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Viral infections in orthopedics: A systematic review and classification proposal

Viral infections in orthopedics. Do we miss something?

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Abstract

BACKGROUND

Although the impact of microbial infections on orthopedic clinical outcomes is well recognized, the influence of viral infections on the musculoskeletal system might have been underestimated.

AIM

The present study aimed to systematically review the available evidence on risk factors and musculoskeletal manifestations following viral infections and to propose a pertinent classification scheme.

METHODS

We searched the MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and SCOPUS for completed studies published before January 30, 2021, to evaluate risk factors as well as bone and joint manifestations of viral infection in animal models and patient registries. Quality assessment was performed using SYRCLE's risk of bias tool for animal studies, Moga score for case series, Wylde score for registry studies, and Newcastle-Ottawa Scale for Case-control papers.

RESULTS

Six human and four animal studies were eligible for inclusion in the qualitative synthesis. Hepatitis C Virus (HCV) was implicated in several peri- and postoperative complications in patients without cirrhosis after major orthopedic surgery. Herpes virus may affect the integrity of lumbar discs, whereas Ross River and Chikungunya Viruses exert a negative impact on bones and joints provoking viral arthritis and bone loss.

CONCLUSION

Evidence of moderate strength suggested that viruses can cause moderate to severe arthritis and osteitis. Risk factors such as pre-existing rheumatologic

disease contributed to higher disease severity and duration of symptoms. Based on our literature search, the proposed clinical and pathogenetic classification scheme is as follows: 1) Viral infections of bone and/or joint; 2) Active bone and joint inflammatory diseases secondary to viral infections in other organs or tissues; and 3) Viral infection as a risk factor for post-surgical bacterial infection.

Key Words: viral infection; musculoskeletal system; bone and joint manifestations; Chikungunya; Zika; Hepatitis C Virus; Herpesviridae; Ross River Virus; Cross-reactivity; classification

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Core Tip: Viral infections can include considerable orthopedic manifestations, thus resulting in significant distress. In addition, the outcome of orthopedic surgeries may be influenced by certain chronic viral infections such as hepatitis C virus. There is evidence of autoimmune-mediated mechanisms, immunosuppression, and perhaps direct viral infection provoking this, although the precise mechanisms have yet to be fully understood. In this review, a classification scheme was proposed, although further research is needed to completely unveil the relative contributions of the identified mechanisms as well as to develop novel preventative and treatment strategies.

INTRODUCTION

Fracture-related and periprosthetic joint infections (PJIs) represent dreadful complications of orthopedic surgery [1]. Although the impact of microbial infections has been well documented, the influence of viral infections on orthopedics might has been underestimated [2]. The potential cause of bone reaction due to viral infections was

firstly studied in 1962 by Marcowa [3] who histologically and radiographically evaluated tick-borne encephalitis virus inducing tibial osteitis in mice. Since then, evidence has suggested that viral agents, such as parvovirus B19, hepatitis B, and C virus, Human Immunodeficiency Virus (HIV), and alphavirus, cause viral arthritis with an estimated incidence of 1% out of all acute arthritides [4].

To elaborate further, an elevated risk of total hip arthroplasty (THA) revision has been documented in HIV patients 90 days post-procedure [5] whereas, sepsis, pneumonia, microbial joint infection, and revision surgery are more ubiquitous in HCV/HBV patients after total joint arthroplasty (TJA) [5]. What is more, orthopedic manifestations of Alphaviridae have been observed [6], with Chikungunya Virus (CHIKV), Ross River virus (RRV), and Sindbis virus being implicated and with viral ribonucleic acid (RNA) being present in joints months post-infection [6]. Flaviviridae are also relevant as arthralgia occurs in 23 - 80% of Zika virus infections [7]. A decrease in Alkanine Phosphatase (ALP) production by osteoblasts post-infection tends to delay their maturation [8].

Arthritis is a major pain generator in HIV patients and is mediated by premature degenerative joint disease through non-specific chronic synovitis and thickening of vessels' wall / tubuloreticular structures [9]. Bone degradation is enhanced by HIV through modifications of the sealing zone and increases in osteoclast-mediated bone resorption [10]. Parvovirus B19, a Deoxyribonucleic Acid (DNA) virus, can cause mono- or polyarthropathy with a preponderance towards adult female patients (80%) [11] and with a duration of symptoms varying from 2 mo to 4 years [11].

Furthermore, it could be possible to broadly classify the orthopedic manifestations of viral infections into three partially overlapping categories. To be more precise, manifestations can be provoked by the inflammatory response and/or direct infection during the acute phase of the illness. This could be the case in Flaviviridae members such as the Zika Virus and alphaviridae member Ross River Virus [7,8]. In addition, Chikungunya virus (CHIKV) perhaps causes orthopedic manifestations mainly *via* autoimmune mechanisms such as cross-reactivity [6]. Lastly, certain viral

infections could predispose to microbial infections due to immunosuppression. Examples would be HIV and HCV/HBV [5]. Of note, in the case of HIV, this was more commonly documented in the pre-highly-active antiretroviral therapy (HAART) era [5].

In this present systematic review (SR), we sought to systematically evaluate not only the risk factors for developing persistent arthritis after a viral infection but also the impact of viral infections on musculoskeletal clinical outcomes. Lastly, we sought to categorize the musculoskeletal manifestations of viral infections according to their causative mechanism and offer insight into novel treatment strategies.

MATERIALS AND METHODS

In this review, human and animal model studies exploring bone and joint manifestations secondary to human viral infections were considered. On the other hand, observational studies, papers not reporting clinical outcomes, rheumatological articles, and papers assessing patients less than 18 years of age were excluded. Moreover, case series with less than 10 subjects were discarded, to increase the validity and credibility of our reporting. We searched the MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and SCOPUS for completed studies published before January 30, 2021. We also considered the trial registries of ClinicalTrials.gov, EU clinical trial register, Australian New Zealand Clinical Trials Registry to search for completed yet unpublished studies. The search terms for MEDLINE were 'clinical trials', 'case series', 'viral infection', 'bone/joint'. KT and KS conducted the literature search independently without any language restrictions. Articles were deduplicated and examined for eligibility using title and article screening. Subsequently, a full-text evaluation of the remainder of the articles was performed. Any discrepancies between authors in the study selection procedure were resolved through discussion. KT and KS independently extracted relevant information from the included full-text articles, including any risk factors for persistent musculoskeletal manifestations.

Quality assessment

Two reviewers (KT and DK) assessed the quality of the included studies using the SYRCLE's risk of bias tool [12] for animal studies, Newcastle-Ottawa Scale for case-control studies [13], Wylde Score for Registry Studies [14], and Moga Score for case series [15]. For the included animal studies, the following domains were considered: sequence generation, baseline characteristics (sex, age, weight), allocation concealment, random housing, identical housing conditions, blinding of caregivers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, other bias (contamination, pooling drugs, influence of funders, units of analysis errors, design risk, new animals added for dropouts). Regarding case-control studies, we assessed the adequacy of case definition, representativeness, control selection and definition, comparability of cases and controls based on design analysis, ascertainment of exposure on the same method for both cases and controls, and non-response rates. For registry studies, we evaluated the following domains: consecutive patients, representativeness, percentage of follow-up, and minimization of potential confounding. In addition, we checked the quality of the included case studies against the 18-criteria checklist included in Moga score [15].

Outcome assessment

The primary outcome measure of the present systematic review was bone and joint manifestations after viral infections other than those associated with abnormal auto-immune response. The secondary outcomes included the impact of viruses on clinical features and secondly the study of any risk factors for developing persistent musculoskeletal manifestations following viral infections.

RESULTS

The literature search yielded 995 potentially relevant records. After the removal of duplicates, the remaining 985 articles were screened for eligibility. Following title and abstract evaluation, 84 articles were found to be eligible for inclusion. The full texts were then assessed, and 10 articles were included for systematic reviewing (Figure

1). Of those papers, two addressed treatment strategies and three dealt with arthroplasties in patients with HCV. Six papers involved human beings looking at Chikungunya, HCV, and Ross River viruses [16-25].

Quality Assessment

For the included animal studies, the domains of follow-up, minimization of potential confounding, representativeness, baseline characteristics (i.e. sex and age), other bias (i.e. contamination, pooling drugs, influence of funders, unit of analysis errors, design risk, new animals added for dropouts) and adequate definitions of cases, selection and definition of controls, ascertainment of the same exposure to control and cases, and comparability of cases and controls were considered to be at low risk of bias (Supplemental table 1). Moreover, the following domains were judged to be at unclear risk of bias: sequence generation, allocation concealment, random housing, blinding of caregivers, random outcome assessment, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting (Supplemental table 1). Furthermore, the domains of identical housing conditions were found to be at an unclear risk of bias (Supplemental table 1). Regarding the case control studies the Newcastle-Ottawa score was used and the only domain which was found to have an unclear risk of bias was the non-response rate for both included papers (Supplemental table 2). On the contrary, the adequacy and representativeness of cases as well as the selection and definition of controls had a low risk of bias (Supplemental table 2). Lastly, the comparability of cases and controls based on design, and the ascertainment of exposure, were deemed to be at a low risk of bias (Supplemental table 2). Following appraisal of the two included registry studies, representativeness was deemed to be adequate because the articles were multicenter in nature with sufficient follow-up (Supplemental table 3). Lastly, the case series of Alpantaki et al 2011 [25] and Soden et al 2000 [22] were evaluated by means of the Moga score (Supplemental table 4) with the former study reaching a sum of 13 and the latter achieving a sum of 10 (Supplemental table 4).

Arthroplasties and major orthopedic surgeries in patients with HCV infection

Three studies related to HCV infection were identified [18][19][20]. In particular, Best *et al* [18] published a retrospective cohort study in 2015 Looking at non-cirrhotic HCV patients subjected to total hip and knee arthroplasty. Half of the included cases referred to THA (ca. 50% males) and the rest patients to TKA (40% males) (Table 1). Likewise, Chowdhury et al published a retrospective study in 2017 to assess the effect of HCV infection 90 days after TKA and/or THA arthroplasty and/or spine surgery. This paper included 2,262 patients, half of whom were HCV positive (Table 1). What is more, Pour et al [20] investigated HCV-positive patients relative to matched controls in 2011 with a 1:2 ratio and included individuals who underwent THA and TKA from 1995-2006 in the US (Table 1). Risk factors in the article published by Best *et al* [18], included length of hospital stay (LOHS), age, gender, comorbidities, postoperative bleeding, thrombocytopenia, transfusion reaction, cardiac complications, respiratory, and renal complications as well as osteomyelitis, and infection. With regard to the article conducted by Chowdhury *et al* [19], age,race, readmission, and death within 30 or 90 days postoperatively were identified as risk factors (Table 1). Lastly, those identified by Pour et al [20] were age, gender, MBI, preoperative platelets, complication rate, and LOHS (Table 1). Best et al noted that patients from the HCV-positive group presented fewer comorbidities such as diabetes Mellitus, hypertension, cardiovascular disease, and osteoporosis as well as shorter length of hospital stay (5.3±3.4 compared with 5.4±5.1 days in the non-HCV group, P<0.001)[18]. In the above study, the overall complication rate was higher in the HCV group with prosthetic joint infection (OR was of 9.5 [95%CI 8.3 to 10.8], p<0.001)[18]. More specifically, acute renal failure and peripheral vascular complications showed an OR of 8 (95%CI 7.4 to 8.6, p<0.001) and 4.8 (95%CI 4.3 to 5.4, p<0.001), respectively[18]. It is underlined that stratification of the patients' cohort into THA and TKA revealed a significant difference in the comorbidities of these patients[18]. Other complications noted in the HCV group were deep venous thrombosis and pulmonary embolism, pneumonia, postoperative bleeding, and a higher blood transfusion rate[18]. Similar results were presented by Pour

et al.[20] who noted a statistically significant difference when the complications of revision hip or knee arthroplasty were compared between the two study groups ($p<0.05$)[20]. When comparing the results between the studies conducted by Best and Pour, the only distinct difference was the length of hospital stay [18,20]. Furthermore, Chowdhury et a reported higher readmission and mortality rates in the HCV group after THA, TKA, lumbar interbody fusion, decompression, and discectomy[19].

Orthopaedic manifestations induced by low-grade viruses

The role of a Herpes virus infection in intervertebral disc degeneration was studied by Alpantaki *et al* [25]. To be more precise, 16 consecutive patients (8 males) with a mean age of 40 years undergoing discectomy within six months of lumbar disc herniation were included. Those individuals constituted the study group, while two patients with thoracolumbar burst fractures formed the control group[25]. What is more, material from the herniated or fractured disc and peripheral blood samples were sampled intraoperatively. Polymerase chain reaction (PCR) was used to detect Herpesviridae DNA in 13 subjects of the study group[25]. Regarding blood samples, seropositivity of patients was assessed with IgM and IgG assays for HSV-1 and CMV[25]. Moreover, the surrounding tissues of the herniated disc were tested by qRT-PCR for mRNA levels of TNF-α and IL-6[25].Herpes Simplex Virus type-1 (HSV-1) DNA was detected in 9/16 subjects and Cytomegalovirus (CMV) DNA was found in 6 subjects while 2/16 subjects had a co-infection of both species[25]. On the contrary, DNA from HSV-2, Varicella-Zoster Virus, Epstein-Barr Virus, Human Herpes Virus 6,7, and 8 were not found in any participant and the control group tested negative for Herpesviridae DNA[25]. In addition, the IgG serological tests were positive in 13/16 subjects with PCR positivity for viral DNA, whereas all subjects were negative for IgM antibodies indicating the absence of an acute reaction at the time of surgical excision [25]. Furthermore, in the study group, the levels of IL-6 and TNF-a mRNA, were two to three times higher than that of the control group [25]. This is the only indication that herpes virus evokes disc herniation in individuals, regardless the age or sex [25].

Ross River Virus infection causes viral arthritis

We note that almost all Alphaviruses can cause joint manifestation. For instance, Ross River virus is detectable in the serum within 7-10 days after the initial symptoms with the synovial fluid infiltration by mononuclear cells being a common phenomenon throughout the disease. Soden *et al* [22] looked at synovial membrane biopsies of inflamed knees weeks after the initial symptoms of Ross River Virus infection (Table 2), whereas Chen *et al* studied the effects of the Ross River virus on human osteoblasts, bone loss in an established murine model, and viral arthralgia[16]. Soden *et al* [22] also utilized RT-PCR to detect viral RNA from synovial membrane biopsy samples and histologically evaluated with standard H&E staining, immunohistochemistry, and TRIzol treatment[22]. Chen *et al* included 21-day-old male and female C57BL/6 WT mice which were inoculated with 10^4 PFU Ross River Virus T48 strain (Table 2). This study replicated bone infection, and implemented µCT to assess bone loss in WT mice (Table 2). It also compared the RANKL/OPG levels in the serum of healthy and RRV infected individuals (Table 2). Soden et al [22], detected RRV RNA in the synovial membrane in 2 subjects 5 wk after the onset of symptoms, with almost all subjects presenting with detectable histological abnormalities including minor lining layer hyperplasia, vascular proliferation, and mononuclear cell infiltration[22]. This study proved that Ross River Virus affects joints by directly triggering an inflammatory reaction and is also detectable weeks after the initial symptoms[22]. Chen *et al* [16] detected high viral titers in the femur, tibia patella, and foot, mainly in osteoblastic bone cells [16]. Of note, high viral levels were detected until day 21 post-infection[16]. By day 15 post-infection µCT imaging showed clear bone loss in the tibial epiphysis, metatarsal joints, and vertebrae, accompanied with a decrease in trabecular thickness, along with a reduction in the growth plate[16]. By contrast, these findings were not noticed in the control group[16]. Lower osteoprotegerin (OPG) and higher RANKL levels were observed in the study group, while serum TRAP5b levels were also higher[16]. These findings indicate

increased osteoclastogenesis in humans similar to that observed in a murine model[16]. It is worthy of note that the Ross River virus also has a tropism for osteocytes[16].

Chikungunya Virus (CHIKV) evokes bone and joint manifestations

Four studies looking at Chikungunya alphavirus joint manifestations fulfilled our eligibility criteria (Table 3). More specifically, Chang *et al* recruited 907 clinically and laboratory-confirmed CHIKV-infected patients. Of those, 38 presented with chronic knee arthritis and were deemed eligible for selection. What is more, a control group with 10

location-matched individuals was considered (Table 3). Chen *et al* studied bone loss after CHIKV infection by recruiting 14 CHIKV patients (6 males) and a control group consisting of 7 healthy individuals (3 males) (Table 3). The second part of the experiment included 25 days old C57BL/6 mice infected with CHIKV- mCherry (Table 3). Goupil *et al* studied the bone and cartilage loss during CHIKV infection by employing two groups of mice featuring IRF 3/7 with deficient type 1 interferon response and adult wild-type C57BL/6. The study group consisted of 11 IRF mice and the control group of 9 C57BL/6 mice [24]. Hawman et al [17] studied the persistence of the viral RNA and its role on joints' pathology. Two groups of 3-week-old C57BL/6J WT mice and Rag1$^{-/-}$ with a lack of T and B cells were formed and a control group was also considered. Chang *et al* collected synovial fluid samples for viral culture and performed qRT-PCR and mass spectrometry for the detection/quantification of viral genome and proteins respectively (Table 3). Moreover, serum samples were analyzed for CRP, IgM, IgM-RF, anti-cyclic citrullinated peptide (anti-CCP), and selected cytokine and chemokine levels[23]. Chen *et al* collected serum from the 3rd to the 22nd post-infection week and compared the RANKL/OPG of the 14 CHIKV patients, and the 7 healthy participants. In the second part of the study, 25 days old C57BL/6 mice were infected with CHIKV- mCherry (20µl of 10^5 PFU at the ventral side of the foot), and a control group was injected with saline (Table 3)[21]. They were subsequently, followed up on the 1st, 3rd, 7^{th,} and 15th days post-infection[21]. Goupil *et al* injected IRF 3/7 mice with IFN-1

deficiency, and C56BL/6 WT mice, with $2x10^4$ PFU CHIKV SVO 476-96 at the caudoventral aspect of the hindfoot[24]. In addition, intact hindlimbs were collected from both groups and scanned via μCT to evaluate differences in the morphology of joints and the trabecular bones post-infection[24]. Furthermore, histopathological analysis was performed with hematoxylin and eosin and Mason's Trichrome staining[24]. Hawman *et al*[17] utilized CHIKV patients' serum to inoculate $Rag1^{-/-}$ mice which lacked T and B cells, as well as WT mice with CHIKV SL 15649 in the left rear footpad[17]. Viral titers were measured, and histopathological analysis was performed[17]. Chang et al found no evidence of viral infection or rheumatoid markers[23], and therefore it was concluded that either CHIKV is exclusively found in synovial tissue cells or it provokes arthritis through autoimmune mechanisms[23]. Chen et al found higher RANKL levels in the CHIKV patients and almost the same OPG levels (Table 3) in the CHIKV and control groups. This finding indicated an osteoclastic condition during the infection[21]. From a clinical examination point of view, edema was greatest on the 3rd day of CHIKV-mCherry mice follow-up, which eventually resolved by day 10[21]. Moreover, the pro-osteoclastic microenvironment was created early after the acute infection as the RANKL/OPG was elevated from day 1 and remained high thereafter [21]. In addition, CHIKV replicated in a murine bone and induced bone loss of 25% relative to uninfected mice[21]. The immune response resulted in arthritis on the 3rd post-infection day featuring elevated MCP-2/CCL8 and increased cellularity [21]. Goupil et al found that C57BL/6J mice on the 7th post-infection day suffered from moderate dermatitis/dermal edema, extensive degeneration/necrosis of skeletal muscles, minimal periostitis, mononuclear/neutrophilic synovitis, and equivocal cartilage necrosis[24]. On day 14 post-inoculation, mild to moderate dermatitis was observed, as well as extensive skeletal muscle degeneration/necrosis with early evidence of regeneration, extensive periostitis, and persistent synovitis with distal joint involvement[24]. On day 21 post-infection the following findings were documented: minimal/mild dermatitis, resolving necrosis/inflammation of muscles (immature fibrosis) extensive periostitis with periosteal bone proliferation, subacute lymphoplasmacytic synovitis, synovial

hypertrophy/fibrosis, and cartilage necrosis[24]. The tendons showed variable mild peritendonitis from day 7 and minimal myocyte necrosis in the contralateral feet [24]. When the IRF type mice were assessed by Goupil et al, the following findings were observed by the 4th-day post-infection: multifocal mild to moderate epidermic necrosis, mild neutrophilic dermatitis/edema, rare vascular necrosis, mild myofiber degeneration, periosteal necrosis, and minimal inflammation of tendons and cartilage[24]. At the same time, the synovium presented with multifocal degeneration/necrosis affecting a few joints. Subsequently, extensive synovitis in multiple joints was documented [24]. By day 7, worsening of those findings was observed with extensive epidermic necrosis, extensive vascular necrosis, moderate myofiber degeneration/necrosis, bone marrow and periosteum necrosis, articular cartilage necrosis, and fibrinosuppurative synovitis in the majority of joints[24]. The tendons only presented with mild inflammation[24]. It was concluded that the bone and joint manifestations were the result of acute viral infection rather than autoimmune-mediated[24]. Hawman *et al* [17] documented that viral inoculation of Rag1$^{-/-}$ mice that lacked T and B cells resulted in higher titers of the virus. In addition, the histopathological analysis presented more intense synovitis, arthritis, and tendonitis[17]. These findings support the notion that joint manifestations of CHIKV infection are the direct result of the infection rather than the host's immune system[17]. It should be noted that possible treatment strategies for CHIKV infection were proposed by authors of the included studies. I particular, Chen *et al* [21] used an inhibitor of monocyte chemoattractant protein (MCPs) (ie, Bindarit) twice daily intraperitoneally (100mg/kg) in mice which reduced joint swelling and bone loss but not viral titers[21]. Hawman *et al* on the other hand proved that tissue-specific administration of monoclonal antibodies reduced the viral RNA in these tissues[17]

DISCUSSION

It is an undeniable fact that a substantial, yet unclear impact on the musculoskeletal system is posed by viral infections. Most of the aspects have not been studied

sufficiently yet, mainly due to the lack of technological advancements until the 21st century. In light of the above, a systematic review was designed to delineate the risk factors and orthopedic clinical outcomes secondary to viral infections. More specifically, the effects of chronic HCV infection on TKA and THA, as well as the role of Herpesviridae on lumbar disc degeneration were addressed. Morevoer, the musculoskeletal effects of the Chikungunya virus and Ross River virus-mediated chronic arthritis were examined.

The impact of viruses on clinical musculoskeletal outcomes

HCV is a cause of arthritis not only due to cross/reactivity but also because of direct infection[26]. A higher level of postoperative complications and a higher mortality rate were noted in the HCV group despite the patients being younger and having lesser medical comorbidities[18]. Nevertheless, the hospitalization of HCV patients was shorter perhaps due to them being transferred to different units to get their complications addressed[18]. A possible explanation behind this would be the circulating autoantibodies leading to decreased lymphoproliferation. As a result of lymphoproliferation, predisposition to infection, leukocytoclastic vasculitis[27], and glomerulonephritis[27,28] develops. In addition to the above features of HCV patients, a hypercoagulability profile was observed[18]. It should be noted that HCV has been shown to induce thrombocytopenia and impaired platelet function[29,30,31], predisposing to higher rates of bleeding[18]. Pour *et al* also documented increased reoperation rates as well as higher number of mechanical complications and hospital stays in the HCV group [20]. To be more precise, complications included periprosthetic femoral fractures, femoral implant loosening and hip dislocation secondary to migration of acetabular implant that required a revision of the total hip arthroplasty[20]. Chronic HCV disease, on the other hand, was found to be associated with multiple extrahepatic manifestations such as diabetes mellitus and thyroiditis, thrombocytopenia, glomerulonephritis, inflammatory myositis, arthralgia, and mixed connective tissue disease, leukocytoclastic vasculitis, and lymphadenopathy. That can be attributed to circulating autoantibodies

that could alter the physiological process of healing[20]. In addition, low-key inflammation could alter the function of platelets, further compounding the pathophysiologic mechanism[20]. Another aspect which is worth mentioning is the potential difference in the socio-economic level of HCV-infected individuals and that of healthy participants[20]. Furthermore, ancillary liver effects were investigated by Chowdhury *et al*, and it was thought that they were implicated in immunosuppression and impaired wound healing[19]. These findings confirm the significance of HCV infection in post-operative outcomes and highlight the importance of including HCV testing in the preoperative workup.

Regarding the potential of Herpesviridae being a possible cause of disc degeneration, Alpantaki *et al* [25] studied 16 patients undergoing discectomy 6 mo after lumbar disc herniation who were thereafter subjected to Herpesviridae DNA testing[25]. Positivity for at least one species (most commonly HSV), was found in 13[25]. Possible mechanisms implicated in disc degeneration could be the vascular channels formed during fetal development that remain patent until the 4th-6th year of life, as well as migrating macrophages and retrograde axoplasmic transport[25]. However, it remains unclear whether degeneration is solely secondary to the upregulation of inflammatory cytokines, or whether viral-induced cell death could also contribute[32]. In addition, it has been postulated that Herpesvirus 6 could be a possible cause of Langerhans Histiocytosis[33]. This rare disease affecting children of 1 to 4 years of age has predominantly bone involvement and more often than not is the first presentation of the disease a pathological fracture[33].

What is more, CHIKV has a cyclical pattern of epidemics with the period from 7 to 20 years and affects countries neighboring the Indian Ocean, Central Africa, China, Italy, and France. After the transmission *via* mosquito bite, the virus multiplies locally and is then transferred to the whole of the host body *via* lymphoid organs and bloodstream. Mononuclear cell infiltration and viral replication in muscles and joints cause severe pain and arthritis. Although CHIKV infection is self-limited in nature, arthritis/arthralgia occurs for a particular amount of time as a result of the immune

response or due to the presence of an active viral reservoir in joints[34]. In 2018, a systematic review and meta-analysis with a total of 2415 individuals suffering from CHIKV infection in America revealed that 52% of the patients appeared persistent arthritis 10 to 72 wk after the primary infection[35]. It has been thought that arthritis may develop due to epigenetic modifications of macrophages which present a more aggressive cell behavior[36]. Another possible cause could be the concomitant presence of seronegative RA although this has been doubted by Chen *et al* Moreover, Chen *et al* noticed that Alfaviridae such as RRV could infect primary human osteoblasts and cause production of inflammatory cytokines, thus promoting osteoclastogenesis[37,38,39]. In addition, when analyzed with μCT it was clear that Alfaviridae could also lead to bone loss. Interestingly enough, following treatment with IL-6 inhibitors bone loss was blocked, thus highlighting the central role of inflammation in the pathogenesis[16]. It is important to be stressed through the impact of CHIVK-mediated arthritis as 82% of chronically infected patients present with arthritis that substantially impacts their quality of life[23].

The proposed clinical and pathogenetic viral infection classification system

In the current review, we have proposed a classification system connected to the pathogenesis of viral infection (Table 4 and Figure 2). Regarding the first proposed category addressing viral infections of bones and/or joints, we noted that the alphavirdae member RRV indeed replicated in murine bones[16]. To buttress this proposed mechanism further, we note that hOBs could be infected with RRV and produce inflammatory cytokines such as IL-6. In addition, in the inflamed knees of affected patients, RRV RNA was present 5 wk after the onset of symptoms [22]. However, some patients presented symptoms in the absence of detectable viruses [22] and this finding is partially congruent with the initial hypothesis that RRV provokes orthopedic manifestations through primary infection and inflammation [22].

As far as the second proposed category is concerned, active bone and joint inflammatory diseases occur secondary to viral infections in other organs or tissues.

CHIKV indeed causes arthralgia/arthritis without being directly detectable[23]. No evidence of it was found neither *via* RT-PCR, mass spectrometry, and culture of synovial fluid, thus agreeing with the initial hypothesis of it causing arthritis principally *via* cross-reactivity and suggesting immunomodulatory agents in its treatment[23]. To support the second proposed category further, productive infection of musculoskeletal cells was also reported by Chen et al [21]. On top of that, animal evidence presented by Hawman et al revealed persistent viral infection but safe extrapolations to human biology cannot be made based on this finding [19].

Lastly, the third proposed category included viral infection as a risk factor for post-surgical bacterial infection. To elaborate, we reported that HCV predisposes to immunosuppression[18] with associated increased post-surgical complications in HCV patients [19], in addition to compromised liver function and wound healing[19]. Pour *et al* confirmed this finding as wound complications requiring antibiotics/wound debridement were noticeably more common in HCV patients postsurgically[20].

Risk factors for chronic disease – The appearance of rheumatologic diseases

The persistence of viral genome or proteins into host cells could represent the major risk factor for chronic manifestations after the initial infection. However, no data are proving any association between Epstein-Barr and rheumatoid arthritis[40]. In the setting of CHIKV infection, joint manifestations resemble inflammatory arthropathies[41] and their severity depends on the levels of cytokines. We highlight that further studies should be performed to clarify that[42].

Study limitations and implications for future research

We recognize that the lack of a consistent definition of virus-induced rheumatoid arthritis as well as the high variety of musculoskeletal manifestations secondary to viral infections complicates the picture for clinicians and health policymakers. On top of that, the limited number of studies addressing the above issues and the uncertainty introduced by the moderate-to-low quality of evidence of the included articles further

contribute to this vagueness. It has been evidenced that some tropism for cells such as osteocytes, synovial cells, and chondrocytes exists. However, the involved mechanisms, the causes of persistent symptoms, and the pathophysiology of the infection/inflammation are yet to be determined. Towards this direction, we advocate that future research should aim for the development of novel treatment options based on the underlying mechanisms.

The role of COVID-19 on the musculoskeletal system

It is highlighted that all articles relating to COVID-19 were excluded due to the vast majority of them being based on expert opinions and observational studies with limited follow-up and sample size. However, some aspects of this pandemic should be commented on. To begin with, it is unknown whether the actual cause of orthopedic manifestations is the virus itself or the antiviral treatment. Osteoporosis and osteonecrosis are two common findings after COVID-19 infection but the potential role of corticosteroids administration as a part of the therapeutic regime cannot be overlooked[43]. Another clinical finding which is worth mentioning is the higher incidence of late (ie a few weeks following COVID-19 diagnosis) spinal epidural abscesses. This could be explained by patients' immunosuppression and/or the occurrence of nosocomial superinfection[44]. The binding of COVID-19 spike protein to functional receptors of ACE2 also expressed in human bone marrow, could also be a possible explanation not only for the decreased bone matrix but also for early muscle disorders[45]. Although the above considerations represent some early indications of the potential connection of COVID-19 with orthopedic clinical outcomes, we underline that a safe conclusion cannot be drawn given the limited available literature and considerable risk of bias.

CONCLUSION

Viral infections pose not only a major concern for microbiologists but also for orthopedic surgeons given the high incidence of chronic arthritis and its detrimental

effect on patients' quality of life[23]. While the literature on this topic was found to be sparse and heterogenous, the negative influence of viruses on orthopedic surgical outcomes is clear[18,19,20]. We highlight that arthralgia, myalgia, and transient arthritis could be the result of the viral infection itself or secondary immune processes although the contribution of each mechanism is still relatively unclear. We advocate that the present systematic review raises awareness of the implications of viral infections in orthopedics and acts as a guide for orthopedic surgeons to classify them in a clinical and pathogenetic fashion.

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1	Konstantinos Tsikopoulos, Konstantinos Sidiropoulos, Dimitrios Kitridis, Elizabeth Moulder et al. " Preventing stainless steel - associated infections in orthopedics. A systematic review and meta - analysis of animal literature ", Journal of Orthopaedic Research, 2021 Crossref	42 words — 1%
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7 Shrikant Tamhane, Rene Rodriguez-Gutierrez, Anoop Mohamed Iqbal, Larry J Prokop et al. "Cardiovascular and Metabolic Outcomes in Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis", The Journal of Clinical Endocrinology & Metabolism, 2018
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8 Brad A. Goupil, Margaret A. McNulty, Matthew J. Martin, Michael K. McCracken, Rebecca C. Christofferson, Christopher N. Mores. "Novel Lesions of Bones and Joints Associated with Chikungunya Virus Infection in Two Mouse Models of Disease: New Insights into Disease Pathogenesis", PLOS ONE, 2016
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