

The effect of experimental hypothyroidism on nasal mucosa

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ABSTRACT

Objectives: This study aims to investigate the histopathological changes in nasal mucosa and alterations in thyroid hormone receptors in an experimental postnatal hypothyroidism model.

Materials and Methods: Twenty-one Wistar albino newborn rats born from the pregnant rats were enrolled in this prospective randomized study and were divided into two groups: Group 1 (n=11, methimazole, MMI -induced hypothyroidism group) given MMI-water, and Group 2 (n=10, control group), normal tap water. When the offspring reached 90 days, they were decapitated and the nasal mucosa was removed. Thyroid hormone receptor (TR- α , TR- β) status was assessed by immunohistochemical staining.

Results: The difference between hypothyroidism and control groups regarding inflammation was statistically significant ($p<0.001$), as were the differences between hypothyroidism and control groups regarding edema and vascular proliferation ($p<0.001$, $p=0.001$). Staining was identified in sebaceous gland structures with immunohistochemical staining for thyroid hormone receptors. No statistically significant difference was found between the hypothyroidism and control groups regarding TR- α and TR- β .

Conclusion: Thyroid hormone receptors are present in nasal mucosa. Edema, inflammation, and vascular proliferation occur in nasal mucosa due to hypothyroidism.

Keywords: hypothyroidism, rhinitis, thyroid hormone receptor, TR- α , TR- β

Numerous factors can lead to anatomical and histological changes that cause rhinitis symptoms by disrupting normal nasal function.^[1] Hormonal rhinitis is discussed within the non-allergic and non-infectious types of rhinitis.^[2] Hypothyroidism, pregnancy, puberty, acromegaly, and oral contraceptive use are among the causes of hormonal rhinitis.^[3]

In addition to clinical features affecting entire body systems in patients with hypothyroidism, clinical changes also occur in the ear-nose-throat region.^[4] Few studies are present in the literature on this subject. In those studies, histological

and physiological changes of nasal mucosa were determined in hypothyroidism.^[5] Hypertrophy of mucous glands and increase in the basal substance of the connective tissue were identified in the nasal biopsies of patients with hypothyroidism and these were reported to be formed with the effect of increased thyroid stimulating hormone (TSH) release in hypothyroidism.^[6]

The aim of our study was to investigate the histopathological changes occurring in nasal mucosa together with the status of thyroid hormone receptors in nasal mucosa in an experimental postnatal hypothyroidism model.

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MATERIALS AND METHODS

Six-month-old pregnant Wistar albino rats weighing 250-300 grams were included in the study. Vaginal smear test was used for determination of pregnancy. The rats in which semen was detected in the vaginal smear test were considered pregnant. Twenty-one Wistar albino newborn rats born from the pregnant rats were enrolled in this prospective randomized study and were divided into two groups. Group 1 (Methimazole (MMI)-induced hypothyroid group, n=11) constituted the group with hypothyroidism, as MMI administration is typically used for inducing hypothyroidism in rats.^[7,8] The mother rats had been fed with normal diet plus MMI-added water. Methimazole (SC-205747A, Santa Cruz Biotechnology, Inc., Dallas, TX) (0.025% wt/vole) was administered in their daily drinking water from birth up to 90 days. The rat offspring were fed with breast milk for 19-22 days, and drank MMI-added water daily up to 90 days, similar to their mothers. Group 2 (n=10) constituted the control group. The mothers of the rats in Group 2 were fed with normal diet and water that did not include MMI. The rat offspring were initially fed with breast milk and then with normal water daily up to 90 days, similar to their mothers. When the offspring were 90 days old, they were decapitated, and the nasal mucosa was removed.

After keeping in 10% formalin for one night, all samples were processed in the automated tissue-tracking device and embedded in paraffin blocks. Sections prepared from the tissues in paraffin blocks were stained with hematoxylin eosin, and conventional morphological evaluation was made. The changes in nasal tissue, surface epithelium and vascular structures, subepithelial edema, inflammation and congestion were evaluated. The scoring was performed as follows: absence of submucosal edema and inflammation was scored as grade 0, light density was scored as grade 1, and moderate density as grade 2. Vascular proliferation and congestion were scored as present or absent.

Immunohistochemical staining evaluated thyroid hormone receptor (TR- α and TR- β) status. Slides with lysine were used for immunohistochemical processing. The process was performed manually, using the streptavidin

- biotin peroxidase method. TR- α 1 and TR- β 1 (1/300; mouse monoclonal; sc-56873, Santa Cruz Biotechnology) were utilized as the primary antibodies. The stained slides were assessed using light microscopy and scoring was made in the presence and absence of staining in the nuclear and cytoplasmic areas. The approval of Medical Faculty of Adnan Menderes University Ethics Committee for Animal Experiments was obtained for the study.

Statistical analysis

All data were analyzed using IBM SPSS version 19.0 (IBM Corp., Armonk, NY, USA) software. Since the number of rats was less than 50, descriptive statistical results were reported as numbers. Mann-Whitney U test was used for determination of the relationship between variables. Fisher chi-square test was used for comparisons between the groups. The level of statistical significance was taken as $p < 0.005$.

RESULTS

Eleven hypothyroid and 10 control group samples were analyzed. While two samples had inflammation in the control group, all of the samples in the hypothyroid group had inflammation. The difference between the hypothyroid and control groups regarding inflammation was statistically significant ($p < 0.001$). None of the samples in the control group had edema whereas nine samples in the hypothyroid group had edema. The difference between the hypothyroid and control groups was statistically significant regarding edema ($p < 0.001$). While vascular proliferation was absent in the entire control group, eight samples in the hypothyroid group had vascular proliferation. The difference between the hypothyroid and control groups was statistically significant regarding vascular proliferation ($p = 0.001$). Increased inflammation and vascular proliferation in the group with hypothyroidism is shown in Figure 1a-c.

Immunohistochemical staining for thyroid hormone receptors revealed staining of sebaceous glandular structures whereas no staining was observed in the surface epithelium and subepithelial tissues. TR- α was detected in one control sample and five hypothyroid samples. TR- β was detected in none of the control samples and in three hypothyroid samples. No statistically

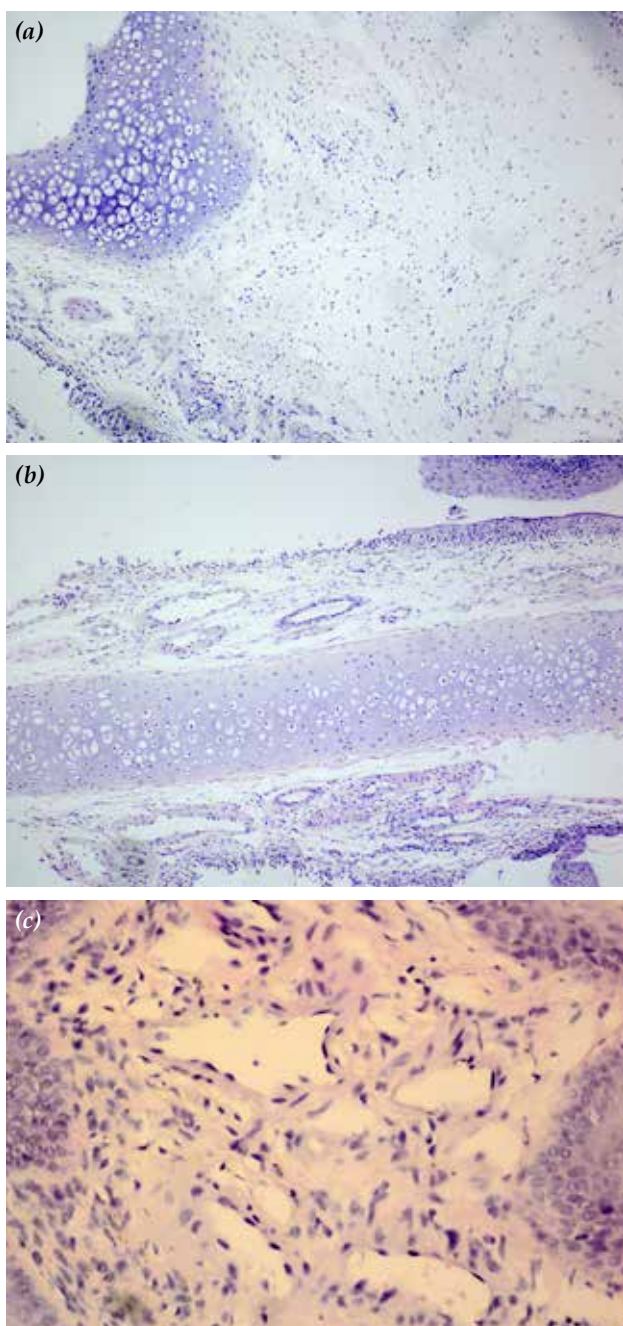


Figure 1. (a) Inflammation observed in the edematous stroma in the group with hypothyroidism (H-E×100). (b, c) Moderate-degree inflammation accompanied by vascular proliferation observed in the group with hypothyroidism (1b; H-E×100 and 1c; H-E×200).

significant differences were found between the control and hypothyroid group samples regarding staining results. Staining with TR- α 1 in the group with hypothyroidism is shown in Figure 2a, b.

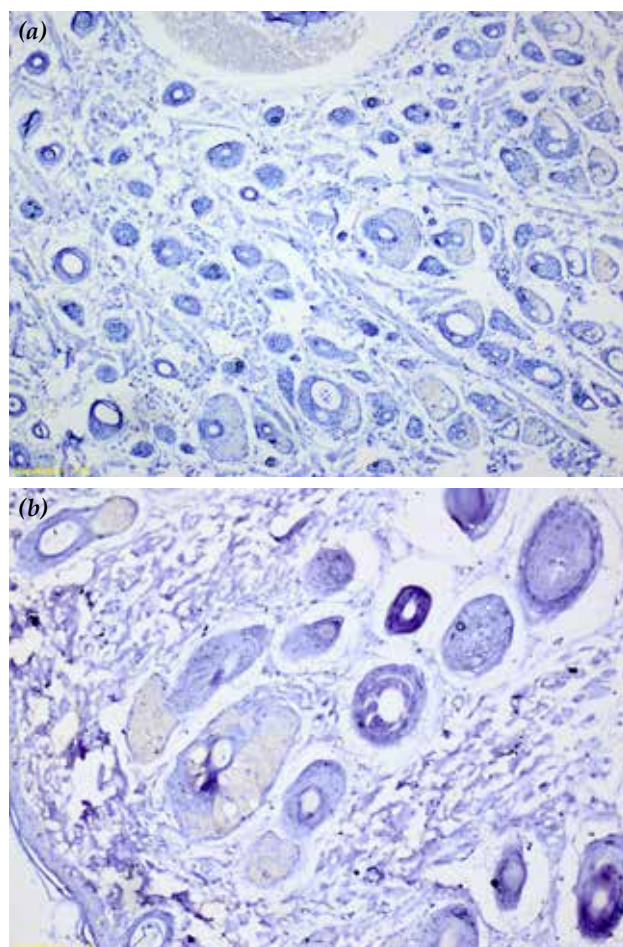


Figure 2. (a, b) Staining with TR- α 1 in sebaceous glandular structures is observed in the group with hypothyroidism (2a; TR- α 1 ×100 and 2b; TR- α 1 ×200).

DISCUSSION

Hypothyroidism has been known to affect the ear, nose, and throat region.^[9] The most frequent symptoms of rhinitis related to hypothyroidism are nasal obstruction and rhinorrhea, which are caused by an increase in submucosal connective tissue and hypertrophy of mucous glands.^[9,10] The pathophysiological mechanism of hormonal rhinitis associated with hypothyroidism has not been clearly identified.^[11] In the hypothyroidism model of Proud and Lange, cilia loss, submucosal infiltration of inflammatory cells and hypertrophy were determined in nasal mucosa.^[12] Few studies on this subject are present in the medical literature.

Thyroid hormone T₃ shows its effect by binding to thyroid hormone receptors, which are found in

the nucleus. These nuclear receptors are important mediators in the physiological activities of thyroid hormones.^[13] Two genes are present for thyroid hormone receptors in humans; the alpha and beta genes. Thyroid beta-receptors are found more likely in brain, heart, liver, kidney, pituitary gland and hypothalamic tissue.^[13]

The presence of TR- α 1 and TR- β 1 receptors was identified in cochlear hair cells.^[14] The TR- α 1 and TR- β 1 receptors were also shown to be present in the human larynx in males and females, but the same study was not able to demonstrate the presence of receptors in laryngeal mucosa and muscles.^[15] The existence of thyroid hormone receptors during embryological developmental was previously determined in the nasal cavities of rats.^[16]

TR- α 1 and TR- β 1 receptors were shown to be increased in the epididymis of rats with hypothyroidism.^[17] Thyroid hormone receptors were shown to be increased in the pituitary glands of rats with hypothyroidism when compared to euthyroid rats.^[18] Also, an increase in thyroid hormone receptors was determined in the brains of rats in which hypothyroidism was created.^[19] An increase of edema findings was determined together with TR- α 1 and TR- β 1 in the larynges of rats in which hypothyroidism was created when compared to the normal group.^[20]

In our study, inflammation, edema, and vascular proliferation were found to be more intense in the group with hypothyroidism when compared to the control group. Hypothyroidism was found to lead to increasing inflammation, edema, and vascular proliferation; these findings were consistent with the literature.

We identified thyroid hormone receptors in sebaceous glandular structures in our study. Although differences were found between the groups regarding thyroid hormone receptors, these differences were not statistically significant. We were not able to encounter any other study in the medical literature that showed thyroid hormone receptors in the sebaceous glandular structures of the nasal mucosa.

Thyroid hormone receptors were shown to have an anti-inflammatory effect in one study.^[21] Thyroid hormone receptors with anti-inflammatory effect

may increase as the hypothyroidism-related nasal inflammation increases. The absence of a statistically significant difference between groups regarding receptors may be related to the duration of exposure to hypothyroidism and the degree of inflammation in our study. A longer duration of hypothyroidism may be considered to increase the significance of the difference regarding the thyroid hormone receptors and new studies may be planned.

In conclusion, edema, inflammation, and vascular proliferation occur in the nasal mucosa due to hypothyroidism. Thyroid hormone receptors are present in the sebaceous glands of the nasal mucosa. Our study suggests that thyroid hormone receptors may play a role in the mechanism of action of hypothyroidism on nasal mucosa and shows that new studies related to thyroid hormone receptors are needed.

Declaration of conflicting interests

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