Research Article

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The effect of fish oil supplementation on the liver and kidney functions of hyperlipidemic and hypothyroid albino rats

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Abstract: Omega-3 fatty acids (Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)) which found in fish oil have been widely recognized due to their beneficial effects on health, and are considered as essential supplements in human food. The present study elucidated the therapeutic effect of omega 3 fatty acids on the liver and kidney functions in hyperlipidemic and hypothyroid albino rats. The current results showed that the liver function parameters were affected by hyperlipidemia which recorded marked improvement after fish oil administration; however, their showed non-significant changes by hypothyroidism. Additionally, serum creatinine and uric acid concentrations were increased significantly while urea level showed non-significant change in the hyperlipidemic and hypothyroid groups. Furthermore, fish oil administration improved the kidney function parameters in both groups. fish oil supplementation showed benefit effects on the liver and kidney functions in both hyperlipidemic and hypothyroid groups which may be due to the beneficial effects of omega-3 fatty acids.

Key words: Omega 3 fatty acids, liver function, kidney function, hyperlipidemia, hypothyroidism.

Introduction

Liver being the major organ responsible for cholesterol transport, metabolism and excretion, it is reasonable to study hepatic oxidative disturbances in hypercholesterolemia (1). Hyperlipidemia is a risk factor for vascular disease such as atherosclerosis and coronary artery diseases (2). It has been suggested that hypercholesterolemia, hypertension and impaired endothelial function in the hypothyroid state augment atherogenesis (3). In addition, several studies suggest that hypothyroidism is associated with the emerging risk factors for atherosclerosis such as hyper-homocysteinemia (4).

Fish oil is oil derived from the tissues of oily fish. Fish oils contain the omega-3 fatty acids Eicosa Pentaenoic Acid (EPA), and Docosa Hexaenoic Acid (DHA), precursors of certain eicosanoids that are known to reduce inflammation throughout the body (5). Omega-3 FAs also show hypotriglyceridemia, anti-aggregatory, anti-inflammatory, and anti-arrhythmatic responses (6). Furthermore, regular consumption of n−3 FAs, particularly docosahexaenoic acid (DHA), has the capacity to ameliorate several cardiovascular risk factors, including elevated blood pressure and triacylglycerols, platelet aggregation, endothelial dysfunction, and arrhythmia (7).

Materials and Methods

Experimental animals:

White male albino rats (*Rattus norvegicus*) weighing between 100-120g were used as experimental animals in the present investigation. They were obtained from the animal house of National Research Institute, El-Giza, Egypt. They were kept under observation for about 15 days before the onset of the experiment to exclude any inter current infection. The chosen animals were housed in metal (stainless steel) separate bottom cages at normal atmospheric temperature (25 ± 5°C) as well as under good ventilation and received water and standard balanced diet.

Hyperlipidemic and hypothyroidism agents:

Cholesterol used as a hyper-cholesterolemic agent, was purchased from Oxford laboratory (India), Cholic acid sodium salt was purchased from Fluka-Biochemical, (Switzerland) and animal lard was purchased from a market in El-Giza. Otherwise, carbimazole used as hypothyroidismic agent, was purchased from Chemical Industries Development "CID" (Egypt).

Fish oil dosage:

Fish oil capsules contain 1000 mg fish oil (13% EPA & 9% DHA) manufactured by SEDICO for pharmaceuticals (Egypt).

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Hyperlipidemic and hypothyroid rats received fish oil in a dose of 0.5ml/kg b.wt./day (8) to rats through gastric intubation for 6 weeks.

Induction of hyperlipidemia and hypothyroidism:
Hyperlipidemia was induced by addition of cholesterol powder, cholic acid and animal lard to the standard diet in percentage of 1%, 0. 5% and 5% respectively (9), to rats for about 45 days. On the other hand, hypothyroidism was induced by injection of 30 mg of carbimazole / Kg b.wt./day (10) to rats through gastric intubation for 6weeks.

Animal grouping:
There are five groups each group contain six rats:

Group (1): was regarded as control group and given distilled water by gastric intubation for 6 weeks.

Group (2): was regarded as hyperlipidemic group and given hyperlipidemic agents for 6 weeks.

Group (3): was regarded as hyperlipidemic group treated with fish oil by gastric intubation for 6 weeks.

Group (4): was regarded as hypothyroid group and given hypothyroid induced agent for 6 weeks.

Group (5): was regarded as hypothyroid group treated with fish oil by gastric intubation for 6 weeks.

All treatments were performed orally and daily between 8.00 and 10.00 a.m.

Biochemical studies:
Glutamate oxaloacetate-transaminase (AST) and glutamate pyruvate transaminase (ALT) activities were determined according to the procedure of (11) using reagent kits purchased from Noble Diagnostic. Moreover, L-γ-Glutamyl-Transferase activity (GGT) was determined according to the procedure of (12) using reagent kits purchased from Centronic (GmbH).

Serum bilirubin concentration was estimated according to the method of (13) but, serum total protein concentration was estimated according to the method of (14), while serum albumin concentration was estimated according to the method of (15) using reagent kits purchased from Bio-Diagnostic, Egypt.

Serum creatinine concentration was estimated according to the method of (16) however, serum urea concentration was estimated according to the method of (17) while, serum uric acids concentration was estimated according to the method of (18) using reagent kits purchased from Bio-Diagnostic, Egypt.

Statistical analysis of the results:
The Statistical Package for the Social Sciences (IBM SPSS for WINDOWS 7, version 20; SPSS Inc., Chicago) was used for the statistical analysis. Comparative analysis was conducted by using the general linear models' procedure (IBM SPSS). Values of $P>0.05$ were considered statistically non-significant, while values of $P<0.05$ were considered statistically significant.

Results

The effect of fish oil on the liver function in hyperlipidemic and hypothyroid rats:
The present study was showed a significant increase in the serum liver enzymes (GOT, GPT and GGT) activities of hyperlipidemic rats as compared to control rats. But the hypothyroid rats showed significant decrease in the serum liver enzymes activities as compared to control rats. Whereas, fish oil administration improved the liver enzymes activities in both groups as shown in tables (1), (2).

In the hyperlipidemic rats, serum total protein concentration was increased significantly, but serum albumin concentration was decreased as compared to control rats and there showed amelioration after the treatment with fish oil. On the other hand, there were non-significant changes in serum total protein and albumin concentrations of hypothyroid rats as compared to control rats as shown in tables (1), (2).

Table 1: shows serum activity of glutamate-oxalacetate transaminase (GOT), glutamate pyruvate transaminase (GPT) and gamma glutamyl-transpeptidase (GGT) and concentration of total protein, albumin, total bilirubin, direct bilirubin and indirect bilirubin of control, hyperlipidemic and hyperlipidemic treated rats with fish oil.

Group	Control	Hyperlipidemic	Treated	LSD
AST(GOT) (u/l)	197.47±3.24^{a}	335±11.92^{c}	227.43±2.53^{b}	29.97
ALT(GPT) (u/dl)	76.53 ± 2.18^{a}	95.2±5.14^{b}	78.7±2.32^{a}	18.67
GGT (u/dl)	2.62 ± 0.12^{a}	11.07 ± 0.93^{b}	4.23 ± 0.33^{a}	8.45
Total protein (g/dl)	5.65 ± 0.52^{a}	7.45±0.36^{b}	5.07±0.57^{a}	1.8
Albumin (g/dl)	2.95±0.20^{b}	2.35±0.15^{a}	2.88±0.09^{b}	0.6
Total bilirubin (mg/dl)	0.95±0.04^{a}	2.37±0.14^{b}	0.9±0.08^{a}	1.43
Direct bilirubin (mg/dl)	0.12±0.01^{a}	0.67±0.04^{c}	0.28±0.06^{b}	0.16
Indirect bilirubin (mg/dl)	0.80±0.04^{a}	1.31±0.05^{b}	0.64±0.06^{a}	0.50

Values significantly different to control at (p≤0.05). Data are expressed as mean ± SE.
Values which share the same superscript symbol are not significantly different. F-Probability: P < 0.05

Table 2: shows serum activity of glutamate-oxalacetate transaminase (GOT), glutamate pyruvate transaminase (GPT) and gamma glutamyl-transpeptidase (GGT) and concentration of total protein, albumin, total bilirubin, direct bilirubin and indirect bilirubin of control, hypothyroid and hypothyroid treated rats with fish oil

Group	Control	hypothyroid	Treated	LSD
GOT(AST) (u/l)	197.47±3.24^{b}	156.02 ± 4.64^{a}	183.53 ± 12.22^{b}	41.5
GPT(ALT) (u/dl)	76.53 ± 2.18^{c}	49.1±2.26^{a}	61.2±1.62^{b}	15.3
GGT (u/dl)	2.62 ± 0.12^{b}	1.13±0.08^{a}	3.27±0.28^{c}	0.65
Total protein (g/dl)	5.65 ± 0.52^{a}	6.72 ± 0.36^{a}	6.27 ± 0.23^{a}	------
Albumin (g/dl)	2.95±0.20^{a}	2.74±0.19^{a}	3.09±0.23^{a}	-----
Total bilirubin (mg/dl)	0.95±0.04^{a}	0.89±0.03^{a}	0.97±0.02^{a}	-----
D.bilirubin (mg/dl)	0.12±0.01^{b}	0.07±0.02^{a}	0.07±0.01^{a}	0.05
In.bilirubin (mg/dl)	0.80±0.04^{ab}	0.73±0.04^{a}	0.85±0.02^{b}	-----

Values significantly different to control at (p≤0.05).
Data are expressed as mean ± SE.
Values which share the same superscript symbol are not significantly different. F-Probability: P < 0.05

Our data showed that serum bilirubin concentrations (total, direct and indirect) of hyperlipidemic rats were increased significantly as compared to control rats. While after fish oil administration serum bilirubin concentrations were improved significantly. On the other hand, the hypothyroid rats showed non-significant change in serum total and indirect bilirubin, however, there was a significant decrease in serum direct bilirubin as compared to control rats which improved significantly after fish oil administration as shown in tables (1), (2).

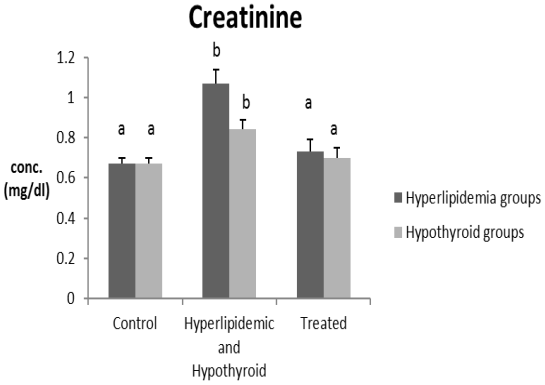

Figure 1: The effect of fish oil administration on serum creatinine concentration in hyperlipidemic and hypothyroid rats

The effect of fish oil on the kidney function in hyperlipidemic and hypothyroid rats:

The present study elucidated a significant increase in serum creatinine concentration of hyperlipidemic and hypothyroid rats as compared to control rats. While, the serum creatinine concentration was improved after treatment with fish oil in both groups as shown in figure (1). Moreover, there was a non-significant change in serum urea concentration of hyperlipidemic and hypothyroid rats as compared to control rats as shown in figure (2). Additionally, serum uric acid concentration was significantly increased in the hyperlipidemic and hypothyroid rats as compared to control rats.

Whereas, fish oil administration ameliorated uric acid level in both groups as shown in figure (3).

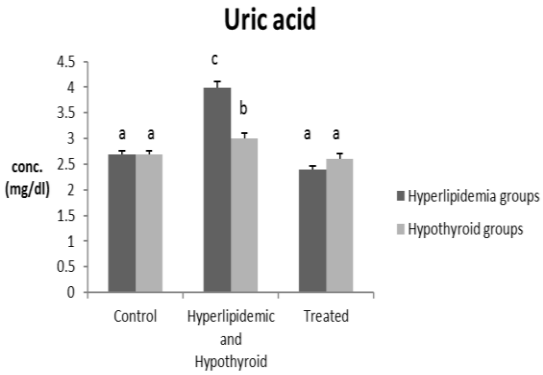

Figure 2: The effect of fish oil administration on serum uric acid concentration in hyperlipidemic and hypothyroid rats

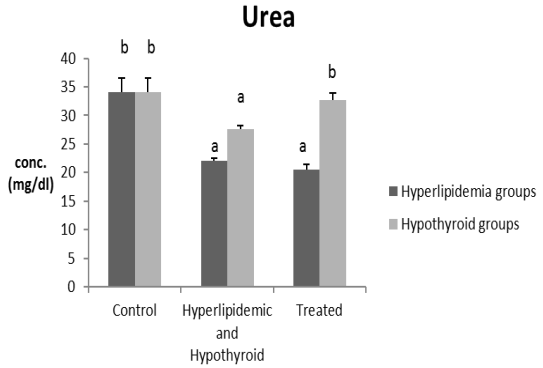

Figure 3: The effect of fish oil administration on serum urea concentration in hyperlipidemic and hypothyroid rats

Discussion

Marine omega-3 fatty acids are very promising dietary supplements used in prevention and therapy of cardiovascular, inflammatory, immunological, psychological and neurological disorders. Already several studies showed efficacy of omega-3 fatty acids in the metabolic syndrome-related conditions (19). The present study shown a significant increase in serum total protein content, a significant decrease in albumin concentration and a significant increase in total bilirubin, indirect bilirubin and direct bilirubin concentration in the serum of hyperlipidemic rats as compared to control rats, these results are in parallel with that of (20).

Increase in serum total protein in hyperlipidemic rats was explained by increased amino acids synthesis and greatly increased concentration of a variety of essential amino acids (21), increase in protein synthesis which in turn may be due to increase in the amount and availability of mRNA, increase in translation factor and increase in ribosomal protein synthesis as a result of hyperlipidemia (22). The decrease in albumin indicates liver dysfunction. These results agree with (23) who reported that the high-fat diet reduced serum albumin. The reduction in serum albumin concentration and elevated bilirubin may be due to hypercholesterolemia - induced liver cell damage (24) as evident in the increase in activities of marker enzymes of liver cell damage. Additionally, cholestasis is a relative indicator of liver excretory function, reflected biochemically by plasma bilirubin, or more specifically direct bilirubin.

In the current study, the hyperlipidemic treated rats with fish oil shown that serum albumin, total protein, total and indirect bilirubin return near to normal values in addition to improve direct bilirubin concentration which were agreement with the data of (25). Increased levels of albumin can be reflecting the synthetic function of the liver. Also, this improvement may be due to increase in liver enzymes and plasma proteins which, in turn, lead to increases in thyroid hormones (26).

Our data showed a significant increase of GOT, GPT& GGT levels in the serum of hyperlipidemic rats as compared to control rats. These results are agreement with several reports (27). Elevation in the levels of diagnostic hepatic serum marker enzymes such as SGOT and GGT in hypercholesterolemia induced rats is due to peroxide formation induced by hypercholesterolemia (28), result in increased cellular membrane permeability, intracellular fluid transfers into intercellular space, resulting in hepatocytes damage which leads to the leakage or release of hepatic marker enzymes from hepatocytes to serum and hence the level of marker enzymes are raised in HCD fed rats (29).

In the current study fish oil administration regarded a significant improvement in GOT, GPT and GGT activities in the hyperlipidemic treated rats, which are agreement with that of (30). It was proved that supplementation with omega-3 PUFA improves biochemical, ultrasonographic and hemodynamic features of liver steatosis (31).

Thyroid dysfunction may perturb liver function, liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs (32). This can explain that the data for the hypothyroid rats had shown a significant decrease in direct bilirubin and non-significant change of total protein, indirect bilirubin, total bilirubin, albumin in the serum as compared to control rats. These agree with (33). On the other hand, the hypothyroid treated rats with fish oil had shown a significant improvement of serum direct bilirubin and a non-significant change of total protein, indirect bilirubin, albumin and total bilirubin as compared to control rats. Otherwise, in hypothyroid group, our data showed that the liver enzymes (SGOT, SGPT& SGGT) were significant decreased as compared to control rats. These are agreement with (34). The low activates of the hepatic enzymes may be due to the low free T3 levels which may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within hepatocytes and preserve liver function and total body protein stores (32). Concerning our study, fish oil administration showed amelioration in SGOT, SGPT and SGGT activities in hypothyroid treated group. (35) attributed the beneficial effects of fish oil administration to hyperlipidemic and hypothyroid rats to its hypolipidemic, antioxidant and hyperthyroid action.

The kidney function in our study showed significant increase in creatinine and uric acid concentrations, and a non-significant change in urea concentration in the serum of hyperlipidemic rats as compared to control rats. These results are agreement with the finding of (36). The hypercholesterolemia leads to reduced renal blood flow and increased renal vascular resistance (37), which are factors directly related with the impairment of renal function.

Dyslipidemia can cause renal fibrosis due to increase in extracellular matrix deposition and reduced matrix degradation (38). The increase in collagen synthesis and activation of pro-inflammatory pathways by oxidized low density lipoprotein (LDL) could be responsible for increased matrix deposition. It has already been shown that renal tubular cells can express scavenger receptors, which are responsible for oxidized LDL uptake, acting as a bridge between hyperlipidemia, oxidative stress and renal fibrosis (39). High-cholesterol-containing diets have been shown to increase focal glomerular sclerosis in guinea pigs and rats (40). Elevated uric acid concentrations are also associated with cardiovascular disease and the relation of hyperuricemia, hypertriglyceridemia has been well recognized for several decades (41).

In the hyperlipidemic treated rats with fish oil, creatinine concentration was ameliorated which may be due to the improvement of glomerular filtration by omega-3 administration which are agree with the data of (42). These indicate that fish oil made improvement in creatinine and uric acid concentrations with non-significant effect on urea level. As, fish oil reduced hyperlipidemia by decreasing serum total cholesterol and LDL-cholesterol concentration, so, creatinine might be decreased due to glomerulosclerosis reduction (40). Some trials found a benefit of fish oil supplementation on renal function (43). Eicosapentaenoic acid (EPA) in fish oil significantly suppresses rate crystal-induced inflammation in the Sprague-Dawley rat subcutaneous air-pouch model.

Thyroid dysfunction causes significant changes in kidney function; both hypothyroidism and hyperthyroidism affect renal blood flow, GFR, tubular function, electrolyte homeostasis and kidney structure. Hypothyroidism-associated kidney dysfunction seems to be more related directly to a reduction in thyroid hormone levels rather than with thyroid autoimmunity (33). Our results recorded that the kidney function in hypothyroid rats showed a non-significant change of urea concentration and a significant increase of creatinine and uric acid concentration as compared to control rats, which are agreement with that of (44). In hypothyroidism, renal blood flow rate, glomerular filtration rate (GFR), and tubular resorptive and secretory capacities are all reduced. The elevation of uric acid level may be due to that the uric acid is negatively regulated by thyroid hormones, especially T3 and therefore tend to increase in overt hypothyroid cases when T3 levels are low. Also, it may be due to a reduction in renal plasma flow and glomerular filtration secondary to thyroid hormone deficiency (45). However, the hypothyroid treated rats with fish oil, creatinine and uric acid were improved significantly after orally fish oil administration. The fish oil effects in the

concentration of creatinine, uric acid and urea/creatinine ratio may due to that fish oil ameliorated thyroid hormones concentrations and improved glomerular filtration (42).

Conclusion

All the above results confirmed the benefit effect of the fish oil on the liver and kidney function in hyperlipidemia and hypothyroidism in albino rats due to the beneficial effects of omega-3 fatty acids.

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