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SYSTEMATIC REVIEW

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The pandemic is gone but its consequences are here to stay: avascular necrosis following corticosteroids administration for severe COVID-19

Filippo Migliorini[1,2*], Nicola Maffulli[3,4,5], Tapish Shukla[6], Riccardo D'Ambrosi[7], Mohit Singla[8], Abhishek Vaish[6] and Raju Vaishya[6]

Abstract

Background In patients with COVID-19 infection and respiratory insufficiency, corticosteroid (CCS) administration is recommended. Among the wide range of complications and interactions, time-limited high-dose CCS administration might promote avascular necrosis (AVN) in a cumulative dose. This systematic review updated the current evidence and characterises the trend of AVN following time-limited high-dose CCS administration in patients who had severe COVID-19, discussing management strategies and outcomes.

Methods This systematic review was conducted according to the 2020 PRISMA statement. In October 2023, the following databases were accessed: PubMed, Web of Science, Google Scholar, and Scopus restricting the search to the years 2019 to 2023. All the clinical studies which investigated the association between time-limited high-dose CCS administration in patients with severe COVID-19 infection and AVN were accessed.

Results A total of 245 patients (9 studies) who experienced AVN following COVID-19 were included in the present investigation. 26% (63 of 245 included patients) were women. The mean age of the patients was 42.9 ± 17.7 years. Four studies focused on AVN of the hip and two on the knee, and the other studies included patients with AVN from mixed areas of the body (spine, pelvis, and shoulder). The mean time elapsed from COVID-19 infection to the development of symptomatic AVN was 79.4 ± 59.2 days (range, 14 to 166 days).

Conclusion It is possible that even time-limited high-dose CCS administration in patients with severe COVID-19 infection increased the incidence of AVN. The mean time elapsed from COVID-19 infection to the development of symptomatic AVN was approximately 80 days. Given the high risk of bias in all the included studies, the quality of recommendations of the present investigation is low, and no reliable conclusion can be inferred.

Keywords COVID-19, Steroids, Avascular necrosis, Osteonecrosis, Hip, Knee

*Correspondence:
Filippo Migliorini
migliorini.md@gmail.com
Full list of author information is available at the end of the article

Introduction

The Coronavirus disease-2019 (COVID-19) emerged in November 2019 in Wuhan, China, and was declared by the World Health Organisation (WHO) a pandemic a few months later [1, 2]. Other coronaviruses caused epidemics in the past decades, including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) [3, 4]. The COVID-19 pandemic imposed healthcare systems worldwide with new challenges and considerable organisational efforts [5–10]. Often far-reaching process changes, such as the management of patient flows, had to be implemented in everyday clinical practice within a very short period [11–15]. The management of COVID-19 is complex and, to date, no shared guidelines exist [16–18]. In patients with COVID-19 infection and respiratory insufficiency, corticosteroids (CCS) administration is recommended [19–21]. CCS administration is indicated in patients receiving oxygen therapy or invasive mechanical ventilation [22–25]. CCS immunomodulates the acute cytokine storm, which is pivotal in the management of COVID-19 [22, 24]. However, depending on the timing of administration, the immunomodulation promoted by CCS might be beneficial (if hyperactivation had already occurred) or detrimental in the case of early immune response inhibition [26–28]. No benefit of CCS administration has been demonstrated in patients with no critical symptoms [22, 29, 30]. However, CCS administration is associated with several complications, including immunodeficiency, diabetes, hypertension, obesity, and thromboembolism [31–33]. Given the high rate of CCS administration and the onset of related complications, the European Society of Endocrinology (ESE) has recently commissioned an urgent clinical guidance document on CCS administration in a COVID-19 period [34]. Among this wide range of complications and interactions, time-limited high-dose CCS administration might promote avascular necrosis (AVN) in a cumulative dose [35–37]. AVN is characterised by the refractory and progressive compromise of bone architecture and vascularisation, which leads to morphological remodelling, premature osteoarthritis (OA), persistent pain, and loss of function [38–42]. This systematic review updated current evidence and characterised the trend of AVN following time-limited high-dose CCS administration in patients who had severe COVID-19, investigating the time elapsed from COVID-19 infection and the development of symptomatic AVN, and discussing management strategies and related outcomes.

Methods

Eligibility criteria

All the clinical studies which investigated the association between time-limited high-dose CCS administration in patients with severe COVID-19 infection and AVN were accessed. According to the author's language capabilities, articles in English, German, Italian, French and Spanish were eligible. Studies with levels I to IV of evidence, according to the Oxford Centre of Evidence-Based Medicine [43], were considered. Posters, abstracts, comments, editorials, opinions, and reviews were not eligible. Only investigations which reported quantitative data on the association between time-limited high-dose CCS administration in patients with severe COVID-19 infection and AVN were eligible.

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the 2020 PRISMA statement [44]. The PICO algorithm was preliminarily set out:

- P (Problem): COVID-19 infection
- I (Intervention): time-limited high-dose CCS administration
- C (Comparison): AVN
- O (Outcomes): risk factors, incidence, management, outcome.

In October 2023, the following databases were accessed: PubMed, Web of Science, Google Scholar, and Scopus. The search was restricted to the years 2019 to 2023. The following keywords were used in combination using the Boolean operators AND/OR: *(COVID* OR *COVID-19* OR *pandemic)* AND *(avascular osteonecrosis* OR *aseptic osteonecrosis* OR *osteonecrosis)* AND *(pain* OR *outcome* OR *incidence* OR *prevalence* OR *symptoms)* AND *(steroids* OR *corticosteroids* OR *cortisone* OR *dexamethasone* OR *hydrocortisone* OR *prednisolone* OR *betamethasone).*

Selection and data collection

Two authors (FM & TS) independently performed the database search. All the resulting titles were screened, and if suitable, the abstract was accessed. The full text of the abstracts which matched the topic was accessed. The bibliography of the full-text articles was also screened for inclusion. Any disagreements were discussed and settled by a third senior author (NM).

Data items

Two authors (FM & TS) independently performed data extraction. Studies generalities (author, year, name of the journal, nature of the study design, and purpose of the study) and data on patient demographics (study size, number of women, and mean age of the patients) were retrieved. Data on the type of CCS, severity of infection, main conclusion, and the time elapsed from COVID-19 infection and the diagnosis of symptomatic AVN were collected.

Study risk of bias assessment

Two reviewers (TS & RDA) independently performed the methodological quality assessment of the extracted studies. Disagreements were solved by a third senior author (NM). The study risk of bias assessment was conducted in accordance with the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions [45]. The risk of bias of the software Review Manager 5.3 (The Nordic Cochrane Collaboration, Copenhagen) was used for Randomised Control Trials (RCTs). The Risk of Bias in Nonrandomised Studies of Interventions (ROBINS-I) tool was used for non-RCTs [46].

Statistical analysis

For descriptive statistics, the SPSS software version 25 (IBM, International Business Machines Corp, Armonk, US) was used.

Results

Study selection

A total of 1221 articles resulted from the literature search. Of them, 277 were duplicates. A further 757 articles were excluded for the reasons: no reported data on COVID-19 patients ($N=158$), no reported data on AVN ($N=571$), type of study ($N=178$), did not report quantitative data on the outcome of interest ($N=28$). Finally, 9 articles were included in the present study. The flow chart of the literature search is shown in Fig. 1.

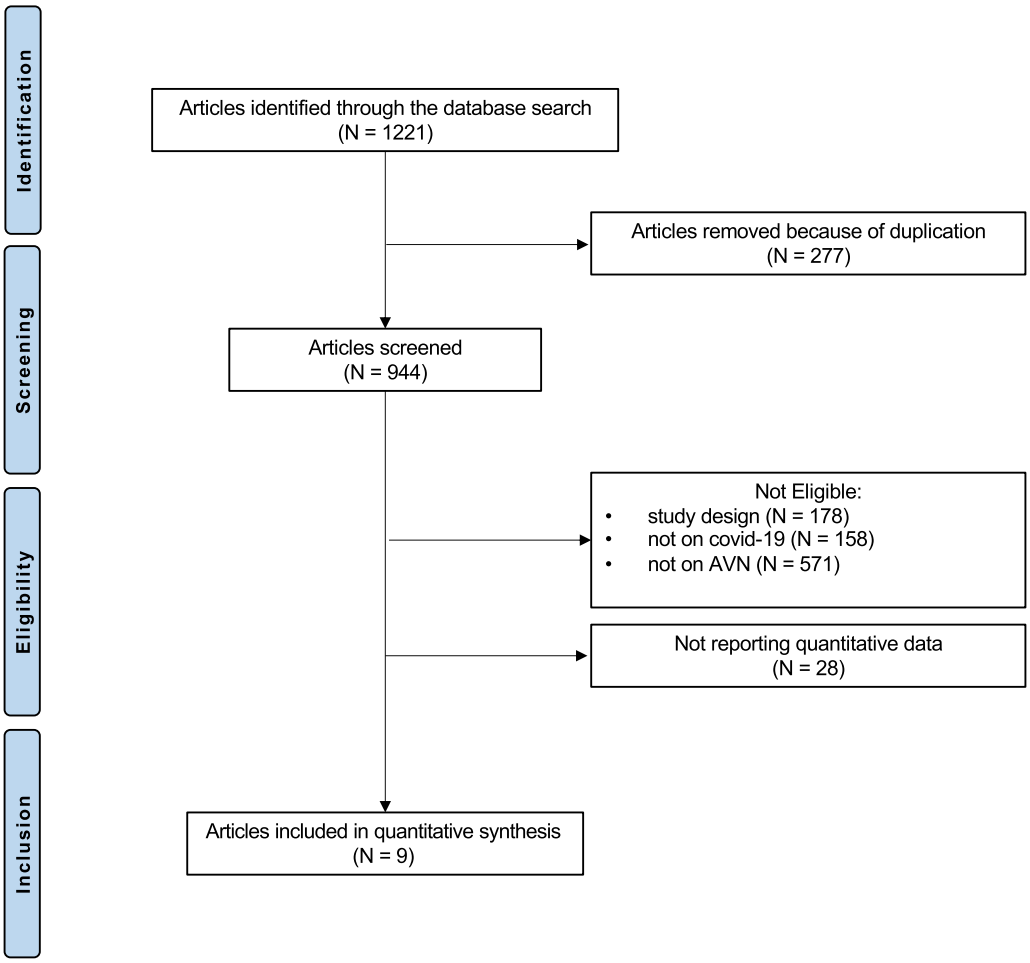

Fig. 1 Flow chart of the literature search

Study risk of bias assessment

The ROBINS-I score evidenced an overall high risk of bias. Most studies were retrospective case series and no RCT was available, with a high risk of selection, detection and performance biases. All the risks of bias investigated in the ROBINS-I score were serious and critical (Table 1).

Study characteristics and results of individual studies

A total of 245 patients who experienced AVN following COVID-19 were included in the present investigation. 26% (63 of 245 included patients) were women. The mean age of the patients was 42.9 ± 17.7 years. Four studies [50, 51, 53, 54], overall involving 228 patients, focused on AVN of the hip, and two studies (5 patients) [47, 48] focused exclusively on the knee. The other studies included patients with AVN deriving from mixed areas of the body (spine, pelvis, shoulder) [49, 52, 55]. Study generalities and data of the patients are shown in Table 2.

Table 3 reports the aims of the studies and the main results of the included studies. The mean time elapsed from COVID-19 infection to the development of symptomatic AVN was 79.4 ± 59.2 days (range, 14 to 166 days).

Discussion

According to the main findings of the present systematic review, there is evidence of increased incidence of AVN after the use of time-limited high-dose CCS therapy in patients with COVID-19 infection. The mean time

Table 1 ROBINS-I of the included studies

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall risk of bias judgement
Agarwala et al., [47]	Critical	Critical	Critical	Critical	Critical	Critical	Critical	Critical
Agarwala et al., [48]	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Alkindi et al., [49]	Critical	Serious	Serious	Critical	Critical	Critical	Critical	Critical
Chacko et al., [50]	Serious	Critical	Critical	Critical	Critical	Critical	Critical	Critical
Daltro et al., [51]	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Ghosh et al., [52]	Critical	Serious	Critical	Critical	Critical	Serious	Critical	Critical
Kachewar et al., [53]	Critical	Critical	Serious	Critical	Critical	Critical	Serious	Critical
Panin et al., [54]	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Sulewski et al., [55]	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious

Table 2 Generalities of the included studies (AVN: avascular necrosis; CCS: corticosteroids)

Author and year	Journal	Study design	Patients (*n*)	Joint	Female (%)	Age (mean)
Agarwala et al., [47]	BMJ Case Reports	Case reports	3	Knee	0	37
Agarwala et al., [48]	BMJ Case Reports	Case series	2	Knee	50	
Alkindi et al., [49]	European Medical Journal	Case report	1	Hip/knee	0	29
Chacko et al., [50]	International Journal of Research in Orthopaedics	Case report	1	Hip	0	23
Daltro et al., [51]	Journal of Regenerative Biology and Medicine	Case report	23	Hip	34	44
Ghosh et al., [52]	Indian Journal of Radiology and Imaging	Case reports	1	Spine/hip/pelvis	0	72
Kachewar et al., [53]	Indian Journal of Musculoskeletal Radiology	Retrospective	200	Hip	23	
Panin et al., [54]	Traumatology And Orthopaedics of Russia	Case series	4	Hip	50	34
Sulewski et al., [55]	Medicina	Case series	10	Spine/hip/pelvis/shoulder/knee	60	61

Table 3 Main findings of the included studies (AVN: avascular necrosis; CCS: corticosteroids; MRI: magnetic resonance imaging)

Author and year	Time to AVN (*days*)	Aim of the study	Main results of the study
Agarwala et al., [47]	49	To report early development of AVN in post-COVID patients	COVID-19-related treatment may induce AVN in approximately two months following the infection
Agarwala et al., [48]	73	To investigate the possible knee AVN as part of long COVID-19 syndrome	After COVID-19, patients are more susceptible to osteonecrosis. Bisphosphonates are effective in early stages of osteonecrosis of knee
Alkindi et al., [49]	166	To report the case of bilateral AVN of femoral heads and proximal tibias after 8 weeks after suffering from severe COVID-19	It is possible that AVN and reactive arthritis are directly linked to the COVID-19 and some superimposed exacerbated it
Chacko et al., [50]	56	To report a case of bilateral femoral head AVN in a post-COVID-19 male patient	There is an increased risk of osteonecrosis of femoral head in COVID-19 case due to hypercoagulability state associated with COVID-19
Daltro et al., [51]	133	To report a case of patient infected with COVID-19 who developed femoral head AVN	CCS and association of hypercoagulability mechanisms related to COVID-19 and AVN
Ghosh et al., [52]	30	To report a case of a man with COVID-19-associated vertebral, femoral and pelvic AVN	The findings are highly suggestive of COVID-19-associated AVN
Kachewar et al., [53]		To study the MRI images of COVID-19 infected patients for spectrum of femoral head AVN	6% incidence of AVN was seen in patients who developed hip pain after being treated for COVID-19
Panin et al., [54]	114	To report a series of patients treated COVID-19 with bilateral femoral heads AVN	Factors associated with COVID-19 and related treatment can influence the development of AVN
Sulewski et al., [55]	14	To report ten patients with AVN following COVID-19	COVID-19 can have a negative impact on bones at 1 to 3 weeks

elapsed from COVID-19 infection to the development of symptomatic AVN was approximately 80 days. Given the high risk of bias in all the included studies, the quality of recommendations of the present investigation is low, and no reliable conclusion can be inferred. However, after the 2003 SARS outbreak, up to 23% of patients receiving CCS developed AVN of the femoral head [56–58]; if the incidence of AVN peaks in these COVID-19 cases at those levels, a pandemic of AVN might happen, considering the massive outbreak of COVID-19 infection across the globe.

Several clinical investigations have explored the time-limited high-dose CCS administration in patients with COVID-19 infection receiving oxygen therapy or invasive mechanical ventilation (Table 4). However, no study reported cases of AVN among time-limited high-dose CCS-treated patients. On the other hand, we were able to identify for inclusion only articles with low levels of evidence in the present study. In this context, no high-quality recommendations can be inferred. Further, high-quality investigations and multi-centre studies are required to establish the actual incidence of AVN following time-limited high-dose CCS therapy in patients with COVID-19 infection.

Previous evidence demonstrated that the use of CCS and their association with AVN is related to cumulative dose [35, 72–74]. However, there is no consensus on their safety threshold. In a recent RCT, the administration of Dexamethasone 6 mg daily for 10 days (600 mg of cumulative dose) in COVID-19 patients was associated with a reduction of the need for mechanical ventilation and 28-day mortality [25, 61]. This dose regime is well below the cumulative dose thresholds described in much of the literature (cumulative dose of 2 g prednisone or its equivalent) [75, 76]. However, there is growing evidence that, if the clinical conditions deteriorate or patients are admitted to critical care, greater pulse doses of CCS (up to 125 mg per day) should be administered [77–80]. However, AVN has been reported even at much lower dose thresholds [81–83]. In a recent meta-analysis of 10 studies (1137 recovered patients with SARS) the risk of AVN was low if the cumulative dose of CCS (methylprednisolone) was $\leq$5 g. Greater cumulative doses of 5 g to 10 g were at high risk for AVN [84].

Osteonecrosis of the femoral head is the most common type of AVN. The management of this condition is challenging and controversial, with unpredictable results [85–87]. A recent systematic review of 88 articles (6112 procedures) evidenced that men, longer symptom duration, and greater pain were negative prognostic factors for AVN of the femoral head [88]. In the early phases of AVN of the femoral head, core decompression, percutaneous drilling and micro-drilling are performed to increase blood supply into the necrotic bone area [89]. However, their efficacy is limited [90, 91]. Core decompression augmented with bone marrow-derived

Table 4 Clinical investigations exploring the time-limited high-dose CCS administration in patients with COVID-19 infection receiving oxygen therapy or invasive mechanical ventilation

Author, year	Country	Journal	Study Design	Sample Size	Treatment
Galvez-Romero et al. [59]	Mexico	*J Intern Med*	Open-label, non-RCT	209	Methylprednisolone or Prednisone
Fernández-Cruz et al. [60]	Spain	*Antimicrob Agents Chemother*	Retrospective, controlled	463	Methylprednisolone
Horby et al. [61]	United Kingdom	*N Engl J Med*	Prospective, controlled, open-label	6425	Dexamethasone
Keller et al. [62]	USA	*J Hosp Med*	Retrospective	1806	Glucocorticoids (not specified)
Mikulska et al. [63]	Italy	*PLoS One*	Retrospective	196	Methylprednisolone
Murohashi et al. [64]	Japan	*Respir Investig*	Retrospective	11	Methylprednisolone
Obata et al. [65]	America	*Jpn J Infect Dis Action Epub*	Retrospective	226	Dexamethasone, Prednisolone
Rana et al. [66]	Pakistan	*Cureus*	Retrospective	60	Dexamethasone or Methylprednisolone
Rodríguez-Molinero et al. [67]	Spain	*Med Clin (Barc)*	Retrospective	418	Methylprednisolone
Spagnuolo et al. [68]	Italy	*Sci Rep*	Retrospective	280	Methylprednisolone
Xiaofan Lu et al. [69]	China	*N Engl J Med*	Retrospective	244	Hydrocortisone
Yan et al. [70]	China	*Biomed Pharmacother*	Retrospective	308	Methylprednisolone
Zhu et al. [71]	China	*World J Clin Cases*	Retrospective	102	Methylprednisolone

The analysis included 13 articles for a total of 10,748 patients treated with steroids for COVID-19. Eleven studies were retrospective, one open-label non-RCT, and one prospective controlled, open-label trial. The steroids used varied from Dexamethasone, Prednisone, or Methylprednisolone. No case of AVN among time-limited high-dose CCS-treated patients was reported

mesenchymal stem cells has been proposed to improve the bone healing activity [92–106]. In a recent meta-analysis of 7 RCTs (579 patients), core decompression combined with bone marrow mesenchymal stem cells showed a lower rate of total hip arthroplasty compared to core decompression in isolation [107]. Additional hip preserving strategies include non-vascularized/vascularized autograft/allograft/synthetic bone grafting, high femoral osteotomies, and drug administration (i.e. bisphosphonates) [108–115]. A recent Bayesian network meta-analysis of 32 clinical trials (2367 procedures) compared several conservative and operative strategies [116]. Conservative management and isolated core decompression were associated with the lowest success rate [116]. Core decompression combined with autologous bone grafting and enhanced with bone marrow concentrate was effective in reducing the rate of failure and progression to hip arthroplasty [116]. Despite these surgical options, AVN of the femoral head often progresses to subchondral fractures, femoral head collapse, and painful OA [117–120]. In those patients, total hip arthroplasty is considered the last resort in the management of AVN [121].

We acknowledge several limitations of this study. Given the high risk of bias in all the included studies, the quality of recommendations of the present investigation is low, and no definite conclusions can be inferred. Given the lack of information on administration protocol and timing of CCS, additional subgroup analyses were not performed. In one included study, only 6% of the entire cohort of patients who had severe COVID-19 developed AVN following time-limited high-dose CCS administration [53]. The definition of severe COVID was not clearly stated in most articles, which poses limits to properly defining the study population. The current literature will benefit future high-quality investigations. Most studies were case reports, with a limited number of patients and not using validated patient-reported outcome measures (PROMs). The surgical procedures and rehabilitation protocols were also biased in most studies, as were general health measures. COVID-19-associated therapies and severity, comorbidities and patient characteristics were also seldom described in most studies. Most patients affected by AVN are young and active, which makes the management of such a potentially devastating condition troublesome. The current treatment strategies are limited, with unpredictable results; despite some new treatment modalities having been introduced with promising results [122, 123], prevention, early diagnosis, and early treatment remain the way to manage AVN. The type of CCS used to manage respiratory insufficiency and the severity of the COVID-19 infection were not reported by most authors. Moreover, the severity and progression of AVN were not classified using validated

classification, such as the Association Research Circulation Osseous (ARCO) for the femoral head.

Conclusion

Some evidence supports that even time-limited high-dose CCS administration in patients with COVID-19 infection increased the incidence of AVN. The mean time elapsed from COVID-19 infection to the development of symptomatic AVN was approximately of 80 days. Given the high risk of bias in all the included studies, the quality of recommendations of the present investigation is low, and no reliable conclusion can be inferred.

Abbreviations

AVN	Avascular necrosis
OA	Osteoarthritis
CCS	Corticosteroids
PROMs	Patients-reported outcome measures
ARCO	Association Research Circulation Osseous

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None.

Author contributions

M was involved in conception and design, literature search and data extraction, interpretation of the data, and drafting; NM contributed to supervision and revision; TS contributed to literature search and data extraction, methodological quality assessment; RDA contributed to methodological quality assessment; AV contributed to supervision; MS contributed to supervision; RV contributed to revision and supervision. All authors have agreed to the final version to be published and agree to be accountable for all aspects of the work.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available throughout the manuscript.

Declarations

Ethics approval and consent to participate

This study complies with ethical standards.

Consent to publication

Not applicable.

Competing interests

The authors declare that they have any competing interests for this article.

Author details

[1]Department of Orthopaedic, Trauma, and Reconstructive Surgery, RWTH University Hospital, Pauwelsstraße 30, 52074 Aachen, Germany. [2]Department of Orthopedics and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), Teaching Hospital of the Paracelsus Medical University, 39100 Bolzano, Italy. [3]Department of Medicine and Psychology, University of Rome "La Sapienza", Rome, Italy. [4]Faculty of Medicine, School of Pharmacy and Bioengineering, Keele University, Stoke on Trent ST4 7QB, England. [5]Barts and the London School of Medicine and Dentistry, Centre for Sports and Exercise Medicine, Mile End Hospital, Queen Mary University of London, London E1 4DG, England. [6]Department of Orthopaedics and Joint Replacement Surgery, Indraprastha Apollo Hospitals Institutes of Orthopaedics, New Delhi 110076, India. [7]Department of Orthopaedics, IRCCS Istituto Ortopedico Galeazzi, 20161 Milan, Italy. [8]Department of Orthopedics, PGIMS, Rohtak, Haryana 124001, India.

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