Systemic anti-inflammatory effects of mesenchymal stem cells in burn: A systematic review of animal studies

Abdullah S. Eldaly*, Sarah M. Mashaly, Eslam Fouda, Omar S. Emam, Amro Aglan, Jumanah Abuasbeh, Aditya Khurana, Hiba Hamdar, Ayman R. Fath

1Division of Plastic Surgery, Mayo Clinic, Jacksonville, Florida, 2Department of Dermatology, El-Menshawy General Hospital, Tanta, Egypt, 3Division of Anesthesia and Perioperative Medicine, Mayo Clinic, Jacksonville, Florida, 4Department of Internal Medicine, Lahey Clinic Beth Israel, Boston, Massachusetts, 5Department of Public Health, University of Arizona, Phoenix, Arizona, 6Department of Internal Medicine, Creighton University Health Education Alliance, Phoenix, Arizona, 7Department of Emergency Medicine, Notre Dame Maritime Hospital, Byblos, Lebanon

Abstract

Background: Despite the advances in burn care, severe burns still impose significant morbidity and mortality. Severe burns are associated with an inflammatory response that ranges from alterations in vital signs to shock, multiorgan failure, and death. Mesenchymal stem cells (MSCs) are known for their anti-inflammatory and immunomodulatory effects. Therefore, MSCs were investigated for their potential benefits in modulating burn-induced inflammation and organ damage in several studies.

Aim: We have conducted a systematic review of the literature to evaluate the efficacy of MSCs in modulating burn-induced systemic inflammation and organ damage in animal models.

Methods: Four databases were searched: PubMed, Cumulative Index of Nursing and Allied Health Literature, Scopus, and Web of Science. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis as our basis of organization.

Results: Eight studies were included in the study. Bone marrow derived MSCs, umbilical cord derived MSCs (UC-MSCs), and UC-MSCs exosomes were used to modulate the burn-induced inflammation. MSCs therapy reduced serum levels of pro-inflammatory cytokines, improved renal function, inhibited tissue damage, and improved survival after burn. Furthermore, MSCs reversed all the burn-induced pathological changes in blood brain barrier (BBB).

Conclusion: MSCs may attenuate the burn-induced inflammation by decreasing serum levels of inflammatory cytokines. However, the effect on anti-inflammatory cytokines is conflicting and mandates more substantial evidence. Furthermore, MSCs reduce tissue inflammation, tissue damage, and apoptosis in the lungs and kidneys. In addition, MSCs reversed the burn-induced pathophysiological changes in the BBB. The underlying mechanisms of these effects are poorly understood and should be the focus of future stem cell research.

Relevance to Patients: Severe burn patients are liable to systemic inflammation due to the release of inflammatory cytokines into the circulation. This inflammatory response has a broad spectrum of severity that ranges from alterations in vital signs to multiorgan failure and death. Despite the advances in burn care, burn-induced inflammation still imposes significant morbidity and mortality. This systematic review evaluates the potential benefits of stem cells in modulating burn-induced systemic inflammation in animal burn models.

1. Introduction

Burn patients with or without inhalational injury are liable to systemic inflammation due to the release of inflammatory cytokines into the circulation. This pathophysiological response takes place immediately or early post-burn and affects long-term outcomes of burn
patients [1,2]. The primary trigger of this inflammatory response is the tissue damage caused by the burn itself, and it has a broad spectrum of severity ranging from physiologic alterations in heart rate, blood pressure, respiratory rate, and body temperature to severe shock, multiorgan failure, and death [3-5].

Mesenchymal stem cells (MSCs) have regenerative, immunomodulatory, and anti-inflammatory potentials that might be of significant value for burn patients [6-11]; therefore, MSCs have been the focus of many preclinical studies to investigate their efficacy in burn animal models [12-15].

Animal models have contributed significantly to our understanding of burn pathophysiology and complications [16-20]. In addition, these models have been the spearhead of exploring new therapies in all aspects of burn care [21-24]. Recently, MSCs were investigated for their potential benefits in modulating burn-induced inflammation with promising results [25-27]. Therefore, we have conducted this systematic review to evaluate the efficacy of MSCs in attenuating burn-induced systemic inflammation and organ damage. Furthermore, we aim to provide researchers with a summary of the current models utilized for this purpose to guide them for the model that best fits their hypothesis-driven experiments.

2. Methods

2.1. Information sources, search strategy, and eligibility criteria

We utilized four electronic databases to run our search: PubMed (including MEDLINE), Cumulative Index of Nursing and Allied Health Literature, Scopus, and Web of Science. The databases were searched from inception to November 2021. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis as our basis of organization (Figure 1) [28]. The following search MESH terms were used: “Burn,” “Animal model,” and “MSCs.” The search terms were adjusted according to each database, and Boolean expressions were used to create a complex search string to conduct our search. Details on search terms used for every database are provided in the supplementary material.

We included studies that (1) investigated the systemic anti-inflammatory effects of, (2) human or animal-derived MSCs, (3) in burn, (4) animal models with, (5) full-text available, and (6) reported in the English language. We have excluded (1) descriptive studies and studies that did not evaluate the outcomes, (2) the pre- and post-studies (studies without a control group), (3) editorials, (4) reviews, (5) conference papers, and (6) letters to the editors.

2.2. Study selection and data collection process

The first two authors independently searched and removed the duplicates using EndNote (Clarivate Analytics). After filtering the studies based on titles, abstracts were then screened according to the aforementioned eligibility criteria. The remaining studies were full text reviewed. Finally, any conflict was solved by a third author; one major conflict between the first two authors was regarding including studies evaluating the use of exosomes, and it was decided by the third author to include these studies.

2.3. Risk of bias (RoB) assessment

To assess the RoB in the included studies, we utilized the systematic review center for laboratory animal experimentation (SYRCLE’s RoB tool [29]. SYRCLE’s RoB tool is based on Cochrane’s RoB tool and was adjusted to detect bias that plays a specific role in animal intervention studies [29]. This tool contains ten entries related to selection bias, performance bias, detection bias, and attrition bias. Two authors independently evaluated the studies using the SYRCLE’s tool, and a third author solved any disagreement.

3. Results

The initial search revealed 2353 non-duplicate results, of which, 40 papers underwent full-text readings resulting in eight studies included in our final analysis (Figure 1). Table 1 summarizes the included studies. In addition, we summarized the animal model, the sample size, the type and source of stem cells, the dose and route of administration, and the outcome variables for each included study.

3.1. Study characteristics

The earliest study was reported in 2010 [25] and the latest in 2020 [26]. All the studies reported using a rodent model; six reported using rats [25,27,30-33] while two reported using mice [26,34]. Sample sizes of 84 [31], 118 [30], and 134 [27] animals were reported in three studies, while the rest did not report the sample size [25,26,32-34]. Six studies reported scald burn injury model [25,26,30,32-34], and two studies reported flame burn injury [27,31]. Three studies did not specify the total burn surface area (TBSA) [26,27,31], while three studies reported a TBSA of 30% [25,32,33], and two studies reported a TBSA of 15 [34] and 20% [30].

3.2. Description of the intervention

One study reported using human bone marrow-derived MSCs (BMMSCs) [25], while Rat [30], mouse [26], and human [31] umbilical cored-derived MSCs (UC-MSCs) were reported in three studies. In addition, mouse BMMSCs [27,34] and human UC-MSC-exosomes [32,33] were reported twice each. The lowest passage for the used cells was 2 [31], and the highest was 7 [25]. The MSCs were administrated intravenously in five studies [26,30,32-34], while intramuscular (IM) [25], subcutaneous (SC) [31], and intradermal (ID) [27] delivery of the cells was reported in one study each.

3.3. Summary of the outcomes

IV administration of UC-MSCs and ID administration of BMMSCs improved survival in two studies [30]. IV and IM administration of rat UC-MSCs and human BMMSCs, respectively, reduced tissue damage and apoptosis in kidneys in two studies. Furthermore, a significant reduction in serum creatinine and blood urea nitrogen after MSCs administration was reported [25,30]. IM and IV administration of human MSCs and
In two studies, IM and IV administration of human MSCs [25] and mouse BMMSCs [34], respectively, was associated with a significant reduction in inflammation in lung tissue. In a third study, IV administration of human UC-MSC-exosomes reduced the concentration of inflammatory cytokines in serum and lung tissue. Furthermore, histological analysis revealed a significant reduction in lung tissue damage and apoptosis compared to the control group [33].

One study investigated the effect of burn and MSC therapy on the blood–brain barrier (BBB) [26]. Histological analysis of the brain tissue post-burn revealed increased BBB permeability and transcytosis. Furthermore, a marked increase in inflammatory markers, particularly interleukin (IL)-6 and IL-1β, was noted in serum and brain tissue. All these effects were reversed with a single dose of IV mouse UC-MSCs administrated 1 h after-burn.

Three studies attempted to evaluate the effect of MSC therapy on serum levels of pro- and anti-inflammatory cytokines post-burn. In the first study, Zhang et al. [31] investigated the potential benefits of human UC-MSCs in an SD rat model. SC administration of UC-MSCs in post-burn rats was associated with a significant decrease in serum levels of inflammatory cytokines, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and IL-6 compared to the control group. However, UC-MSC therapy was also associated with lower anti-inflammatory cytokine IL-10. Finally, there was no significant difference in Interferon-gamma (IFN-γ) levels between the treatment and control groups.

In a different study, Caliari-Oliveira et al. [27] investigated the effect of mouse BMMSCs administrated intradermally on the serum levels of pro- and anti-inflammatory cytokines in a rat flame burn model. The treatment group showed significantly higher anti-inflammatory cytokines, tissue growth factor-beta (TGF-β), and IL-10 than the control group. However, the treatment group also showed significantly higher pro-inflammatory cytokines, IL-6, and cytokine-induced neutrophil chemoattractant 1 (CINC-1).

The third study by Li et al. [32] investigated the influence of human UC-MSC-exosomes on pro- and anti-inflammatory cytokines in a burn rat model. This study showed that UC-MSC-exosomes administrated intravenously were associated with lower levels of TNF-α and IL-1β. Furthermore, the UC-MSC-exosomes were associated with the lower expression of toll-like receptors 4 (TLR-4), which further inhibits the inflammatory response. Finally, the treatment group showed higher levels of IL-10 compared to the control group.

3.4. RoB

The RoB is summarized in Table 2. All the included studies were liable to a high risk of selection and performance bias. For selection bias, none of the included studies described how the allocation sequence was generated and applied. This is true even for the studies that stated that the animals were randomized. However, the authors know that reporting the sequence generation process is not a common practice in animal studies.

Regarding performance bias, none of the studies attempted to blind the investigators or caregivers to the treatment and control groups.
### Table 1. Summary of the included studies.

| Author and Date     | Animal Model | Number | Burn Type, Degree and TBSA | Stem Cell Therapy | Source | Passage | Dose and route of administration | Target of Therapy | Outcome Variables | Results | Summary |
|---------------------|--------------|--------|----------------------------|-------------------|--------|---------|-----------------------------------|-------------------|-------------------|-------------------|----------|
| Yagi et al.[25] (2010) | Sprague-Dawley rats | -      | Scald 3rd 30% | BMMSCs Humans | 3-7 | $2 \times 10^6$/rat IM | Kidney, Lung, Liver. | Gene expression in MSCs, BUN, AST, histological analysis. | MSCs versus Control MSCs gene expression in response to inflammation: ↑IL-10, ↑Akt1, ↑RAF1, ↑MAP3K1, BUN: ↓ AST: no difference from control. Histology: ↓ tissue injury, ↓ apoptotic cells in kidney and lung. | MSCs react to inflammation on a genetic level. MSCs provide anti-inflammatory and anti-apoptotic effects in the lungs and kidneys of burned rats. |
| Caliari-Oliveira et al.[27] (2016) | Wistar rats | 134    | Flame 3rd | BMMSCs Mice | 3-4 | $5 \times 10^6$/rat ID | Inflammatory cytokines | TGF-β, IL-10, IL-6, CINC-1, survival rates | BMMSCs versus Control TGF-β, IL-10, IL-6, CINC-1: ↑ Survival rates: ↑ | ID administration of BMMSCs increased both pro- and antiinflammatory cytokines and prolonged survival in rats. |
| Curtis et al.[34] (2019) | C57BL/6 Mice | -      | Scald 3rd 15% | BMMSCs Mice | 4 | $5 \times 10^6$/mouse IV | Liver, Lung | IL-6, AST, ALT, histological analysis | BMMSCs versus Control IL-6: ↓ AST, ALT: no difference from control. Histological analysis: no difference from control. | IV administration of BMMSCs provided antiinflammatory effects in lung and liver in a mouse model of binge ethanol and burn. |
| Lu et al.[30] (2013) | Sprague-Dawley rats | 118    | Scald 3rd 20% | UC-MSCs Rats | 3-5 | $1 \times 10^6$/rat IV | Kidney | Serum creatinine, BUN, histological analysis, survival analysis. | UC-MSC versus Control Serum Creatinine: ↓ BUN: ↓ Histological analysis: ↓ tissue damage, ↓ apoptotic cells. Survival: ↑ | IV administration of UC-MSCs protects from death caused by burn-induced acute kidney injury in rats. |
| Zhang et al.[31] (2015) | SD rats | 84     | Flame 3rd | UC-MSCs Humans | 2-4 | $2 \times 10^6$/rat SC | Inflammatory cytokines | WBCs, CRP, IFN-γ, TNF-α, IL-6, IL-10 | UC-MSC versus Control WBCs, CRP, TNF-α, IL-6, IL-10: ↓ IFN-γ: No significant difference | SC administration of UC-MSCs suppresses secondary inflammatory reaction by lowering inflammatory cytokines. |

(Contd...)
4.1. Burn induced systemic inflammatory response syndrome (SIRS)

The term SIRS was first coined by the American College of Chest Physicians/Society of Critical Care Medicine in 1992 to describe
a state of systemic inflammation, regardless of its cause [38]. SIRS diagnosis mandates the presence of two or more of the following criteria: body temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20/min or a PaCO₂ <32 mmHg; leukocyte count >12,000/µL, <4000/µL, or >10% immature (band) forms. These criteria must occur as an acute alteration from baseline that cannot be explained by any other cause. SIRS can be caused by a broad spectrum of infectious and non-infectious etiologies. The most common non-infectious causes include trauma, ischemia-reperfusion injuries, pancreatitis, and burn.

Burn patients commonly experience SIRS, with several factors influence the outcomes. Although the presence of SIRS in the first 24 h after burn does not predict mortality [39,40], the persistence of SIRS criteria for more than three days is associated with worse outcomes [41-43]. Furthermore, Talmor et al. [40] revealed that the persistence of SIRS for 2 days postoperatively in high-risk surgical patients was associated with an increased incidence of multiple organ dysfunction syndromes (MODS). In addition, the number of SIRS criteria existing in a patient seems to have a prognostic value. An analysis by Rangel-Frausto et al. [44] showed that the mortality rates for patients exhibiting two, three, and four SIRS criteria were 6%, 10%, and 17%, respectively. In addition, several factors affect the prognosis of burn-induced SIRS. The magnitude of this inflammatory response depends on burn surface area and degree, presence of inhalation injury or other traumatic injuries, and patient-related factors such as age, pre-existing co-morbidities, and drug or alcohol intoxication [4]. Moreover, several other factors may compromise the patient’s ability to adapt to SIRS. These factors include delayed or inadequate fluid resuscitation during the acute phase, infections, tissue necrosis, and bacterial translocation across the bowel [45].

Burn-induced SIRS occurs as a result of direct thermal trauma to tissues [5]. Severe burns result in an inflammatory response characterized by increased levels of pro-inflammatory cytokines, including TNF-α, IL-1, and IL-6 [3]. Although the cellular and molecular mechanisms of trauma-induced SIRS are complex, they are becoming increasingly understood. TLRs are expressed on leukocyte surface and respond to specific patterns of microbial components, named pathogen-associated molecular patterns (PAMPs), to initiate an innate immune response [46]. Furthermore, TLR can recognize damage-associated molecular patterns (DAMPs), which are endogenous particles released from cells upon their destruction by a burn injury, and they include heat shock protein, histones, mitochondrial DNA, extracellular ATP, and eosinophil-derived neurotoxin [47]. Since DAMPs are normally located intracellular, their presence in the extracellular matrix after cell damage can initiate the same TLR-mediated signaling pathway as PAMPs [48]. TLR activation by DAMPs/ PAMPs up regulates the transcription of pro-inflammatory gene products, including TNF, IL-1, and IL-6 [49].

The two-hit hypothesis concept was proposed by some researchers to explain the exaggerated response to secondary stimuli (e.g., infections) in severely burned patients. Although the exact mechanism of the two-hit hypothesis is not fully understood, monocytes and macrophages are thought to play a critical role in mediating this effect [5]. For example, IFN-γ, which is produced early in SIRS might prime macrophages for an exaggerated inflammatory response if a second stimulus(hit is encountered. For example, TNF-α protein is not produced in significant amounts after the first inflammatory stimulus. However, if a second stimulus, such as bacterial infection, takes place, macrophages become primed by IFN-γ to produce large amounts of TNF-α [50]. Following burn, macrophages have increased sensitivity to ligands for TLR2 and TLR4. TLR2 and TLR4 are important components of receptor complexes of DAMPs, peptidoglycans, and lipopolysaccharides (LPS). After the initial burn injury, TLR2 and TLR4 responses become enhanced for secondary stimuli leading to the two-hit phenomenon [50].

On the other hand, SIRS is also thought to be associated with an anti-inflammatory response to restore immune homeostasis and prevent systemic inflammation. This response is referred to as the counter anti-inflammatory response syndrome (CARS) [51]. The hallmark of CARS is increased production of anti-inflammatory cytokines such as IL-10 and TGF-β, which results in leukocyte apoptosis and blunting of systemic inflammation [50,52]. However, prolonged CARS can result in excessive immunosuppression and predispose the patient to infections [5]. Furthermore, prolonged coexistence of SIRS and CARS results in persistent inflammation, immunosuppression, and catabolism syndrome, which can be further complicated by infections leading to MODS and death [53]. Therefore, the current models suggest that patients who rapidly resolve SIRS and CARS have more favorable outcomes.

4.2. The potential role of MSCs in controlling SIRS

MSCs are multipotent stem cells that can differentiate into multiple cell lines, including adipocytes, osteoblasts, chondrocytes, and pancreatic islet cells [8]. MSCs can be isolated from multiple tissues, including bone marrow, umbilical cord tissue, adipose tissue, menstrual blood, fallopian tubes, and endometrial polyps [54,55]. The anti-inflammatory and immunomodulatory effects of MSCs have been heavily investigated, mainly in the context of transplantation tolerance and allergic disorders [56-59]. Recently, several MSCs products were approved for clinical use, including Cartistem for degenerative arthritis, Cupistem for anal fistula in Korea, and Prochymal for graft versus host disease in Canada [8].

Current evidence from preclinical models and human studies suggest that MSCs influence the immune response in several ways, including inhibition of T-cell proliferation, cytokine production, and cytotoxicity [60,61]; induction and regulation of regulatory T cell (Treg) [62] and regulatory B cells (Breg) [63]; induction of IL-10 production [64-67]; inhibition of B cell proliferation and antibody production [68]; inhibition of antigen-presenting cells [69]; and inhibition of IL-2 mediated natural killer cell activation [70].

Although the exact mechanisms of immunomodulation by MSCs are not fully understood, several studies have attempted to investigate those mechanisms. In one model, MSCs’ immunomodulation is explained by multiple soluble factors released from MSCs to mediate the immunosuppressive effects [8].
These soluble factors include TGF-β1, prostaglandin E2 (PGE2), nitric oxide, IL-10, and indoleamine-pyrole 2,3-dioxygenase. MSCs release these factors in response to pro-inflammatory cytokines, including IFN-γ, TNF-α, and IL-1 [71-74]. In other models, MSCs’ immunomodulatory effect relied on their cellular activities, such as secretomes and cellular cross-talk. Instead, the cells functioned through a mechanism involving phagocytosis of MSCs by monocytes cells [75]. After phagocytosis, monocytes produce less TNF-α and more IL-10. Thus, MSCs trigger other cells to perform the immunomodulatory effects [65,75].

Li et al. [32] investigated the potential role of human UC-MSC-exosomes in ameliorating burn-induced inflammation in a rat model. Exosomes are bilaminar membrane vesicles that can originate from any cell type and have the capacity to communicate with other cells and modulate local and distal microenvironments [76]. Exosomes are produced by double invagination of the plasma membrane and formation of intracellular multivesicular bodies (MVBs). These MVBs contain intraluminal vesicles which will be finally secreted as exosomes with a size that ranges from 40 to 160 nm in diameter through exocytosis [77]. Exosomes exhibit high levels of heterogeneity according to their size, content, functional impact on the recipient cells, and cellular origin [78]. The microenvironment and the cellular origin influence the content and the biological markers of exosomes. Exosomes contents vary and include membrane proteins, cytosolic proteins, nuclear proteins, metabolites, mRNA, and DNA [79]. In addition, exosomes exert biological activities similar to their parent cells [80]. Li et al. [32] showed that the exosomes lowered the burn-induced rise in leukocytes and serum levels of TNF-α and IL-1β. Moreover, exosomes induced the secretion of anti-inflammatory cytokine IL-10.

In addition, the exosomes inhibited the TLR-4 signaling pathway and reduced TLR-4 expression. The investigators attempted to investigate the mechanisms of TLR-4 signaling pathway inhibition. Quantification of TLR-4 mRNA and protein revealed higher levels in the burn group compared to sham controls. Although the administration of UC-MSC-exosomes reduced TLR-4 protein levels in the burned rats, they did not affect the TLR-4 mRNA levels. Therefore, the exosomes should have mediated their effect post-transcriptional (i.e., before the protein was produced). The investigators hypothesized that this effect is mediated through miRNA. Comparison of miRNA levels showed significantly lower levels of miR-181c in burned animals than sham controls. Furthermore, the levels of miR-181c in burned rats significantly increased after the administration of exosomes. To further investigate the integrity of this theory, the investigators transfected the exosomes with miR-181c and compared their effects on the TLR-4 pathway with control exosomes. The transfected exosomes showed higher miR-181c expression and significantly lowered TLR-4 protein levels compared to the control groups (Figure 2).

In a different study [27], mice BMMSCs - injected intradermally - were utilized to modulate the inflammatory response to burn in a rat model. Interestingly, the MSC therapy increased the serum levels of both anti-inflammatory cytokines TGF-β and IL-10 and pro-inflammatory cytokines IL-6 and CINC-1. The serum levels of TGF-β and IL-10 were significantly higher in the MSC-treated animals compared to the control group on post-burn day 15 and 30, respectively (P < 0.05). On the other hand, the serum levels of IL-6 and CINC-1 were significantly higher in the MSC-treated animals on post-burn day 30 (P < 0.05 and 0.02, respectively) [27]. The late rise in pro-inflammatory cytokines may indicate that MSCs can reverse the systemic immunosuppression allowing the immune system to respond to bacterial infections. In other words, MSCs might play a role in inhibiting both SIRS and CARS at different time points. However, there is little evidence to support such a theory, and further studies should further expand on this point.

Zhang et al. [31] utilized human-derived UC-MSCs administrated subcutaneously to modulate the inflammatory response in a rat model. Although the MSC-treated animals showed significantly lower levels of the pro-inflammatory cytokines IL-6 and TNF-α at day 7 post-burn (P < 0.01 and 0.05, respectively), the same animals had lower serum levels of the anti-inflammatory cytokine IL-10 at the same timepoint (P < 0.01). The authors explained this contradictory effect as a weaker CARS due to a weaker inflammatory response. In other words, the MSCs blunted the inflammatory response to burn to level that is below the threshold to initiate CARS. Another explanation is that the MSCs unequally increase the production and consumption of IL-10, leading to the lower levels. Another
potential explanation is that MSCs might have different effects on pro- and anti-inflammatory cytokines at different time points. In one study investigating the effects of IV UC-MSCs on IL-10 levels in Sprague-Dawley rats, stem cell therapy was associated with a marked increase followed by marked reduction of IL-10 levels compared to control groups on days 3 and 14, respectively [81]. However, all these explanations lack substantial evidence and mandate further testing. Furthermore, the short follow-up period in this study (7 days) might have led to an inaccurate presentation of the MSC effects.

It is also worth mentioning that the studies included in this review show a marked variability regarding the type of stem cells, the dose, the route of administration, the experimental endpoints, TBSA, and the animal model used. This variability is expected to significantly affect the outcomes. Unfortunately, determining the stem cell type, dose, and route of administration that is associated with best outcomes requires conducting meta-analysis which is not possible currently due to the rarity of the studies.

4.3. Burn-induced liver, lung, and kidney injuries

4.3.1. Liver

Liver injury is a well-documented complication of severe burns [82]. Liver markers such as total bilirubin, glutamate-pyruvate transaminase, glutamic-oxaloacetic transaminase, alkaline phosphatase, and activated partial thromboplastin time may have a prognostic value [83].

Liver edema is the earliest sign of liver injury in severe burns and starts as early as 12 h postburn [84]. Edema of hepatocytes may result in cellular damage or altered membrane permeability, leading to the release of hepatic enzymes into the circulation. Therefore, a rise in plasma levels of liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may indicate a possible burn-induced liver injury. After severe burns, an elevation of 50–200% of AST and ALT is expected, with the peak happens early in the first 24 h postburn [3,85].

Burn-induced hepatocyte death is mediated through two pathways: apoptosis (programmed cell death) and necrosis [86]. An autopsy study of burned children revealed that 10–15% of severely burned descendants had signs of liver necrosis [82]. The molecular mechanisms of hepatocyte apoptosis are not entirely understood; however, several theories emerged to explain the phenomenon. In one theory, the post-burn decrease in blood flow to the bowel and possibly to the liver [87] was considered to be the initiating event of apoptosis. However, the theorized decrease in hepatic blood flow was not confirmed in human studies. Another theory suggests that the early rise in pro-inflammatory cytokines such as IL-1 and TNF-α mediate apoptosis [88,89]. This was endorsed by the synchronous rise in the serum levels of these cytokines with the liver injury onset.

Furthermore, some studies suggest that the elevation in the pro-inflammatory cytokines is not limited to the plasma as increased levels of IL-1, TNF-α, and IL-6 were also detected in the liver [90,91]. Since MSCs are known for their immunomodulatory effects, they can modulate the hepatic burn response. Therefore, several animal studies evaluated the effects of MSCs on burn-induced liver injury.

4.3.2. Kidney

Severe burns can lead to acute kidney injury (AKI) within the first 24–48 h of injury [92,93]. Although burn-associated AKI most commonly occurs as a result of hypovolemia, and it can develop despite aggressive fluid resuscitation and normal urine output [93]. Therefore, several other factors are believed to contribute to burn-associated AKI including systemic inflammation, extensive tissue destruction, iatrogenic agents as antibiotics, and cardiac dysfunction [92,94]. Some of the inflammatory mediators released in response to burn including TNF-α and endothelin compromise renal perfusion and can result in profound injury [95,96]. Therefore, MSCs can potentially ameliorate this injury by inhibiting inflammatory mediator release.

4.3.3. Lung

Lung injury in burn patients can result from inhalation of toxins, systemic inflammation, fluid overload and heart failure from aggressive fluid resuscitation, and iatrogenic ventilator injury [97]. The current guidelines of preventing pulmonary complications depend on early ventilator weaning, oral hygiene, and chest physiotherapy. Current treatments include nebulized heparin, albuterol, cortisol, epinephrine, and mucolytics; these treatments were found to improve pulmonary functions and outcomes [98].

4.4. The potential role of MSCs in reducing burn-induced liver, lung, and kidney injuries

Yagi et al. [25] evaluated the effects of human-derived BMSCs in preventing organ damage induced by LPS or burn. The investigators conducted one ex vivo and another in vivo experiment. The ex vivo experiment was conducted to investigate the molecular response of MSCs to the inflammatory signals present in LPS-derived serum and burn-derived serum. Therefore, quantitative real-time RT-PCR was performed for four genes in MSCs after being incubated for 24 h in either burn-derived or LPS-derived serum. The four genes are IL-10, V-akt murine thymoma viral oncogene homolog 1 (Akt1), Mitogen-activated protein kinase kinase kinase 1 (MAP3K1), and V-raf-1 murine leukemia viral oncogene homolog 1 (RAF1); all of these genes are known for their anti-inflammatory and cell regulatory roles and should play a role in reducing organ injury. Gene expression analysis revealed an increased expression of IL-10, Akt1, and RAF1 in MSCs incubated in either type of inflammatory sera. However, MAP3K1 expression was increased in the MSCs incubated in LPS serum while decreased in the MSCs incubated in burn-derived serum (Figure 3). The results from the ex vivo experiment suggest that MSCs can alter their gene expression in response to the inflammatory signals present in their microenvironment.

The in vivo experiment involved IM injection of MSCs in endotoxemic and severely burned rats. Although MSCs

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significantly reduced tissue injury and apoptotic cells in the lungs and kidneys in both groups, the effect in the liver was not similar. In the endotoxemic animals, the MSCs therapy was associated with significantly lower serum AST levels indicating less liver damage. However, in the burn model, AST levels were not significantly different from the control group suggesting a different response of MSCs in the burn model. These findings were further investigated in another study evaluating the effects of BMMSCs IV administrated in a mouse binge alcohol intoxication and burned model [34]. Although MSC therapy was associated with statistically significant lower levels of IL-6 and neutrophil chemokine, KC (CXCL1) gene expression in the liver, it did not significantly lower the AST and ALT serum levels compared to controls. Furthermore, the reduction in the number of apoptotic cells in the liver and lung was not significantly different from the control group.

The effects of UC-MSCs and UC-MSC-exosomes in preventing burn-induced lung and kidney injuries, respectively, were evaluated in two studies [30,33]. In both studies, UC-MSCs and their exosomes effectively reduced tissue inflammation and apoptosis in the lung and kidney. Furthermore, in the second study, the anti-inflammatory and anti-apoptotic effects of the exosomes were attributed to miRNA-451 expression, as these effects were reversed when the miRNA-451 expression was inhibited. The underlying mechanism is similar to that reported by Li et al. [32] as it is believed that miRNA-451 plays a role in reducing TLR4 protein levels.

4.5. Effects of burn on BBB

There is a lack of information on the effects of burn injury on the central nervous system in humans. However, neurological complications following inhalational injuries with or without coetaneous burn have been reported. These complications are variable and include persistent headaches, memory loss, paresthesia, impaired concentration and learning abilities, and anhedonia [99,100].

In a sheep model, Randolph et al. [101] investigated the pathophysiologic changes induced by inhalational smoke injury with or without third-degree skin burn. The results showed that smoke inhalation alone or in combination with third-degree skin burns was associated with a significant increase in the number of congested blood vessels in the brain compared to the sham-injured controls. Furthermore, damage to the basement membrane and rupture of blood vessels was also noted on histopathologic examination. These findings show that smoke inhalation can disrupt the BBB and lead to significant neurological consequences.

Yang et al. [26] utilized a mouse model to investigate the pathophysiologic effects of third-degree skin burns on BBB and whether these effects can be reversed with UC-MSCs treatment. BBB permeability was evaluated using several methods, including dextran tracer and transmission electron microscopy, to detect transcellular vesicular transport in BBB.

Burn injury increased BBB permeability to 10-kDa and 70-kDa dextran. Furthermore, burns decreased the level of tight junction proteins (TJs), including claudin-5, occludin, and ZO-1, which indicated increased BBB permeability due to the paracellular pathway. Administering UC-MSCs 1-h post-burn successfully reversed all these effects and restored the integrity of BBB. In detail, UC-MSCs decreased IL-1β and IL-6 in blood and brain; attenuated the decrease of TJs; and inhibited transcytosis in cerebral endothelial cells. However, the underlying mechanisms of these effects are yet to be investigated.

4.6. Clinical trials reporting systemic administration of MSCs in patients with sepsis

The favored effects of MSCs on animal models encouraged investigating its safety and efficacy in clinical trials. Multiple studies investigated the safety of escalating doses of different types of MSCs and its effect on inflammatory mediators in septic and healthy patients (Table 3). He et al. [102] investigated the effect of different doses of freshly cultured UC- MSCs in patients with severe sepsis in the intensive care units (ICU). Although there was no significant change in the clinical outcomes, 100% of the patients tolerated the doses of MSCs with an evidence of a decreased level of inflammatory biomarkers L-6, IL-8, TNF-α, and CRP at day 8 after treatment. Two other studies [103,104]
Table 3. Summary of clinical trials utilizing mesenchymal stem cells in patients with septic conditions.

| Study            | Stem Cells Type                  | Dose                              | Administration Route | Type of Patients              | Results                                                                 |
|------------------|----------------------------------|-----------------------------------|----------------------|------------------------------|-------------------------------------------------------------------------|
| McIntyre et al. 2018 [103] | Freshly cultured allogeneic bone marrow–derived MSCs | 0.3×10^6 cells  
1.0×10^6 cells  
3.0×10^6 cells | IV                           | ICU patients refractory   | septic shock treatment (enrolled within 30 h of admission) Intra-venous delivery of a single dose of freshly cultured MSCs is safe and well tolerated up to a dose as high as 250 million cells in patients with septic shock that do not have significant severe comorbid illnesses No adverse safety (e.g., spike in cytokine concentrations after MSC administration) or efficacy signals in the measured cytokines |
| He et al. 2018 [102] | Allogeneic freshly cultured Umbilical cord-derived MSCs | low (1×10^6 cells/kg), intermediate (2×10^6 cells/kg), High (3×10^6 cells/kg) | IV                           | Intensive care units (ICUs)  
Age >18 years  
Onset of severe sepsis, defined as the presence of at least 2 of the 4 criteria of the systemic inflammatory response syndrome within the previous 24 h | A single intravenous infusion of allogeneic MSCs up to a dose of 3×10^6 cells/kg was safe and well tolerated in 15 patients with severe sepsis Reduced inflammatory biomarkers (L-6, IL-8, TNF-a, and CRP) at day 8 after MSC treatment |
| Perlee et al. 2018 [106] | Allogeneic adipose derived MSCs | 0.25×10^6  
1×10^6  
4×10^6 | IV                           | Healthy male subjects  | Intravenous infusion of MSCs, at any dose, was well tolerated. MSCs infusion has mixed proinflammatory (enhanced IL-8 release) and anti-inflammatory (trend to reduce IL-12p40 and increased IL-10 and TFG-β release) effects on the cytokine network during human endotoxemia |
| Schlosser et al. 2019 [104] | Allogeneic bone marrow–derived mesenchymal stem/stromal cells | 0.3×10^6  
1×10^6  
3.0×10^6 | IV                           | Septic shock patients      | No significant increase in pro-inflammatory cytokines was detected after MSC infusion  
MSC treatment appeared to attenuate levels of several pro-inflammatory cytokines in a dose-specific manner |
| Swaminathan et al. 2021 [105] | SBI-101 is a combination of the allogeneic cells (bone marrow-derived) and a Food and Drug Administration-approved hollow fiber plasma separator | Low dose of SBI-101 (250×10^6 MSCs) | Ex vivo administration | Patients with AKI of any etiology and had been, in the Investigator’s opinion, stable for at least 12 hafer commencement of CRRT and were likely to require CRRT for an additional 48 h | Treatment with SBI-101 elicits an immunotherapeutic response that triggers an accelerated phenotypic switch from tissue injury to tissue repair |

MSCs: Mesenchymal stem cells, IV: Intravenous, ICU: Intensive care unit

Table 3. Summary of clinical trials utilizing mesenchymal stem cells in patients with septic conditions.

- McIntyre et al. [103] used escalating intravenous doses of allogeneic BMSCs on ICU patients with refractory septic shock. Both studies concluded the safety of using MSCs in this patient population with no change or attenuation in the level of pro-inflammatory cytokines.

- Swaminathan et al. [105] studied a combination of the allogeneic BMSCs and a Food and Drug Administration-approved hollow fiber plasma separator (SBI-101). They concluded that infusion of this combination in patients with AKI on continuous renal replacement therapy triggered an immunotherapeutic response that promotes tissue repair. The effects of MSCs on healthy subjects were investigated through an IV infusion of allogeneic adipose MSCs. In that study, Perlee et al. [106] conclusion came in line with the previously mentioned studies regarding the safety of different doses and the mixed cytokine response. All these human clinical trials which concluded the safety of MSCs were limited to small number of subjects in the interventional arm ranging from 9 to 24 (Table 3). We believe that this will open the door for more studies that investigate on a wider scale the effects of MSCs treatment modalities on different patient populations.

5. Conclusion

Although the anti-inflammatory and immunomodulatory characteristics of MSCs have been extensively investigated, only few studies investigated their potentials in burn. The evidence from the existing literature suggests that MSCs may attenuate the burn-induced SIRS by decreasing serum levels of inflammatory cytokines, including IL-1, IL-6, and TNF-α. However, the effect on anti-inflammatory cytokines such as IL-10 is conflicting and mandates more substantial evidence. Furthermore, MSCs reduce tissue inflammation, tissue damage, and apoptosis in the lungs and kidneys. However, these effects were not present in the liver. In addition, MSCs may reverse the burn-induced pathophysiologic effects.

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changes in the BBB. The underlying mechanisms of these effects are poorly understood and should be the focus of future stem cell research.

Limitations

As with most systematic reviews, this study is liable to the potential bias of misinterpreting data and results and bias in the study selection process. Specific to this study, the significant heterogeneity among the included studies, particularly the MSCs source and route of administration, precluded the possibility of conducting a sound statistical analysis. Furthermore, the small number of the included studies compromised the quality of driven conclusions.

Conflict of interest

The authors report no conflict of interest.

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