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The Potential Ameliorating Effect of Bone Marrow Derived Mesenchymal Stem Cells on the Tongue Papillae of Rats with Experimentally Induced Hypothyroidism

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ABSTRACT

Purpose: This study aimed to evaluate the potential ameliorating effect of bone marrow derived mesenchymal stem cells (BM-MSCs) on tongue papillae of rats with experimentally induced hypothyroidism using environmental scanning electron microscope (ESEM) and fluorescent microscopic evaluation.

Material and Methods: For this study 30 adult male albino rats were divided into three groups (ten rats each): (1) Control group: The rats allowed to access freely balanced diet and freshwater supply during the course of the experimental period (8 weeks). (2) Hypothyroidism group: To induce hypothyroidism the rats received carbimazole dissolved in distilled water (5 mg/250g body weight/day) for 35 days. (3) BM-MSC treated group: The rats received carbimazole for 35 days and after confirmation of hypothyroidism the rats received a single intravenous injection of BM-MSCs (1× 106 cells) via tail vein. At the end of the experiment, all rats were sacrificed; tongue was dissected and prepared for fluorescent and scanning electron microscopic evaluation.

Results: Tongue papillae of hypothyroidism group showed marked morphological alterations, unusual variable orientation, loss of the regular hornified keratin coverage and atrophied papillae with apparent wide inter-papillary regions and atrophy of gustatory pits. The tongue papillae in BM-MSCs treated group revealed apparent improvement in their architecture.

Conclusion: Hypothyroidism has degenerative effects on tongue papillae. BM-MSCs administration reduces the damaging effects of hypothyroidism on the papillae.

1. INTRODUCTION

Thyroid disorder is the second most common glandular disorder of the endocrine system which may affect any system in the body [1,2]. Hypothyroidism is the most common thyroid disorder in which synthesis of thyroid hormones decrease below the normal level. It may result from dysfunction in thyroid gland itself, from impairment in the mechanisms that control the development of thyroid hormones, or can occur as a result of complications during the treatment of hyperthyroidism [3]. Macroglossia, dysgeusia, delayed wound healing, altered tooth morphology and delayed eruption of teeth are the most common oral findings in hypothyroidism [1].

Carbimazole is an anti-thyroid drug used to prevent thyroid hormone synthesis and is described medically to treat hyperthyroidism. Yet, when it is prescribed in continuous dosage, it can block thyroid hormone synthesis and produce hypothyroidism [4]. Several studies reported that drugs that induce hypothyroidism can cause marked cellular damage in several tissues including; salivary gland tissues, liver, lung, kidney, pancreatic and gastric mucosal tissues [5-7].

Regenerative medicine is a research field that deals with replacing and regenerating cells, tissues and organs to re-establish normal function[8]. Stem cells have an important role in regenerative medicine for their self-renewal capability and because of their differentiation potentiality. Mesenchymal stem cells (MSCs) are the most favourable resource for the cell-based therapy of inflammatory and degenerative diseases due to their immuno-modulatory properties, multi-lineage differentiation potential and pro-angiogenic characteristics. Furthermore, they have the capacity to home into damaged tissue and act as a reservoir of growth factors and regenerative molecules [9,10].

Among the MSCs, BM-MSCs are the foremost readily available source of stem cells because they are easy to harvest, they are able to home into specific tissues, and they can differentiate into mesodermal, ectodermal and endodermal cells. Additionally, they have the ability to stimulate a local repair response [11, 12].

From the fore mentioned; this research aimed to evaluate the effect of experimentally induced hypothyroidism on the morphology and architecture of adult rat tongue papillae and to focus on the possible ameliorating effect of BM-MSCs.

2. MATERIALS AND METHODS:

Materials:

- **Carbimazole:** An anti-thyroid drug used for treatment of hyperthyroidism. It is supplied as film coated-tablets under the trade name "Carbimazole Tablets" (Chemical Industries Development (CID), Giza, A.R.E.). Each tablet contains 5 mg of carbimazole as an active ingredient.
- **Bone Marrow Derived Mesenchymal Stem Cells (BM-MSCs):** Allogenic BM-MSCs were isolated from tibiae and femurs of albino rats. Samples of bone marrow were assembled and were flushed carefully using a syringe with 3ml L-DMEM supplemented with FBS (10%) and L glutamine (1%) and antibiotics. To generate a single-cell suspension, the syringe was gently drawn up and down and the BM suspensions were then cultured in polystyrene dishes. The non-adherent cells were removed from the culture by a series of washes in PBS, whereas the adherent cells were expanded and incubated as monolayer cultures at 37°C in 5% humidified CO_2 for 12–14 days. At 80–90% confluence, the cells were dissociated using 0.25% trypsin and 0.01% EDTA then sub-cultured in new culture dishes (first passage cultures). In the third passage, MSCs were identified by their adhesiveness, fibroblastic shape, expression of CD90 and CD29 but not CD45 and also by their power for osteogenic and adipogenic differentiation. Stem cells were then labeled with PKH26 dye which is a red fluorescent linker that binds to the cell membrane of stem cells. Isolation of BM-MSCs was done in the Biochemistry Department, Faculty of Medicine, Cairo University.

Animals:

Thirty adult male albino rats weighing between 200-250 grams were used in this study. The animals were housed individually in the animal house of the Faculty of Medicine, Cairo University. The rats were kept under controlled temperature, humidity, and dark-light cycle. They were allowed to access freely adequate balanced diet and freshwater throughout the experimental period. The experiment was performed under the supervision of a specialized veterinarian since their housing till getting rid of the sacrificed bodies. This experiment was approved by the Research Ethics Committee, Faculty of Dental Medicine for Girls, Al-Azhar University (REC18- 037).

After one week acclimatization period, the rats were randomly divided into three groups (ten rats each):

- **Control group (GI):** Rats allowed to access a freely balanced diet and fresh water supply throughout the course of the experimental period (8weeks).
- **Hypothyroidism group (GII):** Rats received a single daily dose of carbimazole (5mg/ 250g body weight/ day) dissolved in (3 ml) of distilled water for 35 successive days (5 weeks) [7].

Blood samples were drawn from retro-orbital veins using capillary tubes after five weeks from the start of carbimazole treatment. These blood samples were collected to measure the serum T3 and T4 levels to verify induction of hypothyroidism [13]. Serum T3 and T4 concentrations were markedly reduced in this group. The mean ±SD serum T3 levels were (99±11.2 ng/dl) (The reference value of the kit used for the T3 assay ranged between 205 and 269 ng/dl). On the other hand, the mean serum levels of T4 were (4.08 ±0.6 µg/dl) (The reference value of the kit used for the T4 assay ranged between 7.3 and 15 µg/dl). (Table1)

Table 1—The mean ±SD levels of the results for the estimation of T3 and T4 hormones.

Hormone estimated	Control of the laboratory	Recorded data
T3	205 - 269 ng/dl	99±11.2 ng/dl
T4	7.3 -15 µg/dl	4.08 ±0.6 µg/dl

- **BM-MSCs treated group (GIII):** Hypothyroidism was induced by carbimazole the same as group II. Then, the animals received a single injection of (1×10^6 cells) of BM-MSCs per rat via tail vein. The cells were labeled with PKH26 fluorescent linker dye and were suspended in (1ml) phosphate buffer saline (PBS) [14].

Five microns of paraffin-embedded unstained sections were prepared then examined by fluorescent microscopy **(Sigma-Aldrich, Saint Louis, USA)** to ensure homing of PKH26 labeled-MSC cells into the hypothyroid rat's tongue papillae. The labeled cells appeared as red dots on a dark background. (Fig.1) Fluorescent microscopic examination was done at "The Tissue Culture Unit", Biochemistry Department, Faculty of Medicine, Cairo University, Egypt.

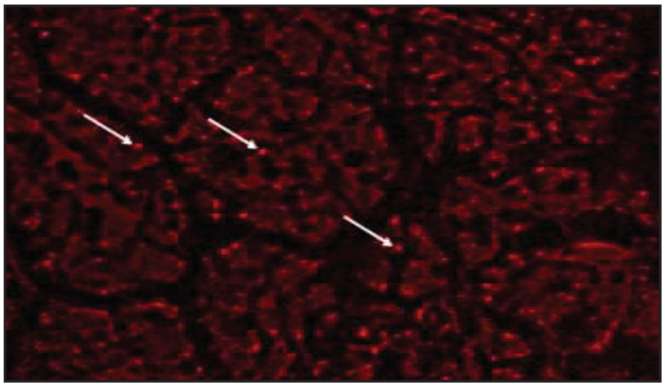

Figure 1 — Photomicrograph of the dorsal surface of the tongue of BM-MSC group showing: red fluorescent PKH26 labeled cells in the tongue tissues 3 weeks following injection (white arrow). (PKH26, Original Mag.×200

Three weeks after stem cells injection, rats of all groups were euthanized separately by an intra-peritoneal anesthetic overdose (sodium thiopental 80 mg/kg). Thus, the total experimental period was 8 weeks; 5 weeks of hypothyroidism induction in addition to 3 weeks of stem cells injection. The tongues were immediately dissected from the most posterior part to separate the circumvallate and foliate papillae.

3. RESULTS

Scanning Electron Microscopic Results:

A. Filiform Papillae:

1. **Control group:** Scanning electron microscopic examination of filiform papillae of GI revealed numerous papillae covering the entire dorsal surface of the tongue. The papillae appeared as conical projections with uniform pointed keratinized tips and smooth surface. They were arranged in parallel rows showing regular orientation in one direction with an antero-posterior direction curving backward towards the tongue root. (Fig.2)
2. **Hypothyroidism group:** In comparison to the control group; the filiform papillae of the hypothyroidism group appeared fewer in number and atrophied with apparent wide interpapillary regions. The papillae exhibited an unusual, variable orientation and inclination. Most of them were disfigured and some were bifid. Moreover, loss of the regular hornified keratin coverage could be identified in the examined specimens. (Fig.3)
3. **BM-MSCs treated group:** Unlike the previous group; ultra-structural examination of BM- MSCs treated specimens revealed nearly normal architecture and orientation of the filiform papillae as was stated in GI. The papillae were arranged in parallel rows with regular antero- posterior curvature backward towards the tongue root. The majority showed narrow uniform keratinized tips; yet was unapparent in others. (Fig.4)

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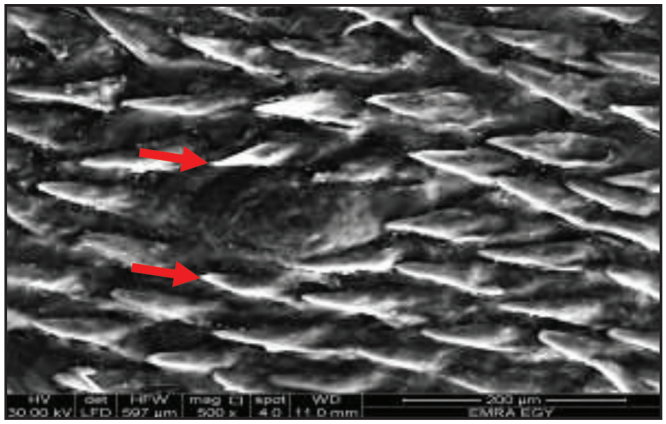

Figure 2 — Scanning electron micrograph of the dorsal surface of the tongue of control group (GI) showing; filiform papillae with uniform pointed keratinized tips (red arrows). (Orig. Mag ×500)

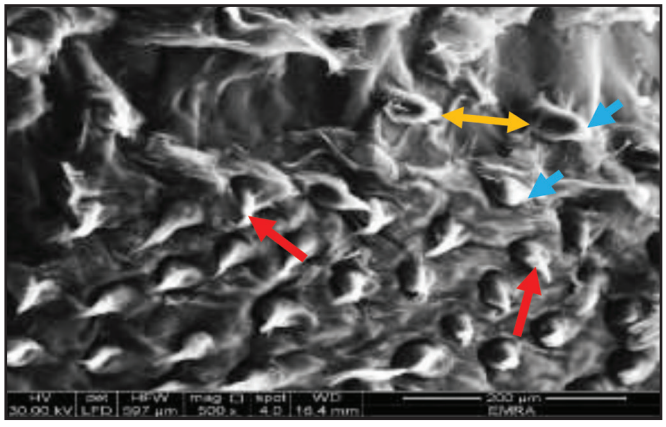

Figure 3 — Scanning electron micrograph of filiform papillae of hypothyroidism group (GII) showing; papillary disfigurement; some were bifid (red arrow), wide interpapillary regions (double arrow), and loss of the regular hornified keratin coverage (blue arrows). (Orig. Mag ×500)

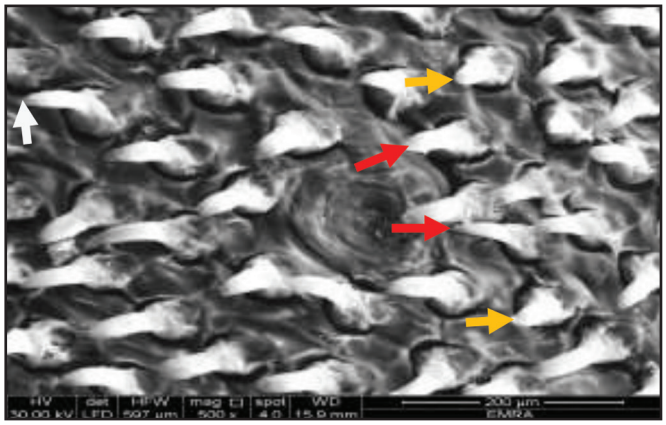

Figure 4 —Higher Magnification of the dorsal surface of the tongue of BM-MSCs treated group (GIII) showing; the majority of the filiform papillae with narrow uniform keratinized tips (red arrows); yet was unapparent in others (yellow arrows). (Orig. Mag ×500)

B. Fungiform Papillae:

1. **Control group:** Scanning electron microscopic examination of fungiform papillae of control group revealed their random distribution in between the filiform papillae; particularly on the anterior and middle regions of the tongue. The papillae assumed cauliflower-like in shape; with circular boundaries, raised edges covered by thin keratin scales and shallow indentations. A depressed, well-defined, regular taste pore was evident in the central region of the papillae. (Fig.5)
2. **Hypothyroidism group:** Unlike the control group, the fungiform papillae of GII appeared atrophied and lost their regular architecture. The papillae were shrunken in size and depressed. Their surface was smooth with disappearance of keratin scales. Furthermore, the gustatory pore appeared narrow and eccentric. (Fig.6)
3. **BM-MSCs treated group:** The examined tongue specimens of BM-MSCs treated group showed the fungiform papillae with the characteristic cauliflower shape and an obvious well-defined taste pore which appeared depressed in the central region and surrounded by shallow indentation; closely resembling that of the control group. (Fig.7)

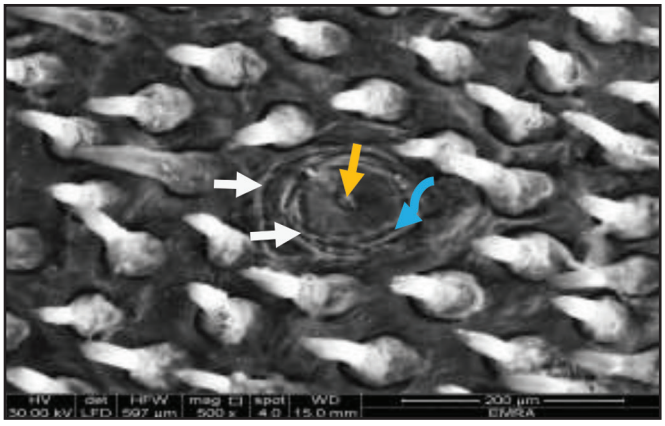

Figure 5 — Scanning electron micrograph of the dorsal surface of the tongue of control group (GI) showing; fungiform papilla with cauliflower-like appearance, circular boundaries, raised edges covered by thin keratin scales(white arrows), shallow indentations (blue arrow) and depressed, well-defined, regular taste pore in the central region of the papillae (yellow arrow) . (Orig. Mag.×500)

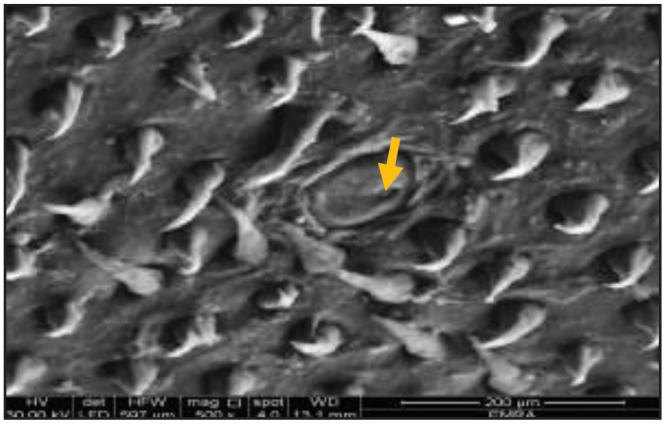

Figure 6 — Scanning electron micrograph the dorsal surface of the tongue of hypothyroidism group (GII) showing atrophied, shrunken and depressed fungiform papilla with smooth surface, disappearance of keratin scales and a narrow, eccentric gustatory pore (yellow arrow). (Orig. Mag. ×500)

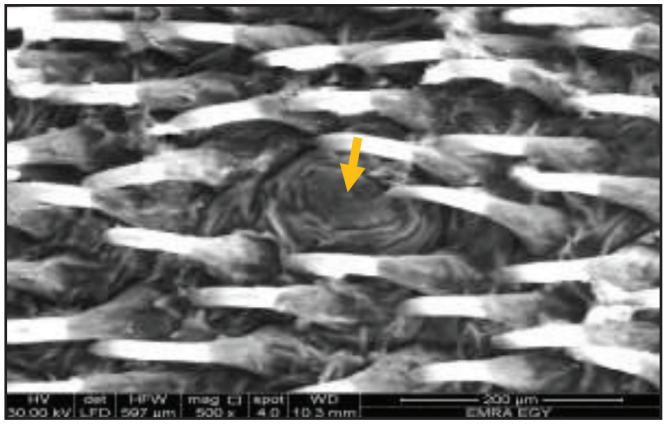

Figure 7 — Scanning electron micrograph of the dorsal surface of the tongue of BM-MSCs treated group (GIII) showing the fungiform papillae with the characteristic cauliflower shape and obvious well-defined taste pore depressed in the central region (yellow arrow).. (Orig. Mag ×500)

C. Circumvallate Papilla:

1. **Control group:** On examination of GI specimens, the circumvallate papilla appeared as a huge central circular structure buried within the substance of the tongue. The papilla's surface exhibited micro ridges together with well-defined minor gustatory pores. Moreover, a well-defined horseshoe-shaped depression simulating a trough was detected along the circumference of the vallate papilla. (Fig.8)
2. **Hypothyroidism group:** Scanning electron microscopic examination of this group revealed slight disfigurement of the circumvallate papilla with areas of distorted papillary ridges. Moreover, some papillae exhibited highly smooth surface with widened trough. Yet, all specimens showed atrophy of their superficial gustatory pits previously detected in the control group. (Fig.9)
3. **BM-MSCs treated group:** Regarding the papillae of BM-MSCs treated group; restoration of the characteristic surface micro ridges was detected together with fine rudimentary gustatory pits. In some of the examined specimens, the papillary trough was apparently wide. However, in others narrowing of the trough could be detected; though still with uneven width. (Fig.10)

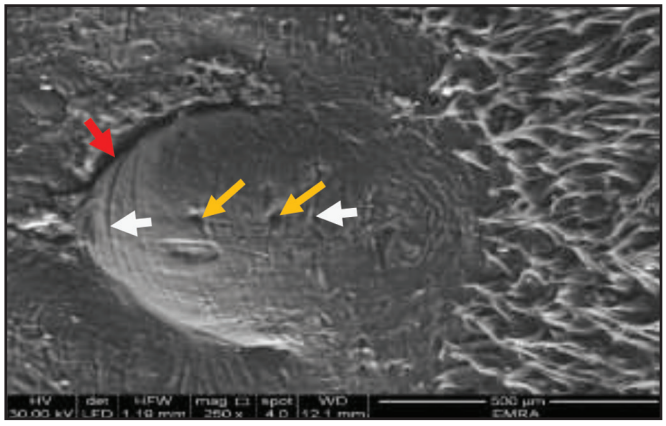

Figure 8 — Scanning electron micrograph of the dorsal surface of the tongue of control group (GI) showing; circumvallate papilla buried within the substance of the tongue, surface micro ridges (white arrows), well-defined minor gustatory pores (yellow arrows) and a well-defined horseshoe-shaped depression simulating a trough along the circumference of the vallate papilla (red arrow). (Orig. Mag. ×250)

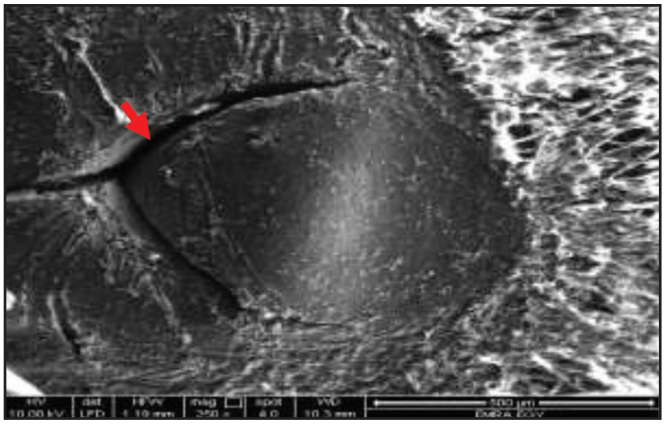

Figure 9 — Scanning electron micrograph of the dorsal surface of the tongue of hypothyroidism group (GII) showing; disfigured circumvallate papilla with areas of distorted papillary ridges, widened trough (red arrow), smooth surface and atrophy of their superficial gustatory pits. (Orig. Mag. ×250).

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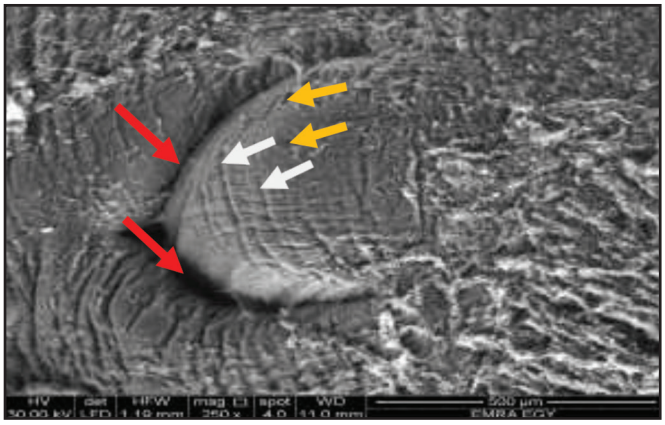

Figure 10 — Scanning electron micrograph of the dorsal surface of the tongue of BM-MSCs treated group (GIII) showing; another circumvallate papilla with surface micro ridges (white arrows), gustatory pits (yellow arrows) and narrow papillary trough with uneven width (red arrows). (Orig. Mag. ×250)

4. **Foliate Papillae:**
    1. **Control group:** Scanning electron microscopic examination of the foliate papillae showed parallel arrangement of numerous prominent ridges on the lateral sides of the tongue; accompanied by a groove at the centre of each ridge. (Fig.11)
    2. **Hypothyroidism group:** Specimens of the hypothyroidism group revealed smoothened surface with disfigured foliate papillae. The examined folia appeared as slightly elevated ridges with loss of the characteristic grooves previously detected in the control group. (Fig.12)
    3. **BM-MSCs treated group:** On examination of the specimens of this group; an improvement in the papillae's architecture has been recorded. They appeared as a series of parallel ridges with narrow grooves at the centre of each ridge. (Fig.13)

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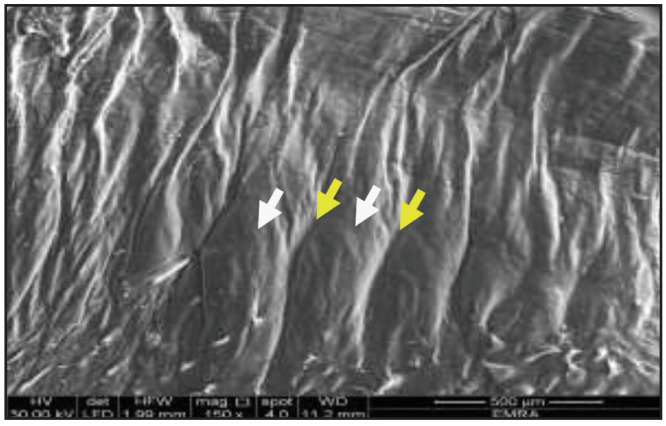

Figure 11 — Scanning electron micrograph of the lateral surface of the tongue of control group (GI) showing; foliate papillae arranged as numerous parallel prominent ridges (white arrows); accompanied by a groove at the centre of each ridge (yellow arrows). (Orig. Mag. ×150)

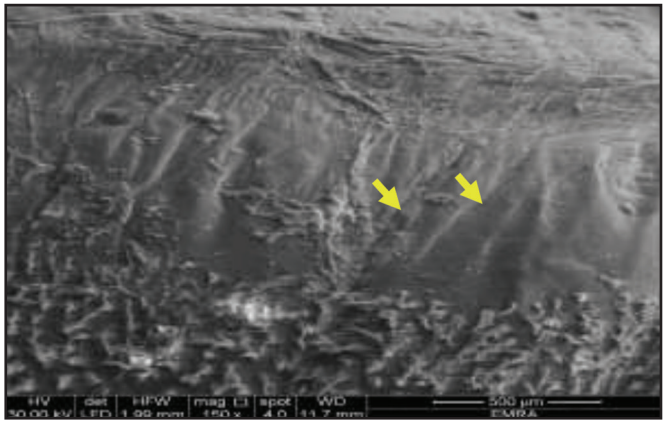

Figure 12 — Scanning electron micrograph of the lateral surface of the tongue of hypothyroidism group (GII) showing; smoothened surface with disfigured foliate papillae, slightly elevated ridges (yellow arrows) with loss of the characteristic grooves. (Orig. Mag. ×150)

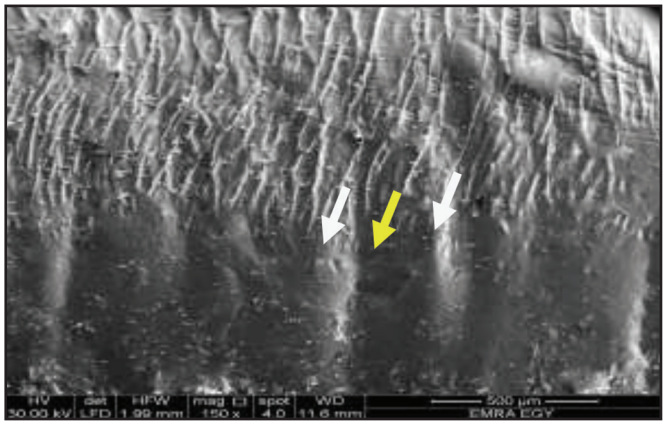

Figure 13 — Scanning electron micrograph of the lateral surface of the tongue of BM-MSCs treated group (GIII) showing; foliate papillae as a series of parallel ridges (white arrow) with narrow grooves at the centre of each ridge (yellow arrow). (Orig. Mag ×150)

4. DISCUSSION

The association between oral and systemic diseases, especially those causing hormonal disorders such as thyroid dysfunction and diabetes had received pronounced attention particularly in the last few decades [15]. Since hypothyroidism is a systemic disease it has been suggested that histological changes would affect the tongue tissues.

The present study was designed to provide a new research platform by exploring the effect of experimentally induced hypothyroidism on the adult rat tongue and assessing the possible ameliorating effect of BM-MSCs.

In this study, hypothyroidism induction was provoked by carbimazole; the most preferentially and frequently used drug in the treatment of hyperthyroidism. The drug was given to the rats through a stomach tube therefore the dose could be accurately adjusted [5]. After absorption of carbimazole, it is converted to the active form methimazole. Methimazole work as a false substrate for thyroid peroxidise, thus, blocking the iodination of tyrosine residues within thyroglobulin thereby reducing the production of the thyroid hormones T3 and T4 serum levels [16]. In the ongoing study, hypothyroidism was confirmed by measuring serum levels of T3 and T4 hormones as there was a significant decrease in their levels.

The SEM results of the present work revealed atrophic changes in the filiform papillae of the hypothyroidism group. The papillae appeared fewer in number with apparent wide interpapillary regions and an unusual, variable orientation and inclination. Most of them were disfigured and some were bifid. Moreover, loss of the regular hornified keratin coverage could be identified in the examined specimens.

On the other hand, the fungiform papillae appeared atrophied and lost their regular architecture. The papillae were shrunken in size and depressed. Their surface was smooth with disappearance of keratin scales. Furthermore, the gustatory pore appeared narrow and eccentric.

The circumvallate papilla showed disfigurement with areas of distorted papillary ridges. Moreover, some papillae exhibited smooth surfaces with widened troughs. Yet, all specimens showed atrophy of their superficial gustatory pits previously detected in the control group. Specimens of the hypothyroid group also revealed smoothened surface with disfigured foliate papillae. The examined folia appeared as slightly elevated ridges with loss of the characteristic grooves previously detected in the control group.

These observed changes were in accordance with previous author who reported epidermal thinning in the skin of hypothyroid rats which received methimazole compared with control rats[17]. Similarly, another study reported that epidermal thinning and hyperkeratosis are common histological changes in hypothyroidism. The study also mentioned that thyroid hormone is an important regulator of epidermal homeostasis as thyroid receptors have been detected in epidermal keratinocytes[18].

Furthermore, a previous study reported vacuolation of the cytoplasm and darkly stained nuclei in the epithelium of renal cortex tubules of hypothyroid rats treated with methimazole. The authors suggested that this effect was accompanied with oxidative stress [13]. Other studies found that hypothyroidism is associated by oxidative stresses due to insufficient anti-oxidant production[7],[19]. In addition, an earlier study revealed cellular changes in the parotid gland of hypothyroid rats and mentioned that these cellular changes could be found to stem from the adverse effects of hypothyroidism upon the metabolic systems within the cell[20]. Moreover, Previous findings have determined that the two isoforms of thyroid hormone receptors (TRα and TRβ) are present in epidermal keratinocytes[21]. Furthermore, It was mentioned that hypothyroidism affects the development of lamellar granules (Odland bodies) which are essential for the formation of a normal stratum corneum[22].

In this study, the taste buds of gustatory papillae of hypothyroid rats were atrophied. Clinically, an altered taste perception was documented in patients with thyroid dysfunction[23],[24]. Hypothyroidism was listed as one of the chronic medical conditions that contribute to dysgeusia[25]. In addition, it was mentioned that thyroid hormones have a well-known effect on the maturation of fungiform papilla. Thus, hypothyroidism could act as a damaging factor for the development of the papillae with a subsequent decrease in taste

perception[26]. On the other hand, it has been proven that neurons and nervous system are highly thyroid hormone sensitive. Taste buds are highly dependent on innervation for maintenance and function. Accordingly, it is expected that taste neurons that induce and maintain the taste buds will be affected[27].

Examination of the specimens of group III revealed improvement in the architecture of the papillae. The papillae of this group showed a close picture to that of the control group. This improvement revealed nearly normal architecture and orientation of the filiform papillae with narrow uniform keratinized tips, the characteristic cauliflower shape of fungiform papillae with its obvious well-defined taste pore, the characteristic surface micro ridges of circumvallate papilla together with fine rudimentary gustatory pits and the parallel ridges of foliate papillae with narrow grooves at the centre of each ridge.

A prevous study showed that systemic intravenous injection of 1×10^6 BM-MSCs/ body via tail vein reduced the damaging effects of diabetes on filiform and fungiform papillae of albino rats [14]. Similarly, other auther reported that intravenous injection of 1.5×10^6 BM-MSCs/ body reduced the severity of induced stomatitis in rats receiving chemotherapy [28].

The improvement in BM-MSC treated group might be explained by several potential mechanisms. First; indirectly as systemic injection of BM-MSCs may cause regeneration of the thyroid gland [29]. An earlier study confirmed that the thyroid gland partially restored its normal functional and histological pattern and became nearly similar to the control group after injection of a single dose of 1×10^6 BM-MSCs in adult male albino rats following induction of hypothyroidism by carbimazole[16]. Secondly; directly by homing of injected BM-MSCs in the tongue papillae and trans-differentiation into a diversity of cell types needed for tissue regeneration [14], this explanation was supported here by the fluorescent PKH26 labeled cells detection within the tissues of the tongue. Moreover, another study mentioned that MSCs revealed a powerful chemotactic migration toward epidermal keratinocytes, dermal fibroblasts and endothelial cells[30]. Concomitantly, is the paracrine factors produced by BM-MSCs and the high expression of several pro-healing genes that ensure growth factors and cytokines production which regulate and enhance various cellular processes as endogenous stem cells proliferation, cell signaling and formation of extracellular matrix[30],[31]. Besides, BM-MSCs have the ability to secrete angiogenic cytokines including Basic Fibroblast Growth Factor (bFGF) and Vascular Endothelial Growth Factor (VEGF), which are favourable to the growth of vessels to promote the repair of damaged mucosa[32],[33]

5. CONCLUSION

From the results of this study, it could be concluded that:

1. Hypothyroidism induced by carbimazole caused degenerative changes and alteration in the morphology and regular architecture of tongue papillae in albino rats.
2. Intravenous injection of BM-MSCs could successfully restore the integrity of damaged tongue papillae.
3. Bone marrow derived mesenchymal stem cells are considered as a promising therapy for reducing the complication associating hypothyroidism.

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