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Thyroid hormones and hepatorenal function in Diabetes Mellitus: A conclusion from Indian study

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RESEARCH

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Abstract

Background

Presence of hypothyroidism in Diabetes Mellitus (DM) is a foundation for development of complications. Thyroid hormones have been hypothesised to affect and be affected by hepatorenal function. These hypotheses warrant further study into the topic.

Materials & methods

81 diabetics and 81 age & sex-matched healthy volunteers participated in the study. Their blood samples were analysed for Fasting Blood Glucose (FBG), Glycosylated Hemoglobin (HbA1C), total Triiodothyronine (T3), total Thyroxine (T4), Free T3 (FT3), free T4 (FT4), thyroid-stimulating hormone (TSH) and liver & renal function tests. Data was analysed using appropriate statistical tests.

Results

42 males and 39 females each were recruited as cases and controls. FBG, HbA1c, FT4, TSH, serum Alanine Transaminase (ALT), Alkaline Phosphatase (ALP) and Serum Creatinine (CR) were higher in diabetics. T3 and FT3 were lower in diabetics. T3, FT3, and albumin (ALB) were lower in diabetics with CR ≥ 1.30 mg/dL. FBG, Direct Bilirubin (DBIL), ALP and CR were higher and T3 and FT3 were lower in hypoproteinemic diabetics. Total Proteins (TPRO) and ALB positively correlated with T3 and FT3. TBIL positively correlated with FBG. ALP positively correlated with HbA1c.

Conclusion

Hypoproteinemia predicts poor glycemic control, renal dysfunction and hypothyroidism. High-normal circulating levels of T3 and FT3 being correlated with lower levels of CR may imply that a thyroid-sufficient state is largely protective against renal dysfunction in DM. In summary, routine LFT and RFT investigations can be indicative of subclinical hypothyroidism and thus an underlying cause of resistance to anti-hyperglycaemic therapy; treating the same may improve therapeutic outcomes.

Key Words

Diabetes Mellitus.

Introduction

Diabetes Mellitus (DM) is a metabolic disorder that has troubled humankind for many millennia. Even Sushruta and Charaka, ancient proponents of Indian Ayurvedic medicine, acknowledged the disease with the name 'Madhumeha' (literally translated as honey urine) owing to the presence of sugars in urine (glycosuria).

Long-standing uncontrolled DM is a particularly dangerous condition. Most complications of DM such as nephropathy, neuropathy, retinopathy, peripheral vascular diseases, etc. arise essentially due to hyperglycemia[1]. Particularly talking about nephropathy, its pathology is understood as the non-enzymatic glycosylation and subsequent disruption of the glomerular basement membrane, leading to hyperfiltration and detectable changes such as microalbuminuria, glycosuria, recurrent urinary tract infections, acute tubular necrosis etc[2].

Blood glucose levels are regulated by a myriad of intrinsically produced hormones and other chemical regulators. These include hormones produced by endocrine pancreas and thyroid gland, catecholamine's etc. Among these, endocrine pancreas and thyroid appear to play a major role in regulation of blood glucose. Thyroid hormones have been shown to improve the ability of insulin to stimulate glucose disposal related to insulinemia[3]. This phenomenon may be highly sensitive, because it was only apparent at low thyroid hormone levels

Hence, variation in levels of their hormones in circulating blood has several effects on the glycemic status of the patient.

The liver is arguably the focal centre of metabolism in the human body. It is of high importance in regard to carbohydrate metabolism and is sensitive to insulin and thyroid hormone levels in the blood[4]. Thyroid hormones have a profound effect on nutrient metabolism in the human body. They have both catabolic and anabolic effects on nutrients and hence are responsible for regulation of various processes like gluconeogenesis, glucose oxidation, and glucose reabsorption among others.

In India, a routine serum LFT usually includes the following parameters: total proteins, albumin, globulin, bilirubin, transaminases, and alkaline phosphatase. Hence, a variation from the normal levels of these analytes is sometimes seen in DM.

It has been noted that thyroid hormones affect renal function by various mechanisms[5]. Such as increasing glucose reabsorption, regulation of sodium-potassium-chloride transport channel, regulating tubular reabsorption etc. Therefore, thyroid dysfunction may be associated with disruption of renal function seen in DM. A reliable routine laboratory indicator of renal function is serum creatinine (CR). Hence, it is expected that thyroid hormones would be correlated with CR.

The pathological increase in the aforementioned analytes is easy to measure in routine practice. Investigating the association of thyroid hormones with LFT and RFT may help to suggest systematic changes in laboratory monitoring of DM.

The presence of thyroid dysfunction in DM, especially subclinical hypothyroidism, is a near perfect foundation for the development of microvascular and macrovascular complications. Correlation of thyroid with the LFT and RFT parameters may prove to be a useful tool for establishing the prognosis of the disease and taking early steps to manage any possible complications as they may go otherwise unnoticed for long periods of time[6].

Implications of these hypotheses regarding association of thyroid dysfunction with LFT and RFT parameters warrants further study into the topic.

Materials & Methods

Data groups

Diabetic subjects were randomly selected from the cases presenting to various OPDs and wards of Tertiary Healthcare Centre in the Mumbai Metropolitan Region of the state of Maharashtra, India. Written informed consent was taken from the subjects in their preferred language prior to blood collection.

The study population consisted of 81 diabetic patients (of Type 2 DM) and 81 age- and sex-matched non-diabetic, healthy volunteers. All patients had been diagnosed according to the standard ADA guidelines.

Inclusion criteria for cases were: (i) age > 18 years, (ii) known case of DM, (iii) hemodynamically stable. Controls were included if they were otherwise healthy adults with no known diseases or symptoms.

Exclusion criteria common for cases and controls were: (i) age < 18 years, (ii) pregnancy and puerperium, (iii) females taking oral contraceptive pills.

Data collection

Permission to conduct this study was obtained from the Institutional Clinical Ethics Committee (ICEC No. RGMC/CSMH/IEC/A/185/03/2021). Patient's basic medical history was taken and information regarding age/sex, medication regimen, known complications etc. was recorded. Blood was collected using standard venepuncture procedure and immediately analysed for various parameters.

Fasting blood glucose (FBG), serum creatinine (CR) and Liver Function tests (total proteins i.e. TPRO, albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), serum aspartate transaminase (AST), serum alanine transaminase (ALT) and alkaline phosphatase (ALP) were all measured by photometric methods. Serum globulin i.e. GLB and indirect bilirubin i.e. IBIL were calculated as GLB = TPRO - ALB and IBIL = TBIL - DBIL respectively.

Total triiodothyronine (T3), total thyroxine (T4), free T3 (FT3), free T4 (FT4) and thyroid-stimulating hormone (TSH) were measured by chemiluminescence immunoassay (CLIA) method. Glycosylated hemoglobin (HbA1c) was measured by high performance liquid chromatography (HPLC) method.

Statistical analysis

Collected data was analysed on IBM SPSS version 26 software. Histograms, Pearson correlation coefficients and t-tests were used to analyse the data.

Results

42 diabetic males (M) and 39 diabetic females (F) were recruited as cases for this study. The age was 57.64 ± 10.74 years in males and 57.00 ± 11.72 years in females. Analysed parameters were found to be normally distributed separately in diabetic and non-diabetic groups, verified by Shapiro-Wilk test.

70.37 Per Cent of the diabetic cases (30 M, 27 F) were euthyroid , while the rest (29.63 Per Cent) had some form of thyroid dysfunction. The categories of thyroid dysfunction were: subclinical hypothyroidism in 24.7 Per Cent of total cases (10 M, 10 F), clinical hypothyroidism in 2.47 Per Cent (1 M, 1 F), and subclinical (1 M) and clinical (1 F) hyperthyroidism in 1.23 Per Cent each.

90.12 Per Cent of the controls (38 M, 35 F) were euthyroid, while the rest, i.e. 9.88 Per Cent, had subclinical hypothyroidism (4 M, 4 F).

The mean values of the various analysed parameters are given in Table 1. Independent samples t-tests were performed to evaluate the equality of means between various parameters between cases and controls. Mean values of FBG, HbA1c, FT4, TSH, ALT, ALP and CR were significantly higher in diabetics than in controls. Mean values of T3 and FT3 were significantly lower in diabetics compared to controls. Other parameters did not differ significantly between the two groups.

Independent samples t-tests were performed for diabetic cases grouped as having CR ≥ 1.30 mg/dL and CR < 1.30 mg/dL. Age (t = 2.535; p = 0.013) was higher and T3 (t = -2.512; p = 0.014), FT3 (t = -2.230; p = 0.029), TPRO (t = -2.159; p = 0.034) and ALB (t = -2.206; p = 0.030) were lower in diabetics with CR ≥ 1.30 mg/dL.

Independent samples t-tests were performed for diabetic cases grouped as hypoproteinemic (TPRO < 6 g/dL or ALB < 3.5 g/dL or both) and euproteinemic (TPRO ≥ 6 g/dL and ALB ≥ 3.5 g/dL). FBG (t = 2.313; p = 0.023), DBIL (t=2.550; p=0.013), ALP (t=3.029; p=0.003) and CR (t=2.499; p=0.015) were higher and T3 (t= -4.512; p = 0.000) and FT3 (t=-4.310; p=0.000) were lower in hypoproteinemic diabetics than euproteinemic diabetics.

Paired samples t-tests were performed for pairs of variables in diabetic cases.

CR was positively correlated with age and negatively correlated with T3 and FT3 (Table 2).

TPRO was positively correlated with T3, FT3, ALB and GLB, and negatively correlated with age. ALB was positively correlated with T3 and FT3, and negatively correlated with ALP. GLB was positively correlated with FT3 and negatively correlated with IBIL (Table 3).

TBIL was positively correlated with FBG, DBIL, IBIL, AST and ALT. DBIL was positively correlated with FBG, IBIL, AST and ALT. IBIL was positively correlated with AST and ALT (Table 4).

AST and ALT were positively correlated with each other. ALT was positively correlated with T4. ALP was positively correlated with HbA1c (Table 5).

Discussion

Histopathological changes of diabetic nephropathy are irreversible. Hence serum markers of renal function such as CR and urine markers such as micro albumin are routinely investigated during follow-up. In our study, CR was found to be negatively correlated with T3 and FT3. We also found that thyroid hormone levels were lower in diabetics with creatinine levels ≥ 1.30 mg/dL.

Elevated CR has been attributed to hypothyroidism. Few explanations for this association have been hypothesised, viz. direct effect of thyroid hormones on transporters, reduced renal plasma flow, and indirect effect due to comorbidities, etc.

Diabetic nephropathy starts off as a hyperfiltration injury due to non enzymatic glycosylation of the glomerular basement membrane which subsequently leads to hypoalbuminemia and further progression of the disease. Mariani, et al[7].Reported that hypothyroid state causes decreased activity of the Na+-K+-2Cl- (NKCC) and other transporters due to direct influence of thyroid hormones on renal transporters. This increases the risk of hyponatremia. As hyponatremia is associated with adverse renal outcomes, decreased activity of the NKCC transporter could exacerbate existing renal disease.

Ahmed found that hypothyroidism can change the hemodynamic processes related to renal function such as decreased release of renin and decreased erythropoietin production. Moreover, hypothyroidism can decrease the expression of renal vasodilators, and increase the matrix Gla protein, CR levels and permeability of glomerular capillaries. It can change tubular functions such as: (1) increase the sensitivity to vasopressin and level of Na+ excretion; (2) decrease the activity of Na+/K+ ATPase and Na+/H+ exchanger, negatively impact urinary acidification, cause hyponatremia and impair excretion of free water.

Van Welsem et al. also reported that hypothyroid patients have reduced GFR and renal plasma flow which are completely reversible by thyroid hormone administration [8]. Reduced GFR leads to reduced creatinine clearance; this may help to explain relatively increased CR in hypothyroid diabetics.

Hypothyroidism predisposes diabetics to various other comorbidities such as dyslipidemia, neuropathies and cardiovascular disease. The RENAAL study showed that dyslipidemia is an independent risk factor for progression of renal dysfunction[9]. As dyslipidemia is famously more prevalent in hypothyroid diabetics than euthyroid diabetics, hypothyroidism may exacerbate the extent of renal dysfunction in DM.

Taking the cue from available literature as well as our findings as mentioned above, it may be advisable to regularly monitor thyroid function of all diabetics with a deranged RFT. Newer markers such as cystatin C may be used to detect early and impending onset of renal dysfunction whenever feasible.

As renal dysfunction typically develops after hypothyroidism, periodic screening of thyroid function is essential in diabetic patients to detect subclinical hypothyroidism as early as possible to initiate therapy for the same. Thyroid hormone replacement therapy was shown to reduce the decline in renal function in CKD patients with subclinical hypothyroidism, including those with diabetic nephropathy[10].

Progression of diabetic nephropathy also has an effect on anti-diabetic pharmacotherapy. Impaired renal function decreases the clearance of sulfonylurea and glinide drugs - which are prescribed very frequently - due to which the risk of hypoglycemia is increased [11].

High-normal circulating levels of T3 and FT3 being correlated with lower levels of CR, as seen in our study, may imply that a thyroid-sufficient state is largely protective against renal dysfunction in DM. Hence, we reiterate the importance of regular screening for subclinical hypothyroidism in diabetic patients and providing adequate pharmacotherapy for the same.

Our study also showed significant correlations between thyroid hormone levels and Liver Function Test parameters. T3 and FT3 levels were positively correlated with total proteins and albumin levels. FBG, DBIL, ALP and CR were higher whereas T3 and FT3 were lower in hypoproteinemic diabetics than euproteinemic diabetics.

Hypoproteinemia is a well-documented sign of hepatic dysfunction. We found that bilirubin levels were directly correlated with FBG as well as ALP was directly correlated with HbA1c. This implies that worsening of glycemic control is associated with deterioration of hepatic function. We also found that CR was higher in hypoproteinemic diabetics, implying that impairment of hepatic and renal function go hand-in-hand.

Thyroid hormone levels were lower in hypoproteinemic diabetics, i.e., those with hepatic dysfunction. DM is a known cause of sustained oxidative stress which leads to hepatic parenchymal and epithelial cell injury. Reactive oxygen species (ROS) are the most validated mechanism of secondary injury [12].

Hypothyroid subjects also displayed higher levels of cholesterols and triglycerides. Increased free fatty acids as seen in the insulin-resistance are directly hepatotoxic, probably due to cell membrane and mitochondrial dysfunction, toxin formation and disruption of key steps of metabolism [13]. Oxidative stress caused by lipid peroxidation, peroxisomal β-oxidation and increased activity of cytokines like tumour necrotic factor-α (TNF-α) leads to elevation of ALT [14].

Thyroxine is a major stimulator of hepatic autophagy and mitochondrial function leading to increased hepatocellular damage. Our finding of increased ALT activity in diabetics compared to controls is clinical evidence for increased hepatocellular injury in DM. Recent literature suggests that dysregulation of mitochondrial homeostasis and autophagy play critical roles in hepatocyte injury and insulin resistance of nonalcoholic fatty liver disease (NAFLD), which is the most common cause of elevated LFTs in DM [15].

Homeostasis model of assessment for insulin resistance (HOMA-IR) is a method used to quantify insulin resistance and beta-cell function. Singh, et al[16]. Reported that hypothyroid subjects demonstrated higher insulin resistance, as assessed by HOMA-IR, compared to their euthyroid counterparts. Hanley, et al [17].Reported that AST and ALT were associated with insulin resistance. Elevated levels of these enzymes in patients of T2DM may result in worsening of glycemic control.

An alternative explanation for increased transaminases in DM was given by O'Brien & Granner who showed that the gene transcription of ALT, a gluconeogenic enzyme, is suppressed by insulin. Hence, an elevation in ALT could be due to an impairment in insulin signalling rather than purely hepatocyte injury [18].

While LFT is investigated routinely (though not in all diabetics), thyroid profile is rarely monitored during follow-up unless clinical symptoms are present. Hence, in diabetics

with deranged LFT or values close to the either limits of normal, monitoring of thyroid profile would help to diagnose subclinical hypothyroidism very early on. diagnose subclinical hypothyroidism very early on.

Hypothyroidism as well as worsening of glycemic control are indicators of deteriorating hepatic function. From a clinical perspective, the liver has an important role in metabolism of anti-diabetic drugs. Moreover, hepatic dysfunction is associated with hypoproteinemia which is a poor prognostic factor for diabetic nephropathy, which in turn can be associated with metabolic dysregulation such as abnormal lipoprotein metabolism[19]. Hence, monitoring of thyroid function is essential to detect early onset of both hepatic and renal impairment. This is specifically advocated in high-risk patients such as those with family history of thyroid dysfunction, known history of other endocrine disorders etc.

Our findings therefore, have two reciprocal implications.

On one hand, hypothyroidism is a poor prognostic factor for hepatorenal function in DM; treatment of hypothyroidism can improve glycemic control, reduce hepatic oxidative stress and decrease the risk of nephropathy. As LFT and RFT have a lag time between actual onset of dysfunction and change in laboratory values, thyroid profile monitoring may be beneficial.

On the other hand, deranged LFT and RFT are associated with hypothyroidism and can help to limit screening to a smaller group of patients, thereby reducing patient expenses and resource expenditure [20].

Conclusion

Optimal state of hepatorenal function is essential in DM as various therapeutic methods depend on these organs for metabolism and excretion. Euthyroid status is also an important factor for increasing the success of glycemic control. However, frequent monitoring of thyroid profile is expensive and resource-intensive.

Routinely investigated LFT and RFT panels can help to predict or gauge the risk of subclinical hypothyroidism early on. Its treatment, in turn, can help to improve glycemic control as hypothyroidism is causally associated with poor glycemic control.

Routine LFT panel helps to gauge the glycemic control and thyroid profile. Hypoproteinemia, for example, is associated with poor glycemic control, renal dysfunction and hypothyroidism. Increased levels of bilirubin as well as ALP, both of which indicate hepatic injury, are correlated with poor glycemic control. Routine RFT panel, mainly CR, predicts hypothyroidism. High-normal circulating levels of T3 and FT3 being correlated with lower levels of CR, as seen in our study, may imply that a thyroid-sufficient state is largely protective against renal dysfunction in DM.

In summary, routine LFT and RFT can be indicative of subclinical hypothyroidism and thus an underlying cause of resistance to anti-hyperglycemic therapy; treating the same may improve therapeutic outcomes. While it would be ideal to investigate thyroid function regularly, routinely doing so is expensive and impractical. Thus, hepatorenal investigations are of great value to limit thyroid profile testing to those who really need the same.

References

1. Balaji R, Duraisamy R, Kumar MP. Complications of diabetes mellitus: A review. Drug Invention Today. 2019;12(1).
2. López-Novoa JM, Rodríguez-Peña AB, Ortiz A, et al Etiopathology of chronic tubular, glomerular and renovascular nephropathies: Clinical implications. Journal of translational medicine. 2011;9:1-26. Doi: https://doi.org/10.1186/1479-5876-9-13
3. Rochon C, Tauveron I, Dejax C, et al. Response of glucose disposal to hyperinsulinaemia in human hypothyroidism and hyperthyroidism. Clinical science. 2003;104(1):7-15. Doi: https://doi.org/10.1042/cs1040007
4. Park SE, Park CY, Sweeney G. Biomarkers of insulin sensitivity and insulin resistance: Past, present and future. Crit Rev Clin Lab Sci 2015;52(4):180-90. Doi: https://doi.org/10.3109/10408363.2015.1023429
5. Ahmed RG. Association between hypothyroidism and renal dysfunctions. IJRSMHS. 2017;2(11):1-4.
6. Chen HS, Wu TE, Jap TS, et al. Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. Diabetic medicine. 2007;24(12):1336-44. Doi: https://doi.org/10.1111/j.1464-5491.2007.02270.x
7. Mariani LH, Berns JS. The renal manifestations of thyroid disease. J Am Soc Nephrol. 2012;23(1):22-6.
8. Van Welsem ME, Lobatto S. Treatment of severe hypothyroidism in a patient with progressive renal failure leads to significant improvement of renal function. Clinical nephrology. 2007;67(6):391-3. Doi: https://doi.org/10.5414/cnp67391

9. Keane WF, Brenner BM, De Zeeuw D, et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: The RENAAL study. Kidney international. 2003;63(4):1499-507. Doi: https://doi.org/10.1046/j.1523-1755.2003.00885.x
10. Shin DH, Lee MJ, Lee HS, et al. Thyroid hormone replacement therapy attenuates the decline of renal function in chronic kidney disease patients with subclinical hypothyroidism. Thyroid. 2013;23(6):654-61. Doi: https://doi.org/10.1089/thy.2012.0475
11. Zanchi A, Lehmann R, Philippe J. Antidiabetic drugs and kidney disease. Swiss Med Wkly. 2012;142(3738):w13629-. Doi: https://doi.org/10.4414/smw.2012.13629
12. Xu JJ, Wang YL. Propofol attenuation of hydrogen peroxide-mediated oxidative stress and apoptosis in cultured cardiomyocytes involves haeme oxygenase-1. Eur. J. Anaesthesiol. 2008;25(5):395-402. Doi: https://doi.org/10.1017/S0265021508003542
13. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology. 2003;37(5):1202-19. Doi: https://doi.org/10.1053/jhep.2003.50193
14. Lu S, Wang Y, Liu J. Tumor necrosis factor-α signaling in nonalcoholic steatohepatitis and targeted therapies. Journal of Genetics and Genomics. 2022;49(4):269-78. Doi: https://doi.org/10.1016/j.jgg.2021.09.009
15. Sinha RA, Yen PM. Thyroid hormone-mediated autophagy and mitochondrial turnover in NAFLD. Cell & bioscience. 2016;6(1):1-6. Doi: https://doi.org/10.1186/s13578-016-0113-7
16. Singh BM, Goswami B, Mallika V. Association between insulin resistance and hypothyroidism in females attending a tertiary care hospital. Indian J Clin Biochem. 2010;25:141-5. Doi: https://doi.org/10.1007/s12291-010-0026-x
17. Hanley AJ, Williams K, Festa A, et al. Elevations in markers of liver injury and risk of type 2 diabetes: The insulin resistance atherosclerosis study. Diabetes. 2004;53(10):2623-32. Doi: https://doi.org/10.2337/diabetes.53.10.2623
18. O'Brien RM, Granner DK. Regulation of gene expression by insulin. Bioche J. 1991;278(Pt 3):609.Doi: https://doi.org/10.1042/bj2780609
19. Hirano T. Abnormal lipoprotein metabolism in diabetic nephropathy. Clin Exp Nephrol. 2014;18:206-9. Doi: https://doi.org/10.1007/s10157-013-0880-y
20. Jain VN, Ghanghurde S, Carvalho SR, et al. Effect of Thyroid Hormone Levels on Glycemic Control: The Indian Context. Iran J diabetes obes. 2022. Doi: https://doi.org/10.18502/ijdo.v14i3.10738

Tables

Table 1: Mean values of analysed parameters

Parameters	Diabetics (Mean ± SD)	Controls (Mean ± SD)	Test statistic (t)	Significance (p-value)
FBG (mg/dL)	189.56 ± 78.94	98.86 ± 12.41	10.152	0.000*
HbA1c (Per Cent)	9.17 ± 2.17	5.41 ± 0.54	14.409	0.000*
T3 (ng/mL)	1.36 ± 0.32	1.46 ± 0.24	-2.111	0.036*
T4 (ng/mL)	84.94 ± 19.77	85.51 ± 13.75	-0.212	0.832
FT3 (pg/mL)	3.12 ± 0.48	3.36 ± 0.36	-3.574	0.000*
FT4 (pg/mL)	15.50 ± 2.52	14.34 ± 1.48	3.56	0.001*
TSH (µIU/mL)	3.81 ± 3.90	2.79 ± 1.82	2.126	0.036*
TPRO (g/dL)	7.11 ± 0.65	6.99 ± 0.51	1.21	0.228
ALB (g/dL)	3.94 ± 0.53	4.02 ± 0.26	-1.207	0.23
GLB (g/dL)	3.13 ± 0.60	2.97 ± 0.44	1.901	0.059
TBIL (mg/dL)	0.60 ± 0.32	0.59 ± 0.25	0.276	0.783
DBIL (mg/dL)	0.26 ± 0.15	0.24 ± 0.10	0.821	0.413
IBIL (mg/dL)	0.34 ± 0.18	0.34 ± 0.16	-0.231	0.817
AST (IU/L)	20.45 ± 9.61	20.90 ± 6.28	-0.351	0.726
ALT (IU/L)	20.27 ± 16.12	15.66 ± 7.72	2.306	0.023*
ALP (IU/L)	96.54 ± 39.84	81.80 ± 23.46	2.853	0.005*
CR (mg/dL)	1.19 ± 0.36	1.07 ± 0.16	2.658	0.009*

Table 2: Correlations of CR

Analyte pair	Pearson Correlation coefficients	Significance (p-value)
CR & Age	0.229	0.040*
CR & T3	-0.222	0.046*
CR & FT3	-0.225	0.043*

Table 3: Correlations of protein parameters of LFT

Analyte pair	Pearson Correlation coefficients	Significance (p-value)
TPRO & T3	0.401	0.000*
TPRO & FT3	0.525	0.000*
TPRO & ALB	0.669	0.000*
TPRO & GLB	0.511	0.000*
TPRO & Age	-0.304	0.000*
ALB & T3	0.431	0.000*
ALB & FT3	0.423	0.000*
ALB & ALP	-0.28	0.011*
GLB & FT3	0.258	0.020*
GLB & IBIL	-0.244	0.028*

Table 4: Correlations of bilirubin parameters of LFT

Analyte pair	Pearson Correlation coefficients	Significance (p-value)
TBIL & FBG	0.264	0.017*
TBIL & DBIL	0.928	0.000*
TBIL & IBIL	0.95	0.000*
TBIL & AST	0.427	0.000*
TBIL & ALT	0.407	0.000*
DBIL & FBG	0.287	0.009*
DBIL & IBIL	0.765	0.000*
DBIL & AST	0.474	0.000*
DBIL & ALT	0.457	0.000*
IBIL & AST	0.34	0.002*
IBIL & ALT	0.32	0.004*

Table 5: Correlations of enzyme parameters of LFT

Analyte pair	Pearson Correlation coefficients	Significance (p-value)
AST & ALT	0.753	0.000*
ALT & T4	0.23	0.039*
ALP & HbA1c	0.225	0.044*