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Adipose Derived Stem Cells and Wound Healing in Patients with Diabetes: a Promising Therapeutic Modality

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Abstract: Wound healing is a complex process resulting in restoration of the structural integrity and functionality of injured tissue. Any disruption or delay in this process results in a chronic wound, which is a challenge to treat even with currently available therapy. Diabetic foot ulcers are a prime example of difficult-to-treat wounds. Despite the millions of dollars spent annually on ulcer management, individuals with diabetes are still at risk for amputations and ulcer recurrence. Adipose derived stem cells (ADSCs) have been investigated as a means to aid the wound healing process. These cells function in a paracrine manner, stimulating surrounding cells and promoting angiogenesis. The studies reviewed highlight the benefit of ADSCs in chronic wounds in both animal models as well as in humans. Research on ADSC in chronic wounds is still in its infancy. Further studies are required to understand their exact mechanism of action, their potential utility in diabetic wounds, and to confirm their safety and efficacy in before this promising therapeutic can be translated to large-scale human therapy.

Introduction

Diabetes affects nearly 10.9% of the American population, which translates to 24.4 million people in 2013.[1] According to the International Diabetes Foundation, $263 billion (USD) was spent on diabetes management in USA in 2013[1]. Approximately 33% of this amount was spent on the management of foot ulcers[2]; the chronic wound most commonly associated with diabetes. Foot ulcers occur as a result of structural foot abnormalities, peripheral neuropathy and peripheral arterial disease. The combination of these processes significantly inhibits wound healing, predisposing individuals to infection, gangrene and subsequent amputations. Individuals with diabetes have a 15% life time risk of developing ulcers[3] and an increased likelihood of ulcer recurrence compared to the general population[4]. Over $5 billion (USD) is spent world-wide annually on advanced wound care products to treat poor wound healing and minimize scarring[5].

Several steps are involved in proper diabetic foot ulcer (DFU) management including controlling infection, assessing the need for revascularization, minimizing the pressure to the affected area (offloading) and applying local therapeutic agents to revascularize the wound bed[6]. Once the wound has healed, the focus then shifts to preventing wound recurrence. Recently, stem cell therapies have been investigated as a means of promoting wound healing and revascularization[7]. Their proposed mechanism of action has shifted from the idea of terminal differentiation to one in which the cells function in a paracrine fashion, secreting growth and angiogenic factors to promote wound healing[8]. This, combined with their ability to differentiate into various cell types, recruit cells into the injured area and stimulate surrounding cells, all serve to augment the healing process[9]. Embryonic stem cells (ESCs) are pluripotent cells that have been shown to enhance wound healing in animal models of diabetic wounds[10]. ESCs, however, are limited in their utility due to ethical considerations, potential for malignant transformation[13] and concerns regarding immunocompatiability[11].

Mesenchymal stem cells (MSCs) have also demonstrated promising results in clinical trials with non-healing wounds. These cells do not have the same limiting factors as ESCs, are found in various

tissues throughout the body, are readily accessible, and easily isolated[9]. MSC's by definition are adherent, fibroblast-like cells that are also multipotent, capable of differentiating into different cell lines, such as osteoblast, chondrocytes and adipocytes in vitro and can be autologously transplant and can be autologously transplanted as they are immunocompatible[15]. Though MSC's can be harvested from different sites, they have been shown to have specific characteristics and studies have shown that they originate from a perivascular niche[5].

Adipose derived stem cells (ADSCs) are a subtype of MSC that are easily accessible and can be harvested in large quantities with minimal patient discomfort and morbidity[9]. The use of ADSC's to treat diabetic wounds has been demonstrated to be safe and efficacious in numerous animal and human trials (Tables 1 and 2). In the three steps of diabetic foot ulcer healing, the use of stem cells play a role in the revascularization as well as the prevention of recurrence[7]. Current methods of revascularization include angioplasty, thrombolysis and distal bypass procedures to improve the macroavascular supply[7]. Effective treatment of diabetic ulcers should also include improvement of the microvascular supply[19]. Efficient treatment with stem cells aimshopes to improve angiogenesis, neoangiogenesis and to promote tissue regeneration, thus improving the microvascular supply and preventing future ulcers. This review aims to elaborate on the current advances in research associated with ADSCs and wound management and to highlight possible directions for future research and clinical practices.

ADSC's in wound healing

Wound healing is a complex process categorized into three overlapping phases: inflammation, proliferation, and maturation/remodeling[5,16]. Disruption of any of these phases results in delayed wound healing and subsequent chronic wound development. Factors preventing or delaying the normal progression of wound healing include underlying systemic disorders (e.g. diabetes), infections, tissue hypoxia, necrosis, excess exudate and elevated levels of pro-inflammatory cytokines[17].

During the normal healing process, it is thought that endogenous stem cellsMSCs (found in the bone marrow, blood and local tissue) are attracted to areas of injury in response to inflammatory mediators and cytokines released from injured tissue[5]. Bone marrow derived endothelial progenitor cells (EPCs) are endogenous stem cellsMSCs, which are attracted to sites of injury by tissue ischemia, cytokine and chemokine release that play an important role in angiogenesis and wound healing[18]. Tissue hypoxia resulting from injury and healing results in the release of EPC attractant molecules such as granulocyte colony-stimulating factor (G-CSF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), placental growth factor (PGF), erythropoietin (EPO), and stromal derived factor-1 (SDF-1)[19]. EPCs are attracted to target tissues through their expression of the CXCR4 receptor which binds to the SDF-1 ligand[20]. Hypoxia-inducible factor-1 (HIF-1), a transcription factor from endothelial cells, in turn regulates CXCR4 expression on EPCs and SDF-1 expression on ischemic tissues, resulting in the adhesion, migration and honinghoming of EPCs to ischemic tissues[20]. Once the levels of the EPC attractant factors increases above the bone marrow threshold, nitric oxide sythetase is activated[19]. This results in the synthesis of nitric oxide which in turn, regulates the activity of matrix metalloproteinases (MMP)[9]. MMP-9 in the bone marrow results in a ligand release from EPCs, which allows them to mobilize to the site injury. SDF-1, together with interleukin 8 (IL-8), CXCR2, growth-regulated oncogene-a, CXCR1, CCL5, CCR5, C-C chemokine and chemokine (C-C motif) receptors 2 and 5, activate and hone EPCs to injured sites[19]. The activated EPCs migrate through the endothelium into sites of injury via intergrin-mediated adhesion to then contribute to angiogenesis and tissue regeneration in a paracrine fashion[19].

The activated progenitor cellMSCs have an anti-inflammatory effect at the site of the wound by reducing the activity of mast cells, natural killer cells T cells and B cells[5,16]. The immunomodulating effect favors fibroblast activity and results in better granulation tissue deposition, allowing progression of the healing process[5]. In the proliferative phase, MSCs have a proangiogenic function, releasing mediators such as VEGF, which promotes vessel formation in the wound bed[5]. Cytokines and growth factors are also released by MSCs which help in the production and deposition of collagen in the extracellular matrix (ECM) and prevent wound contraction by inhibiting myofibroblast differentiation[5]. In the remodeling phase, progenitor cellsMSC inhibit excessive fibroblasts differentiation into myofibroblasts and also help to control cell differentiation in other cells. This helps to produce a more functional ECM, which is structurally similar to uninjured tissue[5].

Table 1. Studies using MSCs for wound healing in animals.

Investigators	Cell Type and Source	Method of Delivery	Wound type	Outcome	Proposed Mechanism
Moon et al (2006)	Human ADSC	Local intramuscular injection	Femoral artery ligation resulting in hind limb ischemia	Muscle injury recovery, increased vascular density. Healing was noted even when ADSC were injected 7 days later.	Paracrine effect via secretion of cytokines and pro-angiogenic factors. Possible transformation of ADSCS to regenerate vessels
Kwon et al (2008)	Rat BMSC	Systemic administration	5mm Fascial wound	Improved healing with SC	Improved collagen metabolism and improved functionality of growth factors
Nambu et al (2009)	ADSC and fibroblasts	Topical administration	Full thickness wounds with wound splinting	Improved wound healing, greater with fibroblasts compared to ADSC	Proangiogenic growth factor release.
Ebrahimian et al (2009)	ADSC	Intravenous vs intramuscular	Full thickness punch biopsy	Improved wound healing, visco-elasticity, and collagen deposition. Increased vascularity and capillary density	Paracrine effect via growth factors and differentiation into keratinocytes and endothelial cells
Amos et al (2010)	Human ADSC	Multicellular cell aggregates vs cell suspension	Full thickness dermal wounds	Increased rate of wound healing with aggregates compared to suspension	Increased deposition of matrix elements and increased production of growth factors
Cianfarani et al (2010)	Mouse ADSC	Topical administration	Full thickness punch biopsy	Improved wound healing with use of non-diabetic ADSC compared to diabetic ADSC	Cell differentiation, recruitment of cells and paracrine effect via growth factors
Lim et al (2010)	Mouse ADSC and cell extract	Local intradermal injection	Wound healing splint model	Improved healing in ADSC group compared to control and extract groups	Paracrine effect via growth factor release and differentiation into other cell lines
Nie et al (2011)	Rat ADSC	Local intradermal injection	Full thickness punch biopsy with wound splinting	Accelerated wound healing	Paracrine effect and local differentiation of ADSC
Lee et al (2011)	Human ADSC and dermal fibroblasts	Topical administration collagen gel vs ADSC and collagen gel vs human dermal fibroblast and collagen gel	Wound healing split model	Improved healing in both dermal fibroblast group and ADSC, but more effective with fibroblast	Paracrine effect via growth factors. Fibroblast work via stimulation proliferation and differentiation of keratinocytes and formation of basement membrane
Elsharawy et al (2012)	Human umbilical cord SC	Local injection	Right front leg punch biopsy	Decreased wound size, increased collagen, thicker epidermis and dermis with increased vascularity	Paracrine effect via growth factor and differentiation into endothelial cells
Shin et al (2013)	Human BM SC	Local injection	Excisional wound splinting	Improved wound healing	Recruitment of endogenous stem cells via cytokines and paracrine effect via growth factor release

Table 1 *continued*. Studies using MSCs for wound healing in animals.

Investigators	Cell Type and Source	Method of Delivery	Wound type	Outcome	Proposed Mechanism
Shrestha et al (2013)	Human umbilical cord MSC	Local administration of PBS vs CM vs MSC	Excisional wound healing model	Improved wound healing in CM and ADSC, complete healing in CM	Paracrine effect via growth factors
Zhang et al (2013)	Human ADSC	Systemic		Decreased proteinuria, inhibited glomerular hypotrophy and interstitial lesions and reduced podocyte injury	Paracrine effect via growth factor release

Diabetic ulcers occur due to poor vascularity and neural damage resulting in areas of inflammatory infiltrate and necrosis[16,21]. Moreover, diabetic patients have fewer endogenous MSCs[23,24] and a lower percentage of these cells express stem cell specific markers[25]. Lee et al[26] reported that this reduction in MSCs was also seen in ADSCs populations. Not only are MSC and ADSC populations depleted in diabetes, their ability to proliferate is severely impaired[24,26]. This impairment influences general cellular functioning, as well as their ability to migrate to sites of injury[23,27,37]. Multiple factors associated with hyperglycemia result in MSC dysfunction. These factors include oxidative stress due to the generation of reactive oxygen species, the accumulation of Glycosylation end products and the reduced expression of growth factors[19]. MSCs in wound sites show perturbations in the inflammatory phase resulting in extracellular matrix breakdown and decreased production and functionality of various growth factors[17,27,25]. In addition, the wound itself demonstrates diminished granulation tissue deposition with increased fibroblast apoptosis[24]. These factors lead to impaired wound healing in people with diabetes.

HIF-1 plays such a vital role in coordinating wound healing that disruption of its functioning would affect the healing process. Xiao et al[28] reported that methylglyoxyl, a byproduct of glycoly-

Table 2. The use of ADSCs in human wounds.

Investigators	Cell Type and Source	Method of Delivery	Wound type	Outcome	Proposed Mechanism
Collawn et al (2012)	Human ADSC	Inoculation into organotypic graft	Laser injury	Improved healing compared to control	Paracrine effect via release of growth factors and differentiation into other cell types
Lee et al (2012)	Human ADSC	Local injection	Chronic wound and necrotic wounds of patients with TAO and DM	Improved pain score and wound healing, increased vascularity	Paracrine effect of pro-angiogenic factors and antiapoptotic effect
Karaaltin et al (2012)	Human ADSC	Local injection	DM plantar wound	Improved healing	Not mentioned
Sung et al (2012)	Human ADSC	Local injection	Nasal necrosis	Complete resolution of necrosis	Paracrine effect and differentiation
Jo et al (2013)	Human ADSC	Local injection with a scaffold	Full thickness facial wounds	Improved wound healing	Paracrine stimulation with growth factor release, differentiating into endothelial cells and producing stromal contents.

sis, affects HIF-1 functioning. Elevated levels of methylglyoxyl is seen in hyperglycemia and affects the stability of HIF-1 and its activation[28]. Impaired HIF-1 functioning results in reduced transcription of SDF-1, VEGF and CXCR4 and affects the activation of nitric oxide synthetase, ultimately resulting in impaired EPC honinghoming and migration to areas of injury[28]. Tecilazich et al[18] added that inflammatory cytokine levels [IL8, tumor necrosis factor α (TNFα) and C-reactive protein (CRP)] are higher in individuals with DFUs. The study demonstrates that wounds in diabetics that healed completely have lower baseline levels of IL-1α and CRP, and higher levels of GM-CSF. The study[18] suggests that these could be used as prognostic indicators of ulcer healing in diabetics.

ADSCs are an alternative source of MSCs for use in chronic wounds. These stem cells are harvested from whole fat and lipoaspirate, and are found in larger quantities in fat compared to the quantity of stem cells available from the bone marrow[9] (over 500 to 1000 fold more plentiful when equivalent amounts are compared[16,29]). Cultured ADSCs also have a higher proliferative capacity compared to bone marrow derived stem cells (BMSCs)[9]. ADSCs have been reported to share some surface markers with BMSCs but the exact surface markers are still unknown.[16,30]. In 2006 the International Society for Cellular Therapy (ISCT) set 3 minimum criteria to identify MSCs[31]. The first being adherence to plastic while in standard culture conditions[31]. Secondly these cells should express surface markers for CD73, CD90 and CD105 and lack CD11b, CD14, CD19, CD34, CD45, CD79α and HLA class II[31]. Thirdly to be identified as MSCs, these cells need to show multipotent differentiation potential[31]. In 2013, the International Federation for Adipose Therapeutics and Science (IFATS) and ISCT included CD13, CD29 and CD44 as positive markers and denoted CD31, CD45 and CD235a as primary negative ADSC markers[32].

Similar to BMSCs, ADSCs can also function in a paracrine manner to promote wound healing. They have been demonstrated to secrete hepatocyte growth factor (HGF),VEGF, TGF-β, insulin-like growth factor (IGF)-1, bFGF, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNFα, interleukin-6, -7, -8, and -11, adiponectin, angiotensin, cathepsin D, pentraxin, pregnancy zone protein, retinol-binding protein, and CXCL12[9]. These factors stimulate and regulate surrounding cells to aid in healing[33], which make ADSCs a promising alternative for cell therapy in chronic wounds.

Use of ADSC's in animal models of wound healing

ADSCs and other MSCs have been demonstrated to enhance wound healing in multiple animal models. Initially it was thought that ADSCs improved wound healing by differentiating into the various cell types that were deficient in the injured area[9]. More recent research has reported that ADSCs and other MSCs function in a paracrine fashion, stimulating surrounding cells by secreting growth factors and cytokines as well as recruiting endogenous cells[34,35]. Shrestha et al[36] reported that stem cells improved healing of diabetic wounds by secreting growth hormones such as VEGF, platelet derived growth factor (PDGF), and keratinocyte growth factor (KGF). Ebrahimian et al[37] demonstrated the paracrine nature of ADSCs in the healing of radiation wounds and reported that wound healing was enhanced with the use of stem cells. ADSCs can also stimulate neovascularization by the production of VEGF, differentiate into ketatinocytes, and produce KGF to stimulate surround cells[37].

Shin et al[38] demonstrated that administration of MSCs enhanced wound healing in a mouse model, and that transplanted MSCs secrete cytokines that attracted endogenous MSCs to the wound site[38]. The transplanted MSCs, however, did not migrate to other areas of the body[38]. Therefore, it was postulated that ADSCs did not directly influence wound healing as previously thought, but worked indirectly via local mediators.

These beneficial effects of ADSCs have been reported to work even if therapy was initiated days after injury. Moon et al[30] injected ADSCs into the limbs immediately and 7 days after inducing hind limb ischemia in nude mice. Both groups demonstrated improved vascularity and muscle repair compared to controls. The mechanism of healing was demonstrated to be due to the proangiogenic growth factor secretion by ADSCs (increased levels of GRO, PGF, EAN-78, MCP-1, IL-6, IL-8, TIMP-1, TIMP-2, MMP-1, MMP-9 and uPAR) which improved the blood supply and prevented apoptotic death of endothelial cells in the injured area[30].

The use of stem cells has also been shown to benefit chronic non-healing wounds such as diabetic ulcers. Kwon et al[27] investigated the effect of BMSCs in diabetic rat wounds and reported that diabetic wounds treated with BMSCs healed as well as wounds in control normal non-diabetic rats. Wounds induced in diabetic rats demonstrated poor healing, pronounced

polymorphonuclear (PMN) cell infiltration in the inflammatory phase, limited granulation tissue formation, deficient growth factor and collagen release and weak wound architecture. However, wounds treated with BMSCs improved healing by improving collagen metabolism and deposition as well as improving growth factor secretion and functionality[27].

Cianfarani et al[25] investigated the effect of autologous versus allogenic ADSC use in wound healing and reported that both the intrinsic properties and functions in diabetic ADSCs were affected, potentially discouraging the utilization of autologous ADCS administration in diabetic ulcers. Fewer stem cells isolated from diabetic mice expressed ADSC markers (CD49e, CD54, CD73, CD90, and Sca-1) and their ability to proliferate, migrate and exert paracrine effects were also decreased[25]. The study also reported that ADSCs from diabetic mice demonstrate decreased granulation tissue and collagen deposition and poor wound healing compared with non-diabetic ADSCs. The authors[25] concluded that if autologous ADSCs were to be used in diabetic patients the cells may require modification to improve their functionality (see future considerations).

Other cells types have also been assessed for their healing benefits in chronic wounds. Nambu et al[39] compared wound healing with use of ADSC contained in a collagen gel matrixgel verses fibroblast which were contained in a collagen gel matrix and reported that while the wounds in both groups of mice healed, the fibroblast group was more effective. Despite their observations, ADSCs were the preferred therapeutic option due to their greater ease of acquisitioning and their immunocompatibility[39]. Lee et al[40] had similar findings in mice when comparing the effect of ADSCs with dermal fibroblasts.

The method of transplanting stem cells into the host niche is an important variable when considering the efficacy of different cell therapies. Most of the studies in this review administered the stem cells locally; either by intradermal injection or topical application. Amos et al[41] further examined topical methods of ADSC application, namely multicellular aggregates versus cell suspension in diabetic wounds. The study reported that multicellular aggregates have better healing compared to cell suspensions, related to their increased secretion of ECM components and growth[41]. This is an area that needs to be further studied to address the most effective application method of ADSCs. In addition, a multitude of possibilities exist in relation to regenerative potential of the 'stromal' vascular fraction', the undifferentiated conglomerate of progenitor cells and stromal cells that are present in early uncultured lipoaspirate. It is thought that this combination of cells may provide cross talk and synergy with themselves and with host tissue to promote successful regeneration in many clinical situations. These progenitor cells, mostly derived from perivascular sites have potent regenerative capabilities. Although this is a step earlier than ADSCs and not the focus of this paper, it should however also be kept in mind as a potential regenerative tool[32,37,41]This is an area that needs to be further studied to address the most effective application method of ADSCs.

Use of ADSC's in human wound healing model

Multiple animal models have demonstrated the benefit of using ADSCs in chronic wounds (Table 1); however, only a limited number of studies have been performed on humans (Table 2). Lee et al[26] reported that intramuscular application of ADSCs in individuals with refractory critical limb ischemia is a safe and effective alternative to other treatment modalities. Nearly two-thirds of study subjects reported improvement, with improved pain rating scales, claudication distance and collateral vessel formation[26]. The authors[26] hypothesized that the mechanism of action was due to paracrine effect via pro-angiogenic and antiapoptotic factor release.

Both Sung et al[12] and Jo et al[42] reported that the injections of ADSCs locally into full thickness facial wounds resulted in healing without complication and minimal scar formation. The exact mechanism of healing was not evaluated in the study, but it was inferred to be due to the paracrine effect of ADSCs. Karaaltin et al[43] reported a case study in which a patient received local injections of ADSCs into a non-healing DFUs resulting in complete wound healing in four weeks. These and other studies have corroborated the potential of using ADSCs in individuals with chronic wounds, but further studies are necessary to elucidate the exact mechanism of action and most appropriate application of ADSCs in treatment of poor wound healing.

Future considerations

The effect of diabetes on the function of endogenous stem cells needs to be taken into consideration when using autologous ADSCs in the management of diabetic wounds. These cells may require *in vitro* ma-

nipulation to enhance their paracrine activity. Genetic modification is an option, but it poses the risk of inserting a mutation that may affect the safety of the ADCSs use in clinical practice. To overcome this, non-genetic options have been explored to enhance the functioning of diabetic ADSCs[45].

Hypoxic pre-conditioning has been shown to enhance ADSC functioning. Lee et al[44] investigated the effect of hypoxia on ADSCs and wound healing and reported that ADSCs exposed to 2% hypoxic conditions exhibited better survival and proliferative capacity and demonstrated enhanced collagen deposition after application at the wound site when compared to cells culture in normoxic condition. The ADSCs exposed to hypoxia showed enhanced growth factor release (VEGF, bFGF and IGF-1) compared to ADSCs exposed to normoxia[44]. Hiaso et al[45] demonstrated that hypoxic preconditioning of ADSCs *in vitro* enhanced their *in vivo* functioning and upregulated growth factor and cytokine release (VEGF, angiogenin (ANG) and IL-8) based on the duration of hypoxia. Subcutaneous implantation of sponges on which pretreated hypoxic ADSCs were cultured, also manifested increased angiogenesis. Both of these studies demonstrated that hypoxic pretreatment of ADSCs enhance their functioning which may lead to improved wound healing in hypoxic, inflamed diabetic ulcers[44.45]. This would be advantageous as diabetic wounds are inherently hypoxic.

Other protocols that have demonstrated ADSC function potentiation include pretreatment with growth factors. ASDCs treated with TGF-β1 reportedly functioned as a wound healing accelerator in a study by Cho et al[46]. The ADSC treated with TGF-β1 influenced fibroblast functioning by increasing proliferation and migration of fibroblasts[46]. Collagen deposition ability was also slightly increased the use of these ADSCs.

ADSC characteristics also vary depending on their source. Cells harvested from the abdominal regions are more resistant to apoptosis. Additionally, greater concentrations of stem cells are found in subcutaneous regions when compared to visceral fat. Interestingly, cells isolated from the inguinal regions are more plastic compared to ADSCs isolated from others[9]. These factors require further investigation so as to optimize and match ADSC harvest and injection sites to achieve therapeutic goals individualized to diabetic recipients.

The best technique for the administration of ADSCs also requires standardization. Current delivery methods include injecting cells with (1) ECM components or scaffold, (2) growth factors or cytokines or (3) as part of re-engineered tissue[23]. Tian et al[47] identified deficient lipid mediators such as 14*S*,21*R*-diHDHA in a murine model of diabetic wounds. The subsequent replenishment of this mediator in combination with ADSCs further enhanced wound healing[47]. The above mentioned are examples of how ADSC can be manipulated and matched to patient requirements. There is an urgent need for additional studies to address enhancement of stem cell function for use in chronic wound management.

Conclusions

Wound healing is a complex process that involves interplay of various biochemical and cellular factors. Stem cells play an important role in modulating the healing process through paracrine interactions. This role is impaired by diabetes resulting in poor wound healing and chronic wounds. ADSCs have been used to enhance the healing process and their benefit has been observed in various animal studies and human trials. They function in a paracrine manner stimulating surrounding cells and promoting angiogenesis. Though diabetes impairs their functionality, diabetic ADSCs can be manipulated to enhance their activity. Further investigation is required intoon ADSCs to determine their potential utility in treating chronic non-healing wounds.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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