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Effects of Stem Cell Therapy on Keloid Treatment: A Literature Review

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Abstract: Fibroblasts that produce excess collagen and growth factors play a role in the pathogenesis of keloid formation. In general, keloids are treated with intralesional corticosteroids alone or with a combination of other modalities, but the recurrence rate is still relatively high, so alternative treatments such as stem cells are being investigated, one of which is Mesenchymal Stem Cells (MSC), which have proven to be useful in healing keloids. Therefore, this literature review aims to discuss the effects of stem cell therapy in the treatment of keloids. In this literature review, 36 journals were used that discussed stem cell therapy in the treatment of keloids taken from various journal sources, namely Google Scholar, Pubmed, Medline, Ebsco, Hindawi, and Cochrane which were published within the last 10 years. According to the source, MSC is divided into 2 types, namely Adipose Mesenchymal Stem Cells (AMSC) and Bone Marrow Mesenchymal Stem Cells (BMMSC). In several studies, AMSC is known to reduce the expression of TGF-β1, COL-1, and COL-2 proteins, and has been shown to inhibit the proliferation of fibroblasts in keloid patients. Whereas in the BMMSC study that was applied with Hydroxybutyl chitosan (HBC) and Arg-Gly-Asp (RGD) hydrogels for 7 days, it was shown to significantly reduce nodular collagen fibers ($p<0.05$). Keloids occur due to excessive production of collagen and are influenced by various factors such as age, gender, skin color, and genetics. Stem cell therapy, such as MSC, has been proven in various studies to be an alternative treatment for keloids.

Keywords: Keloid treatment; Review; Stem cell therapy

Introduction

Keloids result from abnormal wound healing in response to trauma or skin inflammation. The development of keloids rests on genetic and environmental factors. Overactive fibroblasts produce high amounts of collagen and growth factors which are involved in the pathogenesis of keloid formation. As a result, classical histological findings show large, abnormal, hyalinized collagen bundles referred to as keloidal collagen and numerous fibroblasts. Keloids appear clinically as tight, supple nodules in areas of skin previously affected by injury (McGinty et al., 2022).

The main therapies for keloids include intralesional corticosteroid injections, either as monotherapy or in combination with other treatment modalities such as *cryotherapy*, 5-flurouracil, radiotherapy, laser therapy, surgical excision, or silicone occlusive dressings. Although there are many treatment options, results are often unsatisfactory with a recurrence rate of 45%–100%. In addition to the above therapies, there is also one keloid therapy that has not been widely used, namely with stem cells. Stem cells or known as *stem* cells are cells that have unlimited self-renewal capacity and the ability to give rise to daughter cells that are able to differentiate into special differentiated cells. There is increasing evidence of stem cell involvement (Lim et al., 2019).

The incidence of keloids is highest in people with darker skin pigment such as Africans, Asians, and Hispanics and is estimated to range from 5%–16%. Men and women have an equal risk of developing keloids, but their incidence is slightly higher in women, likely because they have more cosmetic procedures such as ear piercing. People aged 10-30 years are also at higher risk

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of keloids. Additional risk factors include people who have blood type A, *hyper-IgE* and hormonal peaks during pregnancy or puberty (Ojeh et al., 2020).

In terms of geographical distribution, it has long been cited that the incidence of keloids ranges from 0.09% in the UK to 16% in Zaire. While the figure does not show how this incident was determined. This is supported by several large-scale studies of geographical events that have been carried out. One was a review of 5735 patients who underwent surgery in 33 health facilities in Zambia between 1993-2008. Research shows that out of 5774 patients who underwent surgery, 514 developed keloids. Thus, keloids accounted for almost 9% of all surgical cases in Zambia during the study period. In Kenya, the prevalence of keloids is 8.5% among people with normal pigmented skin. In contrast, the incidence of keloids in Japan is about 0.1%. Based on world epidemiology, the average incidence of keloids can be estimated at 5–10% in Africa, 0–0.1% in Asia, and <0.1% in other countries (Huang et al., 2020).

Mesenchymal stem cells (MSCs) have shown good potential for healing and wound repair by secreting growth and differentiation factors that accelerate migration, angiogenesis, and regulate epithelialization and collagen remodeling. In addition, MSCs have a number of anti-inflammatory and antifibrotic properties that increase the potential for scar treatment (Elsaie, 2021).

Stem cells are increasingly widely used in the field of dermatology. Stem cell therapy is proven to provide benefits in healing keloids, pemphigus, systemic sclerosis, lupus erythematosus, psoriasis, vitiligo, helping the wound healing process, alopecia, melanoma, and *aesthetic medicine* (Khandpur et al., 2021). Therefore, the use of secretomes is currently more developed as an alternative therapy, especially one of which plays a role in healing keloids. State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Method

The literature sources used come from Google scholar, Pubmed, Medline, Ebsco, Hindawi and Cochrane published within the last 10 years. After searching for keywords, then selection was carried out and selected literature with a literature review method regarding the provision of stem cell therapy in the treatment of keloids and obtained 36 journals. Writing begins with a review of the content of each piece of literature that has been read that meets the criteria. The discussion was arranged in an organized format ranging from the definition, mechanism of keloid formation and effectiveness of stem cell treatment to keloid resolution.

Result and Discussion

Keloids

Keloids are excessive connective tissue growths that exceed the size of the wound in the healing phase (Menaldi et al., 2016). Keloids develop as a result of a mild trauma or trauma of any type in people who have a genetic predisposition (Nangole et al., 2019). Keloid fibroblasts have higher proliferative activity, last longer, and have a lower apoptosis rate. This leads to excessive production of collagen and cytokines where type I and III collagen in keloids synthesis 20 times more than in healthy skin. This process is mainly driven by *Transforming Growth Factor-beta* (TGF-β) and Platelet-Derived *Growth Factor* (PDGF). TGF-β increases fibroblast chemotaxis to the site of inflammation and triggers the production of collagen types I and III. Dysregulation of this pathway leads to fibrosis and an abnormal skar response (McGinty et al., 2022).

The main risk factor for keloid formation is darker skin. It is said that more pigmented skin has a 15-20-fold higher risk of keloid formation due to anomalies in *melanocyte stimulating hormone*. The age of 15-35 years is the peak of keloid formation on human skin because in younger individuals there is more skin tension, faster collagen synthesis and more susceptible to trauma. Women are also more prone to keloid formation than men. This is thought to be due to aesthetic concerns as well as ear piercing procedures that are more widely performed by women (Manoharan et al., 2020). Genetic predisposition also has a role in the development of keloids. In addition, individuals with blood type A have a higher risk for keloid formation that is thought to be due to antigen A on red blood cells. Hypertension causes damage to blood vessels so that it can affect the development of keloids. Keloids are also more likely to develop in more physically active areas such as the shoulders and neck. Infected wounds have a higher risk of developing into keloids (Shaheen, 2017).

*Mesenchymal St**e**m Cells*

Hypertrophic scars are characterized by excessive fibroblast proliferation and *excessive extracellular matrix* (ECM) deposition. Inflammatory cells as well as pro-inflammatory and anti-inflammatory cytokines, play an important role in the formation and maturation of scar tissue. Especially in the early stages of scar tissue formation, many inflammatory cells such as neutrophils, mast cells, macrophages, and T lymphocytes infiltrate tissues and regulate or secrete many proinflammatory factors, including IL-1, IL-6, and TNF-α (H. Wang et al., 2022). Most of the studies looking at wound healing therapies are related to adult stem cells, specifically MSCs. These cells are capable of self-renewal and have been shown to repair tissue damage involving immune responses and can be taken from the patient's bone

marrow, adipose tissue, blood, umbilical cord, and dermis (Hu et al., 2015).

More recently, the origin of MSCs has been associated with *embryonic stem cells* (ESC) that originate from nuclear cell masses in blastocysts and have pluripotent abilities. Several studies have succeeded in inducing *human* ESC (hESC) differentiation into MSCs that can differentiate into adipocytes, osteocytes, chondrocytes, and myocytes (Lim et al., 2019). MSCs produce a broad spectrum of paracrine factors. The main paracrine factors involved in immunomodulation are TGF-β, prostaglandin E2 (PGE2), *hepatocyte growth factor* (HGF), IL-10, IL-6, indolamin 2,3-dioxygenase (IDO), *nitric oxide* (NO), and *human leukocyte antigen* G (HLA-G). Each of these factors is known to regulate different target immune cells. IL-10 is the main anti-inflammatory cytokine that inhibits the infiltration of neutrophils into wounds. NO is known to convert ROS into less toxic reactive nitrogen species. HGF is a growth factor secreted by MSCs that modulates fibroblasts, having a major role in fibrosis. Myofibroblasts are rich in alpha smooth muscle actin, responsible for wound contraction and ECM secretion and undergo apoptosis after wound maturation. Excessive activation of myofibroblasts is seen in the appearance of scarring. HGF downregulates fibroblasts from TGF-1, which promotes myofibroblast differentiation, and collagen types I and III (Lim et al., 2019; Seo et al., 2016).

The nature of MSCs can vary according to the cell source. These cells are divided into Adipose Mesenchymal Stem Cells (AMSC) and *Bone Marrow Mesenchymal Stem Cells* (BMMSC). Both of these cell sources have the relative advantage of being used in treating scars. *Adipose Mesenchymal Stem Cells* offer a greater capacity to multiply ex vivo compared to other cell sources and therefore may be suitable for large-scale preparations with greater cost-effectiveness. In addition, AMSC is easier to obtain, less invasive, and often available as medical waste in many cosmetic surgery procedures (Bojanic et al., 2021). An important thing to consider is that the anti-inflammatory properties of MSCs can differ based on the cell source. Certain studies suggest that AMSC may be superior in promoting the transition of the M1 to M2 phenotype in macrophages that support the resolution of inflammation (Heo et al., 2019).

Adipose Mesenchymal Stem Cells

Adipose Mesenchymal Stem Cells are MSC spinal cord stem cells extracted from adipose or fat cells. These cells are easily available and can be found in large numbers in the human body and have a high rate of proliferation and self-recovery, and show good potential for various diseases, one of which is keloids (Xiong et al., 2020). These cells can secrete bioactive factors that play a role in growth factors and cytokine production, and have the ability to differentiate into osteoblasts, chondrocytes, muscle cells, and neuronal cells. In addition, this cell can also differentiate into keratinocytes so that it can directly differentiate into epidermal and dermal cells that stimulate tissue regeneration and prevent scars in the scar area during the wound healing process. AMSC treatment can also be an approach to treatment of wound healing, soft tissue restoration, and scar remodeling such as keloids and provides quite good results on keloids by inhibiting bioactivity in keloid fibroblasts (Chen et al., 2022; Zhou et al., 2022).

The mechanism of action of AMSC is by inhibiting fibroblast proliferation in hypertrophic scars and helping to relieve the inflammatory process that takes place (Liu et al., 2018; X. Wang et al., 2018; Yang et al., 2021). It also regulates inflammation by regulating the immune system through the paracrine pathway of bioactive factors that inhibit tissue hyperplasia. The immunomodulatory activity of AMSC is also due to paracrine secretion of antifibrotic cytokines, including prostaglandin E2 (PGE2), Interleukin-10 (IL-10), *Hepatocyte Growth Factor* (HGF), and NO. In addition, it activates antifibrotic molecular pathways, regulates primary fibroblast activity and growth factors, and stabilizes the function of prescription fibroblasts and keratinocytes (Luan et al., 2016). This is similar to Chen et al's research that AMSC can reduce hypertrophic scarring through direct differentiation by paracrine mechanisms. Clinically, they can improve the color, elasticity, texture, thickness, and size of hypertrophic scars, as well as have a positive effect in reducing hypertrophic scarring, thus demonstrating their potential as a treatment approach in this condition with broad therapeutic prospects (Chen et al., 2022; X. Wang et al., 2018).

The etiology of keloid formation involves many factors, such as TGF-β1, ECM deposition, as well as excessive amounts of collagen 1 (COL1) and collagen 3 (COL3) (Chen et al., 2022; X. Wang et al., 2018; Zhou et al., 2022). TGF-β1 is recognized as a major factor in the keloid formation process and AMSC administration can significantly improve fibrotic changes induced by decreased TGF-β1 (X. Wang et al., 2018; Zhou et al., 2022). This is in line with other studies that suggest that AMSC is a selective inhibitor of the TGF-β1 signaling pathway and significantly decreases TGF-β1 protein expression. In addition, AMSC also plays a role in reducing COL1 and COL3 expression (Li et al., 2022; Xie et al., 2020). In another study, it was found that giving AMSC can make collagen structures thinner and more regular which shows that AMSC plays a role in reducing the formation of keloid ECM, especially in relation to COL1 (X. Wang et al., 2018).

In line with research conducted by Zhou et al. (2022) on 10 patients with keloids and 9 patients without keloids given AMSC, it was found that there was an

increase in fibroblasts in patients without keloids, while there was a decrease in fibroblasts in patients with keloids . In a study conducted by Liu et al. (2018), 6 keloid samples were used and found a significant decrease in the number of keloid fibroblast cells that migrated significantly within 24 hours after being given AMSC. Meanwhile, in a study conducted by Zahorec et al. (2021) on 8 patients treated with scarred scars, there was an increase in scar healing after AMSC administration.

Bone Marrow Mesenchymal Stem Cells

Bone Marrow Mesenchymal Stem Cells have an inhibitory effect on migration and proliferation in hypertrophic scar tissue and keloids. These cells can also reduce *connective tissue growth factor, plasminogen activator-1*, TGF-β1, and TGF-β2 (Fang et al., 2016). In addition, it also plays a role in the viability and migration of dermal fibroblasts, and can reduce TGF-β3 expression and decrease ECM synthesis, thereby inhibiting the production of skin collagen associated with TGF-β signaling (Fang et al., 2016; Xu et al., 2022).

In a study conducted by Fang et al. (2016) using hypertrophic scar tissue samples and keloids taken from surgical patients suffering from keloids and have not received any keloid treatment. The control group was taken from surgical patients unrelated to keloids. Samples given BMMSC showed results of inhibiting proliferation, weakening profibrotic phenotype, inhibiting extracellular matrix synthesis and not inducing apoptosis of hypertrophic scar tissue and keloids. This is in line with research conducted by (Qu et al. (2019) using a hydrogel made from a bond between *Hydroxybutyl chitosan* (HBC) and Arg-Gly-Asp (RGD). In the study, keloid fibroblasts cultured with HBC-RGD and BMMSC for 7 days were shown to significantly reduce nodular collagen fibers ($p<0.05$), so it can be concluded that it can suppress the proliferation of keloid fibroblasts.

Table 1. Some Research Results on Stem Cell Therapy in Keloid Treatment

Reference	Result
(Chen et al., 2022)	AMSC can reduce hypertrophic scarring, can improve the color, elasticity, texture, thickness, and size of hypertrophic scars, and can reduce hypertrophic scarring.
(Bojanic et al., 2021)	MSC therapy can be an effective method for treating hypertrophic scars and keloids and does not cause significant complications.
(Yang et al., 2021)	Activation of the COX-2/PGE2 cascade in response to ADSC therapy has an important role in mediating ADSC-induced keloid apoptosis and has anti-proliferative effects.
(Fang et al., 2016)	BMSC treatment can speed wound healing and weaken skin collagen deposition.
(Heo et al., 2019)	AMSC can induce M2 macrophages through exosomes that have immunomodulatory and anti-inflammatory functions.
(Hu et al., 2015)	AMSC and BMMSC have an important role in the wound healing process
(Khandpur et al., 2021)	Stem cell therapy can maintain normal skin homeostasis and repair and regeneration during injury.
(Li et al., 2022)	AMSC has been shown to inhibit ECM deposition in keloids.
(Lim et al., 2019)	MSC can relieve inflammation and improve the wound healing process.
(Liu et al., 2018)	The grafted tissue has less collagen connective tissue, and less vascular, after administration of AMSC.
(Qu et al., 2019)	Keloid fibroblasts cultured with BMSCs/HBC-RGD hydrogel had a significant inhibitory effect ($p < 0.05$) on keloid fibroblasts when compared to HBC-RGD hydrogel
(Seo et al., 2016)	MSC is multifunctional as a regulator of the inflammatory process and is the main therapy to treat or prevent excessive scarring.
(H. Wang et al., 2022)	AMSC inhibits hypertrophic formation factors by regulating the balance of explored Th17/Treg cells.
(X. Wang et al., 2018)	AMSC significantly inhibits the associated bioactivity of keloid fibroblasts.
(Xie et al., 2020)	AMSC significantly inhibits cell proliferation and migration and the expression of extracellular matrix proteins (collagen-I, collagen-III, FN and α-SMA).
(Xiong et al., 2020)	AMSC can be an anti-aging skin therapy, overcoming skin inflammation, and scars.
(Xu et al., 2022)	BMSC can inhibit the viability and migration of dermal fibroblasts.
(Zahorec et al., 2021)	Scar healing improved significantly within 6 months after application of autologous lipograft and MSC.
(Zhou et al., 2022)	AMSC increases the rate of wound healing in normal tissue while in keloid fibroblasts, it is reduced.

Conclusion

Keloids are caused by the production of cytokines and collagen types I and III whose synthesis is 20 times the normal. In addition, keloids are also influenced by various factors such as age, gender, skin color, and genetics. One alternative in the treatment of keloids is stem cell therapy such as MSC, which has been proven in various studies to have a positive effect on keloid healing. It is recommended to conduct further research on the application of stem cell therapy against keloids, especially in Indonesia.

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