Review on Osteoporosis A Preventable and management disease in Relation to Diabetes

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Received on:15-04-2017; Revised on: 29-05-2017; Accepted on: 20-06-2017

ABSTRACT

It is a chronic bone disease associated with poor bone remodeling and bone formation. Bone mass and changes in bone structure leads to increased risk of fracture. The pathological condition creates bones to become weak and fracture that commonly affects the parts of hip, wrist and spine. It consist of proteins, collagen, and calcium and associated substances confers the strength. The diabetes is a prolong metabolic disorder associated with multiple complications. The diabetes develop at younger age and suffering from neuropathy, vision problems may reduces the bone mass responsible for risk of bone fracture. The imbalance between osteoclast and osteoblast bone response through out the remodeling buildup the disease. The repeated events promotes bones to meet normal demands and falling more stress on bone advancing the risk of fracture. The diagnosis pattern can be suggested towards X-rays, various vital organ function test, pathological test towards the disease and confirmed by tests to measure bone density. It affects men and women in normal health care scenario. The risk factors include aging, low body weight, low sex hormones and menopause, smoking, alcohol, some medications will impact the development of disease. Current treatment address the medications like bisphosphonates, selective estrogen receptor modulators, calcium and vitamin D supplements. It is a healable disease that can results in devastating the physical, psychosocial, and economic consequences of the patients. The early recognition of the causes and risk factors medication therapy measures impact the outcomes.

KEY WORDS: Calcium, Vitamin D, Osteoporosis, Neuropathy, Bisphosphonates.

INTRODUCTION:

Osteoporosis is a condition of fragile bone with an increased susceptibility to fracture. Osteoporosis weakens bone and increases risk of bones damage. Bone mass decreases after 35 years of age in the patients and bone loss occurs more common in women life after menopause. It affects the bones to become less dense and more susceptible to fractures and breaks. Primary osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural degradation of bone tissue, leading to increase the bone fragility and fracture risk.

Secondary osteoporosis can result from a variety of the chronic health disease conditions that significantly contribute to bone mineral loss and effects of medications and nutritional deficiencies.

Osteoporosis affects the entire skeleton of bone and spongy bone of the spine is most vulnerable. Due to these consequences confining fractures of the vertebrae are common in people with osteoporosis.

Types of Osteoporosis:

Classification on the basis of causative factors and osteoporosis can be divided into:

Primary Osteoporosis: It causes when no specific cause for bone loss can be identified.

The other types of Osteoporosis includes:

Idiopathic Osteoporosis: It is very rare in this condition is seen in children below 14 years of age and young adults.

Postmenopausal Osteoporosis: This type of osteoporosis is most commonly seen in females, usually after about ten years of menopause.

Senile Osteoporosis: It is common in older females and men usually after the age of 65-70 years and is a major cause of hip fractures in this age group.
Secondary Osteoporosis: It is considered to be more specific cause for bone loss such as chronic diseases[9].

Discussion on diabetes and osteoporosis

The younger women with type 1 diabetes have relatively decreased bone mass it may have the nature of increased fracture risk and affects the poor fracture healing capability compared with healthy women without diabetes[61-70]. The higher circulating insulin levels could be expected to increase osteoblast function and have a beneficial effect on bone mass. It has been suggested that hyperinsulinemia may be partially responsible for the association of both diabetes and obesity with a higher body mass index in women[10,11]. Low peak bone mass can increase the risk of developing osteoporosis in future. Some people with type 1 diabetes also suffering from chronic diseases which is associated with reduced bone mass.

Several investigations suggesting that women with type 1 diabetes may strongly associated with an increased fracture risk, since people suffering from visual problems and neuropathy associated with the disease and hypoglycemia have been possible to contribute risk of falls and related fractures[12,13]. The bone density is increased in people with type 2 diabetes it may possible to increase fractures. The improper maintainance of life style common in many people with type 2 diabetes[72-75] also interferes with bone health and the disease affects the older people.

Vitamin D role in association between osteoporosis and diabetes

Vitamin D is an important nutrient to help the body to absorb calcium and it is responsible for maintain the bone density.14,15 It is also there are some studies show that vitamin D may help the pancreas to release more insulin. The person suffering from vitamin D deficiency as well as low bone mass increase the risk of fracture and results in development of osteoporosis.16,17

Causes of secondary osteoporosis include:

Table 1: Medications causes the osteoporosis

<table>
<thead>
<tr>
<th>Glucocorticoids</th>
<th>Hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin[18,19]</td>
<td>Hypogonadism[26,31]</td>
</tr>
<tr>
<td>Excessive intake of vitamin A</td>
<td>Malignancy especially multiple myeloma</td>
</tr>
<tr>
<td>Excessive intake of vitamin D</td>
<td>Prolonged immobilization</td>
</tr>
<tr>
<td>Endocrine disorders[22,23]</td>
<td>Genetic disorders</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Homocystinuria</td>
</tr>
<tr>
<td>Uncontrolled diabetes[24]</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Liver disease</td>
</tr>
</tbody>
</table>

Physiology of Bone formation

Bone Structure

Bone is one of the hardest materials in the body. It is made of collagen and various minerals, such as calcium, that make it strong and hard. Although bones differ in shape and size, they basically have the same structure and function[25,26].

Long bones are made up of two main parts:
- **Diaphysis**: The shaft of a long bone makes up most of the bone’s length.
- **Epiphysis**: The epiphysis is the end of the long bone. There is an epiphysis at each end. The epiphysis is made up of compact and spongy bone tissue[27,28].

Periosteum

The periosteum is a layer of fibrous tissue that covers the bone, except at the ends[29,30].

Compact bone

Compact bone is the dense, hard, smooth outer layer of bone. Compact bone surrounds the yellow bone marrow in the shaft of the bone and gives strength to the hollow part of the bone[31,33].

Medullary cavity

The medullary cavity is the space inside the shaft that contains the yellow bone marrow. The yellow bone marrow mainly serves as a storage place for fatty tissue.[32-35]

Spongy bone

Spongy bone is made up of small, needle like pieces of bone and lots of open space, sort of like a honeycomb. Spongy bone stores the red bone marrow where blood cells are made. In an adult, red marrow is found mainly in the spongy bone of the skull, breastbone, ribs, hip bones, collarbone and spine[36,37].

Cartilage

Cartilage covers the ends of the bones. Cartilage is a tough, fibrous connective tissue mixed with a gel-like substance. It is softer than bone, but firmer than most tissues. Cartilage stops the bones from rubbing together and acts like a cushion to absorb shock[38,39].

Bone cells

Bone is a very active tissue. Bones are constantly being remodelled eventually[40].

Bones respond to:
- Changes in calcium levels in the blood.
- The pull of gravity and muscles on the skeleton[41].

Bones are made up of three types of living cells:
- **Osteoblasts**: It is responsible for build new bone in the body.
- **Osteoclasts**: It will dissolve and remove old bone.
- **Osteocytes**: It will carry the nutrients from the blood to the bone and waste products away from the bone[42].
Functions of Bone

Bones have many functions including:

- Bones form the internal framework that gives the body its shape and provides support to the body’s tissues.
- Bones protect important organs, such as the heart, lungs and brain.
- Muscles, tendons and ligaments work with bones and joints to allow the body to move.
- Storage of fat and minerals.
- Fat is stored inside the cavities of bones.[71]
- Bones also store and release important minerals, such as calcium, phosphorus and magnesium, when they are needed by the body.
- Blood cell production.
- Blood cells are made in the red bone marrow of certain bones.
- Bones give shape and support to the body, and resist all forms of stress.
- They provide surface for the attachment of muscles, tendons, ligaments etc.
- They serve as levers for muscular actions.[76,77]
- Bone marrow manufactures blood cells.
- Bones store 97% of the body calcium and phosphorus.
- Bone marrow contains reticulo endothelial cells which are phagocytic in nature and take part in immune response of the body.[78,79]

Miscellaneous factors like:

Causes

Possible factors involved in the development of the disease include:

- Body mass index: Low Body mass index is most important risk factor to develop Osteoporosis.
- Genetics: At least 30 genes have been implicated in the development of Osteoporosis.
- Immobilization: Prolonged sedentary life causes bone loss.
- Substance abuse: Smoking as well as heavy consumption of alcohol can decrease bone mineral density and precipitate Osteoporosis[80,81].
- Vitamin D deficiency: Mild vitamin D insufficiency is sometimes associated with increased parathyroid hormone production which increases bone resorption, leading to bone loss.
- Poor diet: Low dietary calcium, phosphorus, magnesium, zinc, fluoride, copper and vitamins can contribute to ascendance into osteoporosis.
- Heavy weight training: Large volumes of training can lead to decreased bone density and an increased risk of osteoporosis.[82,83]

The following are some factors that affect at a higher risk of developing osteoporosis:

- Age: The older age getting more risk.
- Gender: Women, especially women in menopause, are more likely to get osteoporosis than men, as low estrogen levels lead to weakening of bones.
- Genetics
- Low levels of vitamin D and calcium levels can lead to bone loss.
- Lack of exercise and long term bed rest can weaken bones.
- Tobacco and alcohol consumption can weaken bones as well.
- Hyperthyroidism[84,85].
- Reduced amounts of sex hormones.
- Disorders of the pituitary gland.[43,44].
- Family history of osteoporosis[45,46].
- History of hip fracture.

Secondary contributing factors includes

- Adverse drug reactions of drug therapy
- Endocrine disorders
- Eating disorders
- Immobilization
- Marrow-related disorders
- Gastrointestinal tract disorders
- Renal disease
- Cancer
- Organ transplantation

Epidemiology

At least 40% of these women and 15-30% of men will sustain one or more fragility fractures in their lifetime. Estimates indicate that the number of osteoporotic hip fractures occurring in the world each year will rise from 1.66 million to 6.26 million by the year 2050, thereby implying an urgent need for preventive strategies. In the United States, osteoporosis is a major public health threat for 24 million Americans, 80% of whom are women. Ten million individuals already have osteoporosis, and 14 million more have low bone mass, placing them at increased risk for this disease[71].

Symptoms

- Fractures: Osteoporosis can result in painful or painless fractures of spine, wrist, hip or shoulder. Hip fractures are among the most serious clinical condition they can result in deep vein thrombosis and clot in the lungs.
- Backache: Back pain may be present along with other symptoms of Osteoporosis.
- Stooping: Multiple vertebral fractures lead to stooped posture, loss of height, and chronic pain with reduction in mobility.
Compression back fracture or sudden collapse: Sudden, severe, shooting back pain, especially in older women may be a dangerous sign of weak bones and a spinal compression fracture.[84]

Osteopenia: It is among the warning symptoms of osteoporosis and is characterized by thinning of bones.

Loss of height: Fracture and collapse of vertebral body contributes to loss of height.

Scoliosis: Lateral curvature of spine may result from bony deformity of spine.

Fracture of bones

Back pain

Stooped posture

Bone pain

Pathophysiology

Bone is an active connective tissue that regularly remodels in relies to mechanical stresses and hormonal changes. The bone remodelling process drives with bone resorption by the conversion of quiescent bone surface into bone resorptive surface.[85]

By transmitting signals to osteoclasts and osteoblasts on the bone surface, osteocytes play a principal role in the initiation of bone remodelling. Osteoclasts resorb bone matrix by first creating a resorption pit. They end their function with apoptosis followed by coupling signals sent to osteoblasts. Osteoblasts then synthesize bone matrix, which undergoes mineralisation.

Bone remodelling is regulated by multiple inflammatory mediators and hormones and genes various cytokines, including interleukins, colony stimulating factors, calcitrophic hormones such as PTH, 1,25-dihydroxy vitamin D, calcitonin, and oestrogen. In postmenopausal women with an oestrogen deficiency, the over expression of RANKL activity responsible for increase the risk of fracture.[47-50]

Bone like a sponge like nature and it is rapidly associated with bone loss and new bone formation. The vertebrae are similarly constructed with a thick cortical layer surrounding sheets of trabecular bone. As a unit each vertebra can compress when temporarily loaded and then return to their original size.

The age progress remodeling leads to a gradual restructuring of the bone. Resorption of the minerals on the inside of the cortical layer and in the bone cavity itself leads to an inexorable loss of trabecular bone and a widening of the bone cavity.[87]

This is partly compensated for by the gradual addition of extra layers of mineral to the outside of the cortical layer. The age progress the bones get slightly thicker. But the danger is that they are not getting any denser. Alterations in bone mineral density almost certainly represents the risk of future osteoporotic fracture. The Changes in hormonal status particularly estradiol, clearly are important factors in both formation and resorption of bone in men and women.

The practice is dawn with like hematopoietic precursors to become osteoclasts and more resorption leads to complete loss of bone structure. The excessive activation of osteoclast is responsible for the destruction of bones. The laking of bone response through out the remodeling causes the osteoporosis.

Diagnosis:

Table 2: WHO criteria for clinical diagnosis of osteoporosis

<table>
<thead>
<tr>
<th>BMD T-score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-score ≥ -1</td>
<td>Normal</td>
</tr>
<tr>
<td>-1 &gt; T-score &gt; -2.5</td>
<td>Low bone mass</td>
</tr>
<tr>
<td>T-score ≤ -2.5</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>T-score ≤ -2.5 with existing fracture</td>
<td>Severe osteoporosis</td>
</tr>
</tbody>
</table>

Baseline laboratory studies include following:

- Liver function tests
- Blood test
- Thyroid stimulating hormone test
- Bone mineral density
- Dual-energy x-ray absorptiometry
- Bone mineral density test

Complications of osteoporosis

- Spinal compression: Sudden, severe back pain, especially in older women may be a dangerous sigh of weak bones and a spinal compression fracture.[51,52]
- Increased mortality: Osteoporosis patients have an increased mortality rate due to complications of fracture.
- Other medical conditions: Hip fracture may lead to serious complications like deep venous thrombosis, pulmonary embolism, and pneumonia.
- Decreased mobility: Hip fractures due to Osteoporosis may lead to decreased mobility which further aggravates the condition.
- Kyphosis: Multiple vertebral fractures can lead to a severe hunchback state called kyphosis. It is quite a dangerous condition since it leads to pressure on lungs and difficulty in breathing.[53]
- Reduced life quality: Fractures lead to severe disability resulting in poor quality of life.

Non pharmacological interventions in treating osteoporosis

The aim of preventive measures is to attain adequate bone mass and...
to maintain it. Preventive measures should be taken right from childhood.

- **Proper nutrition:** Adequate intake of calcium, protein and vitamin D till adult life is important to achieve ample bone mass. Low calcium intake throughout the life may cause decrease in peak bone mass, increasing the risk of fractures\(^{[54,55]}\).

- **Exercise and physical activity:** Exercises especially weight bearing exercises such as walking, dancing, jogging, climbing stairs have been shown to be beneficial in maintaining the bone mass.

- **Weight bearing exercises:** Like walking, jogging, playing tennis, dancing, Free weights, weight machines were practiced\(^{[56,57]}\).

- **Hormone replacement therapy:** Hormone replacement therapy with estrogen may be considered in peri menopausal or postmenopausal females with reduced bone mass, who are likely to develop fractures\(^{[58,59]}\).

- **Stop smoking:** Smoking might reduce the levels of estrogen leading to reduced bone mass.

- **Avoid excessive alcohol intake:** Excessive alcohol intake increases the risk of osteoporosis by decreasing bone formation and possibly due to poor nutrition too\(^{[60]}\).

**Preventing osteoporosis**

Guidelines from the American Association of Clinical Endocrinologists include the following:

- First-line agents: Alendronate, risedronate, zoledronic acid, denosumab
- Second-line agent: Ibandronate
- Second- or third-line agent: Raloxifene
- Last-line agent: Calcitriol

**Medications for treating osteoporosis**

**Calcium and vitamin D**

Getting enough calcium and vitamin D is very important if one affected by osteoporosis:

- Adults under age 50 need at least 1,000 mg of calcium, plus 400-800 IU of vitamin D a day.
- Women over age 50 need at least 1,200 mg of calcium, plus 800 to 1,000 IU of vitamin D a day.

- Sardines and salmon with bones

*Naturally available nutrient foods:

- Fatty fish, like salmon, mackerel, and tuna
- Beef liver, cheese, and egg yolks
- Fortified foods like milk, cereal, and orange juice

The treatment depends on the preventing further loss of bone mass (i.e. resorption of bone) and to stimulate bone formation.

- Raloxifene
- Estrogens
- Calcium and vitamin D supplement
- Calcitriol
- Alpha calcidol
- Biphosphonates includes:
  - Alendronate (Fosamax) is an oral medication people typically take once per week.
  - Ibandronate (Boniva) is available as a monthly oral tablet or as an intravenous injection that you get four times per year.
  - Risedronate (Actonel) is available in daily, weekly, bimonthly, or monthly doses.
  - Zoledronic acid (Reclast) is available as an intravenous infusion once every one or two years.
  - Calcitomin
  - Fluoride
  - Parathyroid hormone
  - Testosterone

**Antibodies**

**Denosumab** is an antibody. It links to a protein involved in body’s process of bone reabsorption. This antibody slows bone re absorption.

**Hormone therapy**

Postmenopausal women are at a high risk for osteoporosis. Estrogen helps protect bones, and estrogen production drops during menopause. For women in menopause hormone replacement therapy is the effective treatment option.

**Selective estrogen receptor modulators**

Selective estrogen receptor modulators can recreate the bone-preserving effect of estrogen.

**Thyrocalcitonin**

It is a hormone of the thyroid gland regulate the calcium levels in the body. The synthetic thyrocalcitonin to treat spinal osteoporosis in people who can’t take bisphosphonates. It can also ease the pain in some people who have spinal compression fractures.
Parathyroid hormone
This hormone controls calcium and phosphate levels in bone. Treatments with a synthetic parathyroid hormone like teriparatide (Forteo) can promote new bone growth. It is available as a daily injection in combination with calcium and vitamin D supplements.

CONCLUSION
It is a healable degenerative bone disease associated with increase loss of bone and decrease in bone density leads to develop risk of bone fracture.

The several mechanism associated with developing the disease includes accumulation of advanced glycation end products and the rising diabetic complications reduces the bone density may contribute the fracture risk[86,87]. The patient suffering from osteoporosis may have the chances to develop the diabetes in future. Early detection screening, prevention guidelines will supports reducing the risk progression. The diabetes is a multiple metabolic burden and progress the vision, neuropathic, kidney problems, musculoskeletal problems and impact on the vitamin D levels in the body. Meeting the national and International prevention guidelines application towards patient community will surely halt the disease burden in the future.[88-90]

Early detection and monitoring of risk factors and educating the patients about disease prevention and treatment is required to treat the disease complications. Driving the awareness programmes and early interventions about the disease among the health care professionals in the community is beneficial for reducing the disease. Approaching the non pharmacological interventions and providing calcium and vitamin D supplements to the community drags the betterment to the patient welfare. Administration of the calcium and vitamin D, antiresorptive therapy, Physical exercise, tobacco avoidance, moderate alcohol intake promotes the management of the disease. Sufficient calcium and vitamin D levels, reducing the consumption of saturated foods and regular monitoring of the cholesterol levels and avoidance of tobacco and alcohol, early screening of postmenopausal women may also helpful for reducing the disease prevalence in the community.

Acknowledgement: We would like to thank Dr. K.S. Lakshmi, Dean, SRM College of Pharmacy, SRM University for her valuable support.

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M.S. Umashankar et al. / Journal of Pharmacy Research 2017, 11(6), 753-761


Source of support: Nil; Conflict of interest: None Declared