# Adipose Stem Cells in Modern-Day Ophthalmology

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Stem cells (SCs) have evolved as an interesting and viable factor in ophthalmologic patient care in the past decades. SCs have been classified as either embryonic, mesenchymal, tissue-specific, or induced pluripotent cells. Multiple novel management techniques and clinical trials have been established to date. While available publications are predominantly animal-model-based, significant material is derived from human studies and case-selected scenarios. This possibility of explanting cells from viable tissue to regenerate/repair damaged tissue points to an exciting future of therapeutic options in all fields of medicine, and ophthalmology is surely not left out. Adipose tissue obtained from lipo-aspirates has been shown to produce mesenchymal SCs that are potentially useful in different body parts, including the oculo-visual system.

stem cells adipose pluripotent regenerative

## 1. The Anatomy of Adipose-Tissue-Derived Stem Cells (ADSC)

Adipose-tissue-derived stem cells (ADSCs) are mesenchymal cells derived from adipocytes, as the name implies [1]. The proliferative actions of these cells were discovered as secondary effects of leptin secretion [2][3][4]. Adipose tissue is distributed normally around the body at sites such as the bone marrow (i.e., red adipose) [5], articular cartilage, and visceral and subcutaneous fat deposits [6][7][8][9][10]. Adipose tissue may also form around the hepatic tissue [11] and cardiac smooth muscle [12]. Adipose tissue obtained via lipo-aspirates can be analyzed in an alkaline medium catalyzed by collagenase enzymes [13]. The subsequent reactions help reveal the base anatomy. Adipose tissue is made up of a stromal vascular fraction (SVF) and mature adipocytes [14].

Various cellular components make up the SVF [15]. These include adipose stromal/stem cells, pericytes, preadipocytes, smooth myocytes, myeloid cells, fibroblasts, endothelial cells, lymphocytes, and macrophages [16]. Of these constituents, adipose stromal cells are identified as being experimentally multipotent [17]. It is important to remember that adult mesenchymal SCs are derived from the stromal vascular fraction component of adipose tissue [18].

Adipose tissue exists in various isoforms that chiefly differ in their thermogenic capacities. These include brown adipose tissue [19] and white adipose tissue [20]. White adipose tissue exists at subcutaneous sites, in the bone marrow, and around the linings of visceral organs [21]. Brown adipose tissue, however, is located all around the body and helps to convert energy from food into heat, especially in cold temperatures [22]. Brown adipose tissue

also contains more mitochondria and capillaries than white adipose tissue, indicating that it is more efficient at supplying oxygen to surrounding tissues [23]. Cadherins, along with integrins, are known receptors that mediate transmembrane adhesion [24].

## 2. ADSCs in Ophthalmic Surgery

Ophthalmic surgery is often necessary for the management of ocular morbidity. Surgery can offer therapeutic benefits; however, ocular complications such as trauma must be considered due to specific procedures, inflammation, and infection. Penetrating keratoplasty and keratoprosthesis are invasive treatment options for visual impairment due to extensive corneal scarring. The use of donor corneas has numerous limitations, which include a lack of donor tissue, the possible rejection of donor tissue, high complication rates, elevated risks of postoperative complications, increased induced astigmatism, etc. [25].

Less invasive options are becoming of increasing interest in the field regarding corneal repair. Studies have shown that exosomal microRNA-19 suppresses the differentiation of corneal stromal keratocytes into myofibroblasts [26]. Ma et al. grafted autologous rabbit adipose stem cells on a poly lactic-co-glycolic acid (PLGA) scaffold following mechanical corneal stromal injury. Marked stromal repair was reportedly observed in vivo [27]. The researchers' group tested the efficacy of topical ADSCs on mouse models with laser-induced photorefractive keratectomy [28]. Homogeneous corneal lesions were created using a laser device. Fluorescein staining and specific corneal photography were used to estimate the extent of the lesions during the entire treatment regimen. The study showed that the group of mice that received supplemental ADSC topical treatment healed faster and with fewer complications when compared to the other groups and the controls.

ADSC therapy has been shown to enhance surgical outcomes and reduce postoperative complications. El Zarif et al. reviewed the laser-assisted intrastromal implantation (via injection) of autologous adipose-derived stem cells in patients with advanced keratoconus to aid in corneal stroma regeneration [29]. They reported an improvement in corneal integrity and function in all of their test groups, which received some form of stem cell therapy. Similar exciting results were reported by Qiu et al., who performed sclerocorneal transplantation of amniotic membranes and autologous ADSCs onto the ocular surfaces of rabbits with limbal stem cell deficiency [30]. ADSC therapy alone performed better than a combined ADSC and amniotic membrane therapy or a third placebo group.

Park et al. utilized a topical cell-free conditioned medium derived from autologous ADSCs on murine models of alcohol-burn-induced keratitis [31]. The ADSC preparation was administered four times daily in the test mice, while other groups of mice received a placebo. Fluorescent biomicroscopy showed the improved expression of corneal epithelial cells. There was also an upregulation of interleukin-6, epidermal growth factor, and C-X-C chemokine receptor type 4 mRNAs. Shadmani et al. injected both autologous and allogeneic ADSCs subconjunctivally in animal models of corneal alkali injury and obtained similar results [32]. Dinç et al. also performed the subconjunctival injection of ADSCs in murine models of acute alkaline corneal burns and demonstrated increased wound healing [33].

Bone-marrow-derived mesenchymal tissue and ADSCs have been compared in several studies in the literature. Demirayak et al. created experimental models to study the mitigating effects of SCs on corneal scarring following penetrating injuries [34]. They performed intracameral injections of allogeneic ADSCs in Wistar rats following induced penetrating corneal injury. They concluded that allogeneic treatment using SCs precipitated the regeneration of damaged cornea stroma and a reduction in subsequent scarring. Shang et al. also assessed the impact of allogeneic ADSCs on the healing response of murine corneas following ethanol exposure via retrobulbar injection and reported that ADSCs were found to promote the clearance of neutrophils in the cornea during the granulation stage [35]. This was highlighted as a key step in a cascade of events that reduced the amount of corneal scarring in their model.

## 3. Therapeutic Applications of ADSCs in Retinal Diseases

ADSCs have been the topic of several studies in the literature that examine the potential therapeutic options for these cells in retinal diseases. Rajashekar et al. found that intravitreal injection of ADSCs in streptozotocin-induced diabetic rats correlated with fewer signs of early vascular derangement characteristic of diabetic retinopathy (DR) [36]. Safwat et al. also reported that adipose-stem-cell-derived exosomes ameliorated characteristic retinal degeneration following intraocular and subconjunctival administration among streptozotocin-induced diabetic rabbits [37].

As with any surgical procedure, ADSC implantation has been assessed for potential risks to the retina. Limoli et al. recorded no complications and an improvement in scotopic electroretinographic scores following suprachoroidal grafting of mature adipocytes and ADSCs in the stromal vascular fraction enriched with platelet-rich plasma (PRP) amongst elderly patients with non-exudative age-related macular degeneration (AMD) [38]. This group also reported objective parameters following the autologous transplantation of adipocytes, ADSCs in the SVF, and platelet-rich plasma (PRP) within the suprachoroidal space of patients with dry AMD [39]. The improved visual performance also correlated with greater retinal thickness averages. Limoli et al. reported that the suprachoroidal transplantation of autologous ADSCs reduced the progression of visual deficits in dry AMD, as shown by an improvement in best-corrected visual acuity (BCVA) and logMAR values 180 days post-treatment. A longitudinal study of visual characteristics from eight patients showed a slight improvement in the visual function of patients with degenerative macula disease following suprachoroidal ADSC implantation [40].

## 4. Future Potential for ADSCs in Retinal Diseases

Genetic and tissue engineering has been hypothesized for the treatment of DR [41]. Vision loss from advanced ischemic or late (proliferative) DR is often irreversible. Therapeutic advantages are best seen with treatment during the earlier stages of DR [42]. Modern-day strategies mostly recommend hyperglycemic control (as well as the control of other vasculopathic patient-specific risk factors) during the mild and early moderate stages of non-proliferative DR. Improving glycemic control following prolonged periods of retinal exposure to hyperglycemic stress, however, can still cause non-reversible effects of previous retinal microvascular damage. Laser or

intravitreal treatments are usually performed when there are signs of active DR. ADSCs have been suggested to provide protective effects against retinal ischemic damage [43] and to retinal extracellular vesicles [44].

Rajashekar et al. proposed a strategy to regenerate the retinal vasculature and neuronal cell integrity via intravitreal injection of ADSCs in streptozotocin-induced murine models of early DR [45]. ADSCs were reported to integrate into retinal perivasculature and, thus, reconstitute the blood–retinal barrier within several weeks.

It has also been postulated that the administration of autologous ADSC exosomes to streptozotocin-induced diabetic rabbits could attenuate diabetic-retinopathy-related neurodegeneration and microvasculopathy via increased microRNA-222 expression [37]. Elschaer et al. subsequently concluded that intravitreal injections of either hADSC- or adipose-SC-conditioned medium primed with cytokines yielded a reduction in vascular permeability and an improvement in electroretinogram scores [46]. ADSCs have also been found to mediate angiogenesis via paracrine mechanisms in retinal endothelial cells and promote retinal regeneration in vitro [47]. ADSC-CM and paracrine factors were associated with better visual functions post-injection in early DR Ins2Akita mouse models.

ADSCs are known to play a role in retinal and photoreceptor cell proliferation [48]. hADSCs have shown a trilineage potential to proliferate, migrate, differentiate into RPE cells when exposed to an RPE-cell-conditioned medium [49]. Yu et al. reported that adipose-derived mesenchymal stem cell exosomes ameliorated laser-induced retinal injury among mice and prevented extensive photoreceptor cell damage via the downregulation of monocyte chemotactic protein-1 [50]. Xu et al. also found that orbital ADSCs isolated via direct explant culture showed the earlier and stronger expression of markers indicating eye field and retinal photoreceptor differentiation than those generated by the conventional enzyme method [51].

## 5. Therapeutic Potential of ADSCs in Neuro-Ophthalmology

Late-phase optic nerve disease yields profound functional limitations, which usually tend to be irreversible [52]. ADSCs, however, may produce a paradigm shift if viable therapies can be established. ADSCs have been reported to offer neuroprotection to retinal ganglion cells and may promote the regeneration of axons in the optic nerve head via the secretion of trophic “paracrine” factors [53]. ADSC exosomes possess bioactive molecules such as microRNAs and immunoregulatory, trophic, and growth factors, which provide pro-angiogenic effects for the possible re-vascularization of ischemic retinal or neural tissue [54]. Faber et al. suggested that ADSCs could be administered intravitreally without adverse consequences [55]. The results were based on clinical findings in a single patient with non-arteritic anterior ischemic optic neuropathy (NAION). Oner et al. reported a slight improvement in visual acuity among patients with optic atrophy following the suprachoroidal implantation of ADSCs. This patient also showed visual field and mfERG recording improvements after treatment [56].

Experiments based on in vivo ADSC transplantation have shown possible therapeutic benefits in rat models with ameliorated optic nerve injury. Treatment showed signs of inhibiting insult-induced inflammation [57][58]. The effects of ADSCs on optic nerve injuries have also been studied in Sprague Dawley rats. Experiments showed that an adipose SC concentrated conditioned medium (ASC-CCM) primed with inflammatory cytokines to induce the

expression of tumor necrosis factor-stimulated protein 6 (TSG-6) improved the retinal barrier function and reduced visual deficits via neuroglial support mechanisms when injected intravitreally following mild traumatic brain injury in mice [59][60]. Jha et al. also highlighted the potential of the ADSC concentrated conditioned medium for regulating retinal neurodegeneration following mild traumatic brain injury [61].

## 6. Potential Applications of Adipose Stem Cells to Periorbital and Orbital Structures

Studies have reported that ADSC therapy could be beneficial in thyroid-associated orbitopathy [62]. It has also been suggested that insulin-like growth factor 1 has pro-adipogenic and pro-proliferative effects on ADSCs extracted from thyroid-associated ophthalmopathy patients via in vitro studies [63]. The topical prostaglandin analog bimatoprost has been reported, however, to inhibit human orbital ADSCs [64].

Wu et al. reviewed the potential of iPSCs derived from autologous adipose tissue to forge patient-specific remedies for degenerative and acquired oculoplastic diseases [65]. Lee et al. reported orbital volume augmentation following the intraorbital injection of ADSCs in rabbits [66]. The rabbits showed an increase in the exophthalmometric value of about 2.5 mm after three months. Li et al. induced autoimmune dacryoadenitis in rabbits via the intravenous infusion of activated autologous peripheral blood lymphocytes. Acute treatment using ADSCs was attributed to the reduced expression of inflammatory markers and increased basal tear volume [67].

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