

EFFICACY OF THYROID DRUGS IN REVERSING ALTERED RENAL MARKERS DUE TO THYROID AILMENTS IN PATIENTS OF PUNJAB, PAKISTAN

Maria Fareed Siddiqui ^{1*}, Zahra Batool ², M.H. Qazi ¹, Sidra Hasnain ³, Sarfraz Ahmad ²,
Muhammad Imtiaz ², Adeela Ali ⁴ and Ismat Fatima ⁴

1. Centre for Research in Molecular Medicine, The University of Lahore, Pakistan.
2. Institute of Molecular Biology and Biotechnology, The University of Lahore, Pakistan.
3. Department of Pharmaceutical Sciences, Superior University, Lahore, Pakistan.
4. Center for Nuclear Medicine, Mayo Hospital, Lahore, Pakistan.

ABSTRACT

Thyroid hormones significantly influence the proper growth, development and performance of kidney, and, in case of hormonal imbalance, kidney function is adversely affected. Many studies have been done on thyroid medication to identify their effectiveness in hyper and hypothyroidism, but the true efficacy of thyroid drug should also be acquainted with their capability in normalizing abnormal renal profiles. The present study was based on identifying the effectiveness of routinely used thyroid drugs in Punjab, Pakistan to distinguish their role in renal dysfunction due to thyroid ailment. Patients of hyper and hypothyroidism were included in this study along with normal subjects as control. Hyperthyroid patients were administered carbimazole and propylthiouracil while hypothyroid patients were given thyroxine. The renal profiles of patients were compared with profiles of normal subjects and results were statistically analyzed by using analysis of variance test to identify significance or insignificance of results based on p-values. Results were found to be more promising with all drugs for creatinine and uric acid while no reversal of altered blood urea and blood urea nitrogen was observed. We conclude that although thyroid drugs reverse some of abnormal renal parameters but adjunctive therapy should be recommended to mask associated risks of renal ailment with thyroid disorder.

Key Words: Thyroid disorder, renal dysfunction, carbimazole, propylthiouracil, thyroxine

Corresponding Author: Maria Fareed Siddiqui, Pharm-D., M.Phil, PhD (Scholar), Centre for Research in Molecular Medicine, The University of Lahore, 1-km defense road, off- Raiwind road Lahore, Pakistan. Tel: +923228493915. Fax: +92-42-35321760. E-mail: maria.pharmacist@gmail.com

RUNNING TITLE: Effect of Thyroid Drugs on Renal Parameters

INTRODUCTION

Human body is comprised of many organs whose anatomy and physiology is really mesmerizing. One such example is Thyroid Gland. Thyroid Gland, in spite of its small size, has profound effect on every organ of the body. Hormones released from this gland are involved in nearly every metabolic reaction taking place inside the body. It is a butterfly shaped gland located on front region of neck just below the larynx, comprises of two lobes; one on right side and the second on the other side of the neck connected by a tissue called isthmus. Its weight is about 12-20g (Brent GA, 1994 and Cheng SY et al., 2010). Thyroid gland makes three hormones:

thyroxine (T4), triiodothyronine (T3) and calcitonin. Upon stimulation of thyroid stimulating hormone (TSH), thyroxine and triiodothyronine are produced from thyroid follicular cells. Thyroid stimulating hormone is released from pituitary gland after being stimulated by thyroid releasing hormone (TRH), produced from hypothalamus. This thyroid stimulating hormone stimulates thyroid gland to express more sodium iodide transporters (NIT) so that iodide metabolism can be initiated which is the first step in the synthesis of thyroid hormones. After iodide uptake by NIT, thyroperoxidase (TPO) enzyme will oxidize it followed by iodination of thyroglobulin (Tg) at tyrosyl residues to produce mono and di-iodinated tyrosyl residues. This iodinated Tg will eventually produce T3 and T4 upon proteolysis inside the lysosome by enzyme T4-5'-deiodinase (Kohrle J, 2000 and Piehl S et al., 2011).

Abnormalities in thyroid gland result in two types of disorders i.e., hyperthyroidism and hypothyroidism. During hypothyroidism low levels of thyroid hormone are produced. Goiter, thyroiditis such as Hashimoto's thyroiditis and un-differentiated thyroid carcinomas are accompanied by Hypothyroidism. Their general signs and symptoms are dry and brittle hair, puffy face, hoarseness and deepening voice, angina, decreased heart rate, constipation, cold dry skin, muscular pain and weakness, cold intolerance, decreased sweating, tiredness and fatigue (Gillet M, 2004, Topliss DJ and Eastman CJ, 2004). During Hyperthyroidism high levels of thyroid hormones are produced. Grave's thyroiditis and differentiated follicular thyroid carcinoma are developed due to hyperthyroidism. Signs and symptoms for hyperthyroidism are fine hair- thinning, goiter, palpitations, diarrhea, hot flushed moist skin, muscular fatigue and weakness, heat intolerance, increased sweating, nervousness, irritability and insomnia (Pinto A and Michael G, 2002).

Syn-thyroid drug used for the treatment of hypothyroidism is Levothyroxine sodium. Starting dose is 0.25mg per day which is carefully monitored after titration to reach maximum dose of 1mg per day. T3 along with T4 may also be used if T3 levels remain abnormal even after T4 replacement. Hyperthyroidism state is normalized by the use of anti-thyroid drugs such as Carbimazole and Propylthiouracil. Initial dosage for Carbimazole is 30-60mg per day divided in two doses, while dosage for Propylthiouracil (PTU) is 300-600mg after 8 hours in a day (Cooper DS, 2005). Levothyroxine is converted into T3 inside liver by deiodinases. Mode of action for anti-thyroid drugs is different. Carbimazole blocks the coupling of iodine residue on thyroglobulin molecule while propylthiouracil blocks the conversion of T4 to T3 (Singer PA et al., 1995).

Thyroid hormones have very dominant effect on proper functioning of kidney by affecting its growth and development. This in turn affects structure and function of kidney. So, any abnormality in thyroid hormone production will affect anatomy and physiology of the kidney (Bradley SE et al., 1982, Bentley AG et al., 1985 and Canavan JP et al., 1994). Renal parameters which are used to monitor structure and function of kidney are glomerular filtration rate (GFR), serum creatinine, uric acid and blood urea nitrogen (Kreisman SH and Hennessey JV, 1999, Iseki K et al., 2001 and Obermayr RP et al., 2008). Since thyroid hormones are involved in the downstream regulation and expression of renin-angiotensin system, and of several ion transporters across nephron membrane, so, variation in their concentrations during thyroid disorders will also affect kidney function by altering the action and number of transporters on plasma membrane (Santos OD et al., 2003 and Wang W et al., 2007).

Patients suffering from thyroid disorders gradually develop renal disorders if their thyroid abnormalities remain untreated. So, as soon as they get treatment for thyroid disorder their renal dysfunction must be settled down automatically. Current study was based on objective to find out role of thyroid drugs in reversing abnormal renal markers due to hyperthyroidism in Pakistani population.

METHODS

Study was conducted on 60 thyroid patients who were recruited from Centre of Nuclear Medicine (CENUM), at King Edward Medical University (KEMU), Lahore, Pakistan. 50 patients were experiencing hyperthyroidism and 10 were of hypothyroidism. Carbimazole and propylthiouracil were administered to patients of hyperthyroidism to avoid thyroid storm and also to prepare those patients for radioactive iodine therapy or surgery. 40 patients of hyperthyroidism were prescribed carbimazole and 10 were given propylthiouracil. Standard doses of carbimazole and propylthiouracil i.e., 15-40 mg /day and 200-400 mg/ day respectively were administered to patients. Patients of hypothyroidism were taking levothyroxine 50-100 micrograms once daily. Patients suffering from concomitant disorders such as hepatitis, diabetes and hypertension etc. and those on multi-drug therapy were excluded from the study and all participants gave their informed consents. Renal parameters such as creatinine, blood urea and uric acid were analyzed through spectrophotometry on micro-lab equipment by using reagents of Crescent Company (Jeddah 21423, KSA) and Human Company (Max-Planck-Ring, Wiesbaden, Germany). Results were compared with levels of 20 healthy subjects and statistical analysis was done by using analysis of variance test (ANOVA). Confidence Interval was 0.95. P-value below 0.05 was considered significant while values above 0.05 were considered non-significant.

RESULTS

Table 1. Values of means (M) and standard error of means (SEMs) of creatinine, blood urea, blood urea nitrogen and uric acid in control, hypothyroidism and hyperthyroidism groups

Sr. No.	Parameters	Control N=20 M $\pm$ SEM	Hypo-medicated N=10 M $\pm$ SEM	Hyper-medicated N=50 M $\pm$ SEM	
				Carbimazole N = 40	Propylthiouracil N = 10
01	Creatinine	0.86 $\pm$ 0.03	0.03 $\pm$ 1.00	0.94 $\pm$ 0.04	0.88 $\pm$ 0.06
02	Blood Urea	17.14 $\pm$ 0.92	29.37 $\pm$ 2.94	25.73 $\pm$ 1.06	22.30 $\pm$ 0.45
03	Blood Urea Nitrogen	7.99 $\pm$ 0.43	13.69 $\pm$ 1.37	11.99 $\pm$ 0.49	10.39 $\pm$ 0.21
04	Uric Acid	5.46 $\pm$ 0.32	6.42 $\pm$ 0.73	5.63 $\pm$ 0.26	4.58 $\pm$ 0.54

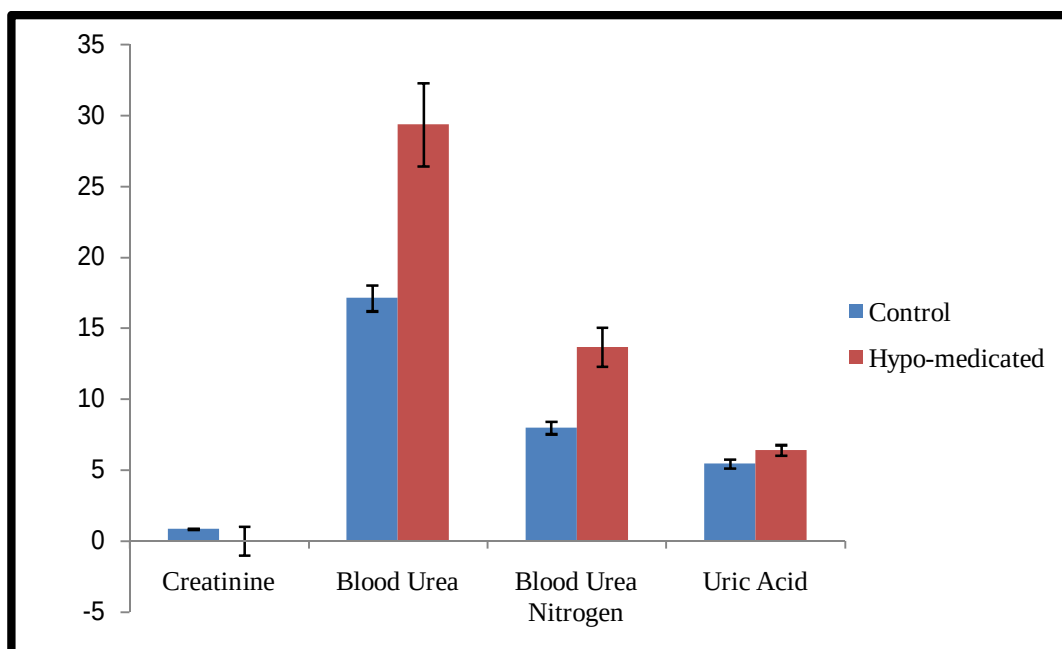


Figure 1. Bar chart representation of Mean values and Standard Error of Means (SEMs) of Renal Markers in Control and Hypo-medicated groups

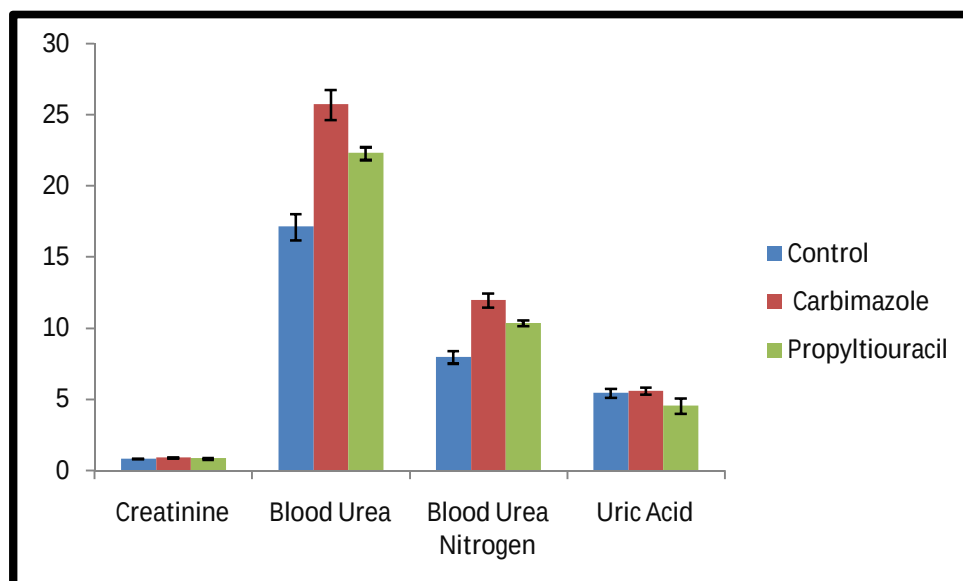


Figure 2. Bar chart representation of Mean values and Standard Error of Means (SEMs) of Renal Markers in Control and Hyper-medicated groups

Table 2. P-values of Hypo and Hyper-medicated groups when compared with Control

Sr. No.	Parameters	p-values for Hypothyroidism patients when compared with Control	p-values for Hyperthyroidism patients when compared with Control
01	Creatinine	0.219	0.337
02	Blood Urea	0.004	0.020
03	Blood Urea Nitrogen	0.001	0.010
04	Uric Acid	0.192	0.198

DISCUSSION

The patients of hypothyroidism were administered levothyroxine. Mean values of control and hypothyroid group for creatinine were 0.86 and 0.03; for blood urea: 17.14 and 29.37; for blood urea nitrogen: 7.99 and 13.69, and, for uric acid: 5.46 and 6.42 for both groups i.e., control and hypothyroid group respectively. The standard error of means for creatinine: ± 0.03 and ± 1.00 ; for blood urea ± 0.92 and ± 2.94 ; for blood urea nitrogen: ± 0.43 and ± 1.37 , and, for uric acid were ± 0.32 and ± 0.73 for both groups i.e., control and hypothyroid group respectively. P-values were identified by comparing hypothyroid group with control and those were 0.219, 0.004, 0.001 and 0.192 for creatinine, blood urea, blood urea nitrogen and uric acid respectively.

Elevated serum creatinine levels in hypothyroid patients decreased to normal levels after treatment with levothyroxine. Statistical analysis also confirmed the results since p-value for creatinine was 0.219 when analyzed for both study groups. Thus, creatinine levels are instantly affected by thyroid status due to effect of thyroid hormones on creatinine synthesis by kidney cells secretion via glomerulus (Den Hollander JG et al., 2005 and Devika T et al., 2009).

Serum urea levels, for control and hypo groups, were found statistically significant with p-value 0.004 representing drug inefficacy to normalize urea levels in hypo group. These raised levels of serum urea are due to possible side effects of L-Thyroxine (Den Hollander et al., 2005).

The levels of uric acid were appeared to be normal after treatment with levothyroxine. Statistical assessment also proved the non-significant difference between control and hypo group. P-value of 0.192 shows the strong effect of drug indirectly on kidney because as the levels of thyroid hormone gets normal, kidney function also tends to be normal. Further we can validate our results by findings of previous studies in establishing a strong correlation between uric acid levels and abnormal thyroid status and effect of L-thyroxine in normalizing thyroid function directly and uric acid levels indirectly (Nakahama H et al., 2001 and Obermayr RP et al., 2008).

Mean and standard error of mean values of hyperthyroid patients with carbimazole treatment were as follows: for creatinine: 0.94 and ± 0.04 ; for blood urea: 25.73 and ± 1.06 ; for blood urea nitrogen: 11.99 and ± 0.49 , and, for uric acid: 5.63 and ± 0.26 . While on treating hyperthyroid patients with propylthiouracil, mean and standard error of mean values for creatinine were: 0.88 and ± 0.06 ; for blood urea: 22.30 and ± 0.45 ; for blood urea nitrogen: 10.39 and ± 0.21 , and, for

uric acid: 4.58 and ± 0.54 . Significance or insignificance was established on the basis of p-values after comparing whole group of hyperthyroid patients with control population and those were 0.337, 0.020, 0.010 and 0.198 for creatinine, blood urea, blood urea nitrogen and uric acid respectively.

Creatinine and uric acid levels were also appeared to be non-significant with p-value of 0.337 and 0.198 respectively. Since the patients included in hyperthyroid group were on anti-thyroid medication and this medication normalized their T4, T3 and TSH so creatinine and uric acid, whose levels are dependent on thyroid profile, also become normalized. Our research findings on Pakistani population are clearly strengthening the previously held notion of renal dependency on thyroid gland as documented by den-Hollander and his coworkers during 2005 that renal anomalies improve as abnormal thyroid function gets better by using anti-thyroid drugs (Iseki K et al., 2001, Den Hollander JG et al., 2005 and Devika T et al., 2009).

Serum urea levels were found to be significant in our study with a p-value of 0.020 when control group was compared with hyperthyroid group through statistical analysis. This increase in urea level was due to side effect of carbimazole and propylthiouracil when used for a long duration as reported in different studies in various timings. Similarly Clara Day and his co-workers presented a case report in 2003 when a male patient under treatment with carbimazole experienced elevated blood urea nitrogen levels. High blood urea nitrogen has also been reported as a side effect of propylthiouracil (Fang T and Chiu-Ching H 1998, Clara D et al., 2003 and Frenais R et al., 2009).

CONCLUSION & FUTURE PERSPECTIVE

During treatment of hypothyroid patients, combination therapy must be recommended to effectively treat the disorder and increase the social and psychological status of the patient. The patients of hyperthyroidism on carbimazole and propylthiouracil may present disturbed renal markers as the associated effects of these drugs, so, adjunctive therapy should be employed to mask related side effects. Furthermore, patients coming with renal disorders must also be examined for thyroid abnormalities so that culprit cause of this renal abnormality could be treated.

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