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ORIGINAL ARTICLE

Risk factors for multi-joint disease in patients with glucocorticoid-induced osteonecrosis

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Abstract

Summary This study investigated risk factors for osteonecrosis involving multiple joints (MJON) among glucocorticoid-treated patients. The best predictor of MJON was cumulative oral glucocorticoid dose. Risk of MJON was 12-fold higher in patients who had a second risk factor for osteonecrosis. Further research is needed into strategies for prevention of MJON.

Introduction Osteonecrosis (ON) is a debilitating musculoskeletal condition in which bone cell death can lead to mechanical failure. When multiple joints are affected, pain and disability are compounded. Glucocorticoid treatment is one of the most common predisposing factors for ON. This study investigated risk factors for ON involving multiple joints (MJON) among glucocorticoid-treated patients.

Methods Fifty-five adults with glucocorticoid-induced ON were prospectively enrolled. MJON was defined as ON in ≥ three joints. Route, dose, duration, and timing of glucocorticoid treatment were assessed.

Results Mean age of enrolled subjects was 44 years, 58% were women. Half had underlying conditions associated with increased ON risk: systemic lupus erythematosus (29%), acute lymphoblastic leukemia (11%), HIV (9%), and alcohol use (4%). Mean daily oral dose of glucocorticoids was 29 mg. Average cumulative oral dose was 30 g over 5 years. The best predictor of MJON was cumulative oral glucocorticoid dose. For each increase of 1,000 mg, risk of MJON increased by 3.2% (95% CI 1.03, 1.67). Glucocorticoid exposure in the first 6 months of therapy, peak dose (oral or IV), and mean daily dose did not independently increase risk of MJON. The risk of MJON was 12-fold in patients who had a second risk factor (95% CI 3.2, 44.4).

Conclusions Among patients with glucocorticoid-induced ON, cumulative oral dose was the best predictor of multi-joint disease; initial doses of IV and oral glucocorticoids did not independently increase risk. Further research is needed to better define optimal strategies for prevention and treatment of MJON.

Keywords Glucocorticoids · Hematologic malignancies · Osteonecrosis · Systemic lupus erythematosus

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Introduction

Osteonecrosis (ON) is a debilitating condition that commonly affects young and middle-aged adults [1]. The disease is characterized by bone cell death that can result in mechanical failure, ultimately necessitating joint replacement [1–5]. ON most frequently develops at the femoral head [4] and accounts for approximately 10% of the total hip arthroplasties performed in the USA annually [6]. However, many other sites are often affected, including the knee, shoulder, and ankle [7, 8].

While glucocorticoids provide systemic relief for over 2 million adults in the USA [9], there are many adverse consequences of glucocorticoid treatment. Exposure to glucocorticoids is the most common risk factor for non-traumatic ON [4, 7, 8, 10, 11]. It has been reported that ON develops in 5–52% of patients receiving long-term glucocorticoid therapy [4, 12] and may also occur with short-term exposure [4, 13, 14]. The association between glucocorticoid use and the development of ON has been well-documented [7, 8, 15, 16]; however, the pathogenesis is poorly understood.

ON that occurs from systemic exposure to glucocorticoids often affects multiple anatomical locations. Patients with ON at multiple sites have increased pain and disability [17]. It remains unclear whether certain aspects of glucocorticoid treatment pose a greater risk for development of ON at multiple sites [7, 18, 19]. In particular, whether the greatest risk relates to glucocorticoid route, dose, duration, and initial or cumulative exposure is unknown. Identifying the specific risk factors for glucocorticoid-induced ON, and for multi-joint disease, may inform treatment regimen and ultimately aid in preventing multi-joint disease and its attendant morbidity.

The goal of this study was to investigate the risk factors for multi-joint disease in a cohort of patients with glucocorticoid-induced ON. Specifically, we studied which factors of glucocorticoid therapy, including route, dose, and duration, pose the highest risk for developing multi-joint ON (MJON). We further investigated which clinical conditions contribute to the risk of glucocorticoid-induced MJON. We hypothesized that a higher cumulative glucocorticoid dose would be the greatest risk factor for the development of MJON.

Methods

We prospectively enrolled adult patients with symptomatic ON who received care at either the Hospital for Special Surgery (HSS) or New York Presbyterian Hospital/Weill Cornell Medical Center (WCMC) between July 2018 and March 2020. Patients were consecutively screened and approached for enrollment in this cross-sectional study. Eligibility criteria included glucocorticoid exposure, as defined below, and clinically diagnosed ON. Patients were categorized as having glucocorticoid-induced ON if they began oral or intravenous glucocorticoid therapy at least 6 months prior to diagnosis of ON. Clinical diagnosis of ON was confirmed by review of medical records including radiographs and magnetic resonance imaging. MJON was defined as ON in three or more joints. This categorization was utilized to reflect a severe clinical picture and high degree of associated disability. The HSS and WCMC Institutional Review Boards approved this study. All subjects provided written informed consent.

Clinical data collection

Medical history was assessed by self-report at the study visit and confirmed by chart review. Demographic data, including age, sex, body mass index (BMI), comorbidities, and social history, was obtained. Social history included alcohol and tobacco use. Alcohol consumption was quantified as daily alcoholic drinks. Patients were further categorized according to consumption of > or < 400 ml/week (320 g/week), the threshold amount associated with ON in prior work [20, 21]. All surgical and medical interventions for ON were recorded. With the exception of glucocorticoids, only medications taken at the time of the study visit were recorded.

Glucocorticoid data collection

History of glucocorticoid use was comprehensively ascertained through review of patient reports and medication logs, office notes, follow-up communication with physicians, and procedure notes for glucocorticoid injections. When details of glucocorticoid therapy were unknown to the patient and not recorded in the electronic medical records at HSS or WCMC, patients were asked to sign a HIPAA compliant authorization for release of health information in order to obtain records regarding glucocorticoid therapy received at other institutions. Historical glucocorticoid data was obtained from the point of glucocorticoid initiation through the time of the study visit permitting full capture of exposure that may have related to multiple occurrences of ON. Total cumulative dose, average dose, peak dose, and duration were calculated separately for the following glucocorticoid routes: oral, intravenous (IV), epidural or intrathecal, intra-articular injection, and inhaled. Further, for intra-articular glucocorticoid injections, calculations were stratified by injection site. Glucocorticoid exposure in the initial 6 months through oral or IV was also separately computed. All doses were converted to prednisone equivalents.

Statistical analysis

Patient clinical characteristics, glucocorticoid exposure, and duration of glucocorticoid treatment were summarized with

means ± standard deviations, or medians and interquartile ranges, for continuous variables or counts (percent of sample) for categorical variables. Subgroup differences in average daily, peak, and cumulative dose and number of days of exposure were evaluated with *T* tests, while subgroup differences in categorized glucocorticoid exposure variables were tested with either Chi-square or Fisher's exact test. Spearman correlation was used for the association between exposure variables and number of MJON sites. Risk factors for bivariate-coded multi-joint osteonecrosis were identified with logistic regression. All statistical evaluations used SAS STAT 13.2 (SAS Institute, Cary, NC).

Results

Fifty-five patients with a history of glucocorticoid-induced ON were enrolled in this study. Demographic characteristics of the cohort are summarized in Table 1. The mean age was 44 ± 17 years. More than half of the patients were women (58%), and the majority was either Caucasian (49%) or Black or African American (33%). Mean BMI was 28 ± 9 kg/m^2. Twenty patients (36%) had MJON, and the remainder had ON involving fewer than 3 joints (non-MJON). The median duration from initial diagnosis of ON to the confirmed presence of MJON was less than 2 years. Caucasian patients were less likely to have MJON. There was no difference in the use of statins, aspirin, anticoagulants, or hydroxychloroquine among the two groups.

Location of ON

The 55 patients enrolled had a total of 136 joints with ON. The average number of joints with ON per patient was 2.5 (range 1 to 6). The most common location of ON was the hip (66%). Other sites included the knee (femoral condyles and proximal tibia), shoulder, and ankle. The majority of patients had ON at more than one site, with 36% having MJON. Bilateral involvement of an anatomic site was common. Of the patients who had ON at more than one site, 51% had bilateral hip, 9% bilateral hip and knee, and 4% bilateral knee. Further, 6% of patients had ON at the hip, knee and shoulder.

Table 1 Clinical characteristics of study subjects.

Characteristics	Total (*N* = 55) Median (IQR), *n* (%)	MJON (*N* = 20) Median (IQR), *n* (%)	Non-MJON (*N* = 35) Median (IQR), *n* (%)	*ρ* value
Age	43 (30–57)	31 (27–58)	45 (39–55)	0.12
BMI (kg/m^2)	26 (22–32)	25 (21–33)	27 (23–30)	0.31
Sex				0.18
Female	32 (58%)	14 (70%)	18 (51%)	
Male	23 (42%)	6 (30%)	17 (49%)	
Race				0.002*
Asian	5 (9%)	2 (10%)	3 (9%)	
Black or African American	18 (33%)	8 (40%)	10 (29%)	
Caucasian	27 (49%)	5 (25%)	22 (63%)	
Other	5 (9%)	5 (25%)	0 (0%)	
Ethnicity				0.73
Hispanic	11 (20%)	5 (25%)	6 (17%)	
Non-Hispanic	44 (80%)	15 (75%)	29 (83%)	
Social history				
Any alcohol use	49 (89%)	17 (85%)	32 (91%)	0.89
Alcohol (g/week)	14 (1-56)	12 (3-28)	14 (2-56)	0.27
Current smoker	2 (4%)	1 (5%)	1 (3%)	1.00
Former smoker	18 (33%)	3 (15%)	15 (43%)	0.07
Primary indication for glucocorticoids				
Rheumatologic Disease	25 (45%)	11 (55%)	14 (40%)	0.43
Malignancy	9 (16%)	6 (30%)	3 (9%)	0.09
Pulmonary Disease	7 (13%)	1 (5%)	6 (17%)	0.38
Other	14 (26%)	2 (10%)	12 (34%)	0.08

*p value ≤ 0.05 for comparison of MJON to non-MJON

Management of ON

The majority of patients (73%) had at least one surgical intervention for ON. Out of the 62 primary procedures performed, 87% involved the hip and 13% the knee. None of the patients had surgery at the shoulder or ankle for ON. Of the 90 femoral heads with ON, 57% was managed surgically with either total hip arthroplasty (THA; 43%) or with a more conservative approach such as a core decompression or fibular graft (14%). Of the femoral heads initially treated with a core decompression or fibular graft, 39% progressed and ultimately underwent THA at an average of 6 years later. A third of the cohort (31%) was medically managed with bisphosphonates.

Clinical risk factors

Clinical risk factors for ON were evaluated in the entire cohort and compared in patients with and without MJON. The most common indications for glucocorticoid treatment in the total cohort are rheumatologic disease (45%), malignancy (16%), and pulmonary disease (13%) (Table 1). In many patients, the underlying condition for which they received glucocorticoids was also known to be associated with an increased risk of ON. These included systemic lupus erythematosus (SLE), hematologic malignancy [acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma], and human immunodeficiency virus (HIV). Other risk factors for ON, in addition to GC use, included a history of alcohol consumption > 320 g/week and a previous deep vein thrombosis (DVT) (Table 2). Only two patients had anti-phospholipid syndrome. No patient had a diagnosis of sickle cell disease or previous radiation therapy.

Glucocorticoid exposure

History of glucocorticoid exposure categorized by route of administration in patients with or without MJON is summarized in Table 3. The mean daily dose of oral glucocorticoids was 29 mg (median 17 mg). The majority (78%) of patients had received daily doses greater than 20 mg, and almost one-quarter (24%) received doses greater than 80 mg. The average cumulative oral dose of prednisone was 29,847 mg (median 15,925 mg) over a span of 5.4 years.

All patients had a history of oral glucocorticoid use except for one who only had IV exposure. All patients with inhaled, intra-articular, epidural, or intrathecal glucocorticoid injection also had oral glucocorticoid exposure. Half of the patients had a history of IV glucocorticoid use. Inhaled glucocorticoids were used by 42% of the total cohort. Moreover, almost half of the patients (44%) had received intra-articular injections. The most common site of injection was the hip. No patient had more than two injections at each hip. One-quarter of patients had also received an epidural or intrathecal spinal glucocorticoid injection.

Predictors of MJON

A higher cumulative dose (r = 0.38, $p < 0.008$) and a longer duration of oral glucocorticoid use (r = 0.28, $p < 0.05$) were associated with an increased risk of MJON. Cumulative oral glucocorticoid dose is the best predictor of MJON (Fig. 1). For each additional increase of 1000 mg in oral cumulative dose, the risk of MJON increased by 3.2% (95% CI = 1.03, 1.67). Oral or IV glucocorticoid exposure in the first 6 months did not independently increase the risk of multi-joint disease. There was no relationship between the total number of locations of ON and IV glucocorticoid factors or glucocorticoid injections. The use of inhaled glucocorticoids was greater in those with MJON ($p < 0.05$).

The presence of a second risk factor, in addition to glucocorticoids, was a strong predictor of MJON. The risk of MJON was 12-fold in patients who had a second risk factor (95% CI = 3.2, 44.4; $p < 0.0003$). In particular, certain underlying conditions, SLE (OR = 6.7; 95% CI = 1.7, 26.5; $p < 0.007$), and hematologic malignancies (OR = 15.6; 95% CI = 2.4, 100.7; $p < 0.004$) were independent risk factors for MJON. We did not find an association between sex, age, and race and increased risk of MJON.

Table 2 Secondary risk factors in patients with glucocorticoid-induced osteonecrosis and multi-joint osteonecrosis

Secondary risk factor	Total ($N = 55$) n (%)	MJON ($N = 20$) n (%)	Non-MJON ($N = 35$) n (%)	ρ value
Systemic lupus erythematosus	16 (29%)	9 (45%)	7 (20%)	0.05*
Hematologic malignancy	8 (14%)	6 (30%)	2 (6%)	0.04*
Human immunodeficiency virus	5 (9%)	1 (5%)	4 (11%)	0.76
Alcohol consumption > 320 g/week	2 (4%)	0 (0%)	2 (6%)	0.73
Deep vein thrombosis	8 (23%)	2 (10%)	6 (17%)	0.75

*p value ≤ 0.05 for comparison of MJON to non-MJON

Table 3 Glucocorticoid exposure in patients with glucocorticoid-induced osteonecrosis

Route	Total ($N = 55$) Median (IQR), n (%)	MJON ($N = 20$) Median (IQR), n (%)	Non-MJON ($N = 35$) Median (IQR), n (%)	ρ value
Oral[a]	54 (98%)	20 (100%)	34 (97%)	1.00
Cumulative dose (mg)	15,925 (3650–48,310)	37,947 (20,360–52,257)	5,755 (1888–24,182)	0.0008*
Average dose (mg)	17 (13–32)	17 (11–38)	18 (13–29)	0.45
Peak dose (mg)	60 (40–100)	60 (40-120)	60 (40–80)	0.45
Duration (d)	300 (90–3,746)	3,457 (229–4,285)	183 (54–1,120)	0.02*
IV[a]	27 (49%)	12 (60%)	15 (43%)	0.30
Cumulative dose (mg)	1520 (100–6177)	2400 (188-6177)	1520 (80–5000)	0.86
Average dose (mg)	80 (32–219)	94 (32–129)	80 (40–267)	0.86
Peak dose (mg)	89 (50–313)	125 (50–267)	80 (53–1000)	0.32
Number	12 (4-28)	14 (7-32)	7 (4-28)	0.33
Intra-articular	24 (44%)	9 (45%)	15 (43%)	1.00
Right hip	15 (27%)	5 (25%)	10 (29%)	1.00
Left hip	11 (20%)	4 (20%)	7 (20%)	1.00
Right knee	5 (9%)	3 (15%)	2 (6%)	0.51
Left knee	4 (7%)	3 (15%)	1 (3%)	0.26
Right shoulder	3 (5%)	1 (5%)	2 (6%)	1.00
Left shoulder	1 (2%)	1 (5%)	0 (0%)	0.77
Right ankle	1 (2%)	0 (0%)	1 (3%)	1.00
Left ankle	3 (5%)	1 (5%)	2 (6%)	1.00
Inhaled	23 (42%)	4 (20%)	19 (54%)	0.03*
Epidural/intrathecal	14 (25%)	3 (15%)	11 (31%)	0.31

[a] All doses are reported as prednisone equivalents. *p value ≤ 0.05 for comparison of MJON to non-MJON

Sex differences in ON

While we did not find sex differences in the prevalence of MJON, glucocorticoid exposure prior to the development of ON differed substantially among men and women. Men who developed glucocorticoid-induced ON had one-sixth of the cumulative exposure of women (7,000 mg in men vs 43,000 mg in women; $p < 0.0001$). Men also had a substantially shorter duration of therapy (6 months in men vs 9 years in women; $p < 0.0001$). There were no differences in exposure to glucocorticoid injections between men and women. There were no significant differences in age, BMI, alcohol consumption, and smoking history. Hematologic malignancies were more common in men; patients with SLE were all female, There were no differences in other underlying conditions or associated medication use according to sex. Since patients with SLE were all women, these analyses were repeated after exclusion of those with SLE. Sex differences remained significant, with substantially lower cumulative dose and shorter duration of therapy in men with MJON.

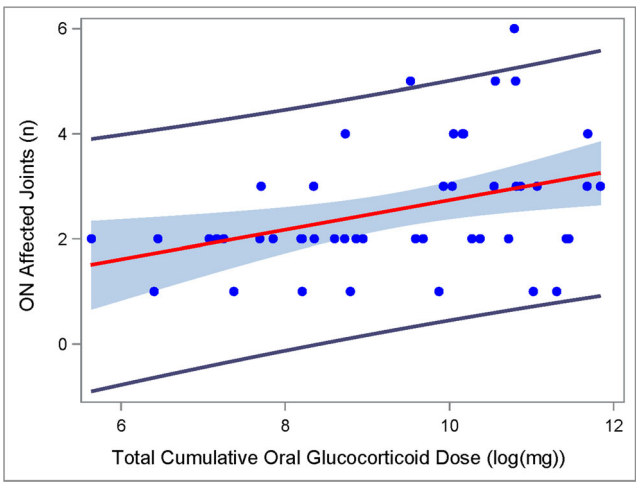

Fig. 1 Cumulative oral glucocorticoid dose (natural log) and prediction of multi-joint osteonecrosis. Shaded areas represent the 95% confidence interval

Discussion

While glucocorticoid exposure is a well-recognized risk factor for ON, the majority of patients who receive glucocorticoids do not develop ON. The patient-specific factors and features of glucocorticoid treatment that most increase the risk of ON are not well-understood. Our study highlights the underlying

factors most associated with increased risk of MJON among patients treated with glucocorticoids. We found that patients who received the greatest cumulative oral glucocorticoid dose had the highest risk of developing MJON. Further, patients with underlying hematologic malignancy and SLE were at markedly increased risk. This may be due to the disease processes themselves, as well as combined effects of medications other than glucocorticoids commonly used to treat these patients. Caucasian patients were at lower risk for MJON. This finding may be due to many factors including comorbidities and racial disparities in access to healthcare fostering earlier detection of disease in Caucasian patients. Our data further suggests that the threshold glucocorticoid exposure for the development of ON may be lower in men.

While the exact pathogenic mechanisms by which glucocorticoids may induce ON remain unclear, the process is most likely multifactorial. Plausible mechanisms include abnormal lipid distribution with resultant microemboli [22, 23], osteocyte apoptosis [22, 23], prolongation of osteoclast lifespan [11], endothelial cell damage resulting in hypercoagulability [11, 23], and inhibition of angiogenesis [11]. In addition to metabolic factors and local environmental effects, genetic predisposition may also play a role in the development of glucocorticoid-induced ON [23, 24]. As a result of cumulative stress resulting from perturbations in these pathways, damage to bone cells cannot be repaired, resulting in necrosis [23]. A higher cumulative oral dose may pose the greatest risk for multi-joint disease, because it represents a prolonged constant insult from which the bone cells cannot recover.

Our findings suggest that higher cumulative dose of oral steroids poses the greatest risk for the development of ON at multiple joints. The amount of detail (i.e., dosage, route, and duration of glucocorticoid treatment) that we captured relating to glucocorticoid exposure in our cohort allowed us to extend the finding of those studies and specifically delineate those features of glucocorticoid exposure that conferred the greatest risk of MJON. To our knowledge, this has not been done in prior work. We found that cumulative oral dose was the strongest predictor. Duration of therapy with oral glucocorticoids was also closely related to risk. We did not observe a relationship between IV dose or number of IV doses and the risk of MJON. This may relate to the fact that the oral exposure for patients in our cohort was far greater than the IV. Prior studies have not compared the contributions of different routes of glucocorticoid administration to risk. We did not find that intra-articular injections or epidural/intrathecal glucocorticoid exposures were related to risk of MJON. The temporal relationship between glucocorticoid injection and ON is difficult to discern in our cross-sectional study, as patients may have had the injections for pain due to undiagnosed ON. Further, the relationship between intra-articular steroid injections and ON may vary by site. We would require a greater number of subjects in our cohort to investigate whether the risk may be greater in individuals who receive injections at the different joints. While there are reports of patients who develop ON after glucocorticoid injections without any IV or oral exposure [25, 26], we may not have detected a relationship because the amount of glucocorticoid from these routes relative to the oral exposure in our cohort was quite small. The use of inhaled steroids was higher among patients with MJON which may suggest that the systemic absorption of inhaled glucocorticoids, although small in relation to oral or intravenous GCs, does contribute meaningfully to total exposure and the development of MJON. More investigation into this topic is needed.

Two prior studies have investigated the relationship between glucocorticoid dose and risk of ON at multiple sites [18, 19]. Flouzant-Lachaniette and colleagues reported that peak glucocorticoid dose > 200 mg (methylprednisolone-equivalent) was the greatest predictor of new lesions in a cohort of patients with multifocal ON, defined as ON at three or more separate sites [19]. Route of glucocorticoid administration and the indication for the glucocorticoid therapy did not predict the development of new lesions. In contrast to our cohort, patients in this study were predominantly male, and all underwent surgery for ON at the hip. It is not clear whether their results are generalizable to women, given our finding of sex differences in the threshold exposure for glucocorticoid induced ON, or to patients with less advanced disease. Further, Zhang et al. investigated multifocal ON in a cohort of patients treated exclusively for severe acute respiratory syndrome (SARS) with glucocorticoids [18]. Similar to our findings, they reported that cumulative dose was a significant risk factor for multifocal ON. These authors also found that peak dose > 200 mg was an independent risk factor. While we did not observe a relationship with the peak dose, our findings suggest that a higher total cumulative oral dose and a longer duration of oral glucocorticoid use were associated with an increased number of joints with ON. It should be noted that Zhang and colleagues [18] confined their analyses to a much younger, smaller, and homogenous cohort. Additionally, they did not separately calculate the cumulative, mean daily dose, peak dose, or duration with respect to the route of administration. The mean cumulative dose and length of glucocorticoid use among patients with multifocal ON in both cohorts [18, 19] were significantly less than that presented in our study. The varying patterns of the glucocorticoid therapy may relate to differences in the underlying comorbidities of the cohorts.

Few studies have investigated the relationship between underlying condition and extent of disease in patients with glucocorticoid-induced ON. Most are case reports or series [27–30]. While these reports describe multifocal ON in patients with SLE [28], HIV [30], leukemia [29], and lymphoma [27], they do not address whether or to what extent these comorbidities individually pose a risk for multifocal ON. In one prospective study of 170 patients with ALL and ON, 85%

had multifocal ON [31]. We found that certain underlying conditions were associated with greater likelihood of having MJON. Both history of SLE and hematologic malignancy significantly increased the risk of MJON. All patients in our cohort with a history of ALL had MJON. While we did not have the numbers to examine these relationships, it is conceivable that the other medications used to treat these conditions, including chemotherapeutic medications like asparaginase, may also contribute to increased ON risk [32]. Our finding, that the risk of MJON is multiplied in patients treated with glucocorticoids who have underlying predisposing conditions, provides further support for a multifactorial pathogenesis for ON.

Our finding that underlying conditions substantially contribute to the risk of MJON raises concern regarding the risk among patients with COVID-19 who are treated with glucocorticoids. As there is mounting evidence supporting glucocorticoid use for the treatment of COVID-19 in hospitalized patients [33, 34], consideration of ON risk in this population and ways to mitigate this risk is necessary. As previously recognized with SARS-CoV-1 [35], the hypercoagulable state induced by SARS-CoV-2 may increase the risk of many thrombotic complications including ON [36–38]. Our results suggest that patients with COVID-19 who receive the highest cumulative doses of glucocorticoids may be at the greatest risk for ON involving multiple joints. Further studies are needed to investigate this important topic.

In addition to the underlying indication of glucocorticoid use, sex may contribute to the risk of ON. Despite some studies reporting sex differences in the development of glucocorticoid-induced ON [15, 39–41], others do not [35, 42, 43]. While sex was not a risk factor for MJON, we found that overall men had significantly less glucocorticoid exposure than women. Our findings suggest that the threshold glucocorticoid exposure that results in the development of ON may be lower in men. The activity of cytochrome P450 3A in the liver, of which women have a higher concentration, promotes the metabolism of steroids and may explain a higher threshold among women [44, 45].

The majority of our cohort underwent surgical treatment for ON. More than a fourth went on to have at least two arthroplasties for ON. Although we did not have a large enough sample size to investigate differences in post-operative outcomes among patients with MJON, or between those with MJON and single joint involvement, this is an important topic for future studies. The prevalence of multiple surgeries in this young population underscores the need for further work investigating the optimal surgical management of ON.

Our study has unique strengths and appreciable limitations. As a tertiary referral center, we had access to a cohort with advanced multi-joint disease. While much of the prior literature on MJON consists of case reports, our study provides comprehensive prospectively acquired data. Our prospective enrollment and methodology permitted us to rigorously capture glucocorticoid exposure. Detailed histories of lifetime glucocorticoid use were obtained from extensive review of patient's records and reports by the patient and/or treating physicians. For this reason, we were able to compare different features of glucocorticoid exposure and evaluate which factors conferred the greatest risk of MJON. However, although we obtained extensive glucocorticoid histories on all of our patients, we did not have the same level of detail regarding prior use of other medications and therefore could not assess whether past use mediated the development or progression of ON or MJON. Whether certain medications may prevent the development of ON is an important topic for future investigation. Our study was limited by its small sample size and cross-sectional design. Further, full body imaging modalities were not implemented in this study to screen for ON. Thus, there may have been patients with asymptomatic ON at other sites which was not diagnosed. A greater number of subjects and longitudinal design, including full body imaging, would have enabled us to further investigate the full extent of disease as well as the timing of progression. Some of the patients who did not have MJON at the time of study evaluation may have progressed to MJON with a longer duration of follow-up. The indication for glucocorticoid therapy varied in this cohort, introducing heterogeneity. We were unable to determine the threshold dose for glucocorticoid-induced MJON as other underlying conditions may have differentially contributed to ON risk in.

However, the inclusion of patients with different underlying conditions was necessary given the rarity of the condition and provided us with insight regarding the relationships of the different secondary risk factors for glucocorticoid-MJON. Histories concerning underlying conditions were collected by self-report and chart review. Thus, comorbidities that are asymptomatic or not clinically diagnosed may have been missed. We were unable to collect data on physical activity among patients and thus could not investigate the role of physical activity in the development and progression of ON in this cohort.

In summary, among patients with glucocorticoid-induced osteonecrosis, cumulative oral glucocorticoid dose was the best predictor of multi-joint disease. Our findings indicate that high initial doses of IV and oral glucocorticoids, which are often necessary to rapidly reduce inflammation, may not increase risk of MJON as much as the total cumulative oral dose. These results suggest that strategies for reducing the risk of MJON in glucocorticoid-treated patients should be aimed at lowering total cumulative exposure. Further research is necessary to define optimal strategies for prevention and treatment of MJON.

Code availability All statistical evaluations used SAS STAT 13.2.

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Approved by Hospital for Special Surgery and the NewYork-Presbyterian Hospital/Weill Cornell Medical Center IRB. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflicts of interest Disclosures, all unrelated to the current work: JL is a consultant for Mesentech, Radius Health, Kuros, and Terumo, BCT. JL is a consultant and Medical/Scienific Advisory Board Member at the ON Foundation. JL also receives research support from Radius Health, Merck and Novartis. GR is a consultant or serves on the Advisory Board or serves on the Data and Safety Monitoring Committee for the following: AbbVie, Actinium, Agios, Amphivena, Argenx, Array Biopharma, Astex, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Celltrion, Daiichi Sankyo, Eisai, Epizyme, Glaxo SmithKline, Helsinn, Janssen, Jasper Therapeutics, Jazz, MEI Pharma (IDMC Chair), Novartis, Orsenix, Otsuka, Pfizer, Roche/Genentech, Sandoz, Takeda (IRC Chair), and Trovagene. GR also receives research support from Cellectis. PD serves on the Advisory Board for Celgene and Sanofi; PD also receives research funding from Janssen. EMS reports research funding from Novartis and Radius. The authors AK, AH, KP, KK, TP, DM, DH, DJM, KAK, and RSB declare that they have no conflict of interest.

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