

Evaluation Pathogenesis Outcomes of Knee and Hip in Patients with Osteoarthritis Based on: Histopathological, Hematological, and Indicators of Inflammation

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ABSTRACT

Introduction: Osteoarthritis (OA) is a biomechanical process in which the joints respond pathologically to mechanical stress, leading to articular cartilage damage and changes in other tissue. The present study focuses on some hematological and inflammatory indicators in both patients and control and histopathological change in the knee and hip of OA patients.

Methods: Tissue samples were obtained from 50 OA patients (25 knee and 25 hip) during knee and hip replacement for histopathological study and 25 as control group for hematological and immune factors analysis. The tissue and blood samples were collected during the period October 2019 to April 2020.

Results: the Histological study of knee and hip OA tissues (Femoral bone tissue and bone marrow tissue) expressed many histopathological changes such as fibrin deposition, congestion of blood vessels, and infiltration of inflammatory cells. There was no significant difference in concentration of Lymphocytes, Monocytes, and Neutrophils between control and tested groups as well there is no significant difference between tested groups in the patients group. Our results showed significant elevation in erythrocyte sedimentation rate (ESR) there was a significant difference in concentration of (ESR) between control and tested groups while there is no significant difference between tested groups in the patients group. While, there was a significant difference in concentration of C- reactive protein (CRP) between control and tested groups while there is no significant difference between tested groups in patients group.

Conclusions: Histopathological, Hematological, and Immune factors are all associated with the progression of OA disease.

Key words Osteoarthritis, Femoral bone, Bone marrow, Knee, Hip

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INTRODUCTION

The knee joint is the largest and most heavily charged human body joint. The knee joint interacts with bone, cartilage, meniscus, joint capsule, ligaments, muscles, and tendons in a special way to provide stability and mobility [1]. The hip joint is the joint between the hemispheric head of the femur and the cup-shaped acetabula of the hip bone. It is a strong, stable multi-axial ball-and socket type of synovial joint. The hip joint is built for flexibility over a wide variety of movements [2].

Osteoarthritis (OA) is the most widespread degenerative joint condition characterized by gradual damage to the articular cartilage, osteophyte formation and alterations of

the subchondral bone [3]. OA is characterized by degradation of articular cartilage, bone hypertrophy at the margins, subchondral sclerosis [4]. Pathological alterations in the late stage of OA include softening, ulceration and focal disintegration of the joint cartilage [5]. Typical clinical symptoms include discomfort, particularly after sustained exercise and weight loss, whereas stiffness is experienced after inactivity [6]. The current study investigates histopathological, hematological, and immunological factors changes in knee and hip OA patients.

MATERIALS AND METHODS

Study has been designed upon Iraqi patients with OA in the Nursing home hospital and Ghazy Al-hariri hospital for surgical specialties/Medical city during the period from October 2019 to April 2020. Subjects involved in this study

include 50 patients, which diagnosed as OA, and 25 as control.

Collection of blood samples

From each 50 patients and 25 control, 7 ml of venous blood was collected from a suitable vein. 3 ml of the blood was transferred to sterile Ethylene diaminetetra acetic acid (EDTA) tubes, 4 ml of blood was used to remove serum, which was insulated by centrifugation at 3000 rpm for 5 minutes, and then collected at -20°C until the period of using it.

Tissue collection

Tissue specimens were obtained during operation involving total replace knee and hip in 50 patients with OA (25 knee and 25 hip) diagnosed by a professional doctor. OA patient's age ranged 35-90 year. The tissue specimens collected were conserved in the fixative solution (formalin10%) for histopathological study which are routinely stained with Hematoxylin and Eosin [7]. Histopathological study was conducted at Mustansiriyah University in the laboratories of Biology department.

The statistical analysis

The data collected were subjected to a one-way variance analysis (ANOVA) test to compare different groups with each other, and values of $p > 0.05$ were considered statically non- significant while $p < 0.05$, < 0.01 and < 0.001 were considered significantly different and highly significantly different. The statistical analysis was carried out by SPSS (V.20).

RESULTS

Histopathological study

Knee tissues

Femoral bone tissue

The results of the histological examination of the sections stained with hematoxylin-eosin stain of the femoral bone tissue in the knee in OA patients indicated that several changes occurred, showed osteocytes death in many areas and abnormal controlling and proliferation of osteocytes (Figure 1A) dilated vascular sinuses with congestion of blood vessels (Figure1B) and necrotic bone cells and empty osteocytic lacunae (Figure 1C).

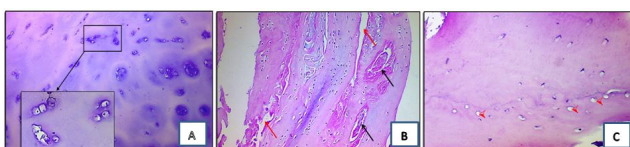


Figure 1: Cross section in the femoral bone of knee OA patient showed. A) Osteocytes death in many areas and abnormal controlling and proliferation of osteocytes (a large figure, X10-small figure, X40). B) Dilated vascular sinuses (red arrows) with

congestion of blood vessels (black arrows) (X4). C) Necrotic osteocytes and empty osteocytic lacunae (head arrows) (X10), (Hematoxylin and Eosin staining).

Bone marrow tissue

Histological sections of f bone marrow tissue in osteoarthritis patients showed in the knee stained with the hematoxylin-eosin stain displayed a number of non-characteristic abnormalities including (Figure 2A) increase in adipose tissue in the bone marrow and decreased cellular portion (Figure 2B) and increase in granulocytes and decrease in erythroid cells.

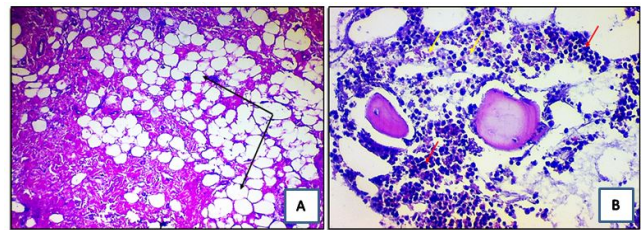


Figure 2: Cross section in the bone marrow of knee OA patient illustrated. A) A mild increase in adipose tissue in the bone marrow and decreased cellular portion, B) An increase in granulocytes (red arrows) and decrease in erythroid cells (yellow arrows) (Hematoxylin and Eosin staining, X10).

Hip tissues

Femoral bone tissue

The results of the histological examination of the sections stained with hematoxylin-eosin stain of the femoral bone tissue in the hip in osteoarthritis patients indicated that several changes occurred, including showed apoptotic osteocytes with condensed nuclei and fragmented chromatin osteocytes (Figure 3A), death in many areas and abnormal controlling and proliferation of osteocytes (Figure 3B). Also, lacunae housing the shrunken remains of osteocytes with increased fibrocytes in outer layers and osteogenic cells in inner layers of Periosteum (Figure 3C).

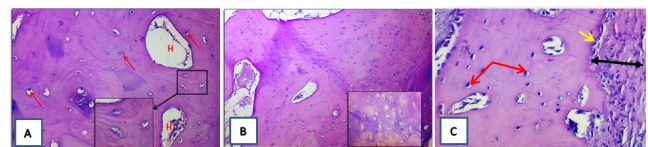


Figure 3: Cross section in the compact femoral bone of hip OA patient showed. A) apoptotic osteocytes with condensed nuclei (red arrows) and fragmented chromatin osteocytes (small figure), H: Haversian canal (large figure: X10, small figure: X40). B) Death in many areas (small figure) and abnormal controlling and proliferation of osteocytes (large figure: X4, small figure: X10). C) Lacunae housing the shrunken remains of osteocytes (red arrows) with increased fibrocytes in outer layers and osteogenic cells (yellow arrow) in inner layers of Periosteum

(double arrow) (X10), (Hematoxylin and Eosin staining).

Bone marrow tissue

The results of the histological examination of the sections stained with hematoxylin-eosin stain of the bone marrow in the hip in OA patients indicated that several changes occurred, including increased formation of erythroid and granulocytes (Figure 4A), hypo cellular areas contain increased reticular strom (Figure 4B) and an increase in the number of megakaryocytes with a mild decrease in bone marrow hematopoietic cellular density (Figure 4C).

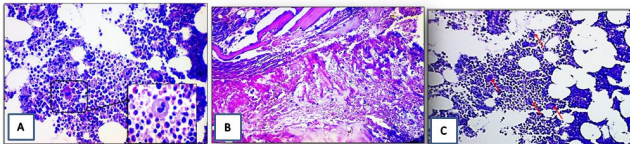


Figure 4: Cross section in the bone marrow of hip OA patient illustrated. A) The increased formation of erythroid and granulocytes (large figure: X10, small figure: X40). B) Illustrated hypocellular areas contain increased reticular stroma (X10). C) An increase in the number of megakaryocytes (red arrows) with a mild decrease in bone marrow hematopoietic cellular density (X10) (Hematoxylin and Eosin staining).

Blood cells count

The result of present study of count blood cells showed in

Table 1: Distribution the level of blood cell distributed in knee and hip OA patients and control group.

Parameters 10 ³ / μl	Mean ± SE
Lymphocytes knee	2.60 ± 1.00
Lymphocytes Hip	2.31 ± 1.15
Control	2.12 ± 0.61
P value between control and tested groups	NS
P value between tested groups	NS
Monocytes Knee	0.41 ± 0.20
Monocytes Hip	0.48 ± 0.31
Control	0.70 ± 0.18
P value between control and tested groups	NS
P value between tested groups	NS
Neutrophils Knee	4.32 ± 0.34
Neutrophils Hip	4.13 ± 0.91
Control	4.10 ± 0.6
P value between control and tested groups	NS
P value between tested groups	NS
SE=Standard Error, NS=No Significant , OA=Osteoarthritis	
Normal value Lymphocyte, 1.5-3.5 10 ³ / μl	
Normal value Monocyte, 0.5-1 10 ³ / μl, Normal value Neutrophil, 2.5-7.5 10 ³ / μl	

Table 1. The lymphocytes count in knee and hip OA patients were 2.60 ± 1.00 10³/ μl and 2.31 ± 1.15 10³/ μl, respectively as compared with control group was 2.12 ± 0.61 10³/ μl. Our result of lymphocyte level was non-significant difference (p > 0.05) in knee and hip OA patients when compared with control group, while no significant difference (p > 0.05) between knee and hip OA patients. While monocytes in knee and hip OA patients were 0.41 ± 0.20 10³/ μl and 0.48 ± 0.31 10³/ μl respectively as compared with control group was 0.70 ± 0.18 10³/ μl. Our result of monocytes level were non-significant difference (p > 0.05) in knee and hip OA patients when compared with control group, while no significant difference (p > 0.05) between knee and hip OA patients.

In addition, the count of the Neutrophils in knee and hip OA patients were 4.32 ± 0.34 10³/ μl and 4.13 ± 0.91 10³/ μl respectively as compared with control group was 4.10 ± 0.6 10³/ μl. Our result of Neutrophil level was non-significant difference (p > 0.05) in knee and hip OA patients when compared with control group, while no significant difference (p > 0.05) between knee and hip OA patients.

CRP test

The level of CRP in serum showed an increase in knee and hip OA patients when compared with control group (Table 2). As the mean value of CRP in knee and hip OA patients were found to be $17.16 \pm 2.7\text{mg/l}$ and $16.41 \pm 2.3\text{mg/l}$ respectively, and in control group was $0.00 \pm$

0.0mg/l . Statistically a highly significant ($p < 0.05$) increased was found in level of CRP between knee and hip OA as compared with control, while no significant difference ($p > 0.05$) in level of CRP of Knee OA as compared with hip OA patients group.

Table 2: Distribution of sample studies according to CRP result of knee and hip OA patients and control group.

Study groups (mg/l)	Mean \pm SE
CRP Knee OA	17.16 ± 2.7
CRP Hip OA	16.41 ± 2.3
Control	0.00 ± 0.00
P value between control and tested groups	0.001
P value between tested groups	NS

SE=Standard Error; NS=No Significant , OA=Osteoarthritis
 CRP=C-reactive protein, Normal value of CRP = $5 < \text{mg/l}$

ESR test

The result of present study showed a highly significant elevation level of the ESR in knee and hip OA patients was $47.12 \pm 5.9 \text{ mm/h}$ and $44.68 \pm 4.2 \text{ mm/h}$ respectively as compared with control group was $11.04 \pm 0.49 \text{ mm/h}$.

Our result of ESR level was with a significant difference ($p < 0.05$) in knee and hip OA patients when compared with control group, while no significant difference ($p > 0.05$) between knee and hip OA patients (Table 3).

Table 3: Distribution of sample studies according to ESR in knee and hip OA patients and control group.

Study groups (mm/h)	Mean \pm SE
ESR Knee OA	47.12 ± 5.9
ESR Hip OA	44.68 ± 4.2
Control	11.04 ± 0.49
P value between control and tested groups	0.001
P value between tested groups	NS

SE=Standard Error; NS=No Significant , OA=Osteoarthritis
 ESR=Erythrocyte sedimentation rate
 Normal value of ESR=($1 - 15 \text{ mm/h}$)

DISCUSSION

Histopathological Study

Knee tissues

Femoral bone tissue

The phenotypes can changes s in bone cells (osteoblasts, osteocytes and osteoclasts) with the progression of OA. Aberrant intercellular communications among bone cell-bone cell and bone cell-chondrocyte are of great importance and might be the factors promoting OA development meanwhile the death of osteocytes is recorded increases in cases of OA increase in immature osteocytes, specifically in regions of active bone formation and MSC accumulation in OA bone [8]. The importance of osteocytes is in the regulation of bone remodelling, osteocytes regulate bone turnover by acting

on bone-forming osteoblasts and bone-resorbing osteoclasts. In addition, osteocytes directly participate in osteolysis, control phosphate homeostasis, and functionally act on the neighboring skeletal muscle and distant organs, the functional and morphological properties of osteocytes appear to be hampered in patients with OA, Indicates that these cells may play an important pathological role in subchondral osteosclerosis [9-11]. Osteocytes die as a result of micro damage or a lack of mechanical stimulus as a result of disuse or weightlessness, which stimulates the recruitment and/or differentiation of osteoclast precursors to the sites of osteocyte apoptosis [12]. On the other hand, a progressive alteration in the subchondral bone is a characteristic of advanced OA, where bone formation leads to the development of osteophytes [13]. Osteophyte formation is significantly correlated with disease progression, and increased local joint space

narrowing is associated with increased osteophyte size [14].

Bone marrow tissue

One of the key changes in bone marrow in patients with knee osteoarthritis is bone marrow fibrosis and necrosis, trabecular bone abnormalities and increased inflammatory cells in sclerotic subchondral bone close to areas of severe cartilage loss, which are known to contain abundant bone marrow, consequently, bone marrow can be regarded as resulting from increased remodelling of subchondral bone and bone marrow [15]. On the other hand, an increase in lesion size strongly associates with progressive cartilage loss and development of OA. Conversely, absence or regression over time of bone marrow is associated with a reduced risk of cartilage loss [16]. There were several fat vacuoles and small blood vessels (sinusoids and venules) often showed erythrocyte aggregation and agglutination. The bone marrow was replaced by fibrous tissue in large areas, The vessels in the Haversian canals were usually open, but areas of erythrocyte agglutination and fibrin thrombi of different ages were not uncommon. Generally, the differences observed in in rheumatoid bone marrow resembled those found in arthritis, except for large aggregations of mononuclear inflammatory cells, sometimes adjacent to vessels clogged [17,18].

Hip tissues

Femoral bone tissue

Osteocyte death occurs as a result of ageing, after the menopause, reduced bone loading and the death of osteocytes is strongly associated with bone resorption, On the other hand, lack of Mechanical loading to apoptosis of osteocytes by oxygen deprivation. It appears that mechanical stimulation provides essential oxygen levels to keep osteocytes viable [19]. Apoptosis of mature osteoblasts is influenced by cytokines such as IL-6 and TGF- β 1, but survival and differentiation of osteoblast into osteocyte was dependent on (matrix metalloproteinase) activity [20]. On the other hand, the current result suggest that the fibrin deposition usually need for mechanical assistance by an increase of osteoclast activity in the in outer circumferential bone lamella in order to causes interruptions in the tidemark with the presence of bony channels carrying inflammatory cells and blood vessels and deposition of blood content involve fibrin this suggestion was explored [21].

Bone marrow tissue

Bone marrow is a source of osteoprogenitor cells, which are key elements in bone formation and fracture healing [22]. An early explanation for the development of Bone marrow considered increased flow and vascular congestion in the setting of capillary wall changes or increased intravascular pressure. It was thought that these factors and the resulting vascular leakage would lead to Bone marrow development [23]. In addition, bone

marrow lesion has reliably been shown to correlate with bone marrow necrosis and fibrosis in OA human knees and hips [24]. This result revealed many of changes that associated with OA, such changes are recorded [25] who mentioned that the bone marrow fibrosis, necrosis, swollen/dying adipocytes, and alterations in trabecular bone structure. Our result contrary to studies of [26] that revealed that the changes of fluid dynamics at subchondral bone represents a part of the mechanism the fluid flow lead to OA and bone marrow.

Blood cells count

The results obtained in the present study showed that there is no effect of OA disease on lymphocytes count, because there is no change in lymphocyte count in that blood. Study of [27] showed that, in the severe knee OA, blood neutrophil, lymphocytes ratio levels found to be elevated when compared to mild to moderate knee OA. The study of [28] reported that, the infiltration into the synovium activation T and B cells and the increased expression of pro inflammatory mediator in both early and late stage of OA which consistent with the current histopathological study [29]. Showed that, T cell may play an important role in the pathogenesis and progression of OA [30] reported the recruited of lymphocyte to the site of inflammation at the late stages of chronic inflammation.

The Monocytes contribute to pathogenesis in OA Low-grade inflammation occurs in OA and correlates with disease severity and progression [31]. A high count of monocyte can be result of several causes, and one of them is acute inflammation, when monocyte increases it indicate that, the body is trying to fight certain diseases [32,33] reported the increase of monocyte, macrophage cells in 24 to 48 hours in most form of acute inflammation, also the chronic inflammation primarily mediated by monocyte and macrophage. It is assumed that the circulating of high numbers of monocyte was occur as a migration of large number of cells into damaged tissues in response to inflammatory signal [34]. When monocytes migrate out of the blood and into peripheral tissue, they immediately undergo to a phenotypic change to aid with the inflammatory response [35].

The neutrophil ratio level as inflammatory marker for indicating the severity of OA [36]. Neutrophils rapidly respond to chemokine's, predominate in the inflammatory infiltrate during 6 to 24 hours [33]. Also it possibly mediates monocyte/macrophage function [37]. After the injury neutrophils, mast cell and macrophages recruited to involved area and can produce variety of pro inflammatory cytokines [38].

CRP test

In this study, all of newly diagnosed OA patients were positive for CRP, this result showed association between CRP and OA were in agreement with the study of [39], CRP is an acute phase protein in synthesized by hepatocytes that stimulates the tumor necrosis factor

TNF- α and fibrinogen that leads to high erythrocytes and stimulates the production of (IL-1), which increases the production of white blood cells and stimulates T cells, and it is considered as an evidence of the severity of the inflammation [40].

ESR test

The ESR is the most commonly used laboratory tests for detecting the acute inflammation [41] and thus diagnosis and monitoring of inflammatory conditions. This study demonstrated the increased ESR levels in OA patients compared to controls, suggesting the presence of an inflammatory response by the immune system against OA [42]. Previous finding demonstrated higher ESR levels in OA patients compared to controls. The failure of various treatments to reverse normalize ESR value is suggestive of presence other mechanisms responsible for the pathogenesis of OA [27].

CONCLUSION

Histopathological changes in Femoral bone and Bone marrow in knee and hip OA patients occurred with the progression of OA disease. The histopathological changes showed the functional and morphological properties of osteocytes appear to be hampered in patients with OA, indicates that these cells may play an important pathological role in OA. Also, the aggregation of inflammatory cells in tissues, thus reflect the role of these cells in inflammatory response. In addition, increase fibrin deposition in much area of tissues. On the other hand, an increase in ESR in OA patients which reflect the present of chronic inflammation in the pathology of OA. While increased CRP in OA patients might be related to present of inflammatory response.

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