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Research Article

Clinical Trends of Hepatic and Renal Profile in Hyperthyroid subjects of Lahore, Pakistan

Muhammad Amir Iqbal[1], Nabila Roohi[1*], Ahmad Qureshy[2]

[1]Department of Zoology, University of the Punjab, Quaid-i-Azam Campus, Lahore- 54590, Pakistan
[2]Department of Nuclear Medicine, Institute of Nuclear Medicine and Oncology, Lahore, Pakistan

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MAI conducted the research, did statistical analysis and wrote the article. NR supervised the research. AQ helped in analysing the samples.

Keywords
Hyperthyroidism, ALT, AST, Creatinine

Abstract | Present study was planned to evaluate the alterations in renal and hepatic profile induced by overt hyperthyroidism as well as its subclinical form. A total of 179 subjects comprising both genders and fulfiling the exclusion and inclusion criteria were recruited for this prospective investigation. Sixty healthy controls, thirty four subclinical, fifty overt hyperthyroid and thirty five follow-up subjects having 3 months of anti-thyroid therapy were recruited. Commercially available diagnostic kits were used to determine the serum levels of FT_4, FT_3, TSH, Creatinine, AST and ALT. Prominent reduction ($P<0.001$) of creatinine was observed in overt hyperthyroid state, when compared with controls. However, significant ($P<0.05$) improvement was noticed in it in post treatment group. Pronounced elevation ($P<0.001$) of ALT was observed in overt state when compared with controls. Subclinical subjects also manifested significant ($P<0.05$) up regulation, whereas, pronounced reduction ($P<0.01$) was observed in ALT in post therapeutic condition. Prominent elevation ($P<0.001$) of AST in both overt as well as subclinical thyroid states have been observed when compared with healthy controls. Whereas, significant reduction ($P<0.05$) of AST was observed in post treatment group. Conclusively, hyperthyroid conditions markedly influence normal hepatic and renal function, whereas, treatments achieving euthyroid state after anti-thyroid therapy also influence these deviations.

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Introduction

Thyroid hormones (TH) are the most important bio-molecules in the realm of human biology. Thyroid is a major endocrine gland located in front of throat below Adam's apple and produces two vital amine hormones, tetra-iodothyronine (T_4) or thyroxin and tri-iodothyronine (T_3) (Yen, 2001; Boeelaert and Franklyn, 2005; Arora *et al.,* 2009). Both T_3 and T_4 are under influence of thyroid stimulating hormone (TSH) a glycoprotein, released by adenohypophysis that in turn is controlled by thyroliberin (also called TRH, thyrotropin releasing hormone) of hypothalamus (Reza *et al.,* 2013). Circulating level of T_3 and T_4 exerts negative feedback effect on anterior pituitary to produce TSH which subsequently acts on the TSH receptor (TSH-R) present on the bio-membranes of thyroid follicles (Chiamolera and Wondisford, 2009). TSH mediates iodine uptake, facilitated through the sodium/iodide symporter (Brent and Koenig, 2010).

T_3 regulates extensive variety of mechanisms like body growth, neural differentiation, development, maintenance of internal environment by activating a series of biochemical reactions after its activation from the precursor, tetra-iodothyronine (Gereben *et al.,* 2008; Williams, 2008; Cheng *et al.,* 2010; Tata, 2013).

Corresponding author: Nabila Roohi
nabilaruhi@gmail.com

Any alteration in the actions of T_3 and T_4 (hypo or hyper activity) influences the normal metabolic pathways of both embryonic and adult life (Mullur *et al.,* 2014). These hormonal actions may range from subclinical, which is asymptomatic with abnormal TSH level but normal free T_3 and T_4 levels, to clinically symptomatic or overt (with abnormal T_3 and T_4 levels) thyroid dysfunction (Krishnamoorthy *et al.,* 2009).

Overt hyperthyroidism is defined as raised serum free T_4 and T_3 concentrations in the presence of an untraceable TSH concentration. Symptoms of hyperthyroidism are increased hunger weight loss, weakness, tremors of hands, elevated heartbeat, goiter, loose stools, irritability, exophthalmos, increased sweating, moist skin and heat intolerance (Khan *et al.,* 2002). Most thyroid dysfunctions are autoimmune in their pathogensis, Hashimoto's thyroiditis is a form hypothyroidism, whereas Graves' disease represents for thyrotoxicosis a type of hyperthyroidism (Sabih and Inayatullah, 2013).

Hyperthyroidism is a prevalent ailment with prominent cardiovascular effects including sinus tachycardia, systolic hypertension, changes in ventricular systolic and diastolic function, changes in peripheral vascular resistance and predisposition to dysrhythmias, especially atrial fibrillation (AF) (Klein and Ojamaa, 2001; Chen *et al.,* 2014). These disorders have been reported in over 110 countries of the world with 1.6 billion people at risk (Iqbal *et al.,* 2016).

Sub-clinical hyperthyroidism represents the earliest phases of thyroid dysfunction (Alam *et al.,* 2010). It exerts various alarming effects on the cardiovascular system (Biondi *et al.,* 2002). Elevated heart rate, enhanced left ventricular mass, raised risk of supraventricular arrhythmias, presumably supplemented by deranged diastolic function and, sometimes, by reduced systolic performance, decreased exercise tolerance are associated with subclinical hyperthyroid disease (Coban and Aydemir, 2008).

In Pakistan, the prevalence of overt and sub clinical hyperthyroidism and hypothyroidism is reported to be 5.1% and 5.8% and 4.1 and 5.4%, respectively (Reza *et al.,* 2013). It is also perceived that the prevalence of both hyperthyroidism and hypothyroidism (subclinical or overt) is higher in females than males. Hyperthyroid situations are often accompanied by the abnormal liver function, even before the start of antithyroid therapy. Such ailments can worsen the intensity of the normal liver biochemistry (Lin *et al.,* 2017). Prevalence of liver biochemical derangements in untreated hyperthyroid situations varies significantly, ranging from 15 to 79 percent (He *et al.,* 2014). Both ALT and AST are two aminotransferases of great clinical importance and indicator of normal liver biochemistry.

Similarly, strong interplay has been reported between thyroid and renal system, thyroid disturbances usually affect renal metabolism (Basu and Mohaptra, 2012). Creatinine, a strong indicator of normal renal metabolism, is a non-protein nitrogenous substance belong to the large group of guanidino compounds (Kumara *et al.,* 2017). Alteration in the level of creatinine indicates pathophysiological condition of renal system.

Present study was planned to evaluate the alterations in renal and hepatic function induced by overt hyperthyroidism as well as its subclinical form. Moreover, the responsiveness of the anti-thyroid treatment was also accessed in a follow-up group of the investigation.

Materials and Methods

Institutional Ethical Review Committee of Department of Zoology, University of the Punjab endorsed the study plan. A total of 179 subjects comprising both genders and full filing the exclusion and inclusion criteria were recruited for this prospective investigation. Sixty healthy age matched controls (Group I: 40 females and 20 males), thirty four subclinical (Group II: 21 females and 13 males) and fifty overt hyperthyroid (Group III: 35 females and 15 males) and thirty five follow-up (Group IV: 25 females and 10 males) subjects having 3 months of anti-thyroid therapy were recruited. A group (n=35; 25 females and 10 males) of newly diagnosed hyperthyroid patients on antithyoid therapy (average of 30-60 mg of Carbimazole/day) was also approached, attaining euthyroid state, after three months for follow-up studies to access the effectiveness of the treatment.

Normal reference ranges of the thyroid profile were as follows

FT_4	11.5 – 23.0 pmol/L
FT_3	2.5 – 5.8 pmol/L
TSH	0.3 – 5 mIU/L

Written informed consent was obtained from each of the participants of the study. A comprehensive proforma was designed to record the demographic parameters of the concerned subjects. Exclusion criteria for subjects with thyroidal dysfunction was obesity, diabetes mellitus, hypertension, cardiovascular complications and family history of these ailments. Subjects having history of liver dysfunction, like hepatitis or drug addiction were also excluded, as these conditions may impair proper liver functioning. Pregnant women were not recruited in this study.

Quantitative assessment of thyroid profile (FT_4, FT_3 and TSH) was made by Immunoassay with commercially available kits of Beckman Coulter of Czech Republic. Commercially available diagnostic kits DiaSys, Diagnostic

Table I: An overall comparison of thyroid, renal and hepatic profile in control, subclinical, overt and follow-up groups.

Parameters	Control	Subclinical	Overt	Follow-up	*P*-value
	Means ± SEM				
FT_4(pmol/L)	17.53 ± 0.36	19.36 ± 0.93	45.65 ± 2.49	14.66 ± 1.08	<0.0001*
FT_3(pmol/L)	3.91 ± 0.09	4.62 ± 0.20	28.77 ± 1.94	4.96 ± 0.16	<0.0001*
TSH(mIU/L)	1.97 ± 0.15	0.09 ± 0.01	0.04 ± 0.007	0.72 ± 0.21	<0.0001*
AST(U/L)	26.16 ± 0.88	36.90 ± 2.24	38.98 ± 1.92	31.15 ± 2.47	<0.0001*
ALT(U/L)	23.61 ± 1.04	27.80 ± 3.24	36.33 ± 2.70	23.50 ± 1.70	<0.0001*
Creatinine(mg/dL)	0.70 ± 0.02	0.62 ± 0.04	0.56 ± 0.02	0.67 ± 0.03	0.0003*
BMI(kg/m^2)	22.02 ± 0.35	21.11 ± 1.18	19.39 ± 0.30	21.31 ± 0.48	<0.0001*

Values are Means ± SEM.*indicates significance at P< 0.001

Systems were used to determine the serum levels of Creatinine, Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) by clinical chemistry analyzer (Model 5010, Robert Riele GmbH& amp; Co KG. D-13467 Berlin, Germany). Demographics including mean systolic, diastolic blood pressure, pulse rate, weight and height for BMI were also measured before phlebotomy of all four studied groups.

Statistical model

Overall biochemical comparisons among overt Hyperthyroid, Subclinical, Follow-up and Control group were carried out by one-way ANOVA (Steel *et al.*, 1997). Significant means (P< 0.05) were compared by using "Student Newman Keuls" (SNK) test assuming following statistical model:

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij}$$

Where,

Y_{ij} = Observation of dependent variable on i^{th} treatment

μ = Population mean

τ_i = Effect of i^{th} treatment (i = 1, 2, 3, 4; Control, Subclinical, Overt and Follow up)

ε_{ij} = Residual effect of j^{th} observation on i^{th} treatment NID ~ 0, σ^2

Results

Table I represents the overall comparison of thyroid, renal and hepatic profile in Control (C), Subclinical (S), Overt (O) and Follow-up (F) groups. Non-significant difference in FT_4 levels was noticed in comparison of control vs subclinical and follow up groups, whereas, highly-significant difference ($P \leq 0.001$) was found in control vs overt hyperthyroid patients indicating 160% elevation in overt state, when compared with control. Highly significant ($P \leq 0.001$) difference was observed with 135% elevation in overt state as compared to subclinical, however, non-significant decrement was observed in follow-up as compared to subclinical group. A comparison of overt vs follow-up groups, indicated highly significant ($P \leq 0.001$) reduction of 68% in follow-up compared to overt hyperthyroid group (Figure 1 a).

Non-significant difference was found in control vs subclinical and follow-up comparison, however, prominent difference ($P \leq 0.001$) was noticed in control vs overt comparison with 635% elevation of FT_3 in overt state when compared with controls. Non-significant difference was present in subclinical vs follow-up comparison, whereas, highly significant difference ($P \leq 0.001$) was observed in subclinical and overt comparison depicting 522% increase in overt state when compared with subclinical. Lastly, overt vs follow-up comparison demonstrated prominent difference ($P \leq 0.001$) with 82% decline of FT_3 in follow-up after anti-thyroid treatment (Figure 1b).

Highly significant difference ($P \leq 0.001$) of TSH was found in control vs subclinical, overt and follow-up comparisons with 95%, 98% and 63% reduction in subclinical, overt and follow-up groups, respectively. Non-significant difference was present in subclinical vs overt comparison, however, prominent difference ($P \leq 0.05$) with 700% increase of TSH in follow-up group, was found in subclinical vs follow-up comparison. In the end follow-up group demonstrated marked ($P \leq 0.05$) elevation of TSH level with 1700% when it was compared with overt group (Figure 1c).

Control vs subclinical and follow-up comparison presented non-significant difference, while, statistically marked difference ($P \leq 0.001$) was found in control vs overt comparison with 54% elevation of ALT in overt group as compared to controls. Non-significant difference was observed in comparison of subclinical vs follow-up, while, significant difference ($P \leq 0.05$) was present in subclinical vs overt comparison with 31% elevation of ALT in overt group as compared to subclinical. Lastly, overt vs follow–up comparison demonstrated significant reduction ($P \leq 0.01$) of 35% in the follow-up group, when compared with overt (Figure 1d).

Highly significant difference ($P \leq 0.001$) was found in

comparisons of control vs subclinical and overt with 41% and 49% elevation of AST in subclinical and overt groups respectively, as compared to controls. However, non-significant difference was present in control vs follow-up comparison. Subclinical vs overt and follow-up comparison did not depicted any significant difference, while, overt vs follow-up comparison demonstrated pounced reduction ($P \leq 0.05$) of AST with 20% reduction in follow-up group after anti-thyroid treatment (Figure 1e).

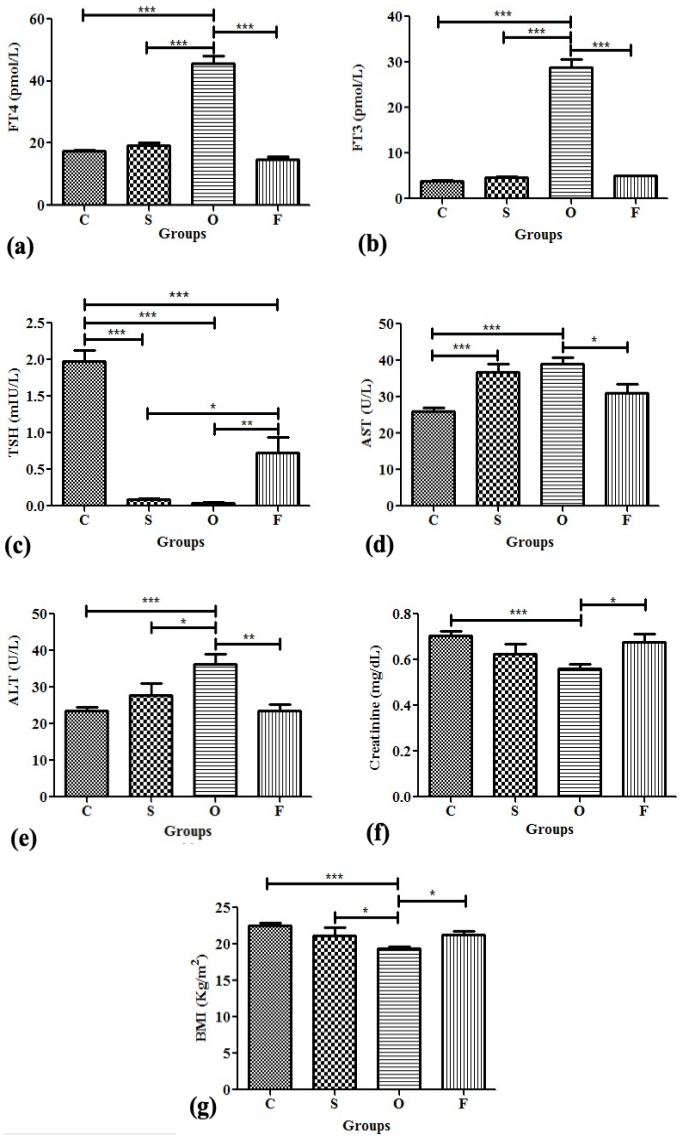

Figure 1: (a-g): Values are Mean ± SEM, Significant at *$P \leq 0.05$, **$P \leq 0.01$ and ***$P \leq 0.001$

Non-significant difference of creatinine was evidenced in control vs subclinical and follow-up comparison, while, control vs overt comparison demonstrated highly significant difference ($P \leq 0.001$) with 20% reduction in overt group, when compared with controls. Subclinical vs overt and follow-up presented non-significant difference, while, in last comparison of overt vs follow-up significant elevation ($P \leq 0.05$) of 20% in creatinine levels was observed in follow-up group, after anti-thyroid treatment (Figure 1f).

Control vs subclinical and follow-up comparison demonstrated non-significant difference, while, control vs overt comparison depicted, highly significant difference ($P \leq 0.001$) with 14% decrease of BMI in overt group when compared with controls. In subclinical vs overt comparison, significant ($P \leq 0.05$) difference was observed with 8% decrease in overt state as compared to subclinical. Moreover, subclinical vs follow–up comparison did not demonstrated significant difference. In last overt vs follow-up comparison, significant difference ($P \leq 0.05$) was found with 10% up-regulation of BMI in follow-up as compared to control group (Figure 1g).

Disscussion

Our findings have shown highly pronounced reduction in the creatinine levels in the overt hyperthyroid patients. Primarily, in overt secretion of thyroid hormones, the cardiac output is enhanced resulting in an increased clearance of creatinine. T_3 has a direct influence on systemic vascular flow, which affects cardiac output (Klein and Ojamaa, 2001), however this could also impact renal blood flow. Moreover, brain natriuretic peptides (BNP) concentrations also have correlation with FT_4 and FT_3 levels (Schultz *et al.*, 2004) which may also modulate cardiac outflow and glomerular filtration rate (GFR). It is an established fact that creatinine clearance is rough estimate of the GFR because of its dependence on muscle mass and active tubular secretion. So it is understandable that the tubular secretion of creatinine is under the influence of thyroid hormones. T_4 also mediates transcription in the sarcoplasmic reticulum, affecting the Na^+/Ca^{2+}exchanger and the Na^+/K^+-ATPase activity in the kidney parenchyme (McDonough *et al.*, 1988). This phenomenon could be of vital importance for the active tubular secretion of creatinine. In addition to that, creatinine production in muscle is dependenton the thyroid status. Some of the authors have reported that increased protein breakdown in hyperthyroid patients is partially balanced by raised GFR (Toshihide *et al.*, 1992). In patients with hyperthyroidism, bodymass is decreased and consequently muscle mass is also decreased,which may result in lower plasma creatinine concentrations (Norrelund *et al.*, 1999).

Furthermore, hyperthyroidism is accompanied by enhanced metabolic activity of the renin-angiotensin-aldosterone system (RAAS) (Ichihara *et al.*, 1998). T_3 also induces relaxation of blood vessel resulting in a reduction in vascular resistance and increases serum levels of renin activity and angiotensinogen concentration (Toshiro and Kenji, 2006). This leads to decrease in TSH with increase in T_3 and T_4 and decreased creatinine levels (Toshiro and Kenji, 2006). Pronounced normalization is observed in the renal functions after having anti-thyroid treatment of three months. So the changes induced in the hyperthyroid subjects are reversible. In case of subclinical hyperthyroid

subjects, despite of non-significant difference compared with control, there was a mild reduction in creatinine level. This mild decrement can be an indicator of future etiology in the renal function of the hyperthyroid patients.

Hyperthyroid situations are often accompanied by the abnormal liver function, hence, even before the start of antithyroidal treatments, these derangements can worsen the intensity of the abnormal liver biochemisty (Lin at el., 2017). The pattern of biochemical liver derangements in hyperthyroidism is variable character in its severity, however, it appears to be predominantly hepatic,with only a few case studies evidencing a cholestatic pattern (Kibirige *et al.,* 2012; Elias etal., 2012; Akande and Balogun, 2013).

In our observation, both AST and ALT were increased in the clinical and subclinical thyroid dysfunction. The similar trends were observed in previous studies (Aydemir *et al.,* 2005; Madani *et al.,* 2014; Hasan *et al.,* 2016). Liver dysfunction in the hyperthyroid patients can be explained by many factors; *in vitro* studies in animals have shown that elevated T_3 activity can provoke apoptosis in hyperthyroidism via mitochondrial dependent cascades (Upadhyay *et al.,* 2004). Furthermore, iodothyronines are also involved in the bilirubin metabolism and there excess concentrations may results in the accumulation of bilirubin precursors, hepatic tissue hypoxia and increased splanchnic oxygen demand (Kubota *et al.,* 2008). Usually thyroid hormones are sulphated and glucuronidated in the hepatic tissue, so as excess of thyroid hormones can over load the liver machinery and injure hapatocytes (Fatima *et al.,* 2017).

Clinical hyperthyroidism is associated with enhanced cardiac output which causes an increased heart mass and acute cardiac failure. Thus liver congestion and cardiac abnormalities can result in the elevation of transaminases (Shimizu, 2008).

Restoration of the thyroid profile causes improvement in the level of serum AST and ALT suggesting that Carbimazole can improve the liver profile towards attaining the euthyroid profile. It is worth mentioning here that during the first month of anti-thyroid treatment transient increase in liver enzymes (AST and ALT) have been reported. Possibly due to increased enzyme production and normalized turnover rate by the effect of antithyroid drugs, serum hepatic enzyme may transiently increase (Kubota *et al.,* 2008).

Conclusion

The study indicates deviations induced by hyperthyroidism, in liver and renal profile. Attaining euthyroid state by Carbimazole treatment helps in improving the creatinine level and reducing the ALT and AST levels towards the normal, in post treatment group.

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