Clinical Sports Medicine Update

Reporting of Mesenchymal Stem Cell Preparation Protocols and Composition

A Systematic Review of the Clinical Orthopaedic Literature

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Background: Mesenchymal stem cells (MSCs) are increasingly being used in the treatment of a wide variety of sports-related conditions. Despite this enthusiasm, the biological properties of MSCs and their effects on musculoskeletal tissue healing remain poorly understood. MSC-based strategies encompass cell populations with heterogeneous phenotypes isolated from multiple tissues and using different methods. Therefore, comprehensive reporting of the source, preparation methods, and characteristics of MSC strategies is essential to enable interpretation of results.

Purpose: To perform a systematic review of levels of reporting of key variables in MSC preparation and composition for clinical studies evaluating MSC-based therapies in the treatment of musculoskeletal conditions.

Study Design: Systematic review.

Methods: A systematic review of the clinical orthopaedic and sports medicine literature from 2002 to 2017 was performed. The following inclusion criteria were used: human clinical trials, published in the English language, involving the administration of MSC-based therapies for orthopaedic or sports medicine applications. In vitro or ex vivo studies, editorials, letters to the editor, and studies relating to cosmetic, neurological, or dental applications were excluded.

Results: Of the 1259 studies identified on the initial search, 36 studies were found to satisfy the inclusion criteria for analysis on comprehensive review. Fifty-seven percent of studies evaluated bone marrow–derived MSCs, 41% evaluated adipose-derived MSCs, and 2% evaluated synovium-derived MSCs. Considerable deficiencies in the reporting of key variables, including the details of stem cell processing, culture conditions, and the characteristics of cell populations delivered, were noted. Overall, studies reported only 52% (range, 30%-80%) of variables that may critically influence outcome. No study provided adequate information relating to all of these variables.

Conclusion: All existing clinical studies evaluating MSCs for orthopaedic or sports medicine applications are limited by inadequate reporting of both preparation protocols and composition. Deficient reporting of the variables that may critically influence outcome precludes interpretation, prevents others from reproducing experimental conditions, and makes comparisons across studies difficult. We encourage the adoption of emerging minimum reporting standards for clinical studies evaluating the use of MSCs in orthopaedics.

Keywords: tissue regeneration; biologics; musculoskeletal healing; novel treatments; MSC

The ability of mesenchymal stem cells (MSCs) to differentiate into multiple musculoskeletal cell types, release pro-regenerative growth factors, and inhibit local immune responses holds great promise for musculoskeletal tissue engineering and the treatment of sports-related pathologic conditions.[42] Promising in vitro data[20,21,41] have further fueled enthusiasm for MSC-based therapies, and more than 150 clinical trials are registered (at clinicaltrials.gov) evaluating the use of MSCs as therapeutic agents in the treatment of musculoskeletal conditions, including anterior cruciate ligament reconstruction and repair, meniscal injury, tendinopathy, chondral defects, and osteoarthritis.

Considerable confusion exists regarding the nomenclature used to describe mesenchymal progenitors. The term *stem cells* should be reserved strictly for populations of cells that demonstrate multipotency and self-renewal in vivo.[5] However, the International Society for Cellular Therapy (ISCT) agreed on a number of characteristics to

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define MSCs, including plastic adherence, mesodermal multipotency, and the expression of defined cell surface markers.[22] Nevertheless, the term MSCs encompasses cell populations with heterogeneous phenotypes and functional distinctions isolated from multiple tissues by use of different methods.[42] The names that have been assigned to these cells include *multipotent adult progenitor cells*,[16] *marrow isolated multilineage inducible cells*,[10] and *multipotent adult stem cells*.[4] Furthermore, the relationship of these populations to each other remains unclear.[45] Given this heterogeneity, accurate descriptions of the provenance, preparation methods, and characteristics of MSC populations are essential to understand the nature of the cells used.

In addition to ambiguity regarding MSC nomenclature, consensus is lacking regarding the optimal preparation, source, delivery, and dosing of MSCs.[42,44] Currently, the most frequently delivered MSC preparations include culture-derived cells isolated from either adipose tissue (ADP-MSCs) or bone marrow (BM-MSCs). Bone marrow aspirate concentrate (BMAC) is an alternative strategy for delivering progenitor cells. However, as these strategies do not require cell culture, they do not meet the defining criteria for MSCs set by the ISCT.[22] The US Food and Drug Administration (FDA) considers the cells delivered within BMAC to be minimally manipulated; however, BM-MSC and ADP-MSC preparations, which are reliant on a period of laboratory culture and expansion, are considered under entirely distinct regulatory criteria.[38] In addition to the characteristics of these different formulations,[54] numerous factors critical to the effect of biologic use, such as the dosage and timing of delivery, remain virtually unexplored. The problem is exacerbated by the lack of information that characterizes most studies, with publications not providing sufficient experimental detail to permit the reader to critically evaluate the results or enable replication of the experiments.[39] This is a particular challenge given the complexity of MSC-based therapies and the lack of familiarity of many clinicians with stem cell biology.

Expert consensus has been reached recently regarding those items that may critically influence outcome and should be reported by clinical studies evaluating MSC-based therapies in orthopaedics and sports medicine.[43] However, the comprehensiveness with which the existing clinical literature reports MSC preparation protocols and composition has not been assessed. We therefore set out to perform a systematic review of clinical studies evaluating MSC-based therapies in the treatment of musculoskeletal pathologic conditions in order to establish levels of reporting. We hypothesized that the reporting of both the formulation and delivery of MSC preparations would be varied and inconsistent.

METHODS

Search Criteria and Article Selection

This study was performed in line with the 2009 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines[40] and was registered using the PROSPERO International prospective register of systematic reviews (Registration No. CRD42017073703). Three databases (PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials) were used to search for relevant clinical studies in July 2017.

The search terms were ("mesenchymal stromal cells" [MeSH Terms] OR ("mesenchymal"[All Fields] AND "stromal" [All Fields] AND "cells"[All Fields]) OR "mesenchymal stromal cells"[All Fields] OR ("mesenchymal"[All Fields] AND "stem" [All Fields] AND "cells"[All Fields]) OR "mesenchymal stem cells"[All Fields]) AND (("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) OR ("cartilage" [MeSH Terms] OR "cartilage"[All Fields]) OR ("ligaments" [MeSH Terms] OR "ligaments"[All Fields] OR "ligament"[All Fields]) OR ("muscles"[MeSH Terms] OR "muscles"[All Fields] OR "muscle"[All Fields]) OR ("meniscus"[MeSH Terms] OR "meniscus"[All Fields])) AND Clinical Trial[ptyp].

The abstracts identified in the search were independently reviewed by 2 authors (P.G.R., C.C.W.). On occasions when it was not clear from the abstract whether studies were relevant, the full text of the article was reviewed. Unanimous consensus was met on inclusion of proposed studies for full text review. The full text of all relevant studies was evaluated against the inclusion and exclusion criteria below. A search of cited references was performed to ensure that relevant studies not identified on initial search were included.

Criteria for inclusion were human clinical trials involving the evaluation of MSCs in the treatment of orthopaedic and sports medicine-related conditions published in English. Studies evaluating concentrated preparations of bone marrow aspirate (including BMAC) were excluded, as were studies evaluating the treatment of dental or maxillofacial conditions. Similarly, laboratory and basic science studies, editorials, letters to the editor, and reviews were excluded.

Data Collection

Expert consensus by use of Delphi methods has recently been reached on items that may critically influence outcome and that should be reported by studies evaluating MSCs in the treatment of musculoskeletal conditions.[43] Data relating to these 61 items were collected under 12 subheadings (Table 1). A number of variables included

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TABLE 1
Variables Which May Critically Influence Outcome That Were Collected in the Assessment of Reporting Standards[a]

1	**Study Design**
1.1	Study conducted in accordance with CONSORT, STROBE, or PRISMA guidelines
1.2	Relevant institutional and ethical approval
2	**Recipient-Based Details**
2.1	Age
2.2	Sex
2.3	Preexisting condition
2.4	Comorbidities
2.4.1	Specifically diabetes
2.4.2	Specifically inflammatory conditions
2.5	Use of anti-inflammatory medication
2.6	Smoking status
3	**Details of Injury**
3.1	Diagnosis
3.2	Relevant grade or measure of severity
3.3	Chronicity specified
3.4	Results of preoperative imaging (if performed)
3.5	Previous treatments for current injury
4	**Details of Intervention/Surgery**
4.1	Intervention for each group described in sufficient detail to enable replication
4.2	Relevant operative findings
5	**Details of Donor (if not autologous)**
5.1	Age
6	**Stem Cell Source and Harvesting**
6.1	Anatomic location from which tissue isolated
6.2	Equipment used for harvest
6.3	Details of reagents used in harvest process
6.4	Tissue storage media
6.5	Tissue storage environment
6.6	Time between tissue harvest and processing
7	**Stem Cell Processing (if performed)**
7.1	Detailed protocol of tissue processing
7.3	Name and manufacturer of commercial system
7.5	Digestion solution concentrations and volumes
7.6	Duration, agitation, and temperature of digestion phase
7.7	Method of purification
7.8	Details of purification described to enable replication
7.9	Yield expressed with respect to volume of tissue processed
8	**Cell Culture (if performed)**
8.1	Culture conditions
8.2	Number of freeze-thaw cycles to which cells were exposed
8.3	Details of predifferentiation
9	**Stem Cell Characteristics**
9.1	Description of stem cell population within title and abstract
9.2	Autologous/allogenic mentioned within title and abstract
9.3	Cellular composition of preparation
9.4	Stem cell number
9.5	Stem cell immunophenotype
9.6	Details of in vitro differentiation tested on batch
9.7	Passage
9.8	Percentage viability
10	**Stem Cell Delivery**
10.1	Point delivery
10.2	Volume of cell suspension delivered
10.3	Media used for cell delivery
10.4	Concentration delivered to cells
10.5	Concentration of co-delivered growth factors
10.6	Details of scaffold or carrier
11	**Postoperative Care**
11.1	Rehabilitation protocol
11.2	Immobilization or mobilization specified
11.3	Physical therapy specified
12	**Outcome Measures**
12.1	Timing of outcome assessments
12.2	Complications
12.3	Specifically infection
12.4	Specifically tumor
12.5	Specifically further surgery
12.6	Radiographic outcomes (if performed)
12.7	Functional outcomes
12.8	Physical examination findings
12.9	Return to activities
12.10	Satisfaction (if performed)

[a]Adapted from Murray et al.[43]

within this list may not be relevant to any given MSC preparation (eg, the age or sex of allogenic cell source if autologous cells were used). Therefore, when percentages are reported in our study, the denominator is based on the number of studies to which that variable applies. Articles were defined as providing comprehensive reporting when the study reported data on all these metrics.

RESULTS

Identification and Selection of Clinical Studies

The process of article identification and selection is summarized in Figure 1. The initial PubMed, EMBASE, and Cochrane Library search identified 1259 individual studies. After titles and abstracts were screened for relevance, 1213 studies were eliminated after application of the inclusion and exclusion criteria. The full text of the remaining 46 studies was assessed, resulting in the exclusion of 10 studies that did not fulfill the inclusion criteria. Therefore, 36 studies were included in the final analysis (Table 2).

Stem Cell Preparations

Of the 36 studies included, 20 studies (57%) evaluated BM-MSCs, 15 studies (41%) evaluated ADP-MSCs, and 1 study (2%) evaluated MSCs derived from synovium of the knee. The clinical indications for which MSC preparations were used in each study are summarized in Figure 2. The radiological severity of the condition treated (if appropriate) was reported in 29 studies (81%), while the chronicity of the condition treated was reported in 13 studies (36%). The mean age of the recipient patient population was 51 years (range, 25-70 years). The comorbidities of patients were reported in 16 studies (44%), and 16 studies (44%) reported the use of anti-inflammatory medication. Smoking status was reported in 3 studies (8%).

BM-MSCs. Of the 20 studies evaluating BM-MSCs, 15 studies (75%) used autologous BM-MSCs, 3 studies (15%) used allogenic BM-MSCs, and 2 studies (10%) did not report whether cells were autologous or allogenic. The cells were harvested from the anterior or posterior iliac crest in 17 studies (85%), with 3 studies (15%) not reporting the anatomic location of harvest. In 14 studies (70%), stem cell processing was reported in adequate detail to enable replication by others.

TABLE 2
Articles Meeting the Inclusion Criteria That Were Included Within the Present Systematic Review

First Author	Journal	Year
Akgun[2]	*Arch Orthop Trauma Surg*	2015
Aoyama[3]	*Tissue Eng Part B Rev*	2014
Centeno[7]	*J Bioeng Biomed Sci*	2011
Centeno[6]	*Biomed Res Int*	2014
Davatchi[8]	*Int J Rheum Dis*	2011
Davatchi[9]	*Int J Rheum Dis*	2016
Eastlack[12]	*Spine*	2014
Emadedin[14]	*Arch Iran Med*	2012
Haleem[17]	*Cartilage*	2010
Jo[23]	*Stem Cells*	2014
Kawate[24]	*Artif Organs*	2006
Kim[26]	*Osteoarthritis Cartilage*	2016
Kim[30]	*Am J Sports Med*	2013
Kim[29]	*Am J Sports Med*	2014
Kim[25]	*Am J Sports Med*	2015
Kim[28]	*Am J Sports Med*	2015
Kim[27]	*Am J Sports Med*	2015
Koh[31]	*Knee*	2012
Koh[34]	*Arthroscopy*	2013
Koh[35]	*Arthroscopy*	2014
Koh[33]	*Knee Surg Sports Traumatol Arthrosc*	2015
Koh[36]	*Arthroscopy*	2016
Koh[32]	*Am J Sports Med*	2014
Lamo-Espinosa[37]	*J Transl Med*	2016
Nejadnik[46]	*Am J Sports Med*	2010
Orozco[49]	*Transplantation*	2011
Orozco[47]	*Transplantation*	2013
Orozco[48]	*Transplantation*	2014
Pers[50]	*Stem Cells Transl Med*	2016
Sponer[51]	*Biomed Res Int*	2016
Vangsness[52]	*J Bone Joint Surg Am*	2014
Vega[53]	*Transplantation*	2015
Wakitani[55]	*Osteoarthritis Cartilage*	2002
Wong[56]	*Arthroscopy*	2013
Zhao[57]	*Bone*	2012
Zhao[58]	*Biomed Res Int*	2015

Detailed descriptions of culturing conditions including temperature, medium, and CO_2 concentration were reported in 11 of the 20 studies (55%). The mean number of cells delivered was reported in 19 studies (95%) and was 8.7×10^7 (range, 8.5×10^6 to 10×10^8).

The complete cellular composition of BM-MSC preparations (specifically the identification of non-MSC cell types within delivered preparations) was not reported in any studies. For the purposes of this study, reporting of immunophenotype was considered adequate if any analysis of cell surface marker expression was performed regardless of the number of markers used. Seven of the 20 studies (35%) assessed preparations for expression of CD90 and CD105, while 3 studies (15%) reported the absence of CD14 and CD34 using flow cytometry. Two studies (10%) reported both positive expression of CD90 and CD105 and negative expression of CD14 and CD34. The mean time from harvesting to delivery was 18 days (range, 7-37 days). Seven studies (35%) did not report the time between harvesting and delivery.

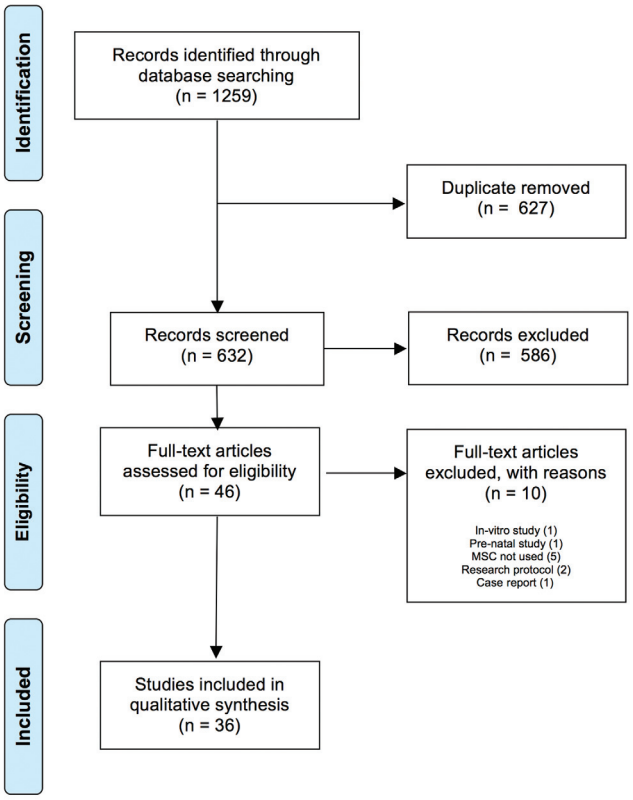

Figure 1. PRISMA flow diagram outlining the systematic review process. MSC, mesenchymal stem cell.

Overall, studies reported information on 50% of the variables that may critically influence outcome when BM-MSCs are used for the treatment of musculoskeletal conditions (Figure 3). No studies provided adequate information relating to all of these variables.

ADP-MSCs. Of the 15 studies evaluating ADP-MSCs, every study (100%) used autologous ADP-MSCs. The cells were harvested from buttock lipoaspirate in 11 studies (73%), abdominal lipoaspirate in 1 study (7%), and the infrapatellar fat pad isolated via extension of arthroscopic portal sites in 2 studies (14%). The anatomic location of tissue harvesting was not reported in 1 study (7%). The equipment used to harvest the adipose tissue was reported in 10 studies (67%), and 8 studies (53%) reported the reagents used for liposuction.

The processing of the stem cells was reported in adequate detail to enable replication by others in 10 of the 15 studies (67%). Six studies (40%) using ADP-MSCs reported laboratory culture, and of those, 5 studies (33%) gave detailed descriptions of their culturing conditions including temperature, medium, and CO_2 concentration. The number of cells delivered was reported in 10 studies (67%), with the mean being 8.7×10^6 (range, 3.9×10^6 to 10×10^6).

The complete cellular composition of ADP-MSC preparations (specifically the identification of non-MSC cell types within delivered preparations) was not reported in any study. The concentration of the MSCs was reported in 5 studies (33%) (mean 9.4%; range, 8.5%-9.9%). Flow

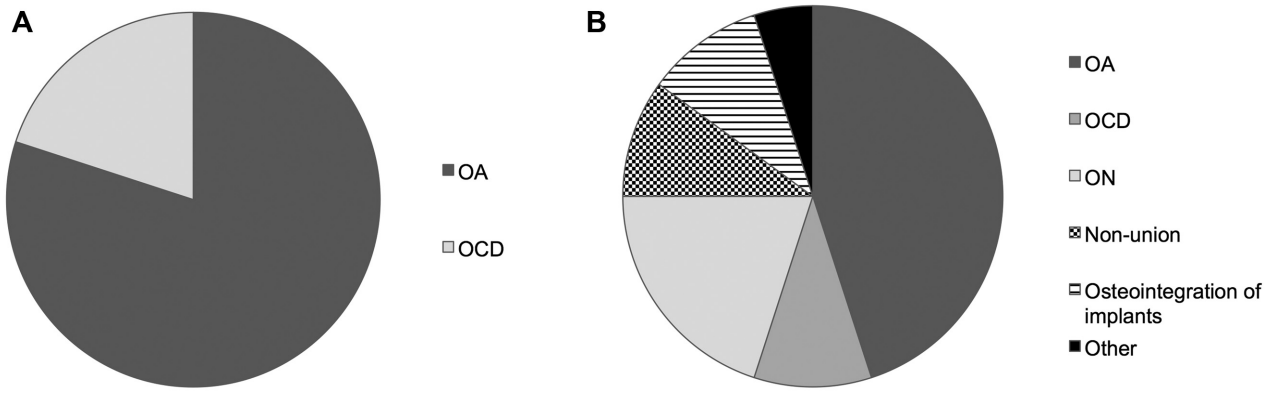

Figure 2. Indication for mesenchymal stem cell (MSC)-based therapy in clinical studies evaluating (A) bone marrow–derived MSCs (BM-MSCs) and (B) adipose-derived MSCs (ADP-MSCs). OA, osteoarthritis; OCD, osteochondral defect; ON, osteonecrosis.

cytometric assessment of CD90, CD105, CD14, and CD34 expression was reported in 5 studies (33%). The timing of cell delivery was reported in all studies, of which 12 studies (80%) delivered the cells immediately intraoperatively. Of the remaining 3 studies, 1 study delivered the cells 11 days after harvesting and 2 studies delivered the cells 1 day after harvesting.

Studies evaluating ADP-MSCs for orthopaedic applications reported information on 53% of the variables that may critically influence outcome (Figure 4). No studies provided comprehensive reporting of all variables.

Overall Reporting

Overall, studies reported a mean of 52% (range, 30%-80%) of applicable variables that may critically influence outcome in clinical studies evaluating MSCs. No study provided adequate information relating to all of these variables. The mean number of variables reported for BM-MSCs and ADP-MSCs is summarized in Table 3.

DISCUSSION

The most important finding of this systematic review was a considerable deficiency in the reporting of variables that may critically influence the outcome of MSC-based therapies. We identified 36 clinical studies evaluating the use of MSCs to treat orthopaedic and sports-related conditions. Of these studies, the average percentage of variables that may critically influence outcomes that were reported was 52%, and no study provided comprehensive reporting of preparation protocols and composition. Inadequate reporting of injury details, MSC preparation protocols, and composition precludes interpretation and makes comparison across studies very difficult.

MSCs are being used in the management of musculoskeletal and sports medicine conditions despite lack of agreement on the optimal composition and lack of standardized reporting of the preparation protocol. This popularity in the use of MSCs in orthopaedics and sports medicine is most likely based on their ability to differentiate into multiple musculoskeletal tissue types, to secrete multiple regenerative cytokines that stimulate tissue resident cell populations, and to regulate local immune environments. MSCs are often regarded as "user-friendly" cells because they can be readily harvested with minimal morbidity from multiple tissue types, can be expanded rapidly in laboratory culture, and can be delivered in isolation or within scaffolds.[15] While a number of clinical studies have reported improved outcomes when MSCs are used to treat a range of pathologic conditions such as chondral defects[29,30] and rotator cuff tears,[13,18] our understanding of the biological properties and effects of MSCs on musculoskeletal tissue healing remains limited.

In this systematic review, we have demonstrated the wide range of MSC preparations being used to treat a variety of musculoskeletal conditions. These preparations vary in terms of tissue source (anatomic sites as well as autologous or allogenic sources), cellular composition, immunophenotype of contained progenitors, and exposure to varying culture conditions. Small differences in a single variable may have a considerable effect on therapeutic characteristics, and comprehensive reporting of variables critical to outcome is essential to allow accurate interpretation of clinical studies. International expert consensus has recently been reached on information items that should be reported by clinical studies evaluating the application of MSCs in orthopaedics and sports medicine.[43] Using heat maps of reporting (Figures 3 and 4), we have demonstrated that most common areas of poor reporting across preparation types include variables relating to stem cell processing, characteristics, and delivery.

Despite efforts from the ISCT to clarify terms relating to these cells,[22] considerable heterogeneity remains in the nomenclature of MSCs. Current systems for classifying MSCs fail to describe basic attributes or the likely effects of each preparation. Furthermore, clinical trials are frequently conducted by clinical researchers who do not have a background in stem cell biology and may not be familiar with the complex scientific variables influencing stem cell behavior. At present, no consensus is available regarding the optimum

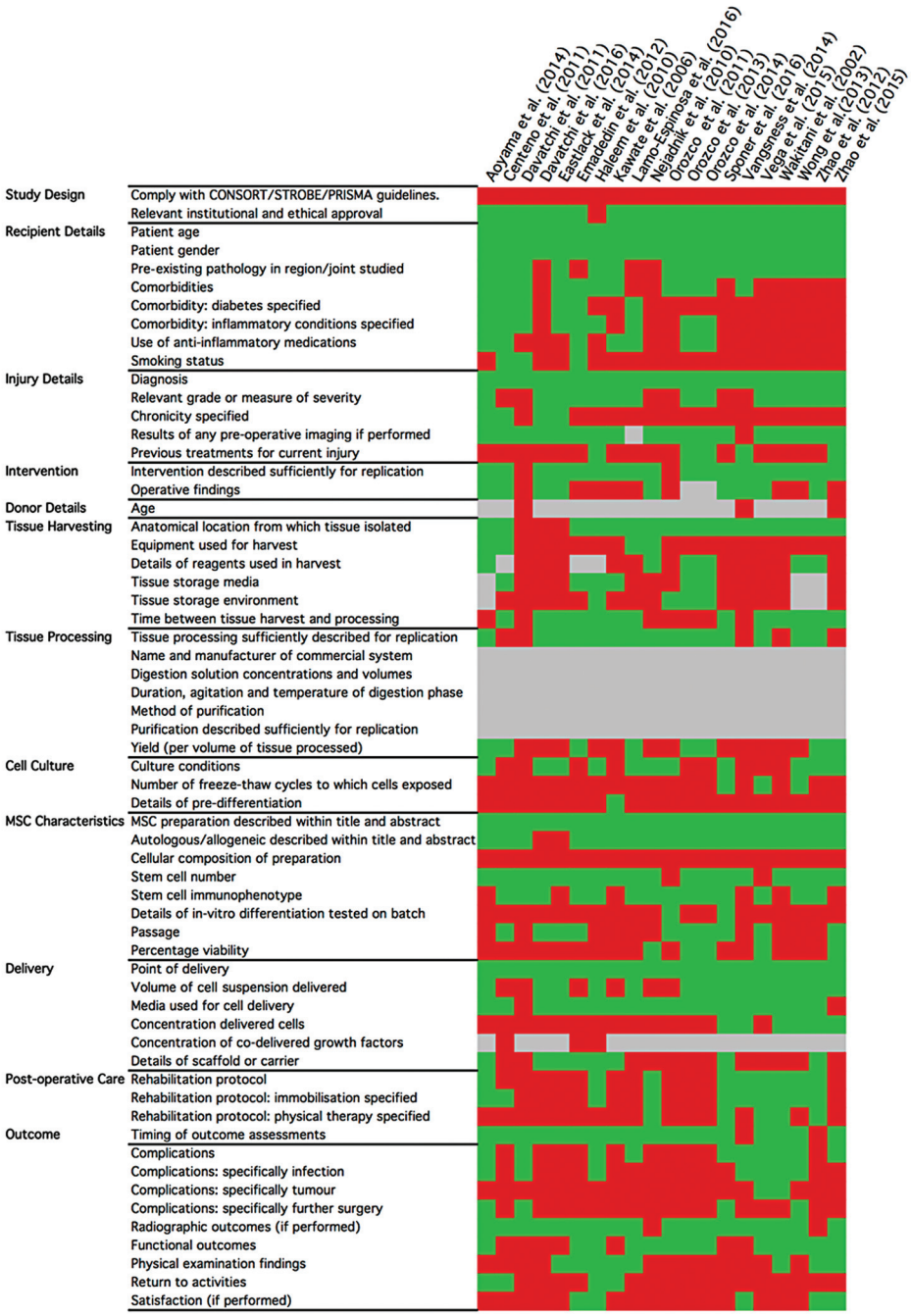

Figure 3. Heat map of reporting in studies of bone marrow–derived mesenchymal stem cells (BM-MSCs). Adequate reporting of variables is indicated by green, while unreported variables are indicated by red. Variables not applicable to individual studies are gray.

dose of MSCs that is deemed therapeutic. In our review, this finding was reflected in the large variation in the number of MSCs delivered. Lamo-Espinosa et al[37] and Jo et al[23] both compared the effects of varying doses in patients with osteoarthritis. Lamo-Espinosa et al[37] compared low (10×10^6) and high (100×10^6) stem cell doses while Jo et al[23] compared low (1×10^7), medium (5×10^7), and high (1×10^8) doses. Both studies found that higher doses were more effective in improving clinical outcomes. Hernigou et al[19] deemed the number of transplanted cells to be the most relevant factor in determining a successful outcome, clinically and radiologically, for tibial non-unions. These results would suggest that a higher dose could be important to achieve efficacy. However, caution must be taken, as free scar tissue formation in doses as low as 1.0×10^7 in the preclinical setting has been reported.[1]

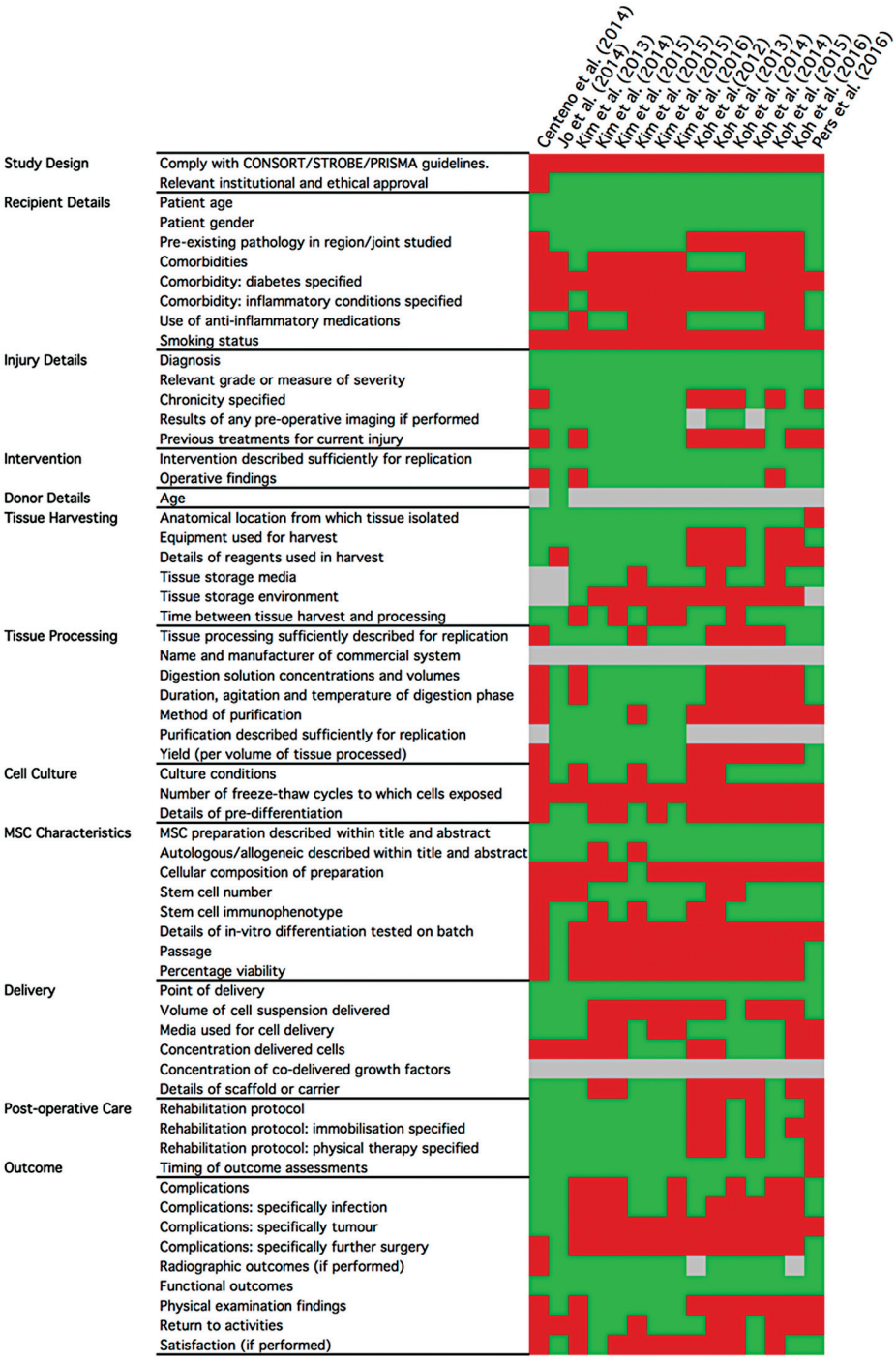

Figure 4. Heat map of reporting in studies of adipose-derived mesenchymal stem cells (ADP-MSCs). Adequate reporting of variables is indicated by green, while unreported variables are indicated by red. Variables not applicable to individual studies are gray.

Contrasting results of MSC-based studies may reflect heterogeneity in composition or attributes of MSC-based therapies. The lack of information on MSC preparation and protocols precludes reasonable comparison across studies or by means of meta-analysis. An immunophenotype for MSCs was proposed as part of the ISCT definition[11] and includes expression of CD105, CD73, and CD90 and lack of expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and HLA-DR surface molecules. Despite widespread use of the ISCT definition, only 1 study in our review reported analysis of all these markers.

It is accepted that the limitations of clinical studies evaluating MSCs in the treatment of musculoskeletal conditions go beyond the reporting of methods and the

TABLE 3
Levels of Reporting for Clinical Studies Evaluating BM-MSCs and ADP-MSCs[a]

	BM-MSCs	ADP-MSCs	Total
Mean no. of variables reported (%)	28 (46)	32 (53)	29 (48)
Minimum (%)	18 (30)	21 (34)	18 (30)
Maximum (%)	33 (54)	48 (77)	38 (62)
No. of studies providing comprehensive reporting (%)[b]	0 (0)	0 (0)	0 (0)

[a]ADP-MSCs, adipose-derived mesenchymal stem cells; BM-MSCs, bone marrow–derived mesenchymal stem cells.
[b]*Comprehensive reporting* defined as the reporting of all 61 essential information items.

characterization of delivered populations. In contrast to research regarding hematopoietic stem cells, research on MSCs lacks rigor regarding fundamental definitions of the cells and the means of characterizing them. This creates considerable challenges to the wider collaborative effort.

Our systematic review has some limitations. We did not attempt to correlate processing methods or composition of MSC-based preparations with outcomes. We believe that this assessment would be confounded by the dramatic variation in indications, processing, and composition variables. Accurate comparisons across studies can be achieved only if sufficient information is reported to enable characterization of the preparations delivered. Furthermore, we identified few studies of level 3 evidence or higher.

CONCLUSION

All existing clinical studies evaluating MSCs for orthopaedic or sports medicine applications are limited by inadequate reporting of both preparation protocols and composition. Deficient reporting of the variables that may critically influence outcome precludes interpretation, prevents others from reproducing experimental conditions, and makes comparisons across studies difficult. We encourage the adoption of emerging minimum reporting standards for clinical studies evaluating the use of MSCs in orthopaedics.

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