Title

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What are the long-term outcomes of using mesenchymal stem cells from different sources (e.g., adipose-derived, bone marrow,) in reconstructive skin grafts, and how do these sources compare in terms of regenerative capabilities and immune compatibility?

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Abstract

Mesenchymal stem cells (MSCs) are increasingly used in reconstructive skin grafts due to their ability to promote tissue regeneration and regulate immune responses, helping to improve graft integration and healing.This paper examines the long-term outcomes of MSCs derived from adipose tissue, bone marrow in skin graft applications. We predicted that both adipose tissue and human bone marrow (which are both types of adult tissue) are good sources for mesenchymal stem cells, and would have similar long-term outcomes when used in clinical settings.
While each MSC source demonstrates distinct advantages, variations in cellular proliferation, differentiation potential, and immunogenicity influence their overall effectiveness in clinical applications. Stem cell-based treatments have become a viable option for reconstructive skin grafts, as they allow for improved regeneration of the skin and leave less scarring. However, the long-term effects of using stem cells obtained from various sources such as bone marrow, umbilical cord, and adipose tissue are still a crucial topic of research. In this study, the regenerative capacity, immunological compatibility, and clinical effectiveness of a few different sources of mesenchymal stem cell sources used for skin graft regeneration are examined and contrasted. This study focuses on mesenchymal stem cells instead of other types of stem cells as they have the most wide application within clinical practice. Bone marrow mesenchymal stem cells (BM-MSCs) show a great capability for differentiation, they may be scarce and vary with donor age. Adipose-derived mesenchymal stem cells (AD-MSCs) are easily obtained and have excellent angiogenic qualities. The goal of this paper is to compare and contrast these different sources of mesenchymal stem cells, and conclude which sources are the most efficient and

effective to draw from in order to give life-saving treatment to patients as quickly as possible within the clinical setting.

Introduction

Stem cells (specifically mesenchymal stem cells) are found throughout the body. They are especially present throughout tissues. They are multipotent stem cells, meaning they can differentiate into many different cell types. This is why they are found throughout bone marrow as both cartilage, fat, and bone cells. Mesenchymal stem cells are also easy to take out of both adult and fetal tissue, which correlates with bone marrow, adipose, and umbilical cords, respectively. Adult tissue exists throughout the body after development, and fetal tissue is typically described as tissue retrieved from a dead human embryo or fetus. Still, it can also be taken from the umbilical cord. Given their remarkable differentiation capabilities and ease of extraction, mesenchymal stem cells have become an important focus in regenerative medicine, particularly in skin graft applications. These cells not only facilitate faster wound healing but contribute to reducing inflammation and minimizing scar formation. However, current limitations of skin grafting—such as donor site morbidity, immune rejection, and insufficient vascularization—highlight the need for more effective regenerative solutions. Despite their shared regenerative properties, AD-MSCs, BM-MSCs, and UC-MSCs exhibit distinct characteristics that may influence their suitability for skin grafts. Recent studies suggest that variations in MSC sources may significantly impact clinical outcomes, making it essential to compare their regenerative efficacy and immune compatibility. By systematically analyzing the

long-term outcomes of MSCs derived from different sources, this paper aims to provide valuable insights into their optimal application in reconstructive procedures.

In addition to differentiation potential, MSCs also exhibit immunomodulatory effects, which play a crucial role in graft survival. Furthermore, recent research has highlighted the immunomodulatory properties of MSCs, demonstrating their ability to suppress pro-inflammatory responses while enhancing regulatory T-cell expansion. For example, both adipose-derived MSCs (AD-MSCs) and bone marrow-derived MSCs (BM-MSCs) have been shown to decrease Th1 and Th17 cell activity, thereby reducing the production of inflammatory cytokines such as IL-17 and IFN-γ. This modulation of the immune response plays a critical role in graft survival, as it helps minimize rejection and promotes long-term tissue integration. By exploring these immunological mechanisms in greater detail, this study seeks to offer a comprehensive comparison of the therapeutic potential of MSCs from different sources and their long-term viability in reconstructive skin grafts. Additionally, understanding the biological interactions between MSCs and the recipient's immune system will allow for future advancements in the field of regenerative medicine, potentially reducing the dependence on immunosuppressive therapies.

Methodology

This research paper was written collaboratively, with a structured approach to reviewing literature and analyzing data. We worked to find research in fields related to our research question and reviewed these thoroughly. To ensure the relevance and credibility of our sources, we included only peer-reviewed studies published within the last 10 years, focusing on clinical

trials, preclinical studies, and systematic reviews. We primarily used reputable biomedical databases such as PubMed, ScienceDirect, and Google Scholar. Key search terms included “mesenchymal stem cells,” “skin grafts,” “AD-MSC,” “BM-MSC,” “UC-MSC,” “regenerative medicine,” and “immune response.” We started by reviewing general research surrounding the different types of stem cells and how they have been used to treat serious issues in clinical settings. Then, we slowly honed in on existing findings most directly related to the answers we wished to find. This included the decision to focus on mesenchymal stem cells as the most applicable to our research, investigating how they have been used in clinical practice, and identifying their sources. By looking into AD-MSCs, BM-MSCs, and UC-MSCs, we conducted a comparative analysis of which of these provide the best regenerative capabilities and immune compatibility, while also evaluating their ease of access and long-term effectiveness. To ensure a robust comparison, we considered specific criteria such as cell proliferation rate, differentiation ability (particularly into skin-relevant lineages), cytokine expression profiles, immunomodulatory effects, graft survival rates, and patient outcomes from clinical trials.

Our methodology relied on a combination of clinical trials, systematic reviews, and preclinical studies gathered from reliable sources, particularly those hosted by the U.S. National Library of Medicine through PubMed. We also referenced comparative studies, such as Thanaskody et al.'s analysis of MSCs versus iPSCs, and broader foundational overviews of stem cell progression, such as Zakrzewski et al.’s review of the field’s development.We incorporated a systematic review approach by compiling and synthesizing data from multiple peer-reviewed studies to ensure a well-rounded and evidence-based conclusion. Both qualitative and quantitative data were evaluated to provide a nuanced assessment of the long-term viability of

different MSC sources in clinical applications. We prioritized regenerative outcomes, ease of harvesting, and long-term tissue integration, particularly in clinical and preclinical graft settings.Overall, our process showcases our immense dedication to the scientific process of understanding existing research and implementing it in innovative ways to help transform clinical practice. This reflects the importance of intensive research and inquiry, rigorous commitment, and scholarly progression within the sciences.

Mesenchymal Stem Cell Applications in Skin Graft Reconstruction

MSCs were first identified in bone marrow by Cohnheim in 1867, who recognized that these cells might serve as the source of fibroblasts involved in wound healing (Knight, et al.). A while afterward, A. J. Friedenstein isolated and propagated MSCs for the first time in 1968. Using cells derived from murine bone marrow, he found that transplanting cell colonies into semi-syngeneic animals could lead to the possible formation of fibrous tissue, bone, and bone marrow. Years later, it was evident that Friedenstein's creations were the result of cells with multipotent abilities. In 1991, following his study on human bone marrow, Caplan coined the phrase "mesenchymal stem cells." From that point on, due to their ease of isolation, ability to expand, and multipotent nature, MSCs have quickly gained popularity as a promising therapeutic tool in regenerative medicine. This historical foundation laid the groundwork for the current clinical exploration of MSCs in wound healing and skin graft applications.

Today, they remain a leading area of research, being investigated for a wide range of applications. Some factors that make MSCs ideal for cell therapy are 1) they possess stemness

potency; 2) they pose fewer ethical concerns compared to embryonic stem cells (ESCs); 3) unlike induced pluripotent stem cells (iPSCs), they present a lower risk of teratoma formation; and 4) they can migrate to damaged tissues via chemoattraction, making them versatile for various therapeutic applications. For this reason, MSCs hold promise for treating tissues of diverse origins. Their unique properties are paving the way for novel therapies in regenerative medicine, offering the possibility of repairing damaged tissues without the need for complex surgical procedures or donor organs, thus improving patient outcomes. Research into MSCs continues to evolve, with exciting clinical trials showing progress in the application of MSCs for conditions like bone and cartilage regeneration, wound healing, and even nerve repair. Given their wide-ranging therapeutic potential, MSCs are becoming a cornerstone of modern regenerative medicine, with ongoing studies aimed at optimizing their use for a broader spectrum of medical conditions.

Although MSCs can be acquired from a variety of tissues, bone marrow is the main source of MSCs. MSCs are defined by three key characteristics: first, their ability to differentiate into osteoblasts, adipocytes, and chondrocytes. Second, they should cling to plastic surfaces under standard culture conditions in a tissue culture flask. Lastly, MSCs exhibit specific surface markers, including CD105, CD73, and CD90, which can be detected through flow cytometry. Figure 1 illustrates a summary comparison of MSCs derived from bone marrow (BM-MSCs), adipose tissue (AD-MSCs), and umbilical cord (UC-MSCs), highlighting differences in proliferation rate, immunogenicity, ease of harvesting, and clinical utility. This comparison helps contextualize their respective advantages and limitations in regenerative applications such as skin grafting.

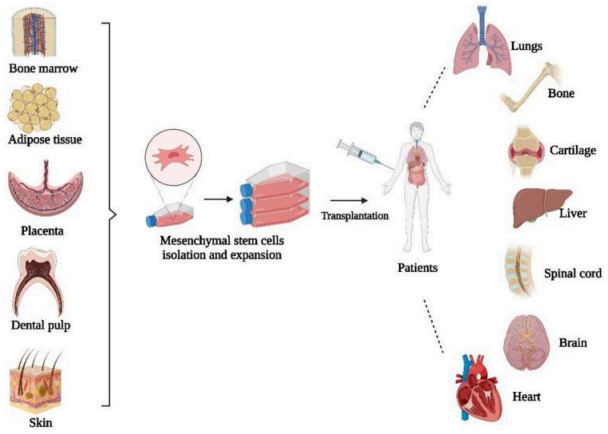

Figure 1. Comparison of mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) for therapeutic applications. Adapted from Thanaskody K, Jusop AS, Tye GJ, Wan Kamarul Zaman WS, Dass SA, Nordin F. "MSCs vs. iPSCs: Potential in therapeutic applications." *Frontiers in Cell and Developmental Biology*. 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9666898/

In the field of skin graft reconstruction, MSCs offer significant advantages due to their ability to enhance wound healing, promote angiogenesis, and modulate immune responses. Their regenerative properties are particularly valuable in cases of extensive burns, chronic ulcers, and traumatic skin loss, where conventional grafting methods may be insufficient for complete tissue restoration. By secreting bioactive molecules and cytokines, MSCs accelerate the formation of new blood vessels, reduce inflammation, and stimulate the proliferation of keratinocytes and fibroblasts, all of which contribute to improved graft integration and durability. Moreover, MSCs have demonstrated the potential to overcome some of the key challenges associated with traditional skin grafts, such as graft rejection and poor vascularization. Their immunomodulatory effects help suppress excessive immune responses, thereby reducing the risk of graft-versus-host disease (GVHD) and improving graft acceptance, even in allogeneic transplant settings. This capability makes MSCs particularly promising for patients who lack viable autologous donor sites or require large-scale skin grafting procedures.This research examines AD-MSCs, BM-MSCs, and UC-MSCs based on clinical parameters such regenerative performance,

immunogenicity, harvesting feasibility, and long-term efficacy in order to determine which MSC source is most suited for various applications. Current research is exploring various techniques to enhance MSC-based skin graft reconstruction, including pre-seeding MSCs onto bioengineered scaffolds or decellularized dermal matrices to create cell-enriched grafts with improved mechanical and biological properties. Additionally, advances in three-dimensional (3D) bioprinting are integrating MSCs into custom-designed skin substitutes, offering the potential for more personalized and functional graft solutions. As clinical trials continue to evaluate the efficacy and long-term safety of MSC-based therapies, the future of skin graft reconstruction appears increasingly promising. By leveraging the unique properties of MSCs, researchers and clinicians are working toward developing more effective, durable, and cosmetically favorable grafting techniques that can significantly improve the quality of life for patients requiring skin reconstruction.

Comparing the effects of hBM-MSCs and hAD-MSCs on allogeneic skin grafts in rhesus monkeys

In 2021, an in vivo study investigating the effects of hBM-MSCs (human bone marrow-derived mesenchymal stem cells) versus hAD-MSCs (human adipose-derived mesenchymal stem cells) was published. Although the study was limited to eight rhesus monkeys and only examined the immunomodulatory effects for the first 96 hours, it found no statistically significant differences in xenogeneic immunomodulatory properties, histopathological scores, or inflammatory response between skin grafts treated with hBM-MSCs and hAD-MSCs. To find out if these effects last over the long term, more research is required because of the limited sample size and brief observation time. By using flow cytometry to analyze the levels Th1, Th17, and Tregs cells, the study found that both hBM-MSCs and hAD-MSCs reduced Th1 and Th17

proliferation and increased the presence of Tregs. Th1 and Th17 are linked to inflammatory responses, while Tregs are responsible for regulating and suppressing inflammatory responses. Therefore, both types of MSCs were shown to possess anti-inflammatory properties, potentially leading to longer skin graft survival due to suppressing rejection mechanisms.

However, this experiment did find significant differences in the levels of different types of Treg cells, FoxP3+ and CD4+CD25+ T cells, at different time points. This indicates a difference between hBM-MSCs and hAD-MSCs, even though their overall immunomodulatory properties were shown to be similar. These molecular-level differences may stem from variations in cytokine secretion profiles, as adipose- and bone marrow-derived MSCs are known to differ in their expression of immunomodulatory factors such as IL-10, TGF-β, and PGE2. This showcases that there are molecular-level differences between these two, which could be worth further exploration, as these distinctions could be important in better determining their effects on skin graft tolerance. However, in this context the difference is not so significantly impactful to be further contextualized for the purposes of this paper. However, this work underscores the need of selecting an MSC type appropriate for particular therapeutic applications and advances our understanding of how MSC source may affect immune modulation in grafting procedures.

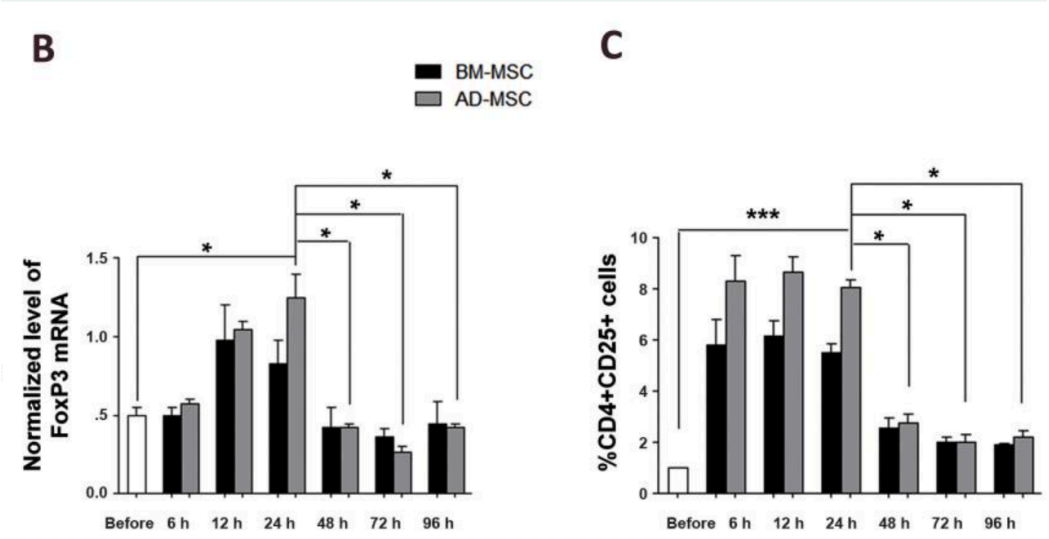

Figure 2. *Immunomodulatory effects of human adipose-derived MSCs (hAD-MSCs) and bone marrow-derived MSCs (hBM-MSCs) on rhesus T cells over time.*
(B) Normalized mRNA levels of the Treg marker **FoxP3** increased in both MSC groups, peaking at 24 hours, with hAD-MSCs showing a significantly stronger early effect ($p<0.05$).
(C) The percentage of **$CD4^+CD25^+$** cells, indicative of regulatory T cell induction, was also higher in hAD-MSC-treated cultures at 12 and 24 hours (**$p<0.001$, $p<0.05$), before declining after 48 hours in both groups. These results highlight the superior early immunosuppressive potential of hAD-MSCs compared to hBM-MSCs. Data are presented as mean ± SD.
https://pmc.ncbi.nlm.nih.gov/articles/PMC7944119/

This study provides insight into the potential of both hBM-MSCs and hAD-MSCs in reconstructive skin grafts, revealing their immunomodulatory properties and ability to extend the survival of the skin grafts. Other studies have obtained similar results, finding decreased Th1 and Th17 production and increased Treg quantities in response to MSCs.Larger and longer-term studies are necessary to better evaluate the long-term effects on immune response and skin graft survival, as well as to ascertain whether the noted immunomodulatory effects result in long-lasting enhancements in graft viability and function, considering the small sample size and brief observation period.**.** While both hBM-MSCs and hAD-MSCs exhibited comparable abilities to regulate inflammation in the early post-transplant period, it remains unclear whether

differences in their mechanisms of action could influence graft stability over time.While hBM-MSCs are known for their bone formation and chondrogenic potential, which may make them more appropriate for composite grafts involving multiple tissue types, hAD-MSCs have been reported to have a higher proliferation capacity and release larger amounts of angiogenic growth factors like VEGF and HGF, potentially improving vascularization and graft integration.

Given this small sample size and short observation period, further research is also required to determine whether the observed immunomodulatory effects translate into long-term improvements in graft viability and function. While both hBM-MSCs and hAD-MSCs exhibited comparable abilities to regulate inflammation in the early post-transplant period, it remains unclear whether differences in their mechanisms of action could influence graft stability over time. For instance, previous studies suggest that hAD-MSCs possess higher proliferative capacity and secrete greater amounts of growth factors such as VEGF and HGF, which could enhance vascularization and improve graft integration. On the other hand, hBM-MSCs are known for their strong osteogenic and chondrogenic potential, which may be advantageous in reconstructing composite grafts involving multiple tissue types. Additionally, the microenvironment in which MSCs are introduced may play a crucial role in their therapeutic efficacy. Factors such as donor variability, age, and the inflammatory status of the recipient could influence the extent of immune modulation exerted by each MSC type. Future studies should explore personalized approaches that consider patient-specific variables to optimize MSC-based therapies for skin graft reconstruction.

Additionally, the microenvironment in which MSCs are introduced may play a crucial role in their therapeutic efficacy. Factors such as donor variability, age, and the inflammatory status of the recipient could influence the extent of immune modulation exerted by each MSC type. To improve clinical results and optimize MSC-based therapies for skin graft regeneration, future research should investigate tailored strategies that take these patient-specific factors into account. Long-term studies evaluating graft histology, vascularization, and fibrosis formation will be critical to understanding whether hBM-MSCs or hAD-MSCs offer superior benefits for allogeneic skin grafts. Moreover, advanced imaging techniques and molecular analyses could help elucidate the specific signaling pathways involved in MSC-mediated immune regulation. As research in this field progresses, refining MSC application methods—such as preconditioning strategies or co-delivery with biomaterials—may further enhance their efficacy. Although further research is required before these findings can be translated into clinical practice, it does add to the fundamental understanding of MSC behavior in graft contexts and helps guide MSC selection for human skin grafts.

Stem Cells Use in Wound Healing

Wound healing is a complex biological process that entails the coordinated interaction of several cell types, such as fibroblasts, keratinocytes, endothelial cells, and inflammatory cells. A series of growth factors and cytokines that control angiogenesis, inflammation, and tissue remodeling propel the process. Impaired healing may result from disturbances in these processes, which are frequently brought on by coexisting illnesses including diabetes, vascular diseases, chronic inflammation and require for advanced therapeutic strategies. By utilizing regenerative

and immunomodulatory qualities of stem cells produced from sources such as bone marrow and adipose tissue, stem cell treatment has become a viable method for improving wound healing in clinical cases.

Hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are two types of bone marrow-derived stem cells (BM-SCs) that are essential for wound healing and tissue regeneration. MSCs have shown the capacity to develop into a variety of cell types, including fibroblasts and keratinocytes, which aid in skin restoration. These cells are a vital resource in regenerative medicine because the bone marrow, especially in long bones like the femur and tibia, is a rich repository for them. Bone marrow aspiration, a safe technique, is used to harvest BM-derived cells, which enables their therapeutic use in wound healing techniques.

The effectiveness of BM-MSCs in healing chronic wounds has been convincingly demonstrated by a number of clinical investigations. In comparison to patients who received only saline dressings, those treated with allogeneic BM aspirate, either fresh or cultured, exhibited a substantial decrease in wound surface area, according to a case-control study involving 75 patients (Gupta G.J, et al.). Interestingly, this improvement persisted through week 4 and was noticed as early as day 7 (Gupta G.J, et al.).The regeneration ability of BM-MSCs in wound healing was further supported by the fact that patients with chronic leg ulcers treated with these cells showed decreased wound size, increased vascularity, and improved skin thickness (Sen C.K. et al.). In addition, three patients with persistent wounds that lasted more than a year were given BM-derived cell treatments in a study by Badiavas et al.; this led to complete wound closure, skin rebuilding, and less scarring (Badiavas E.V. et al.). Similarly, in a case series

research, Rogers et al. found that BM-derived cells applied topically and injected both dramatically decreased the size of chronic lower-extremity wounds (Rogers L.C. et al). Additionally, Jain et al. discovered that BM-MSC therapy reduced the wound area after two weeks by 17.4% in diabetic patients with chronic lower-limb wounds, while the control group only had a 4.84% reduction (Jain P. et al).

Both clinical and experimental research provide strong evidence for the regenerative capacity of BM-MSCs in wound healing. They are a potent tool in regenerative therapy because of their capacity to develop into vital skin cell types, regulate the immune response, and stimulate angiogenesis. Significant increases in wound healing rates have been repeatedly demonstrated in clinical trials, especially for ischemic injuries, diabetic ulcers, and chronic wounds. BM-MSCs are anticipated to play a significant role in cutting-edge wound-healing treatments as research into stem cell application methods advances, providing patients with difficult and non-healing wounds with fresh hope.

Discussion

This study compares MSCs derived from bone marrow (BM-MSCs), and adipose tissue (AD-MSCs) to determine their effectiveness in skin graft healing and integration. All three types of MSCs helped improve skin graft healing by reducing inflammation, speeding up recovery, and lowering the chances of rejection. However, they each have unique strengths that make them better suited for different situations.

Because of their great osteogenic and chondrogenic differentiation capacity, BM-MSCs are well-known for their potent tissue regeneration qualities, especially in supporting the repair

of bone and cartilage. The invasive aspect of bone marrow extraction and the relatively low cell yield somewhat limit their clinical usage, despite the fact that their immune modulation capabilities are effective—particularly in controlling Th1 and Th17 cells and boosting Treg populations. On the other hand, because AD-MSCs may be obtained by less invasive techniques like liposuction, they are more readily available and exhibit a greater rate of growth. Growth factors like VEGF and HGF, which promote angiogenesis and quick tissue healing, are also secreted in greater amounts by these cells. Their high secretory activity and simplicity of collection make them a viable alternative for treating superficial wounds or instances requiring quick recovery, even though their differentiation potential may be a little less than that of BM-MSCs.

Despite being less commonly employed, UC-MSCs have an attractive profile because of their potent immunomodulatory qualities and high proliferation potential. They are a promising option for allogeneic applications due to their low immunogenicity and non-invasive harvesting method, which usually takes place at birth without raising ethical or procedural issues. To ascertain their complete therapeutic potential and stability over time, more research is required as there is currently a dearth of long-term evidence on their application in skin grafting.

When choosing MSC types, it is important to take into account both their biological traits and useful therapeutic considerations. While BM-MSCs are better suited for complex restorations needing long-term structural regeneration, AD-MSCs may be preferred in time-sensitive therapies requiring quick healing and low invasiveness. Particularly in pediatric or allogeneic settings, UC-MSCs offer a new alternative for patients in need of immunocompatible,

commercially available treatments. The significance of choosing the right MSC source to meet certain clinical requirements in skin transplant procedures is highlighted by this comparative analysis.

Healing and Regrowth

BM-MSCs are good at turning into different cell types, which makes them useful for complex tissue repair. However, they don't multiply as quickly as AD-MSCs, and their quality decreases with age, making them harder to use in some patients. Despite this, BM-MSCs still help in reducing inflammation and making grafts last longer.

AD-MSCs, which come from fat tissue, grow and multiply much faster than BM-MSCs. They also release helpful growth factors that improve blood vessel formation, making them great for skin graft healing. Since fat tissue is easy to collect, AD-MSCs are widely available and easy to use in medical treatments. UC-MSCs, taken from umbilical cords after birth, have a special advantage: they are less likely to trigger an immune response. This makes them a great option for patients who need donor cells instead of their own. UC-MSCs also multiply quickly and reduce inflammation, but they are not as good at turning into specialized tissue like BM-MSCs.

In terms of differentiation potential, UC-MSCs exhibit a more limited ability to develop into certain cell types compared to BM-MSCs, which are derived from bone marrow. While both UC-MSCs and BM-MSCs can differentiate into mesodermal lineages, such as osteocytes (bone cells), chondrocytes (cartilage cells), and adipocytes (fat cells), BM-MSCs generally have a stronger capacity for osteogenic (bone-forming) and chondrogenic (cartilage-forming) differentiation. Studies suggest that UC-MSCs are more inclined toward adipogenic differentiation and may have a weaker ability to generate functional bone or cartilage tissue.

Furthermore, UC-MSCs tend to express lower levels of certain differentiation-related genes and signaling pathways that are crucial for tissue regeneration. This reduced differentiation potential is often attributed to their younger, more primitive state compared to BM-MSCs, which originate from a more mature microenvironment. However, despite these differences, UC-MSCs still hold significant therapeutic promise due to their strong immunomodulatory effects, ability to secrete bioactive factors that promote healing, and ease of collection without invasive procedures. Their reduced differentiation capability may also be mitigated through advanced techniques such as genetic modification, preconditioning with specific growth factors, or co-culturing with other cell types to enhance their regenerative properties.

How They Affect the Immune System

Studies in animals, such as rhesus monkeys, show that both BM-MSCs and AD-MSCs help control the immune system by reducing harmful inflammation and increasing protective cells that help the graft survive. However, BM-MSCs and AD-MSCs seem to work slightly differently, with some differences in how they regulate immune cells over time. More research is needed to understand these differences and how they affect long-term graft success.

UC-MSCs, because of their low risk of immune rejection, can be used in patients without needing drugs to suppress the immune system. This makes them a great option for treatments that require donor cells, though more research is needed to confirm their long-term effectiveness in skin grafts.

Long - Term Effects and Challenges

Clinical studies show that MSCs improve skin graft healing by increasing blood flow, reducing scarring, and helping the graft last longer. AD-MSCs seem to have the best overall effect because they grow fast, release helpful healing factors, and are easy to get. BM-MSCs are useful for rebuilding more complex tissue but can be harder to obtain. UC-MSCs are excellent for donor-based treatments because they don't trigger strong immune reactions, though their ability to fully rebuild tissue needs more study.

There are still some challenges to using MSCs in skin grafts. The way these cells behave can change depending on the donor's age, health, and how the cells are collected. Doctors and researchers also need to develop standard methods to make sure treatments are consistent and effective. Future research should focus on optimizing MSC application methods, overcoming ethical and logistical challenges, and ensuring their large-scale clinical feasibility. Additionally, combining MSC therapy with gene editing techniques or biomaterial scaffolds could enhance their regenerative potential and create more effective treatments for patients requiring skin grafts. Standardizing protocols for isolating, expanding, and delivering MSCs will be crucial in ensuring their reliability and effectiveness in real-world clinical applications.

Conclusion

All things considered, AD-MSCs appear to be the greatest choice for skin graft healing due to their rapid growth, ability to create blood vessels, and ease of collection. Because of their potent immunomodulatory ability and ease of collection, UC-MSCs offer a viable allogeneic alternative, although BM-MSCs are still useful for more complicated grafts requiring specialized tissue repair. According to our research, AD-MSCs provide the most affordable and useful option for clinical skin graft applications, especially where minimal invasiveness and quick healing are

required. To maximize their long-term effectiveness and evaluate their performance across a range of patient demographics, more study is necessary.

Long-term clinical trials to assess graft durability, immunological tolerance, and functional results over time should be the main focus of future research. Examining preconditioning techniques or genetic engineering to increase MSC potency may help to improve therapeutic outcomes. Additionally, integrating MSC-based treatments into mainstream clinical practice will require overcoming obstacles like regulatory approval, large-scale production, and standardization of cell preparation. MSC-based skin grafts may soon move from experimental practices to commonly used therapies when these gaps are filled, providing patients with quicker, safer, and more efficient skin reconstruction choices.

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