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Research Article

The impact of Selenium and Levothyroxine on the Immune System of Hypothyroid Rats

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Abstract:

Background: The immune system and thyroid hormones have an inverse relationship, but both thyroid hormones and selenium play a crucial role in the immune system. However, when the levels of thyroid hormones decrease (known as hypothyroidism), their effect on immune system cells and their relationship with selenium supplements in the body are not well understood.

Objectives: This study aimed to investigate the impact of Se-nanoparticles on thyroid hormones and the blastogenic response of lymphocytes in various lymphoid tissues in rats with hypothyroidism.

Methods: A group of female Wister rats aged three to four months were randomly placed into five groups (each group has 6 rats) and were given a basal diet on a daily basis. However, the daily water supply given to each group was different. The first group was the control group and received normal water, while the other four groups were given 0.02% methimazole in their drinking water every day for four weeks to induce hypothyroidism. Once the hypothyroidism was confirmed, the 3rd, 4th, and 5th experimental groups were given one of the following three treatments for four weeks, respectively: SC-SeNPs (0.1mg selenium per kg per day) as T1, Levothyroxine (0.9µg per 100g per day) as T2, or SC-SeNPs (0.1 mg selenium per kg per day) and Levothyroxine (0.9µg per 100g per day) as T3. In the end, blood samples were collected from euthanized animals using a high dose of anesthesia, and lymphoid tissue samples (spleen, Peyer's patches and mesenteric lymph node) were preserved in 10% formalin.

Results: Our research has revealed that IgG, a humoral immunity marker, was found to be significantly decreased in hypothyroidism. However, when treated with levothyroxine alone or in combination with Sc-SeNPs, the level of cellular immunity marker, IL-6, was found to be significantly increased in hypothyroidism when compared to the control group. Additionally, we observed histopathological changes in the lymphoid tissue of hypothyroidism rats, which included depletion of the white pulp of spleen with congestion in the blood vessels, a decrease in the lymphoid follicle of Peyer's patches, and a decrease in the primary and secondary follicles of the mesenteric lymph nodes.

Conclusion: Thyroid hormones play a role in regulating innate and adaptive immunity. The combination of selenium with levothyroxine is the most effective treatment for hypothyroidism and improves the activity of the immune system cells.

Keywords: Hypothyroidism, IGg-IL6, Immune system, Levothyroxine, SC-SeNPs

Introduction

Hypothyroidism from endocrinological point of view is depressed T3 and T4 plasma levels and elevated plasma levels of thyroid stimulating hormone (TSH) which is a condition that is quite common around the world. Hypothyroidism has been characterized in a big number of animal species, namely the dogs, cat, horses, etc. (1-3). Hypothyroidism, is either thyroid dysgenesis or dyshormogenesis (4-6). Reduction in circulating thyroid hormones slows cell metabolism and growth (7, 8); memory impairment, and neurological disorder in dogs (9). Hypothyroidism reduces the health-related quality of life in addition to depression and mood disturbances (10). The communication between endocrine system and immune system is a very sensitive issue and the bidirectional relationship between thyroid gland activity and both innate and adaptive immune systems is the most common. In hypothyroidism, both innate and adaptive immune systems are affected (11). From immunological point of view, the immune checkpoints are part of the immune system that controls immune response and not to be so strong to that it attacks body's cell. Endocrinologically, both causes of hypothyroidism ; destructive thyroiditis or hypothyroidism are related to the Immune-related adverse events (IRAEs), which are mainly accompanied by immune checkpoint inhibitors in several organs including the endocrine glands (12). Levothyroxine is typically used to replace thyroid hormone in hypothyroid patients' treatment plans. A significant fraction of levothyroxine-treated people still experience chronic symptoms despite hitting the biochemical therapeutic targets, raising the question

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of whether levothyroxine medication is enough for all patients or whether alternative therapies are more successful (13, 14). Iodine and selenium are both essential minerals for producing thyroid hormones. Selenium insufficiency affects both the amount of levothyroxine required to treat hypothyroid children and the concentration of thyroid hormones in the bloodstream (15). Selenium nano-particles SeNPs also preserve the same effects so that it is regarded as a nano-medicine with promising characteristics. Hence, SeNPs can function as reduce toxicity, antimicrobial, anticancer, antidiabetic, antiparasitic, antioxidant, and reduce the impact of reactive oxygen species (ROS) and free radicals (16-18).

Materials and Methods

Experimental Animals

Female Wister rats, aged three to four months, were placed into 5 groups (6 rats /group) at random. The first group is control group received basal food and water, the 2nd, 3rd, 4th, and 5th groups received basal diet daily and 0.02% methimazole in drinking water for 4 weeks to induce hypothyroidism. Following the confirmation of hypothyroidism, the 3rd, 4th, and 5th experimental groups of rats received one of three treatments: SC-SeNPs (0.1mg selenium per kg per day) as T1, Levothyroxine (0.9µg per 100g per day) as T2, or SC-SeNPs (0.1mg selenium per kg per day)+Levothyroxine (0.9µg per 100g per day) as T3, respectively, for 4 weeks. Blood samples were collected from euthanized animals using high dose of anesthesia, in addition to lymphoid tissue (spleen, Peyer's patches and mesenteric lymph node) samples were preserved in 10% formalin.

Viability of lymphocytes by isolation of lymphocytes using ficoll solution and staining with trypan blue

Fresh blood samples were used for evaluating the viability and count of lymphocytes using a modified ficoll method (19) according to lymphocyte separation medium manufactured by (Capricorn Scientific GmbH. Cat. No. LSM-B (100 ml), Germany).

Evaluation of cellular and humoral immunity

Serum Immunoglobin G (IgG was determined by using commercial Rat IgG (Immunoglobin G) ELISA kit Cat. No: E-EL-R0518). **Serum interleukin (IL6)** measured by intended kit for *in vitro* according to manufacturing procedure (BT LAB Rat IL6 ELISA kit, Cat. No. E0135Ra).

Histopathological study

Lymphoid tissue sections including spleen, Peyer's patches, and mesenteric lymph node were stained by hematoxylin and Eosin. The tissue sections were observed and examined using a light microscope at 100X and 200X magnifications.

Statistical analysis Data obtained from the present experiment were analyzed by One Way Analysis of Variance (ANOVA), in experiment one-way analysis was used and in experiment two one-way analysis using SAS (Statistical Analysis System), and Microsoft Office Excel (Microsoft Office Excel for windows; 2010). Least significant differences (LSD) was performed multiple (multiple comparisons), to evaluate significant differences among means. $P < 0.05$ was considered statistically significant. The results were expressed as means ± SE. Integrate biomarker response (IBR) was also use for analysis of result in both experiments.

Results

Assessment of hypothyroidism

The hypothyroidism was assessed depending on the obtained base-line; which showed a significant reduction in serum levels of T3 (from 1.2 to 0.46) and T4 (from 35.49 to 7.06) as well as an elevation in serum level of TSH (from 2.38 to 5.58) in comparison to healthy control rats. Also, treatment of hypothyroidism in rats with a combination of levothyroxin and SC-SeNPs produced the best thyroid hormone levels when compared to hypothyroidism treated with SC-SeNPs alone and untreated.

Viability and count of lymphocytes

Lymphocytes viability (%) evaluation using Ficoll method in the present study revealed that cells staining with trypan blue are unviable. Table (1) showed that hypothyroidism rats had the lowest lymphocytes viability and lymphocyte ratio (53.74±4.59) among the other experimental groups. On the other hand, lymphocytes viability and count were improved by different treatments to semi normal levels.

Table 1: Effects of Sc-SeNPS alone or in combination with levothyroxine on lymphocytes viability and count of hypothyroidism female rats for 4 weeks

Group	Lymphocytes viability (%)	Lymphocytes count (×10^5/ml)
CONTROL	85.96±1.24 A	3.62±0.05 A
Hypothyroidism	53.74±4.59 B	1.78±0.20 D
T1	84.98±1.23 A	3.3±0.07 B
T2	86.54±1.00 A	3.5±0.07A
T3	86.18±1.07 A	3.23±0.03 B
LSD	6.7540	0.2956

Different capital letters denote significant differences between groups. T1: hypothyroidism and treated with Sc-SeNPs0.1 mg /kg B.W, T2: hypothyroidism and treated with Thyroxin 0.9microgram/100g BW. day, T3: Hypothyroidism and treated with thyroxin+ Sc-SeNPs 0.9microgram/100g BW. Day, and 0.1 mg /kg B.W.

Humoral and cellular immunity

Humeral immunity marker examined in the present study was IgG, in table 2 this marker showed significant decrease in hypothyrpdism (1.85 ± 0.02), on the opposite, levothyroxine alone or in combination with Sc-SeNPs restored the level of serum IgG to the normal level

Cellular immunity marker, IL-6, increased significantly in hypothyroidism (5.9±0.28) when compared to either control (5.01±0.3). Whereas using different treatments, Sc-SeNPs showed the best restoring effects on IL-6 (4.92±0.21) then the levothyroxine (4.79±0.3).

Table.2: Effects of Sc-SeNPS alone or in combination with levothyroxine in humoral (IgG) and cellular immunity (IL-6) of hypothyroidism female rats for 4 weeks

Animal group	IgG (ng/ml)	IL6 (ng/L)
Control	2.08 ± 0.02A	5.01±0.3B
Hypothyroidism	1.85 ± 0.02B	5.9±0.28A
T1	2.06 ± 0.08A	4.92±0.21 B
T2	2.0 ± 0.02A	4.79±0.3C
T3	2.11 ± 0.11 A	4.42±0.16C
LSD	0.187	0.752

Different capital letters denote significant differences between groups. T1: hypothyroidism and treated with Sc-SeNPs0.1 mg /kg B.W, T2 hypothyroidism and treated with Thyroxin 0.9microgram/100g BW. day, T3: Hypothyroidism and treated with thyroxin+ Sc-SeNPS 0.9microgram/100g BW. Day, and 0.1 mg /kg B.W

Integrate of immunity biomarkers shown in Figure (1) revealed the IBR values of the VL, CL, IL6, and IgG over the five tested groups. The measurements illustrated high variation between the four factors, ranging from 15.527 to 0.00015, with the following sequence (VL>IL6>CL>IGg). Another prominent feature is that VL, CL, and IgG are high in all groups except the hypothyroidism group. This feature is opposite in the case of IL6 which shows low values in all groups except the hypothyroidism group

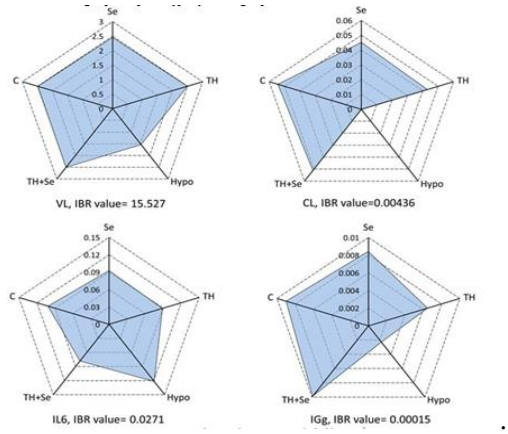

Figure 1: Integrated biomarker response of Vl, CL, IL-6, and IGg for control, hypothyroidism, and hypothyroidism with different treatment.

Histopathological changes in lymphoid tissues

Spleen

Results in figure (2) showed the spleen tissue sections of experimental groups. In figures (2-A and 3-A) control group spleen section showed normal histological architecture; the white pulp (arrow) area was scattered within red pulp area. In figures (2-B and 3-B) sections of rat spleen of hypothyroidism group, showing depletion of some the white pulp (arrow) with congestion of blood vessels. The figures (2-C &3-C) sections of rat spleen of SC-SeNPs group, showing mild activation of lymphoid follicle, the white pulp (arrow) area was scattered within red pulp. Histological section of rat spleen of Levothyroxine group illustrated in figures (2-D and 3-D) showing hyperplasia lymphoid follicles with congestion, the white pulp (arrow) area lymphoid follicles with formation of germinal center was scattered within red pulp area. Histological section of rat spleen of Levothyroxine and SC-SeNPs group (Figures 2-E and 3-E) showing white pulp (arrow) area was scattered within red pulp area showing hyperplasia of white bulb with moderate thickening of central arteriole, formation of gremial center also seen**.**

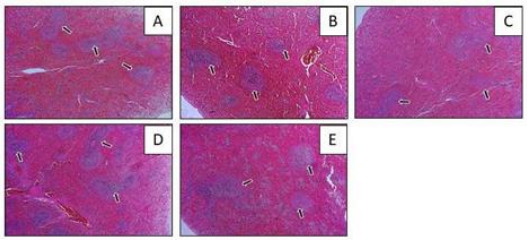

Figure 2: Histological section of rat spleen of A: control group. B: hypothyroidism group. C: Sc-SeNPS-treated group. D: levothyroxine-treated group. E: Sc-SeNPS and levothyroxine group. White pulp (arrow) H&E. 100x.

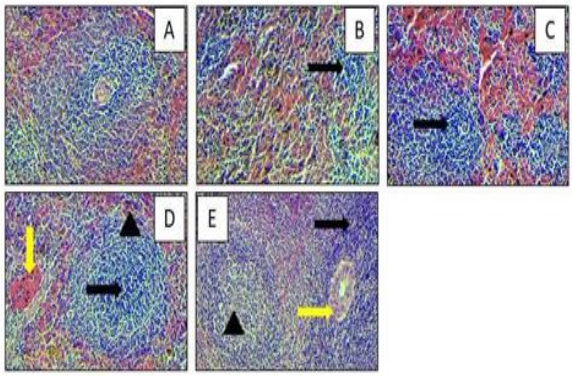

Figure 3: Histopathological section of rat Spleen for a-control group, b- hypothyroidism group B-,C- Sc-SeNPS treated group, D-levothyroxine treated group E-Sc-SeNPS and levothyroxine group, H&E, stains, 400x).

Peyer's patch

Histopathological changes of Peyer's patch of different experimental groups illustrated in figures (4-A and 5-A) showed normal histological architecture. In the hypothyroidism rat's figures (4-B and 5-B) showed decreased Lymphoid follicle of Peyer's patches and depletion in lymphoid tissues when compared with control group figures (4-A and 5-A), and the same were found in hypothyroidism treated with Sc-SeNPs showing decrease Lymphoid follicle of Peyer's patches with hyperplasia of lymphoid tissues fFigures (4-C and 5 -C). Meanwhile, groups had levothyroxine alone figures (4-D and 5-D) or with Sc-SeNPs figures (4-E and 5-E) showed increased lymphoid follicle of Peyer's patches (black arrow), the germinal center showed multiple lymphoid follicle of Peyer's patches (black arrow). The germinal center and lymphoid tissue hyperplasia.

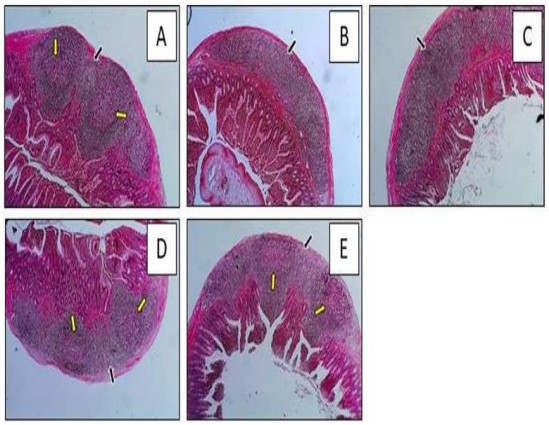

Figure.4- Histological section of Peyer's patches of A-control, B-hypothyroidism, C- Sc-SeNPS treated group, D-levothyroxine treated group E- Sc-SeNPS and levothyroxine group, (black arrow). the germinal center (yellow arrow). H&E.100x

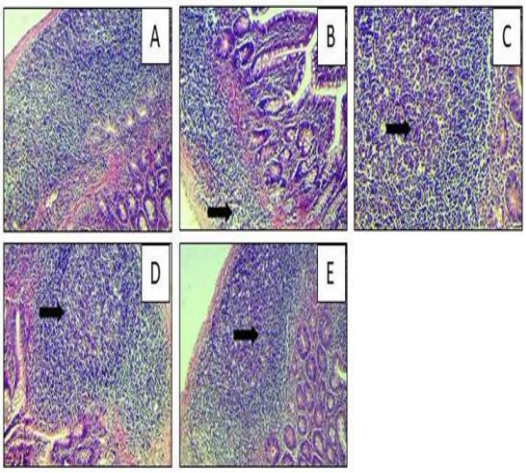

Figure .5 Histological section of Peyer's patches of A-control, B-hypothyroidism, C- Sc-SeNPS treated group, D-levothyroxine treated group E- Sc-SeNPS and levothyroxine group, (black arrow) . the germinal center (yellow arrow) . H&E.200x.

Mesenteric Lymph node

Histological section of mesenteric lymph node from rats of hypothyroidism group, in figures (6-B and 7B), showed decreased primary follicles (black arrow) and secondary follicles (yellow arrow) when compared with control figures (6-A and 7-A). Treatment with Sc-SENPS figures (6-C and 7-C) showed decrease primary (black arrow) and secondary follicles (yellow arrow) and proliferation of multiple lymphoid follicles with active follicular centers, respectively. However, treatment with Levothyroxine alone showed proliferation of multiple lymphoid follicles with active follicular centers and an increase in primary follicles (black arrow) and secondary follicles (yellow arrow) in figures (6-D and 7-D). Treatment with levothyroxine mixed with and Sc-SeNPs treated groups showed increase in primary (black arrow) and secondary follicles (yellow arrow) and formation of active follicular center with presence of numerous histiocytes figures (6-E and 7-E).

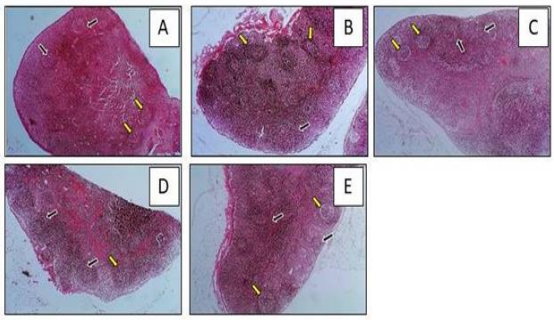

Figure-6 Histological section of mesenteric lymph node from; A-control group B-hypothyroidism, C- Sc-SeNPS treated group, D-levothyroxine treated group E- Sc-SeNPS and levothyroxine group primary follicles (black arrow) and secondary follicles (yellow arrow). H&E. 100x.

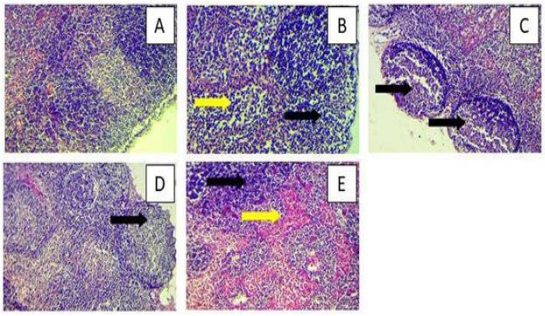

Figure-7 Histological section of mesenteric lymph node of A-control, B-hypothyrodism, C- Sc-SeNPS treated group, D-levothyroxine treated group E-Sc-SeNPS and levothyroxine group, (black arrow). the germinal center (yellow arrow). H&E.200x.

Discussion

The interaction between thyroid hormone and immune regulation has been explored extensively in both physiological and pathological settings. The thyroid hormone demonstrates its effects on the immune system at both nuclear levels by activating transcription factors that are responsible for intracellular signaling and at cellular levels by modulating cytokine release on multiple cells when the innate immune response is taking place (20-22). Immune system components and in particular lymphocytes indicated the innate immune system activity being the defensive line in the body. However, in the present study the effects of hypothyroidism on peripheral blood lymphocytes revealed a lymphopenia indicating immune suppression. Lymphopenia is one of the multi factorial phenomena affected by thyroid hormone level specifically in infection conditions such as Covid-19 infection (23). It is well-established that immunosuppression is associated with hypothyroid conditions (24). Another researchers hypothesized that the thyroid hormones T3 and T4 may encourage T cell proliferation and the decrease in hormones after treatment correlates to the observed decrease in thyroid follicular cells (25). However the imbalance of lymphocytes correlated with thyroid hormones disorder needs more investigation (26).

Humoral immunity, represented by antibodies production by B- lymphocytes, is another form of immune response. Production of antibodies is affected by metabolic disorders resulting in dysregulation of immunological system (27). One of the explanations for the relationship between thyroid hormones and IgG may be the low metabolic rate in hypothyroidism rats. It is well documented the relationship between hypothyroidism and metabolism, the metabolic disorders are common in hypothyroidism (28). Glycosylation, the covalent attachment of sugar moieties to proteins, is the most common and diverse form of post-transcriptional modification of IgG (29). Association of IgG N-glycosylation profiles with metabolic disorder found in hypothyroidism of Hashimoto's thyroiditis patients (30) and cardiovascular disease (31). Result of IL6 in hypothyroidism rat reflect the bidirectional interaction of the thyroid gland activity and proinflammetery activity. It is customary that interleukin 6 increased in response stimulus as acute phase, but it's continuous elevation play pathological effects to induce chronic inflammation and utoimmune disease (32).The increment of IL6 correlated with lower T3 concentration indicated a negative correlation between them (23). This can be attributed to the inflammatory response in hypothyroidism resulted from increased ROS production and the oxidative stress and DNA damage found to be the early events in hypothyroidism (33).
Accordingly, treatment with levothyroxine replaces the thyroid hormone deficiency and restoring the immune system activity as shown by high lymphocytes viability and count. The precise role of the Sc-SeNPs in the lymphocytes and immunity was clearly evident in the present study, even with no thyroid hormones replacement. This result clearly showed that the prepared selenium nanoparticles improved the lymphocytes, increasing evidence suggests that the health benefits of Se can be related to its regulatory capacity of inflammatory response via variable and complex mechanisms (34). It can be concluded that Nano-Se supplementation significantly enhanced the activity of antioxidant enzymes in both serum and liver tissues, with a greater positive influence on immunoglobulin and cytokines production and thyroid activity (35).

The present study aimed to explore the role of Se-nanoparticles thyroid hormones in blastogenic response of lymphocytes of various lymphoid tissue in hypothyroidism rats. The three secondary lymphoid tissues examined in the present study where the cells of the immune system do their actual job of fighting off germs and foreign substances. The most marked histopathological changes denoted in the secondary lymphoid tissues in the present study included lymphoid depletion which is typically characterized by a decrease in the number and size of follicles with few to no germinal centers and/or depletion of paracortical lymphocytes. Defect in thyroid hormones receptors or thyroid hormone deficiency caused suppression in lymphopoiesis (36), because lymphoid cells express thyroid hormone receptors and transporters, configured direct interplay between thyroid hormones and lymphoid cells activity (37). Thyroid hormones activate several cellular signal transduction pathways producing cell activation and proliferation (21). Thyroid hormone deficiency in the present model suggest defect and depression in many genomic responses of lymphoid tissues, because these are important in forming stable complex when binding to DNA triggering activation of transcriptional factors (20). The apoptosis of Peyer's patches lymphoid tissue denoted in the present study could be explained by the absence of thyroid hormones pro apoptotic regulating. Thyroid hormones found to regulate anti-apoptotic activity as demonstrated by (38). In hypothyroidism, the influence of thyroid hormone as a signal molecule to up-regulate the pro-apoptotic protein and thus increase lymphocytic apoptosis rates was clear in Peyer's patches in the group that treated with levothyroxine.
Although, the exact mechanism of Sc-SeNPS in inducing lymphoid hyperplasia in the present study was not fully investigated, but the results indicated appositive role. The Se supplementation as a trace element is important for well immune system performance. However, in the present study there was no Se deficiency, but the supplementation of Se as a nanoparticles improved lymphoid tissue proliferation and reactivated the germinal layers of lymphoid follicles. It was found that Selenium supplementation induced an increase in area of lymphoid tissue (39), on the contrary Se deficiency caused apoptosis and cell cycle arrest in bursa lymphoid tissue (40). All the positive role of selenium may be due to the fact that it is a part of the selenoproteins, antioxidant, anti-inflammatory and anti- apoptotic activities (30).

Conclusion: Thyroid hormones play a role in regulating innate and adaptive immunity. The combination of selenium with levothyroxine is the most effective treatment for hypothyroidism and improves the activity of the immune system cells.

Authors' declaration:
The authors declare no conflict of interest.
We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the Animal care & Welfare committee in College of Vet. Med. University of Baghdad: Ref no. 13021 P.G. 15.06.2023.

Author contributions:
Study conception & design: (Majida A. Al-Qayim). Literature search: (Aryaf M. Sabea). Data acquisition: (Aryaf M. Sabea). Data analysis & interpretation: (Majida A. Al-Qayim). Manuscript

preparation: (Aryaf M. Sabea). Manuscript editing & review: (Aryaf M. Sabea).

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تأثير السيلينيوم والليفوثيروكسين على الجهاز المناعي لجرذان نقص الغدة الدرقية

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الخلاصة:
الخلفية: هناك علاقة عكسية بين جهاز المناعة وهرمونات الغدة الدرقية، لكن كل من هرمونات الغدة الدرقية والسيلينيوم يلعبان دورًا حاسمًا في جهاز المناعة. ومع ذلك، عندما تنخفض مستويات هرمونات الغدة الدرقية (المعروفة باسم قصور الغدة الدرقية)، فإن تأثيرها على خلايا الجهاز المناعي وعلاقتها بمكملات السيلينيوم في الجسم ليست مفهومة جيدًا.
الأهداف: كان الهدف من هذه الدراسة هو دراسة تأثير جزيئات السينانوي على هرمونات الغدة الدرقية والاستجابة الأرومية للخلايا الليمفاوية في الأنسجة اللمفاوية المختلفة في الجرذان المصابة بقصور الغدة الدرقية.
الطرائق البحث: تم تقسيم مجموعة من إناث فئران ويستر، تتراوح أعمارها بين ثلاثة وأربعة أشهر، بشكل عشوائي إلى خمس مجموعات (تحتوي كل مجموعة على 6 فئران) وتم إعطاؤها نظامًا غذائيًا أساسيًا على أساس يومي. ومع ذلك، كانت إمدادات المياه اليومية المقدمة لكل مجموعة مختلفة. كانت المجموعة الأولى هي المجموعة الضابطة وحصلت على مياه عادية، في حين تم إعطاء المجموعات الأربع الأخرى ميثيمازول بنسبة 0.02% في مياه الشرب يوميًا لمدة أربعة أسابيع للحث على قصور الغدة الدرقية. بمجرد التأكد من قصور الغدة الدرقية، تم إعطاء المجموعات التجريبية الثالثة والرابعة والخامسة واحدة من العلاجات الثلاثة التالية لمدة أربعة أسابيع، على التوالي: SC-SeNPs (0.1 ملغ من السيلينيوم لكل كيلوغرام في اليوم) مثل T1، ليفوثيروكسين (0.9 ميكروغرام لكل 100 غرام). يوميًا) مثل T2، أو 0.1) SC-SeNPs مجم من السيلينيوم لكل كجم يوميًا) وليفوثيروكسين (0.9 ميكروجرام لكل 100 جرام يوميًا) مثل T3. في النهاية، تم جمع عينات الدم من الحيوانات الموت الرحيم باستخدام جرعة عالية من التخدير، وتم الحفاظ على عينات الأنسجة اللمفاوية (الطحال، بقع باير والعقدة الليمفاوية المساريقية) في 10٪ من الفورمالين.**النتائج**: لقد كشف بحثنا أن IgG، وهو علامة المناعة الخلطية، وجد أنه انخفض بشكل ملحوظ في قصور الغدة الدرقية. ومع ذلك، عند العلاج باستخدام ليفوثيروكسين بمفرده أو بالاشتراك مع Sc-SeNPs، وجد أن مستوى علامة المناعة الخلوية، IL-6، ارتفع بشكل ملحوظ في قصور الغدة الدرقية بالمقارنة مع المجموعة الضابطة. بالإضافة إلى ذلك، لاحظنا تغيرات نسيجية مرضية في الأنسجة اللمفاوية لدى الجرذان المصابة بقصور الغدة الدرقية، والتي تضمنت استنفاد اللب الأبيض للطحال مع احتقان في الأوعية الدموية، وانخفاض في الجريبات اللمفاوية لبقع باير، وانخفاض في الجريبات الأولية والثانوية للطحال. الغدد الليمفاوية المساريقية.
الاستنتاج: تلعب هرمونات الغدة الدرقية دورًا في تنظيم المناعة الفطرية والتكيفية. يعتبر مزيج السيلينيوم مع الليفوثيروكسين هو العلاج الأكثر فعالية لقصور الغدة الدرقية وتحسين نشاط خلايا الجهاز المناعي.
الكلمات المفتاحية : قصور الغدة الدرقية ، SC-SeNPs ، ليفوثيروكسين ، الجهاز المناعي ،IGg ،IL-6.