Retinopathy

Mesenchymal stem cells: The future of the management of diabetic retinopathy

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In this interesting article, summarised alongside, Ezquer et al consider the use of donor multipotent mesenchymal stromal cells, also known as mesenchymal stem cells (MSCs), as healing agents in diabetic retinopathy (DR). They review the pathophysiological processes in the development of DR in order to identify therapeutic targets for donor MSCs and speculate as to whether MSC-based therapy could prevent or delay the development of DR.

Stem cells are undifferentiated cells that are able to self-renew and give rise to mature cell lines. MSCs are usually harvested from bone marrow but can also be obtained from adipose tissue, and have been shown to be able to differentiate into a variety of cell types, including osteoblasts, chondrocytes, myocytes, adipocytes, beta pancreatic islet cells and even neuron-like cells. Interestingly, MSCs can also be harvested from dental tissue, but these only differentiate into odontogenic cells. This phenomenon has been documented in specific cells and tissues in living animals and their counterparts growing in tissue culture.

MSCs avoid the ethical issues that surround embryonic stem cell research, and it has also been shown that human MSCs are immunoprivileged, reducing the risks of rejection and transplantation complications. When given intravenously, they are able to locate damaged organs, although the mechanisms underlying the migration of these cells remain unclear, and so far there seem to have been no adverse events associated with their use. This all makes MSCs a promising source of stem cells for tissue repair and gene therapy.

So why is the eye a potential candidate site? There are a number of chronic eye conditions, such as age-related macular degeneration and retinitis pigmentosa, that are characterised by loss of neural cells. Bone marrow- and adipose-derived MSCs have been shown to differentiate into photoreceptor cells or retinal pigment epithelium when injected into the eye.

Why DR? Local injection of MSCs in animals with limbal stem cell deficiency is known to greatly reduce the infiltration of inflammatory cells in the cornea. Inflammation is known to be involved in DR, and recently there has been much interest in the use of anti-inflammatory and neuroprotective agents to treat DR. MSCs can also help to reduce oxidative damage by scavenging reactive oxygen species and may be able to differentiate into pericytes and neuronal cells. The authors conclude that MSCs should now be tested in animal models of DR. Stem cell therapy is a newly emerging therapeutic approach but it is clearly the future, even if that future is some way off! ■

Acta Ophthalmol

Mesenchymal stem cells to prevent diabetic retinopathy

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓✓

1 The authors review the literature on the use of mesenchymal stem cells (MSCs) as a treatment to prevent or delay the progression of diabetic retinopathy (DR).

2 Current treatments for the condition all have limitations: laser photocoagulation and vitrectomy are highly invasive and have serious side effects; anti-vascular endothelial growth factor agents have short-lasting effects and are associated with adverse events; intravitreal anti-inflammatory agents require repeat injections and can lead to glaucoma and cataract; and agents that neutralise reactive oxygen species (ROS) require large doses as they have poor oral bioavailability or are unable to cross the blood–retinal barrier.

3 Loss of retinal pericytes, neurons and Müller glial cells is an early characteristic of diabetes that leads to inflammation, angiogenesis and vision loss; therefore, replacement of these cells may be of benefit.

4 Injection of MSCs may result in this regeneration and may be an ideal treatment for DR; in animal models and *in vivo*, they have been shown to differentiate into pericytes and neural cells, modulate inflammation, counteract ROS, induce endogenous tissue regeneration and improve blood–retinal barrier integrity.

5 The principal concerns are that MSCs can secrete angiogenic factors and thus could, in fact, worsen DR; however, they have been administered to >1000 people with no evidence of adverse effects.

Ezquer F, Ezquer M, Arango-Rodriguez M, Conget P (2014) Could donor multipotent mesenchymal stromal cells prevent or delay the onset of diabetic retinopathy? *Acta Ophthalmol* **92**:e86–95

JAMA Ophthalmol

Doxycycline versus placebo in diabetic retinopathy

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓✓

1 This clinical trial investigated whether low-dose oral doxycycline monohydrate can improve retinal function, or induce regression or slow the progression of diabetic retinopathy in people with severe non-proliferative diabetic retinopathy (NPDR) or non-high-risk proliferative diabetic retinopathy (PDR).

2 A randomised, double-masked, 2-year, proof-of-concept clinical trial was conducted to compare the effectiveness of 50 mg of doxycycline monohydrate daily before meals versus placebo among 30 people with diabetes who had one or more eyes with severe NPDR or PDR.

3 Twenty-five people completed the trial. From baseline to 24 months, mean foveal sensitivity, as measured by frequency-doubling technology perimetry, decreased in the placebo group and increased in the doxycycline group (P=0.02); a higher mean foveal sensitivity in the doxycycline group compared with the placebo group was detected at 6 months (P=0.04). This difference persisted at 12 and 24 months.

4 There were no other differences detected between the groups with respect to the other visual function and anatomical outcomes that were assessed.

5 The study suggests a potential link between a low-dose oral anti-inflammatory agent and subclinical improvement in inner retinal function among people with diabetes.

Scott IU, Jackson GR, Quillen DA et al (2014) Effect of doxycycline vs placebo on retinal function and diabetic retinopathy progression in patients with severe nonproliferative or non-high-risk proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol* **132**: 535–43

Br J Ophthalmol

Referrals for eye disease among people with diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 The Scottish Diabetic Retinopathy (DR) Screening service was established in 2006 to prevent vision loss due to DR. The authors report the yield of referable eye disease over the first 5 years of the programme.

2 Among 182 397 people who were screened, the yield of referable disease was 6–7% in the first 2 years and then stabilised at around 4%.

3 Despite initial concerns from ophthalmologists, this workload should be manageable within current ophthalmology provision.

4 Most referrals were for diabetic macular oedema (DMO). With the advent of new treatments that can restore vision even after DMO onset, the authors suggest that including this in the screening programme may be unnecessary.

Looker HC, Nyangoma SO, Cromie DT et al (2014) Rates of referable eye disease in the Scottish National Diabetic Retinopathy Screening Programme. *Br J Ophthalmol* **98**: 790–5

Br J Ophthalmol

Ocular blood flow in T2D and CAD

Readability	✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓

1 Ocular blood flow was compared between people with T2D and coronary artery disease (CAD; n=29), T2D without CAD (n=13) and control subjects without either condition (n=14).

2 Compared with the control group, participants with both T2D and CAD had significantly lower peak systolic velocity and end-diastolic velocity (EDV) in the ophthalmic, central retinal and posterior ciliary arteries; those with T2D but not CAD had a reduced EDV in the ophthalmic artery only.

3 In a subgroup analysis of patients with T2D and CAD, those with diabetic retinopathy (DR) had a further reduction in EDV in the central retinal artery.

4 The authors conclude that the disrupted ocular blood flow in T2D was associated with atherosclerosis regardless of concomitant DR, and that DR was associated with further blood flow impairment in the central retinal artery but not with disruption in the ophthalmic and short posterior ciliary arteries.

Krasnicki P, Dmuchowska DA, Proniewska-Skretek E et al (2014) Ocular haemodynamics in patients with type 2 diabetes and coronary artery disease. *Br J Ophthalmol* **98**: 675–8.

Br J Ophthalmol

Bevacizumab plus laser for DMO

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 In this small pilot study, the authors retrospectively evaluated 18 people (23 eyes) with diabetic macular oedema (DMO) who received a standard regimen of monthly bevacizumab injections followed by macular laser photocoagulation if central retinal thickness (CRT) reached <440 µm.

2 At the time of laser therapy, mean best corrected visual acuity (BCVA) had increased by 10.4 ETDRS (Early Treatment Diabetic Retinopathy Study) letters and mean CRT had decreased by 146 µm.

3 Both BCVA and CRT remained stable up to 12 months after laser; between baseline and final follow-up, the mean increase in BCVA was 7.8 letters (median, 7 letters) and the mean decrease in CRT was 125 µm.

4 Following laser therapy, 43% of eyes required two further bevacizumab injections, whereas 57% required none.

Barteselli G, Kozak I, El-Emam S et al (2014) 12-month results of the standardised combination therapy for diabetic macular oedema: intravitreal bevacizumab and navigated retinal photocoagulation. *Br J Ophthalmol* **98**: 1036–41

> ***"The study suggests a potential link between a low-dose oral anti-inflammatory agent and subclinical improvement in inner retinal function among people with diabetes."***