Antihyperlipidemic Effect of L-Thyroxine Combined with Carvedilol in Induced Hyperlipidemia in Rabbits

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Abstract

Background: Hyperlipidemia is defined as an elevation of one or more of the plasma lipids, including cholesterol, cholesterol esters, triglycerides (TG) and phospholipids .An elevation of plasma lipids may be caused by primary or secondary factors.

Objective: To evaluate the effect of L-thyroxine - Carvedilol combination on hyperlipidemia induced in rabbits.

Material and method: Forty healthy, domestic rabbits of both sexes, weighing (800 – 1100 grams) were used in this study. They were divided into five groups each one contains eight rabbits. The first group (G1) was given a standard diet to be considered as a control group while all other groups fed with high cholesterol diet. The second group (G2) was given high cholesterol diet only, third group (G3) treated with atorvastatin , (G4) treated with L-thyroxine and (G5) received L-thyroxine combined with carvedilol. Then lipid profile, heart rate and body weight were measured for all groups to be compared.

Results: Because atorvastatin is a known antihyperlipidemic drug, the results of using combination of L-thyroxin with carvedilol were compared to those produced by atorvastatin alone. The results showed insignificant ($p<0.05$) difference in all biochemical parameters, heart rate and body weight of the hyperlipidemic group treated with the combination of L- thyroxin and carvedilol (G5) when compared with those treated with atorvastatin alone (G3).

Conclusion: The use of the combination of L-thyroxine and carvedilol has antihyperlipidemic effect similar to that of atorvastatin which is well known antihyperlipidemic drug.

Key words: Hyperlipidemia, L-thyroxin, Carvedilol, Lipid profile, atorvastatin.

التأثير المضاد لفرط الشحوم بالدم لعقار الثايروكسين متحدا بعقار الكارفيديلول على فرط الشحوم بالدم المستحدث في الارانب

الخلاصة:

المقدمة :فرط الشحوم بالدم يعني ارتفاع واحد او اكثر من دهون البلازما متضمنة الكوليسترول, استرات الكوليسترول, الدهون الثلاثية وفوسفات الدهون. ان فرط شحوم البلازما اما ان تنتج عن عوامل اولية او ثانوية.

الهدف من الدراسة:لتقييم تأثير استعمال ال –الثايروكسين متحد بعقار الكارفيديلول على فرط الشحوم بدم الارانب التي استحدث فيها فرط الشحوم.

المواد والطرائق:استخدم في هذه الدراسة اربعون ارنبا بوزن ٨٠٠ -١١٠٠ غم, قسمت الى خمس مجاميع. اعطيت المجموعة الاولى غذاءا مثاليا ليتم اعتبارها مجموعة سيطرة, اما بقية المجاميع فقد غذيت بطعام عالي الكوليسترول. تم اعطاء المجموعة الثانية طعاما عالي الكوليسترول فقط, بينما

عولجت المجموعة الثالثة باستخدام عقار اترفوستاتين, والمجموعة الرابعة عولجت بالثايروكسين بينما عولجت المجموعة الخامسة عقار الثايروكسين متحدا مع ال الكارفيديلول. بعد ذلك اجريت مقارنة صورة الشحوم, وسرعة النبض ووزن الجسم لكافة المجاميع.
النتائج:لكون الاترفوستاتين معروفا بكونه عقارا مضادا لشحوم الدم فقد قورنت نتائج استخدام عقار الثايروكسين متحدا بالكارفيديلول مع تلك التي استخدم لها الاترفوستاتين. اظهرت النتائج عدم وجود اي فرق بشكل معتد في جميع المؤشرات الكيميائية لمجموعة فرط الشحوم المعالجة باستخدام عقار الثايروكسين متحدا بالكارفيديولول عند مقارنتها بتلك التي استخدمت عقار الاترفوستاتين لوحده.
الاستنتاجات :ان تأثير عقار الثايروكسين متحدا بالكارفيديلول في تقليل فرط الشحوم بالدم يساوي ذلك الناتج عن استعمال الاترفوستاتين المعروف بكونه مضادا لفرط الشحوم بالدم.

Introduction:

Atherosclerosis is the most common cause of coronary heart disease (CHD) and related mortality. The first observable event in the process of atherosclerosis is the accumulation of plaque (cholesterol from low-density lipoproteins, calcium, and fibrin) in the endothelium of large and medium size arteries (1).

Lipids are classified according to their structure into simple, compound and derived lipids based on the hydrolysis, which result in breaking off the fatty acids, leaving free fatty acids and a glycerol, using up three water molecules. **Simple lipids** are esters of fatty acids with various types of alcohol. They are distinguished into fats and oils. **Compound lipids** contain an inorganic or organic group in addition to fatty acids and glycerol. They include phospholipids, glycolipids and lipoproteins. Finally, **derived lipids** are obtained by hydrolysis of simple and compound lipids. These lipids contain glycerol and other alcohols (2). The main source of dietary lipids is through the intake of (TG) which can be found as fats or oils.

Lipids are important in maintaining the structure of cell membrane (cholesterol, phospholipids), steroid hormone synthesis (cholesterol), and energy metabolism [TG and fatty acid] (3).

Types of hyperlipidemia:

Hyperlipidemia may basically be classified as either familial (also called primary) caused by specific genetic abnormalities, or acquired (also called secondary) when resulting from another underlying disorder that leads to alterations in plasma lipid and lipoprotein metabolism. Also, hyperlipidemia may be idiopathic, that is, without known cause (4).

Diagnosis of hyperlipidemia:

Many hyperlipidemic individuals are detected as a result of screening procedures, either in the course of 'health-screening' or of 'profiling' of patients. Fasting serum TG concentration is generally >1000 mg/dL (>11.2 mmol/L), and sometimes can exceed 10.000 mg/dL (112 mmol/L) (5). Concomitant lipid abnormalities include a modest elevation in serum total cholesterol, with decreases in low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL- c) (6). A full lipid profile including plasma cholesterol, plasma TG and HDL-c should be obtained following an overnight fast (12-14 hours). In routine practice, LDL concentration (mg/dL) is estimated indirectly from the measured levels of TG, HDL-c, and total cholesterol (TC) using the Friedewald equation: **LDL = TC – HDL – (TG / 5).**When concentrations are expressed in mmol/L, TG is divided by 2.17 instead of 5 (7).

Treatment:

The main aim of treatment in the majority of hyperlipidaemic patients is to reduce the risk of developing premature vascular disease (primary prevention) or the occurrence of further vascular events in those with clinical vascular disease (secondary prevention). The non pharmacological treatment of hyperlipdemia depends on life style modification including diet control, weight loss and exercise (8). While drug therapy includes: ***Statins, Fibrates, Nicotinic acid, Omega-3 fatty acids (fish oils), Ezetimibe*** (9).

Relation between hyperlipidemia and thyroid function:

Thyroid hormone synthesis and secretion is regulated by TSH secreted from the anterior pituitary, which in turn is stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Both TSH and TRH are regulated in a negative feedback loop by circulating T_4 and T_3 (10). The liver, and to a lesser degree the kidneys, play a dominant, although often under- discussed role in the metabolism of thyroid hormones. The majority of the most metabolically active thyroid hormone, 3,5,3'-triiodothyronine (T3), is generated in peripheral tissue (11).

A common problem of thyroid gland is hypothyroidisim which leads to generalized slowing in all metabolic process (12). Thyroid hormone deficiency affects virtually every tissue in the body. Although patients with this disorder can be asymptomatic, some patients have subtle findings, including alterations in lipid metabolism, cardiac, gastrointestinal, neuropsychiatric, and reproductive abnormalities, and an increased likelihood of developing a goiter (13).

Material and Method:

Forty healthy, domestic rabbits of both sexes, weighing (800 – 1100 grams) were used in this study. These rabbits were divided to five groups each one contains eight rabbits. They were supplied by the animal house of the college of medicine / Al-Nahrain University from 2013-2014, in a room where the temperature was 27°C ±1°C and 12 hrs light and dark cycles were maintained. The animals were allowed to acclimatize to the environment for 4 weeks and supplied with a standard pellet diet and water *ad libitum*. Method of blank *et al.* was used with modifications (1963) to produce diet-induced hyperlipidaema. Briefly, normal group (Group 1) received standard chew diet and all other groups received high cholesterol diet consisting of standard pellet diet (92%), cholesterol (2%), cholic acid (1%), and coconut oil (5%) mixed by ether, for 8 successive weeks. At the end of this period, the weight of each of the rabbits was measured and daily consumptions were monitored. The standard pellet diet consist of crude protein (22.06%), crude oil (4.04%), crude fiber (4.0%), Ash (10.0%) and sand silica (0.15%). The standard pellet diet supplies energy of 3620 Kcal/kg (14).

The rabbits were separated in cages, which were provided with a wire mesh floor. The animals were grouped as follows:

- **Group1 (G1):** was given a standard or normal diet to be considered as control group.
- **Group2 (G2)**: The second group (G2) was given high cholesterol diet in standard diet only for eight weeks.
- **Group3 (G3)**: received high cholesterol diet in standard diet with a daily single dose of atorvastatin 10 mg/kg/day (15) for 21 days.
- **Group 4 (G4):** Received high cholesterol diet in standard diet and treated by L-thyroxine in a dose of (50 µg/day) given as single oral dose just before food at morning for 21 days (16)
- **Group 5 (G5):** received high cholesterol diet in standard diet and treated by L- thyroxine in a dose of (50 µg/day) given as single oral dose just before food, combined with carvedilol (3.125 mg/kg, twice daily) orally for 21days.(17)

The blood samples were collected directly from the heart and after centrifugation the serum samples were obtained for biochemical and hormonal parameters (18)

Statistical analysis:

Statistical analysis was performed by using SPSS (Statistical Package for social Science; Version 14), and Microsoft Excel Worksheet 2007. Crude data was analyzed to obtain mean and standard error of mean (SEM). Student paired t- test was used. P-Value was dependent < 0.05 as level of significance

Results

1- **Descriptive data:** For all groups' lipid profile, heart rate and body weight were measured. As shown in table (1)

2- **Comparison between parameters of the normal control group (G1) and those after induction of hyperlipidemia (G2):**

Highly significant ($p<0.001$) difference in parameters (Total serum cholesterol, LDL, VLDL, TG, and body weight) and significant ($p<0.05$) difference in HDL and heart rate were detected between groups G1 and G2, as shown in table (2).

3- **Comparison between parameters of hyperlipidemic untreated group (G2) and the same parameters in the group treated with atorvastatin only (G3)**

The calculated results showed highly significant ($p<0.001$) difference in total serum cholesterol, LDL, VLDL and TG between groups G2 and G3. While significant ($p<0.05$) difference was found in body weight and non significant ($p<0.05$) in HDL and heart rate between these groups (G2 and G3) as shown in table (3) while the changes in lipid profile were shown in figure (1).

4- **Comparison between parameters of hyperlipidemic untreated group (G2) and group treated with L- thyroxine only (G4)**

A highly significant ($p<0.001$) difference in total serum cholesterol, LDL, VLDL, TG, heart rate and body weight were found between groups G2 and G4, whereas no significant difference ($p>0.05$) was found in level of HDL between these two groups (G2 and G4) as shown in table (4).

5- **Comparison between parameters of hyperlipidemic group treated with atorvastatin (G3) and hyperlipidemic group treated with combination of L-thyroxin and carvedilol (G5)**

The results of the present study show insignificant ($p>0.05$) difference in all parameters of group G5 compared to group G3 as shown in table (5).

Discussion

Hyperlipidemia plays a major role in atherogenesis and it is an important risk factor for atherosclerosis (19). Atherosclerosis is the leading cause of mortality in developed countries. This complex disease can be described as an excessive inflammatory, fibro fatty, proliferative response that leads to damage of the arterial wall (20).

In the present study, feeding of rabbits with HFD (2% cholesterol) for 8 weeks resulted in marked hyperlipidemia with a highly significant increase ($p<0.001$) in serum concentration of total cholesterol, TG, LDL, and VLDL, while HDL serum concentration was significantly decreased ($p<0.05$) compared with normal control group (G1) (Table 2). These results are in agreement with those reported previously (21). As cholesterol intake increase, bile acids reabsorption increase too, which leads toan increase in its uptake by the liver. The consequence is an inhibition in the conversion of cholesterol to bile acids by the liver. The resultant elevation in liver cholesterol content leads to an increase in VLDL production, a decrease in lipoprotein receptor activity, and an accumulation of cholesteryl ester rich VLDL and LDL in the plasma. (22).

Another finding is the significant decrease in heart rate which may be due to effect of liver damage by hyperlipidemia that interfere with conversion of T4 to T3 so hypothyroid status will develop in such patients and this will cause decrease in the heart rate. This finding is in accordance with that of (23).

The factors that may contribute to obesity induced by a diet rich in fat include failure to adjust oxidation of fat to the extra fat in the diet (24), increase in adipose tissue lipoprotein lipase activity (25). These facts may explain the highly significant increase ($p<0.001$) in body weight of the rabbits fed with high fat diet as shown in table (2)

In comparison between the HFD group and the HFD group treated with atorvastatin highly significant ($p<0.001$) decrease in total serum cholesterol, LDL, VLDL and TG was noticed in the present study as shown in table (3). The action of atorvastatin is mediated via up-regulation of hepatic LDL receptors (LDL-R) resulting from inhibition of cholesterol biosynthesis in the liver (26). A significant decrease ($p<0.05$) in the body weight was noticed in atorvastatin treated group (G3) as compared to that of hyperlipidemic untreated group (G2). The result of the present study was similar to that shown by Liberopoulos ,et al (27).

Another comparison was done between parameters of the induction group (G2) and the group treated with L- thyroxine only (G4) (Table 4). A highly significant decrease ($p<0.001$) in total serum cholesterol, LDL, VLDL and TG levels were detected in G4 as compared to G2. Generally, hypothyroidism is associated with increased levels of serum TG, cholesterol and LDL cholesterol and *vice versa* hyperthyroidism is associated with their decreased levels (28).

Thyroid hormones (such as 3, 3_,5-triiodo-L-thyronine; T3) are important regulators of lipid metabolism and metabolic rate. They exert their physiological effects by binding to specific nuclear receptors, the thyroid hormone receptors (TR) α and β, which are widely distributed throughout the body (29). The β isoform is the major TR expressed in liver, whereas the α isoform is the major TR expressed in the heart. Beneficial effects of TR activation include lowering of low-density lipoprotein cholesterol and a reduction in whole body adiposity and weight (29). Thyroid hormone stimulated increases in metabolic rate in liver could potentially lead to reduced liver lipid content. However, this beneficial effect could be counteracted by increased lipogenesis in liver (30) or lipolysis in adipocytes either of which could lead to deposition of lipids in the liver (31).

The beneficial decrease in cholesterol after TR activation is driven solely by TR activation in hepatocytes, the only cell in the body capable of cholesterol disposal (32). T3 reduce liver triglycerides and raise acyl-carnitines in plasma. T3 treatment resulted in an increase in liver mitochondrial respiration and changes in hepatic gene expression (33).It increase catecholamine-induced lipolysis rates in adipocytes and increased plasma free fatty acid levels *in vivo*. This lipolysis in adipocytes may have fully or partially counteracted the beneficial hepatic activities. T3 treatment induce changes in gene expression in liver that lead to increased mitochondrial β-oxidation, but T3 treatment appears to over whelm the hepatic catabolism of triglycerides by mobilizing free fatty acid or triglycerides from the periphery. (34)

The measurement of heart rate showed a highly significant ($p<0.001$) increase in rabbits treated with L- thyroxine (G4) compared to hyperlipidemic untreated group group (G2) (table 4). This may be due to an increased sensitivity to noradrenaline. The increase in the noradrenaline content in the heart after treatment with thyroxine may result from the inhibition of mono amine oxidase' by thyroxine, since some drugs which inhibit monoamine oxidase' cause an increase in the noradrenaline content of the rat heart (35).

Highly significant decrease ($P<0.001$) in body weight was detected in the group treated with L-thyroxine (G4) compared to hyperlipidemic untreated group (G2) (table4). Thyroid hormones can shift energy substrates away from their storage as TG, suppressing lipogenesis and promoting the utilization of fatty acids as fuel by increasing lipase activity and β-oxidation in mitochondria and peroxisomes. (28), these actions may explain the reduction in body weight in L- thyroxine treated group detected in this study.

The results of the present study show insignificant ($p>0.05$) difference in all parameters of the hyperlipidemic group treated with combination of L- thyroxine and carvedilol (G5) when compared with those treated with atorvastatin alone (G3) (table 5).This may open a new way in treating hyperlipidemia by L-thyroxine that show clear antihyperlipidemic activity in this study and previous studies (30) with removing its cardiac side effect (tachycardia) by combination with β- blocker (carvedilol) (36), which also had antihyperlipidemic effect in addition to its antioxident effect. (37).

Table (1): Descriptive data of all group (mean± SEM):

Parameters	Normal Group (1)	Hyperlipidemic untreated group (2)	Atorvastatin treated group (3)	L-thyroxine treated group (4)	L-thyroxine+ Carvedilol treated group (5)
Total cholesterol (mg/dl)	43.82 ± 2.29	360.8 ± 11.93	106.09 ± 8.17	123.26 ± 6.24	113.73 ± 8.9
LDL (mg/dl)	22.4 ± 2.29	307.39 ± 17.84	83.63 ± 6.3	100.5 ± 7.07	89.29 ± 8.7
HDL (mg/dl)	23.3 ± 1.07	14.85 ± 1.22	17.23 ± 0.88	16.4 ± 0.41	18.93 ± 1.7
VLDL (mg/dl)	16.78 ± 1.04	62.83 ± 4.16	19.01 ± 2.95	18.99 ± 1.68	23.14 ± 2.7
TG (mg/dl)	83.91 ± 5.22	314.17 ± 20.82	95.06 ± 14.76	94.97 ± 8.4	103.28 ± 9.7
H. R (bpm)	151.13 ± 1.55	148.12 ± 1.3	148.5 ± 1.4	176.2 ± 4.18	146.87 ± 3.7
Wt (gm)	978.75 ± 22.86	1537.5 ± 39.8	1237.5 ± 30.98	1256.25 ± 27.44	1218.75 ± 38.8

Table (2): Comparison of parameters between normal (G1) and hyperlipidemic group (G2) (Results presented in mean± SEM)

Parameters	(G1) Control Group	(G2) Induction Group
Total cholesterol (mg/dl)	43.82 ± 2.29	360.8 ± 11.93**
LDL (mg/dl)	22.4 ± 2.29	307.39 ± 17.84**
HDL (mg/dl)	23.3 ± 1.07	14.85 ± 1.22*
VLDL (mg/dl)	16.78 ± 1.04	62.83 ± 4.16**
TG (mg/dl)	83.91 ± 5.22	314.17 ± 20.82**
H. R (bpm)	151.125±1.55	147.25± 0.16*
Wt (gm)	978.75±22.86	1537.5±39.8**

*= Significant ($p<0.05$) difference
**= Highly significant ($p<0.001$) difference

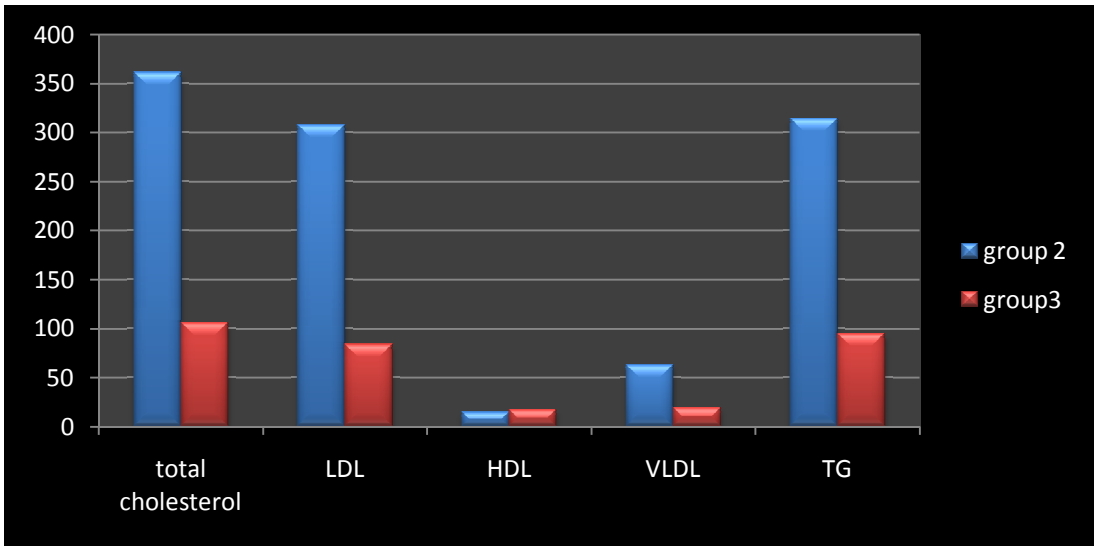

Figure 1: Comparison of lipid profile parameters between hyperlipidemic untreated group (G2) and hyperlipidemic group treated with atorvastatin only (G3).

Table (3): Comparison of parameters between hyperlipidemic untreated group (G2) and hyperlipidemic group treated with atorvastatin only (G3). (Results presented in mean±SEM)

Parameters	hyperlipidemic untreated group (G2)	Atorvastatin treated group(G3)
Total cholesterol (mg/dl)	360.8 ± 11.93	106.09 ±8.17**
LDL (mg/dl)	307.39±17.84	83.63±6.3**
HDL (mg/dl)	14.85±1.22	17.23±0.88
VLDL (mg/dl)	62.83±4.16	19.01±2.95**
TG (mg/dl)	314.17±20.82	95.06±14.76**
H. R (bpm)	147.25± 0.16	148.5±1.4
Wt (gm)	1537.5±39.8	1237.5±30.98*

*=Significant ($p<0.05$) difference
**=Highly significant ($p<0.001$) difference

Table (4): Comparison of parameters between hyperlipidemic untreated group (G2) and hyperlipidemic group treated with L- thyroxine only (G4). (Results presented in mean±SEM)

Parameters	Hyperlipidemic untreated group (G2)	L-thyroxine treated group (G4)
Total cholesterol (mg/dl)	360.8±11.93	123.26±6.24**
LDL (mg/dl)	307.39±17.84	100.5±7.07**
HDL (mg/dl)	14.85±1.22	16.5±0.41
VLDL (mg/dl)	62.83±4.16	18.99±1.68**
TG (mg/dl)	314.17±20.82	94.97±8.4**
H. R (bpm)	147.25± 0.16	176.2±4.18**
Wt (gm)	1537.5±39.8	1256.25±27.44**

*Significant ($p<0.05$) difference
**Highly significant ($p<0.001$) difference

Table (5): Comparison between parameters of hyperlipidemic group treated with atrvostatin (G3) and hyperlipidemic group treated with combination of L- thyroxine and Carvidilol (G5)

Parameters	Atorvastatin treated group (G3)	L-thyroxine+carvedilol treated group (G5)
Total cholesterol (mg/dl)	106.09±8.17	113.73±8.9
LDL (mg/dl)	83.63±6.3	89.29±8.7
HDL (mg/dl)	17.23±0.88	18.93±1.7
VLDL (mg/dl)	19.01±2.95	23.14±2.7
TG (mg/dl)	95.06±14.76	103.28±9.7
H. R (bpm)	148.5±1.4	146.87±3.7
Wt (gm)	1237.5±30.98	1218.75±38.8

*= Significant ($p<0.05$) difference
**= Highly significant ($p<0.001$) difference

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