BIOLOGIA (PAKISTAN)
June, 2019, 65 (I), 113-119

PKISSN 0006 – 3096 (Print)
ISSN 2313 – 206X (On-Line)

Variations in Hepatorenal profile in Hypothyroid subjects of Lahore, Pakistan

ZAHRA NASEEM[1], MUHAMMAD AMIR IQBAL[1], SHAAF AHMAD[2] & NABILA ROOHI[1*]

[1]Department of Zoology, University of the Punjab, Lahore-54590, Pakistan
[2]King Edward Medical University, Neela Gumbad, Anarkali, Lahore-54000, Pakistan

ARTICLE INFORMAION

Received: 21-02-2019
Received in revised form: 27-03-2019
Accepted: 08-05-2019

***Corresponding Author:**

Nabila Roohi:
nabilaruhi@gmail.com

Original Research Article

ABSTRACT

Effects of hypothyroidism on liver and renal parameters and effectiveness of thyroid treatment (thyroxine) on these factors in hypothyroid subjects were assessed in the present investigation. A total of 140 subjects (30 subclinical and 50 overt hypothyroid) between the ages of 15-50 years from INMOL, Lahore and 60 healthy euthyroid controls of the similar age groups from local population were recruited. Additionally, follow up studies of nearly thirty five overt hypothyroid patients was also carried out after taking thyroxine for three months. Serum levels of fT_4, fT_3 and TSH were analyzed through Radioimmunoassay (RIA), whereas, levels of AST, ALT and creatinine were assessed using chemistry analyzer. Levels of ALT and AST were found significantly increased ($P \leq 0.05$) in overt hypothyroid patients compared to controls and after treatment the concentrations of both enzymes were decreased non-significantly in post therapeutic group. Subclinical group also exhibited non-significant elevation in ALT and AST levels. Creatinine levels were significantly ($P \leq 0.05$) increased in both subclinical and overt hypothyroid patients and mildly decreased in follow up group as compared to overt group. Conclusively, positive association of ALT, AST and creatinine with TSH and inverse relationship with fT_3 and fT_4 were observed in hypothyroid patients that reversed moderately after thyroxine therapy.

Keywords: ALT, AST, Creatinine

INTRODUCTION

Hypothyroidism is a clinical syndrome, caused by thyroid hormone (TH) deficiency due to reduced production, deranged distribution, or absence of thyroid hormone effects (Chakera *et al*., 2012; Xu *et al*., 2012; Akinsete *et al.,* 2019). Clinical spectrum for hypothyroidism ranges from an overt state of myxedema, end-organ damage and multisystem failure to a subclinical asymptomatic condition (Cooper, 2001; Biondi & Klein, 2004; Roberts & Ladenson, 2004; Krassas *et al*., 2010). Subclinical hypothyroidism or mild thyroid failure is characterized by raised serum thyroid stimulating hormone (TSH) in combination with normal free tetra-iodothyronine (fT_4) and free tri-iodothyronine (fT_3) levels without clinical symptoms or signs of hypothyroidism (Stenzel & Huttner, 2013). Whereas, overt hypothyroidism is characterized by elevated TSH, in combination with subnormal level of fT_4 (Ross, 2001; Surks *et al*., 2004; Garber *et al*., 2012; Pearce *et al.,* 2013).

Thyroid hormones modulate the functioning of all body cells including hepatocytes. Concomitantly, liver metabolizes thyroid hormones and regulate their systemic effects (Malik & Hodgson, 2002). Normal hepatic circulation is reliant on normal concentration of thyroid hormones and any perturbation in thyroid disturbs its function. Liver injuries are linked with thyroid dysfunction and release of Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) into the bloodstream. ALT is found predominantly in the liver, whereas, AST is also found in skeletal muscles and erythrocytes. Hence, elevations in ALT levels usually are more precise for assessment of hepatic damage than AST. The interaction between thyroid and liver may results in diagnostic misunderstandings and abandonment of these facts may cause over or under diagnosis of associated liver or thyroid diseases. Hence, to exclude concurrent possibility of thyroid dysfunction in patients with unexplained liver biochemical abnormalities, measurement of free T_4 and TSH levels are recommended (Huang & Liaw, 1995).

Thyroid gland and kidneys are interlinked with each other in several aspects. Thyroid hormones are responsible for the development and functioning of kidneys. Conversely, kidneys effect the concentration and metabolism of thyroid

Author's Contribution: Z.N. Conducted experiment work; **M.A.I.** Helped in experiment work and wrote up the manuscript; **S.A.** Helped in data analysis and blood sampling; **N.R.** Supervised whole investigation

hormones (Lippi *et al*., 2008; Kimmel *et al*., 2012). Being cardiotonic, thyroid hormones increase cardiac output while lowering systemic vascular resistance, resulting in increased renal blood flow and increased glomerular filtration rate (GFR) which is associated with serum creatinine level (Montenegro *et al*., 1996; Nakahama *et al*., 2001). Experiments on animals have shown that hypothyroidism results in reduced GFR, however, insufficient data exist on how hypothyroidism influences renal function in human beings (Arora *et al*., 2009). Reduction of cardiac output due to paucity of inotropic and chronotropic effect of thyroid hormones and increased vascular resistance diminish renal blood flow, hence reduce GFR (Montenegro *et al*., 1996; Jayagopal *et al*., 2003; den Hollander *et al*., 2005). In addition to this, histological changes in nephrons, especially basement membrane thickening that physiologically effects renal hemodynamics also results in decrease in renal blood flow and GFR (Montenegro *et al*., 1996; Lippi *et al*., 2008).

Present investigation was designed to evaluate the alterations in renal and hepatic profile induced by overt as well subclinical hypothyroidism. Moreover, effectiveness of thyroid treatment was also assessed in the follow-up group.

MATERIALS AND METHODS

The study was commenced after taking approval from the Institutional Ethical Review Committee (D/1581-ACAD). Subjects visiting Institute of Nuclear Medicine and Oncology Lahore (INMOL) during January 2015 to December 2016, with apparent signs and symptoms of hypothyroidism, were interviewed after taking their written consent. Thyroid Function Test (TFT) was performed to ascertain the diagnosis. Demographic features and detailed history of all the participants were taken by means of pre-designed questionnaire. A mercury sphygmomanometer was used for measuring blood pressure of all the subjects enrolled in the study. Patients having cardiovascular disease, diabetes mellitus and hypertension were eliminated from the study. A total of 140 individuals, satisfying the inclusion criteria comprising sixty healthy controls (48 females and 12 males), thirty subclinical (21 females and 9 males) and fifty overt hypothyroid subjects (38 females and 12 males) were recruited in the study. To evaluate the efficacy of thyroid treatment, follow up study of thirty five (28 females and 7 males) selected subjects, undergone thyroxine treatment for three months, was also carried out. The average daily dose of thyroxine varied from 100-300 mg according to the intensity of the disease.

Subjects having obesity, smoking habit, primary or secondary dyslipidemia, diabetes mellitus, renal and hepatic failure or other systemic maladies were excluded from the investigation. Subjects for blood collection were categorized into following groups.

Control group: Healthy age and sex matched volunteers (60)
Group I: Newly diagnosed overt hypothyroid patients (50)
Group II: Newly diagnosed subclinical hypothyroid patients (30)
Group III: Follow up (35)
Standard 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

Blood samples were collected from the participants and analysed statistically for evaluation and comparison of their renal and hepatic profile before and after treatment. Thyroid profile was studied using commercially available RIA (Radio Immunoassay) kits of Beckman Coulter of Czech Republic, in INMOL Lahore, Pakistan. Whereas, biochemical analysis of ALT, AST and creatinine was performed using commercially available kits of DiaSys Diagnostic System, Holzheim Germany.

Statistical analysis

Overall biochemical comparisons among control (Cn), subclinical (Sb), overt hypothyroid (Ot) and follow up (Fll) groups were accomplished by one-way ANOVA. Newman-Keuls Multiple Comparison Test was applied to compare the group means and statistical significance was achieved when the *P* value is <0.05.

RESULTS

free-thyroxine (fT_4)

Comparison of overt group with control group showed a highly significant ($P \leq 0.001$) reduction of 56% in overt group and after treatment the level of fT_4 increased significantly ($P \leq 0.001$) in follow up group up to 100% as compared to overt group. Whereas, the value of fT_4 was decreased up to 12% in follow up group as compared to control group. A non-significant decrease of 8% was observed in subclinical group when compared with control group. Overt group showed highly significant ($P \leq 0.001$) decrease of 53% in contrast to subclinical group and comparison of follow up group

with subclinical group presented a non-significant decrease of 5% in follow up group (Fig.,1).

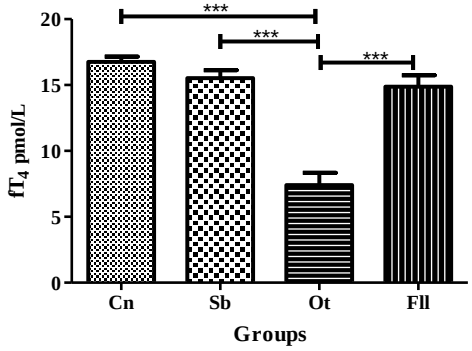

Fig. 1: Mean ± SEM of fT_4 (pmol/L) in study groups.*** significant at $P \leq 0.001$

free tri-iodothyronine (fT_3)

Highly significant ($P \leq 0.001$) variation was recorded in overt group when compared with control group showing 42% decrease in fT_3 in overt group, whereas, subclinical group exhibited non-significant decrease of 7% compared to control group. Similarly, in follow up group 13% decrease in fT_3 was recorded with respect to subclinical group. In comparison between subclinical and overt group, prominent ($P \leq 0.001$) reduction of 37% was observed in overt group. After medication, marked ($P \leq 0.001$) increase of 39% was detected in follow up group in comparison with overt group. A pronounced ($P \leq 0.01$) decrease of 19% was witnessed in follow up group in comparison with control group (Fig., 2).

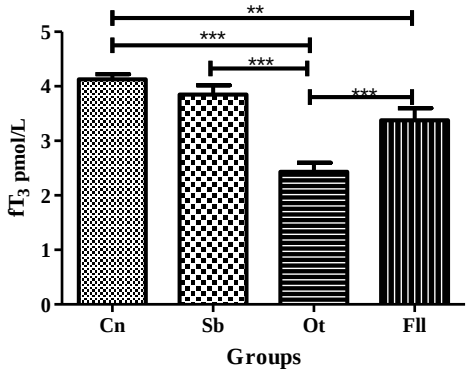

Fig. 2: Mean ± SEM of fT_3 (pmol/L) in study groups. **, *** significant at $P \leq 0.01, 0.001$

Thyroid Stimulation Hormone (TSH)

The analysis of variance showed significant variations in comparable groups. The comparison of overt group with control group revealed a significantly ($P \leq 0.001$) enhanced level of TSH up to 1896% in overt group. A significant ($P \leq 0.05$) rise of 371% was shown by follow up group in contrast to control group. However, after treatment the value of TSH significantly ($P \leq 0.001$) declined up to 77% in follow up group related to overt group. A significant ($P \leq 0.01$) increase of 346% was recorded in subclinical group related to control group. Overt group also presented a highly significant ($P \leq 0.001$) elevation of 346% as compared to subclinical group. However, comparison between subclinical and follow up groups showed a non-significant up regulation of 5% in follow up group (Fig., 3).

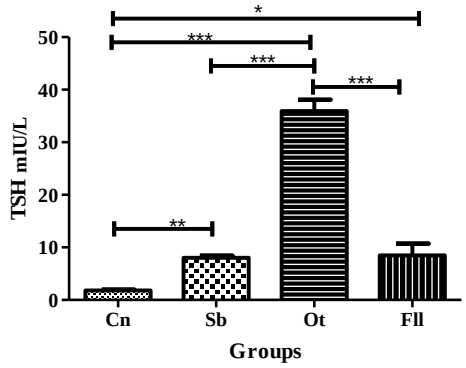

Fig. 3: Mean ± SEM of TSH (mIU/L) in study groups. *, **, *** significant at $P \leq 0.05, 0.01, 0.001$

Alanine Aminotransferase (ALT)

Comparison between control and overt group had shown significant ($P \leq 0.001$) elevation of 58% in concentration of ALT in overt group compared to control group. Similarly, significant ($P \leq 0.05$) elevation of 40% was recorded in follow up group related to control group and non-significant increase of 8% was recorded when subclinical group was compared with control group. In the same way, comparison of subclinical group with follow up group presented an increase of 30% in follow up group. Statistically significant ($P \leq 0.05$) increase of 47% was found in overt group compared to subclinical group. After medication the concentration of ALT was decreased up to 12% in follow up group as compared to overt group (Fig., 4).

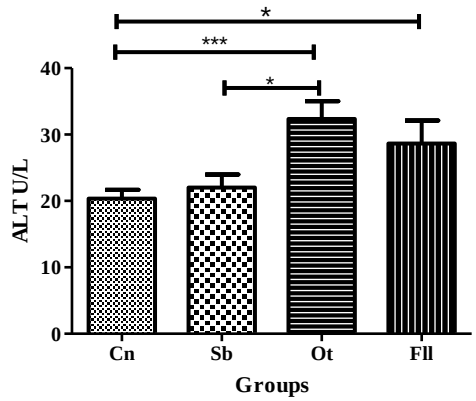

Fig. 4: Mean ± SEM of ALT (U/L) in study groups. *, *** significant at *P* ≤ 0.05, 0.001

Aspartate Transaminase (AST)

Intergroup comparison for AST concentration showed a significant (P ≤ 0.05) increase of 21% in overt group as compared to control group. After medication, this concentration was decreased non-significantly up to 7% in follow up group as compared to overt group. Subclinical group also presented non-significant elevation of 14% in AST value compared to control group. Comparison between control group and follow up group exhibited a non-significant elevation of 14% in follow up group. Similarly, an increase of 5% was recorded in overt group when compared with subclinical group. Whereas, comparison of subclinical group with follow up group showed a slight decrease in AST concentration up to 1% in follow up group (Fig., 5).

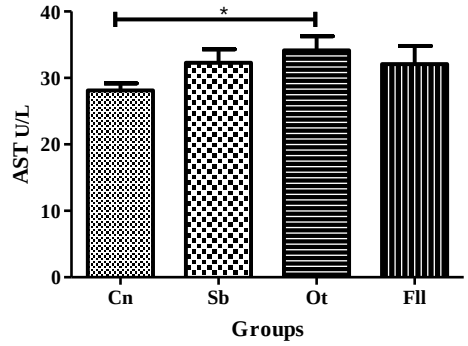

Fig. 5: Mean ± SEM of AST (U/L) in study groups. * significant at *P* ≤ 0.05

Creatinine

The analysis of variances showed significance variations in comparable groups. Overt group showed 20% significant (*P* ≤ 0.001) rise in creatinine level when compared with control group. Comparison of control group with subclinical group presented significant (*P* ≤ 0.05) elevation of 18% in subclinical group compared to control group. In the same way, the concentration of creatinine showed 15% significant (*P* ≤ 0.05) elevation in follow up when compared with control group. The concentration of creatinine was found to be decreased in follow up group as compared to overt group up to 5%. Similarly, overt group exhibited an increase of 1% compared to subclinical group and follow up group presented a decrease of 3% when compared with subclinical group (Fig., 6). Comprehensive presentation of the studied biochemical parameters is summarized in Table I).

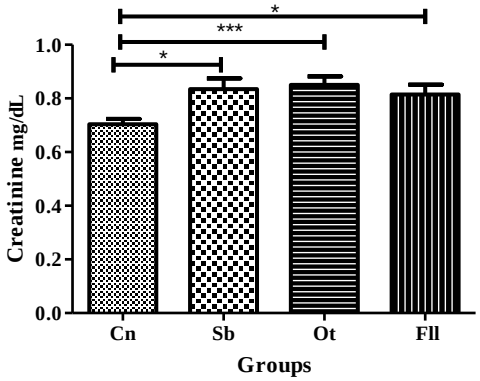

Fig. 6: Mean ± SEM of Creatinine (mg/dL) in study groups. *, *** significant at *P* ≤ 0.05, 0.001, respectively

Table I: A comprehensive presentation of the studied parameters

Para-meters	Control	Sub-clinical	Overt	Follow up	*P*-value
fT4 (pmol/L)	16.76 ± 0.39	15.53 ± 0.6	7.416 ± 0.92	14.88 ± 0.85	< 0.0001***
fT3 (pmol/L)	4.13 ± 0.09	3.85 ± 0.17	2.43 ± 0.17	3.38 ± 0.22	0.0001***
TSH (mIU/L)	1.8 ± 0.16	8.04 ± 0.40	35.93 ± 2.18	8.48 ± 2.26	< 0.0001***
AST (U/L)	28.12 ± 1.06	32.3 ± 2.02	34.15 ± 2.14	32.1 ± 2.73	0.0593
ALT (U/L)	20.36 ± 1.31	22.00 ± 1.98	32.35 ± 2.66	28.65 ± 3.47	0.0002***
Creati-nine (mg/dL)	0.704 ± 0.02	0.835 ± 0.04	0.85 ± 0.03	0.815 ± 0.04	0.0003***

DISCUSSION

Our investigation recorded significantly higher serum ALT levels both in overt and subclinical hypothyroid cases than in the control subjects. Treatment with thyroxine moderately

decreased its level in follow up group. Several studies have described increased level of ALT in hypothyroid subjects and few of them have also reported that level of ALT become normal after treatment (Goncales *et al*., 1998; Targher *et al*., 2008; Chung *et al*., 2012; Ohkubo *et al*., 2012; Khan *et al*., 2013). Contrary to this, Gow *et al*. (1989) reported increased activity of ALT after orally given thyroxine.

Metabolic imbalances due to thyroid dysfunction might be the reason for increased level of ALT. This might be due to increased synthesis of liver enzymes or increased penetrability of liver cell membrane owing to derangement of biochemical reactions inside liver cells in hypothyroidism (Khan *et al*., 2013).

In our study, level of AST was found to be significantly increased in overt hypothyroid group as compared to control subjects. This elevation in aspartate transaminase (AST) level in hypothyroidism may be accredited to myopathies (Liangpunsakul & Chalasani, 2003).

Thyroxine treatment reduced AST level to some extent in our study but studies have shown that the hepatic abnormalities associated with hypothyroidism can be reversible over a matter of weeks with thyroxine treatment, with no residual liver damage. Higher concentration of AST could be linked with thyroid hormone activity. Serum AST level also rises in acute myocardial infarction, muscular dystrophies and myositis because of its abundance in myocardium and skeletal muscles. Probability of increased AST due to cardiac abnormality is quite less because clinical or subclinical evidence of myocardial infarction is not presented in any hypothyroid patients. As AST is also distributed in skeletal muscles, raised AST level in serum of hypothyroid patients is more likely due to release of AST from the skeletal muscles and not due to myocardial infarction (Mane & Bhagwat, 2011).

In our study, level of creatinine was found considerably up regulated in hypothyroid patients compared to control subjects that were found to be improved after thyroid treatment. Similar results were also reported by other investigators regarding serum creatinine levels in hypothyroidism (Diekman *et al*., 2001; Giordano *et al*., 2001; Camacho *et al*., 2003; den Hollander *et al*., 2005; van Welsem & Lobatto, 2007; Iglesias, 2009; Abdella *et al*., 2013).

Saini *et al*. (2012) explored association between renal function and different degrees of thyroid dysfunction and reported that subclinical and overt hypothyroid patients showed significantly elevated serum urea and creatinine level as compared to controls.

TSH exhibited significant positive association with creatinine and uric acid values. Elevated serum creatinine in hypothyroid patients can be associated with increased risk of chronic kidney disease (CKD) (Montenegro *et al*., 1996; Kreisman & Hennessey, 1999; Zhang *et al*., 2014). So, renal function should be frequently examined in hypothyroid patients that seemed to be more related directly to a reduction in thyroid hormone levels rather than with thyroid autoimmunity (Suher *et al*., 2005).

Substantial imbalances in biochemical factors of renal function in hypothyroidism arise due to physiological effects. Hypothyroidism influences renal structure and function, glomerular filtration rate (GFR), transport systems functionality along the nephron and sodium and water balance through direct renal effects as well as through systemic hemodynamics, metabolic and cardiovascular effects.

Clinically, significant reductions in GFR and myopathies associated with hypothyroidism alter glomerular filtration rate of certain constituents of blood plasma such as creatinine that results in elevated serum creatinine level. Mostly these manifestations are reversed after thyroid treatment (Kreisman *et al*., 1999; den Hollander *et al*., 2005; Mariani & Berns, 2012). Increased production of serum creatinine because of its immediate release through muscle break down also results in increased serum creatinine level (Ingbar & Braverman, 1986).

Functioning of kidney is estimated through GFR that can be measured in various ways. The most common marker for the estimation of GFR is plasma levels of creatinine. However, decline in kidney function influences tubular secretion, and effects clearance rate of creatinine. Differences in creatinine level in the blood also occur due to individual variations in muscle mass, dietary habits and numerous drugs (Cabarkapa *et al.,* 2012).

Conclusively, hypothyroid associated Hepatorenal dysfunction poses a risk for a number of maladies and treatment with thyroxine is helpful in attaining euthyroid state, hence maintaining normal renal and hepatic functions.

ACKNOWLEDGEMENT

Authors gratefully acknowledge the Higher Education Commission of Pakistan for financing this investigation via letter number 112-35045-2bm1-513(50022879).

REFERENCES

Abdella, A. M., Ekoon, B. S. & Modawe, G. A.,

2013. The impact of thyroid dysfunction on renal function tests. *Saudi Journal of Kidney Diseases and Transplantation*, 24(1):132-134.

Arora, S., Chavla, R., Tayal, D., Gupta, V. K., Sohi, J. S. & Mallika, V., 2009. Biochemical markers of liver & kidney function are influenced by thyroid function-a case controlled follow up study in Indian hypothyroid subjects. *Indian Journal of Clinical Biochemistry,* 24: 370-374.

Akinsete, A., Oyenusi, E., Odugbemi, B., Odugbemi, T. & Temiye, E., 2019. Spectrum of Thyroid Abnormalities among Children Living with HIV in Lagos, Nigeria. *Journal of Thyroid Research*, 2019; Article ID 1096739, 6 pages. https://doi.org/10.1155/2019/1096739

Biondi, B. & Klein, I., 2004. Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine*, 24(1): 1-13.

Cabarkapa, V., Mijovic, R., Stosic, Z., Curic, N., Zeravica, R. & Ilincic, B., 2012. Estimation of glomerular filtration rate from serum cystatin C and creatinine in patients with thyroid dysfunction. *Journal of Medical Biochemistry*, 31: 88–93.

Camacho, G. D., Ceballos, L. T., Angelin, B. P., Moreno, J. A. R., Nieto, M. L. H. & Gonzalez, J. R., 2003. Renal failure and acquired hypothyroidism. *Pediatric Nephrology,* 18(3): 290-92.

Chakera, A. J., Pearce, S. H. S. & Vaidya, B., 2012. Treatment for primary hypothyroidism: current approaches and future possibilities. *Drug Design, Development and Therapy,* 6: 1-11.

Chung, G. E., Kim, D., Kim, W., Yim, J. Y., Park, M. J., Kim, Y. J., Yoon, J. H. & Lee, H. S., 2012. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. *Journal of Hepatol*ogy, 57(1): 150-156.

Cooper, D. S., 2001. Clinical practice. Subclinical hypothyroidism. *The New England Journal of Med*icine, 345(4): 260-265.

Den Hollander, J. G., Wulkan, R. W., Mantel, M. J. & Berghout, A., 2005. Correlation between severity of thyroid dysfunction and renal function. *Clinical Endocrinology,* 62(4): 423-427.

Diekman, M. J., Put, N. M., Blom, H. J., Tijssen, J. G. & Wiersinga, W. M., 2001. Determinants of changes in plasma homocysteine in hyperthyroidism and hypothyroidism. *Clinical Endocrinology,* 54: 197-204.

Ford, H. C., Lim, W. C., Chrisnall, W. N., 1998. Renal function and electrolyte levels in hyperthyroidism. *Clinical Endocrinology,* 30: 293-301.

Garber, J. R., Cobin, R. H., Gharib, H., Hennessey, J. V., Klein, I., Mechanick, J. I., Pessah-Pollack, R., Singer, P. A. & Woeber, K. A., 2010. American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocrine Practice*, 18(6): 988‑1028.

Giordano, N., Santacroce, C., Mattii, G., Geraci, S., Amendola, A. & Gennari, C., 2001. Hyperuricemia and gout in thyroid endocrine disorders. *Clinical and Experimental Rheumatology,* 19(6): 661-665.

Goncales, J. F. L., Stucchi, R. S., Papaiordanou, P. M., Pavan, M. H., Goncales, N. S. & Pinho, J. R., 1998. Elevated alanine aminotransferase (ALT) in blood donors: an assessment of the main associated conditions and its relationship to the development of hepatitis C. *Revista do Instituto de Medicina Tropical de São Paulo*, 40(4): 219-224.

Gow, S. M., Caldwell, G., Toft, A. D. & Beckett, G. J., 1989. Different hepatic responses to thyroxine replacement in spontaneous and 131I-induced primary hypothyroidism. *Clinical Endocrinology*, 30(5): 505-512.

Huang, M. J. & Liaw, Y. F., 1995. Clinical associations between thyroid and liver diseases. *Journal of Gastroenterology and Hepatology*, 10: 344-350.

Iglesias, P. J. J., 2009. Thyroid function and kidney disease. *European Journal of Endocrinology*, 160(4): 503-515.

Ingbar, S. H. & Braverman, L. E., 1986. In: The Thyroid, a fundamental and clinical text. *Philadelphia Lippincott*, 865-888.

Jayagopal, V., Keevil, B. G., Atkin, S. L., Jennings, P. E. & Kilpatrick, E. S., 2003. Paradoxical changes in cystatin C and serum creatinine in patients with hypo- and hyperthyroidism. *Clinical Chemistry*, 49(4): 680-681.

Khan, M. A. H., Rahman, M. R. & Jahan, R., 2013. Alanine Aminotransferase Activity in Hypothyroid Patients: A Cross Sectional Study. . *Chattagram Maa-O-Shishu Hospital Medical College Journal*, 12(3): 49-51.

Kimmel, M., Braun, N. & Alscher, M. D., 2012. Influence of thyroid function on different kidney function tests. *Kidney and Blood Pressure Research,* 35: 9-17.

Krassas, G. E., Poppe, K. & Glinoer, D., 2010. Thyroid function and human reproductive health. *Endocrine Reviews*, 31: 702-755.

Kreisman, S. H. & Hennessey, J. V., 1999. Consistent reversible elevations of serum creatinine levels in severe hypothyroidism. *Archives of Internal Medicine,* 159: 79-82.

Liangpunsakul, S. & Chalasani, N., 2003. Is hypothyroidism a risk factor for non-alcoholic steatohepatitis? *Journal of Clinical Gastroenterol*ogy, 37(4): 340-343.

Lippi, G., Montagnana, M., Targher, G., Salvagno, G. L. & Guidi, G. C., 2008. Relationship between thyroid status and renal function in a general population of unselected outpatients. *Clinical Biochemistry*, 41(7-8): 625-627.

Malik, R. & Hodgson, H., 2002. The relationship between the thyroid gland and the liver. *QJM: An International Journal of Medicine,* 95: 559-569.

Mane, A. Y. & Bhagwat, V. R., 2011. Serum enzymes and liver function tests in thyroid disorders. *Biomedicine*, 31(4): 517-522.

Mariani, L. H. & Berns, J. S., 2012. The renal manifestations of thyroid disease. *Journal of the American Society of Nephrology,* 23: 22-26.

Montenegro, J., Gonzalez, O., Saracho, R., Aquirre, R., Gonzalez, O. & Martinez, I., 1996. Changes in renal function in primary hypothyroidism. *American Journal of kidney diseases*, 27(2): 195-198.

Nakahama, H., Sakaguchi, K. & Horita, Y., 2001. Treatment of severe hypothyroidism reduced serum creatinine levels in two chronic renal failure patients. *Nephron*, 88(3): 264-267.

Ohkubo, K., Ihara, K., Ohga, S., Ishimura, M. & Hara, T., 2012. Hypothyroidism and levothyroxine-responsive liver dysfunction in a patient with ring chromosome 18 syndrome. *Thyroid*, 22(10): 1080-1083.

Pearce, S. H., Brabant, G., Duntas, L. H., Monzani, F., Peeters, R. P., Razvi, S. & Wemeau, J. L., 2013. ETA guideline: management of subclinical hypothyroidism. *European Thyroid J*ournal, 2(4): 215-228.

Roberts, C. G. P. & Ladenson, P. W., 2004. Hypothyroidism. *Lancet,* 363(9411): 793-803.

Ross, D. S., 2001. Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. *Endocrinology and metabolism clinics of North America*, 30(2): 245-264.

Saini, V., Yadav, A., Arora, M. K., Singh, R. & Bhattacharjee, J., 2012. Correlation of creatinine with TSH levels in overt hypothyroidism: A requirement for monitoring of renal function in hypothyroid patient. *Clinical Biochemistry*, 45: 212-214.

Stenzel, D. & Huttner, W. B., 2013. Role of maternal thyroid hormones in the developing neocortex and during human evolution. *Frontiers in Neuroanatomy,* 7: 19.

Suher, M., Koc, E., Ata, N. & Ensari, C., 2005. Relation of thyroid dysfunction, thyroid auto antibodies, and renal function. *Renal Failure*, 27: 739-742.

Surks, M. I., Ortiz, E., Daniels, G. H., Sawin, C. T., Col, N. F., Cobin, R. H., Franklyn, J. A., Hershman, J. M., Burman, K. D., Denke, M. A., Gorman, C., Cooper, R. S. & Weissman, N. J., 2004. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *The Journal of the American Medical Association*, 291: 228–238.

Targher, G., Montagana, M., Salvagno, G., Moghetti, P., Muggeo, M. & Lippi, G., 2008. Association between serum TSH, free T_4 and serum liver enzyme activities in a large cohort of unselected outpatients. *Clinical Endocrinology*, 68(3): 481-484.

Van-Welsem, M. E. & Lobatto, S., 2007. Treatment of severe hypothyroidism in a patient with progressive renal failure leads to significant improvement of renal function. *Clinical Nephrology*, 67(6): 391-393.

Xu, C., Yang, X., Liu, W., Yuan, H., Yu, C., Gao, L. & Zhao, J., 2012. Thyroid stimulating hormone, independent of thyroid hormone, can elevate the serum total cholesterol level in patients with coronary heart disease: a cross-sectional design. *Nutrition & Metabolism*, 9(1): 44.

Zhang, J., Jiang, R., Li, L., Li, P., Li, X. & Wang, Z., 2014. Serum thyrotropin is positively correlated with the metabolic syndrome components of obesity and dyslipidemia in Chinese adolescents. *International journal of endocrinology*, 289503.