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THE RELATIONSHIP BETWEEN OSTEOPOROSIS AND CHRONIC URINARY TRACT INFECTION

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Abstract: Osteomyelitis is an infection of the bone. The infection can reach the bone by traveling through the bloodstream or spreading from nearby tissue. The infection can also start in the bone itself if the injury exposes the bone to germs Smokers and people with chronic health conditions, such as diabetes or kidney failure, are more likely to get osteomyelitis. People with diabetes may develop osteomyelitis in their feet if they have foot ulcers. Osteomyelitis used to be considered incurable, but today osteomyelitis can be successfully treated. Most people need surgery to remove the dead bone. After surgery, strong intravenous antibiotics are needed.

1.1. INTRODUCTION

Osteoporosis is a systemic skeletal disorder that causes vulnerability of bones to fracture due to reduction in bone density and degradation of the microstructure of bone tissues [1]. Osteoporosis is the most common metabolic bone disease and affects half of female and one-third of male in their sixties and seventies. Prevention and treatment of osteoporosis are critical because the increased prevalence of osteoporosis and fragility fractures, along with aging of the global population, result in significant clinical, economic, and social burdens [2-3]. One in two women and one in five men who are over 50 years old are expected to experience a bone fracture as a consequence of bone weakness. Therefore, women are more likely to develop osteoporosis than men (Ediriweera de Silva et al., 2014). First, the nature of women's bodies has a lower peak bone mass compered to men. Second, women experience rapid decrease of bone mass resulting from hormone changes linked to menopause. Third, women usually live longer than men; therefore, they are more likely to experience loss of bone mass linked to aging for a long period of time [4- 5].

Urinary tract infections (UTIs) also called cystitis or infectious cystitis, are infections that can occur in the urethra (urethritis), bladder (cystitis), or kidneys (pyelonephritis) and are one of the world's most common infectious diseases, affecting 150 million people each year, with significant morbidity. Women are at greater risk of developing urinary tract infections compared to the men. In women, the urinary tract infections are frequently caused by bacteria such as Escherichia coli, or Staph commonly found in bowel flora and may move through the urinary tract, causing infections in the bladder or the other components of urinary tract [6-7]. Majority of UTIs are of bacterial etiology. UTI has been diagnosed by urine culture since decades. UTI, if left untreated, can progress to worsen renal function, cause pyelonephritis, sepsis, septic shock and death. Hence, it is important to treat UTI in earlier stages to prevent significant morbidity and mortality [8].

Both urinary tract infection and osteoporosis are widespread infections among women with numerous possible risks for complications. The appropriate diagnosis, as well as management of these illnesses, is essential to provide the best patient outcomes. The treatment of a UTI in women involves the use of antibiotics that include Fosfomycin, nitrofurantoin, sulfamethoxazole / trimethoprim and ciprofloxacin. In contrast, the treatment of osteoporosis may involve the utilization of antibiotics that comprise bisphosphonates, Fosamax, Raloxifene, teriparatide and denosumab. The management of UTIs among women requires good personal hygiene, getting plenty of vitamin C, drinking plenty water, changing sanitary pads and tampons throughout menstruation. Conversely, the management of osteoporosis among women necessitates regular exercise, healthy eating and avoiding smoking. The risk factors for UTIs include diabetes, pregnancy, poor hygiene, use of spermicides, recent antibiotic use, and sexual activity. On the other hand, some widespread risk factors for osteoporosis are family history, inadequate activity, age, Gonadal hormone deficiency, low calcium and vitamin D intake, smoking, and of the Caucasian or Asian race [9].

1.2. THE AIM OF THIS STUDY

The aim of this study is to determine the relationship between osteoporosis and chronic urinary tract infection

2.1. LITERATURE REVIEW

2.2. OSTEOPOROSIS

Osteoporosis is a bone disease that is characterized by low bone density and reduction of bone mass. It may lead to fragile bone and increase the risk of fracture. Most of the time, fracture is a life-threatening outcome of osteoporosis, the loss of bone happens silently and gradually [10].

The World Health Organization (WHO) roughly defines osteoporosis as the value of bone mineral density (BMD) that is more than 2.5 standard deviations below the average of peak bone mass or the mean of normal young healthy women as measured by dual-energy X-ray absorptiometry [11]. Women are at three times higher risk of osteoporosis than men because women experience a change in hormone levels during menopause and a decrease in bone mass. In the early stages of osteoporosis, there are usually no symptoms until the first fracture happens. People predominately will have a fracture, then they become aware that they are suffering from this disease. The pain often begins in any area of the spine, so it can cause fractures in the bones of the spine. These fractures frequently happen without risk of injury, but the pain happens progressively or immediately overtime along with loss of height [12].

Fractures related to osteoporosis are associated with adverse outcomes such as an early death, disability, poor quality of life, and financial consequences. In addition, fractures cause deterioration in physical function and that leads to soreness, distortion, and fear of falling [13]. As the population age gets older, osteoporosis incidences are estimated to increase, particularly the fractures and falls associated with osteoporosis. The risk of falls increases with age and falls can cause fractures in 10% to 15% of older

people. Additionally, a history of fall can increase the prediction of fall risk in the future. Due to higher deterioration in balance and weakness of muscle, older females who suffer from osteoporosis have a higher risk of falls [14].

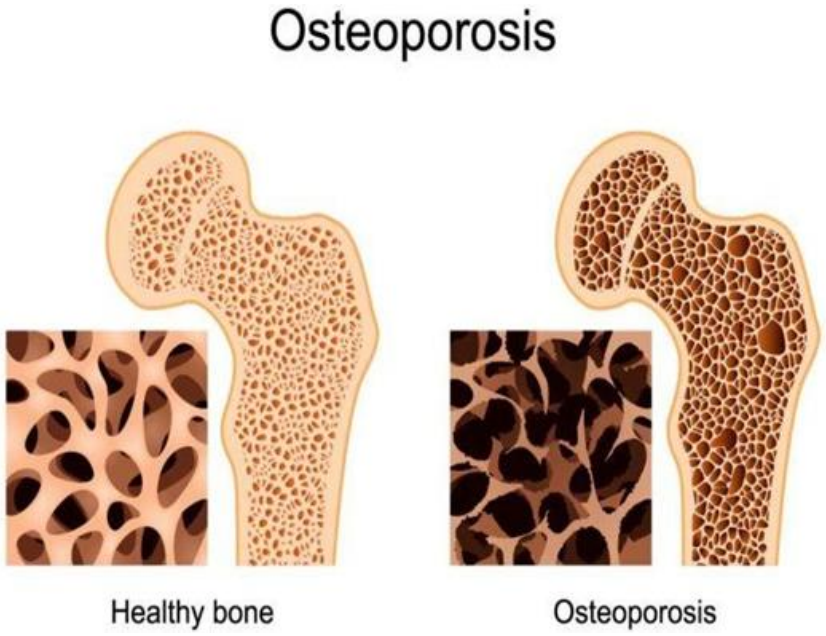


Figure 1: Explains the difference between healthy bone and osteoporosis

A basic understanding of the bone remodelling cycle will facilitate the discussion on the pathophysiology of osteoporosis (Figure 1). Osteoclasts, osteoblasts, and osteocytes are the three main players in bone remodelling. When bone damage occurs, the macrophage polykaryon- derived osteoclasts migrate to the damage site and perform bone resorption. At the end of bone resorption, osteoclasts undergo apoptosis and produce apoptotic bodies that may play a role in the subsequent osteogenesis [15]. After the reversal phase, the mesenchymal stem cell- derived osteoblasts will migrate to the cavity and perform bone formation. Some osteoblasts will be embedded in the bone matrix they synthesise and differentiate into osteocytes. Osteocytes act as a mechanosensor and play regulatory roles in regulating the bone remodelling process through signalling proteins and via perilacunar remodelling directly [16].

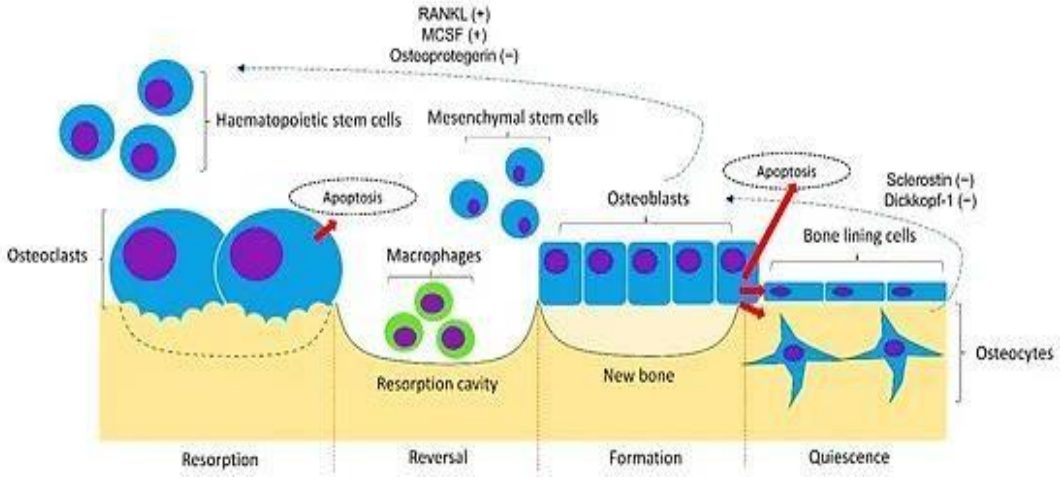


Figure 2: Bone remodelling cycle

(The bone remodelling cycle is governed by osteoclasts, osteoblasts and osteocytes derived from the respective stem cell lineage. The differentiation of osteoclasts is stimulated by the receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (MSCF) and inhibited by osteoprotegerin (OPG) synthesised by osteoblasts and osteocytes. The osteogenesis of osteoblasts is inhibited by sclerostin and Dickkopf-1 synthesised by osteoblasts. Notes: +, promoting factor; −, inhibiting factor.)

The bone remodelling process is coordinated delicately to maintain bone mineral homeostasis and strength. The differentiation of osteoclasts is stimulated by the receptor activator of the nuclear factor kappa-B (NF-kB) ligand (RANKL) and macrophage colony-stimulating factor (MSCF), and inhibited by osteoprotegerin (OPG) synthesised by osteoblasts and osteocytes. The osteocytes synthesised sclerostin and Dickkopf-1 that inhibits the Wnt signalling pathway and osteogenesis by osteoblasts. Bone loss occurs when the rate of bone formation is lower than bone resorption [17].

2.2.1. Causes of osteoporosis

1. Primary Osteoporosis: is often associated with age and sex hormone deficiency. Age-related osteoporosis results from the continuous deterioration of the trabeculae in bone. In addition, the reduction of estrogen production in post-menopausal women causes a significant increase in bone loss. In men, sex-hormone–binding globulin inactivates testosterone and estrogen as aging occurs, which may contribute to the decrease in bone mineral density (BMD) with time [18].
2. Secondary Osteoporosis: is caused by several comorbid diseases or medications. Diseases implicated in osteoporosis often involve mechanisms related to the imbalance of calcium, vitamin D, and sex hormones [19]. For example, Cushing's syndrome has been found to accelerate bone loss through excess glucocorticoid production.21 In addition, many inflammatory diseases, such as rheumatoid arthritis, may require the patient to be on long-term glucocorticoid therapy and have been associated with secondary osteoporosis. Notably, glucocorticoids are considered the most common medications linked to drug-induced osteoporosis. bone mineral density (BMD) has been found to decline rapidly within three to six months of initiation of glucocorticoid therapy.6 The American College of Rheumatology (ACR) has detailed recommendations to aid in guiding therapy selection for the prevention and treatment of glucocorticoid-induced osteoporosis (GIO) [20]. Causes of secondary osteoporosis may differ between genders:

- For men, excessive alcohol use, glucocorticoid use, and hypogonadism are more commonly associated with osteoporosis. For example, men receiving androgen-deprivation therapy (ADT) for prostate cancer are at increased risk of osteoporosis, Studies indicated that those who were treated with ADT experienced a fracture compared with 12.6% of those who were not [21].
- For women, osteoporosis in women is sometimes associated with most often hypercalciuria, malabsorption of calcium, hyperparathyroidism, vitamin D deficiency, hyperthyroidism, Cushing's disease, and hypocalciuric hypercalcemia. Of note, disorders of calcium metabolism and hyperparathyroidism contributed to 78% of the secondary causes [22].

2.2.2. Risk Factors

Risk factors of osteoporosis include increasing age, female sex, postmenopausal status, hypogonadism or premature ovarian failure, low body mass index, ethnic background (white persons are at higher risk than black persons), rheumatoid arthritis (RA), low BMD, vitamin D deficiency, low calcium intake, hyperkyphosis, current smoking, alcohol abuse, immobilization, and long-term use of certain medications, such as glucocorticoids, anticoagulants, anticonvulsants, aromatase inhibitors, cancer chemotherapeutic drugs, and gonadotropin-releasing hormone agonists [23].

2.2.3. Symptoms of Osteoporosis

Osteoporosis is called a silent disease because there are typically no symptoms until a bone is broken. Symptoms of vertebral (spine) fracture include severe back pain, loss of height, or spine malformations such as a stooped or hunched posture (kyphosis). Bones affected by osteoporosis may become so fragile that fractures occur spontaneously or as the result of [24]:

Minor falls, such as a fall from standing height that would not normally cause a break in a healthy bone.

Normal stresses such as bending, lifting, or even coughing

2.2.4. Diagnosis of Osteoporosis

Osteoporosis is a silent disease without obvious symptoms and evidence until a fracture occurs. Thus, screening by dual energy X-ray absorptiometry (DEXA) is important to obtain an early diagnosis and to avoid fractures [25]. All women aged 65 years or older and men aged 70 years or older, postmenopausal women with medical causes of bone loss (e.g., steroid use) regardless of age, postmenopausal women aged 50 years or older with additional risk factors for fracture (e.g., current smoker, RA, history of hip fracture in a parent), and postmenopausal women with a fragility fracture should be screened for osteoporosis by BMD measurement at the hip and lumbar spine as recommended by the

U.S. Preventive Services Task Force (USPSTF), the National Osteoporosis Foundation, and by other guidelines [26].

The gold standard for diagnosing osteoporosis utilizes BMD measurements, especially in the hip and lumbar spine with the dual- energy x-ray absorptiometry (DXA) device or the occurrence of nontraumatic hip or vertebral fractures. Resulting T-scores are used to interpret BMD and to correlate results with fracture risk. For example, low BMD (or a highly negative T-score) is strongly correlated with a high fracture risk (Table 1) [27].

Table 1: T-Scores and WHO Diagnostic Criteria for Osteoporosis

Interpretation	*T-Score*
Normal	−1.0 and higher
Osteopenia	−1.0 to −2.5
Osteoporosis	−2.5 and lower
Severe osteoporosis	−2.5 and lower with one or more fragility fractures

Another diagnostic instrument, available in print or online, is a risk- assessment tool developed by the University of Sheffield in Great Britain called FRAX (Fracture Risk Assessment Tool). It takes into account risk factors such as age, race, alcohol use, gender, body mass index, smoking history, prior personal or parental history of fracture, use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, and femoral neck BMD measurements to predict the 10-year probability of hip fracture and other major osteoporotic fracture. In addition, it assesses country-specific probabilities based on epidemiological data. This tool can be used in conjunction with other diagnostic tools, such as the DXA scan, to determine appropriate patients for treatment [28].

2.3. URINARY TRACT INFECTION

Urinary tract infection (UTI) is defined as an inflammatory response of the urinary epithelium to microbial infection of any anatomical constituent of the upper or lower urinary tract. Technically, upper urinary tract infections (kidneys) are referred to as pyelonephritis and infections of the lower urinary tract (bladder, urethra) are termed cystitis and urethritis respectively [29]. Urinary tract infections (UTIs) are one of the most common bacterial infections worldwide, with an upward trend of disease burden. Globally, more than

404 million individuals suffered from UTIs in 2019 (60% increase from 1990), with approximately 237,000 related deaths and 5.2 million disability-adjusted life-years. The highest number of reported cases was found in the age group between 30 to 34 years [30].

Nonetheless, UTI is far from uncommon in the pediatric population, with an estimated prevalence of 7.8% in children aged under 19 years. UTIs affect mostly females in all age groups, with an estimated one-third getting at least one UTI by the age of 24 and a lifetime UTI risk of 60%. The disease is complex and has heterogenous presentations, ranging from asymptomatic sub-clinical infection to life-threatening urosepsis. Often attributed to anatomical differences, such as the length of the urethra and shorter distance between the urethra and the anus, females are fifty times more likely to suffer from bladder infections than men (Fig. 3). That being said, UTI is far from rare in males, with a third of men over the age of 80 years requiring antibiotic treatment from a general practitioner [31].

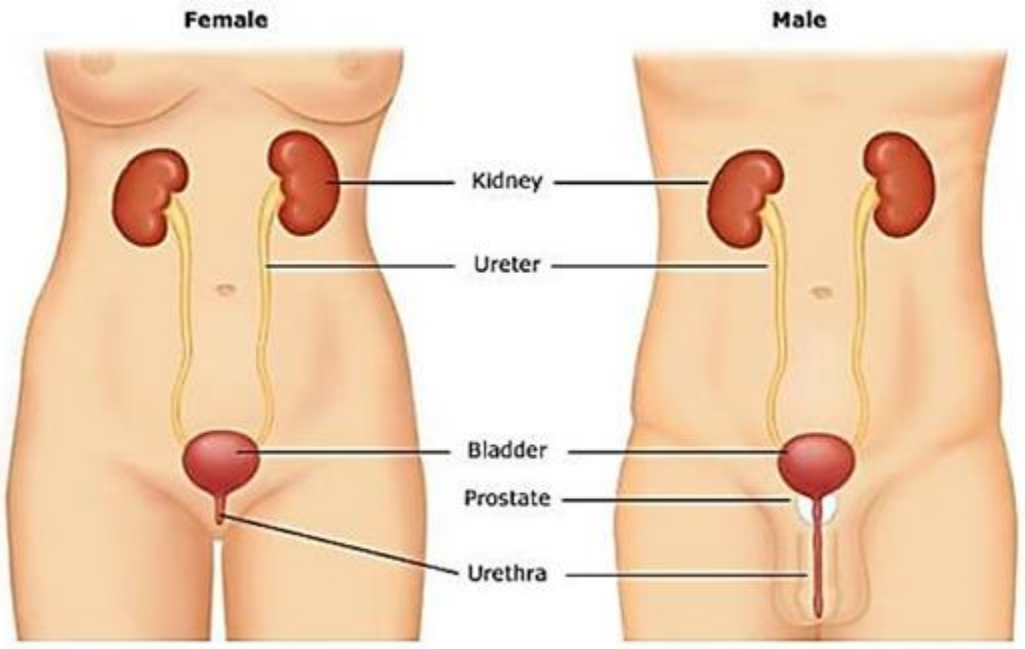


Figure 3: Anatomy of the human urinary tract

(The urinary anatomy is made up of the upper (kidneys, ureters) and lower (urinary bladder, urethra) urinary tracts. The female urethra is significantly shorter than that of males.)

Acute UTI or cystitis, its commonest form, is typified by the onset of lower urinary tract symptoms (LUTS), namely urinary frequency, urgency, and pain4. For those with a history of UTI, the risk of recurrence is around 26% within 6 months in adults5 and 17.3% in children aged between 2 to 6 years within 2 years. These recurrent or chronic UTIs have a significant negative impact on quality of life and are especially difficult to treat [32] A chronic urinary tract infection (UTI) might also be called a persistent or recurring UTI. A UTI can persist or recur because of reinfection or if treatment does not clear the infection entirely. chronic urinary tract infections are a common cause of morbidity, especially in young women. Chronic UTI are defined as having 3 or more UTIs in a year [33].

2.3.1. Symptoms of urinary tract infection

An inflammation of the urinary tract can occur in urethra (urethritis), bladder (cystitis), kidneys and renal pelvis (pyelonephritis), epididymis (epididymitis) or prostate gland (prostatitis). In extreme cases infection overspills to the bloodstream and manifests as sepsis, severe sepsis or septic shock. For clinical management, UTIs are classified into four categories: asymptomatic bacteriuria, uncomplicated UTI,

complicated UTI and catheter-related UTI. Depending on the location of the infection, symptoms vary ranging from mild irritation during voiding to sepsis (Table 1) [34].

Table 2: Clinical symptoms and signs of upper and lower urinary tract infection.

Lower urinary tract infections	Upper urinary tract infections
Dysuria	Systemically unwell
Burning with urination	Nausea and vomiting
Frequency of urination	Uncontrollable shivering Hypotension or shock
Malodorous urine	Loin pain and tenderness in the upper
Suprapubic, and rectal (men) pain	back and sides
Normal temperature	Fever
Haematuria	+/- Features of lower urinary tract infection

2.3.2. Risk factors of urinary tract infection

Factors that may make increase the risk for UTI [35]:

1. Infrequent voiding – The bacteria spend a greater amount of time in the bladder allowing it time to replicate and take hold.
2. Incomplete voiding – An excess amount of urine is left in the bladder and the bacteria is not completely flushed out with each void.
3. Personal Hygiene – Perineal contamination with faeces increases the risk of coliform bacteria in the vagina and near the urethra will increase the risk of urinary tract infections.
4. Sexual Activity – Trauma to the urethra and surrounding tissue may increase susceptibility to infection and also the bacteria can be mechanically pushed into the urethra.
5. Use of spermicidal contraception–The actual spermicide changes the normal flora in the vagina and more coliform bacteria colonize the area. The presence of these strains of bacteria leads to a greater risk of a UTI.
6. Genetics – Certain cells on the vaginal mucosa and the urethra can express receptors that actually allow certain bacteria to attach and pull themselves into the bladder causing an increased risk of a UTI.
7. Hormonal Status - A lack of estrogen allows for thinning and deficiency of the tissue in the vagina and urethral that may allow for greater susceptibility to UTIs. This lack of estrogen also changes the pH of the vagina which allows for colonization with more coliform bacteria and increases the risk of UTIs.
8. Diabetes– Persistently high blood sugar levels cause immunosuppression which allows for greater susceptibility to UTIs.
9. Immunosuppression – There are a variety of causes of immunosupression which decreases a person's ability to fight off infections.
10. Factors that predispose to recurrent uncomplicated UTI include menopause, family history, sexual activity, use of spermicides and recent antimicrobial use [36].

2.3.3. Diagnosis of urinary tract infection

When working up recurrent uncomplicated UTI, culture and sensitivity analysis should be performed at least once while the patient is symptomatic. This workup confirms a UTI as the cause for the patient's recurrent lower urinary tract symptoms. Additionally, adjustment of empirical therapy based on sensitivity may eradicate resistant bacteria as a cause for bacterial persistence and recurrent UTI.

A midstream urine bacterial count of 1 × 105 CFU/L should be considered a positive culture while the patient is symptomatic. Potential for contamination with midstream urine collection necessitates careful evaluation of the cultured species reported. A negative culture, while maintaining a response to treatment, may be present in a minority of women. A negative culture and lack of response to treatment suggest another diagnosis. Patients may then be re-cultured 1 to 2 weeks after initiating therapy adjusted to sensitivity to evaluate for bacterial persistence [37].

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