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High-Dose Corticosteroid Use and Risk of Hip Osteonecrosis: Meta-Analysis and Systematic Literature Review

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ABSTRACT

The effect of varying corticosteroid regimens on hip osteonecrosis incidence remains unclear. We performed a meta-analysis and systematic literature review to determine osteonecrosis occurrences in patients taking corticosteroids at varying mean and cumulative doses and treatment durations, and whether medical diagnoses affected osteonecrosis incidence. Fifty-seven studies (23,561 patients) were reviewed. Regression analysis determined significance between corticosteroid usage and osteonecrosis incidence. Osteonecrosis incidence was 6.7% with corticosteroid treatment of >2 g (prednisone-equivalent). Systemic lupus erythematosus patients had positive correlations between dose and osteonecrosis incidence. Each 10 mg/d increase was associated with a 3.6% increase in osteonecrosis rate, and >20 mg/d resulted in a higher osteonecrosis incidence. Clinicians must be wary of osteonecrosis in patients on high corticosteroid regimens, particularly in systematic lupus erythematosus.

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Osteonecrosis can lead to destructive arthropathies affecting the hip, knee, shoulder, and other joints, and it occurs most commonly in the first four decades of life [1–3]. This disease represents 2% to 10% of total hip arthroplasties performed in the United States and Europe, but may be as high as 50% to 60% in Korea and Japan [1,4–6]. The etiology of atraumatic osteonecrosis remains multifactorial, and no consensus exists on common pathophysiologic mechanisms. Vascular impairment, abnormal cellular reparative processes, and genetic point mutations

have been implicated [7–10]. Risk factors include direct causes such as trauma, radiation exposures, hematologic diseases (sickle cell), and dysbarism (Caisson disease), as well as numerous indirect associated factors, such as rheumatologic or metabolic diseases, corticosteroids, alcohol, and/or smoking [1–3,7].

Heimann and Freiburger [11] were among the earliest to report cases of osteonecrosis in patients treated with high corticosteroid doses. Multiple studies since then have implicated prolonged, high-dose corticosteroid use as an independent factor associated with osteonecrosis, and it has been reported that doses greater than 2 g within three-months present a risk for developing osteonecrosis [3,12]. However, there are marked heterogeneities in patient demographics and epidemiologic variabilities between studies. Furthermore, few reports have examined differences in osteonecrosis incidences as functions across different medical diagnoses.

A systematic literature review and a meta-analysis were conducted to investigate the association of high-dose corticosteroid therapy with osteonecrosis incidences. Primary research questions were: (1) what were the overall osteonecrosis incidences in patients taking high-dose corticosteroids; (2) does the underlying disease for which corticosteroids are used affect osteonecrosis incidences; (3) whether mean doses, cumulative doses, or treatment durations were associated with incidences; and (4) whether pulsed therapies affected incidences.

Methods

Publications in peer-reviewed literature were identified by searching medical databases: Medline (1966-to-present); EMBASE

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(1947-to-present); SCOPUS (1966-to-present); and Web-of-Science (1945-to-present). Boolean search queries included following search keys: (osteonecrosis[title] OR avascular necrosis[title] OR bone necrosis[title] OR aseptic necrosis[title]) AND (corticosteroid*[title] OR steroid*[title] OR prednisone[title] OR prednisolone[title] OR methylprednisolone [title] OR cortisone[title] OR hydrocortisone[title] OR dexamethasone[title] OR betamethasone[title]).

Data were independently extracted and recorded by two authors (RP and SB) into spreadsheets (Excel; Microsoft Corporation, Redmond, Washington). For inconsistencies in numerical values, a third author (KI) reviewed manuscripts and corrected potential errors. Each study was evaluated sequentially. Two authors reviewed manuscripts and if inconsistencies were identified, these were clarified before the next manuscript was reviewed. Inconsistencies recognized were typographical in nature (incorrect number accidentally inputted) and had minimal impacts on reporting quality.

Extracted data included study level-of-evidences, patient demographics, medical diagnoses, corticosteroid types, time-to-diagnoses, mean corticosteroid doses, maximal daily doses, cumulative doses, and treatment durations. Studies that reported differing corticosteroid agents and doses were normalized to relative potencies in prednisone-equivalent doses in milligrams [13]. For analyses of osteonecrosis incidences between high- and low-dose corticosteroids, a 10,000 mg prednisone-equivalents cut-off was utilized because several studies reported doses at or below this level, or substantially above this level (e.g. > 15 g). Thus, this level represented cut-offs in published literature. A third investigator (KI) independently reviewed data accuracy and inter-reviewer consistencies to aid in standardization of pooled data.

The literature search yielded 372 articles between 1960 and 2011, of which twenty-one were review articles. Following assessment of abstracts, 319 *in vitro* studies on histological changes associated with corticosteroids or non-clinical data (e.g. review articles) were excluded, leaving fifty-three studies for review. Reference list examinations identified four additional reports, for a total of fifty-seven studies that were included in the systematic review. There were two level-I, seven level-II studies, and forty eight level-III studies (see Appendix 1) [10,12,14–68].

We evaluated the association of certain disease entities for which systemic corticosteroids were used with the development of osteonecrosis. Specifically, we assessed the association in patients with cardiac, liver, or renal transplants; myeloproliferative diseases (multiple myeloma, acute lymphoblastic leukemia); systemic lupus erythematosus (SLE); or severe acute respiratory syndrome (SARS). No studies assessed corticosteroid effects in other potentially at-risk populations, such as alcohol-users or smokers.

For the meta-analysis, our review resulted in the exclusion of 50 studies due to incomplete outcome reporting, such as inadequate information on mean daily corticosteroid intake, cumulative doses, and duration of treatment, which prevented estimation of odds ratios (i.e. odds that an outcome occurs, given a particular exposure, compared to odds of the outcome occurring in absence of the exposure). Seven studies remained for the meta-analysis [19,20,23,34,52,55,57,69], and these consisted of 1 high-level prospective cohort study, as well as 5 case-control studies (Level III) and 1 case series (Level IV), from which odds ratios could be deduced (Fig. 1). Studies not included in the meta-analysis were used for multivariate analyses to answer secondary questions. The seven studies included 1515 patients undergoing treatment with corticosteroids for SLE ($n = 140$), renal transplantation ($n = 774$), or bone marrow transplantation ($n = 601$; see Table 1 for further details). The mean age of patients in these studies was thirty-three years (range, 15 to 60 years). Studies were performed in the United States ($n = 4$), the United Kingdom ($n = 1$), Canada ($n = 1$), and Denmark ($n = 1$).

Validity assessment of RCTs was conducted independently by two authors (RP and SB) utilizing the Detsky scale cutoff score of 75% [70,71]. Extracted data were pooled from studies meeting inclusion criteria to calculate treatment effects (odds ratio and 95% confidence

intervals) and weights utilizing statistical software (Comprehensive Meta-Analysis v2; Biostat, Englewood, New Jersey) to calculate effects of corticosteroid treatments and doses on incidences. Linear regressions and correlation statistics determined osteonecrosis incidences relative to corticosteroid doses (mean, cumulative, and duration; refer to Appendix for breakdown of included studies for each diagnosis category). Regression analysis was performed to find the quantitative relationship and its significance between the variables, corticosteroid daily dose, cumulative dose, and duration of treatment, and the incidence of osteonecrosis as a dependent variable. Due to the lack of complete dosage data in several studies, we were only able to assess this in SLE and renal transplant patients. The reported R- and R-square results were un-adjusted and reported only for simple linear regressions, rather than for multiple linear regressions to avoid distortion by strong associations between average doses, cumulative doses, and durations. A random effects model was used in the meta-analysis, with publication bias assessed using Orwin's fail-safe N and Duval and Tweedies trim and fill statistics. Furthermore, heterogeneity was assessed using Cochran's Q and I^2 statistics. Statistical analyses were performed utilizing SSPS 17.0 statistical software (IBM, Armonk, New York). Significance was defined as P values ≤ 0.05 (Appendix 2 Statistics).

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There were no external sources of funding for this meta-analysis and systematic literature review.

Results

Incidence of Osteonecrosis

The systematic review demonstrated overall osteonecrosis incidence of 6.7% (range, 0.3% to 52%) in patients taking high-dose corticosteroids. Two level I studies proved a significant positive correlation between cumulative dose and the incidence of osteonecrosis, whereas, five level II studies failed to show it.

Disease and Incidence of Osteonecrosis

Osteonecrosis incidence for SARS was 21.8%, SLE 15.7%, renal transplant 14.7%, and BMT 6.6% (Fig. 2). Across all diagnoses, we observed positive associations between mean corticosteroid doses and osteonecrosis (Fig. 3). This was irrespective of underlying disease, as analysis of variance of osteonecrosis incidence between patients with different medical diagnoses (SLE, severe acute respiratory syndrome, bone marrow transplantation, renal transplantation) demonstrated no differences between diagnostic categories ($P = 0.16$). The regression analysis demonstrated a significant positive correlation in SLE patients ($r = 0.81$; $R^2 = 0.67$; $P < 0.05$), however, this was not significant in renal transplant recipients ($r = 0.32$; $R^2 = 0.09$; $P > 0.05$). It was also noted that renal transplant recipients and SLE patients were more likely to develop osteonecrosis if they were younger than 35 years compared to those who were older (22 versus 13%; $P = 0.04$, and 33 versus 7%; $P = 0.02$, respectively).

Mean Dose, Cumulative Dose, Duration of Treatment and Osteonecrosis Incidence

Meta-analysis of osteonecrosis in patients treated with greater than 20 mg per day demonstrated significantly higher odds than less than 20 mg per day corticosteroid users (OR 9.1; 95% confidence interval, 4.6 to 19.8) (Fig. 4A). For patients treated with high cumulative corticosteroid doses (greater than 10 g), the odds ratio for developing osteonecrosis was 2.4 (95% CI. 0.8 to 6.4), and lower dosing regimens were associated with a lower osteonecrosis incidence (OR 0.4; 95% confidence interval 0.25 to 0.54) (Fig. 4B). Additionally, we observed that

Fig. 1. CONSORT flow diagram demonstrating the study selection methodology. *We excluded studies such as *in vitro* studies on histological changes associated with corticosteroids and manuscripts that were not clinical studies (e.g. review articles). **Additional reports were those retrieved from reference lists of other manuscripts.

10 mg per day dose increases resulted in a 3.6% increase in the rate of osteonecrosis. Due to the lack of data and control groups, the meta-analysis could not be performed comparing other dosing regimens or treatment duration effects on osteonecrosis risks.

Cumulative doses and treatment durations had negative associations with incidence for both SLE and renal transplant patients. In SLE patients, cumulative dose and the duration of treatment showed negative trends ($r = -0.85$, $R^2 = 0.65$ and $r = -0.53$, $R^2 = 0.29$, respectively) with the incidence of osteonecrosis, but these were not significant ($P > 0.05$) and may not represent a true trend. In renal transplant recipients, there was no evidence of a significant correlation between cumulative doses and incidence of osteonecrosis ($r = 0.31$; $R^2 = 0.42$; $P > 0.05$).

Pulsed Corticosteroid Therapy and Incidence of Osteonecrosis

Mean osteonecrosis incidence was 33% in twenty studies evaluating the effects of pulsed corticosteroids based on data from the systematic review.

Discussion

Our aim was to evaluate the available literature and to assess the association between corticosteroids and hip osteonecrosis, utilizing statistical methodologies. In particular, we assessed the effect of dosing

regimens and treatment durations, as well as the role of different disease entities. This study builds upon individual reports that have demonstrated independent risk factors for osteonecrosis, which were not observed in earlier studies [2,20,66,72]. Our results showed that osteonecrosis incidences were affected by treatment with corticosteroids, corticosteroid doses, and patient age. Specifically, patients treated with high-dose corticosteroids may be up to ten times as likely to develop osteonecrosis, and cumulative doses greater than 10 g may increase the likelihood of developing osteonecrosis by two-fold, compared to cumulative doses less than 10 g. In addition, it was observed in the regression analysis that the correlation between corticosteroid dose and osteonecrosis incidence was most evident in SLE patients. However, no differences between diagnoses were noted using the analysis of variance, and further study is needed before a stronger conclusion can be drawn.

Multiple studies have demonstrated that corticosteroids are independent risk factors for osteonecrosis. Shibata et al, in a study of 150 patients, noted a significant association between the total dose of corticosteroids and osteonecrosis incidence in patients during the first two months following renal transplantation ($OR = 4$, $P = 0.02$) [60]. Nakamura et al reported a 10.3 odds ratio of developing osteonecrosis in SLE patients, which compared similarly with the results of the present study ($OR = 9.1$) [73]. We also observed strong correlations ($R^2 > 0.8$) between mean daily corticosteroid doses, cumulative doses, and treatment durations and osteonecrosis incidences. However, no single factor

Table 1

Description of the Studies of Osteonecrosis Incidence in Patients Treated with Oral or Intravenous Corticosteroids Included in the Meta-Analysis.

Author (Year)	Level of Evidence	Study Design	Diagnosis	Incidence ON Steroid vs. Control (%)	Mean Age In Years (Range)	Affected Sites (%)	Mean Daily Steroid Dose mg/day	Mean Cumulative Steroid Dose (Duration of Treatment)	Duration (Months)	Mean Time to Onset In Months (Range)
Jagasia et al (2010)	III	Case control	BMT	50 vs. 156	ON: 37 (N/A), no ON: 48 (N/A)	N/A	1.6 mg/kg/d vs. 1.4 mg/kg/d	N/A	24 (10 to 40) vs. 13 (1 to 21)	7 (4 to 13)
McAvoy et al (2010)	III	Case control	BMT	74/3786 (2%) vs. 147	ON: 28 (4 to 60), no ON: 28 (4 to 60)	hip (54%), knee (36%)	N/A	7043 mg (range, 2352 to 12,755) vs. 1800 mg (range, 0 to 7895)	N/A	16 (2 to 80)
Gladman et al (2001)	III	Case control	SLE	95/744 (13%)		hip (N/A)	Maximum daily dose in + AVN/– AVN: 44.4/28.1 mg	IN + AVN/– AVN: 23.1/15 g	N/A	NA
Lausten et al (1998)	III	Case control	Renal Transplant	High dose: 42/374 (11%), Low dose: 4/124 (3%), vs. 46	overall: 41 (6 to 66)	hip (100%)	High dose: 34 mg/day, Low dose: 17 mg/day vs. (same daily doses for controls) PDS	High dose: 12,540 mg, Low dose: 6481 mg, Controls: 11,200 mg	N/A	26 (N/A) vs. 21 (N/A)
Fink et al (1998)	III	Case control	BMT	87/1939 (5%) vs. 87	ON: 27 ± 1.2, no ON: 27 ± 1.2	hip (62%), knee (38%), shoulder (9%)	N/A	N/A	N/A	26 ± 2
Morris et al (1982)	I	Prospective cohort	Renal Transplant	High dose: 8/39 (21%), Low dose: 1/33 (3%)	High dose: 40 ± 10, Low dose: 39 ± 11	N/A	High dose: 100 mg PSL for 5 days, then 90 mg for 5 days, then tapered 5 mg every 5 days to 20 mg, then tapered 1 mg every 2 weeks to a maintenance dose of 10 mg/day. Low dose: 30 mg PSL for 60 days (with additional 1 g IV MPST on days 6, 7, and 8 after transplantation), then 25 mg daily for 2 weeks, then 20 mg/day, then tapered 1 mg every 2 weeks to a maintenance dose of 10 mg/day.	High Dose: (3 months) 13,500 ± 5830 mg, (6 months) 17,040 ± 5765 mg; Low Dose: (3 months) 13,178 ± 3905 mg, (6 months) 15,450 ± 5110 mg	N/A	N/A
Harrington et al (1971)	IV	Case series	Renal Transplant	High Dose: 16/50 (32%), Low Dose: 2/101 (2%)	ON: 24 (15 to 48)	hip (78%); knee (28%); talus (11%); elbow (17%)	High Dose: (Initial 3 weeks) 120 to 200 mg/d, followed by taper to 30 mg/d; Low Dose: (Initial 4 days) 120 to 200 mg/d, followed by the same taper	High Dose: (3 weeks) 2960 mg (N/A); Low Dose: (3 weeks) 1180 mg (N/A)	N/A	N/A

Mg = milligrams.

predicted variability in osteonecrosis incidences, which pointed to possible synergistic effects between all three factors.

The underlying diagnoses may potentially affect the risk for developing osteonecrosis. However, it is unclear which plays the dominant role, the underlying disease or the effects of corticosteroids, which may have stronger negative synergistic effects for some disorders compared to others. A prospective magnetic resonance imaging (MRI) study by Shigemura et al demonstrated that SLE patients had significantly higher risk (RR 2.1) of osteonecrosis than non-SLE patients (37 versus 21%; $P = 0.001$) [66]. However, they excluded organ transplant recipients due to higher mortality rates, and relied primarily on other systemic inflammatory diseases (e.g. inflammatory bowel diseases, vasculitides, dermatologic autoimmune diseases) as comparison groups. Furthermore, Leiberman et al reported low incidences (3%) of osteonecrosis diagnosed with MRI at a mean of 31 months post-liver transplantation [47]. Presently, the true effect of underlying disease on osteonecrosis incidence remains to be determined, and additional prospective studies are needed.

In addition to differences in diagnosis, it is important to highlight the effects of demographic factors and race on the development of

osteonecrosis. Although it is difficult to specify osteonecrosis rates in a whole population, some studies have evaluated osteonecrosis in Asian populations and have shown higher disease incidence, particularly in those who have corticosteroid-dependent conditions. For example, Yamaguchi et al demonstrated a rising trend in the incidence of nontraumatic ON in Japanese patients, particularly in those who had corticosteroid-dependent conditions, with rates of up to 44% in SLE patients who were on high-dose corticosteroids [74]. However, it was inconclusive whether this was a true trend or just an improvement in diagnostic capabilities. In addition, Fukushima et al observed that according to the Research Committee on Idiopathic Osteonecrosis of the Femoral Head in Japan, roughly 2200 new patients per year were diagnosed with ON. Comparatively, United States-based studies have shown much lower ON rates, with roughly a 15% ON prevalence in SLE patients [75]. Race-specific differences in gene mutations, such as factor V Leiden and prothrombin, have been implicated, however, definitive causes for disparities in incidence remain unclear, and may also be idiopathic or attributed to lifestyle [76]. Nevertheless, it is still important to highlight that there may be fundamental differences in the way certain patients respond to corticosteroids.

Pooled Osteonecrosis Incidence Per Medical Diagnosis Category

Fig. 2. Box-plot of pooled osteonecrosis incidence in patients treated with corticosteroids compared across multiple different primary medical diagnoses based on systematic review data. No significant difference is observed between groups (ANOVA; $P = 0.158$). SLE: systemic lupus erythematosus; SARS: severe acute respiratory syndrome; BMT: bone marrow transplant.

Several studies published in the last two decades have demonstrated associations between high corticosteroid doses and osteonecrosis incidences, although others did not have this trend [12,42,50]. Similar to results observed in this meta-analysis, a prior systematic review found a 4.6% increase in the rate of osteonecrosis for every 10 mg per day increase in corticosteroid doses (Fig. 2; present study had 10% increase per 10 mg/day) [67]. In addition, mean daily doses of greater than 40 mg per day (prednisone-equivalent) have been associated with a higher risk for developing osteonecrosis. One prospective study demonstrated 4-fold higher incidences of osteonecrosis in patients treated with mean daily corticosteroid doses of greater than 40 mg ($P < 0.05$) [66]. Nagasawa et al, in a study of 45 patients diagnosed with SLE and treated with oral prednisolone (40 mg/day), observed dose–response relationships with osteonecrosis over five years [77]. Based on yearly MRI scans, they found that administration of high corticosteroid doses (>1000 mg/day) was more frequently found in patients with early stage osteonecrosis than those without osteonecrosis (87% versus 37%; $P < 0.01$). It is possible that discrepancies between studies may be attributed to recent increases in MRI use for the diagnosis of early-stage osteonecrosis, which may have otherwise been undetectable on radiographic assessment.

Fig. 3. Scatter plot of osteonecrosis incidence as a function of mean daily corticosteroid dose, irrespective of underlying medical disease or diagnosis based on systematic review data. Black line represents the linear regression model; gray lines represent the 95% confidence interval of the model.

Multiple studies have also reported on the association between cumulative corticosteroid doses and osteonecrosis. For example, previous reports suggest that patients receiving greater than 2 g of cumulative corticosteroid doses are at a higher risk for developing osteonecrosis [1,3]. However, it is unclear whether this represents a ceiling above which patients develop osteonecrosis at the same rates irrespective of total doses, or a floor, above which risk for osteonecrosis increases with higher cumulative doses. Additionally, Nakamura et al evaluated 201 patients with SLE over 13 years and observed that osteonecrosis risk was associated with increasing cumulative corticosteroid doses, with 15% of patients requiring increased corticosteroid doses developing the disease [39]. Shibata and colleagues evaluated renal transplant recipients who underwent multiple rejection cycles, and they demonstrated associations between osteonecrosis and cumulative corticosteroid doses (OR 4.2; $P = 0.008$), but not with rejection episode numbers, which allude to the likelihood that higher cumulative doses, rather than systemic effects of host-versus-graft disease, may be implicated in osteonecrosis pathogenesis [60]. However, accurate differentiation between effects of mean daily corticosteroid doses and cumulative doses on the osteonecrosis risk is difficult, since patients with the highest cumulative doses often receive higher mean daily doses and/or are treated for longer durations.

Treatment durations have also been implicated as independent risk factors for developing osteonecrosis. Nakamura et al evaluated 201 patients (537 joints) with SLE who were treated with prednisone doses of greater than 40 mg per day [39]. Of the 537 joints, 238 (44%) developed osteonecrosis. They concluded that progression of osteonecrosis was associated with higher doses of corticosteroid treatment for longer durations.

The association between pulsed corticosteroid therapy and osteonecrosis has been reported to be variable. Oinuma et al, studying 72 patients with SLE, found no differences in osteonecrosis incidences in patients treated with pulsed methylprednisolone therapy in combination with minimum daily corticosteroid doses of 40 mg/day [38]. Of the 32 patients who developed ON, 17 were treated with pulsed corticosteroids while of the 40 patients who did not develop osteonecrosis, 18 were treated with pulsed corticosteroids. However, this study did not specify pulsed corticosteroid dosages. However, in a study by Ce et al, 60 multiple sclerosis patients, who did not have any risk factors for osteonecrosis, were treated with pulsed corticosteroids and were compared to a matched group of patients who did not receive corticosteroids [72]. Cumulative pulsed corticosteroid doses received by the treatment group was greater than 10 g, and they only received pulsed-corticosteroids and were not treated with any maintenance doses between pulses. It was observed that treatment patients had significantly higher incidences of femoral head osteonecrosis as diagnosed on MRI (15.5%; $P < 0.05$) compared to the non-corticosteroid group (0%). Similar results were observed in a study of 498 renal transplant patients, which demonstrated a significantly greater incidence of osteonecrosis in those receiving pulsed therapies (11%) compared to patients receiving non-pulsed therapy (3%; $P < 0.01$) [55].

There were several limitations of this study. The lack of prospective randomized-controlled trials may have contributed to both study-design and reporting bias in individual reports, which may have skewed the observed outcomes. Although double-blinded, prospective randomized-controlled trials are gold standards for evidence-based medicine, in certain situations, such as renal transplantation or SLE, where the first-line therapy is corticosteroids, it would have been unethical to design studies denying treatment. Thus, we relied primarily on case-control studies. There was also a lack of consistency in osteonecrosis diagnostic methods. Studies published after 1990 utilized MRI, while earlier studies relied on patient symptoms, radiographic findings, biopsies, and bone scanning, which due to low diagnostic sensitivity [78] may have underestimated the true osteonecrosis incidence. In addition, lower quality studies on medical diagnoses other than renal transplantation or SLE prevented multivariate analysis due to insufficient degrees

Fig. 4. (A and B) Comparison studies of osteonecrosis incidence included in the meta-analysis: (A) patients who did not receive any corticosteroids and those receiving greater than 2 g of corticosteroids; and (B) patients treated with less than 10 g of cumulative corticosteroid treatment (all patients received at least 2 g of corticosteroid). Horizontal error bars represent the 95% confidence interval of the odds ratio for each individual study. The diamond represents the pooled odds ratio for all the studies with a corresponding horizontal bar representing the 95% confidence interval. A pooled odds ratio > 1 represents higher-odds of having osteonecrosis if treated with greater than 2 g of corticosteroid (A) while an odds ratio of less than 1 is associated with lower odds of having osteonecrosis if treated with less than 10 g of corticosteroid (B).

of freedom in the statistical analyses. This was evident in studies on bone marrow transplant recipients, cardiac transplants, and SARS. However, we were able to analyze two common patient groups (SLE and renal transplantation). Furthermore, almost all studies reported using high cumulative corticosteroid doses. This study did not consider incidental corticosteroid doses, such as the use of dose-packs or corticosteroids in minimal doses that are typically not associated with osteonecrosis. We have focused on patients who received minimum cumulative doses of 2 g or 30 mg daily doses for less than 2 months. Thus, these results may not be indicative of patients given low cumulative doses (<2 g) of corticosteroids for medical conditions that were not directly associated with osteonecrosis.

These meta-analysis and assessment of the available literature demonstrated that high-dose corticosteroid treatments may increase risk for developing osteonecrosis up to ten-fold. Patients treated with daily doses >40 mg were at higher risk, with 3.6% increase in incidences for every 10 mg increase in doses. Effects of cumulative corticosteroid doses and treatment durations are less clear, but are likely to have synergistic relationships with daily doses and underlying diagnoses. Pulsed-therapy has effects on increasing osteonecrosis risk. As molecular and genetic bases for this disease evolves, further knowledge of risk factors for osteonecrosis with prospective MRI-based studies will assist medical practitioners in educating patients. Presently, we would advise erring on the side of caution and using the lowest possible corticosteroid doses, while still maintaining clinical efficacy and minimizing risks.

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Appendix 1. Studies of Osteonecrosis Incidence in Patients Treated with Oral or Intravenous Corticosteroids

Author (Year)	Level of Evidence	Diagnosis	Incidence ON Steroid vs. Control (%)	Mean Age (Years)	Affected Sites (%)	Mean Daily Steroid Dose (mg/day) ^a	Mean Cumulative Steroid Dose (mg) ^a	Duration (Months)	Mean Time to Onset (Months)
Mattano et al (2000)	III	ALL	111/1409 (9.3%)	ON: 33 (16 to 45)	knee (33%); hip (28%); ankle (15%); shoulder (10%); elbow (8%); wrist (3%)	Induction: 60 mg/sqm PO PDS for 28 days with taper; Intensification: 10 mg/sqm DX for 21 days with taper; Maintenance: 40 mg/sqm PO PDS for 5 days every 28 days	Groups A & B: (Males) Total 8850 mg/sqm, (Females) Total 6250 mg/sqm; Group C: (Males) Total 8090 mg/sqm, (Females) Total 5409 mg/sqm	Groups A & B: 32.4 months (N/A) for males, 20.4 months (N/A) for females; Group C: 28.8 months (N/A) for males, 16.8 (months) for females	N/A
Vaidya et al (1998)	III	ALL	5/850 (0.6%)	ON: 25 (14 to 41)	hip (100%)	Induction: 40 mg/sqm PDSL for 29 days, Maintenance: 3 monthly pulses of PDSL (unspecified)	N/A (2900 mg/sqm to 4000 mg/sqm)	N/A (24 to 30)	29 (9 to 46)
Enrici et al (1998)	III	Hodgkin's disease	9/784 (1%)	ON: 31 (23 to 42), overall: 31 (4 to 83)	hip (94%); shoulder (6%)	N/A	4116 mg (2725 to 5250)	N/A	35 (23 to 97)
Freeman et al (2000)	II	IBD/Crohn's	4/877 (0.5%)	N/A (19 to 36)	hip (100%), shoulder (50%)	N/A	N/A	N/A	N/A
Klingenstein et al (2005)	III	IBD/Crohn's	23/(N/A)	22 (N/A)	hip (91%), knee (40%), shoulder (22%)	21 mg (12 to 35.5)	15,403 mg (<8000 to 59,000)	25 (3 to 81)	168 (36 to 504)
Talamo et al (2005)	I	Multiple myeloma	49/553 (9%)	ON: 52 (34 to 72), overall: 58 (25 to 77)	hip (100%); shoulder (8%)	First dose: One 12-day course and two 4-day courses of 40 mg PO DXM; Second dose: Four 4-day courses of 40 mg PO DXM; Third dose: DXM pulses every month (unspecified)	median 7000 mg (5000 to 18,000)	N/A	12 (2 to 41)
Fink et al (1998)	III	BMT	87/1939 (5%) vs. 87	ON: 27 ± 1.2, no ON: 27 ± 1.2	hip (62%), knee (38%), shoulder (9%)	N/A	N/A	N/A	26 ± 2
McAvoy et al (2010)	III	BMT	74/3786 (2%) vs. 147	ON: 28 (4 to 60), no ON: 28 (4 to 60)	hip (54%), knee (36%)	N/A	7043 mg (2352 to 12,755) vs. 1800 mg (0 to 7895)	N/A	16 (2 to 80)
Atkinson et al (1987)	III	BMT	5/50 (10%)		hip	N/A	14 mg/kg		18 (8.3 to 24)
Enright et al (1990)	III	BMT	28/902 (3%)	ON: 26 (1.5 to 47)	hip (64%), knee (61%), ankle (29%), shoulder (21%), elbow (7%)	All patients: (1 month) 0.82 mg/kg/d PDS, (2 months) 2.2 mg/kg/d, (>2 months) N/A	19,800 mg (9000 to 70,000)	N/A	median 12 (1 to 62)
Jagasia et al (2010)	III	BMT	50 vs. 156	ON: 37 (N/A), no ON: 48 (N/A)	N/A	1.6 mg/kg/d vs. 1.4 mg/kg/d	N/A	24 (10 to 40) vs. 13 (1 to 21)	7 (4 to 13)
Socie et al (1994)	III	BMT	27/727 (3.7%)	ON: 25 (5 to 43)	hip (69%), knee (11%), shoulder (11%)	N/A	14,300 mg (2500 to 50,500); 200 mg/kg (60 to 840)	N/A	13 (4 to 58)

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Author (Year)	Level of Evidence	Diagnosis	Incidence ON Steroid vs. Control (%)	Mean Age (Years)	Affected Sites (%)	Mean Daily Steroid Dose (mg/day) ^a	Mean Cumulative Steroid Dose (mg) ^a	Duration (Months)	Mean Time to Onset (Months)
Socie et al (1997)		BMT	77/4388 (4%)	ON: 25 (5 to 43)	hip (87%), knee (13%), shoulder (9%), other	N/A	N/A	15 (N/A)	median 22 (2 to 132)
Torii et al (2001)	III	BMT	19/100 (19%)	ON: 27 (16 to 51), overall: 33 (16 to 51)	hip (100%)	N/A	ON: 10,300 mg (981 to 20,900); no ON: 4020 mg (128 to 20,600)	N/A	22 (8 to 45)
Wiesmann et al (1998)	III	BMT	17/272 (6%)	ON: 33 (16 to 45)	hip (89%); knee (4%); shoulder (6%)	N/A	189 mg/kg for single-site disease, 313 mg/kg for multifocal disease (range 13–555 mg/kg)	N/A	13 (3 to 29)
Griffith et al (2005)	III	SARS	12/254 (5%)	N/A	hip (100%)	N/A	ON: 4570 mg (760 to 8740), no ON: 2220 mg (50 to 10,020)	N/A	7 (3.3 to 9.7)
Hong et al (2004)	III	SARS	28/67 (42%)	overall: 32 (21 to 55)	hip (57%), knee (71%)	N/A (80 to 800) MP SL then unspecified PDS taper	4117 mg (640 to 20,000)	N/A	10
Chan et al (2006)	III	SARS	7/71 (10%)	ON: 31 (30 to 48), overall: 33 (17 to 89)	N/A	143 (81.5 to 187.25) mg/d PDS	2380 mg (1145 to 4150)	17 (15 to 21)	N/A
Li et al (2004)	III	SARS	12/40 (30%)		N/A	N/A	6186 ± 3700 mg MP SL	0.8 (0.5 to 1)	
Abeles et al (1978)	III	SLE	17/365 (4.7%)	ON: 30 (19 to 55), no ON: 27 (N/A)	hip (N/A), knee (N/A)	N/A	ON: 31,985 mg (14,800 to 63,012), no ON: 31,799 mg (2700 to 71,495)	52 (12 to 108) vs. 96 (48 to 180)	53 (6 to 108)
Dimant et al (1978)	III	SLE	22/234 (9%)						
Dubois et al (1960)	III	SLE	11/400 (2.8%)	overall: 31 (N/A)	hip (89%); knee (11%)	N/A	N/A	N/A	60 (N/A)
Gladman et al (2001)	III	SLE	95/744 (13%)		hip (N/A)	Maximum daily dose in + AVN/–AVN: 44.4/28.1 mg	IN + AVN/–AVN: 23.1/15 g	N/A	
Massardo et al (1992)	III	SLE	17/190 (9%)		hip (N/A)				
Migliaresi et al (1994)	II	SLE	7/69 (10%)		N/A	N/A	Total corticosteroid dose including MP SL therapy in + AVN vs. –AVN was 20.6 +/– 14.9 g vs. 29.1 +/– 29 g Total corticosteroid therapy in those not treated with MP SL pulse therapy in AVN + vs. –AVN was 20.6 +/– 14.9 vs. 15.8 +/– 17.7	N/A (3 to 12)	
Mok et al (2000)	III	SLE	38/320 (12%) vs. 143	ON: 27 (10 to 54), no ON: 28 (12 to 57)	hip (95%); knee (13%); humerus (3%); carpals (3%)	15.6 ± 2.0 vs. 9.3 ± 0.5 mg PDSL	17,700 ± 2800 mg vs. 14,100 ± 1200 mg	50 ± 11.3 vs. 52 ± 4.4	50 (4 to 198)
Mont et al (1997)	III	SLE	31/103 (30%)	N/A	N/A	Mean maximal prednisone dose was 60 vs. 37 mg for SLE patients + AVN vs. –AVN	N/A	N/A	
Nakamura et al (2010)	II	SLE	169 (18 pediatric, 25 adolescent, 126 adult)	N/A	hip (N/A); knee (N/A)	N/A	N/A	N/A	N/A
Oinuma et al (2001)	II	SLE	32/72 (44%)	overall: 35 (13 to 66)	knee (84%), hip (72%)	ON: 58.2 ± 10.1 mg, no ON: 58.6 ± 16.6 mg	N/A	N/A	N/A (16 to 40)

Ono et al (1992)	II	SLE	9/62 (15%)	ON: 31 (N/A)	hip (100%)	42 mg/day PDSL	4000 mg	3.2 (N/A)	21 (N/A)
Rascu et al (1996)	III	SLE	9/280 (2.1%)		hip (N/A)	21.3 mg	38,614 mg	N/A	
Smith et al (1976)	III	SLE	7/99 (7%)	overall: 41 (15 to 74)	hip (85%); knee (14%); shoulder (14%)	11.9 (1.5 to 27.5) vs. 13.2 (1.8 to 24.3) mg	13,830 mg (6200 to 27,500) vs. 18,200 mg (9900 to 27,900)	20 (2 to 47) vs. 23 (3 to 60)	N/A
Uea-areewongsa et al (2009)	III	SLE	20 vs. 20	ON: 33 ± 6, no ON: 32 ± 8	hip (100%)	16.47 ± 7.11 vs. 10.82 ± 4.38	20,270 ± 17,780 mg vs. 17,210 ± 15,990	53 ± 45.1 vs. 54 ± 42.8	N/A
Weiner et al (1989)	III	SLE	28/172 (16.3%)						
Zizic et al (1985)	II	SLE	28/54 (52%)	ON: 35.9 (18 to 67)	hip (N/A), knee (N/A), shoulder (N/A)				
Zonana-Nacach et al (2000)	III	SLE	47/539 (8.7%)	N/A	N/A	N/A	N/A	N/A	N/A
Lieberman et al (2008)	III	Cardiac Transplant	6/204 (3%)	ON: 44 (20 to 58), overall: 55 (16 to 72)	hip (88%); knee (13%)	All patients: (initial 2 days) 125 mg/d MPSSL every 12 h; (days 2 to 14) 70 mg/d PDS, tapered down to 20 mg/d; (days 14 to 180) tapered to 5 mg/d PDS — most completely weaned off by 1 to 2 years	ON: (1 month) 2010 mg (1085 to 5190), (1 year) 4979 mg (3839 to 8719); no ON: (1 month) 1511 mg (926 to 5914), (1 year) 4649 mg (2920 to 13,280)	N/A	39 (21 to 52)
Bradbury et al (1994)	III	Cardiac Transplant	5/168 (3%)	overall: 45 (7 to 66)	hip (60%), knee (20%), shoulder (20%)	Pre-operatively, 500 mg MPSSL + 125 mg every 12 h until on oral medications. Then, 50 mg PDS twice a day, tapered by 10 mg each day down to 15 mg/day, then 25 mg/d, 20 mg/d, 12.5 mg/d, and 10 mg/d at 6 weeks, 8 weeks, 3 months, and 12 months post-transplant. Combined heart-lung transplants received 100 mg PDS on day 14, tapered down by 10 mg/d to 30 mg/d, then further reduced as for the previous group.	ON: (1 month) 1767 mg, (6 month) 7973 mg, (1 year) 9477 mg; No ON: (1 month) 3174 mg, (6 month) 5746 mg, (1 year) 7808 mg	12 (N/A)	5 (2 to 11)
Lieberman et al (2000)	III	Liver Transplant	4/203 (2%)	ON: 50 (32 to 59), overall: 56 (25 to 77)	hip (100%)	Pre-operative: 50–1000 mg MPSSL, followed by 6-day taper (200 mg; 160 mg; 120 mg; 80 mg; 40 mg; 20 mg MPSSL); Post-operative: 30 days of 20 mg/day PDS, followed by taper of 15 mg/day down to 2.5 mg at 180 post-operatively.	ON: (1 month) 1303 mg (180 to 2770), (2 year) 9678 mg (7221 to 6277); no ON: (1 month) 2208 mg (40 to 8900), (2 year) 10,552 mg (2935 to 21,348)	N/A	31 (26 to 38)
De Graaf et al (1982)	III	Renal Transplant	52/170 (30%)						
Elmsted et al (1981)	III	Renal Transplant	19/125 (15%)	ON: 46 ± 11, no ON: 40 ± 14	hip (N/A); knee (N/A)	ON: 1.9 ± 0.9 mg/kg/d at 1 month, to 0.5 ± 0.1 mg/kg/d at 12 months; no ON: 1.8 ± 0.6 mg/kg/d at 1 month, to 0.5 ± 0.2 mg/kg/d at 12 months	ON: 6800 ± 3100 mg at 1 month, 18,600 ± 5600 mg at 12 months; no ON: 6200 ± 2800 mg at 1 month, 17,200 ± 6200 mg at 12 months	12 (N/A)	median 12 (5 to 27)
Haajanen et al (1984)	III	Renal Transplant	29/546 (5.3%)						
Harrington et al (1971)	III	Renal Transplant	High Dose: 16/50 (32%), Low Dose: 2/101 (2%)	ON: 24 (15 to 48)	hip (78%); knee (28%); talus (11%); elbow (17%)	High Dose: (Initial 3 weeks) 120 to 200 mg/d, followed by taper to 30 mg/d; Low Dose: (Initial 4 days) 120 to 200 mg/d, followed by the same taper	High Dose: (3 weeks) 2960 mg (N/A); Low Dose: (3 weeks) 1180 mg (N/A)	N/A	N/A
Hedri et al (2007)	III	Renal Transplant	15/326 (4.6%) vs. 15	ON: 41 (31 to 65), no ON: 38 ± 6	hip (80%); knee (20%)	Initially MPSSL 1 to 2 mg/kg/day, tapered down to 10–15 mg/day.	24,240 mg ± 16450 vs. 14,243 mg ± 7530	N/A	42 (6 to 156)
Ibels et al	III	Renal	40/194 (21%)	ON: 30.3	hip (86%); knee	15.9 mg/d (2.5 to 40)	ON: 6000 ± 5000 mg at 30 days,	N/A	19 (1 to

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Author (Year)	Level of Evidence	Diagnosis	Incidence ON Steroid vs. Control (%)	Mean Age (Years)	Affected Sites (%)	Mean Daily Steroid Dose (mg/day) ^a	Mean Cumulative Steroid Dose (mg) ^a	Duration (Months)	Mean Time to Onset (Months)
(1978)		Transplant		(7 to 64)	(35%); tibia (N/A); talus (N/A); shoulder (N/A); humerus (N/A); radius (N/A); ulna (N/A)		9000 ± 7500 mg at 90 days		126)
Lausten et al (1998)	III	Renal Transplant	High dose: 42/374 (11%), Low dose: 4/124 (3%), vs. 46	overall: 41 (6 to 66)	hip (100%)	High dose: 34 mg/day, Low dose: 17 mg/day vs. (same daily doses for controls) PDS	High dose: 12,540 mg, Low dose: 6481 mg, Controls: 11,200 mg	N/A	26 (N/A) vs. 21 (N/A)
Metselaar et al (1985)	III	Renal Transplant	61/248 (24%)	N/A	hip (49%), shoulder (24%), knee (23%), elbow (3%), ankle (1%), N/A	30 mg/day	N/A	N/A	N/A
Morris et al (1982)	I	Renal Transplant	High dose: 8/39 (21%), Low dose: 1/33 (3%)	High dose: 40 ± 10, Low dose: 39 ± 11		High dose: 100 mg PSL for 5 days, then 90 mg for 5 days, then tapered 5 mg every 5 days to 20 mg, then tapered 1 mg every 2 weeks to a maintenance dose of 10 mg/day. Low dose: 30 mg PSL for 60 days (with additional 1 g IV MPSTL on days 6, 7, and 8 after transplantation), then 25 mg daily for 2 weeks, then 20 mg/day, then tapered 1 mg every 2 weeks to a maintenance dose of 10 mg/day.	High Dose: (3 months) 13,500 ± 5830 mg, (6 months) 17,040 ± 5765 mg; Low Dose: (3 months) 13,178 ± 3905 mg, (6 months) 15,450 ± 5110 mg	N/A	N/A
Patton et al (1988)	III	Renal Transplant	52/444 (16%)						
Pierides et al (1975)	III	Renal Transplant	11/78 (14%) vs. 11 (age & surgery matched) vs. 11 (transplant characteristics matched)	ON: 32 (22 to 47)	knee (55%); hip (55%); talus (18%); shoulder (18%); elbow (18%); scaphoid (9%); metacarpal (9%)	N/A	(estimated) ON: 65 mg/kg (20 to 110) at 3 months, 200 mg/kg (80 to 240) at 12 months PDS; control group 1: (significant difference only at 3 months, 65 mg/kg vs. 45 mg/kg); control group 2: (no significant difference)	N/A	17 (5 to 35)
Potter et al (1978)	III	Renal Transplant	11/100 (11%) vs. 11	ON: 11 (5 to 16), no ON: 11 (2 to 16)	hip (72%); knee (45%); talus (9%); navicular (9%)	All patients: 27.5 mg/d (0 to 60) at diagnosis, 10.5 mg/d (0 to 30) at final followup	ON: 3400 mg/sqm at 3 months, 11,900 mg/sqm at 24 months; no ON: 3500 mg/sqm at 3 months, 14,100 mg/sqm at 24 months	N/A (3 to 24)	23 (5 to 55)
Shibatani et al (2008)	III	Renal Transplant	37/150 (24%)	ON: 37 (16 to 63), no ON: 32 (16 to 63)	hip	All patients: 500 mg MPSTL during surgery; PSL taper from 50 mg down to 7.5 mg in 7 day increments; maintenance dose 10 mg/d	Middle tertile steroid use at 2 weeks: 550–650 mg, 4 weeks: 895–1130 mg, 6 weeks: 1165–1488 mg, 8 weeks: 1400–1795 mg	N/A (0.5 to 2)	N/A
Tang et al (2000)	III	Renal Transplant	16/397 (4.2%) vs. 31	ON: 40 ± 11, no ON: 34 ± 7	hip (100%)	16.2 mg ± 2.8 vs. 14.4 mg ± 1.3	N/A	N/A	19 (6 to 121)
Tervonen et al (1992)	II	Renal Transplant	6/100 (6%)		hip	N/A	40,900 mg vs. 32,100 mg	114 (N/A) vs. 97.2 (N/A)	
Troch et al (1972)		Renal Transplant	13/90 (14%)		N/A		N/A	N/A	

N/A: not available, ACTH: adrenocorticotrophic hormone, CS: cortisone, HCS: hydrocortisone, PDS: prednisone, PDSL: prednisolone, MPSTL: methylprednisolone, DXM: dexamethasone, ON: osteonecrosis, ALL: acute lymphoblastic leukemia, BMT: bone marrow transplant, CVD: collagen vascular disease, IBD: inflammatory bowel disease, SARS: severe acute respiratory syndrome, SLE: systemic lupus erythematosus, IV: intravenous, PO: per os (by mouth)

^a All doses are reported as published; doses without accompanying abbreviation are in milligrams of prednisone (PDS), all other corticosteroid agents utilized are noted with corresponding corticosteroid abbreviation

Statistical Appendix (2)

Random effects model was used in the meta-analysis due to variations in studies with respect to age, diagnoses, and comorbidities as it was assumed that it was unlikely that single effect sizes would be consistent across all studies. Orwin's fail-safe N and Duval and Tweedie's trim and fill statistics were used to investigate publication bias. The adjusted odds-ratio for developing osteonecrosis with corticosteroid use was 6.4 (95% CI, 3.3 to 12.3). Using the criteria for trivial odds (i.e. not clinically important) ratio as 1.1 and mean odds ratio of 1.0 in missing studies, we found that 89 additional studies were necessary to reduce odds ratio to 1.1. Similarly, adjusted odds-ratios for developing osteonecrosis with high corticosteroid doses compared to low-dose corticosteroids were 2.4 (95% CI, 0.8 to 6.4). An additional 42 studies with mean odds ratio of 1.0 would be necessary to reduce odds-ratios of developing osteonecrosis with high-dose corticosteroids to under 1.1 suggesting that there exists nominal publication bias. Heterogeneity was investigated by conducting subgroup analyses and the extent evaluated using Cochrane Q and I^2 statistics with higher values suggestive of greater heterogeneity. There were substantial heterogeneities among 4 studies evaluating effects of low- and high-dose corticosteroids in osteonecrosis development (Cochrane Q = 7.8; I^2 = 61.4%; P = 0.05). Substantially less heterogeneities were found in subgroup analyses involving 3 reports on renal transplant recipients (Cochrane Q = 2.3, I^2 = 12.2%; P = 0.32). Marked homogeneity was found between 4 reports evaluating corticosteroid effects on osteonecrosis development (Cochrane Q = 2.1; I^2 = 0%; P = 0.32). In addition, substantial homogeneity was found in the subgroup of 3 reports investigating effects of corticosteroids on osteonecrosis incidences in hematopoietic stem cell transplant recipients (Cochrane Q = 1.8; I^2 = 0%; P = 0.4).