Research Article

Exploring the Link between Fasting And Postprandial Thyroid Function Tests In Clinical Euthyroidism

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Abstract

Background: Thyroid disorders are common but testing is not standardized for time and prandial state. Subclinical hypothyroidism may be underdiagnosed in postprandial samples.

Objective: This study aimed to determine effects of fasting and postprandial state on thyroid function tests (TFTs) in clinically euthyroid patients and to develop a prediction model for fasting TSH if only postprandial levels are available.

Methods: This predictive correlational study conducted in King Edward Medical University in 2021 included 95 clinically euthyroid individuals between 18 and 60 years. After obtaining fasting TFTs, mixed-nutrient 400-500 calorie supervised meal was given. After 2 hours, postprandial TFTs were obtained. Data was analyzed using SPSS- 20.0 keeping significant level at p-value <0.05. Chi-square test, paired sample t-test & one-way ANOVA was used for initial analysis, Pearson product moment correlation and simple linear regression for prediction models.

Results: The mean age of participants was 27.94±5.90 years with 54(56.84%) being male. Mean Fasting and Postprandial FT3 and FT4 were 4.89±0.99 pmol/L, 4.82±1.05 pmol/L (p= 0.328) & 19.34±4.15, 19.03±3.97 pmol/L (p=0.225) respectively. Fasting (FTSH) and Postprandial TSH (PPTSH) was 1.69±2.34 and 1.48±1.15 mIU/L (p=0.162). Compared to fasting, PPTSH declined in 54(56.8%), rose in 36(37.9%) and remained unchanged in 5(5.3%) cases. There was negative correlation between FTSH and postprandial change (r -0.92, p<0.001) and positive correlation between FTSH & PPTSH (r=0.87, p<0.001). PPTSH predicted FTSH as Fasting TSH = 1.765 PPTSH – 0.923 (p <0.001).

Conclusions: PPTSH may predict FTSH but FTSH should be preferred especially in patients with strong suspicion of subclinical hypothyroidism.

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Introduction

Hypothalamo-pituitary axes are noteworthy for following circadian patterns and being sensitive to fasting & post-prandial states.[1] Early morning, fas-

ting sampling is routinely prescribed for gonadal, cortisol axis as well as prolactin. It is interesting to note that similar homogeny is not practiced for thyroid axis.

Thyroid disorders are common and associated with significant morbidity. More than 200 million people in the world have thyroid disease.[2] Goiter has a high prevalence (28.7%) in Pakistani population.[3] Thyroid hormone deficiency affects all tissues of the body, including multiple endocrine changes that alter growth hormone, corticotrophin, glucocorticoids, and gonadal function.[4]

The clinical manifestations are non-specific with very few diagnostic features (apart from Grave's ophthalmopathy). Hypothyroidism, the state of inadequate thyroid hormone production, results in slowed metabolism.[5] Although frequently encountered in clinical practice, the actual prevalence may be higher as manhy patients remain undiagnosed. 4.6% of Americans and up to 10% of the subcontinent population is reported to suffer from the condition.[2] it has been estimated that more than 10% of women worldwide have some degree of thyroid hormone deficiency.[6] -The clinical spectrum of hypothyroidism ranges from nonspecific symptoms to cardiac and neuropsychiatric disorders. Overt It is also linked to dyslipidemia, endothelial dysfunction and ASCVD.[7] Even the subclinical hypothyroidism (SCH) has various long-term effects like dyslipidemia, hypertension, sub fertility and is an independent risk factor for coronary heart disease.[8]

The diagnosis and classification of thyroid pathology therefore relies on accurate analysis of TSH, free T3 and free T4. The importance of early morning fasting sampling for thyroid axis hormones is largely disregarded.[9] In research done in Chennai, TSH levels of the patients measured in fasting and postprandial states was significantly different (p-value <0.05) resulting in re-classification of "normal" individuals as SCH and vice versa.[10] TSH was suppressed in all subjects after food irrespective of the fasting levels. Free T4 and Free T3 values did not change significantly. This resulted in reclassification of as many as 75% subjects as subclinical hypothyroidism (SCH) based on fasting values whose TSH values were otherwise within range in the postprandial sample.[10] However, this study was limited by a small sample size. Postprandial suppression of TSH has been reported in several other studies.[11-14]

Random thyroid function tests are the most commonly prescribed with no specific instructions about time and prandial state. We could not identify how these "random" levels may be converted to fasting levels to obtain some form of standardization.

The present study aims to determine the effect of fasting and postprandial state on thyroid function tests in clinically euthyroid patients. The study also aims to develop a prediction model for determining fasting TSH if only postprandial levels are available by determining the correlation between these two values.

Methods

After approval from institutional review board, this correlational study was conducted in the Department of Medicine, Mayo Hospital, Lahore, a tertiary care teaching hospital affiliated with King Edward Medical University from 1st July 2021 to 31st December, 2021. Sample size of 95 patients was estimated by using Gpower 3.1.9.7 at 1 % level of significance, 99% power of test with expected mean fasting TSH as 2.46±1.32 mIU/L and expected postprandial TSH as 1.89±1.01 mIU/L.[11] Using non-probability purposive sampling, clinically euthyroid individuals of any gender between ages 18 and 60 years were included. For the purpose of this study, euthyroidism was classified as clinical and biochemical. The term clinically euthyroid was reserved for individuals having no clinical features or history of hypothyroidism or hyperthyroidism and not taking any medications for these disorders while the term biochemically euthyroid was applied when individuals exhibited normal Free T3 (FT3) and Free T4 (FT4) and Thyroid Stimulating Hormone (TSH). Patients with pre-existing thyroid dysfunction or taking thyroxine or antithyroid drugs, congestive heart failure, ischemic heart disease, dyslipidemia, diabetes mellitus, acute or chronic renal failure, acute or chronic liver disease, pre-existing autoimmune disease, systemic steroid therapy within last 6 months, pregnancy, lactation, active malignancy within last 6 months, epilepsy or psychiatric disorder were excluded from the study.

Written informed consent were obtained from all enrolled individuals. Demographic characteristics were noted and venous blood samples were collected after overnight fasting of 8-10 hours between 7:30 am and 8:30 am and were sent to laboratory for Thyroid Function Tests

(Serum TSH, FT4 and FT3). All participants were given similar breakfast i.e., a mixed nutrient 400-500 calorie supervised meal after obtaining the fasting sample. 2 hours after the meal, postprandial venous blood sample were collected from each patient between 10:30 am to 11:30 am on the same day and were sent to laboratory for Thyroid Function Tests (Serum TSH, FT4 and FT3). Samples were analyzed by the radio-immunoassays (RIA/IRMA) technique. Machines GAMA Counters (GENESYS – 5000 Made 2009, STRATEC – PC – RIA Made 2004) were calibrated and the serum was collected and processed according to manufacturer's instructions and their outcomes were recorded. All the data was transferred to a pre designed proforma (attached).

Data was analyzed on SPSS- 20.0. Quantitative variables like ages were presented as mean and standard deviation while qualitative variables like gender were presented as frequency and percentages. For comparison of fasting and postprandial values, paired sample t-test. One-way ANOVA was used when the data was regrouped for postprandial change in postprandial TSH. The qualitative variables like gender and diagnosis were analyzed by chi-square test. The correlation between fasting, postprandial and change in TSH was determined by Pearson's correlation coefficient. Simple linear regression was used to predict fasting TSH from postprandial TSH. For the analyses, p-value < 0.01 was considered significant.

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

The mean age of participants was 27.94 ± 5.90 years with 89 (93.68%) of the cases being less than 40 years of age, while only 6(6.32%) between 40 and 60 years. With 54(56.84%) male and 41(43.16%) female participants, the M:F ratio of the study group was 1.3:1.

The mean Fasting and Postprandial FT3 was 4.89 ± 0.99 pmol/L and 4.82 ± 1.05 pmol/L (p-value 0.328). The mean Fasting and Postprandial FT4 was 19.34 ± 4.15 pmol/L and 19.03 ± 3.97 pmol/L (p-value 0.225). The mean Fasting and Postprandial TSH was 1.69 ± 2.34 mIU/L and 1.48 ± 1.15 mIU/L (p-value 0.162).

In fasting euthyroid was diagnosed in 74(77.9%), subclinical hypothyroidism was diagnosed in 2(2.1%) and other diagnoses were made in 19(20.0%) cases while Postprandial euthyroid was diagnosed in 74(77.9%), subclinical hypothyroidism was diagnosed in 2(2.1%) and other/unclassified in 19(20%) cases. The diagnosis of 2 (2.1%) cases changed between fasting & postprandial states; one from euthyroid to other/unclassified and the second one was vice versa.

Analyses of change in TSH showed that as compared to fasting state TSH declined in 54 (56.8%) cases, rose in 36 (37.9%) and remained unchanged in 5 (5.3%) cases. Table I shows the comparative characteristics of individuals grouped on the basis of change in TSH levels.

The greatest difference was observed in the 2 patients with subclinical hypothyroidism; both showed a decline in postprandial states from 22.20 to 9.56 IU/ml and from 6.92 to 4.65 IU/ml.

Fasting TSH and the postprandial change in TSH had a strong negative correlation with r = -0.92, p < 0.001. Fasting TSH and postprandial TSH had a strong positive correlation (r=0.87, p<0.001). The correlation between postprandial TSH and the change from the fasting level

Table 1: *Participant Characteristic Based on Change in TSH from Fasting to Postprandial State*

Characteristics		Postprandial Decline in TSH (n=54)	Postprandial Constant TSH (n=5)	Postprandial Rise in TSH (n=36)	p-value
Age (years)		28.11 ± 9.49	29.4 ± 3.21	27.47 ± 5.278	0.753
Gender	Male (n)	32	4	18	0.385
	Female (n)	22	1	18	
Fasting TSH (mean±SD) mIU/L		2.1087 ± 2.99	1.05 ± 0.43	1.15 ± 0.71	0.134
Postprandial TSH (mean±SD) mIU/L		1.4 ± 1.36	1.05 ± 0.43	1.66 ± 0.82	0.411
Fasting FT3 (mean±SD) pmol/L		4.79 ± 0.9	5.14 ± 0.63	5.00 ± 1.16	0.524
Postprandial FT3 (mean±SD) pmol/L		4.66 ± 1.07	5.21 ± 0.55	5.00 ± 1.06	0.209
Fasting FT4 (mean±SD) pmol/L		19.36 ± 3.63	17.46 ± 1.37	19.59 ± 5.05	0.566
Postprandial FT4 (mean±SD) pmol/L		19.39 ± 3.94	17.42 ± 1.89	18.71 ± 4.21	0.476

was also negative but was less robust ($r = - 0.61$, $p < 0.001$).

Simple linear regression was used to test if the post-prandial TSH predicted the fasting TSH levels. The fitted regression model was:

Fasting TSH = 1.765 PPTSH – 0.923

The overall regression was statistically significant ($R2 = .758$, $F (1,93) = 290.778$, $p <0.001$. It was found that postprandial TSH significantly predicted fasting TSH ($\beta = .87$, $p <0.001$).

Discussion

"To fast or not before thyroid function testing" is a common question asked by patients, laboratories and health care providers. However, concrete authentic scientific answer is lacking. A circadian rhythm can be noted for circulating TSH between 11 pm to 5 am, and nadir between 5 pm to 8 pm.[15] The low amplitude of pulses along with elongated half-life of TSH brings about variations in blood levels. The results for thyroid function test may vary widely due to differing values of TSH. Thus, it is important to bring about uniformity in the testing under standard conditions. Endocrine pathways are by and large regulated by hypothalamo-pituitary axes and these pathways are affected not only by the time of the day but also by fasting and fed states.[16] Interestingly, this awareness is not reflected in testing of thyroid function testing. The present study revolves around a clinically important query that whether fasting state is necessary for thyroid function tests including Free T3, Free T4 and TSH.

The present study analyzed thyroid function tests of young, clinically euthyroid individuals with no prior history of thyroid dysfunction in fasting and postprandial states. This subset of individuals was chosen as we hoped to investigate our study question without the effect of disease or drug as either of these may alter the rhythmicity of TSH and thyroid hormone production.

The present study group comprised of 54(56.84%) male and 41(43.16%) female participants with a mean age of 27.94 ± 5.90 years. The inclusion of young patients was somewhat deliberate for the reasons stated above but the M:F ratio of 1.3: 1 may be a reflection of more frequent thyroid dysfunction among females[2] allowing more frequent enrollment of males.

Majority (77.9%) of our clinically euthyroid group were also biochemically euthyroid while 2.1% had subclinical hypothyroidism with no suggestive clinical features. The remaining 20% who were grouped together as other/unclassified diagnosis did not neatly fit into either euthyroid or primarily thyroid disorders. They were not further tested to establish the reason for variation in thyroid function tests as it was beyond the scope of the study. However, they were informed of the aberrant results and their care was transferred to relevant physicians/endocrinologists.

It was observed in the study that thyroid function tests tended to show a downward trend in the postprandial as compared to the fasting states, although the differences were insignificant when compared directly. TSH is a hormone that is produced in pulsatile manner. The research works of Nair et al, Mahadevan et al, Dong et al, Wang et al and Futela et al[10-14] depicted TSH reduction during postprandial stage, as indicated in present study. The production of TSH is influenced by two factors called somatostatin and Thyrotropin releasing hormone (TRH); somatostatin is TSH inhibitor, whereas TRH is TSH stimulator.[17] The TSH reduction may result from increased somatostatin and suppressed TSH. Somatostatin secretion is stimulated by luminal gastric acid especially in the presence of fatty and protein diet.[18]

We stratified the data on the basis of change in TSH in postprandial state. TSH was chosen because it is the most commonly recommended test for evaluation of thyroid status.[9] In the postprandial state, TSH tends to regress to a mean regardless of the fasting TSH. It is interesting to note that participants with fasting TSH level below 2.0 mIU/L showed little variation post-prandially but those with fasting TSH was above 2.0 mIU/L, the variations also became widely spread. The only consistency identified was a significant decrement in the 2 participants who biochemically turned out to have subclinical hypothyroidism.

It is worthwhile pointing out that the greatest decline in TSH was seen in patients with subclinical hypothyroidism. The diagnosis did not change per se but the therapeutic decision is different. In both cases, the decline in TSH implied less severity of subclinical hypothyroidism; treatment may have been delayed in first one while the surveillance protocol would change in the

2nd case. We applied correlation coefficient and regression models to predict these variations and results were statistically significant.

The study has some limitations. First and foremost, the results should be reconfirmed in larger samples. This study has evaluated levels of TSH after 2 hours of meal. However, it is uncertain that the results would remain consistent if TSH is checked at any other times. An important consideration is that it is not possible in the current study to predict whether the effects are due to the feeding state only or also influenced by circadian rhythmicity. Some studies have pointed out that timing of sampling is crucial for reduction in TSH.[13] In present study TSH reduction may be the outcome of sample timing or food related change in blood chemistry. The timing of phlebotomy and fasting status of patients are not emphasized by clinical guidelines. Another limitation is that although we were able to generate a prediction equation with a very low p-value (<0.001) but the variations were all over the place being positive, negative or even constant. In the current study we did not identify which subset of patients would show a positive or negative deflection between fasting and postprandial levels. The only exception were patients with subclinical hypothyroidism who always reported a decline from fasting to postprandial TSH. We recommend that future studies may be designed to address these unexplored areas.

Conclusion

In conclusion, fasting TSH is the preferred mode of testing. If fasting TSH is not available, an attempt may be made to predict it from the postprandial levels. However, in patient with strong suspicion of subclinical hypothyroidism, fasting values are the preferred choice. Otherwise, patients with mild subclinical hypothyroidism may be missed on initial screening tests which may significantly add to the morbidity of these individuals.

Ethical Approval: The Institutional Review Board, King Edward Medical University, Lahore, approved this study vide letter No. 17/RC/ KEMU. .

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Authors' Contribution:

MR: Acquisition of data, conception & design, analysis & interpretation of data, drafting of article

JT: Acquisition of data, conception & design, analysis & interpretation of data

SL: Acquisition of data, conception & design, analysis & interpretation of data

AAK: Acquisition of data, conception & design, analysis & interpretation of data, revising it critically for important intellectual content

SUM: Acquisition of data, conception & design, analysis & interpretation of data

MAK: Acquisition of data, analysis & interpretation of data

SA: Drafting of article, final approval

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