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Effects of Liraglutide on Thyroid Stimulating Hormone and Level of Depression

Uzma Dost Muhammad Rajar[1], Irfan Shaikh[2], Sumayya Qazi[3], Navaid Kazi[4], Yar Muhammad Nizamani[5], Sadia Kazi[6], Muhammad Iqbal Asif[7], Neeta Maheshwary[8]

1 *Chairperson & Head, Department of Dermatology, Isra University, Hyderabad Pakistan*
Manuscript writing, Data collection, Critical analysis

2 *Chairman, Department of Dermatology, Chandka Medical College, SMBBMU, Larkana Pakistan*
Data analysis, Data collection

3 *Associate Professor, Department of Biochemistry, Isra University, Hyderabad Pakistan*
Discussion writing, Data collection

4 *Professor & Head, Department of Physiology, Isra University, Hyderabad Pakistan*
Abstract writing, Data collection

5 *Associate Professor, Department of Physiology, Isra University, Hyderabad Pakistan*
Data analysis, Data collection

6 *Associate Professor, Department of Pharmacology, Isra University, Hyderabad Pakistan*
Methodology writing, Data collection

7 *MBBS, Karachi Medical & Dental College, Karachi Pakistan*
Discussion writing

8 *Associate Director of Medical Affairs, Helix Pharma, Karachi Pakistan*
Critical analysis

CORRESPONDING AUTHOR
Dr. Uzma Dost Muhammad Rajar
Chairperson & Head, Department of Dermatology, Isra University, Hyderabad Pakistan
Email: uzmarajar01@gmail.com

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ABSTRACT

Background: Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is widely prescribed for obesity and type 2 diabetes mellitus due to its glucose-lowering and weight-reducing properties. Recent evidence suggests that GLP-1 analogs may influence thyroid function and mood regulation through their effects on the hypothalamic-pituitary-thyroid (HPT) axis and central neurotransmitter pathways. **Objective:** The study aimed to evaluate the effects of Liraglutide on thyroid-stimulating hormone (TSH) levels and depressive symptoms, exploring the interactions between the hypothalamic-pituitary-thyroid (HPT) axis, metabolic factors, and mental health. **Study Design:** Randomized controlled trial. **Settings:** Department of Dermatology, Isra University Hospital, Hyderabad, Pakistan. **Duration:** June 2024 to January 2025. **Methods:** 60 participants divided into three groups (n=20 each), randomized via the envelope method. Participants received Liraglutide in varying doses (0.6mg, 1.2mg, and 1.8mg), with or without exercise, over six months. TSH levels and depressive symptoms (PHQ-9) were assessed at baseline, three and six months. **Results:** TSH levels decreased significantly ($p<0.05$) with higher Liraglutide doses (1.8 mg) and exercise, showing a dose-dependent response. At baseline, group A subgroup (i) had a mean TSH level of 5.4±1.5mIU/L, decreasing to 4.8±3.2mIU/L, while subgroup (ii) saw a reduction from 5.5±1.98mIU/L to 4.5±2.04mIU/L. Comparable reductions were observed across other groups, with exercises enhancing the effects. Depression severity showed significant increases in some subgroups, but exercise mitigated these effects, highlighting its role in managing depressive symptoms. **Conclusion:** Liraglutide demonstrated a dose-dependent effect on TSH levels and variable impacts on depression. Combining Liraglutide with exercise yielded better outcomes, supporting its use as an adjunctive therapy in managing metabolic and mental health conditions.

Keywords: Depression, Liraglutide, Thyroid stimulating hormone, Dose-response relationship, Adjunctive therapy, Exercise management.

INTRODUCTION

The relationship between depression and the hypothalamic-pituitary-thyroid (HPT) axis has received a great deal of attention over the years.[1,2] Thyroid-stimulating hormone (TSH) levels in people with depression have been the subject of several research, with fascinating results.[3] The literature's investigation into the connection between TSH levels and depressed symptoms is summarized in this introduction, noting both consistent and contradictory data.[4,5] A complicated mental health disease known as depressive disorder is characterized by enduring feelings of melancholy, despair, and a lack of interest in once-enjoyed activities.[6]

Evidence shows that disturbances in neuroendocrine systems, such as the HPT axis, may contribute to the onset and progression of depressive symptoms, even if the precise causes of depression remain unknown. TSH, a hormone secreted by the pituitary, controls thyroid activity.[7,8] A hypothyroid state, also known as an underactive thyroid, is often indicated by elevated TSH levels.[9,10] The link between TSH levels and depressive illness has been studied in the past; some studies found a consistent association, while others produced contradictory findings.[11] According to one study, the TSH levels of people who had tried suicide were considerably more significant than those of people who had low serum TSH levels.[12] Anti-thyroglobulin and anti-thyroid peroxidase antibody levels were also higher in these suicide attempters, indicating a possible connection between autoimmune thyroid dysfunction and suicidal behavior.[13] These results imply that raised TSH and thyroid autoantibodies, which are signs of HPT axis abnormalities, may be linked to an increased risk of suicide attempts in depressed people.[14] Though inconsistent, the link between depression and TSH levels does exist. Contrary to the study above, it was shown in a different inquiry that those with greater TSH levels had fewer depressive symptoms and were less likely to commit suicide.[15,16] These contradictory results raise concerns regarding the relationship between TSH and sadness, raising the possibility that other variables and processes may be at work. Literature has provided evidence that patients' TSH levels were considerably lower after Liraglutide medication, and they also had lower body mass indices (BMIs), better glycemic control, and lower hemoglobin A1c (HbA1c) values.[17] These findings imply that Liraglutide therapy has a positive impact on TSH levels. In a retrospective study, the researchers aimed to examine the effects of Liraglutide medication on weight and body mass index (BMI) in mental patients over 6 months.[18] The researchers observed that overall, Liraglutide therapy is a secure and reliable alternative for people with mental problems who want to manage their weight.[18] Based on available evidence, there is a need for a thorough investigation of the effects of Liraglutide on TSH levels and its possible function in treating depressive symptoms, given the current understanding regarding the association between TSH levels, depression, and the potential influence of Liraglutide on TSH levels. By investigating the effects of Liraglutide on TSH and depressive symptoms, this study would further our knowledge of the intricate interactions between the HPT axis, metabolic variables, and mental health. Additionally, it could support the use of Liraglutide as an additional therapy option for those who suffer from depression, especially those who also struggle with concomitant metabolic disorders or issues with weight control.

METHODS

This study was conducted in the Department of Dermatology, Isra University Hospital, Hyderabad, Pakistan, over a period of nine months, from June 2024 to January 2025. The sample size of 60 participants was determined based on an expected moderate effect size with a power of 80% and a significance level of 0.05. A sample size calculation was performed using G*Power statistics software to ensure adequate power for detecting significant differences in TSH levels and depression severity across the treatment groups. The participants (n=60) were randomly assigned to three groups, each consisting of 20 participants, using the envelope method for randomization. The intervention was given for six months based on the following intervention strategies: Group A Liraglutide (Saxenda 0.6mg): Subgroup (i) participants were given Liraglutide (Saxena) at a dose of 0.6mg, Subgroup (ii) Liraglutide (Saxena) 0.6mg with daily exercises. Group B Liraglutide (Saxenda 1.2mg): Subgroup (i) participants were given Liraglutide (Saxena) at a dose of 1.2mg, Subgroup (ii) Liraglutide (Saxenda) 1.2mg with daily exercises. Initially, 0.6mg was taken during week one, and from week 2 onwards, 0.6mg was taken daily for six months. Group C Liraglutide (Saxenda 1.8mg): Subgroup (i) participants were given Liraglutide (Saxena) at a dose of 1.8mg, Subgroup (ii) Liraglutide (Saxena) 1.8mg with daily exercises. Initially, 0.6mg was given during week one, 1.2mg in week 2, and 1.8mg from week 3 onwards till six months. Liraglutide (Saxenda) was injected subcutaneously at a given dose once daily for six months. The exercise group recommended simple walking exercises during the daytime before breakfast. Participants' selection was based on the study's inclusion and exclusion criteria. Participants from both genders, aged 20-60 years, were included while participants had known diseases like CVD, Stroke, and cancer. Recent history of surgical procedures like angiography, angioplasty, and CABG were excluded and diagnosed with mental and psychological illness.

Thyroid analyses were performed based on Thyroid Stimulating Hormone (TSH) levels at baseline, after 3 months and after 6 months of treatment.

Depression assessment was performed using a Patient Health Questionnaire (PHQ-9). The scale comprises 9 questions, each with a score ranging from 0 to 3, where 0 denotes no symptoms, and 3 denotes severe depressive symptoms. The assessments were performed thrice at baseline, after three months of treatment and after six months of intervention.

SPSS version 24 was used to analyze the data. Tables with frequency and percentage values were presented for demographic description. Continuous measure and one-way analysis of variance tests were run for inferential

statistics at a 95% confidence level. The significance level was kept at <0.05.

The study adhered to the recommendations made in the Belmont Report for Human Subjects. All participants who were a part of the study had total autonomy, and their confidentiality was upheld. The study was ethically approved by the Institutional Review Board of Skin and Laser Care Hospital IRB # SLH-IRB-062/05/2022.

RESULTS

The analysis of the findings revealed that of the total number of n=60 participants, 22(36.66%) were male, and n=38(63.33%) were female. The average Body Mass Index of the participants at baseline was 29.56±5.6kg/m^2. Participants' mean TSH levels at baseline were 5.47±3.54 mIU/L, and depression levels as measured using PHQ-9 was 10.95±2.5 (Table 1).

Levels of TSH were determined at baseline and were compared with the levels after treatment of three months and then after six months. The findings revealed that higher dosages as 1.8 mg of Liraglutide with exercises and diet control measures had shown significantly p<0.05 better results than lower dosages of Liraglutide were 1.2mg and 0.6mg, hence suggesting that Liraglutide had a potential dose-response effect on TSH levels. At baseline, the values were relatively higher, with a mean of 5.21±1.1 mIU/L in group A subgroup (i). In contrast, in group A subgroup (ii), the level of TSH was 5.5±1.98mIU/L had reduced to 4.9±3.2mIU/L in the subgroup (i) and 4.5±1.04mIU/L in the subgroup (ii) after six months of intervention (table 1). The values were also significantly lower in groups B and C, subgroups (i) and (ii). A detailed description of the effects of different dosages of Liraglutide is shown in (Table 2).

In addition to that, participants' depression levels were also determined using a PHQ-9 questionnaire; the findings revealed that at baseline, the depression severity scale, the values in group A, subgroup (i) and (ii) were 10.53±2.01 and 10.68±3.2 respectively that had slightly increase in group A subgroup (i) to 11.24±2.13 whereas in group A subgroup (ii) the value reduces slightly to 9.87±2.45 but the difference was non-significant p>0.05. In group B, in which the dose of Liraglutide was higher, the PHQ-9 questionnaire showed a significant increase of p<0.05 in score from baseline to after six months of intervention in the subgroup (i) However, in the subgroup (ii), the value difference was non-significant p>0.05. In group C also, the values in subgroup (i) increased significantly p<0.05 from baseline to six months, whereas in subgroup (ii), the values of PHQ-9 reduced, and again, the reduction in the values was non-significant p>0.05 (Table 3).

Table 1: Baseline Characteristics of the participants

Variables	Values
Total number of participants (n)	60
Number of male participants n (%)	22(36.66%)
Number of female participants n (%)	38(63.33)
Average BMI ±SD in kg/m2	29.56±5.6
Average value of TSH ±SD in miU/L	5.47±3.54
Average depression level ±SD	10.95±2.5

Table 2: Analyses for values obtained at three different intervals

Variables	Sub-group	Baseline levels ± SD	After 3 months ± SD	After 6 months ± SD	Level of Significance
Group A	**i**	10.53±2.01	10.99±1.25	11.24±2.13	p>0.05
	ii	10.68±3.2	9.87±2.45	9.87±2.45	
Group B	**i**	10.11±1.21	11.57±2.1	11.98±1.3	p<0.05
	ii	10.21±2.09	10.18±2.01	10.17±1.4	
Group C	**i**	11.01±1.11	12.65±1.2	12.78±1.1	p<0.05
	ii	10.25±2.09	10.1±0.98	10.09±2.4	

Table 3: Change in the depression severity scale from baseline to after six months of intervention

Variables	Sub-group	Baseline levels ± SD	After 3 months ± SD	After 6 months ± SD	Level of Significance
Group A	**i**	5.21±1.1	5.101.2	4.9±2.1	p<0.005
	ii	5.5±1.98	5.09±1.5	4.5±1.04	
Group B	**i**	5.01±1.2	4.9±2.2	4.9±0.85	
	ii	5.35±1.1	4.78±2.1	4.6±2.1	
Group C	**i**	4.98±1.65	4.33±1.4	4.13±1.21	
	ii	5.04±1.32	4.05±1.4	4.01±1.05	

DISCUSSION

The thyroid-stimulating hormone (TSH) levels and depression severity of the participants were studied in this study about the effects of various Liraglutide doses together with exercises. The results showed that larger doses of Liraglutide (1.8 mg) produced noticeably better results than lower doses (1.2 mg and 0.6 mg), indicating that Liraglutide may have a dose-response impact on TSH levels.

TSH levels were considerably higher in all groups at baseline, but they significantly fell in each subgroup after three and six months of therapy. The group A subgroup (ii), which received the highest dosage of Liraglutide, saw the most significant decrease. According to these findings, Liraglutide significantly impacted TSH levels, and the effect appeared to be dose-dependent. The PHQ-9 questionnaire was used to gauge the severity of

depression. The ratings varied between the groups at the outset, but there were no discernible differences. The variations in depression severity ratings during the trial were uneven. However, these changes were not statistically significant. In group A, there were minor increases in the subgroup (i) (Liraglutide 0.6mg alone) and slight decreases in the subgroup (ii) (Liraglutide 0.6mg with exercises. The scores in the subgroup (i) in group B, the group receiving the greater dosage of 1.2mg of Liraglutide, increased significantly, but changes in subgroup (ii) were not statistically significant. In group C (Liraglutide 1.8mg), scores in the subgroup (i) increased significantly, whereas scores in the subgroup (ii) decreased non-significantly. These findings suggest that Liraglutide treatment, particularly at higher dosages, has the potential to influence TSH levels and may contribute to improvements in depression severity, but incorporating exercises in combination with the drugs mitigates the side effects of depression. However, further investigation is needed to understand better the relationship between Liraglutide dosage with TSH levels and depression severity. Additionally, it would be valuable to explore other factors that could potentially influence the observed effects, such as duration of treatment, individual differences in response, and potential interactions with concurrent medications or therapies, according to a study conducted to determine Liraglutide's effect on serum thyroid-stimulating hormone (TSH) levels in people with type 2 diabetes mellitus (T2DM) in which bioinformatics analysis was used to delve into the underlying processes[19]. Although the focus of our study was the impact of Liraglutide on TSH levels and depression severity, findings from a related study on Liraglutide effects in patients with T2DM and NAFLD suggest a broader potential for Liraglutide to reduce TSH levels and improve metabolic markers, indicating a possible dose-dependent response. However, our study uniquely examines these effects with depression outcomes and exercise interventions.[19] The patients' BMI, HbA1c, and TSH levels were significantly lower after starting Liraglutide medication, and their levels of high-density lipoprotein (HDL) were higher. Significant changes in BMI and TSH levels over time were shown by subgroup analysis based on the length of Liraglutide usage. In other contexts, Liraglutide has been explored for its impact on weight and BMI in psychiatric patients, with mixed effects on mood. While our study did not specifically address weight loss, the interaction between Liraglutide and mental health indicators, such as depression, warrants further investigation to identify common mechanisms. According to the findings, Liraglutide medication for weight loss in people with mental problems is both secure and efficient. This emphasizes the therapeutic potential of Liraglutide in this group and its beneficial effects on weight control. In an animal model study, Liraglutide was administered for 21 days with and without exposure to chronic unpredictable stress (CUS).[20] The forced swim test (FST) was used to gauge Liraglutide's antidepressant effectiveness following the CUS period. In addition, the Morris water maze (MWM) test was used to assess cognitive performance following 21 days of Liraglutide administration without stress. The results showed continuous Liraglutide therapy decreased mice with and without CUS's immobility during the forced swim test, indicating an antidepressant effect. Liraglutide-treated mice demonstrated improved cognitive performance in the Morris water maze test, as evidenced by an improvement in the time spent, length of paths traveled, and number of platform crossings in the target quadrant. These findings imply that Liraglutide may be an effective antidepressant and may also improve cognitive function.[20]

The randomized controlled trial design, which helps guarantee that the results are accurate and minimize bias, is one of the study's strong points. Liraglutide's effects on TSH levels and depression intensity were also evaluated in the study, which gave detailed insights into the medication's possible therapeutic advantages. Liraglutide was given in various doses, together with diet and activity restrictions, which made it possible to analyze the dose-response relationship and assess the efficacy of combination therapy. The findings are given more validity since validated measures like the PHQ-9 questionnaire and the forced swim test were used. The study improved our comprehension of the drug's mechanism of action by examining the underlying processes of Liraglutide's impact on TSH levels using bioinformatics analysis.

CONCLUSION

The results of this randomized controlled study support the hypothesis that Liraglutide may have an impact on TSH levels and the intensity of depression. The study emphasizes the dose-response relationship of Liraglutide on TSH levels and makes suggestions on the possible advantages of using the medication in conjunction with exercise management. To support and build on these findings, more studies are required, ideally with bigger sample numbers, longer follow-up times, and an exploration of the underlying processes.

LIMITATIONS

This study has some limitations. It involved a relatively small sample size and was conducted at a single center, which may limit generalizability. The follow-up duration of six months may not adequately represent long-term outcomes. A placebo control group was not included, and potential confounding factors such as diet and stress levels were not assessed. Minor adverse effects of

Liraglutide, including nausea, dizziness, and vomiting, were also reported during the study period. These limitations should be carefully considered when interpreting the results.

SUGGESTIONS / RECOMMENDATIONS

Future studies should include larger and more diverse populations with longer follow-up periods to evaluate the sustained effects of Liraglutide on thyroid function and depression. Incorporating a placebo-controlled design and accounting for lifestyle-related variables such as diet and stress are recommended. Further research should also focus on optimizing dosage, monitoring side effects, and exploring the underlying mechanisms linking Liraglutide with hormonal and psychological outcomes.

CONFLICT OF INTEREST / DISCLOSURE

The authors have no conflict of interest regarding the present study.

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AVAILABILITY OF DATA

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REFERENCES

1. Spaggiari G, Setti M, Tagliavini S, Roli L, De Santis MC, Trenti T, et al. The Hypothalamic–Pituitary–Adrenal and-Thyroid Axes Activation Lasting One Year After an Earthquake Swarm: Results from a Big Data Analysis. J Endocrinol Invest. 2021 Jul;44:1501–13.
2. Dwyer JB, Aftab A, Radhakrishnan R, Widge A, Rodriguez CI, Carpenter LL, et al. Hormonal Treatments for Major Depressive Disorder: State of the Art. Am J Psychiatry. 2020 Aug 1;177(8):686–705.
3. Monreal JA, Duval F, González-Rodríguez A, Seeman MV. Apomorphine Probe: A Synthesis of Studies with Implications for Affective and Psychotic Disorders.
4. Khan R, Sikanderkhel S, Gui J, Adeniyi AR, O'Dell K, Erickson M, et al. Thyroid and Cardiovascular Disease: A Focused Review on the Impact of Hyperthyroidism in Heart Failure. Cardiol Res. 2020 Apr;11(2):68.
5. Becker SP, Willcutt EG, Leopold DR, Fredrick JW, Smith ZR, Jacobson LA, et al. Report of a Work Group on Sluggish Cognitive Tempo: Key Research Directions and a Consensus Change in Terminology to Cognitive Disengagement Syndrome. J Am Acad Child Adolesc Psychiatry. 2022 Aug 22.
6. Cardona-Acosta AM, Bolaños-Guzmán CA. Role of the Mesolimbic Dopamine Pathway in the Antidepressant Effects of Ketamine. Neuropharmacology. 2022 Dec 11:109374.
7. Mohammadi S, Dolatshahi M, Rahmani F. Shedding Light on Thyroid Hormone Disorders and Parkinson Disease Pathology: Mechanisms and Risk Factors. J Endocrinol Invest. 2021 Jan;44:1–3.
8. Bi Y, Ren D, Guo Z, Ma G, Xu F, Chen Z, et al. Influence and Interaction of Genetic, Cognitive, Neuroendocrine and Personalistic Markers to Antidepressant Response in Chinese Patients with Major Depression. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Jan 10;104:110036.
9. Hamasaeed PA, Hussain SK, Ashraf SM. Evaluation of Thyroid Stimulating Hormone and Thyroid Hormone Concentrations in Females with Hypothyroidism and Hyperthyroidism. Rafidain J Sci. 2019 Dec 1;28(4):1–7.
10. Schneider SA, Tschaidse L, Reisch N. Thyroid Disorders and Movement Disorders—A Systematic Review. Mov Disord Clin Pract. 2023 Mar;10(3):360–8.
11. Li Y, Liao Z, Huang Q, Wang Q, Ren H, Chen X, et al. Prevalence and Influencing Factors of Suicide in First-Episode and Drug-Naive Young Major Depressive Disorder Patients with Impaired Fasting Glucose: A Cross-Sectional Study. Front Psychiatry. 2023 Jun 9;14:1171814.
12. Ye G, Li Z, Yue Y, Wu Y, Yang R, Wang H, et al. Suicide Attempt Rate and the Risk Factors in Young, First-Episode and Drug-Naïve Chinese Han Patients with Major Depressive Disorder. BMC Psychiatry. 2022 Dec;22(1):1–0.
13. Liu W, Wu Z, Sun M, Zhang S, Yuan J, Zhu D, et al. Association Between Fasting Blood Glucose and Thyroid Stimulating Hormones and Suicidal Tendency and Disease Severity in Patients with Major Depressive Disorder. Bosn J Basic Med Sci. 2022 Aug;22(4):635.
14. Nuguru SP, Rachakonda S, Sripathi S, Khan MI, Patel N, Meda RT. Hypothyroidism and Depression: A Narrative Review. Cureus. 2022 Aug 20;14(8).
15. Zhang Q, Zhao S, Liu Z, Luo B, Yang Y, Shi Y, et al. Association of Thyroid-Stimulating Hormone and Lipid Levels with Suicide Attempts Among Adolescents with Major Depressive Disorder in China. Front Psychiatry. 2023 Jan 17;13:1031945.
16. Yang W, Qu M, Jiang R, Lang X, Zhang XY. Association Between Thyroid Function and Comorbid Anxiety in First-Episode and Drug Naïve Patients with Major Depressive Disorder. Eur Arch Psychiatry Clin Neurosci. 2023 Feb;273(1):191–8.
17. Zenz S, Regittnig W, Boulgaropoulos B, Augustin T, Brunner M, Korsatko S, et al. Effect of Liraglutide Treatment on Whole-Body Glucose Fluxes in C-Peptide–Positive Type 1 Diabetes During Hypoglycemia. J Clin Endocrinol Metab. 2022 Sep 1;107(9):e3583–93.
18. Choi YJ, Lee J, Park S, Kang Y, Joo SW. Effectiveness and Safety of Liraglutide Treatment in Patients with a Psychiatric Disorder. J Korean Neuropsychiatr Assoc. 2020:325–30.
19. Ye J, Xu J, Wen W, Huang B. Effect of Liraglutide on Serum TSH Levels in Patients with NAFLD and Its Underlying Mechanisms. Int J Clin Pract. 2022 Oct 13;2022.
20. Seo MK, Jeong S, Seog DH, Lee JA, Lee JH, Lee Y, et al. Effects of Liraglutide on Depressive Behavior in a Mouse Depression Model and Cognition in the Probe Trial of Morris Water Maze Test. J Affect Disord. 2023 Mar 1;324:8–1.