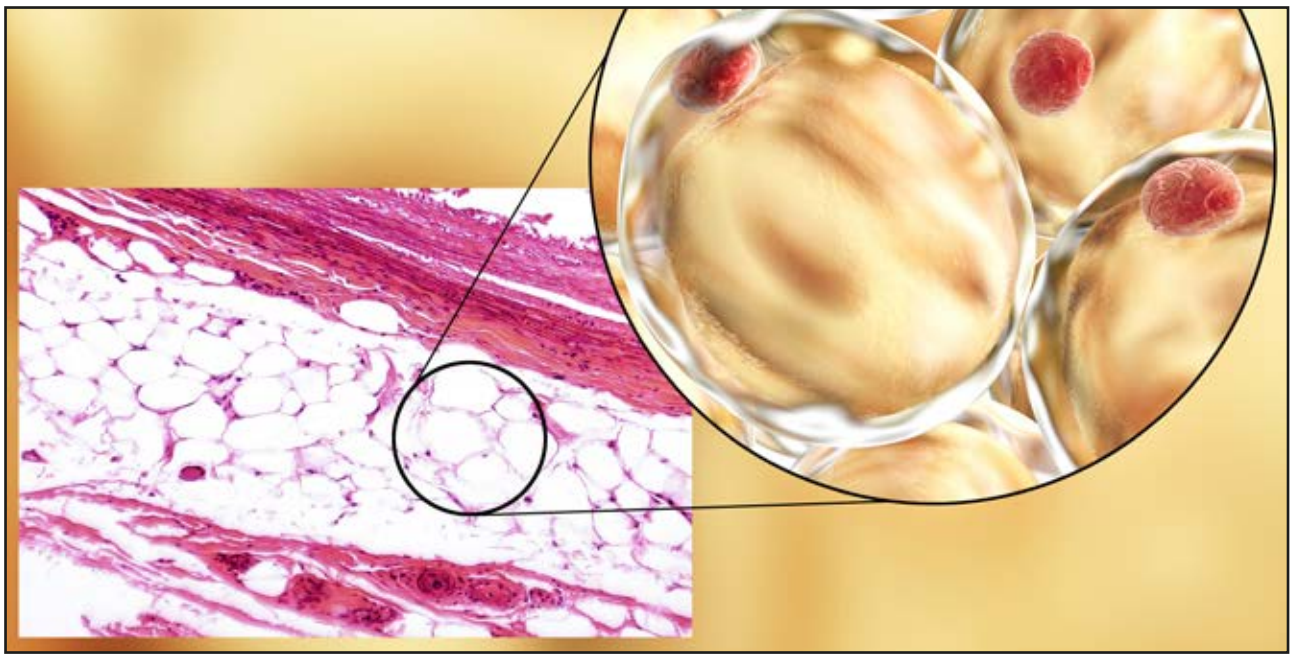

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NANO-FAT & ADIPOSE DERIVED STEM CELLS

Mr Ali Ghanem and Mr Ansar Mahmood discuss the use of fat as a regenerative tool

When it comes to cell therapies and harvesting stem cell components, the beautiful thing about fat is that fat is very easily accessible, and most patients are happy to lose some of it!

A surgeon will find it a lot easier, and more ethically agreeable, if they harvest adipose-derived stem cells, as compared to conducting a bone or deep tissue harvest to achieve the same aim. Almost all of us have a little bit of extra fat, usually around the abdomen, which is perfect for the task, hence adipose-derived stem cells (ADSCs) are the most frequently referenced in aesthetic medicine, often used in conjunction with fat transfer or rejuvenation procedures.

Similarly, unlike other sources of stem cells, such as bone marrow, the quality and volume of stem cells found in fat does not diminish with age as much as bone or blood derived. With modern harvesting techniques, the fat pericyte complex within the vascular niche in the fat tends to stay intact, and thus the number of mesenchymal stem cells MSCs) will be significantly higher. As physicians, what we are interested in capturing for most treatments is not fat (progenitor) stem cells, but the stem cells within the microvasculature of the fat – the vascular endothelial pericytes as these are in fact dormant stem cells. There is also evidence that the fat itself - if we take a fat cell or adipocyte and denude it from the stem cells - has a biological advantage on its own. There appears to be a protective role within the 'padding' that surrounds humans, and it can have a therapeutic effect. There is also a metabolic effect, and the fat progenitor cells have potential regenerative capabilities, regardless of their pericytes. But when we are referring to fat or ADSCs, these are the pericytes which are very strongly adherent to the blood vessels within the fat.

The pericytes are very robust, which is a helpful characteristic when it comes to harvesting ADSCs for treatment. We can extract them out as little 'parcels' which vary between approximately one millimetre and four millimetres in size. We need to dissociate the pericytes from the vascular niche, and we have two ways of achieving that – enzymatic digestion or mechanical dissociation.

With enzymatic digestion, we are adding enzymes to the harvested fat, and it is these enzymes which digest the relationship between the pericytes and the vascular niche. The solution is then washed and spun in a centrifuge. This causes the pericytes to sink to the bottom of the tube as they are heavier than the adipocytes breakdown products.

With mechanical dissociation, we agitate the fat parcels mechanically by either crushing or cutting them, or by using extremely high centrifugal forces, without the combined use of enzymatic digestion, which strips the stem cells out of the vascular niche.

Enzymatic digestion is very efficient when it comes to cell numbers and is regarded as the gold standard. Yet, mechanical dissociation, which is approximately two thirds as efficient, is favoured by regulators because there is minimal manipulation and no additives. Both methods aim to isolate the pericytes from the rest of the fat cell structure, however, too much manipulation can effectively stun them and render them less functional. Enzymatic digestion is viewed as a gentler process, but we must still be mindful of the pressures used in the centrifuge. Similarly, although you will achieve more pericyte cells per millilitre of fat processed with an enzymatic digestion process, than with a mechanical process, it is difficult to say currently whether those cells will

necessarily be better in terms of their function; more studies are needed.

The resultant 'pellet' of pericyte cells is our stromal-vascular fraction. This can be used to treat a patient, in the case of arthritis, burns, scarring, or for rejuvenation, or it can be taken to the lab to be fed and nourished in a petri dish to expand them into pure stem cells for research use. Once within the laboratory environment however, we can no longer give them to the patient without a research licence.

Nano-fat treatments are another descriptive way of generating regenerative cells for therapy which are marketed a lot in aesthetic medicine. Nano-fat is created by emulsification, another type of mechanical dissociation. The fat parcels – which include the adipocytes and the pericytes – are processed through vortexing forces which destroy the fat cells. The result is a cocktail made up of the oil, or lipids, from the fat cells which includes all the debris (e.g., the cell membranes), and the pericytes. Thus, you have a concentrated stromal-vascular fraction, but no centrifugation is used to remove the debris. This is a quick option for clinicians and allows for superficial reinjection into the face without causing lumps from visible fat cells. When this nano-fat cocktail is injected into the skin, there will be a visible yellowing, but the body quickly metabolises the lipids and the remaining stromal-vascular fraction, the pericyte (stem) cells can get to work; generally, there are fewer of them with this process than the ones described earlier.

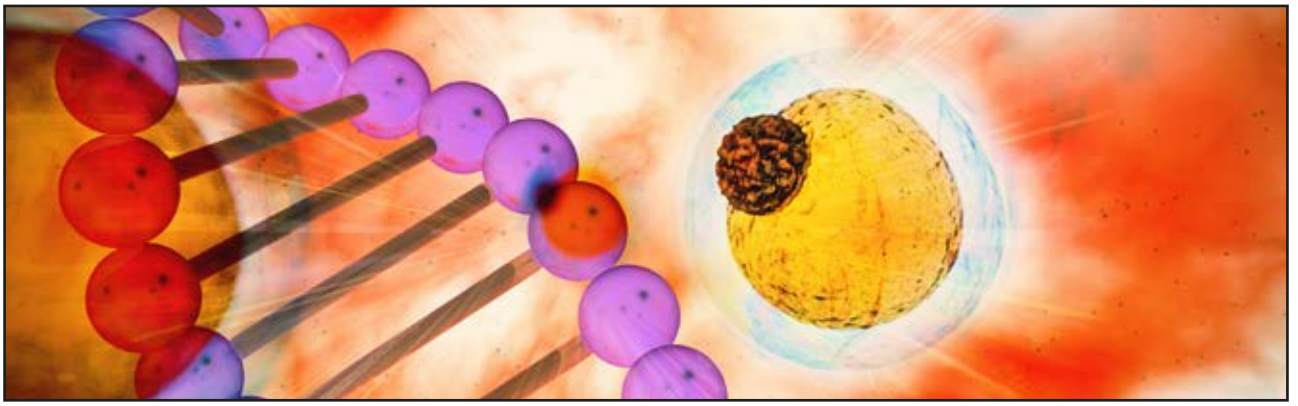
Some examples of the different systems used within the aesthetic sector for cell therapies or nano-fat grafting procedures include Cytori™ (enzymatic digestion), Kerastem™ which uses fat as a treatment for hair loss (enzymatic digestion), Lipogems™ (mechanical dissociation) and Lipocube™ Nano (mechanical dissociation). The resultant combination of the key components – the adipocytes, the pericytes (stem cells), and the vascular niche – within the product created by each system varies. Sadly, clinical validation and comparison studies between the different methods are lacking in the published literature.

Although, there is promising data, albeit not high level, to suggest that fat and adipose-derived stem cells have a role in all aspects of aesthetic rejuvenation. This includes addressing surface damage such as pigmentation, vascular problems, as well as lines and wrinkles.

Good evidence also exists for use in volume restoration and contouring which shows that the enrichment of transferred or grafted fat with SVF and/or PRP combinations leads to better survival of the fat graft. However, this is again in the context of aesthetics, and high-level evidence is not yet available. The use of fat for volumising is regarded as a good option though because we are augmenting like with like; this is a much better option than using silicone implants. However, come caveats and issues need to be addressed, for example, using fat grafts in the breast. For a long time, there were concerns related to latent, active cancers and the way that they can grow with fat grafting. Thankfully, this has been put to bed after several systematic reviews showed that physicians must exclude existing cancer because the fat graft can stimulate existing cancer, but it does not **cause** cancer. In fact, for women who have breast cancer and undergo excision and reconstructive surgeries, fat is often used in the reconstruction process. There is no evidence to suggest that they will have a higher recurrence rate of cancers compared to those who received a silicone implant reconstruction.

Finally, concerning tissue laxity and collagenesis, we have also enough rationale and evidence to support the role of ADSCs in collagen deposition and induction - where by other beneficial molecules are attracted to the area to support the tissue. Beyond that, there are lots of pathologies being researched, but these are not specific to aesthetic medicine. They tend to relate to wound healing or alopecia, and all these inflammatory and degenerative conditions have variable degrees of clinical evidence to support the use of ADSCs, but we need more high-level evidence.

In conclusion, the options for the utilisation of fat and fat-derived cell therapies in aesthetic medicine and surgery are growing exponentially year on year, however, it must be approached like any other medical tool at our disposal - with competency, assessment, and validated protocols - so that we protect the patients and the clinicians alike. Similarly, more characterisation, optimisation and standardisation of these therapies is necessary for our and our patients' future success.



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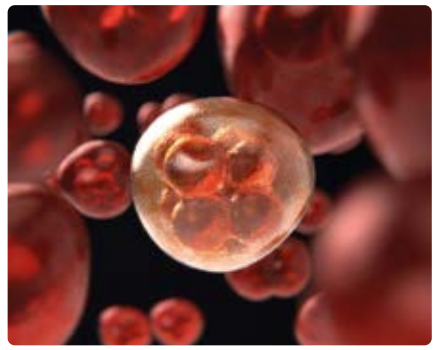

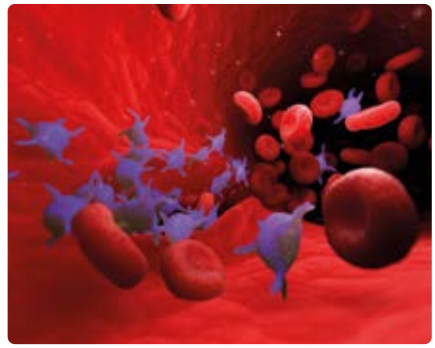

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