporosis in ovariectomized female rats. In vitro eggshell powder stimulates chondrocyte differentiation and cartilage growth. Clinical studies in postmenopausal women and women with senile osteoporosis showed that eggshell powder reduces pain and osteoresorption and

increases mobility and bone density or arrests its loss. The bioavailability of calcium from this source, as tested in piglets, was similar or better than that of food grade purified calcium carbonate. Clinical and experimental studies showed that eggshell powder has positive effects on bone and cartilage and that it is suitable in the prevention and treatment of osteoporosis.

The vivo study Arif *et al.,* (2022) affirmed the absorption of calcium from eggshell powder and it was found highest (41.83 percent) at five percent supplementation level. Supplementation of biscuits with eggshell powder might be an attractive source of dietary calcium intake without any significant adverse effects on biscuits quality up to 10 percent supplementation level.

In some developed countries, egg shell powder has already been widely used as a source of calcium (Brun *et al.,* 2013 and Hassan *et al.,* 2015). However, no study has so far been performed in Bangladesh to explore the use of egg shell powder as a dietary source of calcium. This study showed that the local egg shell is rich in calcium and it is possible to use egg shell powder as a promising and alternative cheap source of calcium for human nutrition. This inexpensive source of calcium may play a greater role in the health sector, particularly by strengthening the bones of people suffering from osteoporosis.