

## Response to Reviewer 1 Comments

All response for reviewer are highlighted in yellow.

Reviewer Comments: “Specific Comments to Authors: The review on empty nose syndrome is well conducted and set up. The observations on the use of MSCs and NCSCs are very thorough and updated. On pag 6 the Authors say "Insert clinical data about adipose tissue derived graft application": I believe that some clinical aspects relating to the use of adipose tissue in this contest should be included which due to an oversight has not been added; I thinkl the Authors need to review this part of their work”

Thank you! Changes made to the text:

“Adipose tissue derived extracellular matrix and methylcellulose hydrogels are new alternative biomaterials that could be potently used for the inferior turbinate reconsctruction. Strong limitation of fat transplantation despite of excellent biocompatibility is its high resorption up to 90% during 5 month <sup>[33]</sup>. Decellularized adipose derived extracellular matrix (ECM) is a new alternative to fat transplantation. It was shown that combination of ECM and methylcellulose hydrogels are promising material for injection laryngoplasty for stable vocal fold augmentation. ECM/MC hydrogel did not cause inflammation or fibrosis in injection site, but number of collagen fibers and fatty granules increased <sup>[34]</sup>. Other study demonstrated that ECM/MC hydrogels are excellent scaffold for injectable stem cell delivery. Transplantation of ADSCs in ECM/MC hydrogels in cutaneous would led to rapid re-epithelialization, neovasculation and minimal scar formation <sup>[35]</sup>. The main advantages of ECM/MC hydrogel composition are high biocompatibility, thermosensitivity that allow to inject material with minimal traumatization for patients, stability and possibility to combine with stem cells.”

Thank you for your review!

Sincerely authors!

## Response to Reviewer 2 Comments

All response for reviewer are highlighted in yellow.

Reviewer Comments: “Specific Comments to Authors: The manuscript “EMPTY NOSE SYNDROME PATHOGENESIS AND CELL-BASED BIOTECHNOLOGY PRODUCTS AS A NEW OPTION FOR TREATMENT” introduces empty nose syndrome (pathogenesis, symptomatology, comorbid psychiatric disorders) and the perspective of stem-cell-based technologies in ENS management. 1, The main body of this review is about the regenerative medicine and biotechnology contributes to the development of new cell-based products in combination with various materials. However, the related details are not included in Abstract and Core tips with a proper volume. The abstract should be re-constructed. 2, Regarding the perspective of stem-cell-based therapy, the authors introduce the underlying molecular mechanisms. I suggest the authors provide one Figure to describe the mechanisms for better reading and understanding.”

Thank you! We tried to make changes regarding all comments!

1. Changes made to the text of Abstract:

Empty nose syndrome (ENS) is a rare complication that develops after partial or complete turbinectomy. The main feature of ENS is paradoxical nasal obstruction feeling despite objectively wide nasal airway. ENS pathogenesis is multifactorial and includes changes in laminar physiological airflow, disruption of mucosa functions and deficient neural sensation. This leads to the development of ENS symptomatology such as dyspnea, nasal dryness, nasal burning, nasal obstruction, feeling of suffocation and even comorbid psychiatric disorders that significantly impairs life quality. Specific effective treatment of ENS does not exist up to date. In this review we outline existing biomaterial for surgical reconstitution of nasal anatomy and discuss the perspective of stem-cell-based technologies in ENS management. The main focus is directed to justification of rationality application of adult mesenchymal stem cells (MSCs) of different tissues origin and neural crest-derived stem cells (NCSCs) based on their intrinsic biological properties. MSCs transplantation may stimulates mucosa tissue regeneration via trophic factors secretion, direct reprogramming in epithelial cells and pronounced immunosuppressive effect. From the other hand, NCSCs based on their high neuroprotective properties may reconstitute nerve structure and functioning leading to normal sensation in ENS patients. We postulate that application of cell-based and tissue-engineered product can help to significantly improve ENS symptomatology only as complex approach aimed at reconstitution of nasal anatomy, recovery the nasal mucosa functionality and neural tissue sensation.”

2. Figure 3 with describe the mechanisms was added: “**Fig. 3. Realization of stem cells therapeutic potential in management of ENS. (Possible mechanisms).** The therapeutic effect of stem cell transplantation could be realized by two main ways. The first one is direct differentiation of transplanted stem cells under the impact of specific environmental factors, such as hypoxia and inflammation. MSCs have the ability to transdifferentiate in mucosa epithelial cells, while NCSCs can form peripheral neurons. However, very small amount, around 1-3%, of transplanted stem cells can differentiate. The 95% of stem cells therapeutic potential are implemented in indirect way via secreting plethora of paracrine factors and extracellular vesicles. MSCs-derived secretory factors promote neovascularization, immunomodulatory anti-inflammatory effect, anti-apoptotic and anti-fibrotic effect, and reduce oxidative stress that create favorable environment for mucosa regeneration. NCSCs, in particular, have strong neuroprotective properties, thus local NCSCs injection in ENS patients could also stimulate nerve recovery by trophic support or direct reintegration in damaged tissue.”

Thank you for your review!

Sincerely authors!