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# Wound Healing By Stem Cell Based New Treatment Modalities.

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**Abstract:** Wound healing is complex phenomenon which influence by many factors like Age, nutrition, chronic diseases, blood supply, microbial contamination. The wound which is not healed in conventional line of treatment and older than 3 months, called as chronic wound. Stem cell based treatment has potential of cutaneous regeneration by trophic and paracrine factors. Autologous cell-based treatment has minimal immune rejection but age decline cellular function. Another approach is deliver of cell by scaffold based application to wound which help in engraftment and paracrine activity of stem cells. Here we are discussing recent advances in stem cell based therapies and their limitations as concerned to wound management.

## SUMMARY

### INTRODUCTION:

Skin is most important organ of human body, it is heaviest one also. Skin is divided into two parts epidermis and dermis. Epidermis is outermost layer of skin which mainly form by keratinocyte type of cells, it is functional and structural barrier. Dermis rest below epidermis which is made of fibroblast cell mainly. Hypodermis lies below dermis which is subcutaneous layer .epidermis acts as barrier for environmental substrates. (1).

Wound is defined as loss of anatomic structural integrity as well as functional loss of skin (2). Due to loss of structure of skin, barrier disintegrate. Wound is mostly subdivided into two types 1.acute 2.chronic.acute wound is heal with conventional line of treatment with antimicrobial agent. Chronic wound is defined as wound which are not heal in 3 months of post injury with conventional medical help. Wound healing depends on underlining causes, nutritional factor, immunity status, blood supply to wound area. Pressure ulcer, radiation wound are chronic type of wounds (3, 4). The healing of wound depends on size, depth, anatomic location, type, cause of wound. Wound healing involves cellular, pathological, physiological principles. Wound healing depends on oxygen status of wound area. In ischemic non- healing

wound, due to deprivation of blood supply to concerned area, oxygen level in wound is less which ultimately inhibit angiogenesis, migration ,reepithelization,remodelling.oxygen concentration in wounded area is average 20 to 30 % but in chronic ,non- healing wound it found it was 10 -15 %(5) .we can measure transcutaneous oxygen pressure. Oxygen deprivation causes colonisation of anaerobic bacteria (gut, oral cavity) at wound area. Which are later causes foul smelling, necrosis .persistence of inflammation is responsible for non-healing of wound. Proinflammatory cytokines like  $TNF\alpha$ ,  $IFN\ \gamma$ ,  $TGF\ \beta$  causes type 1 response which later on convert into anti-inflammatory cytokines in normal wound healing cascade. Chronic diabetes causes diabetic foot ulcer (DFU) which is also non-healing type of wound. In long standing diabetes ,atherosclerotic plaque causes deprivation of blood supply to diabetic foot ulcer .proteins are most important for formation of proteoglycan, hyaluronic acid, growth factors. Protein intake helps in wound healing. (6).

Wound healing is sequential procedure which includes four important stages of healing mechanism.1.homostasis.2.inflammation.3.proliferation and tissue formation .4. Remodelling. Immediate after injury coagulation cascade activates. Due to injury, endothelium layer of blood vessels lacerate, rupture which ultimately causes extravasation of platelet into wound bed. Platelet secretes sticky surface glycoprotein which adhere nearby platelets, accumulate and form plaques to stop bleeding. Ultimately homeostasis occurred (5-8).

### Inflammation:

Injured platelet secretes cytokines and growth factors endothelial growth factor (EGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factor beta ( $TGF\beta$ ), vascular endothelial growth factor (VEGF) (9, 10, and 11). PDGF attracts neutrophils to wound bed to engulf bacteria, foreign particles, devitalised tissue to clean wound. Migrated neutrophils kills and engulf bacteria and debris, neutrophils have short

life span up to 1 -2 days after that neutrophils undergo apoptosis (12). This apoptosis of excessive neutrophils causes pus in wound. Pus is nothing but collection of apoptosed neutrophils, bacteria, virus and debris. Neutrophils secrete growth factor TGF $\beta$  which attracts monocytes toward wound bed, TGF $\beta$  also forms ECM in wound bed. Macrophages have long life span than neutrophils. Macrophages are doing cleaning work of wound bed. TGF $\beta$  convert monocytes to macrophages. Macrophages are potent reservoir for PDGF, TGF $\beta$ , FGF, VEGF, EGF. Macrophages secrete proinflammatory cytokines interleukin 1 and 6 which are helpful for keratinocyte, fibroblast, endothelial cell activation and migration. As inflammatory process subside then neutrophil and macrophages number also decreases which later on promotes sequential stage of proliferation. (6-8, 13-16).

#### **Proliferation:**

This one is sequential stage after inflammation. After few hours of injury, fibroblast crawling towards wound bed. These fibroblast are travelling from deep dermis. TGF $\beta$ , PDGF are important factor which activates fibroblast. This stage forms extracellular matrix (ECM), fibroblast proliferation, angiogenesis. Fibroblast secretes proteoglycan, hyaluronan, elastin, procollagen type 1 & 3, fibronectin. At 1 week of post injury enough ECM formed. Collagen play pivotal role in ECM formation (18). Endothelial cells are activated and migrated to injured side due to FGF. Subsequently endothelial cell released growth factor VEGF which initiate angiogenesis (8, 17, and 22). During this process macrophages supply growth factor for fibroblast proliferation. In hypoxic condition due to activation of FGF, endothelial cell migrate to hypoxic area and forms network of capillaries to supply required oxygen and nutrients, when oxygen and nutrient level is sufficient then these formed unnecessary capillaries destroy by apoptosis (23). Neoangiogenesis means formation of new small blood vessel network from existing resident endothelial cells. Next step is reepithelisation, after week of post injury, sufficient ECM forms then start reepithelisation. Epithelial cell in epidermis and surrounding wound bed, starting proliferation by activation of Epidermal growth factor (EGF), they accumulate and forms epithelial layer (24). Damaged basement layer also starting to reform by cells from side of wound edges. (25). Last step of proliferation is wound contraction, after 2 week of post wound sequel, sufficient fibroblast cells differentiate into myofibroblast which express  $\alpha$  smooth muscle actin, behave like smooth muscle.  $\alpha$  smooth muscle actin protein is responsible for contraction of wound, apposing

wound edges to close (26). Wound contraction is organised sequence of ECM, cytokines, fibroblast.

#### **MATURATION AND REMODELING**

Next sequential step is maturation, maturation phase of wound healing depends on many factors age, sex, type of injury, underlying diseases, nutrition, anatomic location, immunity. After 2 weeks of post injury, collagen type 3 degrade and converted into collagen type 1, this is most important for maturation. Collagen remodelling is most important for transition from granulation to scar. It depends on balance of collagen synthesis and degradation. Continue collagen synthesis and degradation are equal then maturation phase starts (27).

Collagen degradation depends on proteolytic enzymes like metalloproteinase secreted by macrophages, endothelial cells, fibroblast. PDGF, FGF, TGF $\beta$  are also helpful for collagen degradation (28). In unwounded dermis collagen type 1 concentration is 80 % and collagen type 3 is 20 % but in granulation dermis 40 % of collagen type 3 at 1 week post injury healing. As maturation phase progress, capillary formation inhibited, metabolic activity at wound side decreases, cell number decreases which ultimately form scar (29). In uncomplicated wound, proportionally following all these sequential phases of wound healing end with fine scar formation (29-31). But in nonhealing wound there will be long phase of inflammation which hamper wound maturation (32).

#### **Materials and Methods**

##### **Amniotic membrane Stem Cells Vs. Bone Marrow Stem Cells**

The recovery and in vitro expansion of MSC from amniotic membrane is much greater than MSC isolated from any other source like Bone Marrow Stroma. Also the number yield of MSC from amniotic membrane through ex vivo expansion is much higher than other sources like bone marrow and it is non-invasive procedure [33]. Complete regeneration from stem cell is depends on Age of MSC from donor tissue [34]. Progenitor cells and Bone marrow mesenchymal stem cells unlike AM mesenchymal cells show decreasing proliferative potential with increasing age [35-37]. The flow cytometry analysis has even shown an immunophenotypical profile of AM-hMSCs positive for CD29, CD44, CD73, CD105 and CD166 while negative for CD45, CD34, CD14 like bone marrow derived MSC [38]. In addition, AM-isolated cells undergo in vitro myogenin,

osteogenic, adipogenic, chondrogenic expression along with von willebrand factor and CD34 positive cells which permits unrestricted use, distribution and reproduction of these MSC in culture medium [38]. These cells also express the surface markers associated with embryonic stem cell, e.g. TRA-1-60, TRA-1-81, SSEA-3, SSEA-4 pluripotent stem cell-specific transcription factors such as Oct-4 and Nanog [39]. The AECs may be a superior source of MSC than the adult bone marrow. AECs create their own feeder layer of cells, the basal layer of AECs act as feeder layer by possibly providing secreted factors that help induce or maintain undifferentiated AECs or serving as substrate for attachment. These cells don't require second type of cells as feeder layer. Average yield of AECs per amnion is 100 million that is much higher than any other stem cell reserve [39].

#### **AMNIOTIC FLUID:**

Amniotic fluid is collection of proteins, phospholipids, carbohydrates electrolytes, hormones, foetal gastrointestinal, nasal, lung secretion and foetal urine. Amniotic fluid is sterile. As foetus grows amniotic fluid volume increases due to urine content of foetus, at 34 wks. Of gestation amniotic fluid volume is 800 ml that will reduce to 600 ml at term. Amniotic fluid content foetal cells coming from gastrointestinal, nasal, oral, lung secretion as stated above. In 2003, Prusa et al found small population of cells in amniotic fluid, which are actively dividing cells and express OCT4 pluripotent stem cell marker as well as stem cell factors alkaline phosphatase and vimentin. In same year Anker et al. isolate amniotic fluid derived mesenchymal stem cell which differentiate into adipogenic, osteogenic, chondrogenic, myogenic type of cells. Apart from stem cells, amniotic fluid content growth factors, and anti-inflammatory and pro-inflammatory cytokines like IFN  $\gamma$ , TGF  $\beta$ ,

#### **WHARTON'S JELLY:**

Wharton's jelly is named after seventeenth century by English physician and anatomist Thomas Wharton. Predominant molecule in Wharton's jelly is hyaluronan, higher concentration approximately 4 mg/ml. 1 gm. of Wharton's jelly contains approximately 2-5 mg of sulphated glycosaminoglycans with decorin, strongly predominating over biglycan. It was found that Wharton's jelly matrix is stronger source of mesenchymal stem cells

#### **UMBILICAL CORD**

Umbilical cord connects foetus to the placenta, normally contains two arteries and one vein which

surrounded by Wharton's jelly. The umbilical vein supplies oxygenated, nutrient rich blood to foetus and arteries return the nutrient-depleted, deoxygenated blood from foetus to the placenta. The length of umbilical cord varies but study by Malpas reviewed shows an average length of umbilical cord is 61 cm in total of 538 normal cords, published in the British medical journal. Human umbilical cord contains three structures Wharton's jelly described above, vessels which are potent source of endothelial stem cells, epithelium which contains single layer of epithelial cells. Intact vessels have been investigated as potential scaffolds for tissue engineering constructs.

#### **CLINICAL APPLICATION OF BM-MSC IN WOUND HEALING:**

BM contains heterogeneous cell population including fibroblast, adipocytes and mononuclear cells (38, 39). BM-MNC (mononuclear cells) contains endothelial progenitor cells (EPC), mesenchymal stem cells (MSC), haematopoietic stem cells (HSC) and cellular precursor's cells (39).

HSC forms erythrocytes, platelets, white blood cells. MSC are group of stem cells originated at mesodermal germinal layer (39, 40, 41). MSC population constituent of bone marrow is very less (0.001 -0.01 %) (42). MSC can be differentiated further into adipogenic, chondrogenic, osteogenic lineages (43). When wound occurred, SC and MSC stem cells are mobilised from bone marrow and migrate to injured side, homing there. They manage cell migration and proliferation during inflammation phase of cicatrization. Both these cell types have highest plasticity, they can differentiate into haematopoietic and non-haematopoietic type of cells (44-46). Recent studies reveal that bone marrow stem cells, especially MSC have highest capacity of skin regeneration (47-49) and vascularization (50).

MSC influence wounds ability to progress inflammatory phase and avoid regression of chronic wound stage. MSC increases secretion of anti-inflammatory cytokines and decreases secretion of proinflammatory cytokines which progress wound beyond anti-inflammatory stage to remodelling of wound phase (51). Recent study shows antibacterial property of MSC (52). MSC secretes growth factors which eventually help in dermal fibroblast proliferation, collagen synthesis, and angiogenesis (53). Diverse mechanism proposed for regenerative property of wound healing of MSC. Evidenced show that MSC migrate to wound site, differentiate with phenotype and functional properties of cells (54,55) which help in wound healing process and ultimately help in

healing. Other group believe the paracrine effect of MSC. Baldivas et.al (56), shows result of autologous BM-MSC local application on wound helps in closure of wound and reconstruction of tissue. He claimed that in 3 chronic wound patient, injection of freshly collected bone marrow into edges of wound with local application of cultured autologous MSC shows complete healing of wound which fail to heal by traditional therapy. Biopsy shows that increase in vascularization and dermal thickness with collection of matured, immature inflammatory cells.

In 2009, Dash et.al (57), published a result carried out on 24 patients having non-healing wound on lower extremities due to diabetes or vasculitis. They injected autologous BM-MSC intramuscularly into edges of wound after 12 wks. They noticed that ulcer size decreased by 70 % as compared to control group 30 %. Biopsy of tissue shows dermal fibroblast and matured and immature inflammatory cells. The clinical significance of systemic transplanted MSC also shows dramatic improvement in study carried out by Lu et.al (58), selected diabetic patient with critical lower limb ischemia. He was injected autologous BM-MSC or BM-MNC in one leg and saline serum in contralateral leg as control group, after 24 wks. Of transplantation result shows there was significant improvement in pain and healing of ischemic ulcer where stem cells transplanted as compare to control group. Much better improvement in BM-MSC transplanted patient than BM-MNC. But in pressure ulcer patients BM-MNC transplantation are superior as compare to BM-MSC.

Furthermore remarkable results achieved with BM-MSC transplantation with tissue engineering principles (59). Idea behind this is culturing of BM-MSC on appropriate scaffold. A trial performed on 5 patients with acute or chronic type of wound treated with autologous BM-MSC with fibrin spray as cell delivery system. Biopsy noted that MSC migration in wound bed occurred with stimulation of expression of elastin which help in ECM formation. In another similar study collagen sponge used as cell delivery system in 20 patients having chronic wounds. Results shows that collagen compound helps in healing of wound in 18 patients out of 20 (60).

#### **Clinical Application of Adipose derived MSCs (ASCs) in Wound healing:**

MSC can be harvested from different tissues as we know (61). Bone marrow MSC harvesting procedure is painful one. In 2001, ZUK et.al (62), identified and characterized adipose tissue derived MSCs, ASCs are easily isolated from a section of

whole fat (biopsy) or lipoaspirate (63), which means less painful procedure is needed to obtain the cells. BM-MSC reside in bone stroma but very few nucleated cells in bone marrow stroma are MSCs, equal amount of adipose tissue contents 500 fold MSCs as compare to Bone marrow stroma. ASCs are not express identical surface antigen like BM-MSCs (64). ASCs can be differentiate into adipogenic, chondrogenic, myogenic, osteogenic lineages. Also they secrete growth factors and cytokines like BM-MSC but not identical (65). Study on ASCs clinical application revealed that these are important stem cells as alternative for BM-MSCs, in case of wound healing too (66,67). In 2012, Lee et.al (68), published study report on 15 critical limb ischemia patients, they inject ASCs intramuscularly in affected limb, they observed improvement in 66.7 % cases, pain rating scale decreases and claudication distance improves. This study shows that ASCs transplantation are sufficient for angiogenesis.

In 2008, Garcia – Olmo et.al (69). Transplant ASCs in complex perianal fistula. They were collected ASCs from lipoaspirate then washed with phosphate buffer solution (PBS), culture and expand with human serum and DMEM medium in CO<sub>2</sub> incubator at 4 degree centigrade until confluency reaches 80% and more. They transplanted ASCs into local target lesion along with fibrin glue. They compare outcome of ASCs and fibrin glue transplant and only fibrin glue transplant, ASCs with fibrin glue are effective in healing of perianal fistulas. There were no recurrence up to 3 years follow up. In 2010, Garcia – Olmos group, published a case report of rectovaginal fistula. In which they injected heterologous ASCs into targeted lesion, ASCs were not rejected or causes any immunological or GVHD to recipient, according to author it was first case in which heterologous ASCs were transplanted, however fistula was not closed but there was improvement in healing (70). Riggoti et.al (71) used ASCs to treat side effects of radiation treatment in patients with severe symptoms or irreversible function damage (LENT-SOMA grade 3 & 4). Purified autologous lipoaspirate applied to irradiated areas. Significant clinical improvement was observed in most treated patients with Neovessel formation and ultra-structural tissue regeneration (72).

#### **Umbilical cord Blood derived stem cells transplant clinical application in Wound Healing:**

Luo et.al in 2010, published case report on mice cutaneous wound study, they transplanted umbilical cord blood derived MSCs on cutaneous wound of

mice .for that they labelled MSCs with 5-bromodeoxyuridine (BrdU).the distribution and differentiation into keratinocytes were studied by immunohistochemistry staining. The outcome of study contributing to draw conclusion that MSCs isolated from umbilical cord blood were differentiated into keratinocytes and help in wound healing in mice models. HSCs isolated from umbilical cord blood helps in angiogenesis in critical limb ischemia and ischemic limb ulcer patients, ultimately helps in wound healing, it was studied in mice and human models.

A group of scientist isolated new type of stem cells called as Unrestricted Somatic Stem Cells (USSC) from umbilical cord blood ,they were studied application of USSC into Recessive Epidermolysis Bullosa (RDEB) wound mice model ,published in 2011 by Liao et.al. Like HSCs and MSCs, endothelial progenitor cells (EPCs) also isolated from umbilical cord blood .EPCs are helpful in neoangiogenesis in non-healing wound due to deprivation of blood supply .ABO Rh matched umbilical cord blood transfusion also helps in healing of wound. As we know umbilical cord blood is cocktail of cytokines, growth factors and progenitors cells. Nucleated stem cells constitutes of umbilical cord blood is 0.001 % .but remaining 99.99 % of non- nucleated part of umbilical cord blood contents red blood cells, cytokines ,growth factors if we transfused cord blood then it was noted, it will help in wound healing

Umbilical cord blood contents naïve T lymphocytes which doesn't causes immunological reaction so there were not noted single case of GVHD in 1000 patients in which umbilical cord blood was transfused by Dr,Niranjan Bhattacharya in India(73-78) .

#### **Foetal tissue/derived Stem cell transplant application in Wound Healing:**

Dr Bhattacharya. et. al(79) published papers on foetal tissue(neuronal,skin,liver,pancreas ,spine, thymus) heterotopic (under axilla ) transplant for various disorders like neurological,diabetes,parkinsonism,DiGorge syndrome etc.(80-82). He was noted dramatic improvement in disease condition. Foetal skin transplant under axilla can be adopted treatment for wound healing. Firstly collect foetal tissue from aborted 1 trimester foetus from mother who undergone for hysterectomy and ligation procedures. Obtain skin from foetus, cut into small pieces collect small piece of skin and implant it in pocket created in axilla by incision taking i.e. 3 ×2 cm in size under local lignocaine anaesthesia. Then put skin tissue inside pocket and sutured skin edges. This is one mode of using foetal tissue for

wound healing purpose, as we know axilla has good blood supply network so foetal tissue selected to be put under axilla.as we know ,stem cell travels to injured site and homing there. Transplanted foetal skin released bioactive molecules cytokines and growth factors which help for repair of wound by paracrine mechanism this is one hypothesis or MSCs, EPCs, early progenitor cells, embryonic like cells differentiate themselves into fibroblast and keratinocytes which help in regeneration of wound. Early 1 st trimester foetal tissue is hypoantegenic, they express low nonclassical HLA molecules like HLA E, HLA F and HLA G, early foetal tissue before 12 wks. Express very low HLA.T lymphocytes in foetal tissue are naïve or immunologically immature. Early foetal tissue stem cells express Klf 4, Nanog, Oct 4 embryonic stem cell markers. Some peoples isolated MSCs, EPCs, HSCs from foetal tissue in vitro.protocols of stem cell isolation from foetal skin is easy. Take small part of foetal skin, washed it with phosphate buffer solution thrice, digest it in collagen, centrifuged after that culture in CO2 incubator at 4 degree centigrade with growth media .collect isolated MSCs and inject into edges of wound. Foetal tissue MSCs are more potent than BM-MS or ASCs.

A group of scientist, dressed burn and other types of wounds with foetal skin. Outcome is amazing. Also we can used engineered foetal skin as dressing for wound. Most important thing is that collect foetal tissue from healthy donors who undergone for hysterectomy and ligation procedures but in the world many centres took spontaneous aborted foetus for study purpose ,possibility of chromosomal abnormality in spontaneous abortion is high so transmission of mutation genes possibility is also high.

As we know there are disparity between demand and supply of adult human organs. Demand increasing every year but organ donor are increasing very slowly, so there are shortage of adult organ.fetal tissue is the ultimate alternative option for adult organ. Xenotransplantation of pig skin was also tried by people for coverage of burn wound. They used cadaver pig skin for burn wound coverage which was processed and engineered. Culture keratinocytes application also help in wound healing.

#### **Tissue Engineered Skin Substitutes for wound Healing**

Skin was the first tissue application to be successfully engineered in the laboratory. Live culture skin products developed by combination of development of biodegradable matrix materials and

subsequently the development of keratinocyte culture techniques

**Matrix based products:** First engineered skin substitutes which are still used today. Porous matrices used as templates spread on wound bed, which later on integrate and vascularised, after sufficient revascularization matrix covered with autografts. INTEGRA® is the first commercially available skin substitute it consists of matrix of cross-linked collagen and chondroitin-6-sulfate copolymer are mixed to form the dermal matrix.it is used for deep burn wound especially. Matrix undergoes degradations but host cells proliferate and help in healing of wound. Another one is Alloderm® which was made by decellularized donor skin. Removing all donor cells and content only protein structure, prevent disease transmission as well as immunological reaction to host.it is used for wound repair and reconstructive surgery

#### **Cell Based Products:**

In 1988, EPICEL™ is cultured autologous epidermis. Skin biopsy tissue taken from patient and expanded it in laboratory to form autologous cultured Epidermis to cover wound.it was costly (\$800 per a 50 cm<sup>2</sup> area.it was not content dermis so its use were restricted. Another tissue engineered skin products is allogeneic neonatal dermal fibroblasts cultured on polyglactin mesh.it is called as DERMAGRAFT ©®, which used for diabetic foot ulcers.APLIGRAFT® is bilayer construct using fibroblasts and keratinocytes to create a dermis and epidermis. Cells are taken from neonatal foreskin. Fibroblasts mixed with collagen and form matrix on which keratinocytes are seeded. Minced micro graft is new approach in which small area (2 cm<sup>2</sup>) full thickness skin excised, it was minced and mixed with a hydrogel and applied over wound bed. The stem cells in skin proliferate and help in wound healing

#### **Human Induced Pluripotent Stem Cells application in Wound healing:**

As we all know the controversy by using embryonic stem cells in trials or clinical application ,it was noted that embryonic stem cells(ESC) are totipotent and these cells have highest plasticity so in vivo study on mice models they formed teratoma ,there are some ethical, political ,social, ritual issues behind used of these ESCs for research. In August 2006, Shinya Yamanaka and colleagues in Kyoto University demonstrated that murine embryonic fibroblast can be reprogrammed to iPSCs by overexpression of OCT3/4, KLF4, SOX2, and C-MYC with retroviral system (84).in 2007, a milestone achieved by creating iPSCs from

adult human fibroblast. Two groups published there work one in science by James Thompson and team at Wisconsin Madison University (86) and another one in cell by Shinya Yamanaka, Kyoto University, and japan (85). Shinya yamanaka successfully created iPSCs from human skin fibroblasts by overexpression of four genes OCT3/4, KLF 4, SOX 2, and C-MYC with a retroviral system. James Thompson created iPSCs from human skin fibroblasts by using

OCT4, SOX2, NANOG and Lin 28 with lentiviral system. IPSCs can be developed from any human postnatal somatic cells including MNCs (87, 89, 90), skin fibroblasts, EPCs, exfoliated renal epithelial cells isolated from urine. Mononuclear cells have favourable epigenetic profile for iPSCs to develop .MNCs can be isolated from cord blood, bone marrow.EPCs isolated from peripheral blood (88). IPSCs colony formed in culture at 14 days derived from blood MNCs as compare to 28 days for age matched fibroblasts. So blood MNCs are potent source for iPSCs (91, 92). Properties of iPSCs are like embryonic stem cells (ESCs).iPSCs are pluripotent stem cells which can be self-renew themselves and differentiate into three germ layers neuroectoderm,mesoderm ,endoderm.in a recent study ,the feasibility of generating iPSC cells from fibroblasts of patients with recessive dystrophic epidermolysis bullosa (RDEB),an inherited genetic disease characterized with recurrent blistering skin wounds has been demonstrated.RDEB derived iPSC cells are functional and forms 3 D skin structure.iPSC is the potent type of stem cells which are useful for curing genetic RDEB diseases. iPSC have pluripotent property ,they can be differentiate into genetically modified ,patient specific keratinocytes which helpful in RDEB .but role of iPSC is limited in burn wound. Other drawbacks to generate iPSC is time consuming, intensive and high cost process.

#### **CONCLUSION**

Cutaneous wound in aged patients is challenge to manage, need to be properly design therapies for their repair. Stem cell based therapies for wound management are promising one. Stem cell released soluble growth factors and cytokines that stimulate new blood vessel formation and has anti-inflammatory properties. Significant hurdle occurred in progenitor cell selection and their delivery. Following selection of appropriate cell population, effective delivery vehicle are needed which protect them in wound bed and provide additional functional enhancement.clinical studies are need to be carry out in basic and translational research so stem cell based therapy will be first preference of wound management in next 5 years

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