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KNEE OSTEOARTHRITIS: MEASUREMENT OF DISABILITY AND ASSOCIATIONS WITH CHRONIC VENOUS INSUFFICIENCY OF THE LEGS AND OSTEOPOROSIS

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ABSTRACT

Osteoarthritis (OA) is the most common musculoskeletal problem in individuals older than 50 years. It is the fifth most common health problem among 21 conditions. It is the most common joint disease, characterized by pain, inflammation and stiffness due to degeneration of the articular cartilage, bone abnormalities and involvement of soft tissues .It is a slowly progressive disorder which represents failure of diarthorodial movable, synovial lined joint. One-hundred patients aged 50 years or older (82 females and 18 males) patients complaining from unilateral or bilateral knee pain (fulfilling the clinical classification criteria of idiopathic knee OA of the American College of Rheumatology ACR) were included in this study. Case collection was haphazard (convenience) sampling. The conversational Arabic version of WOMAC questionnaire is reliable and valid; therefore bit can be use as an outcome measure in following patients with knee OA. Knee osteoarthritis is significantly associated with increasing BMI, clinical venous insufficiency and relative increase in inflammatory markers. The inter-relationship with osteoporosis is complicated and needs further studies. However the study's findings suggests that osteopenia may be a protected against OA. These findings could have an important therapeutic implications. For example the evidence is accumulating that low grade inflammation plays an important role in OA. Proinflammatory state may then need to be targets of treatment when associated with OA.

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INTRODUCTION

Osteoarthritis

Osteoarthritis (OA) is the most common musculoskeletal problem in individuals older than 50 years (Beary III and Luggen, 2006). It is the fifth most common health problem among 21 conditions (Americans academy of orthopedic surgeons, 2004). It is the most common joint disease, characterized by pain, inflammation and stiffness due to degeneration of the articular cartilage (Shiller 2002), bone abnormalities and involvement of soft tissues (De Filippis *et al*., 2004; Sharetto, 2004). It is a slowly progressive disorder (Vogelgesang, 2002) which represents failure of diarthorodial movable, synovial lined joint (Brandt, 2005). OA importance derives from its economic impact, in terms of both productivity (single greatest cause of days lost from work) and cost of treatment (Lane EN and Schnitzer, 2007). Knee OA is the most frequent form of arthritis (Murphy *et al*., 2008). Overall, 15% of population have problems with OA, with women outnumbering men by a ratio of 2 to 1 for nearly all age groups (Americans academy of orthopedic surgeons, 2004). Thousands of people each year experience symptoms related to subchondral defect of the knee that often threaten quality of life, especially in an active population (Anderson *et al*., 2005). The incidence of OA begins to rise in the mid-40s (long before senility); thus this disorder is a common cause of joint symptoms and loss of work-time long before someone is considered elderly (Lane and Altman, 2009). The most common form of OA is primary (idiopathic) where no predisposing factor is apparent. Secondary OA is pathologically indistinguishable from the idiopathic and it is attributable to underlying causes (Brandt, 2005). Although the initiating insult in OA is not well understood, there are well documented pathogenetic and risk factors (Andriacchi *et al*., 2000). Risk f]actors are broadly dividable into those that are

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constitutional or genetic and those that are local and driven by biomechanical elements, such as excessive joint usage. The incidence of knee OA is expected to rise as the proportion of elderly population continues to increase. Several epidemiological studies in Western and Oriental countries have investigated risk factors of knee OA, finding a consistent association between the incidence or progression of knee OA and age, obesity, history of knee injury, occupational physical demands, physical activity, and excessive sport activities (Mounach *et al*., 2008).

Age is the most powerful risk factor for OA (Brandt.2005) that the disease is uncommon before the age of 40s; its prevalence rises rapidly with age to the degree that most individual over the age of 70 have the pathological changes of OA in some of their joints; although many of them may remain asymptomatic (Dieppe, 2008). Sex is an important risk factor. From the age of 40 to 55, there is a little difference in the prevalence of OA between men and women (Beary and Lugge, 2006). In those < 55 years, the joint distribution of OA in men and women is similar, although symptomatic knee OA, is more common in women than men even for the same degree of pathological severity (Brandt, 2005). OA is frequently considered a localized, rather than systemic disease. Joint involvement is usually asymmetric with a predilection for weight- bearing joints. The common sites of joints involvement are the knee, hip, distal and proximal inter-phalangeal joints and the spine (Shiller, 2002). It has a substantial impact on activities of daily living (Mounach *et al*., 2008). Knee OA is one of the most common causes of chronic disability among elderly persons (Shiller, 2002; Andriacchi *et al*., 2000) particularly if it is associated with quadriceps muscle weakness (Brandt, 2005). One of the various instruments that have been used to measure the functional disability due to knee OA is the Western Ontario and McMaster University WOMAC score that consist of four subscales and measure function difficulties in addition to pain ,stiffness and symptoms. WOMAC is a validated instrument designed specifically for the assessment of lower extremity OA (Wolfe, 1999), it is one of clinical outcomes measurement that can be used for follow up in patients with knee and/or hip OA. It is recommforended for this purpose by the Osteoarthritis Research Society International (Harrison and Mandl, 2006). Although OA is considered to be a non-inflammatory arthritis, as cartilage destruction proceeds, mild to moderate inflammatory reactions are found in the synovial membrane (Garstang and Stitik, 2006) Histologic evidence clearly shows ongoing inflammation and cartilage destruction in osteoarthritis, although not to the same degree as in other arthritides and may have a role in the pathogenesis and severity of OA (William and Wilke, 2010).

Chronic Venous Insufficiency: The reason behind studying chronic venous insufficiency (CVI) in this context is that it provides a pro inflammatory state in the lower limb circulation (Stvrtinova *et al*., 2001) Furthermore there is similarity in the risk factors between knee OA and CVI of the legs as will be discussed in the literature review. CVI is a progressive disorder, resulting from dilatations of the veins of the lower limbs, incompetence of their valves & resultant venous hypertension (UL-Islam *et al*., 2008). Thus venous blood deviate from a normal flow path to a retrograde direction (Weiss 2010, 2007).

Osteoporosis: Osteoporosis (OP) is also an age related disorder. several previous studies reported a negative association between OA and low bone mineral density BMD (Felson, 1988) thus OP may be an alleviating factors for OA. On the other hand osteopetrosis, a condition that stiffen the cartilage or subchondral bone, is associated with sever OA that usually apparent by the age of 40; furthermore, if the subchondral bone is stiffened experimentally by repetitive impact loading soon lead to breakdown of overlying cartilage (Brandt, 2005).

The major aims of this study are

- To evaluate Arabic face to face interview version of the WOMAC questionnaire which measure function and symptoms in knee OA.
- To study whether knee OA has a sort of association with chronic venous insufficiency of the legs and osteoporosis.

REVIEW OF LITERATURE

Osteoarthritis (OA)

Definition and Major Characteristics: OA is a chronic disorder involving the entire joint organ (bone, cartilage, and supporting elements); inflammation is not a prominent clinical feature. It is characterized by focal degeneration of the cartilage of synovial joints, now bone formation in the form of osteophyte at the base of cartilage lesion and at the joint margin, in addition to remodeling of the joint contour. It is strongly associated with ageing and is a major cause of pain and disability in older people (Doherty and Ralston, 2010). Other names for OA are degenerative arthritis, hypertrophic arthritis or age-related arthritis (William and Wilke, 2010). It's most prominent feature is the progressive destruction of articular cartilage which results in severe pain, impaired joint motion, and, ultimately, disability (William and Wilke, 2010) while inflammation is not a prominent clinical feature (Doherty and Ralston, 2010). OA is characterized clinically by pain and stiffness that is aggravated by prolonged activity (Sandmeier, 2000), bony or soft tissue swelling, tenderness, crepitus, peri-articular muscle atrophy, bony hypertrophy, deformity and marked loss of joint motion (Mahajan *et al*., 2005), radiographically by osteophytes and joint space narrowing (JSN), and histopathologically by alterations in cartilage and subchondral bone integrity (Lane and Schnitzer, 2007), ongoing inflammation (William and Wilke, 2010) and remodeling of joint contour. OA is a degenerative disease of the cartilage of the joints (Weiss, 2006). Its earliest pathological manifestation is loss of cartilage. When extensive, this loss is visible on radiograph as joint space narrowing. Subsequent bony changes consist of increased sclerosis of underlying bone, osteophyte formation, and occasionally, subchondral bone cysts (Felson, 1988).

OA Classification: OA is classified into two groups, primary and secondary disorder, the disorder is considered primary when the joint was apparently normal (intact joint) previously and there is no underlying causes. While secondary OA describe OA occurring in previously diseased joints such as after calcium pyrophosphate arthropathy or when there is systemic an underlying (metabolic, endocrine, congenital and developmental, rheumatologic, hematologic) causes. However the lines distinguishing primary and secondary OA are becoming more blurred (American academy of orthpeadic surgeons, 2004). The more common is the primary OA and it is related to the aging process "occurs in older individuals,

becoming worse in frequency and severity with aging" (American academy of orthpeadic surgeons, 2004; Mahajan *et al*., 2005). Secondary OA more likely to show at an earlier age than 1ry OA. Post traumatic secondary OA, for example, accounts for only 12% of the overall prevalence of symptomatic OA (Brandt, 2010).

***OA Epidemiology (Prevalence and Incidence*):** OA is the second most common rheumatological problem (Mahajan *et al*., 2005), it is prevalent in all racial group (Doherty and Ralston, 2010). Irrespective of race, geographical location and climate (Cicuttini and Spector, 1998). The prevalence of OA in under 45 years, 45-64 years and over 65 years is 2%, 30% and 68% respectively in women and 3%, 24.5% and 58% in men (Cicuttini and Spector, 1998). Two-thirds to three-fourth of adults with OA knee are women after menopause (American academy of orthpeadic surgeons, 2004), Men have more knee OA before age 50 (Neustadt, 2006). Radiographic prevalence is about 30% of people older than 50 years and increasing to up to 80% after age 65. Though only 25-30% is symptomatic (Doherty and Ralston, 2010). The life time risk of symptomatic knee OA is estimated to be nearly 1 in 2 overall, more than 1 in 2 among those with history of a knee injury, and nearly 2 in 3 for obese persons (Murphy *et al*.,2008). For the same degree of pathologic severity, women are more likely to be symptomatic than men, those on welfare more likely than those who are working, and those who are divorced more likely than those who are married (Brandt, 2006). In men, being married was associated with a significantly lower risk for OA. Non-smokers had a slightly higher rate than smokers (Anderson and Felson, 1988).

OA Risk Factors and Etiopathogenesis: The exact etiology of OA is not known, but there are many heterogenous factors which need to interact to produce this complex disorder (Mahajan *et al*., 2005b; Kraus *et al*., 2007). These etiopathogenic factors include molecular and mechanical changes related to many gross risk factors such as advancing age, obesity, history of knee injury, physical activity, and regular sport activities, occupational physical demands (Mounach *et al*., 2008) bending and lifting, and previous knee surgery (Felson, 2006), and female sex (Anderson and Felson, 1988). Therefore, it was postulated that if some of the systemic etiopathogenetic factor are operating, the joint may be considered more vulnerable to local biomechanical processes that produce joint degeneration or OA (Garstang and Stitik, 2006). Thus, the etiopathogenetic mechanics can be divided into:

- Systemic risk factors.
- Local risk factors.
- Local pathological processes (the development of OA):
- Molecular processes.
- Tissue changes.
- Systemic risk factors:

Age: the main common factor in OA is increasing age. As a people age, the prevalence of clinical OA in 60 years or older individuals are estimated to be approximately four times that of persons age 20 years and older, (Lim *et al*., 1996). Elderly people are found to have rapid radiological progression of OA. (Mahajan *et al*., 2005b) at all joint sites." (Garstang and Stitik, 2006) particularly in women (Cicuttini and Spector. 1998)

Ethnicity and Race: OA occurs in all populations, irrespective of race, geographical location and climate, but for unknown reason the pattern of disease varies in different ethnic groups; for example, hip disease is less common in Chinese and Asians than in those of Western origin (Cicuttini and Spector, 1988; Garstang and Stitik, 2006).

Gender: gender has a role in OA, particularly at specific sites. Below 45 years of age, OA is more common in men involving one or two joints (Garstang and Stitik, 2006). Above 55 years (55–74 years) the prevalence of knee OA is greater in women involving several joints principally the interphalangeals, the first metacarpal and the knees (Cicuttini and Spector, 1998). While the prognostic factors for the two sexes appear to be somewhat different (American academy of orthopedic surgeons, 2004). Females after the menopause are found to have more severe OA, more number of involved joints, and more symptoms and increased hand and knee OA (Mahajan *et al*., 2005b). Hormonal Status, sex hormones (estrogen) deficiency as around menopause and after hysterectomy may increase the risk of OA. (Mahajan, *et al*., 2005; Garstang and Stitik, 2006).

Genetic Factors: OA has a major genetic component (Garstang and Stitik, 2006) a strong genetic component is thought to be present, particularly in women. The influence of genetic factors was estimated to be 35–65%, independent of known environmental and demographic confounders (Cicuttini and Spector, 1998).

Bone Density: high bone density is believed to be a risk factor for developing OA of the knee, while low bone density mat be a risk factor for more rapid progression (American academy of orthopedic surgeons, 2004). There is a negative association between osteoporosis and OA at certain sites particularly the hip (Mahajan *et al*., 2005b; Garstang and Stitik, 2006).

Other factors: an increased risk of OA in persons with low levels of vitamin D&C (Garstang and Stitik, 2006), Psychosocial factors may include Low personal self-efficacy and depression. (American academy of orthpeadic surgeons, 2004; Cuttini and Spector, 1998).

Local risk factors

Obesity: Obesity is an important modifiable risk factor. (Cicuttini and Spector, 1998) A dose-response relationship has been found (Le Graverand *et al*., 2008) even in individuals with asymptomatic radiological knee disease (Cicuttini and Spector, 1998). The weight effect is stronger in women than in men, in women the risk is proportional to the degree of overweight (American academy of orthpeadic surgeons, 2004). It has been estimated that OA attributable to obesity is 63% in the middle-aged and 25% in the elderly (Cicuttini and Spector, 1998). The obesity can increase risks for OA two to seven folds even in non-weight bearing joints. Obesity may predispose to OA, perhaps via an inflammatory or metabolic intermediary. i.e. obesity plays a role not only as a local process but systemically as well (Garstang and Stitik, 2006).

Altered joint biomechanics: Loss of normal joint biomechanics make joint more vulnerable to OA (Garstang and Stitik, 2006). This topic include:

- Ligamentous laxity as hypermobility syndrome. (Brandt *et al*., 2006).

- Joint misalignment or malalignment or residual joint instability: Poor posture or bone alignment, wearing high heel, thick or narrow, varus alignment a fivefold increase in the risk of progressive knee osteoarthritis among patients who reported a history of bow legs or knock knees in childhood. (Brandt *et al*., 2006; Garstang and Stitik, 2006).
- Muscle weakness (Garstang and Stitik, 2006).
- Impaired proprioception With aging, this decline cause decreased neurologic responses (Garstang and Stitik, 2006; Brandt *et al*., 2006)

Prior joint injuries: these can be accidental, occupational, surgical or sport injury. A previous knee injury that alter mechanical can lead to development of OA knee (American academy of orthopeadic surgeons, 2004). post traumatic OA has been estimated to the 12% of symptomatic OA prevalence. (Brandt, 2010). Repetitive occupational stresses increase risk of OA; This include knee-bending in men, kneeling or squatting, regular weight lifting, miming and others (Garstang and Stitik, 2006; Cicuttini and Spector, 1998; American academy of orthopeadic surgeons, 2004). In the absence of systemic factors, moderate exercise such as regular long-distance running has been shown to reduce the incidence of knee OA (Americans academy of orthopeadic surgeons, 2004). Howerver Intense exercise can accelerate cartilage breakdown and development of premature OA (Sandmeier, 2000; Garstang and Stitik, 2006). Developmental abnormalities (Garstang and Stitik, 2006) seldom are a basis for knee OA (Brandt, 2010).

Joint location: OA is more common in hip and knee joint but occur rarely in ankle. Alteration in chondrocyte responsiveness to different cytokines may be the reason eg. knee chondrocytes exhibit more IL-1 receptors and mRNA for matrix MMP-8 than ankle chondrocytes (Mahajan *et al*., 2005b).

The local pathological processes

Molecular processes: the exact sequence of pathogenetic processes in OA is not yet clear. the following processes are well described:

- ***Chondrocytes senescence:*** the molecular markers of chondrocyte senescence have been found in chondrocytes taken from OA patients (Krasnokutsky *et al*., 2008).
- ***Oxidative injury:*** chondrocyte apoptosis and cartilage matrix degradation mediated by reactive oxygen species (ROS) have been implicated in the OA process (Krasnokutsky *et al*., 2008; Kapoor *et al*., 2011).
- Mechanical stress by both static and intermittent compression, increases nitric oxide (NO) production by chondrocyts (Krasnokutsky *et al*., 2008).
- Low grade synovial inflammation dose occur even in early OA. It can be subclinical as suggested by arthroscopic studies. This synovial reaction is mostly confined to areas adjacent to pathological damaged cartilage and bone (Krasnokutsky *et al*., 2008).
- The role of cytokines: proinflammatory cytokines role in OA has been reviewed by Kapoor *et al*., 2011 in summary:
- IL-1B, TNF and IL-6 are believed to be a major cytokines involved in the pathogenesis of OA.
- IL-1B and TNF are produced locally by chondrocytes, mononuclear cells, osteoblasts and synovial tissue.
- These cytokines induce the production of a number of inflammatory mediators and catabolic factors including several proteolytic enzymes among which are matrix metalloproteinase (MMP) including MMP-1 (interstitial collagenase) and MMP-13 (collagemase 3).

In vitro studies showed that treatment of chondrocyts with IL-1B and TNF enhance the release of NO and prostaglandin E_2 (PGE_2). There are any other cytokines in the OA joint, growth factors and enzyme inhibitors which can be looked at in (Kapoor *et al*., 2011; Mahajan *et al*., 2005b).

Tissue changes: these are summarized by Mahajan *et al*., 2005b and Beary and Luggen, 2006, they include:

CARTILAGE changes: occurs in stages: reduction in proteoglycan, superficial fibrillation and fissuring, focal and diffuse erosions of the cartilage surface and finally thinning and complete denudation of cartilage.

Subchondral bone Changes: new bone formation in the subchondral areas and at joint margins (osteophytes), subarticular bone cysts. Focal synovial thickening and inflammation.

OA Clinical Aspects

OA Clinical Features:- Clinical features of OA summarized by Stone, 2008 are:

- Joint pain with activity
- Brief stiffness in the morning or after rest
- Reduced range of motion
- Joint crepitus and/or peri-articular tenderness swelling.

Pain is an essential component of clinical OA and is a requirement of the American College of Rheumatology (ACR) knee OA criteria (Wolfe and Lane, 2002) and in the vast majority of cases, it is the clinical feature that leads patients with OA to seek medical attention (BRANDT, 2010). Although it often does not correlate well with radiographic abnormalities (William and Wilke, 2010). Typically, the pain is deep, dull ache, an insidious, slowly progressive in and around the knee, localized to the involved joint, aggravated by use of that joint (weight bearing in knee OA) and relieved by rest, it is intermittent initially then may become constant even at rest, increasing in severity, and disabling with disease progression (Hochberg *et al*., 1995). The source of the OA pain may be any of the three knee compartments, lateral and/or medial tibiofemoral and the patellofemoral compartment that is most often the source of pain (Felson, 2006). Although quadriceps weakness is common in patients with knee OA, it arise as a consequence of the painful knee OA or it may be a risk factor for incident radiographic knee OA (Brandt *et al*., 2006) Stiffness is another early symptom of OA (William and Wilke, 2010) described as gelling of joint after inactivity with difficulty in initiating movement (Mahajan *et al*., 2005b). It usually subsides rapidly and becomes more prolonged with progression of the disease (Brandt, 2010). Other symptoms include joint instability (knees give way) (Felson, 2006), crepitus (the sensation of cracking or popping of tissues with movement), deformity such as bowing (Brandt, 2010) and limitation of joint motion. (Hochberg *et al*., 1995). Systemic

manifestations (e.g., fever, anemia, weight loss) are not features of primary OA (Brandt, 2010).

OA Physical Examination: The swelling may be resulting from Synovial effusion, which usually is not large, or synovial thickening, or osteophytes, or bone remodelling both can alter joint contour (Brandt, 2010), or deformity (Mahajan *et al*., 2005b). Atrophy of periarticular muscle (may be caused by disuse) may exaggerate the appearance of joint swelling. Palpation may reveal some warmth over the joint (Brandt, 2010). Tenderness over the medial or lateral joint lines and/or Patellofemoral articulation often signals the location of pathology (Felson, 2006; William and Wilke, 2010). Crepitus, which may be diffuse or localized, is characteristic of OA. It either soft as fibrillated cartilage in the patellofemoral joint, or hard (coarse), sharp crepitus due to irregularity of articular surface in knee OA (Mahajan *et al*., 2005b; Brandt, 2010). In the advanced stages of OA, gross deformity, palpable bony hypertrophy, subluxation, and marked loss of joint motion, often with noticeable contracture, may be striking (Brandt, 2010) The result is a deformed, poorly functioning, painful joint which is unstable in some patients (Cicuttini and Spector, 1998).

OA Investigations

OA Labroratay Examination: No blood tests or arthrocentesis are routinely indicated (Felson, 2006), and generally they are not diagnostic. Their utility lies mainly in excluding other causes for the patient's symptoms (William and Wilke, 2010; Stone, 2008) and may help to identify an underlying cause of secondary OA (Punzi *et al*., 2004). When there is a need to investigate for systemic or local inflammation and disease activity, analysis of blood and synovial fluid may be informative (Bramlage *et al*., 2006). Inflammation is reflected serologically by increased production of acute phase reactants as ESR and C-reactive protein (Clarke and Kirwan, 1998). Examination of synovial fluid is indicated if inflammatory arthritis or gout or pseudogout or joint infection is suspected. A white-cell count below 1000 per cubic millimeter in the synovial fluid is consistent with OA. The presence of crystals is diagnostic of either gout or pseudogout (Felson, 2006).

OA Radiography: Although OA can be diagnosed clinically and there is limited correlation between radiological changes and patient symptoms, X-ray is a very useful diagnostic tool in addition to the clinical picture (Mahajan *et al*., 2005; Stone, 2008). Radiographic status at baseline has been shown to predict future disability (Creamer *et al*., 2000) and reveal clues to a missed diagnosis (William and Wilke, 2010). It is indicated in patient with persistent or a typical nocturnal or not activity-related pain. There is little to be gained from routine serial radiography of joints affected by OA (Clarke and Kirwan, 1998). Radiological findings of Knee: summarized by Mahajan *et al*., 2005b.

Views: Standing anteroposterior (weight-bearing), Lateral, Notch patellar views (sunrise view), Posteroanterior intracondylar (PAIC) And Tangential patellar.

FINDINGS

- Joint space narrowing (Medial tibiofemoral, Patellofemoral, and/or Lateral joint space narrowing to lesser extent.
- New subchondral bone formation.
- Tibia lateral subluxation.

Medial osteophytes formation is most prominent Initially

Loose bodies, joint alignment abnormality, chondrocalcinosis, collapse due to avascular necrosis are also noticed (Mahajan *et al*., 2005b). The X-ray may be normal in persons with early disease (Felson, 2006). Radiograph primarily detects cartilage loss in the medial compartment. This may be because cartilage loss in the medial compartment causes the lateral joint space to open 1-2mm as weight is shifted medially. Joint space widening in the lateral compartment as seen on radiograph, therefore, does not necessarily reflect the actual thickness of the cartilage. This may account for the lower frequency and severity of cartilage loss in the lateral compartment discernible on radiography, and it also may explain the higher occurrence rate of tricomparmental cartilage loss on MR compared with radiography (Chan *et al*., 1991). The severity of OA should be assessed on the basis of JSN, subchondral sclerosis, and subchondral cysts (Kijowski *et al*., 2006). In all imaging techniques subchondral cysts were shown most often in the medial compartment and they frequently were missed. This may be due to local osteopenia. Many cysts were detected by CT and MRI (Chan *et al*.,1991). Ultrasound, CT, MRI, arthroscopy, and radionucleide studies are generally unhelpful to the practicing physician (William and Wilke, 2010) and may detect abnormalities before radiographic signs (Mahajan *et al*., 2005). CT provides an assessment of soft-tissue and osseous changes and shows only bicomparmental changes (Chan *et al*., 1991). MRI has multiplanar imaging capability, more sensitive and detect tricomparmental disease (Chan *et al*., 1991). It shows more joint detail as changes in soft tissue, cartilage and early subchondral changes as bruising or marrow edema (William and Wilke, 2010).

OA Treatment: The main goals of therapy are pain relief and improved physical and social function, maintaining or improving joint mobility (Fang *et al*., 2006). However, treatments do not modify the course or progression of the disease and are not considered curative. (American College of Rheumatology, 2000; Felson, 2006). Medical management of OA consists of both non-pharmacologic and pharmacologic therapies (American College of Rheumatology, 2000; Doherty *et al*., 2003).

Non-pharmacologic therapies, including education, exercise, various appliances and braces, and weight reduction

- Pharmacologic therapies: Acetaminophen is the first-line. If pain relief is inadequate, analgesic-dose NSAIDs may be used (e.g., ibuprofen, naproxen), even high dose may be used if inadequate response. If symptom relief is insufficient or the patient have NSAIDs adverse effects, Intra-articular corticosteroid injection may be considered but it should be limited to three to four times per year per joint to prevent the progressive cartilage damage (Neustadt, 1992).
- Invasive treatments may be considered, if symptom relief is inadequate with conservative measures. Operative treatments include arthroscopic lavage and cartilage debridement, osteotomy, and, ultimately, total joint arthroplasty (Day, 2005).

OA Prophylaxis: It is essential for the prophylaxis and treatment of OA to use:

- Low-calorie diets for weight loss with exercise (Stone, 2008).
- Increasing the intake of vitamins A, E, C and D. Due to their antioxidant properties, they could have beneficial effect in OA (Povorozniuk and Grigorieva, 2007; Ameye and Winnie, 2006).

OA Progression: The cartilage loss may be episodic in OA but once knee OA is established, knee cartilage tends to be lost more rapidly than in healthy adults. Over 2 years, the annual rate of loss of total tibial cartilageis estimated to be between 4.4% and 6.2% in people with symptomatic knee OA, nearly double the rate of loss in asymptomatic subjects. (Wluka *et al*., 2006). Approximately 50% of the patients described worsening of symptoms with time; this deterioration is associated with change in radiographic features (Ledingham *et al*., 1995). Some do not deteriorate neither radio graphically nor symptomatically overtime (Brandt, 2010). Risk of knee progression by alternate joint site: There was a 2-3 fold increased risk of knee JSN progression if there was disc space narrowing (DSN) (Hassett *et al*., 2005).

OA Alleviating Factors

- Cigarette smoking: Protective influence of smoking on knee osteoarthritis has been reported from various studies (Mahajan *et al*., 2005b; Anderson and Felson, 1988).
- Bone density: several studies have found an association between higher BMD and either hip or knee OA, primarily in women. In an editorial the question was raised whether treatment of one such as OP could increase the risk for the other (Amin, 2002). On the other hand women using anti-resorptive agents experienced less knee pain, according to the WOMAC scores, than non-users and had significantly fewer bone abnormalities associated with severe knee OA - including subchondral bone thickening, osteophytes, and bone marrow edema-like lesions than the women not taking these medications, although no cartilage changes were detected by MRI or radiographic changes of OA of the knee. This suggests that these medications may protect against the development of bone abnormalities associated with knee OA, which may a beneficial effect on the overall course of the disease. (Mahajan, *et al*., 2005).
- Hormonal replacement therapy (HRT). Combined estrogen and progestin replacement therapy can significant reduce night pain and knee tenderness in knee OA patients (Mahajan *et al*., 2005).
- Some studies revealed low vitamin D intake and low serum calcidiol level increase the risk of knee OA development and progression. (Povorozniuk and Grigorieva, 2007; Lau *et al*., 2007).

WOMAC: WOMAC provides an excellent look at a patients functional capacity and complements the more objective data provided by MRI, arthroscopy, cartilage biopsy and radiograph (Dinçer *et al*., 2006), it is designed to reflect the individuals problems with lower limb OA (Creamer *et al*., 2000). WOMAC is the Western Ontario and McMaster University (WOMAC) osteoarthritis index, a multidimensional health status instrument that quantifies pain, stiffness, and limited function specifically in knee and hip OA patients (Link *et al*., 2003) It is a sensitive (Clarke and Kirwan, 1998), well established scale, valid (Creamer *et al*., 2000), reliable and responsive measure of outcome, and it has been widely used in diverse clinical and interventional environments for evaluation of knee and hip OA. It is available in different language in both 5-point likert scale and 100mm visual analogue format (Dinçer *et al*., 2006). Because of its greater length and for improving patient compliance, response rates, and quality of the response, a reduced version of the WOMAC has been developed as alternative to the full WOMAC scale. It is practical, valid, reliable and responsive. The short form WOMAC function scale, which consist of seven items of function, that were selected by conducting interview with orthopedic and rheumatology staff (Yang *et al*., 2007). It is a self-reported subjective questionnaire "not require patients to undergo any formal functional test". The mean responses are taken as the overall disability score. The worse knee, as selected by the patient, was "index" knee. Pain severity was measured using the pain section of the WOMAC OA index (Creamer *et al*., 2000).

OA Comorbidity: Age related disorders are numerous; the finding of an association between some of these disorders independent of age will raise the possibility that there are common processes which can predispose to several disorders. The study of these associations can therefore improve our understanding of pathogenesis and may have important therapeutic implications. Clinical conditions associated with OA are many and include musculoskeletal and non-musculoskeletal disorders as obesity, cardiac disease, phlebitis and thrombophlebitis, liver disease, endocrine and metabolic diseases, renal disease, gastritis, etc (Kadam *et al*., 2003; Dijk *et al*., 2008). Among these disorders, BMD effect on OA need further studies because it carries theoretically therapeutic implication; while the interest in chronic venous insufficiency in this context is because it adds a low grade inflammatory environment in the lower limb which may have an impact on knee OA.

Chronic Venous Insufficiency (CVI)

CVI Definition:-CVI of the legs is an important health-care problem; it is an advanced stage of venous disease *resulting from structural or functional abnormalities of veins leading to chronic inflammatory state. It* affects large veins and cutaneous microcirculation (Fink *et al*., 2003; Nicolaides, 2000) characterized by dysfunctional, incompetent venous valves and persistent venous hypertension with significant consequences to the small venules and capillaries (Stvrtinova, 2001). It is one of the most common vascular diseases (UL-islam *et al*., 2008; Lan *et al*., 2007) forming a major problem in many countries with considerable morbidity (Bawakid *et al*., 2004) and invalidates the lifestyle and the patients quality of life (Andreozzi *et al*., 2005).

CVI Prevalence: It is one of the most prevalent, frequently unrecognized and under estimated disease worldwide (UL-islam *et al*., 2008) occurs frequently in the working population (Flore, 2004). Total prevalence of CVI was approximately 25-40% among women and 10-20% among men. With annual incidence of 2.6% in women and 1.9% in men (Bawakid *et al*., 2005). The prevalence of edema and skin changes (hyperpigmentation and eczema) due to CVI is 3%-11%,

venous ulcer about 0.3% of the adult population (Nicolaides, 2000) with higher prevalence of CVI in Saudi population. The mean age of CVI patients was higher compared to the population without any sign of CVI (Bawakid *et al*., 2005).

CVI Risk Factors: These include increasing age, female sex, obesity, a family history of CVI, prolong standing and sitting (UL-islam *et al*., 2008), hormonal influences (pregnancy, post-menopausal HRT, oral contraceptive) and previous leg injury or trauma (Eberhardt and Raffetto, 2010).

CVI Pathology: CVI progresses usually over a number of years, associated with calf muscle pump failure forming dysfunctional valves that reduce venous return, leading to sustained venous hypertension and venous blood flow become bi-directional, resulting in inefficient venous outflow. Very high venous pressure is exerted at the ankle and the venules become the final pathway for the highest venous pressure. (Coghlan, 2004) leading to a chronic inflammatory state (Pappas, 2001).

CVI Pathogenesis: CVI associated with hemodynamic and metabolic changes, such as modification of blood flow, tissue hypoxia, and platelet and leukocytes activation. Platelets contribute to the inflammatory response and activate the coagulation cascade.Leukocytes may play an essential role in the etiopathogenesis of CVI. White blood cells cause a reduction in capillary perfusion pressures and hence the capillary flow rate, resulting in trapping of WBCs in the leg (trapping hypothesis) these cell may then modify the microcirculation by plugging of the capillaries, inducing cell damage and areas of localized ischemia, releasing toxic oxygen metabolites, proteolytic and other lysosomal enzymes, chemotactic substances and other mediators of inflammation (Stvrtinova, 2001). The reactive oxygen species is able to initiate atherogenesis through several important enzyme systems and other degenerative disorders, etc (Flore, 2004).

CVI Classification and Etiology

- The most frequent causes of CVI are primary abnormalities of the venous wall and valves.
- Secondary due to previous DVT, that caused damage to the valves of deep veins and perforators leading to reflux, obstruction, or both**.**
- Congenital venous abnormality that is a rare cause (Nicolaides, 2000; Lew *et al*., 2010; Coghlan, 2004). The most common etiology of chronic venous diseases is reflux in the superficial, deep, or perforator veins. The superficial venous system is the site most commonly affected in which reflux may be reported in approximately 90% of limbs with CVI, whereas reflux in the deep system is detected in only 30% of limbs (Labropoulos *et al*., 2000).

***CVI Clinical Features (Symptoms and Signs)*:** The most common features of CVI are attributed to the progressive syndrome of chronic venous stasis and venous hypertension, these include a wide range starting from asymptomatic (Bawakid *et al*., 2004), dull ache pain that worsens after prolonged standing and improves by walking and elevating the legs, soreness, burning, throbbing, heavy legs, cramping, muscle fatigue, pruritus, night cramp, and restless legs. Pain and other symptoms are usually may worsen with menstrual cycle, pregnancy, and in response to exogenous hormonal therapy as oral contraceptive (Lew *et al*., 2010). The important physical signs are telangiectasia, varicose vein, edema, and skin changes such as pigmentation, lippdermatosclerosis, eczema, ulceration (Coghlan, 2004; Nicolaides, 2000) and delay wound healing. Long standing CVI may lead to the development of lymphedema (Eberhardt and Raffetto, 2010).

CVI Diagnosis: Diagnosis of CVI is based on the characteristic clinical manifestations and ultrasound features of the superficial and deep veins. The classification of clinical manifestations associated with CVI was based on the objective scoring system of C criteria in the CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification specially when there is no clinical suspicion of a systemic cause of bilateral leg edema such as heart failure, nephrotic syndrome, etc (Tokoro *et al*., 2009). Venous duplex ultrasonography using a high resolution duplex ultrasound machine with pulsed and color Doppler is used for determining reflux in the superficial, deep, and perforating venous systems and demonstrate incompetent valves with retrograde blood flow where varicose veins are not clinically apparent (Osinbowale, 2009).

CVI Treatment: Conservative: horse chestnut seed extract is safe and effective for symptomatic CVI but can cause some side effect as headache and dizziness. Bandaging has been a mode of treatment since Hippocrates. Graduated compression stocking (GCS) combined with exercise regime have been shown to control reflux and improve calf muscle pump function in the setting of CVI. Although patients may not tolerate the compression from the garments. Identifying patients with surgically treatable venous incompetence remain an essential component of CVI management (Osinbowale, 2009). Surgical: In 90% of cases where venous hypertension is from superficial and perforator vein reflux, removal or obliteration of the great saphenous vein alone can resolve the venous hypertension, however, In remaining 10%, additional treatment to the incompetent perforator veins may be needed. In severe cases, subfascial endoscopic perforating vein surgery (SEPS), perforator vein ablation and /or venous reconstruction can be attempted (Lew *et al*., 2010).

CVI Prognosis: With appropriate treatment, the vast majority has a good outcome and the progression of the disease is arrested.

Osteoporosis (OP)

OP Definition:-OP is a common systemic skeletal disease, resulting in an insidious bone loss leading to decline of bone mass and strength, increase of bone fragility and subsequently, an increase in risk of fractures (Wu *et al*., 2003) and characterized by deterioration of bone tissue (Rizzoli *et al*., 2001; Fukunga *et al*., 1997; Heijckmann *et al*., 2008). It is a silent epidemic disease as it is under recognized, it is undertreated. Its clinical significance lies in fracture. Fracture may be the first and only manifestation, making OP a major contributor to morbidity and mortality worldwide. In the absence of a defining fracture, the diagnosis of OP is based on the measurement of BMD by dual energy X-ray absorptiometry (DEXA). The world health organization provides a definition of OP as BMD T-score equal or greater than 2.5 standerd deviations (SD) below ideal bone mass (Krawiecki *et al*., 2006).

OP Prevalence: It is estimated that between 1 in 3 women and 1 in 12 men over the age 50 worldwide are osteoporotic, and WHO found 16% of post menopause women have OP (Murphee II, 2007). The prevalence of OP increases dramatically with age (Ettinger, 2003) as 50% of white women have OP or osteopenia 10 years after menopause. It is more common in whites and Asians population; up to 90% of all fracture in elderly can be attributed to OP; up to 20% of vertebral fractures and 30% of hip fractures occur in men. Lifetime risk of fracture is 40% (Krawiecki *et al*., 2006); 33% of all osteoporotic fracture occurs in Asia and the number of fracture is rising rapidly in Asian and in many parts of the developing world (Saag, 2008).

OP Pathology: OP occurs when there is imbalance between bone reabsorption (steoclast cell) and bone formation (osteoblast cells). Bone undergoes constant transformation. At any given moment there are from 1-10 million sites where small segments of old bone are being broken-down (reabsorbed) and new bone is being laid down to replace it. When more old bone is destroyed than new bone laid down, bone loss occurs and OP develop (Murphee II, 2007).

OP Risk Factors: OP has risk factors that divide into two groups

Non-modifiable risk factor: personal or family history of fracture, Caucasian race, advanced age, female sex and dementia. Potentially modifiable risk factors: smoking and excessive alcohol intake, low body weight (BMI < 18 kg/m^2), estrogen and androgen hormone deficiency, low calcium intake, low level of physical activity, and chronic glucocorticoid use (Ettinger, 2003), diseases associated with OP include thyrotoxicosis, Cushing disease, hyperparathyroidism, stroke, and inflammatory arthritides and drugs as anticonvulsant, heparin (Jordan and Cooper, 2002; Garnero and Delmas, 2004).

OP Classification

- Primary OP 80%: type I: peak bone mass is reached at the age of 25-30 years, in women accelerated loss during perimenopausal period.
- Type II: senile OP affects men and women older than 70 years.
- Secondary OP 20% is a result of some underlying disease states and may be corrected by treatment of the primary cause.
- Osteopenia refers to decreased bone density, classically T score between 1 to 2.5 SD below ideal (Krawiecki *et al*., 2006).

OP Clinical Features: Patients with OP are asymptomatic until fracture occurs. Osteoporotic spinal fractures may present with acute back pain or gradual onset of height loss and kyphosis with chronic pain. The peripheral osteoporotic fractures present with local pain, tenderness, and deformity, often after an episode of minimal (low energy) trauma. Many patients present with incidental osteopenia on an X-ray performed for other reasons (Doherty and Ralston, 2010) or present with respiratory difficulties as there is 7% decrease in vital capacity for each vertebral fracture, long term disability, depression (Garnero and Delmas, 2004).

OP Investigations: The pivotal investigation is DEXA at the lumbar spine and hip. (Doherty and Ralston, 2010). In primary OP all relevant laboratory tests are normal. The clinical situation may require various investigations including serum calcium and phosphate, bone alkaline phosphatase, renal function, liver function, thyroid function, immunoglobulin and ESR, screening for coeliac disease, serum 25 (OH) D and PTH should be performed (Krawiecki *et al*., 2006).

OP Management

Prevention: healthy diet, healthy life style, weight-bearing exercise and adequate calcium and vitamin D3 (Krawiecki *et al*., 2006).

Treatment: many drugs are used in OP, the most frequently used are alendronate and risedronate, in addition to vitamin D3 and calcium. (Fallon community health plan, 2010).

OP Prognosis: If fractures can be avoided, the prognosis is good and the loss of BMD can be arrested or even reversed with appropriate treatment. Fifteen percent of women and 30% of men with OP die within one year of fracturing their hips. (Krawiecki *et al*., 2006).

MATERIAL AND METHODS

The present study had approval from regional health administration and the collection of cases started from December 2010 in the out-patients department in ibn-sina teaching hospital in Mosul, Iraq.

Study design: A controlled case-series study.

Subjects

OA Patients: One-hundred patients aged 50 years or older (82 females and 18 males) patients complaining from unilateral or bilateral knee pain (fulfilling the clinical classification criteria of idiopathic knee OA of the American College of Rheumatology ACR) were included in this study. Case collection was haphazard (convenience) sampling.

Clinical criteria of idiopathic OA according to ACR.

Knee pain plus at least three of six of the followings

- Over 50 years of age.
- <30 minutes of morning stiffness.
- Crepitus on active movement
- Bony tenderness
- Bony enlargement
- No palpable warmth of synovium.

The sensitivity and specificity of these criteria per se is 95% and 69% respectively (klippel *et al*., 2008). However the specificity was augmented by exclusion criteria and radiology.

Control Group: Fifty individuals who do not complain from knee pain and have no clinical signs of asymptomatic knee OA and matching in their age and sex with the patients group.

Exclusion Criteria

- Secondary OA patients (who have inflammatory joint disease, gout or trauma).

- Recent attack of radicular low back pain. (presenting complaint)
- Organ failures (heart, liver, kidney).
- Endocrinopathy-endocrine disorders as diabetes mellitus and thyroid dysfunction.
- Recurrent steroid use.
- Neoplastic disorders.

Data Collection

History: Data were obtained directly from the individuals of the study sample. A questionnaire form was designed to record the subject's general and medical information, which included subject name, age, sex, occupation, marital state, smoking state, body weight in kilogram and body height in meters (the last two for BMI measurement)(*), and a detailed description of knee pain (site, character, onset, aggravating and relieving factors and association with post rest stiffness specially at morning and its duration, crepitus on active movement, locking and / or giving away) and a detailed medical history including history of low back pain with or without root symptoms, muscular symptoms (generalize fatigability, proximal muscle weakness), whether the subjects have osteoporosis or not, any period of immobilization (cause and duration), personal history of fragility or low energy fracture (site and time), personal history of venous disorders (haemorrhoid, DVT). Females in the study sample were asked about their gynaecological history, including number of pregnancies and number of abortions or miscarriages that occurred during their fertility period, age of irregular menses, time or duration after menopause, history of hormonal replacement therapy and whether they were operated for oophorectomy and /or hysterectomy.

WOMAC Scores: Western Ontario McMaster Universities Osteoarthritis Index. (WOMAC) which is recommended by Osteoarthritis Research Society International for use in clinical trials of knee OA. Twenty four items (parameters) are grouped into four subscales: symptoms, stiffness, pain, and functional difficulties of daily living (WOMAC function short form subscales). Patients were instructed to answer for the condition of the studied knee joint over the last 48 hours. Answers that were directly obtained from the patients followed a Likert Scale in which patients were asked to choose one of the following answers (none, slight, moderate, very and extreme) and Scores can be presented as the mean within each subscale or as a total instrument score (Harrison and mandl, 2006; Auw, 2007).

Clinical Examination: Both study sample groups (patient and control) were examined clinically for signs of knee OA including redness over the joints, scar of old trauma or surgery, joint line (medial, lateral, patello-femoral and popliteal) tenderness, warmth over the knee (s), palpation to determine whether there was fluid (intra-articular or extra-articular), soft tissue or bony swelling, knee movement (full or limited) and also they were evaluated for sensory disturbance, deep tendon reflexes of knees and ankles, straight leg raising test (SLRT), quadriceps wasting, Perthes maneuver, femoral stretch test, proximal muscle weakness and bone tenderness.

CEAP classification for chronic venous insufficiency: For uniformity in diagnosing CVI, CEAP classification developed by international consensus, was used. Clinical and aetiology subscales were used in the present study (Tokoro *et al*., 2009).

Investigative Instruments

- The laboratory instruments were used for measurement of biochemical parameters are: Automatic micropipettes, Spectrophotometer (APPLE), Centrifuge (HETTICH), Incubator (Memmert) and Shaker.
- For (radiographic study) X- ray image (SIEMENS).
- For osteoporosis diagnosis: Bone densitometer (DEXA) dual energy X-ray absorptiometry (HOLOGIC).
- For venous disorders colour duplex ultrasonograpy (MEDISON).

Investigations

Blood Sampling: All the investigations were done in the out-patients laboratory department in ibn-sina teaching hospital except MDA test for oxidative stress which was done in the college of medicine (department of pharmacology).

Approximately 10 ml of peripheral venous blood from the arm was drawn using disposal syringe from all study sample subjects. Blood sample was divided into:

- Two ml of the blood sample was transferred into EDTA tube for ESR measurement by westegren method.
- One ml of the blood sample was transferred into plastic tube for CRP measurement (Serological study-CRP latex test kit).
- About seven ml of blood sample was transferred into plastic tube. The sample was left at room temperature until it clotted, serum was aspirated after centrifugation of the blood at 3000 rpm for 10 minutes then the serum was used to measure levels of:
- Alkaline phosphatase (Colorimetric determination of the ALP activity method).
- Calcium (O-Cresol Phtalein Complexone method).
- Phosphorus by Gamst O.K. and Try K. method.
- Malondialdehyde(MDA)test see below.
- Maloindialdehyde MDA test was done using the arm venous blood (mentioned above) on a haphazard (convenience) consisting of for 114 subjects (80 of patients and 34 of control sample).

From the 114 subject just mentioned, 48 (27 patients and 21 controls) were haphazardly (according to test availability) sampled for MDA test on an ankle venous blood (saphenous vein) after instruction to stand upright and keep stationary for 15 minutes to induce lower extremity venous hypertension. Blood samples were collected from greater saphenous vein (Lan *et al*., 2007), and divided into:

- Two ml of blood sample was transferred into EDTA tube for ESR measurement by westegren method.
- Two ml of blood sample was transferred into plastic tube, processed as arm sample, to measure MDA.

X-Ray Imaging: X-ray with anterio-posterior weight bearing image of the both knees and lateral view for lumbar vertebra were taken for all subjects in patient's sample and read by the same radiology. The X-ray images used to assess the presence, site and severity of joint space narrowing (JSN), the presence

and size of osteophytes, the presence of sclerosis for knee joints. Subcortical cysts have been looked for but they cannot be seen in study plain radiograph for patients sample (Dieppe, 2008). The site of JSN for each knee focused on medial, and bicompartmental. The severity of JSN of the knees and intervertebral spaces were graded as 0=no JSN, 1-33% mild, 34-66% moderate and 67-100% severe (Chan *et al*., 2008). lateral views X-ray for the lumbar spines were done for 71 patients who complaining from LBP either localized or with radicular symptoms and assessed according to radiographic grading of lumbar disc degeneration on lateral views described by lane *et al*. 1993 for the presence and severity of disc space narrowing (DSN), presence, location and size of osteophytes and lumbar sclerosis (Kettler and Wilke, 2006). Reporting the x-ray findings for both knee and lumbar radiograph was done jointly by another and a single radiology expert.

DEXA: DEXA scan of trabecular and cortical bone provides rapid and precise measures of bone mineral density at multiple sites with minimal radiation exposure. DEXA scan was done for lumbar spine and proximal femur for all subjects (patients and controls). For an accurate BMD measurements and to avoid misguided clinical judgements based on suboptimal bone densitometry result, DXA system be properly calibrated. DXA manufacturers provided phantoms for use with their devices ways to monitor and, if necessary, correct for any drift in scanner performance. To prevent day-to-day variance, scanning the phantom once a day for 15 to 25 consecutive days and the averaging these scan before starting this study. A T score value of -2.50 was chosen for the diagnosis of osteoporosis and -1.00 to less than -2.50 are osteopenia by DXA. The site for diagnostic purposes are the hip, total hip and lumbar spines. Each scan last about 2-5 minutes. All removable metallic objects are outside the scanning region, the subjects lie supine on imaging table with dual energy photon beam beneath the table. X-ray passing through patient are picked up by detector on C shape arm above the table. To obtain scan of L1-L4, subjects arms are put down by the side and legs elevated with a foam block to knee flexion position (hip at 90 degree angle with the spine) to flatten pelvis and lumbar spine against scanning table. To obtain hip scan: arms are across their chest, patients should have the femur straight on the table (shaft parallel to the edge of the picture, internal rotation of 15-25 degree achieved by the use of positioning devices (long axis of femoral neck perpendicular to the X-ray beam) and confirmed on the scan by seeing little or none of the lesser trochanter. Results were compared with database contents usually contained in a software processing program.

Color Duplex Ultrasonography (CDU): CDU is a special type of ultrasound that uses Doppler-flow information to add colour for blood flow in the image. Vessels in the blood are coloured red for flow in one direction and blue foe flow in the other, with a graduated colour scale to reflect the speed of the flow. Below knee bilateral duplex evaluation was done for 73 haphazardly sampled subjects of study groups (48 of the patients, 25 of the control group). The CDU was performed by specialized sonographer. The test was used mainly to confirm or to rule out deep vein thrombosis (DVT) causing secondary venous insufficiency. The test was done using an imaging carrier frequency of at least 3.0 to 5.0 MHz for Doppler carrier and for the vein was identified in a transverse plane and sagitally and manual augmentation is applied to evaluate the presence of venous reflux, venous valvular reflux, and perforators.

Statistical Analysis:-The data were delivered into SPSS program (version 17); and the following tests were done:

1. Standard statistical methods were used to determine the descriptive data, mean and standard deviation.
2. Statistical difference between patients and controls data means was done by t test.
3. Statistical difference between patients and controls data was done by 2 proportion test.
4. Correlation coefficient between two random variables was tested by Karl Pearson correlation.
5. Correlation by ranks was tested by Spearman's Coefficient of rank correlation.
6. The internal consistency Arabic version of WOMAC questionnaire was tested by Cronbach-alpha test.
7. P-value ≤ 0.05 was considered statistically significant.

RESULTS

One hundred patients with knee OA and 50 subjects as controls were studied as mentioned in details in the method. Table (4-1) shows the number and percentage of males and females of all subjects included in the study.

Table 4.1. The Number and Percentage of Males and Females in All Studied Groups

Groups	Male		Female	
	No.	%	No.	%
Control n=50	9	18	41	82
Patients n=100	18	18	82	82

Table (4-2) shows the age of control and patients groups included in the study. There was no difference between the groups.

Table 4-2. The Age of Control and Patients Groups. Data Expressed as Mean±SD

Group	Control	Patients	p-value
Age (in years)	58.3±6.31	58.0±6.70	0.820

According to WHO and obesity task force, this study divides the BMI into three subgroups: normal between 18.5 to 24.9, overweight between 25 to 29.9 and obese 30 or above. Table (4-3) shows the Body Mass Index (BMI) of control and patients.

Table 4-3. Body Mass Index (BMI) of Control and Patients Groups

BMI (Kg/m²)	Control	Patients	P. Value
Normal	24	6	0.04*
Overweight	24	25	0.1
Obese	52	69	0.06
Overweight and Obese	76	94	0.04*

OA Criteria According to ACR Table 4.4. Shows that 32% of patients had unilateral symptomatic OA and 68% had bilateral knee OA. The frequency of each criterion is mentioned also.

Smoking State: The study has found that 87.0% of patients and 78.0% of control are non-smoker while the rest (13.0% and 22.0% of patients and control respectively) are excessive-smokers. Table (4-8) is concerned with history of LBP, weakness and osteoporosis related informations.

Table 4-4. OA Criteria According to ACR

ACR criteria	Percentage (%)
Knee pain:	100
Unilateral knee pain	32
Bilateral knee pain	68
Morning stiffness < 30 minutes	92
Crepitus on active movement	85
Bony tenderness	99
Bony enlargement	30
No palpable warmth of synovium	100
Collective occurrence	
Knee pain + 3 criteria	1
Knee pain + 4 criteria	14
Knee pain + 5 criteria	63
Knee pain +6 criteria	22

Table 4-5. Smoking State of Control and Patients

Smoking State	Control	Patients	P.Value
Active Smoker	22%	13%	0.004*
Mean duration (years)±SD	46.82	15.84	0.001*
Mean of cigarette /day±SD	46.81	32.61	0.009*

Table 4-6. Obstetric Characteristics of Studied Females

Obstetric Characteristics	Control n = 41	Patients n = 82	P.Value
Age at menarche (years)	13.3±1.33435	13.5±1.425	0.5
Parity no.	8±2.47475	9±3.359	0.3
Duration of irregular period in months	0.5610±0.79996	3.9±3.372	0.01*
Age at menopause (in years)	47.9±16.434	48.3± 17.2	0.9
Time elapsed since menopause (for menopaused females only) (in years)	8.9512±6.77477	10.5±8.713	0.09

Table (4-7-a) WOMAC Reliability (Cronbach Alpha)

Cronbach's Alpha	
Total WOMAC	0.845
Cronbach's Alpha if Item Deleted	
The deleted item	Cronbach' Alpha
Symptoms scale	0.867
Stiffness scale	0.836
Pain scale	0.727
Difficulties scale	0.738

Table 4-7-b. Result of WOMAC Scoring Of the Studied Patients Data Expressed As Mean±SD

WOMAC	Score
Symptoms	2.0±0.60
Stiffness	1.8±0.93
Pain	1.57±0.67
Difficulties	1.61±0.78
Mean of Total Score	2.17±0.54

Table 4-7-c. Number of Patients According to Severity of The Total WOMAC Score and in Each Subscale

WOMAC	No. Patients sy. Scale*[1]	No. Patients St. Scale*[2]	No. Patients Pain Scale	No. Patients Diff. Scale*[3]	No. Patients Total WOMAC
Negative respons	7	10	0	0	0
Mild	48	14	18	25	9.0
Moderate	40	44	51	42	52.0
Severe	5	29	29	32	38.0
Extreme	0	3	2	1	1.0

♦mild=1, moderate=2, severe=3, and extreme=4, *[1] Sy=symptoms *[2] ST.=stiffness

Duration from menopause till inclusion in this study had astatistically similar mean of for both groups. Table 4.7. (a, b, c) WOMAC questionnaire: the internal consistency (reliability) of our interview Arabic version was high; the chronback alpha value was 0.845, if any one of subscales is deleted chronback value of the rest remains good. The disturbution of patients according to WOMAC severity in shown in table 4.7.c. The validity of this version of WOMAC is reflected by its association and correlation with several clinical and radiological variables which will be shown in this chapter. Localized LBP occurred in 26% of patients and 28% of controls, LBP with root symptoms occurred in 45% of patients and 42% of controls. Symptoms of either generalized fatigability or proximal muscle weakness were reported by 52% and 46% respectively of the patients and 33% and 30% respectively of the controls. Combination of both fatigability and proximal weakness was reported by 30% of patients and 28% of controls.

Table 4-8. History of LBP, Weakness and OP Related Features

Musculo-Skeletal History	Control n= 50 (%)	Patients n=100 (%)	P. value
Lower back pain (LBP):			
Localized back pain	28	26	0.7
LBP with root symptoms	42	45	0.8
Muscular symptoms:			
Fatigability	33	52	0.02*
Proximal muscle weakness	30	46	0.7
Both	28	30	0.
Osteoporosis	8	17	0.04*
Immobilization	10	16	0.01*
Fracture	10	12	0.8
Fracture time (Mean±SD in years before interview)	4.8±2.33	5.6±2.795	0.06

Table 4-9. Result of Clinical CEAP Evaluation and A History of Hamorrhoid in The Studied Sample

Clinical grades seen in	Controls n=100	Patients n=50	P.Value
C1: Presence of telengectesia	32.0	47.0	.038*
C2: Presence of varicose veins	56.0	50.0	0.6
C3:Presence of leg edema	---	6.0	0.03*
C4A: Presence of Skin changes	---	1	0.1
C4B: Lipodermatosclerosis	---	---	---
C5: Healed venous ulcer	---	---	---
C6:Active venous ulcer	---	---	---
Clinical CEAP collectively	58	70	0.03*
Hemorrhoid	20	43	0.015*

Table 4-10. Clinical Signs of The Studied Sample

Clinical Signs	Control n= 50 (%)	Patients n=100 (%)	P.Value
Reflexes			
Diminished knee reflex	10.0%	9.0%	0.2
Diminished ankle reflexes	10%	11%	0.2
Normal Babinski	100%	100%	0.21
Sensation: Diminished			
Big toe (L5)	--	5%	0.02*
lateral foot(S1)	--	4%	0.03*
Above medial mallei(L4)	--	4%	0.03*
Quadriceps wasting	1.0%	18.0%	<0.001*
Positive SRLT	24.0%	40.0%	0.03*
Positive FST	34.0%	32.0%	0.5
Difficulty in standing	10.0%	38.0%	003*
Bone tenderness	16.0%	41.0%	0.02*

Table 4-11. Laboratory Investigations of The Studied Sample Data Expression As Mean ± SD

Parameters	Control n= 50 (%)	Patients n= 100 (%)	P.Value
ESR	15.94±0.53	30.58±11.25	0.005*
CRP	11.5±6.47	38.47±14.68	<0.001*
S.Alkaline phosphate	74.81±28.374	70.15±34.883	0.4
S.Ca	2.18±0.230	2.24±0.2663	0.1
S.phosph	1.06±0.291	1.08±0.383	0.8
MDA	0.51±0.450	2.84±1.390	<0.001*
Ankle MDA	0.83±0.410	3.94±1.922	<0.001*
Ankle ESR	18.44±8.745	30.38±8.120	<0.001*

History of osteoporosis was given in 17% of patients and 8% of controls. Related are shown in Table 4.8. Table (4-9) shows symptoms and signs of CVI in the patients and control groups. Using the clinical contents of CEAP evaluation, it was found that telangiectasia is present in 47.0% of patients and 32.0% of control (p-value=0.03); varicose veins were present in 50% of patients and 56% of controls (p= 0.06); leg edema occurred in 6 patients and in no one of control; skin changes were present in one patients. Within the current work, no case of C4B, C5 and C6 had been found. A history of hemorrhoids was significantly more freguent in the patients groups; actually all patients have either signs of CVI or a history of hemorrhoid or both.

Table (4-10) musculoskeletal signs mainly neuromuscular in the studied sample. The table shows clinical signs, mainly neruromuscular in the patients and controls. Knee and ankle reflexes were similarly normal in most subjects of both groups. Diminished pain sensation in of any 3 sites (big toe, lateral foot and above medial malleolus) was found in 5 % of patients and none of control (p=0.04). Quadriceps wasting was found in 18% of patients and 1% of controls (p-value=0.001).The SLRT was positive in 40% of patients and 24% of controls (p= 0.03). Femoral streatch test was positive in nearly in one third of each group. Bone tenderness was present in 41% of patients and 16% of controls (p=0.02). Table (4-11) shows laboratory investigations of the studied sample.

Table 4-12. Result of DEXA Examination of The Studied Sample

Parameters		Control n= 50 (%)	Patients n=100 (%)	P.Value
T-score Lumbar	Normal	34.0%	34.0%	> 0.05
	Osteopenia	38.0%	45.0%	> 0.05
	Osteoporosis	28.0%	21.0%	> 0.05
T-score hip	Normal	50.0%	66.0%	0.002*
	Osteopenia	48.0%	30.0%	0.002*
	Osteoporosis	2.0%	4.0%	> 0.05
Z-score Lumbar	Below the expected range for age	10.0%	4.0%	> 0.05
	Within the expected range for age	90.0%	96.0%	> 0.05
Z-score hip	Below the expected range for age	---	---	
	Within the expected range for age	100.0%	100.0%	> 0.05

Table 4-13. Radiological Findings of Knees of The Studied Patients

	Radiological Findings of Knee	Right	Left
Site JSN	Medial compartment	80.0	80.0
	Bicompartment changeas	20.0	20.0
Severity JSN	Mild	40.0	39
	Moderate	41.0	42
	Sever	19.0	19
Osteophytes	Lipping osteophytes	39.0	37.0
	Definite osteophytes	21.0	20.0
	Large osteophytes	4.0	5.0
Sclerosis	Present	74	72.0
Sclerosis and/or osteophytes		100%	

Table 4-14. Radiological Findings of Lumbar Vertebrae

	Radiological Lumbar Findings	Patients n=71	%
DSN	Present	40	56.3%
Site DSN	One level	38	53.5%
	Two levels	2	2.8%
Severity DSN	Mild	24	33.8%
	Moderate	12	16.9%
	Severe	4	5.63%
Osteophyte	Anterior small	54	76.0%
	Anterior definite	4	5.6%
	Anterior large	4.	5.6%
Sclerosis	Present	32	45.1%

Correlation Tables

Table 4-15. Shows The Variable with Significant Correlation with Total WOMAC Score

	Variables	Patients No.	R-Value
WOMAC	Knee JSN	100	0.657*
100patients with a mean score	Knee sclerosis	74	0.411*
2.17	BMI	94	0.341*
	Telangiectasia	56	0.289*

The patients mean of ESR was 30.58±11.25 were the controls mean of ESR was 15.94±0.53 (p-value=0.005). The mean CRP was also higher in the patients than controls (38.47±14.68 and 11.5±6.47respectively, p-value= < 0.001).the MDA test showed a mean of 2.84±1.390 in the patients and 0.51±0.450 in the controls (p-value= < 0.001). Ankle MDA and the ankle ESR were also significantly elevated in patients over the controls. All the subjects have ESR less than 40mm/hr. Table (4-12) shows the DXA results of patients and controls. Using the T-score, osteoporosis was less common in patients than control (21% and 28% respectively) in lumbar region; compared with 4% in the patents and 2% in the controls in hip. On the other hand osteopenia was more common in patients than control in both lumbar and hip regions with a significant difference in the hip region (p-value=0.002).

Radiological Findings of the Studied Patients

Radiological Findings of Knee Joints: The next table (4-13) shows the radiological findings of knee joints of the studied patients. All patients had JSN; medial compartmnt narrowing occur in 80%. the JSN was of mild to moderate severity in 81% in either knees. Osteophytes occurred in 64% of right knees and 62% of left knees. Subchondral sclerosis occurred in 74% of right knee and 72% of left knees. All patients have either osteophytes or suncnondral sclerosis.

***Lumbar Radiological Findings*:** Radiological study of lumber vertebrae has done for a71 patients who complained from LBP in addtion to knee pain and the results are tabulated in table 4.14. disc space narrowing occurred in 56.3% most of them in one level. Osteophytes were detected in 62% of LBP subgroup. Subchondral sclerosis occurred in 45.1% of them. There is no significant correlation of total WOMAC score with the following variables: Knee osteophytes, smoking, LBP, lumbar (DSN, osteophytes, sclerosis), muscular symptoms, history of OP, hemorrhoids, varicose veins, edema, CVI signs collectively, DEXA results of lumbar and hip, ESR, CRP, S.alkaline phosphatase, S.Ca, S.phosphorus, MDA, ankle ESR, and ankle MDA.

There is no significant correlations of Symptoms subscale with the following variables: Knee (JSN, osteophytes, sclerosis), smoking, BMI, LBP, lumbar (osteophytes, sclerosis), hemorrhoid, telangiectasia, edema, T-score of lumbar, Z-score of hip and lumbar spine, ESR, S.alkaline phosphatase, S.Ca, S.phosphorus, MDA, ankle ESR, and ankle MDA. There is no significant correlation of Stiffness subscale with the following variables: Knee (JSN, osteophytes, sclerosis), smoking, BMI, LBP, lumbar (osteophytes, sclerosis), hemorrhoid, telangiectasia, edema, T-score of hip, Z-score of hip, ESR, S.alkaline phosphatase, S.Ca, S. phosphorus, MDA, ankle ESR, and ankle MDA.

lumbar, CRP, S. alkaline phosphatase, S.Ca, S.phosphorus, MDA, and ankle ESR. There is no significant correlations of Difficulty subscale with the following variables: Knee (JSN, osteophytes, sclerosis), smoking, LBP, lumbar (DSN, osteophytes, sclerosis), muscular symtoms, history of OP, hemorrhoid, telangiectasia, varicose veins, DXA results of lumbar and hip, ESR, CRP, S. alkaline phosphatase, S.Ca, S. phosphorus, MDA, and ankle ESR.

There is no significant correlation of Knee JSN with the following variables: stiffness scales, difficulty scale, smoking, lumbar sclerosis, muscular symtoms, history of OP,

Table 4-16. Significant Correlations with A Symptoms Subscale

	Variables	Patients No.	R-Value
Symptoms scale 100 patients with a mean sore of 2.0	Knee JSN	100	0.208*
	Smoking	13	-0.212*
	T-score hip	34	-0.373*

Table 4-17. Significant Correlations of Stiffness Subscale

	Variables	Patients No.	R-Value
Stifness scale 100 patients with a	Lumbar DSN	40	0.257*
	Muscular symptoms	52	0.299*
mean score of 1.8	History of OP	17	0.242*
	Varicose veins	50	0.337*
	CVI signs collectively	70	0.289*
	Z-score lumbar	4	0.229*
	T-score lumbar	45	0.358*
	CRP	20	0.208*

Table 4-18. Significant Correlations of Pain Subscale

	Variables	Patients No.	R-Value
Pain scale	Knee JSN	100	0.422*
	BMI	94	0.884*
100 patients with a mean score of 1.57	T-score lumbar	45	0.411*
	ESR	70	0.201*
	MDA	80	0.708*
	Ankle MDA	27	0.535*

Table (4-19): Significant Correlations of Pain Subscale

	Variables	Patients No.	R-Value
Difficulty scale 100 patients	BMI	94	0.564*
	Edema	6	0.210*
with a mean score of 1.6	CVI signs collectively	70	0.368*
	Ankle ESR	27	0.244*
	Ankle MDA	27	0.244*

Table 4-20-a. Significant Correlations of Knee JSN and WOMAC Scores

	Variables	Patients No.	R-Value
Knee JSN	WOMAC	2.17	0.657*
100 patients	Symptoms scale	2.0	0.208*
	Pain scale	1.57	0.422*

Table (4-20-b): Significant Correlations of Knee JSN with Clinical and Radiological Variables

	Variables	Patients No.	R-Value
Knee JSN	Knee osteophyte	64	0.416*
	Knee sclerosis	74	0.277*
100 patients	BMI	94	0.308*
	LBP	71	0.337*
	Lumbar DSN	40	0.341*
	Lumbar osteophytes	62	0.341*
	z-score lumbar	4	0.239*

There is no significant correlations of Pain subscale with the following variables: Knee (osteophytes, sclerosis), smoking, LBP, lumbar(DSN, osteophytes, sclerosis), muscular symtoms, history of OP, hemorrhoid, telangiectasia, varicose veins, edema, CVI signs collectively, DXA results of hip, Z-scor of

hemorrhoid, telangiectasia, varicose veins, edema, CVI signs collectively, DXA results T-sxore of lumbar and hip, Z-score of hip, ESR, CRP, S. alkaline phosphatase, S. Ca, S. phosphorus, MDA, ankle MDA and ankle ESR. There is no significant correlations of Knee osteophytes with the following

variables: Symptoms scale, stiffness scales, pain scale, difficulty scale, WOMAC score, smoking, BMI, lumbar DSN and osteophyte, muscular symtoms, history of OP, hemorrhoid, telangiectasia, varicose veins, edema, CVI signs collectively, DXA results T-sxore of lumbar and hip, Z-score of hip, ESR, CRP, S. alkaline phosphatase, S. Ca, S. phosphorus, MDA, ankle MDA and ankle ESR.

Table 4-21. Significant Correlations of Knee Osteophytes

	Variables	Patients No.	R-Value
Knee osteophytes	LBP	71	0.337*
64 patients	Lumbar sclerosis	32	0.341*
	z-score lumbar	4	0.259*

Table 4-22. Significant Correlations of Knee Sclerosis

	Variables	Patients No.	R-Value
Knee	Total WOMAC (mean score 2.17)	100	0.411*
sclerosis	lumbar DSN	40	0.341*
74 patients	lumbar sclerosis	32	0.337*
	S phosphorus	1.08	0.535*

There is no significant correlations of Knee osteophytes with the following variables: Symptoms scale, stiffness scales, pain scale, difficulty scale, smoking, BMI, LBP, lumbar DSN and osteophyte, muscular symtoms, history of OP, hemorrhoid, telangiectasia, varicose veins, edema, CVI signs collectively, DXA results T-sxore and Z-score of lumbar and hip, ESR, CRP, S. alkaline phosphatase, S. Ca, S. phosphorus, MDA, ankle MDA and ankle ESR.

DISCUSSION

The current study was conducted to evaluate first to measure disability of knee OA, using WOMAC score, to determine its reliability and clinical validity; secondly the study aimed at investigating any relationship between knee OA and two other conditions, namely CVI and osteoporosis (OP). Studying disease-associated or comorbidity conditions has important implications; certain risk factors in OA are potentially modifiable such as obesity, smoking and alignment disorders (Abramson and Attur, 2010). It is clear that in managing medical disorders, the modifiable risk factors are attacked. Furthermore, investigating the comorbid conditions with OA may improve our understanding of OA pathogenesis. This study involved 150 individuals, divided into two groups: 100 patients with knee OA and 50 controls without knee OA, matched for age, sex, race and physical activities. The WOMAC questionnaire is a well established subjective scores of symptoms and disability in hip and knee osteoarthritis (Baron *et al*., 2007; Wolf, 1999; Tubach *et al*., 2005). A face to face interview version of WOMAC questionnaire was used in this study instead of the conventional patient reported form; the reason is the frequent illiteracy in our patients specially females. The internal consistency (reliability) of WOMAC was high (Cronbach alpha value 0.84). It seems that the high reliability is well distributed through the questionnaire since the Cronbach alpha value remained good after omitting any one of the subscales. The validity of the questionnaire is reflected by the associations and correlations with clinical and investigational variables, the details were mentioned in the results; the next discussions will clarify this issue.

Knee OA and Smoking: This study revealed a significant negative association between symptoms subscale and smoking (r-value=-0.212). The duration of smoking and number of cigarettes smoked per day were also less in OA patients. These results suggest that smoking may have a protective property against knee OA. This result is in agreement with a study done by Anderson and Felson in 1988 who demonstrated that knee OA occurs at slightly higher rate in nonsmokers. On the other hand smoking correlated with an increased likelihood of knee symptoms in those with white female in radiographic knee OA (Lawrence in 1966 and Hochberg in 1984).

The Association of Obesity and Knee OA: Obesity and OA have been linked in several cross-sectional studies and found a strong association between obesity and knee OA. In a previous study weight was associated with radiographic OA of the knee after adjustment for age in both men and women (Anderson and Felson, 1988) but this relation is not so consistent (Felson, 1988). The present study had found a significant association between total WOMAC score and high body weight (r-value=0.341), also BMI correlated significantly with pain subscale (r-value=0.884), difficulty subscale (r-value=0.564) and radiographic JSN of the knee joints (r-value=0.308). Spectors in1992 did not find obesity to be a risk factor for progression of established disease (Graverand *et al*., 2008). Traut and Thrift in 1977 studied the prevalence of obesity in a group of arthritis clinic patients and compared this with prevalence in general medical clinic patients; the subgroup with osteoarthritis had a higher rate of obesity than controls. Hartz *et al* in 1979 found no association between obesity and symptoms, and Felson *et al*. in1988 similarly could detect no link between obesity and symptoms in Framingham study also. While Goldin *et al*. in 1976 found that radiographic OA was uncommon in 22 grossly obese male, 15 had minimal degenerative disease and five had had meniscectomies. Miller *et al*. in 1973 assessed 35 patients with clinical knee OA and found obesity was not correlated with severity of radiographic changes. However, there was no non osteoarthritis control group in his study. Hinz and Pohl in 1977 studied a group of hospitalized patients with knee OA and found them to be significantly overweight. Finally, Lawrence *et al*. in 1963 found that obese subjects with knee OA were more likely to have symptoms than non-obese subjects. In a study of Alobaidi, 2007 found that the weight has direct effect on the development of OA of the knee.

WOMAC Score in Knee OA:-WOMAC questionnaire was developed specifically for patients with lower limb OA (Creamer *et al*., 2000). This study revealed a significant positive correlation between WOMAC and radiographic knee JSN (r-value=0.657) and knee sclerosis (r-value=0.411). The study also revealed a strong correlation between symptoms subscale and radiographic JSN (r-value=0.422) but there is no statistically significant correlation between WOMAC (total and each subscale) and osteophyte of the knee. This result is in agreement with Creamer *et al*., in 2000 who were unable to find a significant correlation between disability and osteophyte but correlation with narrowing was also absent in their study. Creamer *et al*. 2000, actually sited several previous studies which showed an increasing radiographic severity with increasing disability, although this relationship may disappear when adjusted for pain.

The Association of Knee OA and Lumbar OA: The prevalence of degenerative spinal disease among the elderly is

difficult to be determined because many patients remain asymptomatic and do not request medical treatment (Horikawa *et al*., 2006). Although the current study exclude subjects who have recent LBP, it demonstrate that radiographic knee JSN correlated significantly with lumbar DSN confirmed statistically (r-value =0.341) and with lumbar osteophytes (r-value=0.341). Sclerosis in the knee joint correlated significantly with lumbar DSN (r-value=0.341) and with lumbar sclerosis (r-value=0.337). This result is in agreement with a previous study showing that study made by Kadam, *et al*. in 2004 who demonstrated that the most prevalent musculoskeletal conditions associated with OA knee was back disorders and spondylosis. It also agrees with Kraus *et al*. in 2006 who found that patients with spinal OA commonly obtained knee OA radio graphics. The result of this study is also consistant with the Baltimore longitudinal study on aging which concluded that there is a highly significant association between OA of one joint and OA in other joints which cannot be explained by chance or age alone (Felson, 1988).

Knee OA and Venous Disorders: All patients in this study had either legs CVI or history of hemorrhoids or both. Leg telangiectasia occurred in 47% of patients and 32% of controls (p-value=0.03); leg edema occurred in 6% patients and none of the controls. This result point to an association between knee OA and CVI. Furthermore, telangiectasia showed a significant positive correlation with the total WOMAC score (r-value=0.289). Varicose veins correlated significantly with stiffness subscale (r-value=0.337). Leg edema and CVI signs collectively correlated significantly with the difficulty subscale (r-value=0.21 and 0.368 respectively). These results are in agreement with a study done by Kadam, *et al*. in 2004 in which they found a strong association between OA (after adjusting for age and sex) and obesity and phlebitis. In a study done by lan *et al*., in 2007, they found that there is inappropriate inflammatory response in CVI patients which may lead to both local tissue and micro vascular damage in the lower extremity. More sever signs of CVI such as skin changes and ulcer were not seen in the study subjects possible because they are less common.

The Association Between Knee OA and OP: The relationship between these two common, age related disorders is relevant. Depending on WHO definition of osteopenia and osteoporosis, the current study used T-score of the hip and lumbar spine.

Lumbar Spines: Using the lumbar T score, Osteopenia occurred in 45% of patients and 38% of controls (p-value=0.06). Osteoporosis occurred 21% of patients and 28% of controls. The small number of osteoporotic T-score in this study and the association of lumbar OA (osteophytes and sclerosis) make the figures not that informative. The study of Peacock *et al*. 1996 dose suggest that osteophytosis at a margins of the intervertebral disc is associated with increased BMD in the anteroposterior plane of the lumbar spine. Lumbar T-score correlated positively with pain subscale (r-value= 0.411) and with stiffness subscale (r-value=0.358), which means more pain and stiffness with increasing BMD.

Hip: Using the hip T score as a reference site (kanis *et al*., 2005). Osteopenia occurred in 30% of patients and 48% of controls (p-value=0.002) which suggests that osteopenia may have a protective effect against knee OA. However, osteoporosis occurred 4% of patients and 2% of controls which may suggest that increasing loss of BMD may reverse the effect of osteopenia, however the very small number of osteoporotic hip T-score in this study make the figures not that informative. Low T-score of the hip has significant correlations with symptoms subscale (r-value=0.373). The results of this study are in agreement with study done by Roux *et al*. in 2008 for the relationship between vertebral fractures and spine OA in post-menopausal women with osteoporosis and found that disc space narrowing and osteophytes are associated with decreased vertebral fracture prevalence in them. In a study made by Schneider *et al*. in 2002 they found women with clinically diagnosed hand OA had significantly lower BMD at the hip. Zhang *et al*. in 2000 found that higher BMD at the hip was associated with knee OA in older women. Among women with established knee OA, high BMD decreased the risk of progression of the disease in the knee (Amin, 2002). An association between OA and bone mass was suggested by Foss and Byers in 1972 who looked for radiographic and pathologic evidence of hip OA in 140 hip fractured patients and they found higher bone masses than expected for age. Pogrund *et al*. in 1982 assessing pelvis radiographs from a random sample, found an inverse association between hip OA and OP. Roh in 1974 who evaluated bone mass in hip OA and controls, found higher bone mass with OA. In comparing symptomatic osteoporotic women, Dequeker *et al*. in 1983 found that women with generalized osteoarthritis were more obese and had increase bone mass in osteoarthritic patients. The same group of investigators have reported, in a short-term longitudinal study, that osteoarthritis patients lose bone more slowly over time than patients with OP. thus, osteoarthritis patients have a greater bone mass than age-matched controls and especially greater bone mass than patients with OP. Much of higher bone mass seen in OA may explained by the association of OA with obesity. Price *et al*. in 1987 measured bone mass in women OA and discovered that, when bone mass was adjusted for age and weight, it was not significantly higher than that in controls. Thus, the link between OA and bone mass may be explained by the fact that both are associated with obesity or bone mass may be an intervening variable. In this view, obesity contributes to OA in postmenopausal women by preventing OP and maintaining bone mass.

The Association of Knee OA and Inflammatory Markers: This study reveals significant difference in ESR between the studied groups (p-value=0.005) and significant correlation between ESR and pain subscale (r-value=0.201). The CRP in patients was also significantly increased compared to controls (p-value=<0.001); there is also a positive correlation between CRP levels and stiffness subscale (r-value=0.208). This result is in agreement with a study done by lime, *et al*., 1996 who found that systemic marker of inflammation are raised in OA. Wolfe, 1997 found that CRP is elevated in OA compared to healthy individuals and this association was not seen with ESR. While murphy *et al*. in 2008 found that systemic markers elevation is common in OA patients particularly knee OA. It is notable that a higher BMI is associated with a higher CRP, suggesting the presence of low-grade inflammation in obesity (Brandt, 2010).

The Association of OA and MDA: Malondialdehyde (MDA) is the a generally used index of lipid peroxidation in the appreciation of the role of oxidative stress in diseases (Gawat *et al*, 2004; Garenova and Gadjeva, 2005). MDA is frequently used in determining oxidant/antioxidant balance in disease (Mahboob, *et al*., 2005). The current study found that mean

serum MDA in 80 patients was 2.8463±1.39092 while in 34 controls 0.5176±0.45091 with a very significant difference (p-value=<0.001) between them. Serum MDA significantly correlated with pain subscale (r-value=0.708). Saphenous vein MDA samples at significantly higher levels in patients over the controls (p-value=<0.001). Ankle MDA levels correlated significantly with pain subscale (r-value=0.535) and with difficulty subscale (r-value=0.244). Saphenous vein ESR correlated significantly with difficulty subscale (r-value=0.244). These findings suggest that an inflammatory component, both systemic and local, do exist in knee OA patients. The implications of this concept, pathogeneticlly and therapeutically, need further research.

Conclusion

The conversational Arabic version of WOMAC questionnaire is reliable and valid; therefore bit can be use as an outcome measure in following patients with knee OA.

- Knee osteoarthritis is significantly associated with increasing BMI, clinical venous insufficiency and relative increase in inflammatory markers. The inter-relationship with osteoporosis is complicated and needs further studies. However the study's findings suggests that osteopenia may be a protected against OA.
- These findings could have an important therapeutic implications. For example the evidence is accumulating that low grade inflammation plays an important role in OA. Proinflammatory state may then need to be targets of treatment when associated with OA.

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