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Effects of Simvastatin on Histomorphological and Biochemical Parameters of the Thyroid in Rats

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Abstract

Objective: This study intended to explore the effect of simvastatin on the thyroid gland's biochemical function and histological structure in a rat specimen.

Methods: An experimental study using a controlled laboratory model from January 2022 to January 2023. This study was conducted at Army Medical College, Armed Forces Institute of Pathology Rawalpindi in collaboration with the National Institute of Health Islamabad, Rawalpindi over one year. Forty male Sprague-Dawley rats weighing approximately 250 grams and between the ages of 3-4 weeks were randomly assigned into identical groups: a control group (A) and an experimental group (B), which received simvastatin for 12 weeks. After the test, rats were euthanized, and their thyroid glands were harvested for analysis. The glands were examined histologically to assess for structural changes, inclusive of size of diameter of thyroid follicles. In addition, serum levels of thyroxine (T4) and thyroid-stimulating hormone (TSH) were assayed. Data have been analyzed using SPSS software version 23. Statistical significance was expressed using Chi-square checks for qualitative records and independent sample t-test for quantitative comparisons, with $P < 0.05$ considered significant.

Results: Simvastatin treatment resulted in noteworthy differences in the biochemical profile, with a noticeable decrease in serum T3 level (p=0.001) s and a rise in thyroid-stimulating hormone (TSH) (p=0.001) levels compared to the control group. Supplementary noticeable histological changes in the thyroid glands of the rats were detected and characterized by decreased diameter of thyroid follicles (p=0.001).

Conclusions: The results of this study specify that Simvastatin induces considerable alterations in endocrine profile and variations in thyroid gland histology in rats. These results propose that the drug could influence thyroid health, with probable implications for long-term statin use in clinical situations.

Keywords: Hypothyroidism, Hyperthyroidism, Thyroid Diseases, Apoptosis, Endocrine Gland, Metabolism

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Introduction

Statins have significantly enhanced the treatment of dyslipidemia, expressively lowering the risk of cardiovascular disease. Regardless of their widespread use, there are continuing fears regarding potential side effects, particularly with long-standing treatment. Muscle-related issues, such as myopathies, are well-known, but the influence of statins on the structure and function of the thyroid gland is less clearly understood.[1] The thyroid is essential for regulating metabolism, growth, and energy production through its hormones, mainly thyroxine (T4) and triiodothyronine (T3). Any disorders of the thyroid's structure can lead to major metabolic problems, such as hypothyroidism or hyperthyroidism, both of which have systemic effects on the body.[2]

Some researchers advocate that statins might alter thyroid function by triggering inflammatory responses, causing cellular damage, or endorsing the buildup of harmful substances in the gland.[3] These mechanisms could lead to structural changes in thyroid tissue, such as modifications in the follicular architecture, colloid content, or blood supply to the gland.[4] However, the results of these studies remain unpredictable. While some studies show a conceivable link between statin use and thyroid variations, others fail to support such a link. The basic structural changes that could elucidate these effects are not well-characterized.[5]

This study aimed to provide a comprehensive examination of how Statins affect thyroid histology and function. By evaluating the thyroid tissue from rats treated with statins, we identified any structural and biochemical fluctuations. Our inclusive assessment focused on modifications in thyroid follicles, epithelial integrity, and vascular patterns, along with biochemical indicators of thyroid function.

The results of this study highlight notable structural changes in the thyroid tissue of statin-treated rats, accompanied by evidence of disrupted thyroid function.[6] These findings suggest a direct toxic effect on the thyroid, which could alter its normal activity and potentially lead to clinical conditions, such as hypothyroidism or metabolic imbalances.[7] The observed changes may also have broader consequences for metabolic control, as thyroid hormones play a crucial role in the regulation of lipid and glucose metabolism.

The results of this study will contribute to an improved understanding of the potential risks associated with long-term statin use, particularly about thyroid health. These insights may help in refining therapeutic strategies and ensuring safer management of patients who require extended statin therapy while diminishing risks to thyroid function. The observed changes may also have broader consequences for metabolic control, as thyroid hormones play a crucial role in the regulation of lipid and glucose metabolism. The results of this study will contribute to an improved understanding of the potential risks associated with long-term statin use, particularly about thyroid health. These insights may help in refining therapeutic strategies and ensuring safer management of patients who require extended statin therapy while diminishing risks to thyroid function.

Materials And Methods

This research study was conducted in the Army Medical College, Armed Forces Institute of Pathology Rawalpindi in collaboration with the National Institute of Health Islamabad, Rawalpindi over one year. The study spanned over a year from January 2022 to January 2023, and it was a laboratory-based experimental design. Before initiation of the study, forty male Sprague-Dawley rats, each weighing approximately 250 grams and between the age of 3-4 weeks,[8] were randomized using a computer-generated sequence with stratification by weight and divided into two groups: control group (A) and experimental group (B). The control group was given a standard diet and water for 12 weeks,[9] while the experimental group was given a standard diet supplemented with 60 mg/kg/day of simvastatin orally for the same period. Drug solutions were prepared and coded by independent pharmacy staff to ensure blinding. Three separate teams were responsible for animal handling and drug administration, tissue collection, and histological analysis, respectively, with all laboratory personnel remaining blinded to group allocation until data analysis was completed. At the end of the study, the rats were euthanized, and their thyroid glands were collected for analysis. Additionally, a 5 ml blood sample was taken via cardiac puncture for the measurement of thyroid hormones and thyroid-stimulating hormone (TSH) levels in both groups. Histological slides were randomly coded to ensure unbiased assessment. Tissue sections were processed, dehydrated in ascending alcohol series, and cleared with xylene. They were impregnated and embedded with paraffin, then sectioned at 5μm. Sections were stained with Hematoxylin and Eosin (H&E) and mounted with Canada balsam and coverslips. Hematoxylin & Eosin-stained tissue sections were examined under a 40X lens to assess the thyroid glands' histoarchitecture. An Olympus® Bx43 microscope with a Digital Camera was used for observation and photography. Images were analyzed using Image J software, and calibrated with a linear stage micrometer. For each animal, two slides were studied, and six random fields from each slide were photographed under 40X magnification.

The diameter of five randomly selected thyroid follicles was measured using a stage and ocular micrometre. Measurements included the maximum transverse diameter and a perpendicular diameter, both taken from the basement membrane to the basement membrane. The average follicular diameter was calculated as the mean of these two measurements, and the average diameter of the five follicles was recorded as the final reading for each animal. Thyroid gland mass was also measured using the Standard Analytical Balance LSAB-A20 model with a weighing capacity of 210 g with a minimum weighing of 0.004 g and 80 mm / 90 mm of pan size. Using a commercial ELISA kit from Pierce-Endogen (Rockford, IL), a sandwich ELISA technique was employed to measure the levels of T3 and TSH in plasma. The concentrations are reported as pictograms per millilitre of plasma, with values obtained using the manufacturer-provided standards and controls. To ensure consistent results and account for potential plate-to-plate variability, control samples were assessed alongside experimental samples on separate analysis days, ensuring stability and uniformity in T3 and TSH measurements. Male Sprague-Dawley rats were indiscriminately assigned to control (Group A) and experimental (Group B) groups. The rats were acclimatized to standard laboratory conditions with free access to food and water. Initial body weights were documented at the start of the study, and final body weights were measured at the end. The weight gain was calculated by subtracting the initial body weight from the concluding body weight for each rat. All measurements were taken using a calibrated digital balance with a precision of up to 0.1 g.

Data analysis was conducted using SPSS software version 23. Qualitative variables were expressed as percentages and frequencies, and Chi-square tests were used to compare these variables between groups, with $P < 0.05$ indicating statistical significance. Quantitative data was expressed as Mean ± SD. The Shapiro-Wilk test was used to assess the distribution of the data, and independent sample t-tests were employed to conclude statistical significance between groups.

Results

A comparative analysis between the control (Group A) and experimental (Group B) groups revealed significant distinctions across several parameters. The general morphological structure of the thyroid gland was consistent across the control and statin-treated groups. Hematoxylin & Eosin-stained sections, examined under 10X magnifications, revealed notable histological differences in the statin-treated group. Initial weight (g) did not differ significantly between groups (280.74±15 vs. 282.30±14; p=0.679); however, Group A exhibited a significantly higher final weight (g) than Group B (333.35±12 vs. 317.19±14; p=0.001). Despite greater weight gain (g) in Group A (49.30±18 vs. 34.94±20), this difference did not reach statistical significance (p=0.006). Thyroid follicular diameter (mm) and gland weight (mg) were both notably greater in Group A compared to Group B (112.52±3 vs. 98.26±3; p=0.001, and 26.78±4.5 vs. 23.21±2.8; p=0.001, respectively). Additionally, serum T3 (ng/dL) and TSH (mIU/L) levels were markedly altered in Group A & B (3.82±1.06 vs. 2.56±1.77; p=0.001 and 4.97±0.3 vs. 3.89±1.02; p=0.001, respectively). These findings underscore pronounced biochemical and morphological alterations in the experimental group, particularly affecting thyroid structure and function as shown in Table 1.

Table 1: Comparative Analysis of Histological and Biochemical Parameters in Control and Experimental Groups

Parameter	Control group A	Experimental group B	p-value
Initial Weight (g)	280.74±15	282.30±14	0.679 NS
Final Weight (g)	333.35±12	317.19±14	0.001*
Weight Gain (g)	49.30±18	34.94±20	0.006 NS
Thyroid Follicular Diameter (µm)	112.52±3	98.26±3	0.001*
Thyroid Gland Mass (mg)	26.78±4.5	23.21±2.8	0.001*
Serum T3 (ng/dL)	3.82±1.06	2.56±1.77	0.001*
Serum TSH (mIU/L)	3.89±1.02	4.97±0.3	0.001*

- *p-value indicates statistical significance ≤0.005
- NS- Not significant

Thyroid Follicular Diameter

The control group had a mean diameter of 112.52±3 µm. The statin-treated group had a mean diameter of 98.26±3µm. The statin-treated group had a significantly lower mean diameter than the control group (p = 0.003).

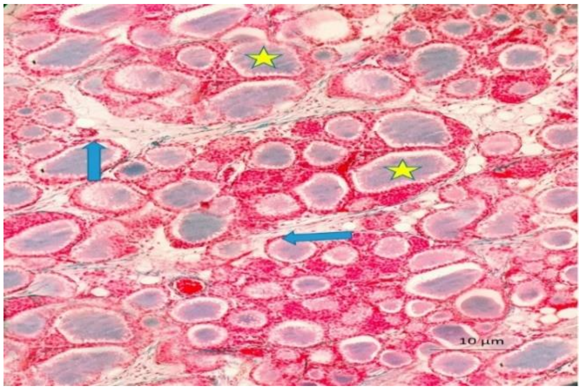

Figure 1: A Photomicrograph of Control Group A showing no disruption of the histological structure of the thyroid (10X, H&E). The follicles (Arrow) are relatively uniform in size and shape. The colloid (Star) appears dense and abundant. The overall thyroid architecture is well-maintained.

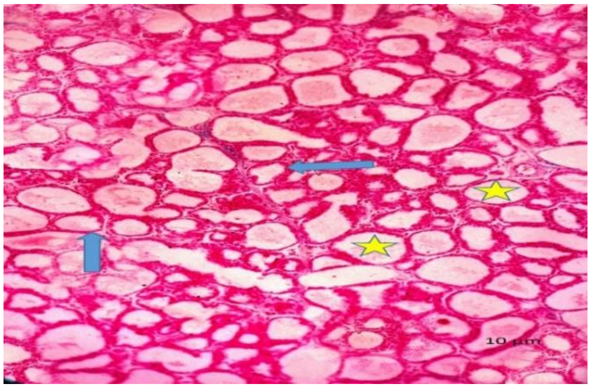

Figure 2: A Photomicrograph of Experimental Group (B) showing disruption of the histological structure of the thyroid (10X, H&E). The follicles (Arrow) are irregular in size and shape, with variability in their diameters. The colloid (Star) content is reduced and appears more fragmented. There is increased interstitial space and disrupted follicular arrangement.

Discussion

Recent studies have explored the effects of statins, particularly on various organ systems, including the thyroid gland. Statins, which are widely used to lower cholesterol, have been shown to influence thyroid function due to their interaction with lipid metabolism. The present study reveals the effects of Simvastatin which is an HMG-CoA Reductase Inhibitor on histological and biochemical parameters of the thyroid gland in the experimental group. The significant differences observed indicate the impact of experimental treatment on thyroid morphology and function.

The absence of noteworthy differences in initial weight between the two groups suggests homogeneity at the commencement of the study. Nonetheless, the prominent increase in the final weight in the control group compared to the experimental group specifies a differential response to the intervention, possibly reflecting changed metabolic rates or energy utilization in the experimental group. The tendency towards an increase in weight gain in the control group, although not statistically significant, is a physiological response or adaptive mechanism in the deficiency of the treatment. The noticeable decrease in serum T3 and an upsurge in TSH levels in the experimental group compared to the control correlates with the histological findings. T3 is vital for metabolic regulation, and its decline is suggestive of compromised thyroid function, which may result from reduced gland mass and changed follicular integrity. Similarly, the decreased TSH levels advocate a feedback mechanism in response to lower circulating T3, further accentuating the functional impairment of the thyroid gland as advocated by Wang et al., 2023.[10] The findings are consistent with previous studies demonstrating that interventions disturbing thyroid morphology can lead to momentous variations in serum hormone levels, reflecting both direct and indirect effects on endocrine regulation as considered by Jasim et al.[11]

Statins seem to influence thyroid hormone levels, precisely by reducing thyroid-stimulating hormone (TSH) levels.[12] This drop in TSH levels is supposed to be mediated by cholesterol variations, representing a direct link between lipid metabolism and thyroid hormone regulation. The current study has shown profound morphological modifications in the thyroid gland of rats treated with simvastatin, characterized by substantial changes in follicular diameter and gland mass. The experimental group showed a prominent reduction in thyroid follicular diameter. This signifies a substantial decrease in follicular size which is a critical indicator of potential thyroid gland damage. A preceding investigation by Khan et al, has reliably linked reduced follicular diameter with hypothyroid states and changed thyroid hormone synthesis.[13] Concomitantly, the thyroid gland weight displayed a substantial decrease further authenticating the observed structural variations. Pharmacological interventions can bring substantial histological deviations in the thyroid gland, leading to alterations in follicular architecture and glandular size.[14] This histological change aligns extraordinarily well with the biochemical indicators observed in this research. The decrease in follicular diameter and gland mass paralleled directly with the noteworthy reduction in serum T3 and TSH levels, suggestive of a complex interplay among structural alterations and hormonal regulation. Wang et al., provide an understanding of the feedback mechanism linked with such changes, emphasizing how reduced circulating T3 levels can activate adaptive responses in the hypothalamic-pituitary-thyroid axis.[15] The perceived decrease in both follicular size and hormone levels specifies a potential comprehensive disturbance of thyroid function which is induced by simvastatin. The diverse nature of the follicular change advocates that the influence of simvastatin on thyroid morphology is varied. J. He et al., have hitherto noted that numerous stressors can lead to histopathological fluctuations in thyroid tissues,[16] often leading to hormone level dysregulation. The histological changes witnessed in this study are consistent with broader consequences for metabolic regulation. The decrease in thyroid gland mass and follicular diameter could elucidate the concomitant changes in body weight and metabolic parameters, supported by observations by Smith et al., and Johnson & Brown vis-à-vis the affiliation between metabolic processes and thyroid function.[17]

Furthermore, the dissimilarities in thyroid parameters detected in this study are in line with the recent bulk of research that deliberates on the gentle nature of the thyroid gland concerning environmental and pharmacological effects. For instance, recent evaluations specify that several stressors can lead to histopathological variations in thyroid tissues, recurrently resulting in dysregulation of hormone levels.[18] These inferences deserve further consideration of the mechanisms by which the intervention affects thyroid morphology and function, as explaining these pathways is critical for developing methodologies to mitigate antagonistic effects. Raised thyroid-stimulating hormone (TSH) levels in the experimental group might be accredited to the early stages of thyroid dysfunction, where increased TSH production compensates for compromised thyroid hormone synthesis.[19] This response specifies an alteration in thyroid physiology, highlighting the necessity for further research on the molecular mechanisms driving these changes.[20]

These findings highlight the probable dual effects of statins on both the histological structure and biochemical function of the thyroid gland, providing a foundation for further studies, particularly in rat models.

In summary, the substantial changes observed in thyroid histology and biochemistry following intervention have profound implications for thyroid health. These findings contribute to the growing body of evidence regarding the impact of various treatments on thyroid function and underscore the importance of monitoring thyroid parameters in experimental and clinical settings. Further research is needed to fully understand the implications of these findings and the potential long-term effects of statin use on thyroid health.

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Conclusions

Conferring to this study, statins have a noteworthy effect on the biochemical parameters and histomorphology of the thyroid gland. Rats served with simvastatin showed multiple changes, including changes to the structure of the thyroid, in contrast to the controls. Worrisome results, comprising changes in thyroid hormone levels, were also shown by chemical analysis, which further suggests that thyroid function may be disturbed. These findings revealed the significant influence that statins have on thyroid health and the necessity of additional research on the long-term effects of these medications on thyroid function.

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Contributions:
A.Q - Conception of study
H.G.K - Experimentation/Study Conduction
M.S.A - Analysis/Interpretation/Discussion
N.A - Manuscript Writing
R.K.Y, A.A - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.