EFFECT OF HYPOTHYROIDISM AND HYPERTHYROIDISM ON LIPIDS PROFILE, GLUCOSE, LACTATE DEYHYDROGENASE, LIVER FUNCTION AND INHIBIN IN RAT

By

Amin, K. A; Kandeil, M.A. and Ali , K.M*

Dept. of Biochemistry Physiology; Faculty of Vet. Med.; Cairo Univ.-Beni- Suef branch*

SUMMARY

The aim of this study is to assess the association of hypothyroidism with lipid abnormalities and to quantify the effect of L-thyroxine therapy on serum lipid profiles (serum cholesterol, triglycerides, high density lipoprotein "HDL" and low density lipoproteins "LDL". Moreover their effect on liver function tests (ALT, AST and γGT), glucose concentration, LDH enzyme activity and inhibin level. These drugs (Carbimazole and Eltroxin) were administered orally for rat through stomach tube daily for 4 weeks. Rats were randomly divided into three groups: control, thyroid hormone deprived (Carbimazole), and Thyroid hormones supplemented group with Eltroxin.

Statistical analysis showed that, the hypothyroidism cause significant increase in cholesterol, triglyceride, LDL concentration, LDH, AST activities and inhibin level .Meanwhile hyperthyroidism showed a significant increase in liver function tests (ALT, AST & γGT) HDL, LDH with significant decrease in serum cholesterol, LDL and glucose concentration.

It could be concluded that, lipoproteins, liver function and inhibin were significantly disturbed in thyroid abnormalities. We recommend monitoring serum total cholesterol and lipoproteins (LDL &HDL) periodically to detect hypothyroidism easily before the appearance of its symptoms and therapy with thyroxine, which normalize lipid profile, preventing obesity and arteriosclerosis with special reference to liver function tests.

INTRODUCTION

Thyroid gland is the source of two essential different types of hormones, thyroxine and triiodothyronine. Both are needed for

normal growth , development and central nervous system maturation (Mosekilde et al., 1990). Normal thyroid function certainly requires a sufficient intake of iodine, which has an effect on its formation. Iodine deficiency has an effect on the physical and mental development of humans in large area of the world (Delange and Burgi 1989).

Thyroid hormones are important regulators of metabolic reactions in animal and human organism (Harper et al. 1993) and participate in the regulatory mechanisms of cell differentiation in several tissues (EL Hardi et al. 1996; Perrin et al. 1997).

The majority of the studies that determined the prevalence of lipid abnormalities in hypothyroidism and the effects of thyroxine replacement on lipids were uncontrolled, remain controversial and varied in inclusion criteria. While hypothyroidism can potentially contribute to a pro-atherogenic lipid profile, thyroxine replacement reduces total cholesterol and low-density lipoprotein cholesterol, with no effect on triglycerides. Effects on HDL, LDL and inhibin require further study (Ineck and Ng 2003). Low-dose methimazole is safer than propylthiouracil while the methimazole toxicity is more common over 40 years old.. Most cases of hepatic injury occur in the first few months of drug therapy as with agranulocytosis (Vitug and Goldman 1985).

The antithyroid drugs, methimazole and carbimazole, are conventionally used in divided daily doses. However, these drugs have a longer intrathyroidal than a plasma half-life. Carbimazole in a single daily dose is an effective method for treating hyperthyroidism in an area of mild iodine deficiency and its efficacy is comparable to that of divided dose therapy. This practical and acceptable method of treatment can be useful in patients who find it difficult to remember to take divided doses (Gupta et al., 1992).

The importance of thyroid hormone has implicated in mammalian reproduction because disturbed thyroid function is frequently associated with abnormalities in sexual function including impaired fertility (Gerhard et al., 1991, and Jannini et al.,1995). Thyroid hormone deficiency also results in alterations in testicular morphology, and these responses can vary greatly from species to another (Weiss and Burns 1988, and Jannini et al., 1995). Despite the apparent importance of thyroid hormone in

mammalian reproduction, little information is available on its role in the regulation of gonadal steroidogenesis and inhibin function.

Inhibin is a dimeric gonadal glycoprotein which consists of α-subunit and βA- or, βB-subunit, and selectively suppresses the follicle-stimulating hormone (FSH) secretion from the anterior pituitary gland. Homodimers of, β-subunits called activin stimulate FSH secretion. Inhibin related proteins, several large forms of inhibin and precursors of the α-subunit have been identified in bovine follicular fluids (Robertson *et al.* 1989) and in fetal bovine testicular extracts (Torney *et al.* 1992), the role of inhibin as a local regulator of spermatogenesis has been indicated in rats (Hakovirta *et al.* 1993).

Sertoli cells undergo important changes in their number and function at different ages in rat and are considered the major source of inhibin secretion in male animals (Culler & Negro-Vilar, 1988, and Rivier et al., 1988) and primary source of circulating inhibin B (Sharpe et al.,1999). Moreover leydig cells secrete inhibin-α-subunit-related proteins during fetal life (Noguchi, et al., 1997).

The present study aimed to determine the effect of hypothyroidism and L-thyroxine therapy on serum lipid profiles, liver function tests (ALT, AST and γGT), glucose level, LDH activity and inhibin levels.

MATERIALS AND METHODS

Experimental animals: Seventy fife male albino rats (150 -200 gm weight) were maintained on a 12 h light/dark cycle was fed adlibitum with normal chow diet with free access to water, rats were allowed to adapt to the new environment at least 1 week before the experiments. Rats were randomly divided into three groups each of 25 comprises 1) Control group giving saline orally 2) Hypothyroidism group giving carbimazol 3) Hyperthyroidism group supplemented with Eltroxin for 4 weeks.

Drugs and doses: - Thyroxine (Eltroxin Glaxo) administered orally in dose of 0.9μg/100 gm Bwt daily for 4 weeks and the dose was calculated according to Paget and Barnes (1964). Antithyroids drugs (Carbimazole) in dose of 100 μg/kg body weights daily for 4

weeks is effective, convenient and has a lower risk (Page et al.,1997). Rats rendered hyper- or hypothyroid by 4 weeks of thyroxine or carbamizol treatment giving orally by special stomach tube (Mano et al. 1995).

Sampling and analysis:- Serum was collected in clean tubes, separated, aliquated and stored at -20 C° until analysis. Serum biochemical variables were analyzed for; total cholesterol using an enzymatic method according to Allain et al., (1974); triglycerides by an enzymatic method according to Fossati and Prencipe (1982), LDL by kits according to Steinberg (1981), HDL by kits according to Burstein et_al., (1970). ALT and AST activities by kits according to Reitman and Frankel (1957), γGT activity, by the method described by Tietz, (1994), LDH by kits according to Kachmar & Moss (1976) and glucose according to Trinder (1969), By using spectrophotometer (*Hitachi 2000).* Serum level of total inhibin was determined by an immunoenzymometric assay depending upon ELISA sandwich technique (Poncelet and Eliard, 1990) using Biosource inhibin ELISA kit which fulfil determination of the total inhibin content in rat samples.

Statistical analysis of the obtained data was carried out by "T" test according to Snedecor and Cochran (1969) using Slide Write plus for Windows v.3 WSWP program.

RESULTS

The results can be summarized as follow:

Table 1) Hypothyroidism causes significant increase serum total cholesterol, triglycerides, LDL. Meanwhile hyperthyroidism showed a significant increase HDL while significant decrease in total cholesterol, triglyceride and LDL. were observed Table 2) Hypothyroidism causes significant increase LDH and inhibin level, meanwhile hyperthyroidism showed a highly significant increases LDH and significant decrease in glucose. Table 3) Hyperthyroidism showed a significant increases ALT, AST γGT. Also data represented in three figures.

DISCUSSION

Effect of hypothyroidism on lipid profile:

The present data showed, significant increased in serum concentration of total cholesterol (table 1) in hypothyroidism

(Boretti et al., 2003). The role of hypercholesterolemia in hypothyroidism indicated as a causal factor for coronary atherosclerosis and there is a very strong negative correlation between plasma HDL cholesterol levels and coronary atherosclerosis (Barbier et al., 1980).

Obvious hypothyroidism resulting in significant increase in LDL which is characterized by hypercholesterolaemia (Table 1) because of a decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver. Moreover, hypothyroidism increases the oxidized plasma cholesterol mainly because of an altered pattern of binding and to the increased levels of cholesterol, which presents a substrate for the oxidative stress. Cardiac oxygen consumption is reduced in hypothyroidism. This reduction is associated with increased peripheral resistance and reduced contractility with endothelium dysfunction, aortic atherosclerosis, and myocardial infarction. Hypothyroidism was often accompanied by diastolic hypertension and in conjunction with the dyslipidemia, may promote atherosclerosis (Duntas 2002).

Hypothyroidism seems to be associated with a decrease in metabolism of serum Remnant-like particles RLPs; the later reflect chylomicron remnants and very-low-density lipoprotein remnants, which are most likely to be atherogenic particles. Such altered metabolism of RLPs may be related to the decreased activities of lipoprotein lipase LPL and hepatic triglyceride lipase (HTGL) and can be corrected by T4 replacement therapy (Ito et al., 2003).

Evidence of an association between subclinical hypothyroidism and cardiovascular disease is mounting. The decrement in T_3 showed that in hypothyroidism may be a result in an increased serum cholesterol (Feld and Dickey, 2001). Alterations of the lipid profile are an important phenomenon in thyroid dysfunction. Thyroid hormones regulate lipid metabolism through various mechanisms, but the LDL receptor pathway plays a key role. It was concluded that plasma Lipoprotein(a) concentrations increase in hypothyroid patients and the observed relationships between thyroid status and Lipoprotein(a) levels can be explained by impaired catabolism of apoprotein B and Lipoprotein(a) in hypothyroidism (Erem et al., 1999).

In mammals, thyroid hormone depletion leads to decrease in LDL receptor expression and elevated serum cholesterol. Thus, we

propose that the decreased LDL receptor and increased serum cholesterol associated with hypothyroidsim is secondary to the thyroid hormone effects on through sterol regulatory element binding protein-2 (SREBP-2), suggesting that the hypercholesterolemia associated with hypothyroidism can be reversed by agents that directly increase SREBP-2. Additionally, mutations or drugs that lower nuclear SREBP-2 would cause hypercholesterolemia. (Shin and Osborne (2003).

The most frequent clinical characteristics observed in hypothyroidism were exercise intolerance, obesity, dermatological, neurological and gastrointestinal signs. In dogs hypothyroidism resulting in increased concentration of cholesterol and triglycerides (Boretti et al., 2003). In many patients the treatment with L-thyroxine reduces LDL, improves cardiac function, reduces symptoms of hypothyroidism, and diminishes neuropsychiatric symptoms. Treatment also reduces the likelihood of statin-induced myopathy (Glueck and Streicher 2003).

Hpothyroidism was associated with an increased risk for atherosclerotic vascular disease (Klein 1990). The dyslipidemia was characterized by elevated serum levels of (LDLc). One of the key processes in the development of atherosclerosis represents the accumulation of cholesterol by macrophages in the subendothelial space of the vessel wall. Oxidation of LDL particles results in modified LDL, which is no longer recognized by the LDL receptor but is taken up by the scavenger receptor on macrophages. Unlike the LDL receptor, the scavenger receptor is not down-regulated with cellular cholesterol accumulation and therefore provides a pathway for the continuous uptake of these chemically modified lipoproteins, which ultimately leads to foam cell formation (Witzum, 1994). In an in vitro model, T_4 inhibited the oxidation of LDL (Hanna et al., 1993), consequently, T_4 deficiency could potentially induce a higher susceptibility of LDL to be oxidized.

Thyroid hormones are involved in the regulation of lipoprotein metabolism, inducing significant changes in the concentration, size, and composition of plasma HDL. Thyroidectomized rats were found to have a 3-fold increase in LDL-C (Huesca-Gomez et al., 2002).

The high-density lipoprotein (HDL) levels are normal or even slightly elevated in hypothyroidism because of decreased activity of cholesteryl-ester transfer protein (CETP) and hepatic lipase (HL), which are decreases in hypothyroidism (Tan et al.,1998). The low activity of cholesteryl-ester transfer protein, and more specifically of hepatic lipase, results in reduced transport of cholesteryl esters from HDL2 to very low-density lipoproteins (VLDL) and intermediate low-density lipoprotein (IDL), and reduced transport of HDL2 to HDL3 (Duntas, 2002).

HDL-C metabolism is a complex, and changes in plasma levels are due, in part, to remodeling of HDL-C particles by hepatic lipase and cholesterol ester transfer protein (CETP) (Tall, 1993). Activity of both enzymes were increased in hyperthyroidism, correlating with plasma HDL-C (Tan et al., 1998).

Elevated total cholesterol and triglycerides levels in hypothyroidism (table 1) were normalized, along with a significant increase in (HDLc) by throid hormone supplementation (Bicikova et al., 2003). Which may be due to decreased activity of cholesteryl-ester transfer protein (CETP) that, results in reduced transport of cholesteryl esters from HDL to VLDL in exchange for triglyceride in addition decreased activity of hepatic lipase the degradation of triglycerides (Duntas, 2002).

Effect of hyperthyroidism on lipid profiles:-

Levels of serum total cholesterol and LDL were significant decreased by thyroxine therapy (Table 1), which in agreement with Barbier et al., (1980) and Ito et al., (2003).

Thyroxine therapy usually leads to a considerable improvement of the lipid profile. Hyperthyroidism exhibits an enhanced excretion of cholesterol and an increased turnover of LDL resulting in a decrease of total and LDL cholesterol (Duntas 2002).

The impact of thyroid hormone on lipid levels explained by as it is primarily mediated through triiodothyronine-bound thyroid protein binding and activation of the promoter regions of the low-density lipoprotein receptor and 3-hydroxy-3-methylglutaryl coenzyme A-reductase genes, leading to a reduction in serum cholesterol levels (Feld and Dickey 2001).

There was a significant reduction in cholesterol level in response to thyroxine. Variation within the LDL receptor gene appears to influence the magnitude of both the hypercholesterolemia of hypothyroidism and, consequently, the reduction of serum LDL cholesterol. Thus, it may be possible to predict that hypothyroid patients are at greatest risk for coronary artery disease (Wiseman et al., 1993).

The decreased plasma cholesterol level is observed despite an enhanced synthetic rate and is thus related to an increased clearance rate. The lack of increased expression of LDL receptor and LDL receptor-related protein suggests that other receptors were implicated. (Cachefo et al., 2001).

Data of HDL-C showed a significant increased in hyperthyroidism compared to the controls, thus suggesting a defect in HDL metabolism. Thyroid hormones modulate lipoproteins, particularly Lp(a). The delay in normalization of HDL but not LDL suggests an effect on HDL production rather than on LDL removal (Kung et al., 1995).

This study revealed that, serum triglycerides were slightly decreased by T_4 therapy, that agree with Ito et al., (2003) which was due to increased hepatic triglyceride lipase (HTGL).

Effect of hypothyroidism on glucose level and LDH activity:

Our data revealed that hypothyroidism cause slight decrease in serum glucose concentration (Table 2). This result was in agreement with, Turakulov et al., (1983) who found that thyroidectomized rats were manifested by a decrease in blood glucose concentrations than control. Also the decrease of gluconeogenesis observed in cells from thyroidectomized rats was reversed by the addition of pyruvate.

Data demonstrated Significant elevation in lactate dehydrogenase (LDH) and (AST) activities in hypothyroidism (table 2,3). Since muscle dysfunction is frequently associated with a hypothyroid state and many clinical reports have indicated that serum enzyme activities derived from the muscle (LDH) and (AST) are elevated. These enzyme activities in the serum of hyperthyroidism, euthyroidism and hypothyrodism have been known to have a good inverse correlation with protein-bound iodine (PBI). The values of myoglobin in untreated hypothyroidism, were

significantly higher than in normal subjects. Myoglobin was significantly correlated to LDH and (AST) abnormalities of these enzyme levels in serum (Shimoda and Kasai 1980). The origin of the increased muscle protein values observed in hypothyroidism, support the view that the muscle enzymes are mainly derived from skeletal muscles. (Roti et al., 1980 and Burnett et al., 1994).

Hypothyroid state was associated with an increase in serum muscle indicators (AST and LDH), and thus with muscle dysfunction encountered in anorexia nervosa (Kumano et al., (1990) and Vaughters 1990).

Effect of hyperthyroidism on glucose level and LDH activity : -

Statistical analysis showed significant decrease (table 2) in serum glucose level in hyperthyroidism, may be attributed to the rate of glucose utilization by every cell may exceed absorption, glycogenolysis and gluconeogenesis (Guyton 1986). Moreover hyperthyroidism increases glucose uptake by the forearm muscles in the postabsorptive state and during an oral glucose challenge, with increased fluxes of glucose through the oxidative and nonoxidative pathways (Foss, 1994), A moderate decrease in serum glucose by T_4 could be recovered (Segermann et al., 1991).

The plasma insulin concentrations in the portal and aortal blood vessels of fed as well fasted hyperthyroid group were higher from the respective values in the control one indicating that, hyperthyroidism increases insulin secretion but does not affect its removal (Gorska et al., 1989). Also the plasma levels of pro-insulin were higher while the glucagon level was normal (Rovira et al., 1987). Insulin is known to decrease plasma levels of both glucose and amino acids whereas in hyperthyroidism glucose disposal and decrease in amino acids levels are closely correlated as in healthy subjects (Barzilai et al., 1993). Moreover hyperthyroidism is characterized by increased levels of circulating free fatty acids (FFA) and increased lipid oxidation and suggest that femoral and abdominal adipose tissue contribute equally to the excessive rate of lipolysis in hyperthyroidism (Riis et al., 2002). Consequently, body fat and weight decreased and body oxygen consumption increased so decreased serum glucose concentrations in mice (Oh and Kaplan 1994).

Thyroxine administration resulted in preferential stimulation of oxidative stages of carbohydrate catabolism, while the activity of

glycolytic enzymes in these cells was less affected. Such effect seems to be similar to thyroid hormone action on the metabolism in several other tissues. While iodothyronines stimulate the processes of oxidative phosphorylation (Nelson, 1990).

The data (table 2) showed an increase in LDH activity that could be confirmed by Hyperthyroidism induced GSH depletion in the liver, with a significant enhancement in the thiobarbituric acid reactive substance (TBARS) formation and the TBARS/GSH ratio. Also an increased in the fractional LDH and GSH efflux (Videla et al., 1995). The results provided the evidence that the energy metabolism is influenced by thyroxine. It was found that a significant changes in the activity of enzymes of energy metabolism occurred simultaneously with the alterations in glucose, after repeated administration of thyroxine.

Effect of hypothyroidism on liver function: -

Data showed a non-significant changes in ALT and γGT activity in hypothyroidism (table 3). Cholestatic jaundice caused by imidazole derivatives is a rare complication of antithyroid therapy. Only 20 cases have been reported in the literature since the introduction of methimazole and carbimazole (Schwab et al., 1996).

The effect of the thyrostatic agent carbimazole decreased the level of serum thyroxine. ALT and γGT activities were apparently normal after carbimazole (Nedvidkova et al., 1991), indicating that the drug was safe by using such dose.

If clinical or laboratorial evidence of hepatocellular injury develops, the drug should be discontinued immediately when the hepatic injury is detected. Recovery is usually complete after the withdrawal of the drug (De Castro et al., 2001).

Effect of hyperthyroidism on liver function: -

This study presented (Table 3) significant elevation in liver enzymes (ALT, AST and γGT) activities, in hyperthyroidism indicating that an abnormal liver function in thyroid disorders may be secondary to thyrotoxicosis or to autoimmune injury to the liver (Bellassoued et al., 2001).

The frequencies of increased levels of AST, ALT, γGT, in the current study group were attributed to liver dysfunction and similar to but somewhat lower than those reported in previous

studies (Biscoveanu and Hasinski, 2000 and Bellassoued et al., 2001).

According to the present data, therapy with levothyroxine caused a significant elevation in mean serum γGT activity in comparison with the control, while decreased in patients with hypothyroidism. Euthyroidism results in restoration of normal γGT levels (Azizi, 1982).

The data suggest that liver biochemical test abnormalities are frequently observed in hyperthyroid. However, presence or absence of these abnormalities does not indicate to the development of subclinical hepatoxicity during 6-week antithyroid therapy (Gurlek et al., 1997).

γGT activity were significantly increased in hyperthyroidism and decreased under treatment by carbamizol, suggesting that variations in γGT levels in hyperthyroidism and hypothyroidism are, at least in part, in relation with variations in thyroid hormone levels (Couzigou et al.,. 1984).

T_3-calorigenesis resulted in elevated rates of O_2 consumption by the liver, together with higher lipid peroxidative processes and GSH depletion, compared to the euthyroid state and marked elevation in γGT, after thyroid hormones treatment, beside an enhancement in lactate dehydrogenase and protein release, suggesting that loss of GSH might be related to a permeabilization of the hepatocyte plasma membrane (Fernandez et al., 1991).

Hyperthyroidism led to Kupffer cell hyperplasia and significant increases in serum (AST). Also increases the susceptibility of the liver to the toxic effects and the rate of formation of thiobarbituric acid reactants, which seems to be accomplished by potentiation of the hepatic oxidative stress status. (Videla et al., 1995).

Effect of hyperthyroidism and hypothyroidism on inhibin: -

In male rats, inhibin levels were increased significantly (1.7- to 2-fold greater) in hypothyroidism, than those in control males, demonstrating that the hypothyroidism induced increases in the testicular size and sperm production were not due to increased levels of FSH at any point in development (Kirby et al., 1992).

Carbimazol treatment increased serum thyroid-stimulating hormone (TSH) levels and reduced serum levels of thyroxine from 5 days onwards, indicative of hypothyroidism. Inhibin levels were increased, with increase in the number of Sertoli cells per testis in treated adult rats (Van Haaster et al., 1992).

Transient neonatal hypothyroidism in the rat causes prolonged Sertoli cell proliferation with delayed Sertoli cell maturation, and increased adult Sertoli cell number, testis weight, and sperm production. Conversely, neonatal hyperthyroidism decreases Sertoli cell proliferation and ultimate testis size. This suggests that thyroid hormones might normally directly inhibit Sertoli cell proliferation while promoting maturation. However, these Sertoli cell effects could be due to secondary hormonal or metabolic effects of hypo- or hyperthyroidism (Simorangkir et al., 1995 and Cooke et al., 1998).

Hypothyroidism, increased Sertoli cell population also stimulates increased Leydig cell proliferation in male rat (Hardy et al., 1996) leading to significant elevation in serum inhibin level (table 2). Moreover hypothyroidism stimulated the expression of mRNAfor inhibin, and the stimulation was suppressed by thyroxine treatment up to control levels, suggesting that thyroid hormone has a direct inhibitory action on inhibin (Tamura, et al., 1998).

The hormonal regulation of inhibin biosynthesis by human benign hyperplastic prostate tissue, testosterone and estradiol had no effect whereas, a decrease in inhibin biosynthesis was noticed on the addition of, thyroid releasing hormone (TRH) (Vanage et al., 1990).

Thyroid hormones are important for growth and development of many tissues. Altered thyroid hormone status causes testicular abnormalities. For hypothyroidism induces macroorchidism, increases testicular cell number (Sertoli, Leydig, and germ cells) and daily sperm production. Although the role of T_3 on sperm, germ, and peritubular cells has not yet been completely studied, it is clear that T_3 directly regulates Sertoli and Leydig cell functions. Further studies are required to elucidate the direct effect of T_3 on sperm, germ, and peritubular cells (Maran, 2003)

It could be concluded that, the obtained data provide an evidence that the thyroid hormones involved in the regulation of glucose level and LDH activity. Cholesterol and LDL, were highest in hypothyroidism indicating progression of atherosclerosis, also carbimazole is effective, convenient and has a lower risk in dose of

100 μg/kg B.wt as a hypothyroidism drug. We recommend monitoring serum total cholesterol and lipoprotins periodically to detect hypothyroidism easily before the appearance of its symptoms and therapy with thyroxine which normalize lipid profile, preventing obesity and artheriosclerosis with special reference to liver function tests.

It could be also concluded that hypothyroidism increased the testicular cell number of sertoli, germ cells, leydig cell and daily sperm production with the increment in serum inhibin level.

REFERENCE

Allain, C.C; Poon, I.S.; Chain, C.S; Richmand, W. and Fu, P.C (1974): "Enzymatic determination of total serum cholesterol" Clin. Chem., 20 (4): 470.

Azizi F. (1982) "Gamma-Glutamyl transpeptidase levels in thyroid disease" Arch Intern Med, 142(1):79-81

Barbier, R; Paffoy, J.C; Venard-Sassolas, A. and Berthezene, F. (1980): "Variation in high density lipoprotein cholesterol during treatment of thyroid gland diseases" Diabete Metab; 6(3):213-7

Barzilai, N; Karnieli, E; Barzilai, D. and Cohen, P. (1993):"Correlation between glucose disposal and amino acids levels in hyperthyroidism" Horm. Metab., Res 25(7):382-5

Bellassoued, M; Mnif, M; Kaffel, N; Rekik, N; Rebai, T; Tahri, N; Krichen, M.S. and Abid, M. (2001) "Thyrotoxicosis hepatitis: a case report" Ann Endocrinol., (Paris); 62(3):235-8

Bicikova, M; Hampl, R; Hill, M; Stanicka, S; Tallova, J. and Vondra, K. (2003): "Steroids, sex hormone-binding globulin, homocysteine, selected hormones and markers of lipid and carbohydrate metabolism in patients with severe hypothyroidism and their changes following thyroid hormone supplementation" Clin Chem Lab Med.;41(3):284-92.

Biscoveanu, M. and Hasinski, S. (2000): "Abnormal results of liver function tests in patients with Graves' disease".Endocr Pract;6(5):367-9

Boretti, F.S; Breyer-Haube I, Kaspers B, and Reusch C.E. (2003) "Clinical, hematological, biochemical and endocrinological aspects of 32 dogs with hypothyroidism" Schweiz Arch Tierheilkd.;145(4):149-56, 158

Burnett, J.R; Crooke, M.J; Delahunt, J.W. and Feek, C.M. (1994): "Serum enzymes in hypothyroidism" N Z Med J. 14;107(985):355-6.

Burstein, M.; Scholnick, H.R, and Morfin, R (1970): "Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions" J Lipid Res.; 11(6):583-95.

Cachefo, A; Boucher, P; Vidon, C; Dusserre, E; Diraison, F. and Beylot, M. (2001): "Hepatic lipogenesis and cholesterol synthesis in hyperthyroid patients" J Clin Endocrinol., & Metab.; 86(11):5353-7.

Cooke, P.S; Zhao, Y.D. and Bunick, D. (1998): "Triiodothyronine inhibits proliferation and stimulates differentiation of cultured neonatal Sertoli cells: possible mechanism for increased adult testis weight and sperm production induced by neonatal goitrogen treatment". Biol Reprod; 59(1):216.

Couzigou, P; Latapie, J.L; Fleury, B; Climas, M.T; Le Moigne, F; Crockett, E; Sauneron, M.F; Richard-Molard, B; Amouretti, M. and Beraud, C. (1984): "Evolution of serum gammaglutamyl transpeptidase activity in treated hyperthyroid and hypothyroid patients" Gastroenterol Clin Biol;8(5):458-63

Culler, M.D. and Negro-Vilar, A. (1988): "Passive immunoneutralization of endogenous inhibin: sex-related diVerences in the role of inhibin during development". Molecular and Cellular Endocrinol., 58 263–273.

De Castro, J.J; Nobre, E.L, Garcia e Costa, J. and Galvao-Teles, A. (2001): "Asymptomatic hepatitis induced by propylthiouracil" Acta Med Port;14(5-6):523-7

Delange, F. and Burgi, H. (1989): Iodine deficiency disorders in Europe. Bull. WHO, 67,317-326.

Duntas, L.H. (2002) "Thyroid disease and lipids" Thyroid, 12(4):287-93.

EL Hadri, K; Pairault, J. and Feve, B. (1996): "Triiodothyronine regulates beta 3-adrenoceptor expression in 3T3-F442A differentiating adipocytes" Eur J Biochem. 239,519-525,

Erem, C; Deger, O. and Bostan, M.; Orem, A; Sonmez, M.; Ulusoy, S. and Telatar, M. (1999): "Plasma lipoprotein (a) concentrations in hypothyroid, euthyroid and hyperthyroid subjects" Acta Cardiol;54(2):77-81

Feld, S. and Dickey, R.A. (2001): "An Association Between Varying Degrees of Hypothyroidism and Hypercholesterolemia in Women: The Thyroid-Cholesterol Connection" Prev Cardiol. ; 4(4):179-182

Fernandez,V.; Simizu, K.; Barros, S.B.; Azzalis, L.A.; Pimentel, R; Junqueira, V.B. and Videla, L.A. (1991): "Effects of hyperthyroidism on rat liver glutathione metabolism: related enzymes' activities, efflux, and turnover" J. Endocrinol.; 129(1):85-91

Fossati, P. and Prencipe, L. (1982): "Determination of triglyceride using enzymatic method" Clin. Chem., 28:2077.

Foss, M.C. (1994): "Peripheral glucose metabolism in healthy subjects and in endocrine diseases" : Braz J Med Biol Res;27(4):959-**79**

Gerhard, I.; Becker, T.; Eggert-Kruse, W.; Klinga, K. and Runnebaum, B. (1991): "Thyroid and ovarian function in infertile women. Hum Reprod., 6:338–345

Glueck, C.J. and Streicher, P. (2003): "Cardiovascular and medical ramifications of treatment of subclinical hypothyroidism" Curr Atheroscler Rep.;5(1):73-7.

Gorska, M.; Lopaczynski, W. and Kinalska, I. (1989): "Effect of acute hyperthyroidism on insulin removal in the rats" Exp Clin. Endocrinol.;94(3):345-50.

Gupta, S.K; Mithal, A. and Godbole, M.M. (1992): "Single daily dose of carbimazole in the treatment of hyperthyroidism" Natl Med J India. ;5(5):214-6.

Gurlek, A; Cobankara, V. and Bayraktar, M. (1997): "Liver tests in hyperthyroidism: effect of antithyroid therapy" J Clin Gastroenterol.;24(3):180-3.

Guyton, A.C. (1986): "Text book of medical physiology" 7 th Ed. W.B. Saunderc Company Philadelphia, London, Mexico, Sydney and Hong Kong. P 897-902.

Hakovirta, H.; Kaipia, A; Soder, O. and Parvinen, M. (1993): "Effects of activin-A, inhibin-A, and transforming growth factor-β-1 on stage specific

deoxyribonucleic acid synthesis during rat seminiferous epithelial cycle" J. Endocrinol., 133: 1664–1668.

Hanna, A.N; Feller, D.R; Witiak, D.T. and Newman, H.A.I. (1993): "Inhibition of low density lipoprotein oxidation by thyronines and probucol" Biochem Pharmacol. 45:753–762.

Hardy, M.P; Sharma, R.S; Arambepola, N.K; Sottas, C.M; Russell, L.D; Bunick, D; Hess, R.A. and Cooke, P.S. (1996): "Increased proliferation of Leydig cells induced by neonatal hypothyroidism in the rat" J Androl.;17(3):231-8.

Harper, M.E; Ballantyne, J.S; LEACH, M. and BRAND, M.D. (1993): "Effects of thyroid hormone on oxidative phosphorylation" Biochem Soc Transact, 21:785-792,

Huesca-Gomez, C; Franco, M; Luc, G; Montano, L.F; Masso, F; Posadas-Romero, C. and Perez-Mendez, O. (2002): "Chronic hypothyroidism induces abnormal structure of high-density lipoproteins and impaired kinetics of apolipoprotein A-I in the rat" Metabolism; 51(4):443-50

Ineck, B.A. and Ng, T.M. (2003): "Effects of subclinical hypothyroidism and its treatment on serum lipids" Ann Pharmacother; 37(5):725-30.

Ito, M; Takamatsu, J; Matsuo, T; Kameoka, K; Kubota, S; Fukata, S; Tamai, H; Miyauchi, A; Kuma, K. and Hanafusa, T. (2003): "Serum concentrations of remnant-like particles in hypothyroid patients before and after thyroxine replacement" Clin Endocrinol (Oxf).;58(5):621-6.

Jannini, E.A; Ulisse, S. and D'Armiento, M. (1995): "Thyroid hormone and male gonadal function" Endocr Rev., 16:443–459

Kachmar, j.F. and Moss, D.W. (1976): "In fundamentals of clinical chemistry" second Ed. N.W. Tietz Editor, W.B. Saunders philadelphia, p. 652.

Kirby, J.D; Jetton, A.E; Cooke, P.S; Hess, R.A; Bunick, D; Ackland, J.F; Turek, F.W. and Schwartz, N.B. (1992): "Developmental hormonal profiles accompanying the neonatal hypothyroidism-induced increase in adult testicular size and sperm production in the rat" J.Endocrinol. ;131(2):559-65

Klein, I. (1990):"Thyroid hormone and the cardiovascular system" Am J Med., 88:631–637

Kumano, H; Kuboki, T; Tawara, R; Sasaki, T; Nomura, S; Suematsu, H. and Ogata, E. (1990): "Interrelationship between serum muscle enzymes and a low T3 in anorexia nervosa" Endocrinol Jpn.;37(4):583-9.

Kung, A.W; Pang, R.W; Lauder, I. and Lam, K.S (1995): "Changes in serum lipoprotein (a) and lipids during treatment of hyperthyroidism" Clin Chem., 41:226 –231.

Mano, T; Sinohara, R; Sawai, Y; Oda, N; Nishida, Y; Mokuno, T; Kotake, M; Hamada, M; Masunaga, R. and Nakai, A. (1995): "Effects of thyroid hormone on coenzyme Q and other free radical scavengers in rat heart muscle" J Endocrinol.;145(1):131-6.

Maran, R.R. (2003) "Thyroid hormones: their role in testicular steroidogenesis"Arch Androl. ;49(5):375-88.

Mosekilde, L; Eriksen, E.F. and Charles, P. (1990): "Effect of thyroid hormones on bone and mineral metabolism" J. Clin. Endocrinol. & Metab., 19: 35-63.

Nedvidkova, J; Stolba, P; Strbak, V; Vanzura, J; Hrabalek, A. and Vinsova, J. (1991): "The effect of 1-p-bromphenyl-5-mercapto-1,2,3,4-tetrazole (Br FMT) on thyroid gland function in rats" Cesk Farm.;40(2):75-7

Nelson, B.D. (1990) : "Thyroid hormone regulation of mitochondrial function. Comments on the mechanism of signal transduction" Biochim Biophys Acta, 1018:275- 277,

Noguchi, J; Hikono, H; Sato, S; Watanabe, G; Taya, K; Sasamoto, S. and Asegawa, Y. (1997): "Ontogeny of inhibin secretion in the rat testis: secretion of inhibin-related proteins from fetal Leydig cells and of bioactive inhibin from Sertoli cells" J. Endocrinol., 155: 27–34

Oh, S. S. and Kaplan, M. L. (1994): "Early treatment of obese (ob/ob) mice with triiodothyronine increases oxygen consumption and temperature and decreases body fat content" Proc Soc Exp Biol Med.;207(3):260-7.

Paget, E.E. and Barnes, J.M (1964): "Evaluation of drug activities" Toxicity tests Chapter 6 p. 135-166 Pharmaceutics vol., I academic press.

Page, S.R; Sheard, C.E; Herbert, M; Hopton, M. and Jeffcoate, W.J. (1997): "A comparison of 20 or 40 mg per day of carbimazole in the initial treatment of hyperthyroidism" Clin Endocrinol., (Oxf);46(2):240.

Perrin, M.C; Blanchet, J.P. and Mouchiroud, G.M. (1997): "Modulation of human and mouse erythropoiesis by thyroid hormone and retinoic acid: evidence for specific effects at different steps of the erythroid pathway" Hematol. & Cell Ther., 39:19-26.

Poncelet, E. and Eliard, P. (1990): "Construction of a sensitive two site immunoinzymatic assay for human inhibin in serum and other biological fluyids" Abst. 2nd Joint Esco-Eshre meeting, Milan, Italy, 110-111.

Reitman, S. and Frankel, S. (1957): "colorimetric determination of glutamic transaminase" Am. J. Clin. Path., 28:56-63.

Riis, A.L.D; Gravholt, C. H; Djurhuus, C.B; Nørrelund. H.; Jørgensen. J.O; Weeke, J. and Møller, N. (2002): "Elevated Regional Lipolysis in Hyperthyroidism" J. Clin. Endocrinol., & Metabolism, 87 (10) : 4747-4753

Rivier, C; Cajander, S; Vaughan, J; Hsueh, A.J.W. and Vale, W. (1988): "Age-dependent changes in physiological action, content, and immunostaining of inhibin in male rats" J. Endocrinol., 123:120–126.

Robertson, D.M; Giacometti, M; Foulds, L.M; Lahnstein, J; Goss, N.H; Hearn, M.T.W. and de Kretser, D.M. (1989): "Isolation of inhibin α-subunit precursor proteins from bovine follicular fluid"J. Endocrinol., 125: 2141–2149.

Roti, E; Bandini, P; Robuschi, G; Emanuele, R; Bolognesi, R; Ciarlini, E; Buzzonetti, P. and Gnudi, A. (1980): "Serum concentrations of myoglobin, creatine kinase, lactate dehydrogenase and cardiac isoenzymes in euthyroid, hypothyroid and hyperthyroid subjects." Ric. Clin., Lab.;10(4):609-17

Rovira, A; Valdivielso, L; Ortega, R; Valverde, I. and Herrera Pombo, J.L. (1987):"Plasma glucose, insulin, proinsulin, C-peptide and glucagon before and after a carbohydrate-rich meal in hyperthyroid patients" Diabete Metab.;13(4):431-5

Schwab, G.P; Wetscher, G.J; Vogl, W. and Redmond, E. (1996): "Methimazole-induced cholestatic liver injury, mimicking sclerosing cholangitis" Langenbecks Arch. Chir.;381(4):225-7

Segermann, J; Hotze, A; Ulrich, H. and Rao, G.S. (1991): "Effect of alpha-lipoic acid on the peripheral conversion of thyroxine to triiodothyronine and on serum lipid-, protein- and glucose levels" Arzneimittelforschung.;41(12):1294-8.

Sharpe, R.M; Turner, K.J; McKinnell, C; Groome, N.P; Atanassova, N; Millar, M.R; Buchanan, D.L. and Cooke, P.S. (1999): "Inhibin B levels in

plasma of the male rat from birth to adulthood: effect of experimental manipulation of Sertoli cell number" J. Androl.; 20(1):94-101.

Shimoda, S.I. and Kasai, K. (1980): "A clinical evaluation of the increased serum myoglobin: creatine phosphokinase and lactic dehydrogenase in patients with thyroid disorders " Nippon Naibunpi Gakkai Zasshi. 20;56(8):1096-106.

Shin, D.J. and Osborne, T.F. (2003): "Thyroid hormone regulation and cholesterol metabolism are connected through sterol regulatory element binding protein-2 (SREBP-2)"J. Biol Chem. 26 [Epub ahead of print].

Simorangkir, D.R; de Kretser,D.M. and Wreford, N.G. (1995): "Increased numbers of Sertoli and germ cells in adult rat testes induced by synergistic action of transient neonatal hypothyroidism and neonatal hemicastration" J Reprod. Fertil;104(2):207.

Snedecor, G.W. and Cochran, G. (1969): In "Statistical methods" 6th ed. Iowa state Univ. Press. Anes Iowa, USA, P. 70.

Steinberg, D.(1981):"Metabolism of lipoproteis at the cellular level in relation to atherogenesis" In lipoproteins Atherosclerosis & coronary heart disease, 1(2):31-48.

Tall, A.R. (1993): "Plasma cholesterol transfer protein" J. Lipid Res., 34:1255–1274.

Tamura, K., M. Hatsuta, G. Watanabe, K. Taya, and H. Kogo. (1998):"Inhibitory regulation of inhibin gene expression by thyroid hormone during ovarian development in immature rat" Biochem. Biophys. Res. Commun., 242: 102–108.

Tan, K.C; Shiu, S.W; Kung, A.W. (1998):"Plasma cholesteryl ester transfer protein activity in hyper- and hypothyroidism. J. Clin. Endocrinol. & Metab., 83:140 –143.

Tietz, N.W. (1994) "Textbook of Clinical chemistry, 2nd ed. W.B. Saunders Co., Philadelphia, P.A, p851.

Torney, A.H; Robertson, D.M. and de Kretser, D.M. (1992): "Characterization of inhibin and related proteins in bovine fetal testicular and ovarian extracts: evidence for the presence of inhibin subunit products and FSH-suppressing protein" J. Endocrinol., 133: 111–120.

Trinder, P. (1969): "Rapid colorimetric method for deteminartion of blood glucose" Annual Clinical Biochemistry, 6:24-27.

Turakulov, IaKh, Mirmakhmudova, S.I.; Gainutdinov, MKh. (1983): "Regulation of pyruvate **transport** in mitochondria by thyroid hormones" Biull Eksp Biol. Med.;96(9):57-9.

Van Haaster, L.H; De Jong, F.H; Docter, R; De Rooij, D.G. (1992): "The effect of hypothyroidism on Sertoli cell proliferation and differentiation and hormone levels during testicular development in the rat" J. Endocrinol.,131(3):1574-6

Vanage, G.R; Phadke, M.A; Bandivdekar, A.H. and Sheth, A.R. (1990): "Hormonal modulation of in vitro biosynthesis of inhibin like peptide by human prostate"Andrologia, 22(1):7-11

Vaughters, R.B. (1990): "Hypothyroidism as a cause of enzyme elevations" J. S. C. Med. Assoc., 86(6):351-2

Videla, L.A; Smok, G; Troncoso, P; Simon, K.A; Junqueira, V.B. and Fernandez, V. (1995): "Influence of hyperthyroidism on lindane-induced hepatotoxicity in the rat" Biochem. Pharmacol, 50(10):1557-65.

Vitug, A.C. and Goldman, J.M. (1985): "Hepatotoxicity from antithyroid drugs" Horm. Res., 21(4):229-34.

Weiss, R.S. and Burns, J.M. (1988): "The effect of acute treatment with two goitrogens on plasma thyroid hormones, testosterone and testicular morphology in adults male rats" Comp. Biochem. Physiol., 90:449–452.

Wiseman, S.A; Powell, J.T; Humphries, S.E. and Press, M. (1993): "The magnitude of the hypercholesterolemia of hypothyroidism is associated with variation in the low density lipoprotein receptor gene" J. Clin. Endocrinol., & Metab., 77(1):108-12

Witzum, J. (1994): "The oxidation hypothesis of atherosclerosis" Lancet, 344:793–795.

Table 1) Effect of hypothyroidism and hyperthyroidism on lipids profiles in serum of rats

Groups	Cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)
Control	76.61 ± 2.3 a	85.51±4.93 a	27.91±2.49 a	31.50±0.74 a
Hypothyroids	87.63 ±2.83 b	102.02±3.15 b	28.31±2.10 a	38.91±1.06 b
Hyperthyroids	69.22 ±1.84 c	80.64±2.76 a	39.5±1.08 b	13.54±0.34 c

Different litter in the same column indicates significant difference at p< 0.05

Table 2) Effect of hypothyroidism and hyperthyroidism on LDH and glucose and inhibin in serum of rats

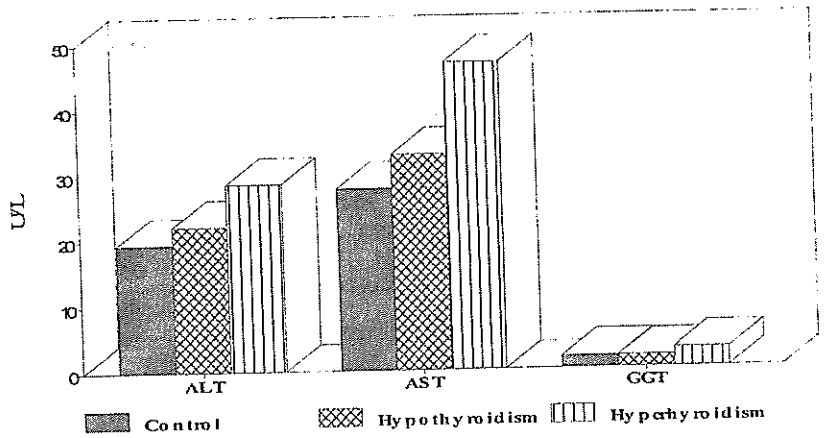
Groups	LDH (U/L)	Glucose (mg/dL)	Inhibin (ng/mL)
Control	309.13±24.59 a	130.13± 9.44 a	4.35±0.41 a
Hypothyroids	391.88±25.42 b	120.68±8.04 a	7.82±0.71 b
Hyperthyroids	580.64±47.80 c	99.59±6.30 b	5.69±0.51 a

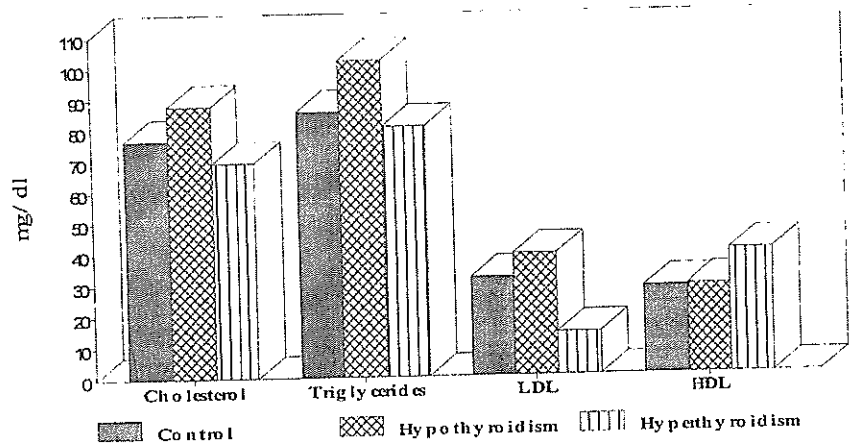
Different litter in the same column indicates significant difference at p< 0.05

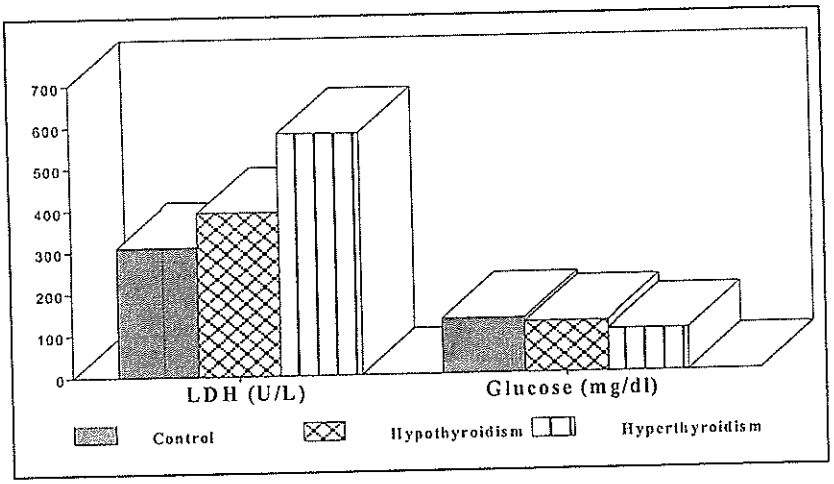
Table 3) Effect of hypothyroidism and hyperthyroidism on Liver enzyme activities in serum of rats.

Groups	ALT (U/L)	AST (U/L)	γGT(U/L)
Control	19.39±2.58 a	27.72±1.07 a	1.80±0.08 a
Hypothyroids	22.10 ± 1.25 a	32.85±1.53 b	1.79±0.21 a
Hyperthyroids	28.54±2.19 b	46.9±1.6 c	2.83±0.39 b

Different litter in the same column indicates significant difference at p< 0.05


U/L
50
40
30
20
10
0
ALT
AST
GGT
Control
Hypothyroidism
Hyperthyroidism


mg/dl
110
100
90
80
70
60
50
40
30
20
10
0
Cholesterol
Triglycerides
LDL
HDL
Control
Hypothyroidism
Hyperthyroidism


700
600
500
400
300
200
100
0
LDH (U/L)
Glucose (mg/dl)
Control
Hypothyroidism
Hyperthyroidism

الملخص العربي

تأثير نقص وزيادة هرمون الغدة الدرقية على مستوى الدهون والطاقة ووظائف الكبد ومستوى الأنهبين فى الفئران

كمال عادل أمين . ؛ محمد أحمد قنديل، * خالد محى الدين علي

*قسم. الكيمياء حيوية * علم وظائف الأعضاء؛ كلية الطب البيطري-بنى سويف- جامعة القاهرة*

تهدف هذه الدراسة الى تقييم علاقة نقص هرمون الغدة الدرقية مع تغيرات فى الدهون وأن تحدد تأثيرالعلاج بالثيروكسين على الدهون (الكلوستيرول والترايجلسريدات والبروتينات الدهنية مرتفعة الكثافه ومنخفضه الكثافه فى المصل). علاوة على ذلك تأثيرهم على إختبارات وظـائف الكبد (أنزيم الألانين أمينوتراسفيريز أنزيم الأسبارتيت أمينوتراسفيريز والجاما جي تي)، وتركيز الجلوكوز وأنزيم الاكتيت ديهيدروجينيز ومستوى الأنهبين.

أعطيـت عقاقـير كاربيمازول وإلتروكسين عن طريق الفم للفئران من خلال إنبوب المعـدة يومـيا لمـده ٤ أسابيع. قسمت الفئران بشكل عشوائي الى ثلاث مجموعات: الأولى ضـابطة ، والثانـية أعطيـت عقـار الكاربيمازول، والثالثه أعطيت هورمون الغدة الدرقية (إلتروكسـين). أظهر التحليل الآحصائي للنتائج أن نقص هرمون الغدة الدرقية أدى الى زيادة معنوية في مستوى الكلوستيرول والترايجلسريدات والبروتينات الدهنية منخفضه الكثافه ونشاط أنـزيمى الاكتيت ديهيدروجينيز وألأسبارتيت أمينوتراسفيريز وكذلك مستوى الأنهبين. بينما زيادة هرمون الغدة الدرقيه (الثيروكسين) أدى الى زيادة معنوية في إختبارات نشاط انزيمات الكـبد (الألانيـن أمينوتراسفيريز والأسبارتيت أمينوتراسفيريز والجاما جي تي)، وتركيزات البروتيـنات الدهنية مرتفعة الكثافه وكذلك أنزيم الاكتيت ديهيدروجينيز. بينما أدى الى نقص معـنوى فى الكلوستيرول والبروتينات الدهنية منخفضه الكثافه ، وتركيز الجلوكوز في مصل الفـئران. ويستخلص أن البروتينات الدهنية ووظائف الكبد، ومستوى الأنهبين يختل بشدة عند حـدوث خلل فى هرمونات الغده الدرقيه. ونوصي بمراقبة مستوى الكلوستيرول والبروتينات الدهنـية منخفضـه ومرتفعة الكثافه بشكل دوري للكشف عن نقص هرمون الغدة الدرقية قبل ظهـور أعراضـه والعـلاج بهرمون الثيروكسين الذى يعيد مستوى الدهون لطبيعتها ويمنع حدوث السمنة وتصلب الشرايين وذلك مع الرجوع الى اختبارات وظائف الكبد .

****