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The Role of Vascular Pathology in the Development and Progression of Deforming Osteoarthritis of the Joints of the Lower Extremities (Literature Review)

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Abstract.

There is growing evidence that vascular pathology plays a role in the onset and / or progression of an underlying joint disease: osteoarthritis deformans (DOA). Possible mechanisms: an episodic decrease in blood flow in small vessels in the subchondral bone at the ends of long bones and a related decrease in the flow of interstitial fluid in the subchondral bone. Blood flow can be reduced due to venous occlusion and stasis or due to the development of microembolism in the subchondral vessels. There are several probable factors of subchondral ischemia: the first of them is a violation of the metabolism of nutrients in the articular cartilage, which is a potential initiator of degradation changes in the cartilage. The second is apoptosis of osteocytes in the regions of the subchondral bone, which initiates the resorption of osteoclasts of this bone and, at least temporarily, reduces the bone support for the overlying cartilage. It may be important to recognize these potential etiological factors in order to develop more effective therapies that prevent progression of OA.

Key words: Osteoarthritis, blood vessels, chronic venous insufficiency, subchondral bone, venous stasis, osteocyte viability, osteoclasts.

Introduction

This review examines the evidence supporting the concept that vascular pathology may play a role in the onset and / or progression of an underlying joint disease: DOA. Although DOA is characterized by progressive degenerative damage to the articular cartilage, as the name suggests, significant changes occur in the bones of the affected joints. Bony changes with established DOA include subchondral cysts, sclerosis, and osteophyte formation.

However, the detection of changes in the subchondral bone by MRI even in the early stages of DOA has led to the assumption that DOA may arise as a bone disease affecting bone structure and remodeling, rather than a disease that directly affects the articular cartilage. It is more likely that DOA has multiple etiologies that converge, leading to the recognized manifestations of joint pain, stiffness, and degeneration of articular cartilage. Genetic and environmental risk factors for DOA, such as weight gain,

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female gender, joint dysplasia, displacement and trauma, undoubtedly contribute to the onset and progression of this condition, however, lack of understanding of the root cause (s) of DOA means that treatment remains largely palliative and replacement joint is possible in the terminal stage of the disease. Although cartilage itself is avascular, there is ample evidence that vascular problems may underlie the development of DOA.

Blood flow and bone

Bone is a highly vascular structure, and the vasculature is directly involved in all aspects of its growth, repair and metabolism. The blood supply to the bones is provided by both bone marrow and calcified bone tissue, and the two tissue types are functionally interdependent with regard to hematopoiesis, bone modeling and remodeling. The vascular supply of the bone has many arteries and veins, including, in the case of long bones, four arteries: the nutrient artery, periosteal, metaphyseal, and epiphyseal arteries. The work of Rhinelander et al highlighted the close relationship that exists between the vasculature and sites of bone exchange. Parfitt wrote persuasively about the role of blood vessels as key agents in bone resorption and formation (62). Blood vessels are appropriately located to participate in the interaction of these processes, and the excellent work of Moller et al. Showed that blood vessels are closely associated with cancellous bone and, in particular, at sites of bone resorption (56). Barou et al. Found in rats a significant relationship between the number of vessels and the rate of bone formation (6).

The subchondral regions of the long bones are especially highly vascularized, which indicates a high requirement for nutrients. A higher rate of blood flow to bone is also associated with an increased rate of bone remodeling. However, the "reserve" system of nutritional and periosteal arteries is not present in the epiphyseal regions of long bones due to the articular cartilage in this area. Therefore, the pineal glands and articular surfaces are especially at risk of circulatory failure. Impaired blood flow in the subchondral bone for any reason can have detrimental effects on the bone, but because of the likely importance of the subchondral bone for nourishing the avascular articular cartilage, it also has implications for its integrity.

Bone blood flow and osteocyte viability

Bone blood flow has a number of functions. These include the exchange of oxygen, nutrients and metabolic waste with the interosseous fluid of the bone, which is of prime importance for the osteocytes found in the bone matrix. Although osteoblasts and osteoclasts play a clear role in episodes of bone remodeling, osteocytes are the most abundant cells in bone, and their important current role in bone health, metabolism, and stress adaptation is gaining recognition. First, osteocytes play a key role in bone mechanosensitivity, probably mediated by the flow of interstitial fluid moving along the osteocyte lacunae, which, in turn, is controlled by both mechanical stress on the bone and pulsating blood flow. Second, osteocytes are ideally positioned to detect and respond to microdamage in the calcified bone matrix, allowing them to exercise important control over bone resorption and formation. Third, recent studies indicate a broader role for osteocytes in systemic mineral metabolism.

Bone remodeling is carried out through the coordinated action of osteoclasts and osteoblasts. The triggering event for sites of bone remodeling is unknown, but it seems likely that these sites are targets, and the basis for this targeting may be areas of loss of osteocyte viability, as described in the review by Noble (58, 59). Intravital imaging has convincingly shown that ischemia decreases osteocyte viability and that osteocyte death leads to resorption of the dead bone segment. Depriving the bone of mechanical stress and, thus, reducing the diffusion of interstitial fluid quickly causes hypoxia of osteocytes.

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Accordingly, serum-deprived osteocytes have an increased rate of in vitro apoptosis, which can be largely overcome by subjecting these cells to fluid shear stress that stimulates the expression of the cell survival molecule. Thus, osteocytes are able to detect mechanical signals in the form of fluid flow, and, importantly, their viability seems to depend on fluid flow. It has also been shown that microdamage to the bone matrix induces osteocyte apoptosis. In bone, the initial response to apoptotic osteocytes appears to be catabolic, with rapid recruitment and differentiation of osteoclast precursors. A cascade of events from osteocyte signaling to bone renewal has been aptly summarized by Parfitt (61-63).

Bone marrow edema

How can vascular pathology be transformed into DOA symptoms? From the above, insufficient fluid flow around osteocytes for any reason, such as unloading of a limb, venous congestion or small vessel occlusion, can sequentially lead to osteocyte apoptosis, osteoclast recruitment, and expulsion of nonviable bone. Recurrent episodes of this process at the ends of affected long bones can lead to changes in bone remodeling and morphology. In extreme cases, partial or complete collapse of the subchondral bone may occur, as in avascular necrosis (AVN). Evidence that such phenomena can occur in the subchondral bone comes from high-resolution magnetic resonance imaging (MRI) of the joints. Areas of the subchondral bone that appear bright on MRI are usually seen in both established and early osteoarthritis, as well as in people with painful joints. They are thought to correspond to areas of bone marrow edema (BME) that occurs idiopathically or in response to bone injury. Longitudinal studies have shown that BME is a potent risk factor for structural deterioration in knee DOA. The increase in these bone marrow lesions is closely related to the increased loss of cartilage. Conversely, a decrease in the degree of bone marrow abnormalities on MRI is associated with a decrease in cartilage degradation. Recently, it has been shown that subchondral cysts, characteristic of high stage DOA, arise from areas of BME.

The origin of BME is unknown, but it may be secondary to episodes of ischemia, possibly exacerbated by reperfusion injury, as Winet et al. Have modeled beautifully (78). Interestingly, similar areas of BME, as identified by MRI, have been described in stress fractures, where it was assumed that their origin is associated with the generation of intramedullary pressure in excess of peak blood pressure during strenuous exercise. In this case, the bone tissue will suffer from ischemia caused by decreased blood flow during exercise and reperfusion injury after exercise. Although it is not possible to examine BME histologically in patients with early osteoarthritis, several studies have attempted to compare MRI results with histology in more severe diseases. BME areas in patients with end-stage DOA during knee replacement were more prone to edema, bone necrosis, and trabecular anomalies than controls. In another study, BME in early nontraumatic AVN of the femur showed areas of edematous bone marrow, empty osteocyte lacunae in cancellous bone, indicating increased bone formation. Thus, there is some evidence that an important early correlate of DOA, BME, is associated with both bone necrosis and cartilage degeneration. There are several possible causes of BME, and its occurrence due to local ischemia has yet to be proven. Similarly, it remains to be determined whether BME is the initiating event in the development of DOA or the driving force behind the progression of DOA.

The consequences of ischemia of the subchondral bone

If ischemia of the subchondral bone is a causative factor in the development of DOA, there are several possible consequences. First, the supply of nutrients and oxygen from the subchondral bone to the overlying articular cartilage will be reduced from areas of ischemia. Imhof et al. Described a dense

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subchondral vasculature in close proximity to cartilage and microchannels that penetrate into the subchondral mineralization zone and provide a connection between bone and cartilage (40-41). These authors also state that more than 50% of the cartilage needs for glucose, oxygen and water are provided by perfusion from the subchondral vessels. In addition, examination of the osteocartilaginous junction of long bones shows that osteocytes and osteocyte tubules, which are also likely to be conductors of nutrients, are closely associated with articular cartilage. Indeed, experimental interruption of the contact between articular cartilage and subchondral bone in baboons led to cartilage degeneration. Interestingly, subchondral osteoblasts in DOA, but not in control bone, induce changes in articular chondrocytes that are consistent with the catabolic effect of osteoblasts on cartilage. This suggests that the connection between bone and cartilage components at the osteochondral junction may be important for health and disease.

What is the evidence that episodes of ischemia in the subchondral bone can lead to increased bone resorption? As indicated above, there is histological and biochemical evidence of increased metabolism in subchondral bone containing RCM. In addition, the increased subchondral bone remodeling found on bone scans has been well described in the established DOA, where joint space narrowing is reported to be predicted. It is not possible to determine whether increased bone turnover is a cause or a consequence of human DOA, but several animal models of DOA are of interest in this regard. In the model of dissection of the anterior cruciate ligament (DACL) in rats with DOA, increased resorption of the subchondral bone is associated with the early development of cartilage damage, which precedes significant thinning of the cartilage and sclerosis of the subchondral bone. It is noteworthy that treatment with the antiresorptive bisphosphonate, alendronate, in this model suppressed both the resorption of the subchondral bone and the later development of DOA symptoms in the knee joint. The authors concluded that subchondral bone remodeling plays an important role in the pathogenesis of DOA. In a canine DACL model, calcitonin reduced levels of circulating markers of bone metabolism and the severity of lesions in DOA. When discussing similar results in dogs treated with calcitonin with DACL, Behets et al. Noted that the loss of the trabecula of the subchondral bone may contribute to cartilage destruction by increasing cartilage deformation under stress on the joint (7). An alternative explanation for the results of these studies is that the antiresorptive agents acted directly on chondrocytes, and none of the studies provided direct evidence for a vascular cause of increased bone metabolism. Human data are consistent with animal models, but not definitive. While they show, for example, increased markers of bone turnover in patients with advanced knee DOA compared with patients with non-progressive knee DOA, there are clearly many contributing factors, such as osteoporosis, vitamin D and vitamin K deficiencies.

The above data confirm an important role in the increase in the turnover of the subchondral bone in DOA. The question to be addressed is whether this could be secondary to episodic ischemia, in turn, due to vascular pathology in the subchondral bone. As detailed below, the literature contains abundant evidence of venous congestion, hypertension, and altered coagulation in human ODA and in animal models of ODA.

Venous congestion

Reducing arterial flow and obstruction of venous outflow has been shown to impair blood flow to bones and reduce the supply of nutrients and oxygen to cells. Violation of venous circulation (venous stasis) and, as a consequence, a decrease in blood outflow, especially from the articular ends of long bones, leading to an increase in intraosseous pressure, has been proposed as a causative factor in osteonecrosis. Although long bone has multiple supply and drainage vessels, if large veins, such as the

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femoral vein, are blocked or experimentally tied, or muscle veins are compressed with a tourniquet, or perhaps malfunctioning, as is the case with varicose veins, the system's ability to drain blood is impaired. Accordingly, in patients with severe degenerative DOA of the hip, venous drainage from the perioscleral cancellous bone through the cortical is reported to be impaired. Arnoldi showed that increasing intra-articular pressure in rabbits increases intraosseous pressure. This is because the drainage veins at the ends of the long bones usually exit inside the joint capsule. For example, the drainage veins from the femoral neck extend to the edge of the cartilage and are initially located in the joint capsule. Thus, even a small increase in joint pressure is sufficient to destroy these thin-walled vessels and block blood flow. These data indicate that increased intra-articular pressure caused by obesity or intra-articular inflammation may be one of the mechanisms causing intraosseous hypertension in OAD, either as a primary cause of the disease, or as an exacerbating factor. In line with animal data, intraosseous hypertension was also observed in the femur in patients with knee DOA.

The concept of venous stasis was developed by Cowin et al. Venous congestion of any cause will result in more blood remaining in the organ, which will be redirected to the remaining functional vessels. These vessels will increase in size to accommodate the increased vascular resistance and, as a result, vascular pressure will increase. It is also accompanied by an increased flow of filtration through the vessel wall, which causes an increase in extravascular pressure, since the bone is a relatively rigid compartment. As the pressure in the system increases with venous congestion, the differences created by the blood pulse and hence the flow of interstitial fluid also decrease in the mineralized matrix.

Because blocked or impaired venous return will reduce the flow of interstitial fluid, the supply of nutrients and oxygen to the bones and the removal of waste products will be reduced, which is extremely harmful to osteocytes. It has been reported that an osteocyte left without nutrient exchange for 4 hours will die, and bone ischemia for more than 6 hours causes significant osteonecrosis. Pedersen et al. Reported that subchondral bone hypoxia was present in the thighs with DOA and the thighs with non-traumatic necrosis (64). Identical signs of subchondral medullary and trabecular necrosis were found in both conditions. Loss of fluid flow in osteocyte lacunae not only removes the stress-sensing ability of osteocytes, but it is likely that osteocytes depend on stress and flow-induced cellular deformation for their viability.

Thus, episodes of venous congestion in OA can lead to loss of viability of osteocytes in bone regions. This is probably especially true for the subchondral region of long bones with a high vascular content. Venous congestion can also lead to a decrease in the supply of the overlying cartilage, as suggested by Imhof et al (40-41). Loss of osteocyte viability in the subchondral bone can lead to an increase in bone turnover to repair damaged and necrotic bone tissue, which, in turn, can lead to changes in the architecture of the subchondral bone and, possibly, to joint degeneration due to disruption of the structural basis of the cartilage.

Hypertension

Patients with end-stage hip DOA show a high prevalence of comorbid vascular disease, and a causal relationship between the progression of DOA and atherosclerotic vascular disease has recently been proposed. This may reflect a higher incidence of hypertension and other vascular conditions with age, but generalized osteoarthritis is significantly more common in older men with high than low diastolic blood pressure. Knee osteoarthritis in women was more common in hypertensive cohorts, regardless of obesity, although many of these patients were overweight or obese. Weinberger et al. Reported that patients with DOA generally exhibited symptoms associated with hypertension and heart disease, which

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is consistent with data linking DOA with potentially preventable health problems such as obesity, hypertension, and heart disease, regardless of trauma. The implication is that reducing the burden of cardiovascular disease may also have positive benefits for the development of DOA.

It is clear that uncontrolled hypertension is a strong risk factor for cardiovascular disease, cardiovascular disease and many other diseases associated with target organs. There is evidence that these consequences of hypertension are associated with impaired vascular capacity for growth and angiogenesis, which, in turn, occurs due to damage or dysfunction of endothelial cells. Although the endothelium of different vascular beds differs, and the characteristics of the microvasculature of the bone have been insufficiently studied, a likely unifying feature of all vascular beds is a reduced ability to synthesize nitric oxide (NO) under conditions of hypertension. Other vascular factors, such as vascular endothelial growth factor (VEGF), may be involved in the pathogenesis of hypertension, although their role in DOA has only been preliminary studied.

Hypercoagulation and hypofibrinolysis

Coagulation disorders have been described in patients with osteonecrosis of the hip joint. Many predisposing factors and generalized disease states have been associated with osteonecrosis of the femoral head, including corticosteroid overuse, alcoholism, hemoglobinopathies, Gaucher disease, pregnancy, hyperbaric exposure, autoimmune diseases, and hip injuries. Intravascular coagulation, activated by a variety of underlying diseases, is postulated as a common link leading to ischemic stroke, intraosseous thrombosis and bone necrosis. Korompilias et al. Examined patients with osteonecrosis of the hip for the presence of thrombophilic disorders to assess whether their presence is associated with an increased risk of osteonecrosis. Only 17% of patients had a completely normal thrombotic profile, and the authors suggested that osteonecrosis may result from recurrent thrombotic or embolic events occurring in the vulnerable vasculature of the femoral head. In a model of steroid-associated osteonecrosis of the femur in rabbits, microangiography of the subchondral bone showed clear evidence of thrombo-blocking and leaking of blood vessels in this disease. Understanding the relationship between the states of hypercoagulability and osteonecrosis may allow pharmacological intervention to prevent this process.

Although there is currently no consensus that DOA is etiologically associated with osteonecrosis, Cheras et al., As well as Ghosh and Cheras reviewed the literature and presented their own data to support the concept that changes in blood clotting may also predispose to DOA (14). Cheras et al. Observed intraosseous intravascular fatty thrombosis, especially in the venous microvasculature, in the femoral heads in patients with degenerative DOA and, to a greater extent, in ischemic bone necrosis, but not in the femoral heads without osteoarthritis (15). Therefore, thrombotic microvessel blockade at the articular ends of long bones is a potential mechanism for bone necrosis and subsequent DOA. Interestingly, early studies of femoral heads in patients with DOA showed frequent widespread loss of osteocyte viability and suggested that episodic osteocyte death and bone collapse in idiopathic femur DOA may be the cause rather than the result of arthritis. It is also possible that bone remodeling caused by this process leads over time to at least some of the articular abnormalities described as causal for primary DOA, especially the hip joint.

A study by Cheras et al. Potentially explaining observations in the bone microvasculature of DOA revealed significant differences between the DOA group and the control group with fibrinogenic and fibrinolytic parameters and lipid profile (14-15). These findings are consistent with hypercoagulability, hypofibrinolysis, and increased fibrin production in DOA. In a follow-up study, Cheras et al. And Ghosh and Cheras described the results obtained in a relatively young group of patients (49 ± 10 years) with a

relatively recent diagnosis of DOA, performed to identify potential markers that could help differentiate DOA from non-DOA. The results of this study show a combination of increased procoagulant factors as well as significant hypofibrinolysis, which was also reported by Glueck et al. In patients with ischemic bone necrosis (30). Violation of fibrinolysis and hyperlipidemia are associated with a tendency to venous thrombosis. The authors suggested that the coagulation and lipid abnormalities described in this study support a possible association with the occurrence of DOA and ischemic bone necrosis. Interestingly, the changes in clotting found in individuals with early osteoarthritis were also associated with signs of increased bone metabolism. Ghosh and Cheras also described a study in dogs in which large breed dogs with radiologically confirmed hip DOA were injected subcutaneously with calcium pentosan polysulfate. Platelet aggregation before treatment was increased compared to the control group. Interestingly, treatment with pentosan polysulfate calcium normalized thrombotic parameters and the dogs showed clinical improvement in terms of DOA symptoms. Qualitatively similar results were obtained in a 24-week study in people with DOA who received calcium pentosan polysulfate, although interpretation of this study was complicated by the strong response to placebo. It has not been determined whether hypercoagulability and hypofibrinolysis precede DOA or are a consequence of the disease. However, family studies by Glueck et al. In patients with ischemic bone necrosis indicated that genetically related hypofibrinolysis associated with elevated PAI-1 levels may be the main cause of osteonecrosis. Similar family studies are shown in DOA in addition to prospective studies in individuals with hypercoagulability or hypofibrinolysis.

Conclusion

This review presents some accumulated information that will help to build a hypothesis about vascular lesion, if not about the cause of DOA, then as a factor in the progression of this condition. Since the vasculature in question is the vasculature of the subchondral bone, it requires more careful consideration. Much remains to be learned about the ways in which bones and cartilage interact in normal bone turnover and how vasculature can affect this. However, the essential knowledge platform summarized here will allow for more informed research and hopefully new treatment options for DOA, which represents such a heavy burden of disease on our aging population.

References

1. Aguirre J.I., Plotkin L.I., Stewart S.A. et al. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. J Bone Miner Res 2006;21:605–15.
2. Alimdjanovich, R.J., Isamiddinovich, K.A., Evgenyevna, L.N., Jasur ugli, O.K., Djamalovna, R.G.Pathomorphological changes in the oral mucosa in patients with colon cancer. European Journal of Molecular and Clinical Medicine. 2020. 7(7), c. 666-672.
3. Arnett T.R., Gibbons D.C., Utting J.C. et al. Hypoxia is a major stimulator of osteoclastformation and bone resorption. J Cell Physiol 2003;196:2–8.
4. Bakker A, Klein-Nulend J, Burger E. Shear stress inhibits while disuse promotes osteocyte apoptosis. Biochem Biophys Res Commun 2004;320:1163–8.
5. Behets C, Williams JM, Chappard D, Devogelaer JP, Manicourt DH. Effects of calcitonin on subchondral trabecular bone changes and on osteoarthritic cartilage lesions after acute anterior cruciate ligament deficiency. J Bone Miner Res 2004;19:1821–6.
6. Berger CE, Kroner AH, Minai-Pour MB, Ogris E, Engel A. Biochemical markers of bone metabolism in bone marrow edema syndrome of the hip. Bone 2003;33:346–51.

7. Brandi ML, Collin-Osdoby P. Vascular biology and the skeleton. J Bone Miner Res 2006;21:183–92.
8. Buckwalter JA, Brown TD. Joint injury, repair, and remodeling: roles in post-traumatic osteoarthritis. Clin Orthop Relat Res 2004;423:7–16.
9. Carrino JA, Blum J, Parellada JA, Schweitzer ME, Morrison WB. MRI of bone marrowedema-like signal in the pathogenesis of subchondral cysts. Osteoarthritis Cartilage2006;14:1081–5.
10. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? Ann Rheum Dis 2005;64:1539–41.
11. Enomoto H, Inoki I, Komiya K et al. Vascular endothelial growth factor isoforms and their receptors are expressed in human osteoarthritic cartilage. Am J Pathol 2003;162:171–81.
12. Felmeden DC, Spencer CG, Belgore FM, Blann AD, Beevers DG, Lip GY. Endothelial damage and angiogenesis in hypertensive patients: relationship to cardiovascular risk factors and risk factor management. Am J Hypertens 2003;16:11–20.
13. Felson DT, McLaughlin S, Goggins J et al. Bone marrow edema and its relation toprogression of knee osteoarthritis. Ann Intern Med 2003;139:330–6.
14. Feng JQ, Ward LM, Liu S et al. Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism. Nat Genet 2006;38:1310–5.
15. Garnero P, Peterfy C, Zaim S, Schoenharting M. Bone marrow abnormalities onmagnetic resonance imaging are associated with type II collagen degradation in kneeosteoarthritis: a three-month longitudinal study. Arthritis Rheum 2005;52:2822–9.
16. Gross TS, King KA, Rabaia NA, Pathare P, Srinivasan S. Upregulation of osteopontin by osteocytes deprived of mechanical loading or oxygen. J Bone Miner Res 2005;20:250–6.
17. Han Y, Cowin SC, Schaffler MB, Weinbaum S. Mechanotransduction and strain amplification in osteocyte cell processes. Proc Natl Acad Sci USA 2004;101:16689–94.
18. Hayami T, Pickarski M, Wesolowski GA et al. The role of subchondral bone remodeling in osteoarthritis: reduction of cartilage degeneration and prevention of osteophyte formation by alendronate in the rat anterior cruciate ligament transection model. Arthritis Rheum 2004;50:1193–206.
19. Hayami T, Pickarski M, Zhuo Y, Wesolowski GA, Rodan GA, Duong le T. Characterization of articular cartilage and subchondral bone changes in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis. Bone 2006;38:234–43.
20. Hunter DJ, Zhang Y, Niu J et al. Increase in bone marrow lesions associated withcartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. Arthritis Rheum 2006;54:1529–35.
21. Johnson EO, Soultanis K, Soucacos PN. Vascular anatomy and microcirculation skeletal zones vulnerable to osteonecrosis: vascularization of the femoral head. Orthop Clin North Am 2004;35:285–91.
22. Karter Y, Aydin S, Curgunlu A et al. Endothelium and angiogenesis in white coat hypertension. J Hum Hypertens 2004;18:809–14.
23. Kasimov, A., Abdullaeva, N., Djurabekova, A., Shomurodova, D.Features of diagnosis and clinic of post-traumatic epilepsy against the background of concomitant somatic diseases. International Journal of Pharmaceutical Research. 2020. 12(3), c. 1788-1792.
24. Khamidov O.A. Radiation methods of research in case of damage to the soft tissue structures of the knee joint. XXI INTERNATIONAL CORRESPONDENCE SCIENTIFIC SPECIALIZED CONFERENCE «INTERNATIONAL SCIENTIFIC REVIEW PROBLEMS OF NATURAL SCIENCES AND MEDICINE » Boston, USA, 2020y. page 30-42.

25. Khamidov O.A. Diagnostics of injuries of the soft tissue structures of thee knee joint and their complications. «EUROPEAN RESEARCH: INNOVATION IN SCIENCE EDUCATION AND TECHNOLOGY » Moscow, 2020y. page 33-36.
26. Khamidov O.A. Optimization of radiological diagnostics of injuries of the soft tissue structures of the knee joint and their complications. American journal of medicine and medical sciences, America, 2020y. page 881-884.
27. Khamidov O.A., Murodullaeva D.M., Yakubov D.Zh., Mardieva G.M. Ultrasonic scanning for knee diseases. Сборник материалов международной научно – практической онлайн конференции «Фундаментальная наука в современной медицине» Самарканд, 2020г. Стр. 468-469
28. Khodzhibekov M.X., Khamidov O.A., Mardieva G.M. Verification of radiation methods in diagnostics of injuries of the knee joint intra-articular structures. International Journal of Pharmaceutical Research. 2020:13(1), p. 302-308.
29. Kiefer FN, Neysari S, Humar R, Li W, Munk VC, Battegay EJ. Hypertension and angiogenesis. Curr Pharm Des 2003;9:1733–44.
30. Korompilias AV, Ortel TL, Urbaniak JR. Coagulation abnormalities in patients with hip osteonecrosis. Orthop Clin North Am 2004;35:265–71.
31. Lajeunesse D, Massicotte F, Pelletier J-P, Martel-Pelletier J. Subchondral bone sclerosis in osteoarthritis: not just an innocent bystander. Mod Rheumatol 2003;13:7–14.
32. Mandalia V, Fogg AJ, Chari R, Murray J, Beale A, Henson JH. Bone bruising of theknee. Clin Radiol 2005;60:627–36.
33. Mardieva G.M., Khamidov O.A., Yakubov D.Zh., Turdumatov Zh.A. Ultrasound semiotics of Biker cysts. Vienna 2018. «European science review» № 1-2 2019, January – February. Volume 2. P. 166-168.
34. Mavlyanov, F.Sh., Mukhammadiev, M.Kh., Kamolov, S.Zh., Shukurov, F.M., Mavlyanov, Sh.Kh.Monitoring of organ failure development in patients with acute pancreatitis. European Journal of Molecular and Clinical Medicine. 2020. 7(3), c. 2523-2528.
35. Mavlyanov, F.Sh., Mukhammadiev, M.Kh., Shukurov, F.M., Kamolov, S.Zh.Laparoscopy in the complex treatment of severe acute pancreatitis. European Journal of Molecular and Clinical Medicine. 2020. 7(2), c. 3003-3007.
36. Mavlyanova, Z., Burkhanova, G., Ravshanova, M., Makhmudov, S., Kholboyev, S.Improving the tactics of treating children with severe cerebral palsy. European Journal of Molecular and Clinical Medicine. 2020. 7(2), c. 1623-1631.
37. Neogi T, Booth SL, Zhang YQ et al. Low vitamin K status is associated with osteoarthritis in the hand and knee. Arthritis Rheum 2006;54:1255–61.
38. Noble B. Bone microdamage and cell apoptosis. Eur Cell Mater 2003;6:46–55.
39. Noble B. Microdamage and apoptosis. Eur J Morphol 2005;42:91–8.
40. Parfitt AM. Misconceptions V-Activation of osteoclasts is the first step in the boneremodeling cycle. Bone 2006;39:1170–2.
41. Sanchez C, Deberg MA, Piccardi N, Msika P, Reginster JY, Henrotin YE. Subchondral bone osteoblasts induce phenotypic changes in human osteoarthritic chondrocytes. Osteoarthr Cartilage 2005;13:988–97.
42. Seeman E. Osteocytes-martyrs for integrity of bone strength. Osteoporos Int 2006;17:1443–8.
43. Sormaala MJ, Niva MH, Kiuru MJ, Mattila VM, Pihlajamaki HK. Bone stress injuries of the talus in military recruits. Bone 2006;39:199–204.
44. Spector TD, MacGregor AJ. Risk factors for osteoarthritis: genetics. Osteoarthr Cartilage 2004;12(Suppl A):S39–44.

45. Tashkenbaeva, E., Nasirova, Z., Ziyadullaev, S., Farzona, K.The role of biopsychosocial risk factors on the intensification of unstable angina. International Journal of Advanced Science and Technology. 2020. 29(5), c. 1948-1952.
46. Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, Moutsopoulos HM. Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. Ann Rheum Dis 2004;63:1159–61.
47. Turdumatov J.A., Mardieva G.M. Clinical and x-ray peculiarities of the course of chronic obstructive pulmonary disease in combination with diabetes. European Journal of Molecular and Clinical Medicine. 2020:7(2), p. 3009-3028.
48. Wang L, Fritton SP, Weinbaum S, Cowin SC. On bone adaptation due to venous stasis. J Biomech 2003;36:1439–51.
49. Winkler DG, Sutherland MK, Geoghegan JC et al. Osteocyte control of bone formation via sclerostin, a novel BMP antagonist. EMBO J 2003;22:6267–76.
50. You LD, Weinbaum S, Cowin SC, Schaffler MB. Ultrastructure of the osteocyte process and its pericellular matrix. Anat Rec a Discov Mol Cell Evol Biol 2004;278:505–13.
51. Zhai G, Blizzard L, Srikanth V et al. Correlates of knee pain in older adults:Tasmanian Older Adult Cohort Study. Arthritis Rheum 2006;55:264–71.
52. Zhang G, Qin L, Sheng H et al. Epimedium-derived phytoestrogen exert beneficial effect on preventing steroid-associated osteonecrosis in rabbits with inhibition of both thrombosis and lipid-deposition. Bone 2007;40:685–92.
53. Jasur A. Rizaev, Ezozbek A. Rizaev, N.N. Akhmadaliev. Current View of the Problem:A New Approach to Covid-19 Treatment. Indian Journal of Forensic Medicine & Toxicology, October-December 2020, Vol. 14, No. 4. PP 7341-7347
54. Rizaev, J.A., Ashirov, Z.Quality management of medical care in the dermatovenerological service based on rational planning of professional activities of dermatovenerologists. European Journal of Molecular and Clinical Medicine7(2), c. 2996-3002
55. Rizaev Jasur, Kubaev Aziz. Preoperative mistakes in the surgical treatment of upper retro micrognatia. International Journal of Pharmaceutical Research | Jan - Mar 2020 | Vol 12 | Issue 1. - P. 1208-1212.
56. Sh.Ziyadullaev, J.Rizaev,I.Agababyan, J.Ismailov h, S.Yuldashev. The effect of budesonide on the quality of life in patients with bronchial asthma. European Journal of Molecular & Clinical Medicine. ISSN 2515-8260 Volume 7, Issue 2, 2020 Pages 1760-1766
57. .Ziyadullaev, S., Elmamatov, O., Raximov, N., Raufov, F.Cytogenetic and immunological alterations of recurrent bladder cancer. European Journal of Molecular and Clinical Medicine7(2), c. 1877-1883
58. MavlyanovF.Sh.MuhammadievH.KhShukurov F.M.Kamolov S.Zh. Laparoscopy in the complex treatment of severe acute pancreatitis European jornal of Molecular & Clinical Medicine. Volume 07.P.3003-3007.
59. Mavlyanov F, Mavlyanov Sh, Shirov T, Khayitov U. Program For Diagnosing The Degree Of Urodynamic Disorders And Kidney Functions And Determining Tactics Of Managing Children With Obstructive Uropathies. *European Journal of Molecular & Clinical Medicine, 2020,* Volume 7, Issue 3, Pages 2546-2554
60. Мардиева Г.М., Муродуллаева Д.М., Хамидов О.А. Ультразвуковая верификация синовита у больнқх артрозом коленного сустава. Научно-методический журнал «Достижения науки и образования» (Иваново, Россия). № 16 (70), 2020. Стр.54-59.

61. Мардиева Г.М., Хамидов О.А., Якубов Д.Ж., Муродуллаева Д.М. Ультразвуковая диагностика травм коленного сустава у спортсменов. Научно – практическая конференция с международным участием. Проблемы биологии и медицины, 2019, №2,1 (110). С. 35-36.
62. Мардиева Г.М., Хамидов О.А., Якубов Д.Ж., Оллаберганов М.И. Возможности лучевых методов исследования при повреждениях мягкотканых структур коленного сустава. «ХАЛКАРО ИЛМИЙ ЖУРНАЛ» БИЛОГИЯ ВА ТИББИЁТ МУАММОЛАРИ №4(104) 2018. С. 197-201.
63. Муродулаева Д.М., Хамидов О.А., Мардиева Г.М. Аспекты ультразвуковой верификации повреждений коленного сустава. Сборник материалов II международной конференции студентов медиков и молодых учёных. Бухара 27 мая 2020г. Стр 89-90.
64. Ризаев Ж.А., Хамидов О.А., Муродуллаева Д.М., Якубов Д.Ж. Ультразвуковая диагностика повреждений внутрисуставных структур коленного сустава и их осложнения. Сборник материалов международной научно – практической онлайн конференции «Избранные вопросы диагностической радиологии и ядерной медицины» Самарканд, 2020г. стр. 102-103.
65. Сафаров У.Б., Ахмедов Я.А., Тоиров Э.С., Хамидов О.А., Аметова А.С. Лучевые показатели ревматоидного артрита в зависимости от периода заболевания. Сборник материалов международной научно – практической онлайн конференции «Избранные вопросы диагностической радиологии и ядерной медицины» Самарканд, 2020г. стр. 72-73.
66. Сафаров У.Б., Ахмедов Я.А., Якубов Г.А., Каримов З.Б., Хамидов О.А. Изменение визуальных показателей ревматоидного артрита в зависимости от периода заболевания. Материалы конференции «Тенденции и перспективы развития науки и образования в условиях глобализации» Вып. 54 2019 стр. 412-416.
67. Хамидов О.А. Результаты обследования пациентов с повреждениями менисков коленного сустава и их осложнений. Биология ва Тиббиёт муаммолари, Самарканд 2020г. № 4 (120), стр. 121-126.
68. Хамидов О.А., Мардиева Г.М., Якубов Д.Ж., Муродуллаева Д.М. Возможности ультразвукового исследования для диагностики синовита и периартрита у больных гонартрозм. «Научно – практический журнал» терапевтический вестник Узбекистана №2 2019. С. 105.
69. Ходжибеков М.Х., Хамидов О.А. Обоснование ультразвуковой диагностики при повреждениях внутрисуставных структур коленного сустава и их осложнений. Тиббиётда янги кун № 3(31). Бухоро, 2020г. Стр. 526-529.
70. Якубов Д.Ж., Муродуллаева Д.М., Хамидов О.А. Артросонография в диагностике синовита и периартрита у больных гонартрозм. Материалы 73 – научно – практической конференции студентов и молодых учёных «Актуальные проблемы современной медицины» № 1.1(108) 2019. С. 71.
71. Якубов Д.Ж., Муродуллаева Д.М., Хамидов О.А., Мардиева Г.М. Ультразвуковое исследование при повреждении мягкотканых структур коленного сустава. Научно-методический журнал «Достижения науки и образования» (Иваново, Россия). № 2 (56), 2020. Стр.96-99.
72. Якубов Д.Ж., Хамидов О.А., Нарзикулов Ш.Ф. Возможности ультразвукового исследование в диагностике артроза коленного сустава. «BIMCO JOURNAL» Abstract book of the congress BIMCO, 2018. С. 394.
73. Якубов Д.Ж., Хамидов О.А., Оллаберганов М.И. Ультразвуковая диагностика кисты Бейкера. Материалы 72 – научно – практической конференции студентов и молодых учёных «Актуальные проблемы современной медицины» № 2.1(101) 2018. С. 177.

74. Irsalieva, F., Razikova, I., Kamalov, Z., Dustbabayeva, N., Nizamov, K. Rationale for sublingual allergen-specific immunotherapy in immunocompromised patients. International Journal of Pharmaceutical Research, 2020, 12(2), p. 230–236
75. Dustbabaeva, N., Irsalieva, F., Kamalov, Z., Ziyadullaev, S., Akhmedov, K. Research of the association of IL-17A RS (2275913) gene polymorphism with allergic rhinitis associated with food co-sensitization. International Journal of Pharmaceutical Research, 2020, 12(2), p. 758–762
76. Yakubova, O., Ayupova, F., Kamalov, Z., Negmatshaeva, K., Mamarasulova, D. Role of COL1A1 and G2046T genes in Uzbeks with juvenile dysmenorrhea in the presence of criteria for undifferentiated connective tissue dysplasia. Journal of Critical Reviews, 2020, 7(2), p. 391–394
77. Tashkenbaeva, E.N, Ziyadullaev, S.K, Kamalov, Z.S, Kadirova, F.S, Abdieva, G.A. Urate regulation gene polymorphisms are correlated with clinical forms of coronary heart disease. International Journal of Pharmaceutical Research, 2019, 11(3), p. 198–202