

Propylthiouracil: An Intriguing Connection Among the Propylthiouracil, Hypothyroidism, and Obesity

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Abstract: Hypothyroidism and obesity both are medical conditions that have been connected closely. 6- Propyl-2-thiouracil (PTU) is an anti-thyroid drug usually used to treat overactive thyroid, but may cause obesity, which rises morbidity and mortality of patients. Object To explore the prevalence of obesity in hypothyroid patients, who were receiving PTU for the management of overactive thyroid. The aims of current research to access the drug utilization and investigation of PTU which aids in attaining rational therapy and other aspects related to patient's safety. Method: A cross-sectional research was conducted and 200 participants with overactive thyroid selected by non-probably consecutive sampling method from POD #4 at Liaquat University of Medical and Health Sciences, Hospital, Jamshoro from May 2016 to April 2017 and all adults with overactive thyroid receiving Propylthiouracil were included. Their Thyroid function tests performed on Immunoassay Elecysis 2010 and entire data was evaluated via SPSS version 22.0. Result: The data revealed that the PTU-induced obesity in 52 hypothyroid patients (n=14 males, n=38 females) and the prevalence of PTU-induced obesity was 26.0%. Conclusion: It was perceived that PTU alters the function of thyroid stimulating hormone (TSH) or thyrotropin and increases the amount of thyrotropin would will be secondary to obesity.

Keywords: Hyperthyroidism, Hypothyroidism, Obesity, Propylthiouracil

1. Introduction

Obesity and underactive-thyroid are two familiar medical manifestations that have been connected together closely. The connection has become more relevant in the circumstances of an uncommon rise in the prevalence of obesity globally [1]. Body organization and thyroid hormones seem to be meticulously related. Thyroid hormones manage basal metabolism, thermogenesis and perform a crucial role in lipid and glucose metabolism, food intake and fat oxidation [2]. Thyroid disorder is correlated with alteration in body weight, body temperature and resting energy expenditure (REE) unconventional of physical activities. Underactive thyroid is correlated with reduction in thermogenesis, reduction in metabolic rate, and

also associated with a higher mass index (BMI) and higher incidence rate of obesity. There is clinical demonstration suggesting that even mild thyroid deviation in the form of hypothyroidism is associated to remarkable alteration in body weight and increases the chances of overweight and obesity [3]. TSH levels are at the upper limit of the normal range or slightly increased in obese males and females and are positively correlated with BMI. Slight variations in thyroid function that are within laboratory reference ranges, also contribute to the tendency to gain weight, Progressive fat accumulation was associated with a parallel increase in TSH [4].

In obese adults, the commonest abnormality observed is hyperthyrotropinemia and it can return back after weight loss either by bariatric surgery or by hypocaloric diet. Weight loss

produces a significant decrease in serum TSH concentration [5].

Most likely, even minute alteration of lifestyle, characterized by increased physical activities and exercise improved in body composition without accompanying changes of BMI lead to reduce the level of TSH [6].

It is also very crucial to consider that even though thyroid hormones have been frequently used in attempts to induce weight loss in obese patients but there is no manifestation for their utilization to control body weight except in obese hypothyroid people. In future, the raising prevalence of obesity may surprise the definition of normal TSH range in population research studies. Mild hyperthyrotropinemia can reasonably be secondary to obesity, so thyroid autoantibody condition may helpful in diagnosis of hypothyroidism in obese population. [7]. Rationale of this research study was to investigate the frequency of over-weight and obesity in underactive-thyroid patients and to identify the potential of this adverse effect in local population.

2. Materials and Methods

2.1. Material

Cross-sectional research was conducted to interpret the selected sample of 200 (female n=168, & male=32) participants and whole particulars were accumulated through Non-probability consecutive sampling method, participants with overactive thyroid identified in Pathology lab at Liaquat University Medical and Health Sciences (LUMHS), Hospital Jamshoro, their thyroid function tests (TSH, T3 & T4), weight and height were measured after the use of PTU. The research was managed between May 2016 to April 2017. Approval (N0. DRUGS/1011) was get hold from ethical board committee. Prior to recruit into the research, all thyroid patients were informed about the study and verbally consents were taken from all participants and their participation into this research was entirely voluntary.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria

Inclusion criteria of research participants: (1) All patients were between age 15 to 80 years old; (2) All participants were medically confirmed to be overactive thyroid (3) All patients receiving chemotherapy (PTU) (4) All participants have complete clinical and follow-up data. (5) All participants were informed about the study and verbally consents were taken from all participants and their participation into this research was entirely voluntary.

2.2.2. Exclusion Criteria

Exclusion criteria: (1) Combined with other diseases (2) All children (3) with other infections and autoimmune disorders (4) medicine other than PTU.

2.3. Methods

2.3.1. Sample Collection

Blood sample: 3 cc blood drawn from patients and put into

gel/plain tube and their Thyroid function tests performed on Immunoassay Elecysis 2010. Thyrotropin, T3 & T4 concentration were assessed before and after the onset of PTU therapy. As the result of PTU therapy underactive thyroid developed in overactive thyroid patients, associated with obesity, testing of Thyroid function profile indicated the hypothyroidism in overactive thyroid patients which develop obesity in these patients.

2.3.2. Procedure of Thyroid Function Tests

Collected blood sample in gel tube became a clot within 5 minutes than serum would be separated after centrifugation in 7 to 10 minutes then this serum provided the results of thyroid after 45 to 50 minutes. Thyroid screening test was done by eletro-chemo-luminescence in this method the rays are produce due to the electrochemical reaction occurs in between molecules, after electrochemically activation, eliminates visible energy when they reached to relax condition. This electrochemical magnetic energy used in Laboratory science to measure the level of chemical in solution form.

2.3.3. Determination of Weight

Out of total 52 (Male, n=14 & (female, n=38) had developed hypothyroidism leading obesity, The Body Mass Index (BMI) can be calculate through division of body mass (Kg) by height (m^2), according to BMI, patients categorized into healthy weight ($18.5-24.9 \text{ Kg/m}^2$, over weight ($25-29.9 \text{ Kg/m}^2$) & obesity ($>30 \text{ Kg/m}^2$).

2.4. Statistical Analysis

A Structured proforma was used to collect particulars from participants and data was coded, entered and evaluated by using SPSS version 22.0. Descriptive statistics via gender (Percentage, mean, (SD) standard deviation and median etc) were computed to present values for the quantitative variables. Pearson's and Spearman's correlation coefficients used to assess correlation between thyroid function, body weight, and BMI between male & female, and hyperthyroid & hypothyroid patients and find out the differences. The p-value considered significant if the findings of difference is > 0.05 . BMI was classified into 3 main classes Healthy (BMI=18.5-24.9). Overweight (BMI $> 25-29.9$), and obesity (BMI > 30), percentages were calculated and presented as well.

3. Results

3.1. Effects of Thyroid Hormones on Body Weight

Out of the total 200 patients, 54 patients developed hypothyroidism, 120 Eu-thyroid and 26 remain hyperthyroid state. Total 168 female patients (Overactive thyroid, n=21, underactive thyroid, n=40 & Euthyroid, n=107) whereas total 32 male patients (Overactive thyroid, n=5, underactive thyroid, n=14 & Euthyroid, n=13). Weight variation observed in female (weight gain, n=38, weight remain same, n=112, & weight loss, n=18) in male (weight gain, n=14, weight remain same, n=14, & weight loss, n=4).

Effects of Thyroid Hormone on body weight

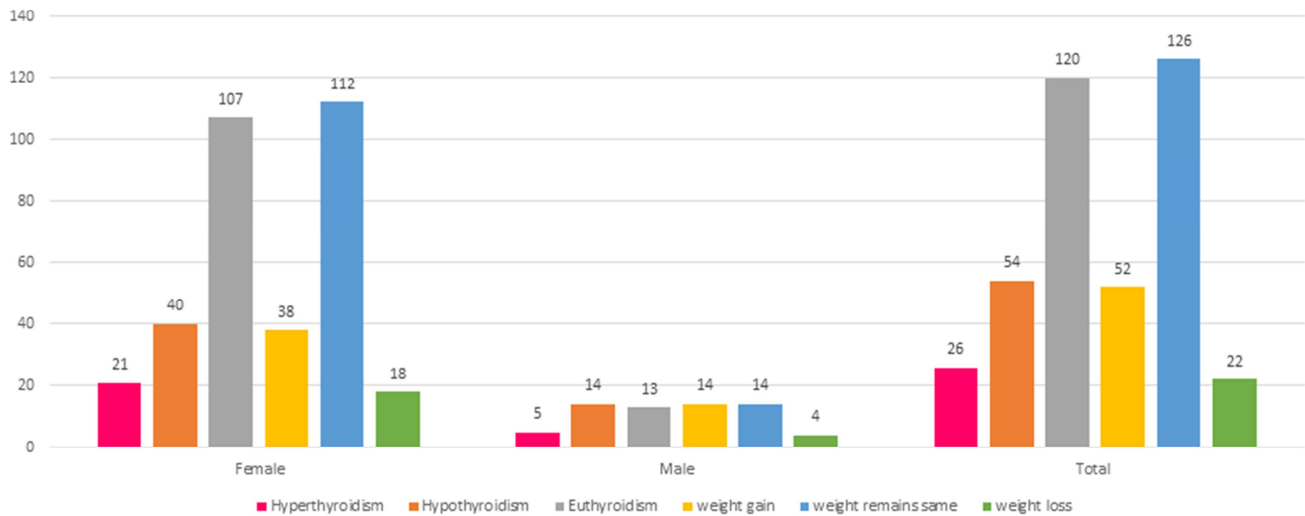


Figure 1. Effects of Thyroid Hormones (TH) on Human Body weight.

3.2. Correlation Between Thyrotropin Concentration and Body Mass Index (BMI) in Hypothyroid Patients

After receiving the PTU for the treatment of Overactive thyroid out of 200 patients, hypothyroidism developed in 54 patients, 7% (n=14) in male whereas, 20% (n=40) in female.

Thyrotropin (TSH) concentration altered in these patients which developed overweight in 32 patients (female, n=28, & male, n=4) and obesity in 20 patients (female, n=10, & male, n=10) while 2 female patients' weight remained same.

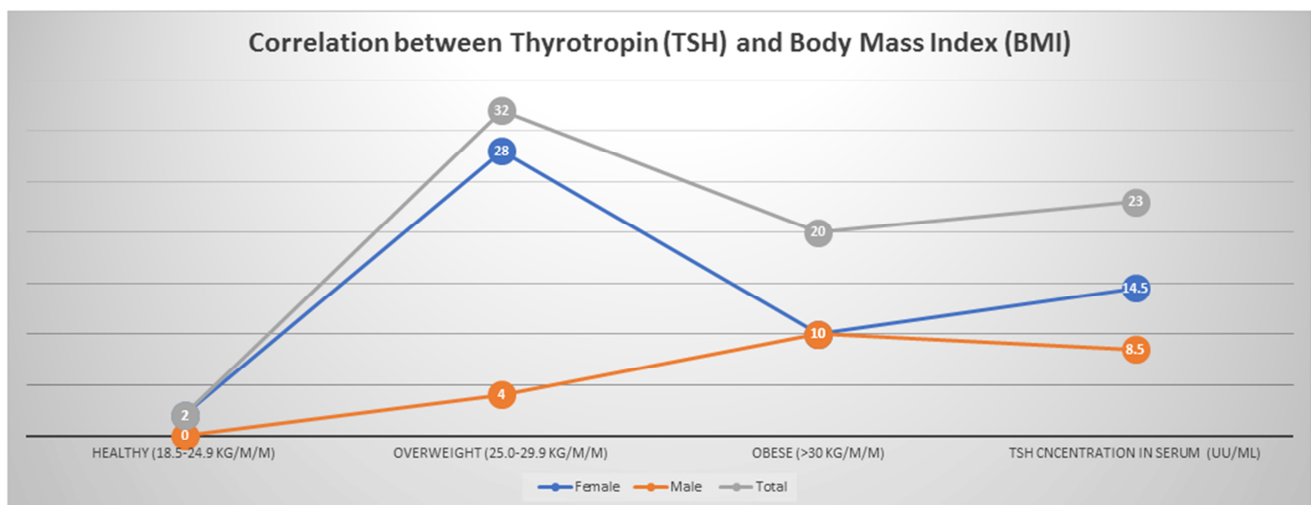


Figure 2. Correlation between the Thyroid Stimulating Hormone (TSH) and Body Mass Index (BMI) in Hypothyroid patients.

3.3. Demographic and Biological Findings of Overactive & Underactive Thyroid Patients

Out of 200 patients, 168 (84%) were female and 32 (16%) were male. The overall mean age was of overactive thyroid and underactive thyroid patients were 36.27 ± 1.16 and 42.38 ± 2.76 years, patients were categorized into three groups, Overactive thyroid 26 (13%), underactive thyroid 54 (27%) and 120 (60%) Euthyroid patients presenting the highest of the total. The most common presenting sign of hypothyroidism was overweight 32 (female, n=28 & male,

n=4) and obesity in 20 ((female, n=20 & male, n=20). PTU associated alteration noticed in Thyrotropin (TSH), body temperature and body weight, there were notable elevation in thyrotropin concentration and weight. The mean weight of overactive thyroid patients (68.34 ± 9.73 Kg) and underactive thyroid (70.83 ± 10.0866 Kg) with $P=0.005$. Slightly reduction in body temperature was also observed in hypothyroid patients and the mean body temperature was (97.60 ± 10.11 °F). Mean value of Thyrotropin (TSH) were (2.87 ± 1.35 uU/ml) and (3.39 ± 1.43 uU/ml) in hyper and hypothyroid patients respectively with $p=0.00022$ shown in table 1.

Table 1. Pre-and post-treatment demographic and biochemical results of the patients with thyroid disorders.

Demographic and biochemical characteristics of patients with thyroid disorders	Overactive thyroid patients (n=26) (Female, n=21 & Male, n=5)	Underactive thyroid patients (n=54) (Female, n=40 & Male, n=14)	P-value
Age	36.27±1.16	42.38±2.76	0.009
Weight prior to medication	66.44±10.84	70.83±10.0866	0.003
Weight after medication	68.34±9.73	68.52±11.70	0.005
TSH level prior to medication	1.97±1.43	2.98±1.55	0.001
TSH level after medication	2.87±1.35	3.39±1.43	0.0002
T3 level prior to medication	1.78±0.23	1.67±0.19	0.001
T3 level after medication	1.36±0.091	1.450±0.17	0.019
T4 level prior to medication	1.78±0.68	0.87±0.19	0.0003
T4 level after medication	0.73±0.23	0.91±0.12	0.007
Body Temperature (°F)	99.6±1123	97.60±10.11	0.0005

Note: TSH: Thyroid Stimulating Hormone or Thyrotropin (normal range=0.35-4.94uU/ml), T3: Tri-iodothyronine (normal range=0.58-1.59 ng/ml) and T4: Tetra-iodothyronine or thyroxine (normal range=4.87-11.72 ug/dl).

All values have been expressed as means ± SD (Standard deviation).

4. Discussion

Hyperthyroidism (overactive thyroid) is a medical manifestation due to the production of elevated amount of hormone. 6-Propyl-2-thiouracil, an anti-thyroid drug, recommended for the management of hyperthyroidism or Grave's disease (GD) due to its suppressive nature, it inhibits the oxidation of iodine in thyrocytes of gland which stop the secretion of hormones [8]. PTU is highly recommended as first choice of drug therapy to cure and manage the overactive thyroid, but can generate hypothyroidism, which induced obesity in participants. Drawback of long-term treatment (12-18 months), can develop obesity due to hypothyroid condition. A research was conducted on 278 Saudi people at the Central Laboratory of Aseer Central Hospital, correlation in between the serum concentration of thyroid-stimulating Hormone (TSH) and BMI was detected. The TSH level was measured via chemiluminescence immunoassay. Approximately, 75% of the adults showed elevated serum level of TSH in obese people with significantly p-value 0.001, but no effect of T3 and T4. Mean TSH serum level increases obesity [9]. In the current study 200 participants were enrolled from OPD (#4) at LUMHS, Hospital, Jamshoro, out of total participants 54 (27%) developed hypothyroidism after the treatment of hyperthyroidism with Propylthiouracil, their thyroid profile tests and BMI data was gathered, mean TSH level of hyperthyroid and hypothyroid were (2.87±1.35 & 3.39±1.43, p=0.0002) with not significant effect on T3 and T4 concentration.

Underactive thyroid basically correlated to obesity, while overactive thyroid associated with reduction in weight. The study was conducted for the assessment of thyroid disorders and body mass index (BMI) in patients who had thyroid anomalies. A cohort, retrospective and observational research was managed at Endocrine Department of Pontevedra University Complex Hospital, Spain. The data of thyroid tests and BMI was gathered and follow up duration was 1 year. Data of 330 participants was accumulated for research and 235 patients were excluded due to variable. Further 61

patients were also eliminated because of incomplete data such as: failure to gain euthyroid state, lost to follow-up and incomplete medical information. Only 34 patients were selected for research (hyperthyroid patients, n=17 & hypothyroid patients, n=17), differences were noticed within mean BMI of hyper & hypothyroid participants (26.09±3.22 vs 25.39±4.6) with p=0.609. Obesity was noted approximately 77.3% in hypothyroid patients whereas, 59% in hyperthyroid patients with (P=0.23), mean BMI was 26.23±3.4 & 27.5±4.99, p=0.361 in both type of participants. Untreated thyroid disorders are not correlated with BMI while treated or normalized thyroid hormone concentration significantly altered the weight of participants [10]. In the present study 200 participants were recruited who had thyroid problem, after the treatment out of total 54 (Female, n=40 & Male, n=14) participant developed hypothyroidism within six months of treatment, their weight also increased due to hypothyroidism then their thyroid profile test was screened by the Elecsys chemiluminescence immunoassay 2010, the elevated TSH (thyrotropin) hormone was noticed whereas, the T3 and T4 level were slightly increases in some patients while no change was observed in most of the hypothyroid patients, means BMI was 68.34±9.73 & 68.52±11.70, p=0.005, hypothyroidism was found in 54 participants whereas, obesity was noted in 52 patients (female (52) & male (14)), 26% participants were overweight and obese.

Obesity can be described as a body mass index (BMI) higher than 30 Kg/m², is affected approximately, 40% population of United States, increased BMI put the negative effects on thyroid hormones and metabolism, hypothyroidism, a hormonal imbalance associated with obesity. Recent researched revealed that the concentration of thyroid stimulating hormones (TSH) could be outcome of obesity. Increased body mass (BMI) is greatly connected with increased Thyrotropin (TSH) in obese people. The case study was conducted on a 38 years old female complain with obesity and fatigue and Thyroid profile indicated the elevated level of TSH and normal T4 concentration. The elevated level of TSH identified the hypothyroidism which can be treated with supplementation of thyroxine [11]. In the current

study the prevalence of obesity was 26% (19% in female whereas, 7% in male) was observed. Imbalance thyroid hormones also noticed in hypothyroid patients specially, elevated Thyroid stimulating hormone (TSH).

Interesting connection exhibits between thyroid function, weight management, and obesity. Cohort research revealed that the balance of weight depended on the thyroid stimulating hormone (TSH), and elevated TSH concentration increases the gaining of weight in hypothyroid patients. TSH level increases due to the activation of hypothalamus pituitary thyroid axis. In contrary, little deviation in thyroid hormones (THs) correlated with up to 5- 10 Kg increased body weight. Majority of the patients treated to cure hyperthyroidism undergo a weight gain than they reduced weight during hyperthyroid state of ailment [12]. In the present study Propylthiouracil used as anti-thyroid drug (ATD) to treat hyperthyroidism which leads to hypothyroidism in 54 (27%) patients and develop obesity. Alteration in THs can cause increase in weight up to 5-8 Kg in present study.

Albeit, connection between thyroid stimulating hormone (TSH) and obesity has been observed in participants but the research on girls throughout adolescence, which is key time period basically associated with imbalance of thyroid hormones and established obesity. Cohort research was conducted of 481 girls who were studying in school and this study was arranged in four regions of East China and duration of study was two years from 2017-2019. Anthropometrically measurement of weight, height and waist circumference (WC) were done then BMI was computed. Blood specimen have been collected to assess TSH and Thyroxin (T4). Out of total, 474 girls have prevalence of BMI was 19.8%, and obese girls had significantly higher TSH concentration as compare to the normal ($p=0.037$), 435 girls followed-up for two years showed that general and central obesity had elevated TSH concentration ($p=0.004$ and $p=0.008$). The TSH concentration for girl with overweight had 0.45mIU/L, higher in comparison to normal weight girls. Thyrotropin was positively connected with obesity amongst girls at adolescence [13]. In present research the prevalence of BMI was 26% and obese females had significantly elevated TSH level ($p=0.005$). TSH concentration of overweight women was 5.94 uIU/ml, higher in obese participants because thyrotropin associated with obesity specially, in child bearing age females.

Hypothyroidism as well as hyperthyroidism associated with alteration in body weight, either the deviation of Thyroid hormones within the reference value are correlated with weight. The research was conducted on 2407 participants and categorized into 2 groups; patients who were not taking any ATD treatment with serum thyrotropin (TSH) level of 0.5-5.0 mIU/L and serum level of 0.5-10.0 mIU/L were enrolled in the research and the changes in body weight has been noticed during 3.5 years of follow-up. The mean weight raised gradually from 64.6 to 70.3 Kg from 0.5 to 10.0 mIU/L concentration of TSH in Female participants ($p<0.001$) and 82.7 to 85.8 Kg in 0.5 to 10.0 mIU/L TSH

level in male participants ($P=0.007$). Mean (SD) body weight elevated 1.5 (5.6) Kg in female whereas, 1.0 (5.0) Kg in male. An elevate in TSH level at follow-up was positively correlated with gaining of body weight in female approximately, 0.5 to 2.4 kg with increasing TSH level; $p<0.001$ while in male almost 0.4 to 1.3 kg with increasing TSH level; $P=0.007$. TSH level with reference range is correlated with raise in body weight in both (Male & Female). The prevalence of obesity was 14.3% [14]. In current research the prevalence of weight gaining is 26% and the prevalence of obesity at TSH level (0.5-8.5 uIU/ml) was 7% whereas, at TSH level (8.5-14.5 uIU/ml) was 19% and mean (SD) body weight 68.52 (11.70) kg in female and 72.45 (12.50) Kg in male; $P=0.005$.

Madani et al conducted the research on population of Saudi Arabia where obesity is become a major health issue and the prevalence of obesity approximately, 23.7% amongst female and 14.1% amongst male, whereas, the prevalence of overweight is almost 28.3% in female and 30.8% in male, this data indicated that the Saudi Arabia has highest incidence rate of obesity and overweight [15]. In current study the prevalence rate of over all obesity and overweight is 26% whereas, the prevalence of overweight is approximately 14% among women and 2.0% in men, while incidence rate for obesity amongst men and women is same 5%. This indicated that the prevalence rate of weight gaining increasing gradually in Pakistan too.

5. Conclusion

Hyperthyroid patients after the treatment developed hypothyroidism the functions of thyroid hormones have statistically significant alteration in body weight as well as BMI, the raising prevalence of obesity may develop due to the mild hyper-thyrotropin-emia could well be secondary to obesity.

Hypothyroidism is connected with reduction in thermogenesis, reduced metabolic rate, and also correlated with higher (BMI) and higher incidence of obesity. Overall thyroid dysfunction was observed more in obese people with varying degree of significance. Obesity is the root cause of all diseases and most important health issue of this time, according to the National Health and Nutritional Examination Survey, the prevalence of obesity was 32.2% in between 2003 to 2004. Obesity is correlated with an increase chances of mental disorders, diabetes, dyslipidemia, kidney failure, cardiovascular disorders, stroke and cancer. Obesity associated with all types of ailment and leading causes of death all over the world.

Thyroid hormones (THs) plays crucial role in metabolism is familiar to us but THs also effects on hypothalamus to control appetite too. Thyroid disorder either hyper or hypo can influence on appetite, body weight, metabolism, body temperature, BMI, lipolysis and reduction of cholesterol and fats, gluconeogenesis etc. Body weight regulate through the fine-tuning between energy intake and energy consumption.

Conflicts of Interest

The authors declare that they have no competing interests.

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