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Effects of Endocrine Disorders on Bone Mineral Density - A Narrative Review of Literature

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ABSTRACT

Introduction: Hormones are primary messengers that regulate the physiological and behavioral aspects of the body. Bone, a dynamic connective tissue, forms the framework of the body alongside its contribution in maintaining homeostasis and hosting the bone marrow. Disturbances in hormonal levels disrupt bone health thereby leading to impaired quality of life.

Aim: To encapsulate the effects of various endocrine disorders on bone mineral density based on previous clinical studies.

Methodology: An electronic search was conducted across PubMed, EMBASE, CINAHL, Google Scholar and Cochrane databases during the period of March to July 2021 by two reviewers independently using Medical Subject Headings (MeSH) terms.

Result: The search yielded a total of 208 articles and further screening based on selection criteria resulted in inclusion of 19 studies to elicit the effects of commonly prevalent endocrine disorders on bone mineral density. Studies revealed that most hormonal imbalances have a negative impact on the bone mineral density (BMD) at varying degrees.

Conclusion: Endocrine disorders have become highly prevalent at present deteriorating the life standards, especially the middle aged and elderly population. Any disruption in this normality will lead to altered bone mineral density and further risks of fracture or immobility. Constant monitoring of hormonal levels and bone health is required to enhance the quality of living alongside an increased life expectancy.

Key Words: Endocrine disorders, Bone Mineral Density, Parathormone, Diabetes Mellitus, Calcitonin, Hormones

INTRODUCTION

The endocrine system is composed of various glands that secrete a set of chemical messengers called hormones, which are instrumental in regulating growth and development, metabolism, electrolyte balance, reproduction and several other important functions.¹ The terms endocrine and hormone are derived from Greek words 'endokrinein' and 'hormaein' respectively. The actual word hormone meant 'to arouse' or 'to excite', which was later defined by Starling (1905) as "the chemical messengers which speed from cell to cell along the bloodstream, may coordinate the activities and growth of different parts of the body".² The endocrine system is principally controlled by hypothalamus which secretes the releasing and inhibiting hormones that in turn influence the release of stimulating hormones from the pituitary gland.¹ These hormones released into the bloodstream may stimulate other glands or directly target distant tissues to bring about cellular

changes. Hormonal imbalance, per se, has become a quotidian term in recent times, and is reported with a high incidence rate. Various physical, psychological and social stresses in day-to-day life have had an adverse impact on the endocrine system leading to multiple systemic manifestations.³ It has led to a growing concern to keep a watch over the hormonal levels not only among the elderly but also among the younger age groups. There is a need to reinstate the former ways of living, with appropriate diet balance, adequate exercise and a relaxed state of mind, body and soul in order to maintain a healthy life. This requires serious attention in maintaining good bone health in order to sustain a quality living.

METHODOLOGY

An electronic search was conducted across PubMed, EMBASE, CINAHL, Google Scholar and Cochrane databases

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during the period of March to July 2021 by the two reviewers independently. The search methodology used a combination of Medical Subject Headings (MeSH) words and keywords such as “Type 2 Diabetes mellitus”, “Estrogen disorders”, “Vitamin D deficiency”, “Osteoporosis”, “Parathormone”, “Thyroid disorders” AND “Bone mineral density” considering synonyms, alternative spelling, and related terms.

Inclusion criteria

1. Articles published dating from 1999 to 2020
2. Clinical trials on humans, cross-sectional retrospective or prospective studies
3. Studies assessing the effects of Type II Diabetes Mellitus, Estrogen, Vitamin D, Osteoporosis, Parathormone & Thyroid dysfunction on bone mineral density.
4. Gender neutral as well as gender-specific studies included
5. Studies done on adult participants alone

Exclusion Criteria

1. Animal trials, In-vitro studies, Case reports, Literature or Systematic reviews
2. Population having any comorbidities or multiple factors affecting bone mineral density.
3. Studies that had methods of measuring bone quality other than Bone mineral density.
4. Publications made in languages other than English

A structured electronic search was conducted by two reviewers independently using the Keywords and MeSH terms yielding a total of 208 articles. Initial screening consisted of a check for duplication during which a total of 56 articles were excluded based on the titles and authors. This was followed by assessment of title and abstract based on article type which led to the exclusion of 73 articles. The final phase of screening involved full text reading based on selection criteria and exclusion of 60 articles was done. A total of 19 studies were included for the final review. The search methodology has been summarized in Figure 1.

PHYSIOLOGICAL BONE REMODELLING

Bone is a highly dynamic connective tissue that undergoes constant remodeling throughout the lifetime. It serves two crucial roles, provision of skeletal support and maintenance of mineral homeostasis. Bone contains three major types of differentiated cells, namely the osteoblasts or the bone-forming cells, osteocytes and the osteoclast or bone-resorbing cells. Bone rigidity and density depends on the deposition of calcium and phosphorus as hydroxyapatite during mineralization. The inorganic content composed of the minerals sum up to 70% while the remaining 30% consist of organic matter, especially Type 1 collagen. The outer layer consists of a dense cortical bone that provides structural support while the

inner trabecular bone forms the reservoir for the bone marrow hosting the active process of bone remodeling.⁴ Bone remodeling is a sequence of seven phases: quiescence, activation, resorption, reversal, formation, mineralization and termination. This activity of deposition and resorption is influenced by local and systemic factors. The major role is played by the systemic factors that include hormones and growth factors. The list of hormones and growth factors that majorly affect the remodeling of bone is mentioned in (Table 1).

BONE MINERAL DENSITY (BMD)

Bone mineral density, in the literal sense, would mean the mass per unit volume of mineralized bone without the organic portion or adjacent tissue. But clinical investigations simply reveal the apparent bone mineral density inclusive of the bone marrow and the overlying tissues. However, bone mineral density is a reliable and non-invasive biophysical parameter that aids in measuring bone quality. It is one of the major diagnostic tools for bone disorders like osteopenia, osteoporosis etc. Investigatory techniques for determining the BMD include: (i) Dual energy X-Ray absorptiometry (DXA), (ii) Single energy absorptiometry (SXA), (iii) Quantitative Computed Tomography (QCT), (iv) High-resolution peripheral quantitative computed tomography (HR-pQCT), (v) Peripheral quantitative computed tomography (pQCT) and (vi) Quantitative Ultrasonography (QUS). DXA is the most popularly used technique for the assessment of BMD, which operates by propagation of two low dose X-ray that provide the density profiles of hard and soft tissues thereby aiding in determination of BMD. Measurements are commonly done at four sites namely, lumbar spine, femoral neck, trochanteric region and Ward's triangle.

The most widely accepted parameter for measuring the BMD is the T-score, which is a unitless value that is calculated as a ratio of the difference between the observed bone mineral density (BMD) and the expected young normal value (YN) to the standard deviation of the population. It is used to compare the BMD of an individual with the healthy, young population of the same gender.

$$T\text{-score} = \frac{BMD (g/cm^2) - YN (g/cm^2)}{SD (g/cm^2)}$$

According to WHO⁵, four general diagnostic categories had been established for women as follows:

1. Normal: Value of BMD within 1 SD below the young adult reference mean (T-score ≥ -1)
2. Low bone mass (osteopenia): Value of BMD ranging from 1 to 2.5 SD below the young adult mean (T-score < -1 and > -2.5)
3. Osteoporosis: Value of BMD more than or equal to 2.5 SD below the young normal (T-score ≤ -2.5)

4. Severe osteoporosis: Value of BMD more than 2.5 SD below young adult mean ($T\text{-score} \leq -2.5$) with the presence of one or more fragility fractures.

While yet another scoring system is the Z-score that compares the BMD of two individuals of the same age and gender. It aids in determining the presence of secondary causes of osteoporosis which is indicated when the score goes below -2.5.

A constant monitoring of the BMD among various age groups that are commonly vulnerable to bone fragility due to endocrine disorders is required in order to prevent disabilities in early stages. Women of perimenopausal age groups and infants lacking adequate nourishment are to be treated with special care to prevent the occurrence of endocrine disorders. Hormones are governed by various internal as well as external factors of which diet, livelihood as well as state of mind plays a crucial role in balancing the homeostasis. Hence, it is necessary to sustain a healthy way of living for a quality life.

ENDOCRINE DISORDERS AND BONE MINERAL DENSITY

1. PARATHORMONE

There are normally two pairs of parathyroid glands, namely, the superior and inferior parathyroid situated in the posterior aspect of the two lobes of thyroid gland. Although the parathyroid glands are small in size, they secrete parathormone that plays a crucial role in Calcium homeostasis. Parathormone (PTH) acts as a scavenger of Calcium ions thereby maintaining a high serum Calcium level by resorbing the bone, preventing loss of Calcium ion through urine and also increasing the intestinal absorption of dietary Calcium ions. PTH acts by induction of osteoclast formation that is mediated through the osteoblast by stimulation of RANKL and inhibition of OPG mRNA expression.⁶ The release of Parathormone normally occurs when there is a decrease in normal serum Calcium levels. Increased level of parathormone in blood leads to bone resorption in order to raise the serum Calcium levels thereby decreasing the bone mineral density.

2. CALCITONIN

Calcitonin is secreted from the parafollicular cells of the thyroid gland that couples with PTH in order to maintain calcium homeostasis in blood. Calcitonin has a hypocalcemic effect that counteracts the activity of parathormone. The normal serum Calcium levels range from 8.5 to 11.5mg/dl. Calcitonin acts by binding to specific receptors located at the sealing area leading to the loss of ruffled border of the osteoclasts required for resorbing bone surface.⁷ These receptors are known as Calcitonin Receptors (CTR) which

cause loss of mobility of osteoclasts (Q-effect) and also lead to retraction (R-effect). Calcitonin acts by two known signaling mechanisms: one using cyclic adenosine monophosphate (cAMP) as the secondary messenger and the other using phospholipase C pathway that aids in influx of serum calcium ions promoting bone deposition.⁸ Calcitonin is usually absent or deficient in patients who have undergone thyroidectomy, which often leads to decreased serum calcium levels, decreased PTH levels and reduced bone formation rates. Capelli et al.⁹ reported that osteocalcin showed decreased bone formation with an increased turnover rate signified by the presence of resorption markers like deoxypyridinoline and N-terminal telopeptide of type I collagen thereby decreasing the bone mineral density.

3. VITAMIN D

Vitamin D is a fat soluble vitamin that is also categorized under steroid hormones since its active form is synthesized in the body. Vitamin D is obtained from the exposure of skin to Ultraviolet rays of sunlight. It undergoes hydroxylation in the liver initially to form 25-hydroxyvitamin D (25(OH)D) and later in the kidney to form an active metabolite as 1,25-dihydroxyvitamin D (1,25(OH)₂D). Vitamin D plays a major role in Calcium and bone homeostasis and has an inverse relation with PTH levels in the blood, thereby counteracting the effects of PTH. Vitamin D binds to the Vitamin D receptor (VDR) on the osteoblasts that increases the Receptor Activator for Nuclear Factor κ B Ligand (RANKL) expression which in turn leads to the binding of RANK on the preosteoclasts. This aids in the conversion of preosteoclasts into mature osteoclasts which release hydrochloric acid that demineralize bone.¹⁰ Chronic vitamin D insufficiency results in hypocalcemia and hyperparathyroidism, thereby a lowered bone mineral density which can contribute to high incidence of osteoporosis and fractures especially in the elderly population. Epidemiological studies by Palacios C et al.¹¹ show that in the United States having vitamin D deficiency sum up to 35% of the total adult population while Pakistan, India, and Bangladesh show about 80% prevalence. Meanwhile, the prevalence of Vitamin D among the elderly population relates to about 61% in the United States, 90% in Turkey, 96% in India, 72% in Pakistan, and 67% in Iran. Hence Vitamin D levels need to be monitored constantly over age. Khadijeh J. Menai et al., in a study assessing the effect of Vitamin D on performance of adult footballers revealing its extended relation on skeletal muscle due the necessity of Vitamin D₃ on maintaining serum Calcium levels that aid in adequate contraction of skeletal muscle.¹²

4. ESTROGEN

Estrogen is an important sex hormone produced predominantly from the ovaries in females and present in trace amounts in males. Apart from its role in regulating the

human reproductive system, it also has its influence on the bone, neuroendocrine and adipose tissues. Estrogen has a down regulatory effect on tumor necrosis factor- α (TNF- α), Interleukin-1 and 6 (IL-1, IL-6), Macrophage Colony Stimulating Factor (M-CSF) and prostaglandin- E_2 (PGE $_2$) that leads to decreased resorption. Estrogen acts on the bone by modulating both osteoclast and osteoblast cells, which result in inhibition of RANKL/M-CSF induced activator protein-1-dependent transcription, thereby preventing osteoclast differentiation.⁶ Vargas et al.¹³ found that TNF- α is the most important mediator in bone resorption by experimenting on TNF-Receptor 1 (TNF-R1) deficient mice which resulted in normal bone physiology even under estrogen deficiency. Post-menopausal women experience a rapid drop in the levels of estrogen produced by the body often leading to osteoporosis and risks of fracture due to the increased activity of the osteoclast stimulating factors and decreased bone mineral density.

5. INSULIN

Insulin, a polypeptide hormone secreted by the pancreas plays a crucial role in regulating glucose levels in blood. It is the only hypoglycemic hormone synthesized by the human body. The normal serum insulin level ranges between 6-15 μ IU/ml. Diabetes mellitus (DM) is of two types: Insulin-dependent DM (Type I DM) and Non-Insulin dependent DM (Type II DM). Type II DM is highly prevalent among the adult population accounting for 85% of the total diabetic population,¹⁴ while Type I DM, which is often a hereditary type, has a trail of concrete evidence in causing retinopathy, neuropathy, cardiovascular disorders, periodontal problems and many other complications. However, studies in recent years revealing the effects of insulin on bone metabolism have led to further prospective research to establish the exact correlation. Wang et al.¹⁵ reported that insulin acted by reducing the osteoprotegerin(OPG) to RANKL ratio, thereby decreasing the osteoblastic and osteoclastic activity in bone resorption. Hence a decrease in insulin leads to Further, hyperglycemia may also induce the formation of advanced glycation end-products (AGEs) through non-enzymatic pathways which have a negative effect on bone quality, affecting the extracellular matrix and the vessels by increasing osteocytic expression of sclerostin, a negative regulator of bone formation.¹⁶

6. THYROID HORMONE

The thyroid is a butterfly-shaped gland that is normally bilobed and is connected by an isthmus. Histologically, it consists of the follicular cells that secrete thyroxine (T4) and triiodothyronine (T3) and the parafollicular cells which secrete Calcitonin, the release of which is regulated by the Thyroid Stimulating Hormone(TSH) secreted from the pi-

uitary gland. Thyroid hormones play a major role in maintaining basal metabolism. Its effect on bone density is still a debatable topic till date. Studies have stated that hypothyroidism reduces osteoblast formation and thereby increases the rate of osteoclastic resorption resulting in a slowed bone remodeling process.⁶ On the other hand hyperthyroidism increases osteoblast and osteoclast activity raising the bone turnover with an impaired bone formation cycle favoring rapid resorption. In adults, hyperthyroidism leads to reduced bone mineral density (BMD), and increased fracture risk, especially in postmenopausal women.

7. GLUCOCORTICOIDS

Glucocorticoids are a class of steroid hormones that are secreted from the zona fasciculata region of the adrenal cortex. They play an important role in immunosuppression as well as metabolic activities. Excess glucocorticoids decrease the bone remodeling rate primarily by reducing the levels of gonadotropins causing an estrogen-deficient state. This results in elevated levels of tumor necrotizing factor- α (TNF- α), increased RANK-RANKL interaction alongside colony-stimulating factor (CSF-1) stimulating osteoclastogenesis and suppressing osteoprotegerin (OPG), a decoy receptor.¹⁷ Glucocorticoids are also known to stimulate the release of matrix metalloproteinases (MMPs) that destroy the collagen matrix of bone leading to further resorption. Weinstein et al.¹⁸ reported that increased levels of glucocorticoids also destroy the osteoblast progenitor cells immensely compared to osteoclast precursors.

8. GROWTH HORMONE

Growth hormone (GH) or somatotropin is a protein hormone made of 190 amino acids and is synthesized and secreted from the adenohypophysis or anterior pituitary gland. It is controlled by Growth hormone-releasing hormone (GHRH) that stimulates the secretion of GH from the pituitary and Somatostatin (SS) counteracts the GHRH by inhibiting the secretion of GH. Ghrelin is yet another peptide hormone secreted by the epithelial cells of the stomach that binds to the growth hormone secretagogue receptor (GHS-R) of somatotroph cells that aids in the synthesis and secretion of GH. GH acts through either direct or indirect mechanisms on the target cells. GH acts on the bone majorly through Insulin-like Growth factor (IGF $_1$ & IGF $_2$) that induce chondrocyte proliferation and differentiation as well as increase the formation of osteoblasts thereby, their activity by OPG expression. They also enhance calcium and phosphate absorption by increasing the activity of calcitriol (D3), thereby elevating the rate of reabsorption of phosphate in the renal tubules.¹⁹ This in turn increases the bone mineral density by increasing the bone mineralization. Murray et al.²⁰ conducted a study with 125 adults having growth hormone deficiency (GHD) revealing higher number of younger adults (<30 year) having

a BMD Z-score < -2.0 compared to the older patients (30 to 40, 40 to 60, >60 years) denoting that the effect of GHD on BMD was less severe among the elderly. This causes an increased risk of fracture of the long bones as well as vertebral column. While in acromegaly, a state of excess GH production in the adults, the bone turnover rate was higher with increased formation and resorption as well as increased bone mineral density at the femoral neck region compared to insignificant change in lumbar spine region as reported by Maffezzoni et al.²¹ which also results in high rates of vertebral fractures especially in males with hypogonadism.

DISCUSSION

Endocrine disorders, once widely been considered as hereditary disorders, have now become a common encounter in the medical field with changing lifestyles disrupting the circadian rhythm and basal metabolism of the body. Apart from their effects on growth, development and regulation of homeostasis, their role in balancing the dynamic remodeling of bone tissue and serum Calcium levels which in turn aid in preserving the functional state of the body. The most commonly prevalent endocrine disorders among the general adult population include Type II diabetes mellitus, hypovitaminosis of VITAMIN D, thyroid and parathyroid disorders among the general population and estrogen deficiency disorders and osteoporosis common among post-menopausal women as listed in Table 2.

Type II Diabetes Mellitus (T2DM) has become an ubiquitous metabolic disorder of the present age, threatening the overall health having a long trail of comorbidities affecting most of the organs. Many studies have been done on the adult population assessing the effect of Insulin-resistant diabetes on bone mineral density. Isaiah et al.²² and Gerdhem et al.²³ had illustrated a decrease in BMD in patients with T2DM compared to the healthy control groups. In contrast to these results, Bonds et al.²⁴ and Schwartz et al.²⁵ demonstrated an increase in BMD with increased risks of fractures. These are common in both male and female populations though the women of perimenopausal age have a higher predilection for bone disorders with multiple risk factors in play.

The role of sex hormones on bone remodeling has been undoubtedly proven by many. Studies by Ho Pham et al.²⁶ revealed that the effects of Estrogen levels on BMD are more pronounced compared to the Testosterone levels thereby reasserting the risk of decreased BMD with reducing estrogen levels among post-menopausal women when compared to the men of similar age. Cauley et al.²⁷ and Popat et al.²⁸ expressed the direct positive correlation between Estrogen levels and BMD and also proved that supplements of Estrogen combined with Progestin greatly improved the BMD and reduced the risks of fractures.

Hypovitaminosis of Vitamin D3 commonly measured in its active form as Calcitriol that was once a concern among countries that are located at the tropical or temperate zones with insufficient exposure to sunlight has now become common among the population in equatorial regions due to the growing sedentary lifestyles inside closed, non-ventilated rooms. Studies by Arya et al.²⁹ and Grados et al.³⁰ reveal that there is a decrease in BMD with decrease in serum Vitamin D levels and vice versa that is contrary to the findings of Brot et al.³¹ who stated that there was an increased bone turnover with increase in Vitamin D3 levels thereby decreasing the BMD. Aloia et al.³² and Nieves et al.³³ demonstrated that there were no significant changes in the BMD with Vitamin D3 supplements.

Siris et al.³⁴ and Pressman et al.³⁵ demonstrated the inverse relation between the severity and chronicity of osteoporosis with the BMD, with high female predisposition increasing the risks of fracture in long bones among post-menopausal women. Osteoporosis has perturbed the health status among the older population thereby resulting in disabilities. Rathod et al. states that Indian studies show the risk of skeletomuscular disorders in post-menopausal women while vasomotor complications are evident in peri-menopausal women.³⁶

Parathyroid disorders usually occur secondary to the discrepancies occurring in thyroid glands resulting in removal of parathyroids during thyroidectomy. Neer et al.³⁷ and Hodsman et al.³⁸ demonstrated the positive correlation between parathormone levels and BMD. Parathormone replacement therapy has proven highly efficient in improvising bone quality.

Thyroid disorders have been rising over the current age due to stress levels and dietary habits. Not many studies have been done to clearly elicit the effect of thyroid dysfunction on BMD, and there are various schools of thought regarding the correlation of serum thyroxine levels on bone quality. Tuchendler et al.³⁹ illustrated a decrease in BMD level among those with hyperthyroidism compared with the hypothyroid group and control group. Jodar et al.⁴⁰ demonstrated a mild deleterious effect of endogenous and exogenous thyroid hormone excess in the axial bone mass with an evident decrease in BMD in male subjects. Further Vestergaard et al.⁴¹ studied a rise in fracture risk hyperthyroidism and hypothyroidism and also thyroid surgery in hyperthyroid patients revealed a decreased fracture risk.

Various states of hormonal imbalance have led to impediment of regular activities among adults. Endocrine disorders that are acquired with age are a global concern and require constant monitoring of health status that are often neglected until impairments set in. A nation's progress hugely depends on the accessibility and affordability of health care services to its people. Bone health apart from general health has a greater impact on the quality of living, which needs to be assessed and kept track of. This narrative review asserts the

effects of endocrinology on bone health therefore, any disturbance in the hormonal levels requires serious attention. Further studies with wider perspectives are required to determine the exact mechanism of action of each hormone on bone health.

CONCLUSION

Apart from their roles in growth and development, hormones play an undoubtedly important role in maintaining the homeostasis of the body vis-à-vis bone health. The bone health in turn is determined by means of measuring the bone mineral density. Endocrine disorders that were once considered as the diseases of old have now become prevalent among the younger generations due to nutritional deficiency, dietary changes, comfortable standards of living as well as increased levels of stress due to work, education and in sustaining a good living. The focus has diverted from a healthy life to a wealthy life, leaving behind ailments among all age groups. A constant record of bone health is important to avoid bone fragility resulting in morbidities among the population, especially in post-menopausal women.

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Table 1: Hormones and Growth factors that regulate bone remodeling

Hormones	Growth Factors
Parathormone	Transforming growth factor – β (TGF- β)
Calcitonin	Bone morphogenetic protein (BMP)
Growth hormone	Platelet-derived growth factor (PDGF)
Insulin	Insulin-like growth factor - I & II (IGF-I, IGF-II)
Vitamin D ₃ (Calcitriol)	Fibroblast growth factor (FGF)
Sex hormones	Tumor Necrosis Factor- α (TNF- α)
Glucocorticoids	Several chemical mediators of Interleukine family
Thyroid hormone	Colony stimulating factor (CSF)

Table 2: Evidences based on experimental studies stating the effect of commonly prevalent Endocrine disorders on BMD among Adult populations

S. No	Author	Objectives	No. of participants	Age (Years)	Outcomes	Conclusion
1	G.C.Isaia et al. ²²	To assess the bone mineral density in patients with Type 2 Diabetes Mellitus	66	51-82	Significant differences were found between the two groups in the levels of mid-molecule PTH (higher in the control group than in diabetics: $P = 0.0003$), in urinary calcium and hydroxyproline (higher in the group of diabetic patients than in controls: $P = 0.001$ and $P = 0.006$, respectively).	Significant decrease in BMD was observed in femoral region among diabetic patients compared to the control group

Table 2: (Continued)

S. No	Author	Objectives	No. of participants	Age (Years)	Outcomes	Conclusion
2	Bonds et al. ²⁴	To determine the risk of fracture in post-menopausal women with type 2 diabetes compared with non-diabetic women.	93676 (of which 271 were excluded)	64 ± 7	Women with diabetes had greater hip and spine BMD. The elevated fracture risk was found at multiple sites (hip/pelvis/upper leg; foot; spine/tailbone) among black women (RR 1.33, 95% CI 1.00–1.75) and women with increased baseline bone density (RR 1.26, 95% CI 0.96–1.66).	Women with type 2 diabetes are at increased risk for fractures. This risk is also seen among black and non-Hispanic white women after adjustment for multiple risk factors including frequent falls and increased BMD.
3	Schwartz et al. ²⁵	To assess the risk of fracture among older female patients with Type 2 diabetes mellitus	9654	≥ 65	BMD among women with diabetes was 5.2% higher at the distal radius ($P < 0.001$), 5.1% higher at the calcaneus ($P < 0.001$), and 2.9% higher at the femoral neck ($P < 0.001$) compared with nondiabetics.	Women with diabetes have a greater risk of fracture despite having higher BMD due to the comorbidities associated with diabetes or also because the decrease in bone strength is not reflected in the measurement of BMD.
4	Gerdhem et al. ²³	To assess the BMD among patients with Type 2 Diabetes Mellitus and the association with 25-OH D and PTH.	1132	75	i) In diabetic women, the BMD of the femoral neck was 11% higher ($p < 0.001$), and BMD of the lumbar spine was 8% higher ($p = 0.002$) than in non-diabetic women. ii) There were no significant correlations between duration of diabetes and bone markers or between duration of diabetes and 25OHD or PTH	Decrease in BMD was evident in diabetic patients compared to non-diabetic patients.
5	Ho-Pham et al. ²⁶	To assess the relative contributions of estrogen (E2) and total testosterone (TT) to variation in bone mineral density in the region of Femoral Neck (FN) and Lumbar Spine (LS) among men and women.	615	18-89	In women, higher serum levels of E2, but not TT, were significantly associated with greater BMD at the FN ($P = 0.001$) and LS ($P < 0.0001$). In men, higher serum levels of E2 were independently associated with greater FNBMD ($P = 0.008$) and LSBMD ($P = 0.086$).	Estrogen is more important than testosterone in the determination of age-related bone mineral density in men and women.
6	Cauley et al. ²⁷	To assess the effect of estrogen plus progestin on Bone mineral density.	16608	50-79	Total BMD increased by 3.7% after 3 years among women treated with estrogen plus progestin compared to 0.14% among the women treated with placebo.	Estrogen plus Progestin therapy among post-menopausal women aids in increased BMD.

Table 2: (Continued)

S. No	Author	Objectives	No. of participants	Age (Years)	Outcomes	Conclusion
7	Popat et al. ²⁸	To assess bone density and associated risk factors for reduced bone density in young, estrogen-deficient women using primary ovarian insufficiency (POI) as the disease model.	512	30-32	i) Women with POI who had onset of menstrual irregularity before age 20 were 2.72 times more likely to have lower BMD ($P < 0.0001$). ii) Women with lower estradiol level and lower ovarian volume showed a trend toward a risk for lower bone density.	Women with POI had significantly lower BMD at all sites compared with controls.
8	Arya et al. ²⁹	To assess the correlation between Vitamin D and Bone mineral density among healthy Indian adults	92	24-53	There was significant positive correlation between serum 25(OH)D concentration and BMD of Ward's triangle and the femoral neck ($r=0.50$, $P=0.020$ and $r=0.46$, $P=0.037$, respectively)	The serum 25(OH)D level is a good indicator of vitamin D status in healthy subjects, unlike the serum 1,25(OH) ₂ D level, which remained within the normal range even in severely deficient individuals. Vitamin D deficiency leads to low BMD and increases the risk of fracture.
9	Aloia et al. ³²	To assess the effect of relatively low doses of supplemental vitamin D on vitamin D and bone status in Pakistani immigrants.	208	50-75 YEARS	There was an increase in BMD of the total body, hip, and radius at 1 year in both groups. Over the 3 years, BMD declined at these sites by 0.26% to 0.55% per year. The BMD of the lumbar spine increased slightly in the placebo and active groups.	There was no observed effect of vitamin D ₃ supplementation on bone mineral density in calcium-replete, postmenopausal African American women.
10	Grados et al. ³⁰	To compare the effect of Vitamin D supplements on Bone mineral density among population with Vitamin D deficiency	192	75 ± 7 YEARS	The median bone mineral density increase was significantly greater in the supplemented group than in the placebo group: +2.98% vs. -0.21% at L2-L4 ($P = 0.0009$), +1.19% and -0.83% at the femoral neck ($P = 0.015$), +0.86% and -0.56% at the trochanter ($P = 0.015$), and +0.99% and +0.11% for the whole body ($P = 0.01$).	Bone density in older women with vitamin D deficiency increases significantly at the lumbar spine, femur, trochanter, and whole body after calcium and vitamin D supplementation for 1 year, and concomitantly bone markers improved as vitamin D levels returned to normal.
11	Brot et al. ³¹	To assess the relation between Vitamin D levels and bone mineral density among perimenopausal women.	510	45-58	A consistent inverse relationship between serum 1,25-(OH) ₂ D and bone mineral density was found ($P = 0.001$), spine ($P = 0.005$) and femoral neck ($P = 0.05$). There was a positive relationship between levels of 1,25-(OH) ₂ D and biochemical bone markers.	Within the normal physiological range, elevated levels of 1,25-(OH) ₂ D were associated with decreased bone mineral density and content, reduced calcium:phosphorus ratio in the diet and increased bone turnover.

Table 2: (Continued)

S. No	Author	Objectives	No. of participants	Age (Years)	Outcomes	Conclusion
12	Nieves et al. ³³	To determine if vitamin D supplementation (1,000 IU/day) would prevent bone loss and whether vitamin D receptor (VDR) polymorphisms modify the response.	127	≥ 50	Average BMD with mean T scores near zero at both the spine and hip. The Z score was between 0 and 1 for all subjects compared to an age-matched black female population.	There were no other significant differences between the vitamin D and placebo groups.
13	Siris et al. ³⁴	To describe the occurrence of osteoporosis and its related risks of fracture.	200,160	≥ 50	Overall, 39.2% women were diagnosed with osteopenia and 7.9% with osteoporosis according to World Health Organization criteria for low BMD.	The risk of osteoporosis increased from 1.79 for a woman aged between 55-59 years to 22.56 for women aged 80 years or older.
14	Pressman et al. ³⁵	The aim of the study was to describe initiation of osteoporosis drug therapy after bone mineral density (BMD) testing and to determine any association with BMD test results obtained.	8020	≥ 45	Prevalence of osteoporosis increased with age; 10% of women aged 45-54 years, 26% of women aged 55-64 years and 40% of those aged ≥65 years were in this category.	Osteoporosis is a highly prevalent bone disorder among the women of perimenopausal age group leading to lowered bone mineral density.
15	Neer et al. ³⁷	To assess the effect of injections of parathyroid (1-34) hormone on the bone mineral density and fracture risk	1637	67 ± 10	The mean bone mineral density of the spine was 2.6 SD below the mean value in normal young white women (mean T score, -2.6). Treatment with parathyroid hormone resulted in significant dose-dependent increases in the bone mineral density of the spine and hip and in total-body bone mineral.	The clinical benefits of parathyroid (1-34) hormone reflects its ability to stimulate bone formation and thereby increase bone mass and strength.
16	Hodsman et al. ³⁸	To assess the efficacy and safety of human PTH-(1-84) (full length PTH) in the treatment of postmenopausal osteoporosis.	217	50-75	Changes in whole body BMD for 0-, 50-, 75-, and 100-µg doses of full-length PTH were 0.3±1.9%, -0.5±2.3%, -0.4±1.9% and -0.9±2.4%, respectively.	Daily injection of full-length PTH resulted in time- and dose related increases in BMD in the lumbar spine.
17	Tuchendler et al. ³⁹	To evaluate the effects of hyper- and hypothyroidism on BMD and selected bone turnover markers at the time of diagnosis and after six and 12 months of treatment.	119	18-52	In the group with hyperthyroidism, a statistically significant decrease in OC and CTx concentration was observed. On initial evaluation, a statistically significant lower femoral neck bone density expressed by the Z-score was found in female patients with hyperthyroidism compared to those with hypothyroidism.	There is a decreased BMD level among those with hyperthyroidism compared with the hypothyroid group and control group.

Table 2: (Continued)

S. No	Author	Objectives	No. of participants	Age (Years)	Outcomes	Conclusion
18	Jodar et al. ⁴⁰	To assess the BMD among male patients with L-Thyroxine suppression therapy and Hyperthyroidism	49	48 ± 10	Bone formation markers (BGP) and total ALP were higher in patients suffering from Graves' disease compared with those on L-T ₄ suppressive therapy. The BMD values of patients with treated thyroid cancer and those with Graves' disease were lower than expected at all sites of measurement.	There is a mild deleterious effect of endogenous and exogenous thyroid hormone excess in the axial bone mass with an evident decrease in BMD in male subjects.
19	Vestergaard et al. ⁴¹	To study fracture risk in patients with hyperthyroidism and hypothyroidism.	16,249	≥ 50	In patients with hyperthyroidism, fracture risk was only significantly increased around the time of diagnosis (incidence rate ratio [IRR] between 1.26 and 2.29), but decreased to normal levels after diagnosis. Surgical treatment of hyperthyroidism was associated with a decreased fracture risk after diagnosis. In hypothyroidism, fracture risk was significantly increased both before and after diagnosis with a peak around the time of diagnosis (IRR between 2.17 and 2.35).	Fracture risk is increased in hyperthyroidism and hypothyroidism. Thyroid surgery seems associated with a decreased fracture risk in hyperthyroid patients.