Effects of Omega-3 on lipid profile and haematological parameters in hyperlipidemic rats

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ABSTRACT

Background: There is good evidence that omega-3 fatty acids found in fish oil can help to prevent and treat atherosclerosis by preventing the development of plaque and blood clots. Omega-3 can also help prevent heart disease, lower blood pressure, and reduce the level of triglycerides in the blood. The present study was designed to evaluate and compare the effects of different doses of omega-3, gemfibrozil and atorvastatin on lipid profile and haematological parameters in hyperlipidemic rats.

Methods: Forty eight rats were divided into two groups. The first groups included 18 rats' they were subdivided into three subgroups each of 6 rats. The first subgroup served as a control. The second and third subgroups received omega-3 (15 mg/kg) and (30 mg/kg) orally (PO) daily respectively. The second group included 30 rats and received atherogenic diet throughout the treatment period and served as hyperlipidemic rats. The hyperlipidemic model rats were subdivided into five subgroups of six rats each. The first subgroup served as a positive control. The second and third subgroups received omega-3 (15 mg/kg) and (30 mg/kg) PO daily respectively. The fourth and fifth subgroups received gemfibrozil (3.5 mg/kg) PO daily and atorvastatin (2 mg/kg) PO daily respectively. At the end of treatment period of all these groups, the rats were subjected to various biochemical and hematological tests.

Results: After four weeks of therapy, (30mg/kg) of omega-3 showed a significant reduction in the level of triglyceride (TG), total cholesterol (TC) and low density lipoprotein (LDL-C) in control rats, whereas (15mg/kg) omega-3 could only reduce the level of TC and LDL-C significantly. Four weeks of daily administration of both doses of omega-3 produced significant reduction in serum (TC, TG and LDL-C) of hyperlipidemic rats. However neither (15mg/kg) of omega-3 nor omega-3 (30mg/kg) could increase the level of high density lipoprotein HDL-C in the treated and non-treated hyperlipidemic rats.

Both doses of omega-3 produced a significant increase in the level of HB, RBC and MCH in normal rats. The same doses of omega-3 showed a significant increase in the levels of hemoglobin (HB), red blood cell (RBC), hematocrit (HTC) and mean corpuscular hemoglobin (MCH) in hyperlipidemic rats after 4 weeks of therapy.

Following four weeks treatment with both gemfibrozile and atorvastatin there was a significant reduction in serum (TC, TG and LDL-C) and a significant rise in serum HDL-C in hyperlipidemic rats.

Conclusion: Omega-3 was effective in controlling lipid profile especially serum (TC, TG and LDL-C). No significant differences were found between the effects of both doses omega-3 and gemfibrozile or atorvastatin on TC, TG, and LDL-C of hyperlipidemic rats. In contrast to omega-3, gemfibrozile and atorvastatin induced a significant raise in the level of HDL-C. Omega-3 was effective in increasing the levels of HB, RBC, HTC and MCH in hyperlipidemic rats.

Key words: Omega 3, Gemfibrozile, Atorvastatin, Lipid profiles, hyperlipidemic rats

Introduction

Hyperlipidemia is a lipid abnormality with genetic or familial origins (primary hyperlipidemia). Hyperlipidemia could also be caused by endocrine, hepatic or renal diseases (secondary hyperlipidemia). Primary hyperlipidemia includes familial or polygenic hypercholesterolemia, familial combined hyperlipidemia, familial hypertriglyceridemia, and dysbetalipoproteinemia (1).

Concomitant elevation of circulating levels of triglyceride-rich VLDL and cholesterol-rich LDL is recognized as being associated with an increased risk of premature coronary artery disease (2).

There is good evidence that omega-3 fatty acids (namely EPA and DHA) found in fish oil can help prevent and treat atherosclerosis by preventing the development of plaque and blood clots. Omega-3 can also help prevent heart disease, lower blood pressure, and reduce the level of triglycerides (fats) in the blood. One preliminary study found that people with high cholesterol who took fish oil and red yeast rice lowered cholesterol levels about as much as people who took simvastatin. People with heart disease or those who need to lower triglycerides may need to take fish oil supplements (3) and are characteristic of subjects who exhibit a lipid phenotype typical of combined hyperlipidemia (4).

Atherosclerosis is a disease of large and medium-sized muscular arteries characterized by inflammation and dysfunction of the lining of the involved blood vessels and the buildup of cholesterol and lipids. This results in the formation of a plaque, obstruction of blood flow and diminished oxygen supply to target organs (5).

This dysfunction may arise due to many factors like vessel injury and collagen exposure, metabolite deposition in the vessel wall (increase in lipid, cholesterol), or change in vascular reactivity due to change in the rate or force with which blood flows (6, 7).

The present study was designed to evaluate and compare the effects of different doses of omega-3, gemfibrozil and atorvastatin on lipid profile and haematological parameters in hyperlipidemic rats.

Materials and Methods

Animals

A total of 48 rats of both sexes were used in the present study. Their weight ranged from (170- 250 grams) and they were aged 60 days, the rats were obtained from Mousil and Abu ghreb. Once received they were kept in the animal house in the College of Medicine under controlled conditions of a 12 hour light / 12 hour dark cycle in a room temperature of 25 C°.

The rats were divided into two groups. The first groups included 18 rats which received standard diet throughout the experimental period and were subdivided into three subgroups each of 6 rats. The first subgroup served as a control. The second subgroup received a daily single dose of omega-3 (15mg/kg) orally (PO). The third subgroup received a daily double dose of omega-3 (30mg/kg) PO.

The second group included 30 rats and received an atherogenic diet (79% standard diet + 21% Butter fat) throughout the treatment period and served as hyperlipidemic rats. The hyperlipidemic model rats were subdivided into four subgroups, each group having six rats. The first subgroup served as a positive control. The second subgroup received daily single dose of omega-3 (15mg/kg) PO. The third subgroup received a daily double dose of omega-3 (30mg/kg) PO. The fourth subgroup received a daily single dose of gemfibrozil (3.5mg/kg) PO, and the fifth subgroup received a daily single dose of atorvastatin (2mg/kg) PO.

At the end of the treatment period, the animals were subjected to various biochemical parameters (biochemical and hematological parameters). The animals were deprived of food overnight, anesthetized using light chloroform and sacrificed by cervical decapitation. Blood samples were collected from the rats for determination of serum total cholesterol, triglycerides, high density lipoprotein-C and low density lipoprotein-C, besides some of hematological parameters (HB, RBC, HTC, and MCH).

Statistical analysis

All data are expressed as means± standard error means (M±SEM) and statistical analysis was carried out using statistically available software (SPSS Version 11.5). Data analysis was made using one-way analysis of variance (ANOVA). The comparison among groups was done using Duncan test. $P<0.05$ was considered as statistical significance.

Results

Effects of omega-3 on lipid profiles

Daily administration of omega-3 (30mg/kg) induced a significant reduction in the level of TG in normal rats. The level of triglyceride of normal rats also decreased by (15mg/kg) of omega-3 but the result turned out to be statistically non-significant (Table 1 - next page).

Both doses of omega-3 (15mg/kg) and (30mg/kg) have the same significant efficacy in reducing the level of both TC and LDL-C of the normal rats, whereas they have no significant effects on the level of HDL-C of normal rats as shown in Table 1.

Effects of omega-3 on lipid profiles of hyperlipidemic rats

There was a marked increase in the level of serum triglyceride and TC and LDL-C in the animals treated with atherogenic diet compared to the control group indicating the induction of hyperlipidemia as shown in Table 2 (next page).

Different letters indicate the significance of the result ($P<0.05$).

Table 1: Effect of different doses of omega-3 (15mg/kg) and (30mg/kg) on the lipid profile of normal rats (n=18)

Parameters	Control	Omega-3 (15mg/kg)	Omega-3 (30mg/kg)
TG mg/100ml	67.25±14.45	44.08±2.55	27.26±2.349 *
TC mg/100ml	58.31±9.70	23.88±1.55 *	24.19±3.78 *
HDL-C mg/100mL	32.96±6.002	24.33±1.38	25.21±2.39
LDL-C mg/100mL	6.51±1.71	2.31±0.25 *	2.76±0.65 *

* (P<0.05) when compared to control group

Table 2: Effect of different doses of omega-3, gemfibrozile and atorvastatin on the lipid profile of hyperlipidemic rats (n=36)

Parameter	Control	Hyperlipidemic rats model	Omega -3 15mg/kg	Omega -3 30mg/kg	Gemfibrozile 3.5mg/kg	Atorvastatin 2 mg/kg
TG mg/100ml	57.25±17.45 a	174.83±53.86 b	33.78±2.34 a	28.83±3.55 a	65.24±9.63 a	65.93±9.31 a
Cholesterol mg/100ml	58.31±9.70 a	104.33±23.91 b	41.006±5.81 a	35.79±3.85 a	68.29±6.04 a	46.51±5.38 a
HDL-C mg/100ML	32.96±6.002 a	32.66±5.77 a	35.08±3.02 a	28.81±2.42 a	70.08±5.96 c	48.02±4.45 b
LDL-C mg/100ML	6.51±1.71 a	21.50±12.62 b	4.4±0.73 a	4.5±0.54 a	11.80±1.95 a	5.81±0.51 a

Different letters indicate the significance of the result (P<0.05).

Table 3: Effect of different doses of omega-3 on the haematological parameters of normal rats

Parameters	Control	Omega-3(15mg/kg)	Omega-3(mg/kg)
HB g/dl	13.1000±0.7895 a	15.7333±0.29515 b	15.6833±0.25221 b
RBC 10^12/ µl	6.5650±0.38125 a	7.2250±0.07873 b	7.4967±0.10834 b
HTC %	37.3333±2.54659 a	41.2000±0.86323 a	41.0167±0.96243 a
MCH pg/L	19.9833±0.44827 a	21.3417±0.19080 b	20.8333±0.21705 b

Table 4: Effects of different doses of omega-3 on the haematological profiles of hyperlipidemic rats

Parameter	Control	Hyperlipidemic rats model	Omega -3 (15mg/kg)	Omega-3(30mg/kg)
HB g/dl	13.1000±0.7895 a	10.9667±0.82610 a	15.1333±0.67856 b	15.2833±0.40118 b
RBC10^12/ µl	6.5650±0.38125 ab	5.9800±0.51046 a	7.1683±0.26196 ab	7.5583±0.18718 b
HTC%	37.3333±2.54659 a	32.4833±2.82683 a	41.0333±2.05340 b	41.5500±1.28705 b
MCH pg/L	19.9833±0.44827 b	18.5000±0.54894 a	21.1000±0.45092 b	20.2167±0.15366 b

Compared to the hyperlipidemic rat model both doses of omega-3 (15mg/kg) and (30mg/kg) produced significant reduction in the level of TG. Moreover the same doses of omega-3 could decrease the level of TC and LDL-C hyperlipidemic rats significantly. Compared to the control group no significant changes appeared in the level of HDL in the treated and non-treated hyperlipidemic rats (Table 2).

Effects of omega-3 on some haematological parameters

Both doses of omega-3 significantly increased the level of HB, RBC and MCH of control rats, while the same doses of omega 3 induced a non-significant rise in the level of HTC as shown in Table 3.

Rats fed with atherogenic diet for thirty days displayed non-significant reduction in the levels of HB, RBC and HTC, whereas it significantly reduced MCH compared to the control group. Both doses of omega-3 (15mg/kg) and (30mg/kg) significantly increased the level of HB, RBC and HTC compared with both normal and hyperlipidemic groups as shown in Table 4.

Compared to the control group both doses of omega-3 showed no significant changes in the level of MCH. However there was a significant difference between the effects of omega-3 with that of hyperlipidemic rats as shown in Table 4.

Effects of gemfibrozil on lipid profiles of hyperlipidemic rats:

Compared to the hyperlipidemic rat model gemfibrozil produced significant reduction in the level of TG, TC and LDL-C (Table 2).

No significant differences were found between the effects of both doses omega-3 and gemfibrozil on TG, total cholesterol and LDL of hyperlipidemic rats. However gemfibrozil unlike omega-3 significantly increased the level of HDL-C as shown in Table 2.

Effects of atorvastatin on lipid profiles of hyperlipidemic rats:

Compared to the hyperlipidemic rat model atorvastatin produced significant reduction in the level of TG, total cholesterol and LDL (Table 2).

No significant differences were found between the effects of both doses omega-3 and atorvastatin on TG, total cholesterol and LDL of hyperlipidemic rats however atorvastatin could significantly increase the level of HDL as shown in Table 2.

Discussion

According to the lipid hypothesis, abnormally high cholesterol levels (hypercholesterolemia), or more correctly, higher concentrations of LDL-C and lower concentrations of functional HDL-C are strongly associated with cardiovascular disease because these promote atheroma development in arteries (atherosclerosis). This disease process leads to myocardial infarction (heart attack), stroke and peripheral vascular disease. Since higher blood concentrations of LDL-C, especially the smaller and denser LDL particles, contribute to this process, they are often termed "bad cholesterol" because they have been linked to atheroma formation, while high concentrations of functional HDL-C, which can remove cholesterol from cells and atheroma, offers protection (8).

Concomitant elevation of circulating levels of triglyceride-rich VLDL and cholesterol-rich LDL is recognized as being associated with an increased risk of premature coronary artery disease (2) and is characteristic of subjects who exhibit a lipid phenotype typical of combined hyperlipidemia (4).

In the present study, serum triglycerides were significantly reduced in hyperlipidemic and normal rats treated with omega-3 at the dose of (15mg/kg) for a single dose and (30mg/kg) for a double dose after 4 weeks of treatment. This result is in agreement with another study by Harris et al (1983) who found that omega-3 significantly reduced serum triglycerides in hypertriglyceridemic patients by 25 % to 35 % after 12 weeks of therapy (9). Similar findings were reported by Sanders and Hochland (1983), Negakawa et al. (1983) and Zucker et al. (1988) (10, 11, 12) who found that fish oil

(< 20 g/d) induced a marked decrease in triglyceride concentration in hyperlipidemic patients.

This antitriglyceridemic effect of omega-3 on hyperlipidemic rats is in consensus with Simopoulos (1991) and Thomas et al. (2000) who observed that triglyceride concentration was reduced considerably by omega-3 in patients with hypertriglyceridemia (13, 14).

The mechanism responsible for the triglyceride-lowering effect of omega-3 is poorly defined. In theory it could be related to decreased VLDL-C production (presumably secondary to decreased availability of hepatic free cholesterol for particle assembly), increased clearance of VLDL-C through the LDL receptor (or other lipoprotein receptors), increased delipidation of VLDL particles via LPL, or a combination of the above mechanisms (15).

In this study, the level of total cholesterol was significantly reduced in hyperlipidemic rats treated with both doses of omega-3 after 4 weeks of treatment. This finding is in agreement with Kobatake et al. (1984) who observed that omega-3 significantly reduced serum total cholesterol after 20 days of therapy in hyperlipidemic subjects (16). Whereas Harris (1997) found that a large dose of omega-3 (4 g per day) has no significant effect on the level of total cholesterol in hyperlipidemic subjects after 2 weeks of treatment so this difference might be due to the short term treatment with omega-3 (17).

In the present study, hyperlipidemic rats treated with omega-3 at the doses of (15mg/kg) and (30mg/kg) showed no significant increase in the level of HDL after 4 weeks of treatment. This result is incompatible with another study by (Mori 2000) who found that HDL-C concentration was increased significantly in hyperlipidemic subjects (18). Furthermore Harris (1997) concluded that 4 g per day of omega-3 increased HDL-C cholesterol levels by 1 to 3 percent after 4 weeks of treatment. This effect of omega-3 could be due to the fact that omega-3 significantly reduced total cholesterol in hyperlipidemic and normal rats (19).

LDL-C was significantly reduced in hyperlipidemic rats treated with both doses of omega-3 after 4 weeks of treatment. This is incompatible with the observation of Mori (2000) who observed that there was usually no significant changes in LDL-cholesterol concentration associated with omega-3 administration in hyperlipidemic subjects (18). On the contrary, especially with high doses of omega-3 FAs used in the treatment of hypertriglyceridemia, LDL levels may rise by 10 %, this effect being even more pronounced in patients with extreme TG elevations at baseline (17. 19).

In another investigation Sanders and Hochland (1983) reported that there were modest decreases in LDL concentration for the normal subjects who received (< 20 g/d) of fish oil after 4 weeks of treatment (10), similar findings were reported by Negakawa et al (1983) and Zucker et al (1988) (11, 12).

In the present study, HB and RBC were noticeably increased in hyperlipidemic rats treated with omega-3 at the dose of (15mg/kg) and (30mg/kg). These results are compatible with another study by Abbas et al (2009) who found that administration of omega-3 was associated with an increase in the levels of HB and RBC in sucrose treated rats (20).

In this study, HTC was significantly increased in hyperlipidemic rats treated with omega-3. This result is incompatible with another study by Ghaderpanahi et al (2010) who found that administration of 1g of fish oil in elderly subjects has no significant effects on the level of HTC (21).

In this research, MCH was increased significantly in hyperlipidemic rats treated with omega-3 (15mg/kg) and (30mg/kg). This result was replicated in another study by Nwabueze et al (2011) who found that (MCH) was significantly ($P<0.05$) higher in Heterobranchus bidorsalis fish fed on feeds containing 2000mg and 1000mg omega-3 than in control fish (22).

Gemfibrozil treatment produced a significant reduction in the serum triglyceride of hyperlipidemic rats similar to that of omega-3. This result was quite similar to that reported by Keijiro Saku et al (1985) who found that gemfibrozil significantly reduced serum triglycerides by 46 % after 12 weeks of therapy in hyperlipidemic patients (23).

Moreover it is accordance with the result of Irish and Thompson (1996) who detected that gemfibrozil lowered serum triglycerides by 44% after 6 weeks of therapy in hyperlipidemic patients (2).

The result of this study showed that total cholesterol was significantly reduced in hyperlipidemic rats treated with gemfibrozil after 4 weeks of treatment. This result is in agreement with another study by Keijiro Saku et al (1985) who found that gemfibrozil significantly reduced total cholesterol by 47% after 12 weeks of therapy in hyperlipidemic patients (23).

In this study, HDL was significantly increased in hyperlipidemic rats treated with gemfibrozil after 4 weeks of treatment. This result is in consensus with studies by Irish and Thompson (1996) who concluded that gemfibrozil significantly increased HDL by 36% and 31% respectively after 12 weeks of therapy in hyperlipidemic patients (2, 24).

In the present study serum LDL was reduced in hyperlipidemic rats treated with gemfibrozil after 4 weeks of treatment. This result is in agreement with another study by Manninen et al (1982) who found that gemfibrozil significantly reduced LDL by 23% after 12 weeks of therapy in hyperlipidemic patients (25), whereas Irish and Thompson (1996) reported that gemfibrozil has no significant effect on the level of LDL in hyperlipidemic patients even after 12 weeks of treatment. Therefore this result is incompatible with the finding of this study (24).

In this study, serum TG was significantly reduced in hyperlipidemic rats treated with atorvastatin after 4 weeks of treatment. This result is in agreement with studies of Athyros et al (2002) and Branchi et al (1999) who found that atorvastatin 20 mg daily dose significantly reduced TG by 31%, 20 % respectively in hyperlipidemic patients after 2 months of therapy (26, 27). In accordance with reports of Stein et al (1998) the effect of atorvastatin on serum TG was largely dependent on the baseline serum triglyceride level and, in patients with low serum triglyceride; there was little if any hypotriglyceridemic response (28). The relationship of the hypotriglyceridemic activity to the baseline serum triglyceride level may explain why some authors found only small effects of statins on serum triglycerides, whereas others reported greater lowering effects.

The differences in the hypotriglyceridemic response among the studies are likely to be due to differences in the patient populations. It is generally accepted that HMG CoA reductase does not play a direct role in the repletion of TG levels. Atorvastatin administration, however, produces marked reduction in TG levels in hyperlipidemic patients (29).

In the present study, atorvastatin as gemfibrozil and omega-3 significantly reduced the level of total cholesterol in hyperlipidemic rats after 4 weeks of treatment. These results are in agreement with results of studies conducted by Nawrocki et al (1995) and Marian et al (2006) who found that atorvastatin reduced plasma cholesterol up to 45% in patients with primary hypercholesterolemia (30, 31).

In this research, LDL-C was significantly reduced in hyperlipidemic rats treated with atorvastatin after 4 weeks of treatment. This is in accordance with the observations of Hing-Chung et al (2006) who found that atorvastatin 20 mg daily for 12 weeks of treatment significantly decreased LDL-C in comparison with 10 and 40 mg of atorvastatin in hyperlipidemic patients (32).

This reduction of serum cholesterol could be due to inhibition of HMG-CoA reductase which catalyzes the conversion of HMG-CoA to mevalonate which decreases the cholesterol synthesis (33, 34).

In the present study, HDL-C was significantly increased in hyperlipidemic rats treated with atorvastatin after 4 weeks of treatment. This result was quite similar to that reported by Jeevan et al, (2008) who found that atorvastatin significantly increased HDL-C for 12 weeks of treatment (35).

The mechanism underlying the increase in HDL-C levels observed during statin therapy is poorly understood. Available evidence suggested that increase in HDL-C with statin therapy results from a combination of increased expression of apoA-I and reduced HDL remodeling as a consequence of lowering triglyceride levels (35, 36).

There is also evidence that increases in HDL-C during statin therapy may be related to the decrease in the activity of cholesteryl ester transfer protein, likely due to depletion of levels of very low-density lipoprotein and LDL particles (37).

No significant differences were found between the effects of both doses of omega-3 with gemfibrozil and atorvastatin on TG, total cholesterol and LDL-C of hyperlipidemic rats, however gemfibrozil and atorvastatin unlike omega-3, significantly increased the level of HDL-C.

Conclusion

1- Omega-3 was efficient in reducing serum TC, TG and LDL-C. However it was not effective in significantly altering serum HDL-C in hyperlipidemic rats.

2- Omega-3 was effective in increasing the levels of HB, RBC, HTC, and MCH in hyperlipidemic rats.

3- No significant differences were found between the effects of both doses of omega-3 and gemfibrozile or atorvastatin on TG, TC and LDL-C of hyperlipidemic rats. In contrast to omega-3, gemfibrozile and atorvastatin induced a significant rise in the level of HDL-C.

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