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# Acceptability of Allogeneic Mesenchymal Stromal Cell –Based Tissue Engineering for the Treatment of Periodontitis: A Qualitative Study in France

Lucas Riazuelo<sup>a</sup>, Valérie Planat-Bénard<sup>b</sup>, Alexia Vinel<sup>a,c</sup>, Sara Laurencin<sup>a,d</sup>, Louis Casteilla<sup>b</sup>, Philippe Kémoun<sup>a,b</sup>, Mathieu Marty<sup>a,e</sup>, Paul Monsarrat<sup>a,b,f\*</sup>

<sup>a</sup> Oral Medicine Department and CHU de Toulouse, Toulouse Institute of Oral Medicine and Science, Toulouse, France

<sup>b</sup> RESTORE Research Center, Université de Toulouse, INSERM, CNRS, EFS, ENVT, Université P. Sabatier, Toulouse, France

<sup>c</sup> I2MC, INSERM UMR 1297, University of Toulouse III, Toulouse, France

<sup>d</sup> Center for Epidemiology and Research in POPulation Health (CERPOP), UMR 1295, Paul Sabatier University, Toulouse, France

<sup>e</sup> LIRDEF, Faculty of Educational Sciences, Paul Valéry University, Montpellier, France

<sup>f</sup> Artificial and Natural Intelligence Toulouse Institute ANITI, Toulouse, France

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## ABSTRACT

**Introduction and aims:** Periodontitis, the main cause of tooth loss in adults, is a public health concern; its incidence increases with age, and its prevalence increases with increasing life expectancy of the population. Innovative therapies such as cell therapy represent promising future solutions for guided tissue regeneration. However, these therapies may be associated with fears and mistrust from the general public. The aim of this study was to estimate the acceptability of an advanced therapy medicinal product combining allogeneic mesenchymal stromal cells from adipose tissue with a natural fibrin hydrogel in the treatment of periodontitis.

**Methods:** The methodology was based on a qualitative study conducted through semi-structured interviews with patients followed for periodontitis in the Oral Medicine Department of the Toulouse University Hospital, Toulouse, France. Qualitative studies are essential methodologies to understand the patterns of health behaviours, describe illness experiences, and design health interventions in a humanistic and person-centred way of discovering.

**Results:** Eleven interviews (with 4 men and 7 women) were required to reach thematic saturation. Analysis allowed 4 main themes to emerge: (1) perception of new treatments, science, and caregivers; (2) conditions that the treatment must meet; (3) patient perception of the disease; and (4) factors related to the content of the treatment.

**Conclusions:** Patients find cell therapy for periodontitis to be acceptable. If they express a need to be informed about the benefit/risk ratio, they are not particularly worried about side effects of the treatment, for either allogeneic or blood-derived products. Periodontitis is a prototypical model of chronic inflammatory pathology and is multitissular, with hard- and soft-tissue lesions. In a patient-centred approach, the success of cell therapy will require a bilateral, informed decision, taking into account potential therapeutic effectiveness and patient expectations for regeneration.

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\* Corresponding author. Oral Medicine Department and CHU de Toulouse, Toulouse Institute of Oral Medicine and Science, 3 chemin des Maraîchers, 31062 Toulouse Cedex 9, Toulouse, France

E-mail address: [paul.monsarrat@univ-tlse3.fr](mailto:paul.monsarrat@univ-tlse3.fr) (P. Monsarrat).

Paul Monsarrat: <http://orcid.org/0000-0002-5473-6035>

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## Introduction

Improvements in public health and health care have resulted in significant life-span extension, with a subsequent increase in the incidence of age-related diseases.<sup>1</sup> Chronic inflammatory age-related diseases (ARDs; eg, cardiovascular,

rheumatic, dermatologic, digestive, oral pathologies) are associated with multitissue disruptions leading to functional loss. These diseases usually silently settle over time; tissues lose their ability to regenerate, and lesion irreversibility and function failure evolve.<sup>2</sup> Tissue damage has particularly disabling consequences, significantly impairs patients' quality of life (eg, chronic pain, disabilities, aesthetic alterations, loss of self-confidence), and represents a significant burden for families, caregivers, and the medical-economic system,<sup>3</sup> which can ultimately lead to dependency.<sup>4,5</sup>

Amongst the therapeutic strategies, transplantation of cultured mesenchymal stromal cells (MSCs) to recover optimal tissue structure/function relationship is a promising strategy for ARD therapy.<sup>6,7</sup> Based on grafted MSCs' pleiotropic trophic capacities driving, amongst others, antidysbiotic,<sup>8</sup> immunomodulation,<sup>9</sup> angiogenic support,<sup>10</sup> and antifibrotic effects,<sup>11</sup> these cells control the critical first steps of tissue repair required for regeneration.<sup>12</sup> These effects explain the popularity of the use of MSCs in many pathophysiologic contexts, in particular the use of allogeneic MSCs from adipose tissue (ASCs) in immunodysregulatory contexts.<sup>7,13</sup> To date, more than 300 clinical trials using MSCs are reported as completed in ClinicalTrials.gov, of which only about 20 are in phase III. The clinical use of MSCs still appears to be safe, with no association between MSC treatment and the development of acute toxicity, death, infection, organ systemic failure, or malignancy.<sup>14–16</sup> However, if intravascular/intravenous injection of MSCs seems safe and a therapeutic advantage for some diseases,<sup>17</sup> therapeutic utility may be limited due to insufficient homing to the target site.<sup>18</sup> For many ARD tissue defects, local administration of allogeneic MSCs is appropriate to support tissue repair by in situ paracrine factor delivery.<sup>18</sup> Moreover, tissue engineering investigations highlighted the importance of materials supporting 3D biomechanics in MSC proregenerative activities and to enhance retention and survival of MSC.<sup>18,19</sup> Indeed, MSC delivery in appropriate biomaterial carrier, such as platelet lysate hydrogel, has been reported to exert effects at several levels, including fibrin clot maintenance resulting from postsurgical coagulation, neovascularisation, immunomodulation, and the recruitment of the endogenous progenitors leading to tissue regeneration.<sup>20–23</sup> Such an association of a carrier hydrogel and ASCs is classified by the European Medicines Agency as a combined advanced therapeutic medical product.

Amongst ARDs, chronic periodontitis exerts a significant burden on our societies. Periodontitis, a tooth-supporting tissue (or periodontium, including gingiva) disease, results from a breakdown of the balance between the microbiota and the host, inducing an inadequate and exacerbated immune response along with the development of dysbiosis.<sup>24</sup> Disease extends as a vicious circle, with an extension of the inflammatory infiltrate from gingiva to deep periodontium (periodontal ligament, cementum together with bone resorption). With disease progression, destruction of deep periodontium leads to formation of complex 3D morphology lesions—called periodontal pockets—and results in irreversible defects.<sup>25</sup> Age acts as a risk indicator of periodontitis, accounting for a substantial part of the variance of periodontitis in the population.<sup>26</sup> Without appropriate and effective management, periodontitis leads to tooth loss, which confers a significant impact on quality of

life. The latest epidemiologic data reported chronic periodontitis prevalence to be around 50% of adults older than 45 years.<sup>27</sup> Periodontitis can also affect systemic health, further increasing all health costs.<sup>28</sup> Unfortunately, despite clinical results, current therapies fail to sustainably restore periodontal tissue homeostasis and regeneration.

However, use of allogeneic ASCs surgically delivered in a suitable vehicle, including blood plasma derivatives, inside diseased deep periodontium seems to be a promising periodontitis therapy.<sup>29</sup> While it is undeniable that regulatory authorities do everything possible to ensure the safety of cell therapy products, it is fundamental to anticipate patients' expectations, sources of information, and fears, especially in a context of mistrust towards new therapies. Studies have suggested that some patients may be misinformed about the science, safety, and efficacy of stem cell therapy.<sup>30–32</sup> The perception of health treatment is a complex and personal phenomenon, and traditional quantitative tools—such as questionnaires—are not sufficiently personalised, especially in the case of new therapies. Qualitative studies are thus essential and suitable methodologies to understand patterns of health behaviours, describe illness experiences, and design health interventions in a humanistic and person-centred way.<sup>33</sup> These approaches often require a small number of participants because the objective is not to quantify but to understand the diversity of themes. The inclusion of participants is stopped when thematic saturation is reached, that is, when no more new themes emerge. Nevertheless, these approaches are lacking in the field of cell therapy.<sup>34</sup>

The objective of this work is to consider the general public's acceptance of tissue engineering procedures using allogeneic MSCs derived from adipose tissue via qualitative analysis.

## Methods

### Research design

A descriptive qualitative research design was followed based on semi-structured interviews. Qualitative methodologies are particularly suited for exploring opinions, habits, or beliefs.<sup>35,36</sup> The questions are open-ended to give participants more freedom to express their ideas and thus to address points that may not have been anticipated by the investigator.<sup>37</sup> The use of semi-structured interviews for data collection leads to the development of knowledge, allowing for an interpretative approach. This approach emerges in constructivist paradigms because it proposes to study socially constructed realities.<sup>38</sup>

### Sampling strategy

Participants whose characteristics were most similar to those who will benefit from the periodontal regenerative procedures being studied were selected/included. Considering that these procedures will be reserved for hospital settings, recruitment was carried out in the Oral Medicine Department of the University Hospital of Toulouse, Toulouse, France. Lesions must be severe and refractory to conventional therapies. Participants should have already benefitted from an initial periodontal therapy and have residual periodontal

lesions (periodontal pocket depth of  $\geq 6$  mm with bleeding on probing) on at least 2 different teeth. Recruitment for new interviews was stopped when data saturation ("the point at which additional data does not improve understanding of the phenomenon under study"<sup>39</sup>) was reached; that is, no new themes emerged during the interviews.

### Data collection

Two experienced interviewers collected data between March and June 2021 through *in-depth*, semi-structured interviews. The interviews lasted between 10 and 20 minutes each and were digitally recorded and later transcribed.

Researchers used an interview guide previously developed with the help of a panel of 7 experts in the fields of periodontal regeneration, cell therapy and tissue engineering, cancer, or cell metabolism, comprising both public and private actors. The interview guide therefore addresses the following concepts: (1) new treatments in the context of therapeutic impasses, (2) the notion of stem/stromal cells, (3) the stem cells' origin (adipose tissue) and donor (allogeneic/autologous), (4) the administration of the therapeutic product (local graft and biomaterial of biological origin), and (5) the notion of therapeutic cost. According to a deductive methodology, questions were formulated to allow exploration of unanticipated but relevant emerging topics. Data obtained in this research will be shared on reasonable request to the corresponding author.

### Data analysis

Thematic analysis has been carried out for identifying, analysing, and reporting patterns (themes) within data.<sup>40</sup> The analysis was carried out following these steps:

1. Debriefing and writing reports of the interviews.
2. Transcribing interviews.
3. Coding data with the NVivo 12 software (QSR International, Massachusetts, USA) and data aggregation affiliated with the same code.
4. Clustering the different codes into general themes.
5. Delineating the themes (modifications, mergers, and/or deletions).
6. Illustrating the themes with data citations.
7. Reporting, interpreting, and discussing the analysis.
8. Submitting the results to some of the participants so they could compare and contrast these with their own experiences and look for similarities and consistencies. Other investigators verified the report and the external validity of the results analysis.<sup>39</sup>

### Ethical concerns

The interviews did not expose patients to any stressful situations, interventions, or risks. All patients provided consent to reproduce the quotations in extenso; the codes were then consolidated into different themes. The study was conducted according to the guidelines of the Declaration of Helsinki. The study is covered by the reference methodology defined by the French National Commission for Informatics and Liberties

(CNIL). Toulouse University Hospital signed a commitment of compliance to the reference methodology MR-004 of the CNIL (number: 2206723 v0). This study adheres to the Standards for Reporting Qualitative Research.

## Results and discussion

As previously mentioned, 11 interviews (with 4 men and 7 women, of different socioeconomic levels, aged between 38 and 71 years) were required to reach thematic saturation. Analysis allowed 4 main themes to emerge: (1) the perception of new treatments, science, and caregivers; (2) the conditions that the treatment must meet; (3) the participant (ie, pt) perception of the disease; and (4) the factors related to the content of the treatment. All themes and subthemes are summarised in the [Figure](#), which is inspired by Aiyegbusi et al.<sup>34</sup> As the term MSC therapy was not known by the participants, the term "adult stem cell therapy" was used during the interviews. Excerpts from the interviews are presented in the [Table](#).

### Theme 1: the perception of new treatments, science, and caregivers

The acceptability of a new treatment will depend on the patient's view of the medical community and research in general. Some will be rather wary of novelty (pt8: "I don't want to be a guinea pig," pt5: "just don't want to be the first one tested"), whilst others will see it as an opportunity to contribute to scientific progress (pt10: "I told myself that I can make things progress," pt7: "medicine advances and we have to take everything that there is, that's how we progress"). Acceptance also depends on the relationship the patient has with their health care team and the trust they have in them. Participant 1 would be willing to try this treatment if an office dentist offered it to him, but not in a hospital setting, expressing a loss of confidence in the medical team. This lack of confidence in both medical innovation and caregivers may be linked to the various previous public health crises, from the thalidomide tragedy to contaminated blood or vaccines,<sup>41–43</sup> which may carry a heavy weight in decision-making. Fear may be further reinforced with the use of blood derivatives for cell culture or as a carrier biomaterial. The latter, is often a pooled products to minimise interdonor variability.<sup>44</sup> Improving awareness amongst the general public, as well as amongst health care professionals, of new therapeutic approaches and implementing communication tools for the general public regarding innovative therapies may lead to increased social acceptance.

The general public's concerns regarding scientific rigour should be considered when communicating to the patient that multiple clinical trials throughout the world have already proven the safety of MSCs in humans, whether by systemic injection<sup>16,45</sup> or by local delivery.<sup>46</sup>

### Theme 2: The conditions that the treatment must meet

#### The need for results

One idea that came emerged from these interviews was the need to experience results: "I am receptive to it as soon as it

#### 4 – Factors related to the content of the treatment

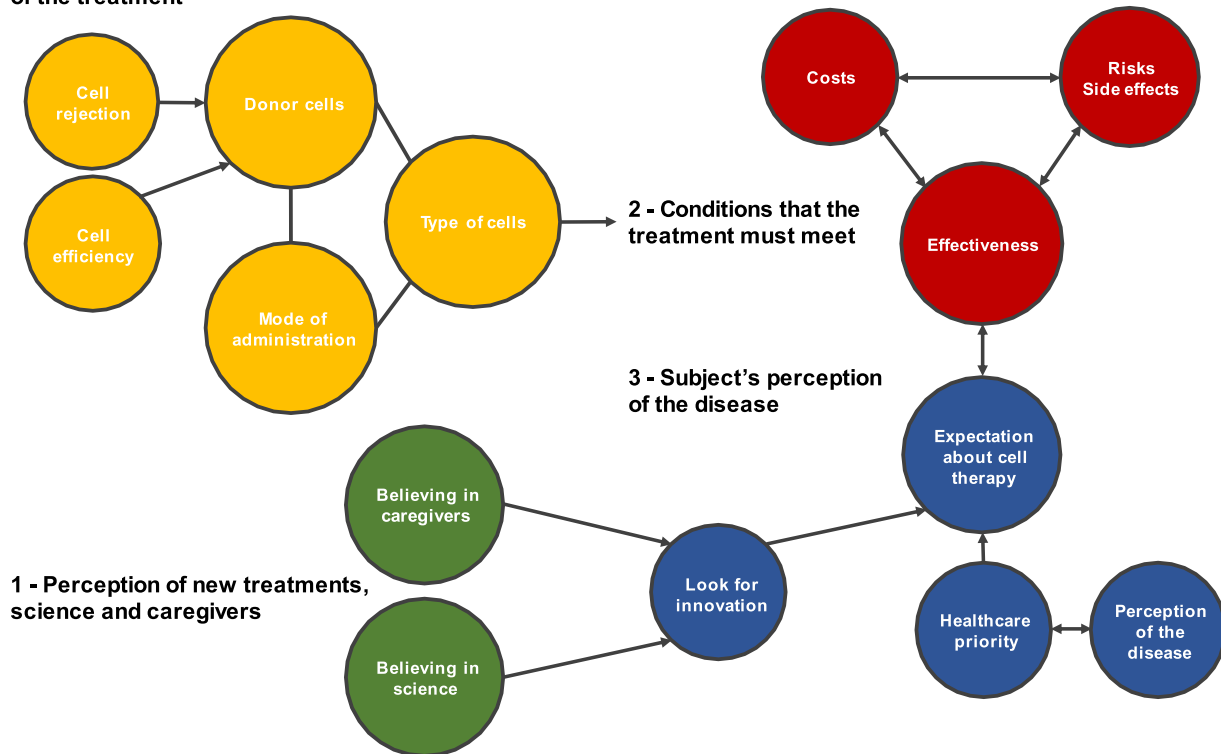


Fig – Themes and subthemes that emerged during the interviews.

heals me” (pt8) or “I am interested in its effectiveness” (pt11). Nevertheless, some patients specified that they wanted to know all the risks and side effects before accepting a treatment, like pt2: “I should have all the necessary information, both good and bad, and so I can summarise it.”

#### Cost and effectiveness

The price, and more particularly the cost/effectiveness ratio, is also necessarily important in the decision (pt8: “It depends on the price, I don’t want to pay a fortune”).

Cell therapies are amongst the most expensive therapies available, and health care systems are not yet prepared to assume the cost of the development of those therapies.<sup>47</sup> It is also necessary to fight against misinformation and unproven stem cell-based interventions.<sup>32</sup> On the one hand, many developments are necessary throughout the production process to achieve scale economies.<sup>48</sup> Allogeneic therapy seems to be the most cost-effective method, by optimising the production process (bioreactor, culture medium),<sup>48,49</sup> allowing standardisation of the product. Unlike with other body areas such as the brain,<sup>50</sup> patients in this periodontitis research did not appear to be worried about potential side effects of the treatment; they just wanted to be properly informed about the benefit/risk ratio.

The development of potency assays and retrospective analysis of multidimensional clinical trial data using artificial intelligence would also allow selection of the most efficient cell batches for a given patient and disease, thus increasing the cost/efficiency ratio.<sup>9,51</sup> On the other hand, given their

high prevalence and systemic health and quality-of-life impacts amongst ageing populations, periodontal diseases weigh heavily in direct and indirect health costs. For example, related expenditures almost doubled in the United States from 1997 to 2006 (\$81 billion in 2006), which is higher than for heart diseases or cancer.<sup>52</sup> A study performed in the United Kingdom demonstrated that for each tooth preserved an additional year, and each millimeter of attachment loss avoided, the incremental cost-effectiveness ratios were of 217€ and 1130€, respectively.<sup>52</sup> Thus, future medicoeconomic studies will have to take into account both the direct and indirect costs of periodontitis in comparing them with the costs of cell therapy, which are expected to decrease.

#### Theme 3: patient perception of the disease

##### Awareness of the personal and collective impact of periodontitis

Acceptance of new treatments depends on patients’ perception of their disease. Some participants are not waiting for new therapies. They may not consider themselves to be disabled by the disease or find that their condition does not justify the use of such a treatment (pt3: “I think it is a lot for the teeth, this is my questioning,” pt5: “I would have cancer, I might not have the choice,” and pt8: “If it is to save a life, we are always tolerant, we should not ask ourselves the question. But if it’s just for personal pleasure, stem cells from a person, that bothers me”).

On the other hand, others are looking for innovations (pt6: “I could try it, it’s very important for the teeth” or pt9: “there

**Table – Excerpts of interviews of the 11 participants (pt1 to pt11).**

Subtheme	Excerpts
<b>1. Perception of new treatments, science, and caregivers</b>	
<i>Fear</i>	<p>"I'll wait to see if it works on other people" (pt5)</p> <p>"I just don't want to be the first one tested" (pt5)</p> <p>"There is always the risk of something unexpected" (pt7)</p> <p>"Tomorrow it exists and we want to try it, I say no" (pt8)</p> <p>"I don't want to be a guinea pig" (pt8)</p>
<i>Confidence</i>	<p>"It doesn't scare me at all, it's a progress" (pt2)</p> <p>"I even think it's a good idea" (pt3)</p> <p>"I got the vaccine so you know" (pt6)</p> <p>"If we ask ourselves too many questions, we don't take care of anything anymore" (pt7)</p> <p>"I got the vaccine by the way" (pt7)</p>
<i>Want to advance the science</i>	<p>"We must advance science" (pt2)</p> <p>"I am for science, I am open to everything" (pt1)</p> <p>"Medicine advances and we have to take everything that there is, that's how we progress" (pt7)</p> <p>"I am for the progress of medicine" (pt7)</p> <p>"I believe in science" (pt9)</p> <p>"I told myself that I can make things progress" (pt10)</p> <p>"My ophthalmologist, every time I see him, I tell him when you have a new thing, you call me" (pt11)</p> <p>"You have to move forward more quickly" (pt11)</p>
<b>2. The conditions that the treatment must meet</b>	
<i>Effectiveness of the therapy</i>	<p>"If it's this or lose your teeth, okay" (pt3)</p> <p>"As long as I am treated, I am open to it" (pt4)</p> <p>"I accept if it is really effective I will not take it immediately, it must prove itself" (pt5)</p> <p>"If it is effective, I am for it" (pt6)</p> <p>"If it can stop everything and allow me to keep my teeth, I will do it" (pt7)</p> <p>"I am receptive to it as soon as it heals me" (pt8)</p> <p>"If it can allow me to keep my teeth for a while, I don't mind going for an appointment. If it's to keep them for 6 months and come every week, that's a shame" (pt8)</p> <p>"As long as it works" (pt9)</p> <p>"I am interested in its effectiveness" (pt11)</p>
<i>Compatibility with other pathologies</i>	<p>"I would report my stroke issues and my Previscan dosages and if all is compatible I would agree to do so" (pt2)</p>
<i>Cost</i>	<p>"It depends on the price, I don't want to pay a fortune" (pt8)</p> <p>"If you tell me 3,000 euros per cell dose, I won't do it. It depends on the price" (pt8)</p>
<i>Detailed information</i>	<p>"I should have all the necessary information, both good and bad, and so I can summarise it" (pt2)</p> <p>"It depends on the treatment, I will look at the side effects. Every treatment has side effects" (pt5)</p>
<b>3. The patient's perception of the disease</b>	
<i>Not being bothered by the disease or finding the treatment excessive regarding the disease</i>	<p>"If it's to save a life, we are always tolerant, we should not ask ourselves the question. But if it's just for personal pleasure, stem cells that come from a person, that bothers me" (pt1)</p> <p>"I think it is a lot for the teeth, this is my questioning" (pt3)</p> <p>"I would have cancer, I might not have the choice. When I see some treatments and their side effects, it's scary" (pt5)</p>
<i>Suffering from the disease or not finding the treatment excessive regarding the disease</i>	<p>"It's not a luxury, it's really necessary. I suffer from it, sincerely" (pt1)</p> <p>"I'll be willing to do it because I'll get out of this mess" (pt2)</p> <p>"I've been getting treatment for 10 years, I don't want to lose my teeth" (pt5)</p> <p>"I could try it, it's very important for the teeth" (pt6)</p> <p>"I would like to be at ease, really, because I am stressed every morning" (pt8)</p> <p>"If it can help us to progress and help with this disease which is really painful and long" (pt8)</p> <p>"There must be something to progress" (pt9)</p>
<i>To want to keep or not to keep teeth</i>	<p>"I would like to feel comfortable because I am stressed every morning" (pt10)</p> <p>"I prefer that to implants that will cost me I don't know how much" (pt5)</p> <p>"I've come to terms with the idea of the removable prosthesis. I am 48 years old, what is the point of going for a bone graft to gain 5 years with teeth but finally pull everything out? If I am told, either we do a graft for a life-span of 10 years, or we give up, well, I prefer to wait and replace by a prosthesis the day I will have nothing left" (pt8)</p> <p>"For the same fee, if I had the choice between trying to save my molar or removing it and putting an implant and a crown on it, I would definitely want to save it" (pt9)</p> <p>"I could not bear to lose my teeth" (pt10)</p>

(continued)



**Table. (Continued)**

Subtheme	Excerpts
<b>4. Factors related to the content of the treatment</b>	
<i>Stem cells: does not disturb</i>	“The fact that there is something alive doesn’t bother me, it is part of us” (pt3) “Cells don’t bother me, on the contrary” (pt10)
<i>Stem cells: drawing a parallel between cell donation and organ donation</i>	“If you have to donate or accept to receive a kidney, in theory, if you are able to give, you are able to receive” (pt2) “Let’s say organ donation, I’m for it, so I think there’s no reason to be against it too” (pt8) “I am in favour of organ donation” (pt9) “I would be happy if they gave me cells or a heart, I am in favour of donation” (pt11)
<i>Donor: does not disturb</i>	“No, I don’t mind, it’s like when you give blood, actually, I don’t mind” (pt6) “No, I don’t mind it coming from someone else” (pt7) “Tomorrow they tell me they are going to take out your eye and implant a new one that works. I won’t say no because it belonged to someone else. I’m not stuck on something like that” (pt11)
<i>Donor: fear</i>	“The fact that it comes from a donor, I don’t know psychologically, it bothers me a little” (pt1) “It’s the fact of receiving something from another person” (pt1) “Personally I would have preferred it to be of animal origin” (pt1) “Is there a compatibility problem?” (pt7) “It’s not even the side effects, but the fact that you gave me a disease that I didn’t have” (pt8) “I would be afraid that the donor would have a disease and that he would transmit it to me” (pt10)
<i>Donor: finding it more relevant to use donor cells</i>	“Well, I’m old, I have an autoimmune disease, well there are a lot of things that make me not have absolute confidence in my cells” (pt3) “If I have this disease it’s because my own cells are not very efficient” (pt9) “If my cells are not correct” (pt9) “If I have to go with an almost new tire, it’s better than an almost retread” (pt11)
<i>Donor: prefer own cells</i>	“I tell myself that with fat I would have less chance of catching something than with blood because it is in the blood that infections circulate” (pt8) “It’s always better if you can repair your body with your own elements” (pt11)
<i>Way of delivering: acceptable in the mouth</i>	“Isn’t it more effective if it’s administered directly into the gum? It may have an immediate effect” (pt1) “Directly on the spot it seems more logical to me” (pt2) “I would find it more logical to go directly to the gum” (pt3) “Directly on the problem, it seems to me faster, it acts immediately” (pt7)
<i>Way of delivering: prefer a systemic administration</i>	“Well, considering my dental problems, it might be better in the blood” (pt6) “In the blood, perhaps it allows to regenerate more things” (pt11) “I have never thought about taking my own cells to repair my eyes, for example. In the blood, I think it could be more generalised” (pt11)

must be something to progress”). Patients referred to the disability that their periodontitis generates in their daily life, for example, pt10: “I would like to feel comfortable because I am stressed every morning” and pt1: “I suffer from it, sincerely.”

#### Health care priority

Some participants may be confused by the fact that they are being offered cell therapy for their teeth but not for a “more serious” disease they may be experiencing. This was the case for pt3, who had nuclear scleroderma, and pt11, who was diabetic and visually impaired and who mentioned MSCs more for their general effects than for their effects on his teeth: “I have never thought about taking my own cells to repair my eyes, for example. In the blood, I think that it could be more generalised.”

#### Expectations about therapy

Acceptance also depends on the desired degree of efficacy. Some participants were resigned to the idea of losing their teeth (pt8: “I’ve come to terms with the idea of the removable prosthesis. I am 48 years old; what is the point of going for a

bone graft to gain 5 years with teeth but finally pull everything out? If I am told, either we do a graft for a life span of 10 years, or we give up, well, I prefer to wait and replace by a prosthesis the day I will have nothing left.”).

Periodontitis affects patients beyond the oral sphere; the main reasons for complaints are psychological discomfort, stress, problems in social relationships, difficulties in daily activities,<sup>53,54</sup> and a putative association with more than 57 systemic diseases.<sup>28</sup> Unfortunately, in its early phase, periodontitis is generally painless,<sup>55</sup> explaining the late entry into care with severe lesions and lower regeneration potential. This study comprised participants who were certainly eligible for this kind of cell therapy, as they had intraosseous defects and disease that was poorly responsive to the usual therapies, and most were referred by their private practitioners. Regardless of the therapeutic efficacy of the cell therapy per se, practitioners must be particularly aware of the quality of the health care relationship, which is a key area in the management of periodontitis. Indeed, the most common reason for patient noncompliance is loss of motivation and a feeling

of lack of importance of treatment. A variable that greatly influences satisfaction is the patient's understanding of their disease and treatment plan.<sup>56</sup> Patient understanding of cell therapy's mechanisms of action and advantages/disadvantages, alongside appropriate psychosocial support, is a key to therapeutic optimisation.

#### **Theme 4: factors related to the content of the treatment**

Finally, acceptance of the treatment will depend on its content and the way it is delivered.

##### *Type of cells*

Some participants had never heard about MSCs and referred to them as embryonic stem cells, cells from the umbilical cord of newborns, or xenogeneic cells. One participant also discussed cell therapy with his ophthalmologist for the treatment of visual impairment. Surprisingly, the ethical, social, and religious issues concerning cell therapy based on embryonic cells<sup>50</sup> were not mentioned by participants. The concern essentially stems from the notion of the cell donor.

##### *Allogeneic or autologous cells*

The presence of cells does not seem to generate fear in itself. But the fact that they come from a donor is more difficult to accept for some patients. When participants were asked whether they would prefer their own cells or those of a donor, some fears were expressed about allogeneic cells (pt1: "The fact that it comes from a donor, I don't know psychologically, it bothers me a little," "It's the fact of receiving something from another person. Why I can't explain it to myself?", pt10: "I would have feared that the donor had a disease and that he would transmit it to me").

Conversely, some participants think that donor cells would be more effective than their own cells (pt3: "Well, I'm old, I have an autoimmune disease, well, there are a lot of things that make me not have absolute confidence in my cells" or pt9: "If I have this disease, it's because my own cells are not very efficient"). Whether because of individual predisposition, age, or an oral manifestation of a systemic pathology, MSCs from patients with periodontitis may have impaired potential for regeneration.<sup>57–60</sup>

Although the notion of cell rejection was not mentioned as such, some participants compared the donation of cells with that of organs. It is then important to specify that although the cells will be recognised by the patient's immune system and will gradually disappear, there can be no rejection as in the case of an organ transplant.<sup>61</sup> This concern regarding rejection has also been observed for Parkinson disease.<sup>50</sup>

##### *Mode of administration*

Local administration of treatment on the lesions, that is, in the mouth, was unambiguous for many patients. A comparison with administration by blood transfusion was mentioned, however. Some participants think that treatment would be more effective if administered directly on the lesions (pt7: "Directly on the problem it seems to me faster it acts immediately"), whilst others would prefer a transfusion (pt11: "In the blood perhaps it allows to regenerate more things").

Interestingly, there were no additional considerations regarding either the source tissue (adipose tissue) or the proposed tissue-engineered biological vehicle (blood-derived product).

In the area of cell therapy, few studies captured patients' experience regarding these therapeutics.<sup>34</sup> However, a better understanding of patients' expectations, apprehensions, and experiences will help to anticipate and optimise therapeutic approaches and even to set up specific and adapted educational programmes.<sup>34,50</sup>

## **Conclusions**

Based on the results and inferences from this qualitative study, participants found use of cell therapy for periodontitis to be acceptable. If the efficacy of the treatment is expected, allogeneic cell composition and the presence of a blood-derived product will require discussion about what the treatment entails and how it is manufactured. The interviewed participants had advanced and refractory pathologies, with previous failure of nonsurgical treatment. It could therefore be interesting to carry out similar qualitative study amongst patients with less advanced lesions, possibly in private practices. Periodontitis can be considered both as a pathology in itself and also as a prototypical model of chronic inflammatory pathology that is multitissular, with hard and soft tissue lesions. This opens up new perspectives to consider the acceptability of cell therapy procedures based on tissue engineering (local delivery of cell therapy by an adapted carrier) for a range of chronic age-related pathologies.

In a patient-centred approach, the success of cell therapy will require a bilateral, informed decision, taking into account potential therapeutic effectiveness and the patient's expectations for regeneration. We have emphasised the importance of information given to the patient. The creation of information leaflets on cell therapy, taking into account the elements mentioned herein and validated by the scientific community and opinion leaders, will be necessary. A particular effort will have to be made in the formulation and aesthetics of these leaflets, with the help of humanities and social sciences to deliver a clear scientific message that is comprehensible and free of conflicts of interest.

## **Author contributions**

Lucas Riazuelo: collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript. Valérie Planat-Bénard: conception and design, data analysis and interpretation, manuscript writing, and final approval of manuscript. Alexia Vinel: provision of study material or patients, collection and/or assembly of data, and final approval of manuscript. Sara Laurencin: conception and design, data analysis and interpretation, and final approval of manuscript. Louis Casteilla: financial support, manuscript writing, and final approval of manuscript. Philippe Kémoun: conception and design, manuscript writing, and final approval of manuscript. Mathieu Marty: conception and design, provision of study material or patients,



manuscript writing, and final approval of manuscript. Paul Monsarrat: conception and design, data analysis and interpretation, manuscript writing, and final approval of manuscript. Mathieu Marty and Paul Monsarrat contributed equally to this work.

### Conflict of interest

None disclosed.

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### REFERENCES

- Carmona JJ, Michan S. *Biology of healthy aging and longevity. Rev Investig Clin Organo Hosp Enfermedades Nutr* 2016;68:7–16.
- Franceschi C, Garagnani P, Morsiani C, et al. The continuum of aging and age-related diseases: common mechanisms but different rates. *Front Med* 2018;5:61. doi: [10.3389/fmed.2018.00061](https://doi.org/10.3389/fmed.2018.00061).
- Beard JR, Officer A, de Carvalho IA, et al. The world report on ageing and health: a policy framework for healthy ageing. *Lancet Lond Engl* 2016;387:2145–54. doi: [10.1016/S0140-6736\(15\)00516-4](https://doi.org/10.1016/S0140-6736(15)00516-4).
- Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges. *Cell Stem Cell* 2015;17:11–22. doi: [10.1016/j.stem.2015.06.007](https://doi.org/10.1016/j.stem.2015.06.007).
- Sui BD, Hu CH, Zheng CX, Jin Y. Microenvironmental views on mesenchymal stem cell differentiation in aging. *J Dent Res* 2016;95:1333–40. doi: [10.1177/0022034516653589](https://doi.org/10.1177/0022034516653589).
- Hoang DM, Pham PT, Bach TQ, et al. Stem cell-based therapy for human diseases. *Signal Transduct Target Ther* 2022;7:1–41. doi: [10.1038/s41392-022-01134-4](https://doi.org/10.1038/s41392-022-01134-4).
- Monsarrat P, Vergnes J-N, Planat-Bénard V, et al. An innovative, comprehensive mapping and multiscale analysis of registered trials for stem cell-based regenerative medicine. *Stem Cells Transl Med* 2016;5:826–35. doi: [10.5966/sctm.2015-0329](https://doi.org/10.5966/sctm.2015-0329).
- Monsarrat P, Kémoun P, Casteilla L, Planat-Bénard V. Broad-spectrum antibacterial effects of human adipose-derived stromal cells. *Stem Cells Int* 2019;2019:5389629. doi: [10.1155/2019/5389629](https://doi.org/10.1155/2019/5389629).
- Planat-Bénard V, Varin A, Casteilla L. MSCs and inflammatory cells crosstalk in regenerative medicine: concerted actions for optimized resolution driven by energy metabolism. *Front Immunol* 2021;12:626755. doi: [10.3389/fimmu.2021.626755](https://doi.org/10.3389/fimmu.2021.626755).
- Bura A, Planat-Bénard V, Bourin P, et al. Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia. *Cytotherapy* 2014;16:245–57. doi: [10.1016/j.jcyt.2013.11.011](https://doi.org/10.1016/j.jcyt.2013.11.011).
- de Bonnecaze G, Chaput B, Woisard V, et al. Adipose stromal cells improve healing of vocal fold scar: morphological and functional evidences. *Laryngoscope* 2016;126:E278–85. doi: [10.1002/lary.25867](https://doi.org/10.1002/lary.25867).
- Bogdanowicz DR, Lu HH. Designing the stem cell microenvironment for guided connective tissue regeneration. *Ann N Y Acad Sci* 2017;1410:3–25. doi: [10.1111/nyas.13553](https://doi.org/10.1111/nyas.13553).
- Monsarrat P, Kémoun P, Vergnes J-N, Sensebe L, Casteilla L, Planat-Bénard V. Spatial and temporal structure of the clinical research based on mesenchymal stromal cells: a network analysis. *Cytotherapy* 2017;19(1) P47–60. doi: [10.1016/j.jcyt.2016.09.005](https://doi.org/10.1016/j.jcyt.2016.09.005).
- Lalu MM, McIntyre L, Pugliese C, et al. Safety of cell therapy with mesenchymal stromal cells (safecell): a systematic review and meta-analysis of clinical trials. *PLoS ONE* 2012;7:e47559. doi: [10.1371/journal.pone.0047559](https://doi.org/10.1371/journal.pone.0047559).
- Rozier P, Maria A, Goulabchand R, Jorgensen C, Guilpain P, Noël D. Mesenchymal stem cells in systemic sclerosis: allogenic or autologous approaches for therapeutic use? *Front Immunol* 2018;9:2938.
- Thompson M, Mei SHJ, Wolfe D, et al. Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: an updated systematic review and meta-analysis. *EclinicalMedicine* 2020;19:100249. doi: [10.1016/j.eclinm.2019.100249](https://doi.org/10.1016/j.eclinm.2019.100249).
- Wysoczynki M, Khan A, Bolli R. New paradigms in cell therapy. *Circ Res* 2018;123:138–58. doi: [10.1161/CIRCRESAHA.118.313251](https://doi.org/10.1161/CIRCRESAHA.118.313251).
- Levy O, Kuai R, Siren EMJ, et al. Shattering barriers toward clinically meaningful MSC therapies. *Sci Adv* 2020;6:eaba6884. doi: [10.1126/sciadv.aba6884](https://doi.org/10.1126/sciadv.aba6884).
- Facklam AL, Volpatti LR, Anderson DG. Biomaterials for personalized cell therapy. *Adv Mater Deerfield Beach Fla* 2020;32:e1902005. doi: [10.1002/adma.201902005](https://doi.org/10.1002/adma.201902005).
- Wikesjö UM, Selvig KA. Periodontal wound healing and regeneration. *Periodontol* 1999;19:21–39 2000.
- Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell* 2018;22:824–33. doi: [10.1016/j.stem.2018.05.004](https://doi.org/10.1016/j.stem.2018.05.004).
- Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. *Npj Regen Med* 2019;4:1–15. doi: [10.1038/s41536-019-0083-6](https://doi.org/10.1038/s41536-019-0083-6).
- Martin I, Galipeau J, Kessler C, Le Blanc K, Dazzi F. Challenges for mesenchymal stromal cell therapies. *Sci Transl Med* 2019;11:eaat2189. doi: [10.1126/scitranslmed.aat2189](https://doi.org/10.1126/scitranslmed.aat2189).
- Bartold PM, Van Dyke TE. Host modulation: controlling the inflammation to control the infection. *Periodontol* 2017;75:317–29 2000. doi: [10.1111/prd.12169](https://doi.org/10.1111/prd.12169).
- Bartold M, Ivanovski S. Stem cell applications in periodontal regeneration. *Dent Clin* 2022;66:53–74. doi: [10.1016/j.cden.2021.06.002](https://doi.org/10.1016/j.cden.2021.06.002).
- Billings M, Holtfreter B, Papapanou PN, Mitnik GL, Kocher T, Dye BA. Age-dependent distribution of periodontitis in two countries: findings from NHANES 2009 to 2014 and SHIP-TREND 2008 to 2012. *J Periodontol* 2018;89:S140–58. doi: [10.1002/JPER.17-0670](https://doi.org/10.1002/JPER.17-0670).
- Eke PI, Dye BA, Wei L, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J Periodontol* 2015;86:611–22. doi: [10.1902/jop.2015.140520](https://doi.org/10.1902/jop.2015.140520).
- Monsarrat P, Blaizot A, Kémoun P, et al. Clinical research activity in periodontal medicine: a systematic mapping of trial registers. *J Clin Periodontol* 2016;43:390–400. doi: [10.1111/jcpe.12534](https://doi.org/10.1111/jcpe.12534).
- Dubuc A, Planat-Bénard V, Marty M, Monsarrat P, Kémoun P. Periodontal cell therapy: a systematic review and meta-analysis. *Adv Exp Med Biol* 2022;1373:377–97. doi: [10.1007/978-3-030-96881-6\\_20](https://doi.org/10.1007/978-3-030-96881-6_20).
- Kingery MT, Schoof L, Strauss EJ, Bosco JA, Halbrecht J. Online direct-to-consumer advertising of stem cell therapy for musculoskeletal injury and disease: misinformation and violation

- of ethical and legal advertising parameters. *J Bone Joint Surg Am* 2020;102:2–9. doi: [10.2106/JBJS.19.00714](https://doi.org/10.2106/JBJS.19.00714).
31. Arthurs JR, Nordan LM, Hultgren BH, et al. Patients seeking stem cell therapies—a prospective qualitative analysis from a Regenerative Medicine Consult Service. *Npj Regen Med* 2022;7:1–6. doi: [10.1038/s41536-022-00215-w](https://doi.org/10.1038/s41536-022-00215-w).
  32. Zarzeczny A, Clark M. Unproven stem cell-based interventions & physicians' professional obligations; a qualitative study with medical regulatory authorities in Canada. *BMC Med Ethics* 2014;15:75. doi: [10.1186/1472-6939-15-75](https://doi.org/10.1186/1472-6939-15-75).
  33. Renjith V, Yesodharan R, Noronha JA, Ladd E, George A. Qualitative methods in health care research. *Int J Prev Med* 2021;12:20. doi: [10.4103/ijpvm.IJPVM\\_321\\_19](https://doi.org/10.4103/ijpvm.IJPVM_321_19).
  34. Aiyegbusi OL, Macpherson K, Elston L, et al. Patient and public perspectives on cell and gene therapies: a systematic review. *Nat Commun* 2020;11:6265. doi: [10.1038/s41467-020-20096-1](https://doi.org/10.1038/s41467-020-20096-1).
  35. Bower E, Scambler S. The contributions of qualitative research towards dental public health practice. *Community Dent Oral Epidemiol* 2007;35:161–9. doi: [10.1111/j.1600-0528.2006.00368.x](https://doi.org/10.1111/j.1600-0528.2006.00368.x).
  36. Lesaffre E. *Statistical and methodological aspects of oral health research*. John Wiley & Sons; 2009.
  37. Chai HH, Gao SS, Chen KJ, Duangthip D, Lo ECM, Chu CH. A concise review on qualitative research in dentistry. *Int J Environ Res Public Health* 2021;18:942. doi: [10.3390/ijerph18030942](https://doi.org/10.3390/ijerph18030942).
  38. Lincoln Y S. In search of students' voices. *Theor Pract* 1995;34(2):88–93. doi: [10.1080/00405849509543664](https://doi.org/10.1080/00405849509543664).
  39. Bedos C, Pluye P, Loinçon C, Levine A. Qualitative research. Lesaffre E, Feine J, Leroux B, Declerck D, editors. *Qualitative research. Statistical and methodological aspects of oral health research* 2009:113–30. doi: [10.1002/9780470744116.ch8](https://doi.org/10.1002/9780470744116.ch8).
  40. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101. doi: [10.1191/1478088706qp063oa](https://doi.org/10.1191/1478088706qp063oa).
  41. Jacobs JW, Bibb LA, Savani BN, Booth GS. Refusing blood transfusions from COVID-19-vaccinated donors: are we repeating history? *Br J Haematol* 2022;196:585–8. doi: [10.1111/bjh.17842](https://doi.org/10.1111/bjh.17842).
  42. Brazier M, Cave E. *Medical products liability*. Manchester University Press; 2020.
  43. Kazarian M. Who should we blame for healthcare failings? Lessons from the French tainted blood scandal. *Med Law Rev* 2019;27:390–405. doi: [10.1093/medlaw/fwz004](https://doi.org/10.1093/medlaw/fwz004).
  44. Viau S, Lagrange A, Chabrand L, et al. A highly standardized and characterized human platelet lysate for efficient and reproducible expansion of human bone marrow mesenchymal stromal cells. *Cytotherapy* 2019;21:738–54. doi: [10.1016/j.jcyt.2019.04.053](https://doi.org/10.1016/j.jcyt.2019.04.053).
  45. Rodríguez-Fuentes DE, Fernández-Garza LE, Samia-Meza JA, Barrera-Barrera SA, Caplan AI, Barrera-Saldaña HA. Mesenchymal stem cells current clinical applications: a systematic review. *Arch Med Res* 2021;52:93–101. doi: [10.1016/j.arcmed.2020.08.006](https://doi.org/10.1016/j.arcmed.2020.08.006).
  46. Ciccocioppo R, Klersy C, Leffler DA, Rogers R, Bennett D, Corazza GR. Systematic review with meta-analysis: safety and efficacy of local injections of mesenchymal stem cells in perianal fistulas. *JGH Open* 2019;3:249–60. doi: [10.1002/jgh3.12141](https://doi.org/10.1002/jgh3.12141).
  47. Shukla V, Seoane-Vazquez E, Fawaz S, Brown L, Rodriguez-Monguio R. The landscape of cellular and gene therapy products: authorization, discontinuations, and cost. *Hum Gene Ther Clin Dev* 2019;30:102–13. doi: [10.1089/humc.2018.201](https://doi.org/10.1089/humc.2018.201).
  48. Jossen V, van den Bos C, Eibl R, Eibl D. Manufacturing human mesenchymal stem cells at clinical scale: process and regulatory challenges. *Appl Microbiol Biotechnol* 2018;102:3981–94. doi: [10.1007/s00253-018-8912-x](https://doi.org/10.1007/s00253-018-8912-x).
  49. Robb KP, Fitzgerald JC, Barry F, Viswanathan S. Mesenchymal stromal cell therapy: progress in manufacturing and assessments of potency. *Cytotherapy* 2019;21:289–306. doi: [10.1016/j.jcyt.2018.10.014](https://doi.org/10.1016/j.jcyt.2018.10.014).
  50. Drevin J, Nyholm D, Widner H, et al. Patients' views on using human embryonic stem cells to treat Parkinson's disease: an interview study. *BMC Med Ethics* 2022;23:102. doi: [10.1186/s12910-022-00840-6](https://doi.org/10.1186/s12910-022-00840-6).
  51. Liu YYF, Lu Y, Oh S, Conduit GJ. Machine learning to predict mesenchymal stem cell efficacy for cartilage repair. *PLOS Comput Biol* 2020;16:e1008275. doi: [10.1371/journal.pcbi.1008275](https://doi.org/10.1371/journal.pcbi.1008275).
  52. Beikler T, Flemmig TF. Oral biofilm-associated diseases: trends and implications for quality of life, systemic health and expenditures. *Periodontol* 2011;55:87–103 2000. doi: [10.1111/j.1600-0757.2010.00360.x](https://doi.org/10.1111/j.1600-0757.2010.00360.x).
  53. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: a call for global action. *J Clin Periodontol* 2017;44:456–62. doi: [10.1111/jcpe.12732](https://doi.org/10.1111/jcpe.12732).
  54. Rawlinson A, Vettore MV, Baker SR, Robinson PG. Periodontal treatment, psychological factors and oral health-related quality of life. *J Clin Periodontol* 2021;48:226–36. doi: [10.1111/jcpe.13405](https://doi.org/10.1111/jcpe.13405).
  55. Lundy FT, Linden GJ. Neuropeptides and neurogenic mechanisms in oral and periodontal inflammation. *Crit Rev Oral Biol Med Off Publ Am Assoc Oral Biol* 2004;15:82–98. doi: [10.1177/154411130401500203](https://doi.org/10.1177/154411130401500203).
  56. Shah R, Thomas R, Bhandari S, Mehta DS. Influence of various factors on patient compliance after periodontal therapy: a pilot study. *J Indian Soc Periodontol* 2017;21:50–4. doi: [10.4103/jisp.jisp\\_254\\_16](https://doi.org/10.4103/jisp.jisp_254_16).
  57. Fafián-Labora JA, Morente-López M, Arufe MC. Effect of aging on behaviour of mesenchymal stem cells. *World J Stem Cells* 2019;11:337–46. doi: [10.4252/wjsc.v11.i6.337](https://doi.org/10.4252/wjsc.v11.i6.337).
  58. Xu J, Zuo C. The fate status of stem cells in diabetes and its role in the occurrence of diabetic complications. *Front Mol Biosci* 2021;8:745035. doi: [10.3389/fmolb.2021.745035](https://doi.org/10.3389/fmolb.2021.745035).
  59. Nguyen LT, Hoang DM, Nguyen KT, et al. Type 2 diabetes mellitus duration and obesity alter the efficacy of autologously transplanted bone marrow-derived mesenchymal stem/stromal cells. *Stem Cells Translational Medicine* 2021;10:1266–78. doi: [10.1002/sctm.20-0506](https://doi.org/10.1002/sctm.20-0506).
  60. Qi Y, Ma J, Li S, Liu W. Applicability of adipose-derived mesenchymal stem cells in treatment of patients with type 2 diabetes. *Stem Cell Res Ther* 2019;10:274. doi: [10.1186/s13287-019-1362-2](https://doi.org/10.1186/s13287-019-1362-2).
  61. Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. *Nat Biotechnol* 2014;32:252–60. doi: [10.1038/nbt.2816](https://doi.org/10.1038/nbt.2816).