DISCUSSION

Thyroid diseases, namely hypothyroidism and hyperthyroidism constitutes one of the most common endocrine abnormality in recent years, diagnosed either in subclinical or clinical form. [58]

Dyslipidemia is a common metabolic abnormality in patients with thyroid disease, either in overt or subclinical forms of disease, and constitutes the end result of the effect of thyroid hormones in all aspects of lipid metabolism. [48]

The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population.This indicates a possible interplay between thyroid status and insulin sensitivity.[71]

In the present study, the mean age of the patients was 33.94 +/- 7.29 years and that of the control group was 35.65 +/- 7.77 years.The selected patients were male (29%) and female (71%) with female predominance .This coincides with Canaries et al. who reported that thyroid disease is much more prevelant in women than men .[31]

In hypothyroid group, cholesterol level (mean 201.54 +/- 49.25) was higher than the control group (mean 192.22 +/- 47.32).There is positive correlation between TSH and cholesterol .LDL level was higher (mean 134.67 +/- 40.98) than in control group (mean 120.44 +/- 38.37) .There is positive correlation between TSH and LDL. The previous results agrees with TZOTZAS et al.[87] and Colorado Thyroid Disease Prevalance Study, who reported that dyslipidemia is a common finding in patients with clinical hypothyroidism consisting of high levels of total and LDL cholesterol. Data regarding T.Gs and HDL components are scarce, reporting higher ,lower or similar to euthyroid subjects level. Effect of overt hypothyroidism on T.Gs and HDL concentration have been variable.[31,88]In the hyperthyroid group, cholesterol level (mean 173.46 +/- 35.46) was lower than the control group (mean 192.22 +/- 47.32) but did not reach statistical significance (p=0.089).There was a positive correlation between TSH and cholesterol level .LDL level (mean 107.29 +/- 33.46) was lower than control group (mean 120.44 +/- 38.37)but did not reach statistical significance (p=0.007).There was a positive correlation between TSH and LDL. This results agrees with Raziel et al.,[88] found lower total and LDL cholesterol levels in patients with hyperthyroidism. Lower T.Gs and HDL levels have been found in those patients compared with euthyroid controls. Liberopoulos E et al.[89] had reported that hyperthyroidism constitutes not only a significant cause of acquired hypobetalipoprotienemia but can also be the underlying cause of unexpected improvement of lipid profile of hyperlipidemic patients.[89]

In subclinical hypothyroidism group, cholesterol level (mean 206.50 +/- 31.11) was higher than the subgroup (1) (mean 158.60 +/-31.77) and statistically significant (p=0.017)..LDL level was higher (mean 137.17 +/- 20.16) than in subgroup (1) (mean 99.60 +/-28.80) and statistically significant (p=0.022).Tagami et al.[90] and Bairaktari E et al.,[91] reported that lipid abnormalities is found in subclinical hypothyroidism including mainly increased total and LDL cholesterol. In contrast, HDL and T.G levels did not exhibit any difference between patients with subclinical hypothyroidism and controls in the majority of the studies which agree with our study.[90, 91]

In subclinical hyperthyroidism, cholesterol level (mean 158.60 +/- 31.77) was lower than the control group (mean 192.22 +/- 47.32) and statistically significant difference (p= 0.047). LDL level (mean 99.60 +/- 28.80) was lower than control group (mean 120.44 +/- 38.37) but statistically not significant (p=0.110) . T.Gs level (mean 92.40 +/-20.22) was lower than control group (mean 134.83 +/- 44.51) and statistically significant (p= 0.004). These results were supported by J.V. Parle et al.,[92] who confirmed that subclinical hyperthyroidism is associated by lower levels of LDL, cholesterol, T.G and HDL. Berghout et al.,[93] revealed normal levels of total LDL, HDL cholesterol and T.Gs.[93]

These changes in the lipid profile are explained by the regulatory effect of thyroid hormones on the activity of some key enzymes of lipoprotein metabolism. Specifically, the thyroid hormone stimulates the hepatic de novo cholesterol synthesis by inducing the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-Co A) reductase that catalyzes the conversion of HMG-CoA to mevalonate, the first step in the biosynthesis of cholesterol. This results in an enhanced intracellular cholesterol concentration in hyperthyroidism and a decreased one in hypothyroidism. Additionally, thyroid hormones activate the LDL receptors; the promoter of the LDL receptor gene contain a thyroid hormone responsive element (TRE) which allows the triiodothyronine (T3) to upregulate the gene expression of the LDL receptor. Moreover, thyroid hormones stimulate the cholesteryl ester transfer protein (CETP), an enzyme which transports cholesteryl ester from HDL2 to the very low density lipoproteins (VLDL) and triglycerides in the opposite direction. Finally, thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the triglyceride-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes HDL2 to HDL3.[94]

Thyroid dysfunction can have an important effect on lipid profile. Biochemical screening for thyroid dysfunction is of paramount importance in all dyslipidemic patients, as well as in all patients with unexpected improvement or worsening of their lipid profile. Underlying thyroid disorders should be recognized and treated in this setting.

In hypothyroid patients,fasting insulin level (mean 17.23 +/- 12.34) is higher than control group (mean 15.42 +/- 7.00) but did not reach statistical significance (p=0.276).HOMAIR level (mean 3.93 +/- 2.98) is higher than control group (mean 2.98 +/- 1.42) but did not reach significance (p= 0.079)

In hyperthyroid patients,fasting insulin level (mean 17.23 +/- 12.05) was higher than control group (mean 15.42 +/- 7.00) but there is no statistical significance between them (p= 0.273).HOMAIR level (mean 4.04 +/- 3.21) was higher than control group (mean 2.98 +/- 1.42) but did not reach statistical significance (p=0.079).

In subclinical hypothyroid patients,fasting insulin level (mean 16 +/-8.29) was higher than control group (mean 15.42 +/- 7.00) but did not reach statistical significance (p=0.441).HOMAIR level (mean 3.23+/-1.25) was higher than control group (mean 2.98 +/- 1.42) but without statistical significance (p= 0.343).

In subclinical hyperthyroid patients,fasting insulin level (mean 9.7+/-4.89) was lower than control group (mean 15.42 +/- 7.00) and there is statistical significance between them (p= 0.033).HOMAIR level (mean 2.12+/-1.49) was lower than control group (mean 2.98 +/- 1.42) but did not reach statistical significance (p=0.111).

Maratou E et al., have proved the association between Insulin resistance and hypothyroidism, but there is controversy as to whether this association is also present in subclinical hypothyroidism. [95] Fommei E et al.,[96] revealed that insulin resistance was comparable to both subclinical and overt hypothyroidism.[96] BM Singh et al.,[97] reported that fasting insulin and TSH were significantly high in hypothyroid group only. HOMAIR was significantly raised in hypothyroid group as compared to controls. [97] Shantha et al.,[98] have observed that females with insulin resistance have significant association with subclinical and overt hypothyroidism. [98] Gimenez-Palop et al.[99] and Owecki et al.,[100] showed that there is no significant difference between the patients with thyroid dysfunction and euthyroid healthy group regarding fasting insulin and insulin resistance which is similar to our data.[99,100] Dimitriadis and Raptis et al.,[68] have reported that thyrotoxic subjects frequently show elevated fasting insulin level, but decreased and normal levels of plasma insulin have been reported.[68] Heemstra KA et al.,[101]showed that subclinical hyperthyroidism has been associated with increased insulin sensitivity.[101]

Liver, is a major target of thyroid hormones. Several genes involved in gluconeogenesis, glycogen metabolism, and insulin signaling that are regulated by thyroid hormones have been identified. Therefore playing an important role in the homeostatic regulation of blood glucose levels. Another study found that hyperthyroidism decrease mRNA expression of the Akt2 (protein kinase B), a serine / threonine kinase that is an essential molecule in the insulin signaling pathway. Akt2 has been shown to promote glycogen synthesis in the liver by inactivating glycogen synthase kinase 3. Thus, a decrease in Akt2 activity would decrese glycogen synthesis explaining the antagonistic insulin effect of thyroid hormones at the liver. Another mechanism is that thyroid hormones oppose the action of insulin and stimulate the hepatic gluconeogenesis and glycogenolysis. They up-regulate the expression of genes such as glucose transporter type-4 (GLUT4) and phosphoglycerate kinase, involved in glucose transport and glycolysis, respectively, thus acting synergistically with insulin facilitating glucose disposal and utilization in peripheral tissues.[102]

Regarding F.B.G, group (1) (mean 92.54 +/- 19.79) and group (2) (mean 90.58 +/- 14.14) have higher level of F.B.G than control group (mean 79.78 +/-15.27) with statistical significance between group 1 and control group (p=0.012) ,as well as group 2 and control group (p=0.012).

Regarding P.P.G, group (1) (mean 163.38 +/- 15.73), group (2) (mean 173.67+/- 14.23) and subgroup (2) (mean 182 +/- 16.42) were having higher level of P.P.S than control group (mean 161.83 +/- 17.47) and there was statistical significance between group (1) and control group (p=0.011), group 2 and control group (p=0.013) as well as between subgroup 2 and control group (p= 0.014).

Regarding HbA1C, all groups were having nearly the same value as control group without statistical significance between them.

Concerning systolic blood pressure, group 1 (mean 116.04 +/-13.35) and subgroup 1 (mean 110.00 +/- 7.07) were having lower levels than control group (mean 124.72 +/- 16.13). with statistical significance between them (p= 0.036) (p=0.004) respectively.On the other hand, group 2 (mean 132.50 +/- 11.61) and subgroup 2 (mean 134 +/- 4.92) had

higher levels than control group (mean 124.72 +/- 16.13) with statistical significance between them (p=0.046) (p=0.019) respectively.

Regarding diastolic blood pressure, group 1 (mean 72.08 +/-7.79) and subgroup 1 (mean 70 +/- 10) were having lower levels than control group (mean 73.33 +/- 9.07) without statistical significance between them. On the other hand, group 2 (mean 81.25 +/- 8.88) and subgroup 2 (mean 89.17 +/- 2.04) had higher levels than control group (mean 73.33 +/- 9.07) with statistical significance between group 2 and control group (p= 0.004) and between subgroup 2 and control group (p=0.000).

Regarding BMI, group 1 (mean 22.02 +/- 2.82) and subgroup 1 (mean 23.82 +/- 1.12) were having lower level than control group (mean 26.88 +/- 4.27) with statistical significance found between them (p= 0.000) (p=0.006) respectively.On the contrary, levels in group 2 (mean 29.18 +/- 3.30) was higher than control group (26.88 +/- 4.27) with statistical significance (p=0.033).

Fazio et al.,[103] demonstrated that in hypothyroidism (overt or subclinical the main functional cardiovascular disturbances involve decreased heart rate, elevated peripheral vascular resistance, increased blood pressure. [103] Biondi et al.,[104] reported that in hyperthyroidism, increased triiodithyronine level exert positive inotropic and chronotropic effects leading to enhanced heart rate, reduces peripheral vascular resistance causing decrease in blood pressure which is similar to our findings. [104] This result coincided with Klein et al.,[105] who recognized that hypothyroidism is a secondary cause of hypertension with similar effect have also been described in SHO.[105] Fommei et al[96] reported that replacement of lacking thyroid hormones reduces high B.P and total cardiovascular risk. [96] On the other hand, Liu et al.,[106] has reported no association between hypertension and hypothyroidism.[106] Park et al.,[107] reported that higher levels of fasting blood glucose is found with increased TSH level. [107] Roos et al,[108] reported that body mass index was significantly associated with TSH level, however individuals with SHO or SHE did not cause any difference.[108]

Most of existing data support that thyroid disease is associated with increase cardiovascular risk and atherosclerosis. This is attributed to the development of dyslipidemia in thyroid disease which in turn induces insulin resistance, hypertension, inflammation and coagulation defect.[104,109] A higher frequency and severity of coronary heart disease and increased ischemic stroke risk have been reported in patients with overt and subclinical hypothyroidism.[110] This is supported by Whickham survey and 3 meta-analyses as well as Razvi et al.[111-114].On the contrary, Rodondi et al.,found no association between subclinical hypothyroidism and prevalence of ischemic stroke compared to general population. On the other hand, clinical hyperthyroidism is associated with hypertension, hypercoagulable state, increased risk of thrombosis and ischemic stroke.[113]

The association between subclinical hyperthyroidism and coronary heart disease is still unclear. Singh et al, Ochs et al. found a possible association. While Jeong et al. found no significant association.[112, 114, 115]

. In our study, hypothyroidism, either overt or subclinical, causes high systolic and diastolic blood pressure as well as higher levels of FBG and PPG. It supports a possible relationship with increased cardiovascular risk.

It worth mentioning, that there was no relationship between subclinical hypothyroidism and BMI, which defines the common mistake that some dieticians fall in by attributing weight gain to subclinical hypothyroidism.

There might a link between SHO and cardiovascular risk, as in patients with full-blown hypothyroidism, serum levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol are elevated. In patients with subclinical hypothyroidism, not surprisingly, the same changes are present but are less marked and less consistent. Some studies, but not others, have shown a decrease in LDL cholesterol and total cholesterol levels after treatment with levothyroxine (Levoxyl, Levothroid, Synthroid).

In several studies, a sensitive measure of myocardial contractility, the ratio of pre-ejection period to left ventricular ejection time (PEP:LVET) was shown to improve significantly in patients with subclinical hypothyroidism who were treated with levothyroxine, compared with patients who were treated with placebo.

SUMMARY

Thyroid diseases, namely hypothyroidism and hyperthyroidism constitutes one of the most common endocrine abnormality in recent years, diagnosed either in subclinical or clinical form.

Dyslipidemia is a common metabolic abnormality in patients with thyroid disease, either in overt or subclinical forms of disease, and constitutes the end result of the effect of thyroid hormones in all aspects of lipid metabolism.

The prevalence of thyroid disease in patients with diabetes is significantly higher than that in the general population. This indicates a possible interplay between thyroid status and insulin sensitivity.

The study was conducted on 71 subjects who were selected from the outpatient clinics of internal medicine department, Alexandria University hospitals.

They were divided into three groups. Group 1 as hyperthyroidism (25 patients), group 2 as hypothyroidism (26 patients) and control group (20 subjects) . SHE and SHO were excluded from group 1 and group 2 and compared to control group as subgroup 1 (5 patients) and subgroup 2 (6 patients) respectively.

We excluded postmenopausal women and patients known to have diabetes and chronic illness as congestive heart failure, renal failure, chronic liver disease and end stage cancer.

All subjects will be submitted to the following:

- Informed consent.
- Full medical history :
  With particular stress on onset, duration of thyroid disease and any associated illness.
- Physical examination:
  With special emphasis on clinical thyroid gland examination Anthropometric measures: weight,height,body mass index.
- Laboratory investigations:
  1- Fasting lipid profile (HDL,LDL,Triglycerides,Serum Cholesterol).
  2- Thyroid function test(TSH,Free T4,FreeT3).
  3- Insulin sensitivity measurement. Using homeostatic model assessment(HOMA-IR).
  4- Modified oral glucose tolerance test (Fasting blood glucose, 2 hours after 75g oral glucose), as well as HbA1c.

The following are the results of this research:

In hypothyroid group, cholesterol level (mean 201.54 +/- 49.25) was higher than the control group (mean 192.22 +/- 47.32) .There is correlation between TSH and cholesterol in (r= 0.511) and statistically significant (p=0.006).LDL level was higher (mean 134.67 +/- 40.98) than in control group (mean 120.44 +/- 38.37) .There is correlation between TSH and LDL (r=0.639) and statistically significant (p=0.001).

In hyperthyroid group, LDL level (mean 107.29 +/- 33.46) was lower than control group (mean 120.44 +/- 38.37).There is correlation between TSH and LDL (r=0.476) and statistically significant (p=0.019).

In subclinical hyperthyroidism, cholesterol level (mean 158.60 +/- 31.77) was lower than the control group (mean 192.22 +/- 47.32) and statistically significant (p= 0.047).There is negative correlation between TSH and cholesterol level (r= -0.476) . T.Gs level (mean 92.40 +/-20.22) was lower than control group (mean 134.83 +/- 44.51) and statistically significant (p= 0.004).

In subclinical hyperthyroid patients,fasting insulin level (mean 9.7+/-4.89) was lower than control group (mean 15.42 +/- 7.00) and there is statistical significance between them (p= 0.033).

CONCLUSION

- Thyroid hormones disorder, including overt and subclinical type have a significant effect on glucose metabolism. In hyperthyroidism and subclinical hyperthyroidism, impaired glucose tolerance may be the result of insulin resistance.
- In subclinical hyperthyroidism, total cholesterol and triglycerides were lower than euthyroid patients. There is no relationship between HDL and thyroid disease.
- There was no statistical significant relationship between thyroid disease and insulin resistance, although it was proven in other studies.
- In thyrotoxicosis and hypothyroidism, there was higher levels of FBG and PPG compared to euthyroid subjects.
- In thyrotoxicosis (overt and subclinical), SBP is lower than euthyroid subjects, while levels were higher in overt and subclinical hypothyroidism.
- DBP was higher in subclinical and clinical hypothyroidism.