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Original Article

Some Metabolic and Organ Function Disturbances Related to Thyroid Dysfunction

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Abstract:

Background: Hypothyroidism and hyperthyroidism are the thyroid disorders that involve adverse metabolic disturbances. The present study aims to investigate the serum lipid profile, glucose levels and the renal function in newly diagnosed hypothyroid (HO) and hyperthyroid (HE) patients.

Methods: This cross-sectional study was carried out in King Khaled hospital, Hail, Saudi Arabia. The database of 72 (M=17, F=55) newly diagnosed patients with thyroid disfunction were included in the study. Based on their thyroid stimulating hormone (TSH) results, the patients were classified into HO (TSH ≥ 4.5 mIU/L), HE (TSH ≤ 0.4 mIU/L) and normal subjects used as control. The levels of serum free triiodothyronine (FT3), free thyroxine (FT4), TSH, serum total cholesterol (TC), triglycerides (TGs), HDL, LDL, glucose, creatinine, blood urea nitrogen (BUN) and uric acid (UA) were assayed in the hospital laboratory. and VLDL calculated by subtraction.

Results: The serum glucose levels were significantly elevated in the HE ($P < 0.01$) and HO ($P < 0.05$) groups compared to control, with significant positive correlation with Log FT4. Whereas,

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the serum TCs of the HO group was significantly ($P < 0.05$) higher than the HE, but not different from control. Similarly, the serum TGs level of the HE group was significantly lower than control ($P < 0.05$) and HO ($P < 0.01$) groups. However, the HDL- and LDL-cholesterol fractions were not significantly altered in any of the groups. The VLDL- fraction of the HE group was significantly ($P < 0.05$) lower than the control, and was lower than the HO group ($P < 0.01$). The TSH showed significant positive correlations with TC and TGs. The serum creatinine in the HE group was significantly ($P < 0.01$) lower than control and significantly ($P < 0.001$) lower than the HO. Similarly, the serum BUN and UA in the HO group were significantly ($P < 0.05$) higher than the HE. Moreover, the TSH exhibited significant positive correlations with serum creatinine and UA. Whereas, the FT4 and FT3 exhibited negative correlations with creatinine.

Conclusion: The existence of insulin resistance in both HO and HE was evidenced by the significantly elevated serum glucose concentrations, whereas, the TC and TGs were significantly elevated in the HO group and reduced in the HE. The renal impairment was confirmed by the elevated renal function markers in the HO, but unaltered in the HE.

We recommend that during treating patients with thyroid disfunction, such related metabolic disturbances should be considered and treated to avoid further progression into chronic complications.

Keywords: Dyslipidemia, insulin resistance, renal function, thyroid dysfunction, TSH.

Running Title: Dyslipidemia and insulin resistance in thyroid disorders.

Introduction:

The thyroid disorders are widely spread worldwide and their prevalence is increasing in populations of both developing and developed countries. The thyroid hormonal regulation is essential for normal cellular metabolism and function. The thyroid hormones directly promotes proliferation of the pancreatic β cell and controls the insulin secretion [1], whereas, TSH reduces the synthesis and secretion of insulin and consequently increases serum blood glucose levels [2]. The hypothyroidism is known to be associated with insulin resistance, dyslipidemia, renal impairment and increased risk of cardiovascular diseases. In hypothyroidism due to the insulin resistance the cellular uptake of glucose and metabolism are slowed down leading to elevated blood glucose levels. This may occur in both overt and subclinical hypothyroidism [3]. Abnormal thyroid hormone levels are also associated with hypercholesterolemia and hypertriglyceridemia due to disturbed lipoprotein synthesis and metabolism [4]. Moreover, the thyroid hormones are involved in the regulation of renal blood flow, and diminished hormonal levels can reduce the glomerular filtration rate leading to renal impairment [5]. Several cardiovascular risk factors such as increased levels of oxidized low density lipoprotein (LDL) particles, and elevated serum homocysteine levels are also detected in hypothyroidism.

The present study aims to investigate the disturbances in the glucose and lipid homeostasis and the altered renal function related to the hyperthyroidism and hypothyroidism, and moreover, to elucidate the correlations of the biochemical markers of the metabolic disturbances with the levels of serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) in these thyroid disorders.

Patients and Methods:

The present cross-sectional study was carried out in King Khaled hospital, Hail, Saudi Arabia. The study was conducted in accordance with the principles of the Helsinki Declaration and written permission was obtained from the Research Ethical Authority in the Deanship of the Scientific Research in the University of Hail, Kingdom of Saudi Arabia. The patient`s electronic database was searched for newly diagnosed patients with thyroid disorders who visited the outpatient clinic of Endocrinology and Diabetes between

January 2018 and June 2018. Inclusion criteria included all newly diagnosed patients, males and females aged ≥ 12 years. Exclusion criteria included patients with abnormal liver function, chronic kidney disease, or overt diabetes mellitus or on thyroid replacement therapy. The number of patients files selected with complete chemistry results were 50 (M=14, F=36). The patients had an average age of 38 ± 14 years (range 10 -74 years). Based on their thyroid stimulating hormone (TSH) results, the patients were classified into two groups; hypothyroid (with TSH ≥ 4.5 mIU/L) and hyperthyroid (with TSH ≤ 0.4 mIU/L). The serum test results of normal fasting subjects visiting the hospital for routine medical check-up were recorded and used as controls (22 subjects; M= 3, F = 19). The missing chemistry results in the control and other clinical groups, including the thyroid function tests of the controls were assayed in hospital medical laboratory using the residual serum samples and commercial kits. The measurements of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH) were carried out using an Autoanalyzer (ELecsys 2010, Cobas E 411, Mannheim Germany). The other biochemical tests of serum total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, glucose, creatinine, blood urea nitrogen and uric acid were carried out by Dimension RxL-Max, Germany. The very low-density lipoprotein (VLDL)-cholesterol was calculated by subtraction of HDL and LDL from total cholesterol.

Statistical analysis: The results are expressed as means ± SD. The differences between the means were computed by one-way analysis of variance (ANOVA) using the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). The significance of differences between the means was carried out by unpaired Student`s t-test. *P* values < 0.05 were considered significant. The regression analysis between the various parameters was carried out by Spearman`s Regression analysis. *P* values < 0.05 were considered significant.

Results:

As shown in Table 1, the patients had an average age of 38 ± 14 years, ranging between 36.51 ± 16.07 in the hypothyroid group and 40.90 ± 18.87 years in the hyperthyroid group with no significant difference between the means.

Table 1: Age, gender and thyroid function parameters in patients with thyroid dysfunction. Presented values are means ± SD. a: significantly different from control, b: significantly different from hyperthyroid. * P < 0.05, † P < 0.01, ‡ P < 0.001.

	Control	Hyperthyroid	Hypothyroid
Age (Years)	37.40 ± 9.68	40.90 ± 18.87	36.51 ± 16.07
Gender	F = 19, M = 3	F= 17, M = 4	F = 19, M = 10
TSH (mIU/L)	2.21 ± 1.20	0.02 ± 0.03 a‡	16.63 ± 10.87 a‡ b‡
FT3 (ng/L)	4.62 ± 0.89	8.18 ± 4.67 a*	4.35 ± 1.18 b†
FT4 (ng/L)	15.99 ± 1.88	24.98 ± 8.40 a‡	14.16 ± 3.65 b†

However, the males constituted only 23.61% of the total patients. The mean TSH value of the hyperthyroid group was significantly (P < 0.001) lower than that of the control, whereas, that of the hypothyroid group was significantly (P < 0.001) higher than the control. On the other hand, the mean value of FT3 in the hyperthyroid group was significantly (P < 0.05) higher than that of control by 77%, whereas, that of the hypothyroid group was not significantly different from control. Similarly, the FT4 of the hyperthyroid group was significantly (P < 0.001) higher than that of the control group by 56.22%, and that of the hypothyroid group was not significantly different from that of control.

Table 2 depicts the changes in serum glucose and lipid profile. The fasting serum glucose level in the hypothyroid group was significantly (P < 0.01) higher than control by 40.69%, whereas, that of the hyperthyroid was also significantly (P < 0.05) higher than control by 27.74%.

Table 2: The serum glucose and lipid profile in patients with thyroid dysfunction. Presented values are means ± SD. a: significantly different from control, b: significantly different from hyperthyroid. * P < 0.05, † P < 0.01, ‡ P < 0.001.

	Control	Hyperthyroid	Hypothyroid
Glucose (mmol/L)	5.48 ± 1.21	a* 7.00 ± 2.73	a† 7.71 ± 3.73
Total Cholesterol (mmol/L)	4.43 ± 0.90	4.07 ± 1.01	b* 4.86 ± 1.20
Triglycerides (mmol/L)	1.43 ± 0.09	a* 1.05 ± 0.17	b† 1.69 ± 0.27
HDL-c (mmol/L)	1.20 ± 0.25	1.29 ± 0.38	1.19 ± 0.39
LDL-c (mmol/L)	2.57 ± 0.65	2.35 ± 0.84	2.79 ± 1.17
VLDL-c (mmol/L)	0.65 ± 0.22	a* 0.47 ± 0.26	b† 0.84 ± 0.39

Similarly, the serum total cholesterol of the hypothyroid group was significantly (P < 0.05) higher that of the hyperthyroid group by 19.41%, but was not different from that of the control. Whereas, that of the hyperthyroid group showed a slight, but nonsignificant, reduction compared to the control. On the other hand, the serum triglycerides level was significantly (P < 0.05) lower in the hyperthyroid group compared to the control by 26.57%, whereas, that of the hypothyroid was significantly (P < 0.01) higher than that of the hyperthyroid group by 60.95%, and not significantly different from the control. However, the HDL- and LDL-cholesterol fractions were not significantly altered in any of the groups, whereas, there was a trend of slight reduction in the LDL of the hyperthyroid group by 8.56% compared to the control, and the LDL of the hypothyroid was higher than that of the hyperthyroid by 18.72%. However, the VLDL- fraction of the hyperthyroid group was significantly (P < 0.05) reduced compared to the control by 27.69%, whereas, that of the hypothyroid

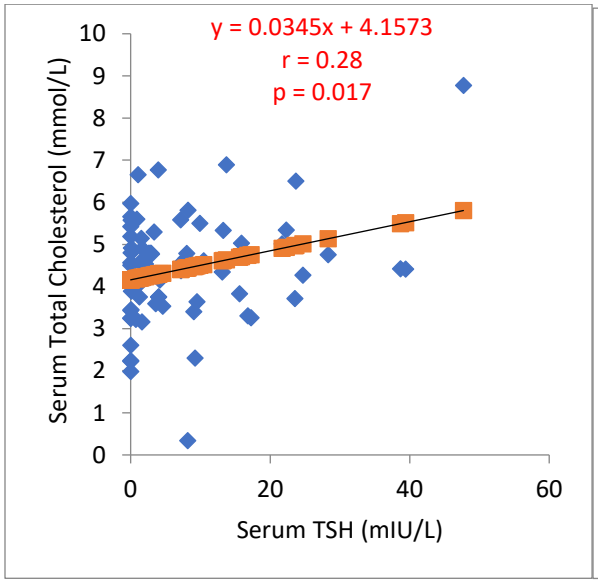
was significantly ($P < 0.01$) higher than that of the hyperthyroid group by 78.72%, but not significantly different from that of control. Table 3 shows the kidney function markers in these groups of patients.

Table 3: Renal function parameters in patients with thyroid dysfunction. Presented values are means ± SD. a: significantly different from control, b: significantly different from hyperthyroid. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$.

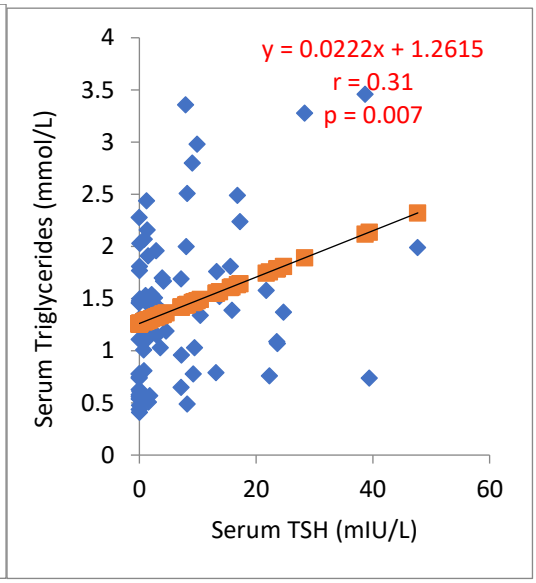
	Control	Hyperthyroid	Hypothyroid
Creatinine (µmol/L)	60.95 ± 12.74	49.96 ± 11.92 a†	68.56 ± 13.55 b‡
BUN (mmol/L)	4.55 ± 0.99	3.69 ± 0.83	4.59 ± 1.24 b*
Uric Acid (µmol/L)	199.23 ± 54.89	200.52 ± 54.01	251.34 ± 72.40 a*b*

The serum creatinine was significantly ($P < 0.01$) reduced in the hyperthyroid group by 18.03% compared to the control, whereas, that of the hypothyroid group was significantly ($P < 0.001$) elevated by 37.23% compared to that of the hyperthyroid group, and was not significantly different from the control. Similarly, the serum blood urea nitrogen in the hypothyroid group was significantly ($P < 0.05$) higher than that of the hyperthyroid by 25.07%. However, none of the two groups were significantly different from that of the control, although there was a slight trend of reduction in that of the hyperthyroid group by 18.9% compared to the control. Similarly, the serum uric acid in the hyperthyroid group was not significantly different from that of control, whereas, that of the hypothyroid group was significantly ($P < 0.05$) higher than that of control and hyperthyroid by 26.16% and 25.34%, respectively. Figure 1 depicts the correlation between the serum TSH, as independent variable, and the total cholesterol, triglycerides, creatinine and uric acid, as dependent variables. TSH showed significant correlations with total cholesterol and triglycerides ($r = 0.28$, $P = 0.01$) and ($r = 0.31$, $P = 0.007$), respectively. Moreover, the TSH exhibited a significant correlation with serum creatinine ($r = 0.26$, $P = 0.028$) and uric acid ($r = 0.34$, $P = 0.04$). Moreover, as shown in Figure 2, the serum

FT4, as an independent parameter, showed significant negative correlations with the total cholesterol, triglycerides and creatinine (r = - 0.24, P = 0.04), (r = -0.31, P = 0.007) and (r = - 0.34, P = 0.004), respectively. Whereas, the serum glucose showed a significant positive correlation with Log FT4 (r = 0.33, P = 0.004). The FT3 also showed significant correlations with creatinine (r = - 0.4, P = 0.0005), and with blood urea nitrogen (r = - 0.27, P = 0.022).



A



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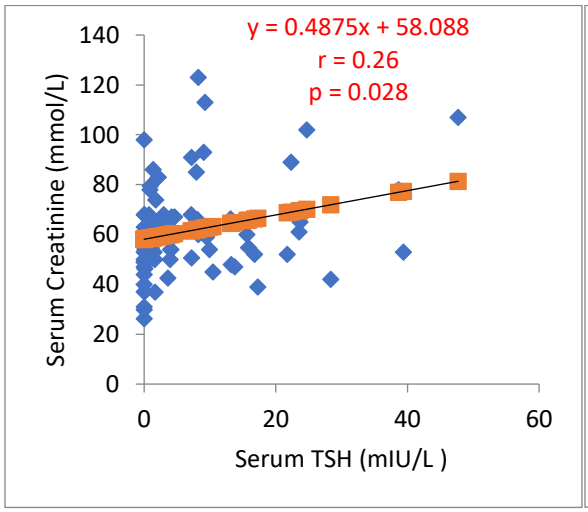

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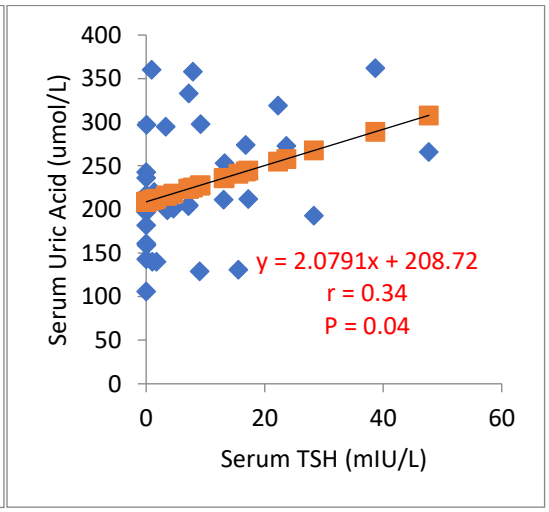
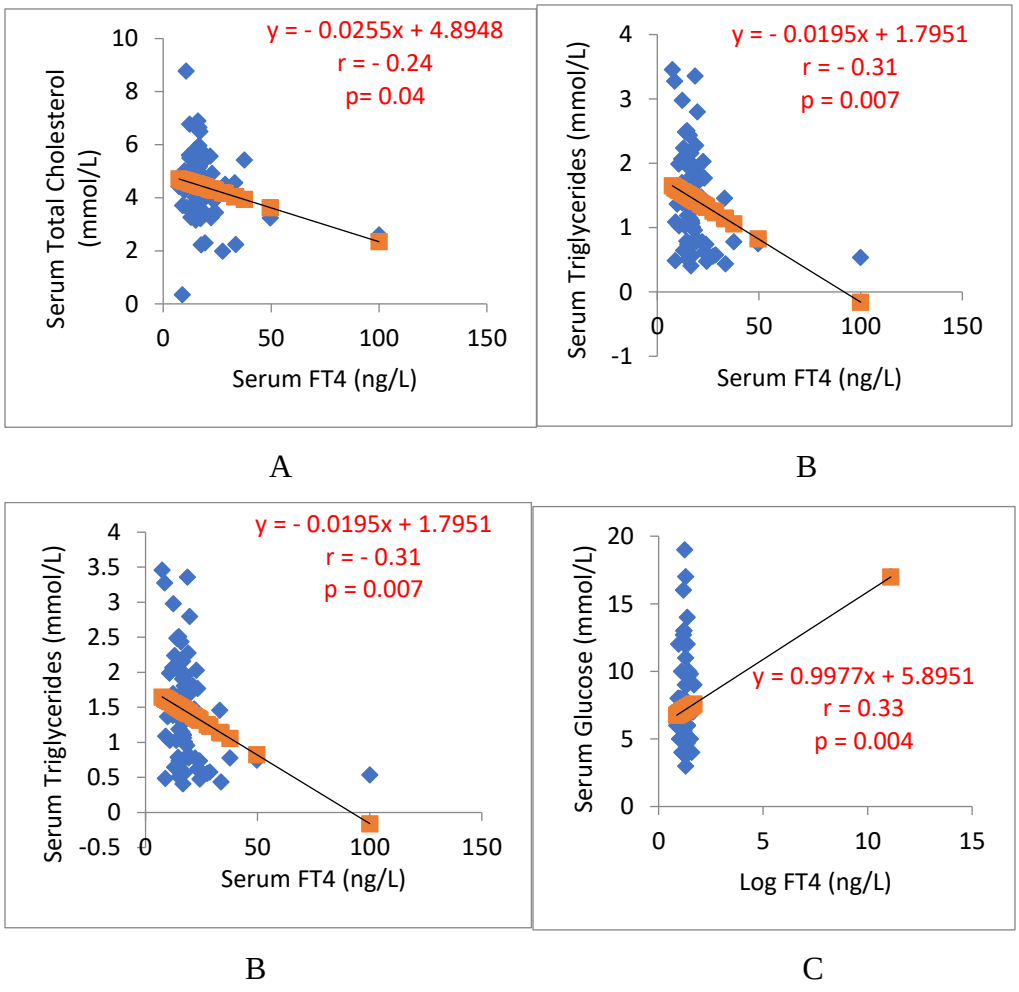
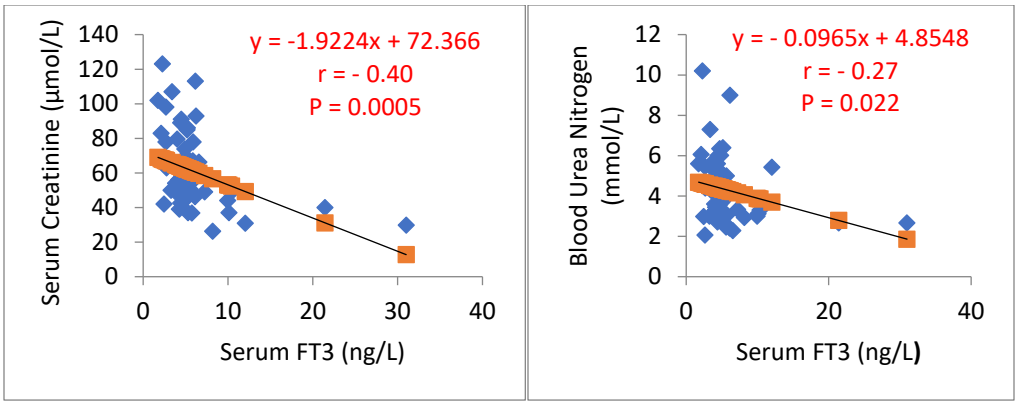


D

Figure 1: Straight line plots of regression analysis between thyroid stimulating hormone (TSH) and: a) total cholesterol, b) Serum triglyceride, C) Serum Creatinine and D) Serum Uric Acid. P values less than 0.05 were considered significant.





E F

Figure 2: Straight line plots of regression analysis between serum free thyroxine (FT4) or log FT4 and: a) total cholesterol, b) Serum triglyceride, C) Serum Creatinine and D) Serum glucose, and between serum free triiodothyronine (FT3) and E) creatinine and F) blood urea nitrogen. P values less than 0.05 were considered significant.

Discussion:

In the present study the majority of the participants were young females with mean age 38 years. The mean TSH value of the hypothyroid group was 16.63 (range 8.06 – 47.7, median 15.5 mIU/L) which was significantly higher than that of control. however, neither the levels of FT3 nor FT4 were different from those of the control. The data showed that 12 out of 29 (41.37%) of the hypothyroid group were subclinical hypothyroids with their TSH range between 4.5 – 9.9 mIU/L. However, even exclusion of the subclinical hypothyroids from the hypothyroid group, did not change the mean values of FT3 (4.35 ± 1.18 before exclusion and 4.23 ±1.08 after exclusion) and the FT4 values (14.16 ± 3.65 before exclusion and 13.22 ± 3.43 after exclusion) and still the values of FT3 and FT4 were not significantly different from those of the control. This probably indicates that in these young patients the triggered release of T3 and T4 induced by the secreted TSH has successfully compensated the fall in the FT3 and FT4 levels. Probably if patients were of older ages the overt hypothyroidism could not be corrected by induced TSH. In a study which involved effects of gender and age differences on the influence of hypothyroidism on lipid disturbances, the

authors found that it was substantially influenced by age, especially in patients with mild thyroid impairment (TSH< 10 mIU/L) [6] . In contrast, our data showed that the TSH values of the hyperthyroid group were significantly lower than that of the control and both FT3 and FT4 were significantly higher than those of the control. The serum glucose was significantly elevated in the hypothyroid group and moderately increased in the hyperthyroid group, and the serum glucose showed a significant positive correlation with Log FT4. Our results were in accordance with investigators who reported that hypothyroidism is associated with insulin resistance and elevated blood glucose levels [7]. In a previous study we also observed significant insulin resistance in both subclinical and overt hypothyroid patients, with highly significant negative correlation between FT4 and serum insulin levels [8]. Several studies have reported an increased risk of insulin resistance and diabetes mellitus in patients with hypothyroidism [9,10]. Moreover, TSH was shown to reduce insulin synthesis and secretion from pancreatic β cells and consequently promote the development of hyperglycemia [2]. It is believed that thyroid hormones stimulate the maturation of the insulin secreting beta cells [11], and the hormones are also known to enhance the cellular uptake of glucose by expressing the glucose transporter-4 (GLT-4) isozyme [12]. On the other hand, the levels of leptin, a neuroendocrine regulator, was shown to significantly correlate with TSH, and its level was elevated in patients with hypothyroidism and with diabetes mellitus [13,14]. Our results also indicated that the serum glucose levels in the hyperthyroid group were also significantly ($P < 0.05$) elevated compared to that of the control. In a previous study we also reported the occurrence of insulin resistance and glucose intolerance in hyperthyroid patients [15]. Elevated thyroid hormone levels are believed to affect the glucose homeostasis in several and sometimes opposing ways. During hyperthyroidism, the half-life time of insulin was found to be reduced due to the increased rate of insulin degradation [16], and a reduced ratio of the C-peptide to proinsulin was detected indicating an underlying defect in the proinsulin processing [17]. Furthermore, in experimental animals the thyroid hormones were found to induce increased synthesis of the hepatocyte membrane glucose transporter 2, the main glucose transporter responsible for the hepatic glucose output

into the blood circulation [18,19]. Moreover, in hyperthyroidism the elevated thyroid hormones induce the release of catecholamines that accelerate lipolysis resulting in elevated levels of circulating free fatty acids for oxidation and the glycerol used for hepatic gluconeogenesis [20], and the enhanced nonoxidative glucose metabolism in hyperthyroidism results in overproduction of lactate used for further gluconeogenesis releasing more glucose into circulation [21,22]. The diabetic patients with hyperthyroidism are known to experience worsening of their glycemic control and thyrotoxicosis precipitating into diabetic ketoacidosis [23], and the authors suggest urgent follow-up and management of these patients. In strptozocin-treated mice, the treatment with T3 at physiologic levels prevented the deterioration of the beta-cells and maintained the islet structure and function, whereas hyperthyroidism resulted in significant impairment of the islets structure and function [24]. Authors suggested that the glucose intolerance observed in patients with hyperthyroidism is prevalently due to hepatic insulin resistance caused by excess thyroid hormones that increases the endogenous glucose production and insulin requirement and reduces the hepatic insulin sensitivity [25].

The present results also exhibited significant elevations of the serum total cholesterol and triglyceride levels in the hypothyroid patients, with significant positive correlations with the TSH and negative correlations with FT4. These findings were in line with the reports of Risal et al, [26], who observed significant elevation of the serum total cholesterol in the hypothyroid patients compared to euthyroid group with a significant negative correlation between the cholesterol and FT4 ($r = -0.197$, $p = 0.010$) and significant positive correlation between total cholesterol and TSH ($r = 0.36$, $p = 0.000$). Thyroid hormones are known to play significant roles in the metabolism of cholesterol and triglyceride. Recently, some authors reported that the mechanism involved in the development of dyslipidemia in the hypothyroidism may be associated with the decreased thyroid hormones and the increased TSH levels via independent effects. This was suggested to involve some newly identified regulatory factors, such as proprotein convertase subtilisin/kexin type 9 (PCSK9), angiogenin-like proteins and fibroblast growth factors [27]. Moreover, investigators

observed significant differences in the serum levels of PCSK9 in the hypothyroid and hyperthyroid groups with a positive correlation between PCSK9 and the TSH levels (r = 0.211, p = 0.019), and a significant negative correlation with FT3 and FT4 (r = -0.239, p = 0.009 and r = -0.218, p = 0.015), respectively [28]. It has been reported that the activities of lipoprotein lipase (LPL) and hepatic lipase (HL) enzymes are diminished in hypothyroidism, and increased in the hyperthyroidism in parallel with the serum T3 concentrations [29], which was accompanied by increased plasma triglyceride concentration in the overt hypothyroid patients. Since the LPL and HL are responsible for the clearance of the residual triglyceride from the VLDL and intermediate density lipoprotein (IDL) particles converting them into LDL, this probably explains the increased accumulation of VLDL in the hypothyroid group and its significant reduction in the hyperthyroid group observed in the present study. Some authors related the elevated LDL levels in the hypothyroid patients to the delayed clearance of the LDL particles due to the reduced number of LDL receptors at the liver cells [30]. The present data indicated that the HDL- cholesterol concentration was not altered in the hypothyroid group compared to the control. Similar findings were also reported by other investigators who related that to decreased activity of cholesteryl-ester transfer protein (CETP) and the HL, which are regulated by thyroid hormones [30]. The diminished activity of CETP and HL result in reduced transport of cholesteryl esters from HDL 2 to the VLDL and IDL. In contrast, in hyperthyroidism excretion of cholesterol is enhanced and an increased turnover of LDL resulting in a decrease of total and LDL-cholesterol, whereas HDL may be decreased or not affected [30].

In the present study the alterations in renal function associated with the thyroid disorders were also investigated. The hypothyroid group showed a significant elevation in the serum creatinine, blood urea nitrogen and uric acid levels compared to the hyperthyroid group, whereas, the serum creatinine level in the hyperthyroid group was significantly lower than the control group. This was accompanied with significant positive correlations between serum creatinine or uric acid and TSH (r = 0.26, P = 0.028) and (r = 0.34, P = 0.04), respectively, and a negative significant correlation between creatinine and FT4 (r = - 0.34, P = 0.004), and FT3 (r = 0.40, P =

0.0005), and between FT3 and blood urea nitrogen (r = 0.27, P = 0.022). These results were in congruence with the reports of several investigators. Naguib R and Elkemary E [[31] compared the kidney function in hypothyroid and hyperthyroid patients before and after treatment and reported that the hypothyroid patients treated with levothyroxine showed significant reduction in their serum creatinine levels and increased eGFR compared to that before treatment, whereas, the hyperthyroid group had their serum creatinine levels increased and the eGFR dropped after treatment, and the TSH had a significant positive correlation with serum creatinine and a significant negative correlation with eGFR in all patients with thyroid dysfunction. Similar results were also reported by other investigators [5, 32]. Thyroid hormones are known to have renal and pre-renal influences by which they increase the renal blood flow and the glomerular filtration rate. Hypothyroid patients are known to experience reduced glomerular filtration rate (GFR), whereas hyperthyroidism is associated with increased GFR and activated renin–angiotensin–aldosterone system (RAAS) [33]. Hypothyroidism imposes adverse effects on kidney function via different mechanisms that include; disruption of the RAAS, reduction of cardiac blood output, and induction of renal vasoconstriction that reduces the renal blood flow [34]. On the other hand, hyperthyroidism results in increased renal blood flow and consequently enhanced GFR [35]. The thyroid hormones accelerate the renal blood flow and GFR by increasing the cardiac blood output by positive chronotropic effects [36], and induction of renal nitric oxide synthase enzyme triggering increased production of endothelial nitric oxide (NO) in the kidney [37]. The GFR was shown to increase by about 18–25% among the hyperthyroid patients [35]. Beside the influence of the thyroid hormone on the renal blood flow, the activation of RAAS also contributes to the increase in GFR. During hyperthyroidism the thyroid hormones stimulate the RAAS activity by increasing the β-adrenergic receptors in the renal cortex [38]. The thyroid hormones are also known to increase the renin gene expression, increase the hepatic angiotensinogen synthesis, stimulate the angiotensin converting enzyme activity and increase the serum angiotensin II level [39]. Thus, the enhanced RAAS activity causes vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole

with consequent increased filtration pressure and enhanced glomerular filtration rate. Taking into consideration all these adverse effects imposed on body functions, many authors agree that beside the overt hypothyroid and hyperthyroid patients, individuals with severe subclinical hypothyroidism (TSH > 10 mIU/L) or grade 2 subclinical hyperthyroidism (TSH < 0.1 mIU/L) should receive treatment, mostly due to the increased risk of cardiovascular morbidity and mortality being reported in these patients [40], and thyroid dysfunction should be taken into account when evaluating and treating dyslipidemic patients or patients with insulin resistance.

Conclusion:

The serum glucose concentration was significantly elevated in both hypothyroid and hyperthyroid patients indicating existence of insulin resistance in both disorders, with glucose showing significant correlation with log FT4 and not TSH.

Total cholesterol and triglyceride were significantly elevated in the hypothyroid group and reduced in the hyperthyroid, with significant correlations with both TSH and FT4 and FT3.

Renal impairment was evidenced by the significantly elevated serum creatinine, BUN and uric acid in the hypothyroid group and reduced in the hyperthyroid group, with significant correlations between serum kidney function markers and TSH.

The author suggests that clinicians and providers of health services should closely monitor the renal function, lipid profile and glucose homeostasis in all patients treated for thyroid disorders. Moreover, to consider the possible involvement of thyroid disorder when treating these metabolic abnormalities.

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