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Review

Steroid induced osteonecrosis: An analysis of steroid dosing risk

Christian Powell ^{a,1}, Christopher Chang ^{b,*}, Stanley M. Naguwa ^a, Gurtej Cheema ^a, M. Eric Gershwin ^{a,*}^a Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, United States^b 1585 Railroad Avenue, Crescent City, CA 95531, United States

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ABSTRACT

Osteonecrosis is a serious condition involving bone destruction that frequently requires surgical treatment to rebuild the joint. While there is an abundance of literature documenting corticosteroid related osteonecrosis, there is no consensus as to the relative risk of osteonecrosis after administration of steroids via parenteral, oral, topical, inhaled and other routes. This risk is an important prognostic indicator because identification and conservative intervention can potentially reduce morbidity associated with aggressive surgical treatment of osteonecrosis. This paper provides insight into establishing guidelines related to the risk of developing osteonecrosis as a result of corticosteroid use. Case studies, retrospective studies and prospective studies in humans on different corticosteroids and varied dosages were assessed. Most cases of osteonecrosis are secondary to systemically administered corticosteroids and/or high dose daily therapy, particularly in patients with underlying comorbidities including connective tissue diseases, hyperlipidemia, or previous trauma. Previous case reports of osteonecrosis related to inhaled or topical use of steroids are complicated by the fact that in the great majority of cases, the patients are also treated with systemic steroids prior to the development of osteonecrosis. Based on the literature, a set of recommendations regarding the risk of osteonecrosis in patients on steroids was formulated.

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* Corresponding authors. Chang is to be contacted at Pacific Coast Allergy, 1585 Railroad Avenue, Crescent City, CA 95531, United States. Tel.: +1 707 464 3430; fax: +1 707 464 4668. Gershwin, Tel.: +1 530 752 2884; fax: +1 530 752 4669.

E-mail addresses: c3chang@yahoo.com (C. Chang), megershwin@ucdavis.edu (M.E. Gershwin).

¹ Contributed equally to the preparation of this paper.

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1. Introduction

Osteonecrosis, otherwise known as ischemic necrosis, avascular necrosis, aseptic necrosis of bone, osteochondritis dissecans or bone death results in collapse of the normal architecture of the skeletal framework, leading to significant clinical morbidity, including progressive joint pain and loss of function [1]. The most common cause of osteonecrosis is trauma, which leads to mechanical interruption of nutrient delivery to the bone, but there are many non-traumatic causes or associations as well. By far the most well known association is related to the use of corticosteroids, but other iatrogenic causes including alcoholism, radiation treatment, bisphosphonate use, and possibly even cigarette smoking, exist. Other etiologies for osteonecrosis include anatomical deformities such as Legg–Perthes–Calves disease, dislocation of a joint and slipped femoral capital epiphyses. Osteonecrosis has also been reported to occur as a result of exposure to hyperbaric conditions, and has been tenuously associated with conditions in which a lipid disorder exists, such as lipid storage diseases and even pregnancy. The list of potential causes is lengthy and beyond the scope of this article, the focus of which is to attempt to navigate the extensive literature on corticosteroid associated osteonecrosis in order to decipher trends in risk related to corticosteroid use.

2. Corticosteroids and osteonecrosis

Harvey Cushing first recognized the adverse effects of hypercortisolism on bone tissue in the early 1930s. Since then, multiple reports of bone death have increased our awareness of the potential for the development of osteonecrosis in patients on corticosteroids [1,2]. Steroid induced osteonecrosis has in fact been described in numerous publications, ranging from case reports to prospective studies. There is no doubt that there is a real risk of osteonecrosis with steroid use. However, it is often difficult to determine the extent of causality between steroid use and osteonecrosis because many of the conditions they are used to treat can also cause or predispose to osteonecrosis. Indeed, there appears to be a significant difference in the incidence of corticosteroid induced osteonecrosis depending on the underlying condition for which corticosteroids are administered. It is also not clear whether the risk of osteonecrosis is more closely related to cumulative dose, maximum dose or duration of therapy. Topical, inhaled and oral glucocorticoids are some of the most frequently used treatments for eczema, asthma, allergic rhinitis, pulmonary diseases, autoimmune disease and other inflammatory diseases, and it is therefore vital to identify those at particular risk for complications.

The association between corticosteroid use and osteonecrosis was first described in renal transplant patients who were undergoing immunoablation or immunosuppression as part of their transplant regimen [3]. Multiple reports elucidating this connection have been published and a cause–effect relationship is now well established. Early diagnosis has proven to be problematic as the majority of patients are asymptomatic until significant damage to bone has occurred. Osteonecrosis tends to occur in a younger, more active age group and because there are limited treatment options for advanced disease, early identification is vital. Multiple treatment options have been explored for osteonecrosis. Presently, the best option for preventing complete joint replacement is the diagnosis of subjects in earlier stages before the joint becomes compromised. Again, this

emphasizes the importance of identifying high-risk patients as early as possible.

3. Epidemiology

The incidence of steroid induced osteonecrosis is estimated to be approximately 10,000 to 20,000 per year in the United States. Steroid induced osteonecrosis accounts for 10% or more of the 500,000 total joint replacements performed annually in the United States [4]. Approximately 75% of patients with steroid induced osteonecrosis are in their 30's to 60's, with the exception of SLE patients who make up a younger cohort [5]. The average age of steroid induced osteonecrosis is 33 and since the only treatment is surgery, these individuals will require multiple surgeries over their lifetime [6]. Male to female ratio is 7:3 with the exception of patients with underlying systemic lupus erythematosus (SLE), in which there is a higher female proportion. Early diagnosis is essential as prognosis and treatment options decline as the disease progresses.

Corticosteroid use now falls behind only trauma as the most common etiology of osteonecrosis, with a prevalence ranging between 3 and 38% [1]. It is estimated that 30 million Americans require glucocorticoids for various conditions. The incidence of steroid induced osteonecrosis may reach 40%, depending on the duration, dose or underlying disease [6,7].

4. The clinical presentation of steroid induced osteonecrosis

The most commonly affected sites of osteonecrosis include the femoral and humeral heads, but osteonecrosis can occur elsewhere as well, including knees (femoral condyles and proximal tibia) [8], small bones of the foot, ankle, and hands (including scaphoid and lunate), vertebrae and bony structures of the face [9]. The onset of steroid induced osteonecrosis is usually insidious or vague in early stages. Symptoms may not occur for weeks to up to a year after cessation of steroid use. The pain may be referred. For example, in osteonecrosis of the femoral head, unilateral hip pain is usually the presenting symptom, but pain may also be referred to the groin, thigh, knees or buttocks. The contralateral hip will become affected within 2 years in up to 55% of cases [1]. Function may be affected as well, and many patients will present with a painful limp, which is aggravated by weight bearing and partially relieved by rest. Progression of pain is common and in advanced disease, pain is also present at rest. Range of motion and disability are progressive in the late stages, and as hip arthroplasty becomes imminent, pharmacologic intervention is of suboptimal effectiveness and is limited to analgesics. Several classification systems have been proposed to grade the severity of osteonecrosis. In the Ficat and Arlet scheme, stages 1–2 are reversible while stages 3–4 denote end stage disease with irreversible damage.

5. Methods

Medline search of published studies with key words “osteonecrosis” and “corticosteroids” from 1961 to 2010 was conducted. From this search and their accompanying references a total of 490 studies dated from 1959 to the present were reviewed, and 396 were determined to be pertinent to our discussion. Studies consisted of animal and human studies. The “human” literature included case reports, reviews, prospective studies and retrospective studies.

Manuscripts were reviewed with particular reference to the pathogenesis, clinical presentations, risk factors, and steroid dose association with osteonecrosis.

6. Results

It has been reported that those at particular risk of development of osteonecrosis have received high dose, long term and long acting preparations of steroid. Similarly, cumulative dosing has also been reported as having a significant risk in pathogenesis. However, multiple studies have also reflected occurrence in those treated with short courses of high dose steroid, and more rarely, with low dose, short duration courses including inhaled and topical preparations. Animal models have helped to establish a cause and effect relationship to steroid dosing.

6.1. Animal studies

The pathogenesis and immunology of osteonecrosis will be discussed in subsequent articles in this series on osteonecrosis. In 2008, Motomura et al. [10] described the relationship between steroid dosing and osteonecrosis in rabbit models. Rabbits were treated with 1, 5, 20, and 40 mg/kg of methylprednisolone (MPSL), resulting in incidence of osteonecrosis of 0, 42%, 70%, and 96%, respectively. Histologically, reparative tissues around the osteonecrosis sites were observed in the rabbits with 5 mg/kg MPSL, but not observed in rabbits with 20 and 40 mg/kg MPSL. On hematological examination, hyperlipidemia and thrombocytopenia were most apparent in the rabbits receiving 40 mg/kg MPSL. Overall, this study highlights the statistically significant association of dose and osteonecrosis occurrence, and suggests that hyperlipidemia is important in its pathophysiology. Similarly, Yamamoto et al. [11], examined the effect of pulsed doses of methylprednisolone acetate on bone and bone marrow tissue in rabbits, and observed the formation of osteonecrosis at 4, 6, 8, and 10 weeks. Forty-three percent of the rabbits developed osteonecrosis in multiple sites by the fourth week after injection with 20 mg/kg of methylprednisolone. Other factors related to altered lipid metabolism also were found to be present, including fatty liver, hyperlipidemia, and intraosseous fat embolism. In 2009, Yang et al. [137], studied mouse models of steroid induced osteonecrosis. Interestingly, the authors found discontinuous therapy was less osteonecrotic than continuous dexamethasone treatment, consistent with the possible benefits of a “steroid holiday” seen in clinical settings.

6.2. Human studies

The case reports of corticosteroid induced osteonecrosis are presented first, followed by groupings of larger prospective, retrospective, case series, or cohort studies, which have been divided by underlying disorder. The underlying diseases with a high reported prevalence of steroid induced osteonecrosis include systemic lupus erythematosus, renal transplant, bone marrow transplant, cardiac transplant, lung transplant, liver transplant, acute lymphocytic leukemia, Hodgkin's disease, multiple myeloma undergoing chemotherapy, severe acute respiratory syndrome (SARS), multiple sclerosis, and neurosurgical patients. The majority of studies of corticosteroid induced osteonecrosis have been reported in SLE patients or renal transplant patients. In most of these and other studies, the steroid administered differs in name and in properties, such as half-life or relative strength. In order to facilitate comparison, a table outlining the difference between commonly used corticosteroids is shown in Table 1.

Table 1
Relative potencies of corticosteroids.

Preparation	Dose (mg)	RP	Duration
Hydrocortisone	10	1	Short
Cortisone	12.5	0.8	Short
Prednisone	2.5	4	Intermediate
Prednisolone	2.5	4	Intermediate
Methylprednisolone	2	5	Intermediate
Triamcinolone	2	5	Intermediate
Paramethasone	1	10	Long
Dexamethasone	0.4	25	Long
Betamethasone	0.3	33	Long

The relative potency relates only to drug half-life, not biologic half-life. In other words, the effect of corticosteroids may persist long after the drug has dissipated from the sera or tissues.

Table 2
Risk factors for the development of osteonecrosis.

Medications
Corticosteroids
Protease inhibitors
Connective tissue diseases
APLS
Ehlers danlos
AS
GCA
PM/DM
PMR
RA
SCL
Sjogrens
SLE
Hematologic diseases
ALL
Aplastic anemia
Lymphoma
PML
Post-BMT
Solid malignancies
Bronchogenic CA
Ovarian CA
Testicular carcinoma
Organ transplant
Heart
Lung
Renal
Hemoglobinopathies
DIC
Hemophilia
Polycythemia
Sickle cell
Thalassemia
Genetic
Gaucher disease
Legg–Calve–Perthes disease
GI
Crohn's/UC
Pancreatitis
Refractory celiac disease
Metabolic/endocrine
Cushing's
Hyperlipidemia
Hyperparathyroidism
ID
HIV
Meningococemia
Misc
Alcohol
Dybaric
Fat emboli
Idiopathic
Pregnancy
Premature ovarian failure
Radiation exposure
Smoking
Spinal cord injury

Table 3
Case reports of steroid induced osteonecrosis with particular attention to steroid dosing. Organized chronologically.

Study/Ref.	No. of pts	Site	Steroid route	Daily dose	Duration	Cumulative dose prednisone equivalent	Other risk factors
Kontovazenitis et al. [78]	1	Knee	IA	Intraarticular steroid not reported	NA	NA	NA
Yildiz et al. [79]	1	Knee/femoral head	IV/PO	MPSL/prednisone 1000 mg × 3 days, 500 mg × 3 days, and 250 mg × 3 days, followed by taper over 3 weeks	4 weeks	6562 mg during pulse.	ITP
Kosaka et al. [80]	1	Bilateral femoral heads	IV/PO prednisolone	Pulse; taper	423 days	Total in taper not described. 7365 mg	Breast Ca; radiation
Gunal et al. [12]	1	Bilateral femoral heads	IM prednisolone	Single IM injection	Single IM injection	75.5 mg	None
Hussain et al. [81]	3	Bilateral femoral head; bilateral knees; bilateral knees	PO	MPSL equivalent. Varied dose.	11 days	981 mg; 1500 mg; 1680 mg	None
Drigo et al. [17]	1	Femoral head	Topical/po/inhaled	3-day treatment with topical steroids (mometasone lotion 0.1%); 10-day course of oral steroid (betamethasone 1 mg/kg for three days with tapering of the dose in the next seven days) and 3 courses of inhaled beclometasone dipropionate (800 µg/day) lasting 2–3 weeks	Topical—3 days; oral—10 days; inhaled—3 courses lasting 2–3 weeks each	NA	None
Yamamoto [13]	1	Femoral head	IA	MPSL 80 mg × 1	Single IA injection	100 mg	None
Tasic et al. [82]	1	Bilateral talus	IV/PO	MPSL/prednisone 40 mg po × 4 weeks; pulse IV 500 mg × 3; prednisone 40 mg/day for 10 days followed by 25 mg on alternate days and then tapered; additional prednisone required	~1 year	4730 mg prednisone and 1500 mg MPSL (1875 mg pred equiv).	Nephrotic syndrome
Lanyi et al. [83]	1	Left “foot”; tibia	PO	Prednisone 40 mg/day with additional ? steroid at onset	12 weeks	>3360 mg	Crohn's
Jafrri et al. [16]	1	Knee	Inhaled/intraarticular	40 mg Depo-Medrone × 1; long term inhaled steroids	NA	NA	?Ethanol abuse
Ito et al. [84] (Japanese study)	1	Knee	PO	Prednisolone	10 years	NA	Ulcerative colitis
Loddenkemper [85]	1	Femoral head	IV/PO	Prednisolone (maximum dose 500 mg/day (pulse therapy; average dose 15 mg/day)	~20 years	~106,800 mg prednisolone	MCTD
Skinner [86]	2	Femoral head	PO	Prednisolone 40 mg × 10 days Prednisolone 40 mg/day × 6 weeks	10 days × 4 courses; 6 weeks 7 days	NA	Infertility Tobacco
Clinkscales [87]	1	Knee/ankle	IV methylprednisolone 7 months prior.	NA	7 days	4.5 g MPSL (5625 mg pred equivalent)	None
Sakai et al. [88]	1	Femoral head	NA	NA	NA	NA	NA
Reichert-Pénétrata et al. [89]	1	Bilateral femoral head	Topical	Betamethasone dipropionate Daily average 30 mg × 5 years; intermittent use × 20 years	~20 years	445,000 mg	None
Nasser et al. [90]	1	Bilateral femoral head	IM	16 total injections of depot corticosteroid: nine of Kenalog (triamcinolone; Bristol-Myers Squibb, Hounslow) 40 mg and seven of Depo-Medrone (MPSL) 80 mg.	Over 10 years	360 mg triamcinolone (450 mg pred); 560 mg methylprednisolone (700 mg pred)	None
Kubo et al. [91]	1	Femoral head	Topical	2–3 g/day of 0.05% clobetasol propionate	2 years and 10 months	~2530 g over time period	None
Abhyankyan et al. [92]	1	Femoral head	IV	Dexamethasone 8 mg q 8 hourly	5 days	800 mg	Acute promyelocytic leukemia
Spencer et al. [93]	1	Femoral head	IM	Betamethasone two doses of 12 mg over 24 h × 6	Over 3 months	1166 mg	Pregnancy
Carter et al. [94]	2	Femoral head	PO	Prednisone 40–80 mg po q day; prednisone 60 mg po q day with taper over 3 months	3–4 months	NA	Crohn's

Braverman et al. [95]	1	Bilateral knees	Enemas	Hydrocortisone 100 mg retention enemas×6	3 months	150 mg	Ulcerative colitis
Hurel [96]	1	Femoral head	IV/PO	Dexamethasone 8 mg/day×2 months; dexamethasone 1 mg/day×?; prednisolone 5 mg po q day×?	~2 months	3200 mg	None
Gogas et al. [97]	1	Femoral head	IV	Dexamethasone 20 mg IV×6; dexamethasone 20 mg IV×12	18 total doses over 3 years	4.32 g	Ovarian Ca; chemotherapy
Hui et al. [98]	4	NA	IV	Dexamethasone	NA	Total dexamethasone dose equivalent to that of prednisone, 3.4–5.0 g/M2	Acute lymphocytic leukemia
Cowan [99]	1	Mandible	PO/IV	Prednisone 60 mg po q day with taper; intermittent pulse therapy	~2 years	NA	Myasthenia gravis
Jones et al. [100]	1	Multifocal knees/hips, ankle	IV	Dexamethasone 10 mg IV q 6 h	10 days	Dexamethasone 200–250 mg (1333–1666 mg pred)	Bronchogenic Ca
Madsen et al. [101]	1	Femoral head	PO	Prednisolone 40 mg po BID	28 days	2–3 g	Ulcerative colitis
Osebold [102]	1	Humeral head	IV	Dexamethasone pulse and taper	26 days	5375 mg	Cord injury
Mizuta [103]	1	Bilateral patella	PO	Prednisolone 25 mg/day	5 years	44,500 mg	Polymyositis
Beyer et al. [104]	1	Bilateral femoral head, capitellum, trochlea	PO	Prednisone 120 mg/day	~5 years	NA	Dermatomyositis
Obrien et al. [15]	1	Femoral head	Inhaled/IM	Inhaled steroids;16 injections of depot cs: 9 of Kenalog 40 mg and 7 of Depo-Medrone 80 mg.	Over ten years	NA	Allergic rhinitis
McCarty et al. [105]	1	Knee	PO/IA	IA injections; 2× MP SL tablets×6 days	~12 days	NA	None
Adleberg et al. [8,106]	1	Talus	PO/IA	Prednisone 5 mg/day; IA "cortisone×3"	NA	NA	None
Kelman et al. [8]	2	Knee	PO	NA	NA	NA	NA
Eghwrujdjakpor et al. [107]	1	Femoral head	PO	Hydrocortisone 60 mg/day with taper	~3 months	NA	None
Archer et al. [108]	1	Knee/femoral head	PO/IV	Dexamethasone. The highest daily dose was 32 mg in four divided doses for a one day period. This was tapered over the remaining two weeks.	15 days	248 mg of dexamethasone over a fifteen day period (1653 mg pred)	None
Gold et al. [109]	1	Bilateral knee	PO	Prednisone 60 mg po×2 months	2 months	3600 mg	IVDA. Did not consent for HIV testing. Steroid treatment for ITP.
Jones et al. [110]	3	Femoral head	IV	High dose pulsed MP SL: single dose of 1 g vs. 500 mg vs. 40 mg (double blind study)	Single dose	1250 mg vs. 625 mg vs. 50 mg	RA
Preston-thomas et al. [111]	2	Bilateral femoral head; left knee and left femoral head	IV/PO	Patient 1: betamethasone 16 mg/day×22 days and then on a "reducing dose"×11 days; patient 2: 1st episode: betamethasone 24 mg×1, followed by 16 mg/day×19 days. 2nd episode: betametasone "again given for 19 days."	33 days; 39 days	352 mg + unknown taper dose; 632 mg (assuming 16 mg/day was administered during 2nd episode (2933 mg; 5266 mg of pred equiv)	Cerebral edema treatment
Yamaguchi [112]	2	Patella	PO	Prednisone?	NA	NA	Asthma;SLE
Kalliel et al. [14]	1	Left femoral head	PO/inhaled	Prednisone 40 mg/day with taper×2; inhaled steroids	>1 year	NA	Asthma
Tang et al. [113]	1	NA	Topical	0.025% Flucinolone topical cream (1 tube–5 g every 2 days)	4 years	3560 g (equivalent to prednisolone 1140 mg)	Psoriasis
Spencer et al. [114]	1	Femoral head	PO	Prednisolone 100 mg BID×(time period not reported); IV "high dose" MP SL (quantity not reported); prednisolone 4 mg maintenance for 10 years	10–15 years	NA	Renal transplant
Hogan et al. [115]	1	Bilateral hip	Topical	Long term use of 0.05% Clobetasol propionate ointment, ave 250 g/month	5 years	15,000 g of clobetasol	Ethanol abuse
Aoki [116]	2	Hip	Oral	Average dose of 150 mg per day; average dose of 53 mg per day	18 days	Prednisolone equivalent 2675 mg and 1050 mg, respectively	None
Roseff et al. [117]	1	Femoral head	IM/IA	Multiple soft tissue and intraarticular injections	>18 years	Estimate of 13 g of MP SL (16,250 mg pred)	None

(continued on next page)

Table 3 (continued)

Study/Ref.	No. of pts	Site	Steroid route	Daily dose	Duration	Cumulative dose prednisone equivalent	Other risk factors
Fast et al. [118]	1	Femoral and humeral heads	NA	Short term treatment for brain edema	NA	NA	NA
Taylor et al. [119]	3	Femoral head	IV/PO	Dexamethasone short term treatment for brain edema or spinal cord edema	Unknown; 43 days; 32 days	Unknown; 2813 mg; 2533 mg	None
Snyder et al. [120]	2	Femoral head	PO	Hydrocortisone 60 mg/day; Hydrocortisone 30–50 mg/day	? Months–1 year	Unknown	None
Williams et al. [121]	2	Multi; humeral head; femoral head	PO	Prednisolone 2–20 mg/day; cortisol 5–12 mg/day	18 months; 14 months	2–7 g of prednisolone; 8 g cortisol	Addison's
Hendry [122]	1	Femoral head	NA	NA	NA	NA	NA
Watkins [123]	1	Femoral head	PO	Prednisolone 60 mg × 14 days q 6 weeks × 6 courses	Prednisolone 60 mg × 14 days q 6 weeks × 6 courses	NA	Hodgkin's
McCluskey et al. [124]	3	Bilateral femur/humeral head	PO	Hydrocortisone for brain edema. After first 32 days, started on 7–9 mg prednisone per day; dexamethasone for brain edema; dexamethasone for spinal cord injury	High dose for 32 days and then 7–9 mg for 7 months; 18 days; 37 days	Dexamethasone 191 mg equivalent for first 32 days and additionally 1680 mg prednisone over 7 months; dexamethasone 216 mg; dexamethasone 172 mg (2953 mg; 1440 mg; 1146 mg of pred)	None
Anderton et al. [125]	1	Bilateral humeral head	PO	Dexamethasone 4 mg po 6 h	1 week	1120 mg	None
Black et al. [126]	4	Patient 1: bilateral femoral head, bilateral humeral head, right tibial plateau; patient 2: bilateral hip, shoulders, right wrist; patient 3: bilateral femoral and left humeral head; Patient 4: Bilateral femoral heads	PO	Dexamethasone for brain edema or spinal edema (daily doses not described)	Patient 1: 24 days; patient 2: 20 days; patient 3: 30 days; patient 4: 15 days	Patient 1: 136 mg dexamethasone; Patient 2: 217 mg; Patient 3: 165 mg; Patient 4: 140 mg (906 mg; 1446 mg; 1100 mg; 933 mg of pred)	None
Richards et al. [127]	6	Femoral Head	PO	1. Prednisone 10–30/day 2. MPSTL 12–36 mg/day 3. Prednisone 40–80 mg/day 4. Prednisone 10–40 mg/day 5. MPSTL 8–32 mg/day 6. Prednisone 5–20 mg/day	1. 20 years 2. 15 years 3. 6 weeks 4. 15 years 5. 3.5 years 6. 2 years	NA	None; patient # 6 ethanol abuse, polycythemia

7. Case reports

Interpreting data from case reports must be undertaken carefully. Gleaning information regarding the effect of exact steroid dose, duration, cumulative dose–risk relationship or preparation on the development of osteonecrosis must be interpreted within the context of confounding factors within a patient. The pathogenesis of osteonecrosis is indeed likely related to a multi-hit theory in a predisposed host. In addition to the type and dosage of steroids, the underlying condition, other concurrent medications, and lifestyle variables such as alcohol and cigarette smoking are likely to be confounding variables. Furthermore, given the volume of prescriptions for intraarticular (IA), intramuscular (IM), topical, oral and inhaled steroids, low numbers of isolated case reports needs to be interpreted within the context of the individual patient's history. Finally, the sheer variety of preparations and dosing, which are potentially prescribed by multiple physicians throughout a patients' lifetime, make calculating and tallying the exact cumulative dose of steroid difficult and fraught with potential error. A list of predisposing risk factors for osteonecrosis is shown in Table 2.

In all, 66 case reports consisting of 1 to 6 patients were identified and included in Table 3. These patients had a wide range of diseases, including idiopathic thrombocytopenic purpura, polycythemia, Addison's, nephrotic syndrome, inflammatory bowel disease, alcohol abuse, renal transplant, autoimmune inflammatory disease (SLE, MCTD, dermatomyositis, polymyositis, rheumatoid arthritis and psoriasis), malignancy (breast cancer post radiation, Hodgkin's lymphoma, bone marrow transplantation, acute lymphocytic leukemia, and bronchogenic carcinoma), asthma, allergic rhinitis, neurosurgical patients, myasthenia gravis, and pregnancy. The femoral head was the most commonly involved site, occurring in 54/85 patients, followed by the knee, humeral head and ankle. The most commonly associated administered route included intravenous (IV) pulse steroids, followed by oral, and rare reports of intramuscular depot ($n=5$), topical ($n=5$) intraarticular ($n=4$), inhaled ($n=4$), and enema ($n=1$) steroid induced osteonecrosis.

Single dose steroid (IM or IA) and subsequent risk of osteonecrosis are of particular concern and were examined. This was found to be uncommon with only 2 case reports of isolated IM or IA injection and subsequent osteonecrosis [12,13]. The remainder of reported IA/IM associated cases includes concurrent or subsequent addition of other steroid routes of administration (inhaled, oral, pulse, topical, and repeated IA/IM injections). Interpretation of case reports of osteonecrosis linked to topical steroids was limited. Of the 5 described cases, 4 were treated with long term topical preparations from 2 to 20 years with rough cumulative doses ranging widely from 1 to 15,000 mg prednisone equivalent. The majority of cases were also treated with additional preparation(s) of oral or inhaled steroids. Thus, osteonecrosis is likely to be an exceedingly rare phenomenon with topical steroids alone and is more likely to occur after prolonged therapy with cumulative doses and concurrent use of additional steroid therapy preparations. The risk of osteonecrosis from inhaled steroids is of concern given the vast number of steroid inhalers prescribed for asthma. In theory, the cumulative dose of inhaled steroid over a lifetime could add up to sizeable amounts. However, conclusions regarding steroid risk are again difficult to draw from the 4 reported cases related to inhaled steroids [14–17] because all cases were concurrently or subsequently treated with oral steroids prior to the diagnosis of osteonecrosis. Though no studies have been performed, the recent unapproved but commonplace use of swallowed ultra high dose inhaled steroids (specifically fluticasone dipropionate) to treat eosinophilic esophagitis will increase the risk of osteonecrosis in these patients.

The majority of case reports involved high dose pulse steroids with dexamethasone or methylprednisolone, followed by varying durations of oral steroids on a daily or repetitive basis. The cumulative

dose was described in most reports (45/66), and ranged from 150 to 445,000 mg of prednisone equivalent (average 5969 mg prednisone). Approximately 1000 mg of oral prednisone administered within a short window will place patients at increased risk. Any addition of parenterally administered steroids, further increases this risk significantly. Parenterally administered steroids are often discussed in terms of their serum half-life but one should remember that the biologic half-life of the drug can often significantly exceed its serum half-life.

8. Risk of steroid induced osteonecrosis in patients with systemic lupus erythematosus

Systemic lupus erythematosus is a multi-organ, multisystem autoimmune disease for which steroids are an essential aspect of therapy. Steroid induced osteonecrosis in SLE is well established [18–20] and is clinically apparent in 4 to 15% of patients, but rises to nearly 40% when asymptomatic, image-proven osteonecrosis is taken into account [21]. Typically SLE patients have multi-joint onset of osteonecrosis, the hips being the most common site, followed by the knees and shoulders [22]. The goal of this amalgamation of prospective, retrospective and cohort studies is to try and establish a pattern of risk of steroid dosing and development of osteonecrosis in SLE patients. A summary of these studies is presented in Table 4.

8.1. Cushingoid habitus and steroid dose

A cushingoid appearance tends to occur with higher or longer-term dosing of steroid therapy. 5/20 studies specifically noted the correlation of cushingoid appearance and development of osteonecrosis. Mont et al. [34], studied clinical and laboratory factors in patients with systemic lupus erythematosus to identify subgroups at higher risk for developing osteonecrosis. 31 out of 103 (30%) patients studied with SLE developed osteonecrosis and were found to have significant increases in cushingoid body habitus (74% with vs. 42% without, $p=0.002$), thrombophlebitis, vasculitis, cigarette smoking, and preeclampsia. Similarly, Gladman et al. [23], Mok et al. [24], Massardo et al. [25] and Zizic et al. [22] found a statistically significant correlation between osteonecrosis and cushingoid appearance (OR 3.8 in Gladman study). However, osteonecrosis can exist in SLE in the absence of cushingoid features.

8.2. Maximum daily dose/pulse therapy

The dose of steroid influences the risk for developing osteonecrosis. In the studies compiled, 16/20 specifically recorded and addressed daily dosing of corticosteroid. Out of these 16 studies, 6 studies did not find a statistically significant correlation between daily steroid dosing (mean or maximal daily dosing) and the development of osteonecrosis [26,27]. Interestingly, the majority of the negative association occurred in papers prior to 1978 [19,28–30]. In 1960, Dubois et al. [28] was the first to recognize a connection between SLE and development of osteonecrosis. However, he did not find a relationship to steroid dosing and occurrence, probably because patients had received high doses and the study was done before MRI. Similarly, in 1974 and 1976, Bergstein et al. [19] and Smith et al. [30], respectively, found no correlation between daily steroid dosing and osteonecrosis. In 1978, Diamant et al. [29] failed to find a correlation between peak dose, duration or cumulative dose of steroid and osteonecrosis. However, since then, only 1 further study in 2010 by Nakamura et al. [26], echoed this negative correlation. The authors of this study concluded that there is no statistically significant difference in the highest daily dose of steroids in osteonecrosis and non-osteonecrosis groups ($p=0.072$), though the p -value did approach significance. A major criticism of this study is that methylprednisolone

Table 4
Prospective, retrospective, case control studies of steroid induced osteonecrosis in SLE.

Study/Ref.	Study design	No. of patients (+ ON/–ON)	Daily dose	Treatment duration	Cumulative dose (steroid equivalent in prednisone)	Site of lesion	Remarks
Uea-areewongsa et al. [35]	Retrospective Case control	41/186 only 20 patient included in data analysis	NA	NA	NA		Use of steroids (recorded as evidenced by maximum and mean daily prednisolone dose) was significantly higher in the ON group than in controls
Nakamura et al. [26]	Prospective	169 pts ON in 260 of 676 pts (38%) Pediatric: 4/72 joints (6%) Adolescent: 49/100 joints (49%) Adult: 207/504 joints (41%)	The mean highest daily corticosteroid dosages were 51.4, 60.4, 57.4 mg/day in pediatric, adolescent, adults, respectively. The mean highest daily corticosteroid dosage according to body weight was 1.5 mg/kg/day (range 0.7–3.0) in pediatric patients, 1.2 mg/kg/day (range 0.6–2.0) in adolescent patients, and 1.1 mg/kg/day (range 0.4–1.9) in adult patients. (P=0.0001).	NA	NA	Hips and knees	Rate of ON and mean highest daily steroid dose significantly lower in pediatrics vs. adolescent and adult (p<0.0001) However: Highest daily dose of steroid not SS different in + AVN vs. –AVN in mean daily dose (P=0.072) and according to body weight. (P=0.820) Limitations: MPPL pulse therapy not studied or reported
Jaovisidha [37]	Prospective	2/11	NA	NA	4920 mg	NA	The 2 AVN patients had longest duration of steroid treatment before MR study (105 and 99 days) and higher cumulative dose of prednisolone compared to non-AVN patients.
Gladman et al. [36]	Retrospective Case control	95/744	Maximum daily dose in + AVN/–AVN: 44.4/28.1 mg	NA	IN + AVN/–AVN: 23.1/15 g	Hip most common	AVN significantly associated with the use of CS (OR=19), maximal dose of steroids (OR=1.02), cumulative dose (OR=1.04) and duration of therapy (OR=1.15); however, in the multivariate analyses, only the use of corticosteroids remained significantly associated with osteonecrosis (OR=18.5). cushingoid appearance OR 3.8
Oinuma et al. [27]	Prospective	32/72 (44%)	40 mg/day or more equivalent prednisolone The initial mean (SD) CS dose 58.2 (10.1)/58.6 (16.6) mg/day in the + AVN/–AVN 17 pts in ON group 18 in non-ON group treated with MPPT	AVN onset after 39.6 and 100.2 days of treatment.	NA	Multi-joint	Early development of ON in SLE was related to an event just after high dose CS treatment, and was not related to the total treatment period, the highest daily dose, a continuous high dose, or the cumulative dose of corticosteroid. SLE ON lesions developed very early (1–2 months) after starting high dose CS treatment.
Zonana-Nacach et al. [32]	Retrospective	47/539 (8.7%)	Prednisone high dose (>60 mg/day for >2 months) in 21% of total cohort Pulse MPPL (1–3 g IV) in 30% of total cohort	NA	Converted to relative risk.	NA	The risk significantly increased with exposure to a high dose of prednisone. Each 2 mo of exposure to >60 mg of prednisone was associated with 1.2-fold increased risk for development of AVN Risk was not associated with cumulative dose or pulse therapy
Mok et al. [24]	Retrospective	38/143 (26%)	NA	NA	AVN+ vs. AVN– in 1 and 4 month cumulative dose: 1.8 vs. 1.1 and 4.5 vs. 2.8 g, respectively; P<0.01 in both	NA	Highest cumulative prednisolone dose in 1 and 4 mo was significantly higher in SLE patients with ON vs. without ON (1.8 vs. 1.1 and 4.5 vs. 2.8 g, respectively). + Correlation with cushingoid habitus and ON

Mont et al. [34]	Cohort	31/72 (43%)	Mean maximal prednisone dose was 60 vs. 37 mg for SLE patients + AVN vs. – AVN	NA	NA	NA	<p>SLE pts with osteonecrosis had significant increases in cushingoid body habitus and higher maximal prednisone doses compared with SLE patients without osteonecrosis. + Correlation between steroid dose and development of AVN, BUT other factors likely play role as well.</p> <p>Drawbacks: only analyzed symptomatic ON + Relationship between AVN and conventional CS treatment.</p> <p>No increased risk of AVN in MPPT-treated patients, even though they cumulated the highest CS doses.</p> <p>Shortcomings: study might have underestimated the true occurrence of AVN because it was performed by radiographs and/or bone scan and in the follow up it included only symptomatic AVN.</p> <p>Patients who developed AVN received a higher dose of steroid in a shorter period of time.</p> <p>+ Correlation with + AVN and cushingoid appearance, use of MPPL ($P < 0.045$), steroid doses $> \text{ or } = 40 \text{ mg/day}$ during the first month of treatment, a ratio of steroid dose in grams/year $> \text{ or } = 12 \text{ SS}$ only with MSPL and cushingoid appearance</p> <p>Both IV pulse CS and oral prednisolone therapy at a dose $> 30 \text{ mg/day}$ for at least 1 month were risk factors for ON. However, it is unclear whether short term high dose MPPL pulse therapy is a risk factor.</p> <p>CS intake during the first 1.5 years after diagnosis of SLE and during the third year after diagnosis was significantly greater for the patients AVN+ vs. AVN–.</p> <p>+ Relationship between oral dose in each time period and development of AVN</p> <p>Comparing steroid dose and bolus steroids indicated that a 9000 mg prednisone (equivalent) cumulative dosage given in a month had a 22% incidence of AVN. Bolus dose was not associated with AVN. This quantitative review strongly suggests that steroid dose is the major predictor of the risk of AVN.</p> <p>The oral dose effect amounts to a 4.6% increase in the risk of AVN for every 10 mg/day rise in oral steroids during the first 6 months of therapy</p> <p>Draw backs: only a small number of non-renal cohorts in study (SLE patients have different risks!)</p>
Rascu et al. [38]	Retrospective	6/280 (2.1%)	Mean daily dose 21.3 mg Max daily dose 72 mg	NA	Mean cumulative dose 38,614 mg IV MPPL in 2/6	Hip most common	
Migliaresi et al. [33]	Prospective	7/69 (10%)	NA	3–12 month	Total corticosteroid dose including MPPL therapy in + AVN vs. – AVN was $20.6 \pm 14.9 \text{ g}$ vs. $29.1 \pm 29 \text{ g}$ Total corticosteroid therapy in those not treated with MPPL pulse therapy in AVN+ vs. – AVN was $20.6 \pm 14.9 \text{ vs. } 15.8 \pm 17.7$	NA	
Massardo et al. [25]	Retrospective	Total 17/176 Group A (MPPL): 7/36 patients (19%) Group B (no MPPL): 10/154 (6%) patients $P < 0.04$	Group A: pulse methylprednisolone Group B: no pulse methylprednisolone Steroid dose $> 40 \text{ mg/day}$ in 1st month: 57%/37% in AVN+/AVN–	NA	NA	Femoral head most common	
Ono et al. [31]	5 year prospective study	9/62 total patients (14%)	Prednisone/MPPL at dose of $> 30 \text{ mg/day}$	> 1 month	NA	NA	
Weiner et al. [39]	Retrospective	28/172 (16.3%)	Prednisone/MPPL	NA	NA	NA	
Felson et al. [21]	Metanalysis of 22 studies (SLE, renal transplant, BMT, Hodgkin's)	AVN range 0–31%	1st month, 3 months, 6 months, and 12 months (total steroid/oral steroid), respectively was 127/80, 74/50, 49/34, 29/25.	1-, 3-, 6-, and 12-month periods	NA	NA	

(continued on next page)

Table 4 (continued)

Study/Ref.	Study design	No. of patients (+ON/–ON)	Daily dose	Treatment duration	Cumulative dose (steroid equivalent in prednisone)	Site of lesion	Remarks
Zizic et al. [22]	Prospective	28/54 total patients (52%) 3/6 patients on MPSL developed AVN	The mean daily dose of prednisone for the highest month of therapy was >40 mg/day in 93% and >20 mg/day in all patients with ischemic necrosis of bone.	NA	NA	Multifocal	Cushingoid changes in 24 (86%) of the 28 patients with AVN vs. 4 (15%) of the 26 patients without AVN ($p < 0.0001$). The duration of steroid therapy, total cumulative steroid dose, and the mean daily prednisone dose for the first 1–12 months of therapy were not significantly different between the two groups. Mean daily prednisone dose for the highest single month as well as the highest consecutive three, six, and 12 months of therapy was significantly higher in patients with ischemic necrosis of bone. A lower mean dose of prednisone was required to produce ischemic necrosis of bone in patients with Reynaud's phenomenon. Severity of disease and duration of therapy were not found to correlate with AN. High initial corticosteroid dosages in patients with SLE seem to be associated with the development of AN. No correlation was found with duration, peak dose, or cumulative dose of corticosteroid therapy. No correlation between steroid dose and AVN.
Abeles [40]	Retrospective	17/365 (4.7%)	NA	1, 3, and 6 months Average duration of therapy 4.3 years	Mean total dose in first 1, 3, and 6 mo in +AVN vs. –AVN: 1.4 vs. 0.6 g; 3.5 vs. 1.9 g; 6.4 vs. 3 g	NA	
Dimant et al. [29]	Retrospective Case control	22/234 (9%)	NA	NA	NA	NA	
Smith et al. [30]	Retrospective case control	7/99 (7%)	Patients with AVN: 11.88 mg prednisone Patients without AVN: 14.18 mg prednisone	Patients with AVN: 19.86 months of treatment Patients without AVN: 22.86 months of treatment	Patients with AVN: 13.83 g prednisone Patients without AVN 18.18 g prednisone	NA	
Bergstein et al. [19]	Prospective	14/35	Prednisone 2 mg/kg per day in divided doses. Following remission of activity prednisone was "tapered."	NA	NA	Most common site distal femur	No difference was found in the age of onset of SLE, the duration of prednisone or the average annual dose of prednisone between patients with and without bone disease. + Correlation with total cumulative dose up until dx of ON No association of AVN with steroid therapy
Dubois et al. [28]	Retrospective	11/400	NA	NA	NA	NA	

pulse therapy was not reported or included in the data analysis and may have in turn, led to this negative conclusion.

Since 1978, the evidence is clear that there is a correlation between mean daily dose, maximal daily dose or high dose steroid therapy and the development of osteonecrosis. Massardo et al. [25], found a positive correlation with osteonecrosis and the use of prednisone doses greater than or equal to 40 mg/day. He further noted that high dose methylprednisolone therapy was also a risk factor and concluded that patients who developed osteonecrosis received a higher dose of steroid in a shorter period of time compared with those who did not develop osteonecrosis. Clearly, a lower dose of prednisone administered over a longer time would carry comparably increased risks. Statistical significance was reached with the MPSTL data, but not the prednisone data. Ono et al. [31], found that both IV MPSTL pulse therapy and prednisone >30 mg/day for at least a month were risk factors for osteonecrosis. Zonana-Nacach et al. [32] also demonstrated that the risk of osteonecrosis significantly increased with exposure to high dose oral prednisone. He found that each 2 months of exposure to >60 mg prednisone was associated with a 1.2 fold increased risk for development of osteonecrosis. In the meta-analysis by Felson et al. [21], there was a positive relationship between oral prednisone dose when evaluated at time intervals of 1, 3, 6, and 12 months, and the subsequent development of osteonecrosis. The authors suggested that steroid dose is the major factor in predicting the risk of osteonecrosis. The oral dose effect amounts to a 4.6% increase in the risk of AVN for every 10 mg/day rise in oral steroids during the first 6 months of therapy. Interestingly, they found no association if only a single bolus dose of steroids was used. In 2000, Oinuma et al. [27], found that osteonecrosis development occurred after high dose corticosteroid treatment, but was not related to highest daily dose. Migliaresi et al. [33] did not find an increase in osteonecrosis in methylprednisolone treated patients, even though they accumulated the highest dose. Mont et al. [34] found that SLE patients with osteonecrosis received higher maximal prednisone doses than those without osteonecrosis. Uea-areewongsa et al. [35] found that the use of steroids (recorded as maximum and mean daily dosing) were significantly higher in the osteonecrosis group compared to control. Gladman et al. [36] concluded that osteonecrosis was significantly associated with the use of steroid (OR = 19), and correlated with the maximal dose of steroids per day (OR = 1.02). In a multivariate analysis, only the use of steroids was statistically significant. Finally, the mean daily dose of prednisone for the highest month of therapy was >40 mg/day in 93% and >20 mg/day in 100% of patients who developed osteonecrosis [22]. The mean daily prednisone dose for the highest single month of treatment, as well as, the maximal dose during consecutive 3, 6, 12 months of therapy was significantly higher in patients with osteonecrosis [22]. This study reflects that higher daily dosing has a positive correlation to osteonecrosis development.

8.3. Cumulative dose

The correlation of higher cumulative dose and development of osteonecrosis has also been studied. In all, 13/20 SLE studies commented on cumulative dosing. Out of these 13 studies, 5 studies did not find an association with cumulative dosing [20,21,36–39], while 8 studies did [19–21,25,36,37,39,40]. With regard to positive correlation, Mok et al. [20] identified 38/143 subjects with osteonecrosis and found that the cumulative dose at 1 and 4 months was significantly higher in the SLE patients with osteonecrosis vs. without osteonecrosis (1.8 vs. 1.1 at 1 month and 4.5 vs. 2.8 g prednisone at 4 months). Jaovisidha et al. [37] found that the 2 patients who developed osteonecrosis had the longest duration of corticosteroid treatment and higher cumulative dose compared to the patients who did not develop osteonecrosis, but this was a small cohort of patients and limited conclusions can thus be drawn from it. In a retrospective,

case control series, Gladman et al. [23] identified 95 patients with osteonecrosis out of a total of 744 SLE patients. Data analysis determined a minimally positive odds ratio of 1.04 for cumulative dose, which did not reach statistical significance. Weiner et al. [39], found that corticosteroid intake during the first 1.5 years after diagnosis of SLE and during the third year after diagnosis of SLE was significantly greater in the osteonecrosis vs. non-osteonecrosis group. Felson et al. [21], was the only meta-analysis available and looked at 22 different studies with underlying disorders including renal transplant, SLE, BMT, and Hodgkin's disease. Limited conclusions can be deduced with respect to SLE and steroid dose as only 3/22 studies looked at an SLE cohort. When Felson et al. [21], compared steroid dose and bolus steroids, they calculated that a 9 g prednisone equivalent cumulative dosing given in a month had a 22% incidence of osteonecrosis. Further discussion of this paper will be included in subsequent sections as it applies. Massardo et al. [25] noted a positive correlation with osteonecrosis when patients were treated with a cumulative dose of ≥ 12 g/year. Finally Bergstein et al. [19], similarly found a positive correlation with cumulative dosing. Overall, the data indicates a correlation between higher cumulative dosing and increased risk for osteonecrosis.

9. Risk of steroid induced osteonecrosis in renal transplant patients

It is in renal transplant patients that the association of corticosteroid induced osteonecrosis was first described [3]. Those with years of chronic renal failure and osteodystrophy are particularly prone to steroid induced osteonecrosis. Between 3 and 40% of renal transplant patients suffer from osteonecrosis, but fortunately there has been a decrease in the prevalence with improvement in dialysis maintenance care. There have been numerous studies examining the relationship between steroid use in transplant patients and the development of osteonecrosis. Of particular interest is the relationship between daily dosing, high dose pulse therapy, cumulative dose and the risk of osteonecrosis. 24 pertinent studies were reviewed and are outlined in Table 5.

9.1. Daily dose

18/24 studies selected looked directly at daily steroid dosing as a potential risk factor of osteonecrosis. 5/18 found no statistically significant relationship to osteonecrosis risk [41–44]. Interestingly, as seen with the SLE studies, the negative relationship, was only found in studies that were greater than 25 years old. Since then, there has been repeated and dramatic evidence of a dosing relationship to risk. In 2008, Shibatani et al. [45], performed a retrospective analysis of 150 renal transplant patients, 37 of whom developed osteonecrosis. The authors found a statistically significant dose–response association at 8 weeks after transplantation. Considerable correlation with cumulative dose was found as will be described in the next section. The finding of significantly higher daily dose and risk was echoed in multiple studies [21,46–50]. Koo et al. [7], found that high dose steroid during the first several weeks was more important than total cumulative dose. Patton et al. [49], noted that the mean linear trend of higher daily prednisone dose was also statistically significant ($p < 0.03$) for the development of osteonecrosis. In contrast to the SLE data, the majority of studies (17 of 22) in the Felson meta-analysis were renal transplant studies. Overall, the general consensus among these studies is that a higher daily dose confers a significant risk for developing osteonecrosis. Unfortunately, due to the variation among studies, a recommendation for a universally “safe” steroid dose cannot be made and in all situations, physicians should exercise caution in using steroids and provide appropriate informed consent.

Table 5
Prospective, retrospective, case control studies of steroid induced osteonecrosis in renal transplant patients.

Study/Ref.	Study design	No. of patients (+ ON/–ON)	Daily dose	Treatment duration	Cumulative dose	Site of lesion	Notes
Shibatani et al. [45]	Retrospective	37/150 (24%)	MPSL 500 mg IV during surgery, PSL 50 mg from the day after surgery, divided into 3 doses a day × 7 days (March 1989–Nov1996) or for 3 days (after Dec 1996). After that, PO dose gradually reduced to 40, 30, 25, 20, and 17.5 mg every 7 days, and maintenance dose of 10 mg was attained by the 6th week. In acute rejection: IV MPSL	2–8 weeks	The steroid doses (lower, middle, and upper thirds) at 2-week period: <550, 550–650, and >650 mg, respectively. At 4-week period: <895, 895–1130, and >1130 mg, respectively. At 6-week period: <1165, 1165–1488, and >1488 mg, respectively. At 8-week period: <1400, 1400–1795, and >1795 mg, respectively MPSL bolus in 24 pts at an average dose of 3111 mg	N/A	SS association between AVN incidence and the total dose of steroids in the first 2 months after transplantation, and there was a dose–response relationship. In the 2-week period after transplantation, odds ratios for AVN in the middle and upper-dose steroid groups rose, though not statistically significantly. In the 4 and 6-week periods after transplantation, ORs for the middle-dose group rose significantly and those for the upper-dose group also rose, but not significantly. In the 8-week period after transplantation, ORs for the middle- and upper-dose groups rose significantly, and a significant dose–response relationship was observed. Cumulative CS dose and the acute rejection rate were higher among the AVN group than the control group (P = 0.04 and P = 0.058, respectively).
Hedri et al. [51]	Retrospective	15/326 (4.6%)	MPSL 1–2 mg/kg/day. CS dose gradually reduced over the next 8–12 weeks to a maintenance of 10–15 mg/day.	AVN diagnosed at a mean of 3.5 years after RT (range, 0.5–13 years)	Cumulative mean dose in AVN group 24,240 mg +/- 16,450 vs. 14,243 +/- 7530 in non-AVN group (P = 0.04)	Hip	The high dose of steroid during the first several weeks seems to be more important than the total cumulative dose.
Koo et al. [7]	Retrospective	22 total Renal transplant (7), aplastic anemia (6) nephrotic syndrome (3) liver transplantation (1), Crohn's (1) eosinophilic granuloma in (1), pemphigus vulgaris (1), MS (1), ALL (1)	During 1st month mean daily dose was 76 mg (range 60–145 mg)	The duration of steroid treatment within this period (mean 4.5 months). Start of steroid treatment to the diagnosis by MRI mean 5.3 months	1800–15,505 mg (mean 5928 mg). During 1st month: mean dose 2267 mg Until the diagnosis on magnetic resonance imaging, the total dose of steroid mean 5928 mg	Femoral head, other	
Tang et al. [46]	Retrospective Case control	16/397 (4.2%) control group 31	NA	NA	IV MPSL cumulative dose in 1st year in + AVN vs. – AVN: 2.97 +/- 2.48 vs. 1.42 +/- 2.01 (P = 0.026)	NA	Significantly higher body weight increments, rejection rate, mean daily oral prednisolone, and cumulative intravenous pulse methylprednisolone consumption in the first posttransplant year in AVN group
Saisu et al. [128]		Group A: 27% Group B: 100%		<3 months	Group A: 0–4000 mg corticosteroid Group B: >4000 mg IV methylprednisolone	Femoral head	
Bradbury et al. [53]	Retrospective	3%	NA	NA	MPSL at 1 month in AVN+ / AVN–: 5371 / 2610 mg (P = 0.0005) MPSL at 1 year in AVN+ / AVN–: 6171 / 2966 mg Cumulative prednisone at 1 year was 5435 vs. 4540 for AVN– vs. AVN+	NA	+ Association between cumulative doses of IV MPSL in the first month after transplantation and the onset of osteonecrosis. No association between the cumulative doses of prednisone during the first year after transplantation and the development of osteonecrosis
Tervoven et al. [47]	Prospective	6/100 (6%)	NA	>6 months mean time of exposure for AVN+ 9.5 years Mean time of exposure for AVN– 8.1 years	Mean 32.1 g for all comers Mean for AVN+ 40.9 g (p = 0.269)	HIP	No significant differences were found regarding the total dose of corticosteroids and AVN, but a trend towards higher dose and development of AVN was evident
Lausten et al. [48]	Retrospective	Group 1 (high dose steroid): 42/374 (11%) Group 2 (low dose steroid): 19/376 (5%) p = 0.002	34 mg/day 17 mg/day	Mean interval between treatment and ON–26 months in first group 21 months in second group	Average prednisone during 1st month, 1st year Group 1: 4224, 12,540 mg Group 2: 1712, 6481 mg	NA	Higher incidence with increased daily and cumulative dose of steroid The incidence of femoral head AVN was more than halved with reduction of cumulative steroid from 12 g to 6.5 g

Patton et al. [49]	Retrospective	52/444 (16%)	NA	NA	NA	ON was associated with a history of early acute rejection (p less than 0.02), higher final serum creatinine (p=0.07), and greater mean prednisone (p<0.0001). The mean linear trend of daily pred dose was also significant (p<0.03)
Felson et al. [21]	Metanalysis of 22 studies	AVN range 0–31% (SLE, renal transplant, BMT, Hodgkin's)	1st month, 3 months, 6 months, and 12 months (total steroid/oral steroid), respectively was 127/80, 74/50, 49/34, 29/25.	1-, 3-, 6-, and 12-month periods	NA	NA + Relationship between oral dose in each time period and development of AVN Comparing steroid dose and bolus steroids indicated that a 9000 mg prednisone (equivalent) cumulative dosage given in a month had a 22% incidence of AVN. Bolus dose was not associated with AVN. This quantitative review strongly suggests that steroid dose is the major predictor of the risk of AVN. The oral dose effect amounts to a 4.6% increase in the risk of AVN for every 10 mg/day rise in oral steroids during the first 6 months of therapy Draw backs: only a small number of non-renal cohorts in study (SLE patients shave different risks!) Cumulative dose of steroids was not predictive of AVN Increase in body weight showed a strong correlation with AVN development at 6 months
Metselaar et al. [50]	Retrospective	61/248 (24%)	Prednisone 30 mg/day after transplantation Rejection episodes treated with MP SL or increasing oral prednisone	NA	NA	Hip, knee, ankle, shoulder, elbow Cumulative dose of steroids was not predictive of AVN Increase in body weight showed a strong correlation with AVN development at 6 months
Haajanan et al. [54]	Retrospective	29/546 (5.3%)	Until 1975, initial MP SL was 100–160 mg/day, where after 68–80 mg/day MP SL 1 month after transplant: 44–60 mg/day; 6 months after: 12–36 mg/day; 12 months after: 0–20 mg/day Rejections treated with IV MP SL 0.5–1 g/day (total 2–5 g)	NA	Total steroid without pulse at 12 months in + AVN/–AVN: 7716/7490 Total steroid with pulse doses at 12 months in + AVN/–AVN: 10,135/8912	Femoral Head No significant difference in + AVN vs. – AVN in cumulative steroid without pulse dose group. Highly significant difference in + AVN/–AVN in cumulative steroid with pulse dose (IV MP SL)
Morris et al. [55]	Prospective	9/72 (12%) 8 patients in HD group and 1 patient in LD group	High dose (HD) regiment: 100 mg prednisolone daily in two doses started on the day after transplantation, reduced to 90 mg daily after 5 days and then by 5 mg every 5 days to 20 mg, after which the dose was reduced by 1 mg every 2 weeks down to a maintenance dose of 10 mg/day. Low dose (LD) regiment: 30 mg prednisolone daily in divided doses for 60 days, reduced to 25 mg daily for 2 weeks, and then to 20 mg/day. Subsequently, same taper as HD group. The LD patients received, in addition, 1 g MP SL IV on days 6, 7, and 8 after transplantation, and all patients were given 100 mg hydrocortisone i.v. during the operation.	NA	Cumulative dose in HD MP SL during first 6 months 8560 +/- 4500 mg; oral prednisone during first 6 months 6340 +/- 140 Cumulative steroid in LD group in first 6 months: methylprednisolone 9200 +/- 4000; prednisone 3950 +/- 110	NA AVN is related mostly to the cumulative steroid dose received during the first few months after transplantation. Problems: low dose group with methylprednisolone may have actually gotten more total steroid. Only SS results were of prednisone data.

(continued on next page)

Table 5 (continued)

Study/Ref.	Study design	No. of patients (+ ON/–ON)	Daily dose	Treatment duration	Cumulative dose	Site of lesion	Notes
De Graaf et al. [52]	Retrospective	52/170 (30%)	Initial prednisone dose posttransplant: 80 mg/day, reduced within 6 days to 25–30 mg/day. Subsequently reduced each month by 2.5 mg until min daily dose of 7.5–10 mg was reached. Rejection: IV MPPL 125–200 mg/day × 5 days and then tapered. Mean prednisone dose in + AVN: 6300 +/- 990 mg	1, 3, and 6 months	Total prednisone in first 3 months: 2380–9230 mg	Hip > knee > ankle	+ Correlation between cumulative prednisone in 1st 3 months and with the incidence of AVN. (p < 0.001) Statistically significant correlation between number of rejection treatments and incidence of AVN Dosages > 5000 mg during first 3 months appears to be critical dose cut off above which AVN may develop
Hely et al. [129]	Retrospective	29 total children; 21% AVN.	NA	NA	NA	Femoral head	The presence of osteodystrophy prior to transplant was strongly correlated with osteonecrosis Extensive reviews of their records failed to clearly identify other predisposing factors A direct relationship between dose of steroids and the development of AVN not consistently demonstrated
Elmsted et al. [130]	Retrospective Case control	19 with AVN compared to 125 without AVN	NA	NA	NA	NA	No significant correlation seen in prednisone dose and AVN even in patients treated with MSPL for acute rejection Although the prevalence of AVN decreased after 1967 coincident with a decrease in prednisone dose, children with AVN received the same cumulative prednisone dose as children in a control group.
Ibels et al. [41]	Prospective Case control	40/194	Prednisone 2.5–40 mg/day (mean 15.9) Rejection treated with MPPL	NA	NA	Multi sites. Hips most common.	No significant correlation seen in prednisone dose and AVN even in patients treated with MSPL for acute rejection
Potter et al. [131]	Retrospective Case control	11/100 (11%)	At the time of transplantation, treatment with prednisone, 2 to 4 mg/kg The prednisone dose is rapidly decreased to 0.8 to 1.0 mg/kg at the end of one month and more slowly thereafter to a minimum dose of 0.1 to 0.3 mg/kg Rejection treated with MPPL	< 12 months	Cumulative prednisone dose at 3, 6, 12, and 24 months in + AVN/– AVN, respectively. 3368/3466, 5018/4211, 8336/8086, 11,893/14,087 Total dose in + AVN/– AVN: 14,207/12,432	femoral heads, 14; femoral condyles, 12; tall, two; and carpal naviculars, two.	Although the prevalence of AVN decreased after 1967 coincident with a decrease in prednisone dose, children with AVN received the same cumulative prednisone dose as children in a control group.
Levine et al. [42]	Retrospective Case control	16 pts with + AVN compared with 16 control	Mean daily steroid dose for each of the first 14 28-day periods after transplantation was calculated for each patient. Exact numbers not described	NA	The total dosage of CS received by each patient with AVN was estimated in an arbitrarily chosen period of the first 392 days following transplantation. Exact numbers not described	Femoral heads, femoral condyles and humerus in 1	No significant difference between AVN+ and control patients in either total steroid dose or average daily dose over the first 392 days following transplant.
Bewit et al. [43]	Retrospective	13 patients developed AVN	NA	NA	NA	NA	No correlation between steroid dose and AVN
Pierides [44]	Retrospective Case control	11/78 (14%) 11 patients with A.N. were compared with two control groups of unaffected renal transplant patients.	Exact mean not recorded	NA	Exact mean not recorded	NA	the cumulative dose of prednisone received by affected patients during the first three posttransplant months was found to be significantly higher than that for both control groups (P less than 0.05 No significant difference was found between the daily dose of prednisone received by affected patients and control group II
Troche et al. [132]		13/90 patients	Prednisolone 50 mg/day with gradual reduction to 10–20 mg/day over one year Rejection treated with high dose prednisolone	NA	NA	NA	No SS difference in amount of CS received by 13 patients with osteonecrosis and unaffected patients over a comparable period.
Harrington et al. [133]	Retrospective	18/150	NA	> 3 weeks	Of 50 patients who had received an average total dose of steroids of 2960 mg in the 3-week period after transplant 16 developed AVN Of 101 patients who had received an average total dose of steroids of 1180 mg in the 3-week period after transplantation, only 2 developed AVN	NA	Total steroid dose in the 3-week period after transplantation was an etiological factor in the development of AVN.

9.2. Cumulative dose

In renal transplant patients, the cumulative dose is of special interest as it takes into account the number of renal transplant rejections and the subsequent administration of high dose pulse therapy. Patton et al. [49], Tang et al. [46], Hedri et al. [51], and De Graff et al. [52] all noted a statistically significant association between acute rejection and the onset of osteonecrosis. In 1992, Tervoven et al. [47] found no statistically significant difference regarding total dose of glucocorticoids, but noted a trend towards higher cumulative dose and occurrence. In fact, prior to 1985, Metselaar et al. [50], Potter et al. [121], Levine et al. [42], and BewickTroche et al. [43] also reported no predictive correlation between cumulative dose and osteonecrosis but again this data must be tempered by the methodology used.

More recently, Shibatani [45] found a statistically significant association between osteonecrosis and the total dose of steroids in the first 2 months after transplantation. Hedri et al. ($p=0.04$) [51], Lausten et al. [48], Felson et al. [21], Morris et al. [55], De Graff et al. [52], Pierrides et al. [44], and Harrington et al. [133] all found similar risk with increased cumulative dose. Several authors demonstrated evidence for increased risk when specifically considering cumulative IV methylprednisolone [21,46,53–55]. Lausten et al. [48], calculated that the incidence of femoral head osteonecrosis was more than halved with reduction of the cumulative steroid from 12 g to 6.5 g. De Graff et al. [52], found that a cumulative dose greater than 5000 mg during the first 3 months was a striking risk. Bradbury et al. [53] found a similar association between steroids used during the first year and subsequent risk of osteonecrosis. In 2002, Koo et al. [7], noted that daily oral dosing was more important than cumulative dose. In summary, the majority of the data on renal transplant-induced osteonecrosis indicates a positive role on cumulative dose and osteonecrosis development. Multiple confounding variables are at play here (i.e. active inflammation during rejection may predispose to osteonecrosis, MPSSL vs. oral cumulative dosages may confer different risks).

10. Risk of osteonecrosis in other conditions

The risk of steroid induced osteonecrosis in bone marrow transplant, cardiac transplant, lung transplant, liver transplant, acute leukocytic leukemia, Hodgkin's disease, multiple myeloma undergoing chemotherapy, SARS, multiple sclerosis, and neurosurgical patients is noted in Table 6. This third grouping of studies consists of non-renal transplant patients (bone marrow transplant, $n=6$; liver transplant, $n=2$; cardiac/pulmonary transplant, $n=2$), malignancy (Hodgkin's, $n=3$; acute lymphoblastic leukemia, $n=9$, multiple myeloma, $n=1$), aplastic anemia ($n=3$), SARS ($n=2$), and neurosurgical disorders ($n=2$). Organ transplantation inevitably requires steroids for rejection prevention and subsequent osteonecrosis has been a rare, albeit, well-documented phenomenon found throughout the literature. In cardiac and liver transplant, an incidence of 2–3% is suggested by several authors [53,56,57]. This is much lower than the incidence reported in renal transplant patients (3–40%) suggesting again that underlying disease has a distinct influence on the incidence of steroid induced osteonecrosis. Fortunately over the last 10 years, alternative immunosuppressants have been increasingly employed, thereby decreasing the overall need for steroids. Regarding neurosurgical patients, steroids have shown to be beneficial in cerebral edema, malignancy, meningitis, cord injury, among others and short courses of high dose corticosteroid (often dexamethasone) are usually employed. The overall incidence of 0 to 0.6% extracted from the scattered case reports and small studies is considerably lower than the other underlying diseases discussed thus far [58,59]. With regard to underlying malignancy and steroid induced osteonecrosis, the incidence varies

widely between 0.6 and 3.4% [60–73]. It is difficult to make generalized statements regarding steroid dosing with these varied underlying disorders, but patterns are evident.

10.1. Daily and cumulative dosing in cardiac and liver transplant

In 2 studies of cardiac and liver transplant, Lieberman et al. [56,57], found no statistically significant relationship between daily prednisone dosing or IV MPSSL and osteonecrosis. The cumulative dosing was also not statistically different. In 2002, Koo et al. [7], suggested that high dose steroids during the first several weeks seems to be more important than the cumulative dose. The major limitation here is that there was only 1 patient out of 22 that had a solid organ transplant (aside from renal). In 1994, Bradbury et al. [53] performed a retrospective study and found 3% of cardiac/pulmonary transplant patients developed osteonecrosis. The author demonstrated a correlation between cumulative dosing of IV MPSSL in the first 1 month after transplant and the onset of osteonecrosis ($p=0.005$). In summary, there is no significant data to make concrete statements regarding dosing relationship to osteonecrosis in solid organ transplant, though clearly there seems to be a trend towards higher daily and cumulative dose.

10.2. Daily and cumulative dose in malignancy (BMT, ALL, MM, NHL, and HL)

Talamo et al. [60], found an osteonecrosis incidence of 9% in patients with multiple myeloma treated with antineoplastic therapy including steroids. When he adjusted for body weight, cumulative dose remained significantly associated with osteonecrosis (OR, 1.030; 95% CI, 1.005–1.055, $p=0.02$). A logistic analysis further predicted that a cumulative dexamethasone dose of 2880 mg had a 20% chance of inducing osteonecrosis which was a 4.2-fold higher probability than a patient treated with a cumulative dexamethasone dose of 800 mg. In acute lymphocytic leukemia (ALL) patients, Arico et al. [61], found that there was an increased incidence of osteonecrosis with chemotherapy regimens where the cumulative dose was higher. Mattano et al. [63], studied a pediatric ALL population and found a 1.4-fold increase in osteonecrosis in patients treated with 2 dexamethasone pulses as compared to those that received just one. However, the results did not reach statistical significance. Vaidya et al. [67], also agreed that the high cumulative doses of steroid were noted to have an increased risk of osteonecrosis in acute lymphocytic leukemia patients. In a small cohort of acute lymphocytic leukemia patients, Chan-Lam et al. [72] reported 5/9 patients with osteonecrosis, which he proposes may be explained by their protocol of higher dose steroids (1.5–1.75 \times greater than in convention chemotherapy). Several other studies state that steroids play a role in osteonecrosis development [64,68,74].

In the 5 bone marrow transplant papers, steroid dosing, including higher cumulative dose, was a significant risk factor for development of osteonecrosis. In a multivariate analysis, Socie et al. [69], found 5 factors conferring statistically significant risk of osteonecrosis development. These factors include chronic GvHD (OR 3.52), acute GvHD (OR 3.73), age < 16 (OR 5.81), aplastic anemia (OR 3.90), and acute leukemia (OR 1.72.) The exact steroid dosage was not addressed, but patients having complications and who are treated with corticosteroids, are at increased risk for osteonecrosis. Enright et al. [73] and Torri et al. [62] echoed these assertions, also finding an increased risk with acute or chronic graft vs. host disease, higher cumulative steroid dose, or use of intravenous (IV) pulse therapy.

10.3. Daily and cumulative dosing in neurosurgical patients

The incidence of osteonecrosis in neurosurgical patients was lower than those with other underlying diseases. This suggests that the pathogenesis of osteonecrosis involves a “multi-hit” theory, which

Table 6
Prospective, retrospective, case control studies of steroid dosing and osteonecrosis in bone marrow transplant, cardiac transplant, lung transplant, liver transplant, acute lymphocytic leukemia, Hodgkin's disease, Multiple myeloma undergoing chemotherapy, SARS, multiple sclerosis, neurosurgical patients.

Study/Ref.	Study design	No. of patients (+ ON/–ON)	Underlying disease	Daily dose	Treatment duration	Cumulative dose	Site of lesion	Notes
Lieberman et al. [56]	Retrospective	6/204 (3%)	Cardiac transplant	Three 125 mg doses of IV MPSTL q 12 h starting immediately after surgical procedure. On postop day 2, prednisone 70 mg/day and then tapered to 20 mg/day by postoperative day 14. Taper regimen over the next 180 days down to a maintenance dose of prednisone 5 mg/day. For transplant rejection: IV MPSTL bolus of 1500 to 3000 mg over 3 days and a bolus of prednisone 770 mg over 16 days.	Most weaned off of steroids by 1–2 years post op. Some required continued maintenance dose prednisone 5 mg/day.	Cumulative steroid (MPSTL and prednisone over 2 years) –in AVN+ 5560 mg; in AVN– 5866 mg. Cumulative dose of MPSTL at 2 years 881 vs. 1188 in AVN– vs. AVN+, respectively. Cumulative dose of prednisone at 2 years was 4984 mg vs. 4372 for AVN – vs. AVN+	N/A	No relationship between either the prednisone or IV MPSTL dose and the development of osteonecrosis of the hip or knee.
Chan et al. [75]	Prospective	7/69	SARS	prednisolone 0.5–1.0 mg/kg of body weight daily, or IV hydrocortisone 100 mg every 8 h with step-down titration starting at the third week of admission. For patients with clinical deterioration including desaturation (oxygen saturation, 90% using pulse oximetry) or development of new infiltrates in chest radiograph, pulse steroid using MPSTL 0.5 g daily × 3 days Daily hydrocortisone equivalent (mg/day) 572 (326–749)	The median hospital-day on maintenance and/or pulse CS therapies was 17	Hydrocortisone equivalent for all corticosteroids (mg)* 9520 (4580–16,600)	N/A	Cumulative doses of >2000 mg of MPSTL, >1900 mg of hydrocortisone, >13,340 mg of hydrocortisone equivalent, and >18 days on corticosteroid therapy are significant risk predictors for ON, while pulse steroid therapy is not. Hydrocortisone and hydrocortisone equivalent not SS
Ce et al. [134]	Prospective cohort	5/33	Multiple sclerosis; tobacco+	N/A	N/A	Total CS dosage varied between 10 and 62 g	N/A	No meaningful relationship between dosing and AVN. Given trends, very high doses of steroids given in a short-time course constitutes an independent risk for AVN.
Wong et al. [58]	Retrospective	4/1352 (0.3%)	Neurosurgical patients	High dose, short course Dexamethasone	Duration of steroid treatment ranged from 15 to 27 days (mean 20 days).	The steroid dose as dexamethasone equivalent ranged from 59 to 150 mg (mean 102 mg)	Femoral head	Though data failed to establish a relationship between steroid dosage and the risk of AVN, experience of long term steroid management indicates that the duration and dosage of steroids are factors contributing to AVN.
Talamo et al. [60]	Prospective	49/553	Multiple myeloma undergoing antineoplastic therapy	Dexamethasone in 4 phases.	N/A	The cumulative dexamethasone dose ranged from 800 to 2880 mg, with a median cumulative dose to onset of AVN of 1120 mg.	NA	When adjusted for body weight, the cumulative dexamethasone dose remained significantly associated with an increased probability of AVN (OR, 1.030; 95% CI, 1.005–1.055; P=0.0201). Higher cumulative dexamethasone dose (odds ratio [OR], 1.028; 95% CI, 1.012 to 1.044; P=0.0006 [per 40 mg of dexamethasone]) A logistic regression equation predicted that a patient receiving a cumulative dexamethasone dose of 2880 mg had a 20% chance of developing AVN, a probability that was 4.2-fold higher than that of a patient treated with a cumulative dexamethasone dose of 800 mg.

Li et al. [135]	Retrospective	12/40	SARS	N/A	average course of treatment was (24 +/- 5) days (16 to 30 days). N/A	average total dosage of methylprednisolone was (4949 +/- 2959) mg AIEOP-ALL-95 regiment: 3250-6420 mg/m ²	N/A	The cumulative dosage and duration of therapy denoted highest risk of AVN
Arico et al. [61]	Retrospective	15/1421 (1/0.1%)	Chemotherapy in childhood acute lymphoblastic leukemia	N/A			N/A	Cumulative dose is a risk factor Noted decreased incidence with comparison between other chemotherapy regimens (CCG vs. DFCI) where cumulative dose is higher (5885-9050 mg/m ² vs. 7600-21,240, respectively) The high dose of steroid during the first several weeks seems to be more important than the total cumulative dose.
Koo et al. [7]	Retrospective	22 total	Renal transplant (7), aplastic anemia (6) nephrotic syndrome (3) liver transplantation (1), Crohn's (1) eosinophilic granuloma in (1), pemphigus vulgaris (1), MS (1), ALL (1)	During 1st month mean daily dose was 76 mg (range 60-145 mg)	The duration of steroid treatment within this period (mean 4.5 months). Start of steroid treatment to the diagnosis by MRI mean 5.3 months	1800-15,505 mg (mean 5928 mg). During 1st month: mean dose 2267 mg Until the diagnosis on magnetic resonance imaging, the total dose of steroid mean 5928 mg	Femoral head, other	
Torii et al. [62]	Retrospective	19/100 (19%)	Post-BMT	NA	NA	NA	Femoral head	Four factors were found to be SS different between patients who had osteonecrosis develop and those who did not: younger age at the time of bone marrow transplantation, chronic graft-versus-host disease, cumulative dose of steroid, and intravenous pulse therapy with methylprednisolone. It was concluded that a low rate of complications and low dose steroid administration would reduce the incidence of osteonecrosis after bone marrow transplantation. No relationship between either parenteral or oral steroid dose and the development of osteonecrosis of the hip
Lieberman et al. [57]	Retrospective	3/203 (2%)	Liver transplant	MPSL preoperative dose 50-1000 mg of MPSL IV, followed by a 6-day tapered dose as follows: day 1, 200 mg; day 2, 160 mg; day 3, 120 mg; day 4, 80 mg; day 5, 40 mg; and day 6, 20 mg IV. On post op day 7, Prednisone 20 mg/day x 30 days. Followed by taper of 15 mg/day down to 2.5 mg at 180 days after transplant.	Up to 2 years	Prednisone + MPSL at 2 years in AVN+/AVN-: 9678/10,552 MPSL alone at 2 years in AVN+/AVN-: 9678/10,552 (mg/m ²) Prednisone alone at 2 years in AVN+/AVN-: 7,688/7,152	Hip	
Mattano et al. [63]	Retrospective	111/140 (9.3%)	ALL-pediatric	NA	NA	(mg/m ²) Induction prednisone: 1815 Delayed intensification dexamethasone 235 in group A and B and 470 in group C Maintenance Prednisone in males/females: 7000/4400 in group A and B and 6200/3600 in group C	NA	Incidence of ON higher for patients randomized to receive two 21-day dexamethasone courses versus one course (23.2% +/- 4.8% vs. 16.4% +/- 4.3%, respectively; P = 0.27). Patients 10-20 years old randomized to receive DDI (2 dexamethasone pulses) exhibited a 1.4-fold higher incidence of symptomatic ON compared with those who received SDI (1 dexamethasone pulse), although this did not reach a conventional significance level. This effect was accentuated in females and in those 16 to 20 years of age at diagnosis of ALL. Conclusion: children ages 10 to 20 years who receive intensive ALL therapy, including multiple courses of corticosteroid, are at significant risk for developing ON.

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Table 6 (continued)

Study/Ref.	Study design	No. of patients (+ ON/–ON)	Underlying disease	Daily dose	Treatment duration	Cumulative dose	Site of lesion	Notes
Ojala et al. [64]	Prospective	9/24 (34%)	ALL	Induction phase: prednisone 60 mg/day; delayed intensification phase, which includes intensive dexamethasone medication.	4–5 weeks for induction phase; unclear duration of intensification phase Interval between treatment and osteonecrosis—within a few months	NA	NA	Corticosteroids may cause osteonecrosis in cancer patients.
Wiesman et al. [65]	Retrospective	17/272 (6%)	Post allogenic BMT	High dose prednisolone The mean maximal dose of prednisolone was 3 mg/kg/day (range 2–27).	NA	Total dose 189 mg/kg (range 13–555 mg/kg) The median total dosage of prednisolone at the time of diagnosis was 189 mg/kg (single manifestation 150 mg/kg; multiple manifestations 313 mg/kg) with a total range of 13–555 mg/kg.	Femoral head most common, multifocal.	Significant difference in median total dosage of prednisolone at the time of diagnosis between single and multifocal AVN
Enrici et al. [66]	Retrospective	9/784 (1%)	Hodgkin's disease	NA	Between treatment and ON—35 months	Prednisone 2725–5250 mg	Head of femur; 1 humeral head	Osteonecrosis is rare in CS treated Hodgkin's disease
Wing et al. [59]	Prospective cohort study	0/59	Spinal Cord Injury	Methylprednisolone	24 h	MPSL 11,000–15,000 mg over 24 h	NA	Using binomial distribution, we conclude that the true incidence of AVN among the methylprednisolone treated group is less than 5% ($\alpha 0.05$) and therefore continue to recommend short term (24 h) methylprednisolone therapy. Shortcomings: very poor follow up. The data suggests that patients receiving combination chemotherapy, especially those with high cumulative doses of steroids, run an increased risk of developing AVN
Vaidya et al. [67]	Retrospective	850 (0.6%)	ALL	NA	Duration of chemotherapy regimen including steroid 24–30 months Between treatment and ON—29 months	Prednisolone cumulative dose from 4.5 to 7 g	NA	Drawback: radiography and bone scans were performed on symptomatic patients only.
Fink et al. [68]	Case control	87/1939 (5%)	ALL	NA	Between treatment and ON—26 months	NA	NA	Corticosteroids are a high-risk factor for developing osteonecrosis in ALL. Posttransplant steroid use was a risk factor for the occurrence of AVN (adjusted OR, 14.4; 95% CI, 2.8–73.2), with the greatest risk associated with those receiving steroids at the time of diagnosis of AVN (adjusted OR, 31.9; 95% CI, 4.4–248.9). There was no further increasing risk associated with increasing duration of steroid use.
Socie et al. [69]	Multicenter retrospective	77/4388 (4%)	Post-BMT	NA	Mean of 15 months Time delay between steroid and ON—22 months	NA	Hip most often affected (88%)	In multivariate logistic regression analysis, five factors remained significantly associated with an increased risk for developing avascular necrosis: chronic GvHD (odds ratio (OR) 3.52), acute GvHD

Ojala et al. [70]	Prospective	9/28 (32%)	ALL-pediatric	High dose dexamethasone 3 different regimen: all the regimens included 4–5 weeks of prednisone at a dose of 60 mg/m ² per day in the induction phase 2/3 regimens with Intensification phase and high dose dexamethasone	NA	NA	NA	(OR 3.73), age > 16 years (OR 5.81), aplastic anemia (OR 3.90), and acute leukemia (OR 1.72) Steroids are part of treatment for GVHD. Steroids dose and exact relation not examined. Steroids are a significant risk factor for developing AVN in post-BMT patients. A significant risk of developing AVN exists in patients on intensive CS treatment for ALL. All of our patients with AVN had been treated with IR or HR protocols, which include a delayed intensification phase with intensive dexamethasone medication, whereas no typical AVN were found in the SR patients, who had not received dexamethasone
Thornton et al. [74]	Retrospective Case series	8/12 patients	ALL or NHL	High dose dexamethasone These phases: 28 days of prednisolone 60 mg/m ² body area daily at the induction phase, 4 weeks of dexamethasone at 10 mg/m ² body area daily at the intensification phase and 5-day pulses of prednisolone 10rag daily every month for 2 years in the maintenance phase.	NA	NA	11 knees, seven hips, five shoulders and five ankles	AVN in these patients is most likely due to the high dose dexamethasone therapy as in all eight cases symptoms followed this stage of the regimen.
Bradbury et al. [53]	retrospective	5/168 (3%)	Cardiac/pulmonary transplant	NA	NA	Total MPSL dose at 1 month: 2610 mg in patients who did not develop osteonecrosis and 5371 milligrams in those patients who developed osteonecrosis (P = 0.0005) Total MPSL at 1 year: 2966 mg vs. 6171 mg for AVN– vs. AVN+. Total prednisone at 1 year: 5435 vs. 4540 for AVN– vs. AVN+	NA	+ Association between cumulative doses of IV MPSL in the first month and 1 year after transplantation and the onset of AVN. No association between the cumulative doses of prednisone during the first year after transplantation and the development of osteonecrosis
Socie et al. [71]	Retrospective	27/727	Post-BMT	First line therapy for GVHD was 2 mg/kg × 10 days and then tapered Severe or progressive GVHD was treated with Prednisone 5 mg/kg	NA	Mean cumulative dose 14.3 g/patient (range 2.5–50.5 g). According to body weight, Mean total dose of 200 mg/kg, range 60–840 mg/kg.	Hip most common in 69%	3 factors with increased risk for developing avascular necrosis by multivariate analysis: male gender (relative risk (RR) 4.72, P = 0.002), age older than 16 (RR = 3.87, P = 0.004), and acute graft-versus-host disease requiring steroid therapy (RR = 6.30, P = 0.0002).
Chan-lam et al. [72]	Retrospective	5/9 (55%)	ALL and high grade malignant Lymphoma	28 days of prednisolone at the dose of 60 mg/m ² daily in the induction phase, 4 weeks of dexamethasone at 10 mg/m ² daily at the intensification phase and 5-day prednisolone pulses every month in the maintenance phase for 2 years.	~2 years	NA	Hips, knees, ankles	The relatively high incidence of AVN in our series could be explained by the dose of corticosteroids used in the BFM protocol which is 1.5–1.75× greater than the doses used in conventional chemotherapy schedules like the MRC ALL × protocol. Three out of the four patients who did not develop clinical AVN did not receive the late intensification block which contains high dose dexamethasone and this would further support the role of high doses of steroids in causing AVN.

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Table 6 (continued)

Study/Ref.	Study design	No. of patients (+ON/–ON)	Underlying disease	Daily dose	Treatment duration	Cumulative dose	Site of lesion	Notes
Marsh et al. [76]	Retrospective	Group A: 21% Group B: 0%	Aplastic anemia	Group A: methylprednisolone 5 mg/kg/day Group B: methylprednisolone 1 mg/kg/day	2–4 weeks	NA	Femoral head most common, knee, 1 patient with humeral head	AVN only seen in high dose group.
Enright et al. [73]	Retrospective	28/902	Post-BMT	Mean dose/day in 1st month: 0.82 mg/kg/day, and was 2.2 mg/kg/day during the second 30 days after transplantation (reflecting increased steroid need for GVHD)	NA	The mean cumulative dose of steroids to onset of avascular necrosis was 19.8 g/patient (range 9 to 70.0 g)	The hip joint was most often involved (64% of patients), followed by knee (61%), ankle (29%), shoulder (21%), and elbow (7%).	Significant correlation between the total cumulative dose of steroids and number of joints involved ($p < 0.01$). A multivariate analysis (allogeneic transplant patients only) identified acute or chronic GVHD requiring steroid therapy ($p = 0.003$), and increasing age ($p = 0.002$) as significant and independent risk factors. + Relationship between oral dose in each time period and development of AVN Comparing steroid dose and bolus steroids indicated that a 9000 mg prednisone (equivalent) cumulative dosage given in a month had a 22% incidence of AVN. Bolus dose was not associated with AVN. This quantitative review strongly suggests that steroid dose is the major predictor of the risk of AVN. The oral dose effect amounts to a 4.6% increase in the risk of AVN for every 10 mg/day rise in oral steroids during the first 6 months of therapy Draw backs: only a small number of non-renal cohorts in study (SLE patients have different risks!)
Felson et al. [21]	Metanalysis of 22 studies	22 pooled studies	AVN range 0–31% (SLE, renal transplant, BMT, Hodgkin's)	1st month, 3 months, 6 months, and 12 months (total steroid/oral steroid), respectively were 127/80, 74/50, 49/34, 29/25.	1-, 3-, 6-, and 12-month periods	NA	NA	
Atkinson et al. [136]	Retrospective	5/50	Aplastic anemia–post-BMT	NA	> 14 days	Total dose of 14 mg/kg	Femoral head	Minimization of steroids in prophylaxis of GVHD to prevent AVN complication

may include underlying disease, increased oxidative stress and high dose corticosteroids. Furthermore, neurosurgical indications for corticosteroids are usually for a short duration (often <24 h) of treatment with high doses. In the 2 studies included in this table [58,59], both authors recognize steroids as a risk factor that should be carefully minimized in duration and dose. However, neither found statistically significant association with daily or cumulative dose. Felson et al., also included 1 neurosurgical study out of the 22 others examined.

10.4. Daily and cumulative dosing in SARS and aplastic anemia patients

In a study of SARS patients, Chan et al. [75], concluded that cumulative doses of >2000 mg of MPST and duration of therapy >18 days were statistically significant risk factors for development of osteonecrosis. Li et al. [135], also concurred that high cumulative dosing and long duration of therapy conferred the highest risk. With regard to aplastic anemia, Marsh et al. [76] found that osteonecrosis only occurred in the high steroid dose group (5 mg/kg/day vs. 1 mg/kg/day of MPST).

11. Discussion

The risk of corticosteroids on the development of osteonecrosis is dependent on daily dose, cumulative dose, maximum dose and route of administration, as well as underlying disease states. In addition, there are genetic factors that have not yet been identified. Parenteral or oral steroids are more likely to lead to osteonecrosis. The highest daily dose, or, to a lesser extent, cumulative dose is directly correlated with the risk of developing osteonecrosis. Osteonecrosis is rare in patients who are on very short course, low dose protocols. Topical and inhaled steroids have been reported to be associated with osteonecrosis, but these cases were confounded by the use of oral or parenteral steroids as well. No cases of osteonecrosis were found that were associated with the use of topical or inhaled steroids alone. Unfortunately, only the minority of affected cases are ever reported.

Due to the absence of subjective and objective findings in the initial phases of the disease, early diagnosis of osteonecrosis depends on the ability of the physician to maintain a high index of suspicion. Once symptoms have presented, the disease may have already progressed to phases of irreversible damage. Treatment in these later stages of the disease is suboptimal and invariably involves surgical procedures, including total hip replacement.

Currently there are no guidelines that define a safe threshold dose of steroids. This paper attempts to establish some recommendations for the administration of steroids. In many cases, the use of steroids is unavoidable, but knowing the likelihood of developing osteonecrosis as a complication of steroid use may help in early detection of the condition.

12. Concluding remarks

The risk of osteonecrosis from corticosteroids remains a significant cause of morbidity. Physicians should be aware of this risk and patients should be informed consumers when corticosteroids are prescribed. Indeed, we suggest the following recommendations:

1. Health care providers should be aware of the potential risk for osteonecrosis in patients treated with corticosteroids, especially parenteral or oral preparations, and with certain specific underlying disease states.
2. Patients who receive steroids via other routes, such as IA, inhaled or intranasal, have a low but not zero risk of developing osteonecrosis. There is the potential for developing osteonecrosis when high doses of inhaled corticosteroids are used, such as in severe persistent asthma or eosinophilic esophagitis.
3. Patients should always be informed of the risk of developing osteonecrosis whenever steroids are used.

A more complete understanding of the pathogenesis of osteonecrosis may help us establish more precise guidelines in the future. Until then, the use of a “therapeutic checklist”, such as that proposed by Weldon et al. [77], may be a useful means of identifying those patients at particular risk and minimizing, whenever able, the use of steroids at every decision crossroad.

Take-home messages

- Corticosteroids remain a life-saving medication but do carry risk factors, including potential development of osteonecrosis.
- Patients with autoimmune disease have themselves an increased risk of osteonecrosis but carry an increased burden secondary to the use of corticosteroids.
- Physicians should be aware of this complication as earlier diagnosis may lead to a significantly improved outcome.
- The risk of development of osteonecrosis is both dose and duration dependent but there are clearly individual differences that explain different patient susceptibility to development of this complication.

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Significance of quantitative measurement of heparin-induced platelet antibodies

Heparin-induced thrombocytopenia (HIT) is a prothrombotic immune-mediated adverse drug reaction. Antigen and platelet activation assays are used for detection of antibodies. Quantitative results from platelet factor 4 (PF4)-dependent immunoassays may lead to inter-laboratory standardization of measurements. The aim of this study, **Javela K. et al. (Eur J Haematol 2010; 84: 169–74)** was to modify a PF4-dependent immunoassay to measure PF4/heparin antibodies quantitatively. Over five consecutive years, 1070 samples from thrombocytopenic, heparin-treated patients were analyzed by a PF4/heparin ELISA and the heparin-induced platelet activation assay (HIPA). Results of ELISA assay were expressed as arbitrary units per liter (AU/L). Precision of ELISA at the concentration of 50 AU/L was 3.6%. Of 1070 samples, 117 were positive for antibodies by ELISA and/or HIPA assay. The higher the antibody concentration was, the higher was the proportion of HIPA positive cases (>140 AU/L, 100%, n = 26; 100–140 AU/L, 55%, n = 20; 50–99 AU/L, 38%, n = 29; 30–49 AU/L, 17%, n = 36). Conclusions: The measurement of anti-PF4/heparin antibody concentration is a new parameter that may improve the diagnosis of HIT. All samples with extremely strong antibody concentration were positive also by HIPA. For accuracy, antibody concentrations must be in the linear range of the assay and an international standard is needed.