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Mob: +92 300 3008585, Fax: +92 41 8815544
E-mail: editorpjn@gmail.com

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Metabolic and Histological Effects of Different Polyunsaturated Fat Types in the Diet: Omega-3 and Omega-6

Maha Hasan Daghestani[1], Promy Virk[1] and Ayman EL-Meghawry EL-Kenawy[2,3]
[1]Department of Zoology, King Saud University,
Women Students-Medical Studies and Sciences Section, Riyadh, Kingdom of Saudi Arabia
[2]College of Medicine, Taif University, Kingdom of Saudi Arabia
[3]Department of Molecular Biology, Genetic Engineering and Biotechnology Institute,
Menofiya University, Egypt

Abstract: The beneficial effects of polyunsaturated fats and omega 3 supplements in human and animal nutrition have been widely discussed and established though clinical and experimental studies. In this study the High-Fat (HF) diet rodent models were used to evaluate the effects high doses of two polyunsaturated fats omega-3 and omega-6 on metabolic parameters and histology of liver and kidney. Male and female Wistar rats were fed High-Fat (HF) diets containing Omega-3 fish oil supplements (HF-F) and Omega-6 corn oil (HF-C) at a level that was equivalent to three times the maximum safe daily dosage and the control group was fed with regular laboratory chow. Body weight and plasma parameters of glucose, cholesterol and triglycerides were measured after a 8 week diet course. Rats fed both the high fat oil based diets (HF-F, HF-C) reported a significantly higher body weight gain than the control group. Plasma triglyceride levels were significantly higher in the high fat diets being highest in the fish oil based diet. Both the high fat diets fed animals (HF-F, HF-C) showed pronounced hepatic micro vesicular steaosis and renal interstitial inflammation in comparison with the control in the histological studies. Thus this study demonstrated that high fat diets with polyunsaturated fats including omega-3 rich fish oil could induce dyslipidemia and obesity in rodent models reflecting signs of metabolic syndrome in the humans.

Key words: High-fat diet, obesity, omega 3, omega-6, corn oil, fish oil

INTRODUCTION

The coincidence of obesity, insulin resistance, hypertension and dyslipidemia commonly referred to as the 'metabolic syndrome' is a condition that affects approximately 20-40% of the world population in the industrialized nations. Its prevalence is expected to rise further in the coming years (Laaksonen *et al*., 2004). Both nutrition and physical activity are major factors contributing to its manifestation. A High-Fat (HF) diet is known to induce obesity in animals and humans. Several rodent models have been used to study the pathogenesis of the metabolic syndrome. It has been evident from the past literature that high fat feeding indicates an elevated feeding efficiency even without a hypercaloric intake (Oscai *et al*., 1984). Analysing the specific fat type, animal derived fats such as lard and beef tallow and also plant fats rich in unsaturated omega-9 and omega-6 fatty acids like corn oil induce the obese phenotype, diets containing a large fraction of marine omega-3 polyunsaturated fatty acids however do not. This cannot be generalized as the results in such HF fed rodent studies have been variable owing to a difference in different laboratories due to animal strain and diet variations. Other research findings have documented that not only quantity, but also fat type used in the diets affects the amount of weight gain as it effects and regulates the body adiposity (Jang *et al*., 2003).

The omega fatty acids are Polyunsaturated Fats (PUFA) and Omega 6 and 3 are two of the forty-nine know essential nutrients. Available data on the effects of different types of PUFAs on body adiposity are controversial. Alterations in dietary fat composition can influence metabolic functions and lead to changes in body weight and/or composition. Although the consumption of omega-3 Polyunsaturated Fatty Acids (PUFAs) has been associated with beneficial health effects various epidemiologic studies have shown an inverse relation between the incidence of cardiovascular disease and the consumption of fish oil (Mori and Beilin, 2001; Hooper *et al*., 2001). Omega-6 fats are the most commonly eaten polyunsaturated Fatty Acids (PUFA) in westernized countries. The top three sources are corn oil, soybean oil and cottonseed oil. Polyunsaturated fats like omega-3 and omega 6 have been used less frequently in high fat diets keeping in mind the current nutrition recommendations of using unsaturated fats in the diet specifically the omega-3 based fish oil. Excessive amounts of omega-6 Polyunsaturated Fatty

Corresponding Author: Promy Virk, Department of Zoology, King Saud University, Women Students-Medical Studies and Sciences Section, College of Medicine and Medical Science, Saudi Arabia

Acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's Western diets, promote the pathogenesis of many diseases under the metabolic syndrome which include cardiovascular disease, cancer and inflammatory and autoimmune diseases. However increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects on the same (Simopoulos, 2008). Also previous animal studies on modelling obesity have shown that animals when fed similar amounts of fat, those fed diets containing fish oil did not gain as much weight as those fed diets with more saturated fats (Wang *et al*., 2002). Many high-fat diets used in laboratory animal research contain more saturated fat such as lard, beef tallow, or coconut oil and these diets are quite capable of inducing obesity insusceptible strains (Buettner *et al*., 2006).

The main objective of the present study was to evaluate the effects of high-dose consumption of polyunsaturated fats (omega-3 and omega-6) in male and female Wistar rats. A direct comparison of high-fat diets based on the main polyunsaturated fatty acid subtypes (omega-3 and Omega-6) and the laboratory chow has been made with respect to morphometric and physiologic parameters as well as histological changes in the liver and kidney.

MATERIALS AND METHODS

Animals: 60 Wistar (both male and female) rats were obtained from the animal house facility of the Department of Zoology, King Saud University, Riyadh. The animals were 2 months old at the start of the experiment and were housed in conventional wire-mesh cages at a room temperature regulated at 21±1°C, humidity at 45-50% and light/dark cycles (12 hrs). Environmental conditions (humidity, heat, light, ventilation etc.) were kept constant during the period of the study.

Experimental design: The animals were divided into three groups, with 20 rats (10 of each sex) and each experimental group, received different diet compositions. The control group was fed standard laboratory chow consisting of 24% protein, 3.62% fat, 7% cellulose, 10% ash and 12% water. The other two experimental groups were named High-Fat Corn (HF-C) rats receiving corn oil and High-Fat Fish (HF-F) rats receiving a fish oil supplement of omega-3. Corn oil and omega 3 oil were mixed with the chow in different diets to obtain a homogeneous mixture. Each oil group was fed *ad libitum* a chow containing 60 g oil/100 g of chow, for a period of 8 weeks. The mixtures were prepared daily and unused chow was discarded within a period of 24 hrs in order to prevent spontaneous peroxidation. Oils were reported to have no significant peroxide content at room temperature for 24 hrs (Klaus *et al*., 1995). Animals were weighed before and after the study period. At the end of the in-life phase of the study, the animals were anaesthetized with CO_2 and humanely killed by exsanguinations after an overnight fast (16 hrs). Venous blood was drawn from the heart into red top tubes and serum was prepared and stored at -20°C for the determination of triglycerides, cholesterol and glucose levels.

Biochemical assays: Plasma glucose, triglycerides and cholesterol levels were analyzed by commercially available kits using ReflotronAssays(Roche).

Histology: Liver and kidney tissue samples were fixed in 10% formaldehyde before embedding in paraffin, sectioned at a thickness of 3-5 µm. The sections were then stained with haematoxylin and eosin (H&E) for microscopic examination.

Statistical methods: To obtain representative data, all experiments were performed on 10 animals. Data are presented as means±SD. One-way ANOVA was used. Group differences were analyzed with an unpaired Student's t-test. Numerical data were correlated with SPSS 16.0 statistics software (Chicago, IL, USA). The significance level was set to $p<0.05$.

RESULTS

Weight gain: Initial body weight was the same in all groups, with a combined mean of 116 g for both sexes. The weight gain after 8 weeks is shown in Fig. 1 for all diet groups. The HF-C rats showed the highest weight gain of all groups which was 136.6±0.6 g (Table 1) There was a highly significant difference in the weight gain observed among the three groups, HF-F, HF-C and the control group ($p\leq0.05$) (Fig. 1). Both the oil groups showed a significantly higher weight gain as compared to the control group. The mean difference in the weight gain between rats in the HF-F and control group being 93.65 g and those in the HF-C and control being 117.1 g (Table 2). The mean weight gain however showed a gender based difference in all the three groups being significantly higher in the males as compared to females. The highest value was observed in the male rats from the HF-F group (190.4 g) which was highly significant to that of the females (82.7 g) ($p\leq0.001$) (Fig. 2).

Table 1: Basal characteristics of the dietary groups after 8 weeks. The values represent the means±SD of three independent experiments

	Omega-3 (HF-F)	Corn oil (HF-C)	Control
Weight gain (g)	136.55±14.5	160±5.0	42.9±4.1
Plasma characteristics			
Glucose (mmol/l)	6.6±0.14	6.3±0.13	5.5±0.09
Triglycerides (mmol/l)	1.4±0.06	1.2±0.02	1.0±0.01
Cholesterol (mmol/l)	2.8±0.05	2.9±0.04	2.8±0.05

Table 2: Multiple comparisons of Basal characteristics within the dietary groups

Dependent variable	(I) Group	(J) Group	Mean difference (I-J)	Std. Error
Triglyceride mmol/l	HF-F	HF-C	0.201***	0.051043
	HF-F	Control	0.39***	0.051043
	HF-C	Control	0.189**	0.051043
Cholesterol mmol/l	HF-F	HF-C	-0.0245	0.065126
	HF-F	Control	0.035	0.065126
	HF-C	Control	0.0595	0.065126
Glucose mmole/l	HF-F	HF-C	0.133421	0.177396
	HF-F	Control	1.0849210***	0.177396
	HF-C	Control	0.95150***	0.175107
Weight gain	HF-F	HF-C	-23.45	12.91597
	HF-F	Control	93.65***	12.91597
	HF-C	Control	117.1***	12.91597

*Significant at the 0.05 level; **Significant at the 0.01 level; ***Significant at the 0.001 level

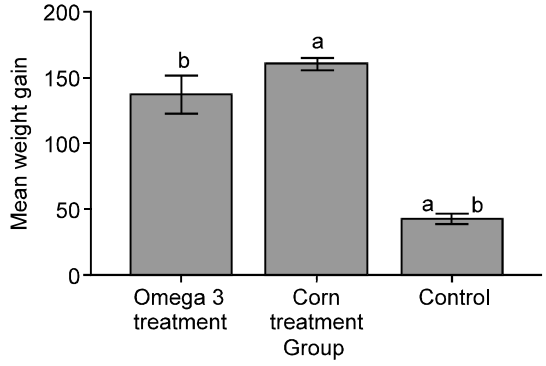

Fig. 1: Effects of dietary fat on weight gain in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means±standard error of the mean. Bars with different letters are significantly different from one another at p≤0.05 as determined by t-test. Error bars: +/- 1 SE

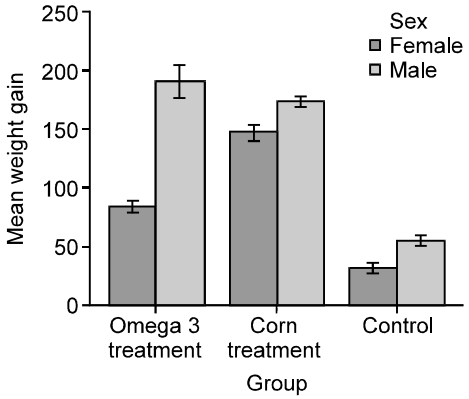

Fig. 2: A gender based comparison on the effects of dietary fat on weight gain in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means±standard error of the mean. Error bars: +/- 1 SE

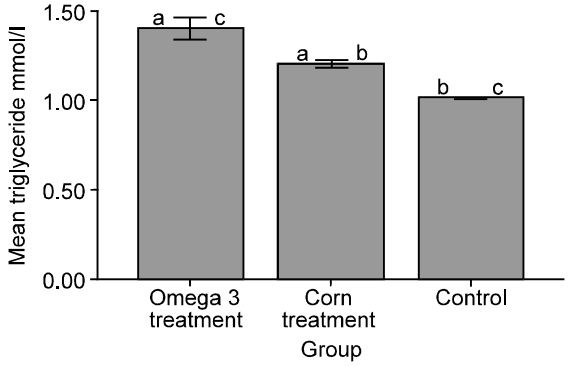

Fig. 3: Effects of dietary fat on plasma triglycerides in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means± standard error of the mean. Bars with different letters are significantly different from one another at p≤0.05 as determined by t-test. Error bars: +/- 1 SE

Plasma characteristics: The plasma characteristics are given in detail in Table 1. Plasma triglycerides were elevated in rats of both the oil groups. Highest mean value was observed in rats from the HF-F group (1.4035 mmol/l) which was highly significant over the HF-C and control groups (p≤0.001) (Fig. 3). There was no statistically significant gender based difference observed in the mean values of plasma triglycerides in rats from the HF-C and Control group. However, the males from the HF-F group showed a significantly higher value than the females (p≤0.01) (Fig. 4). The glucose levels were elevated in the rats from the HF-F and HF-C groups with the highest mean value recorded for the HF-F group, 6.57 mmol/l. The glucose values in the rats of the two oil groups were highly significant in comparison to the control group (p≤0.001) (Fig. 5). The mean values of plasma glucose did not reach a statistically significant difference between the males and females in all three experimental groups (Fig. 6). However; there was no statistically significant difference

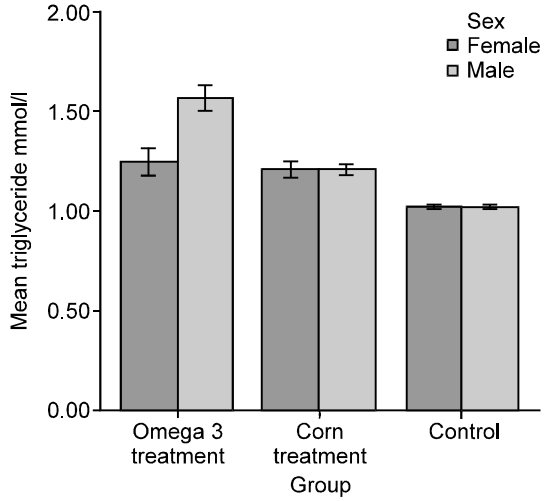

Fig. 4: A gender based comparison on the effects of dietary fat on plasma triglycerides in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means±standard error of the mean. Error bars: +/- 1 SE

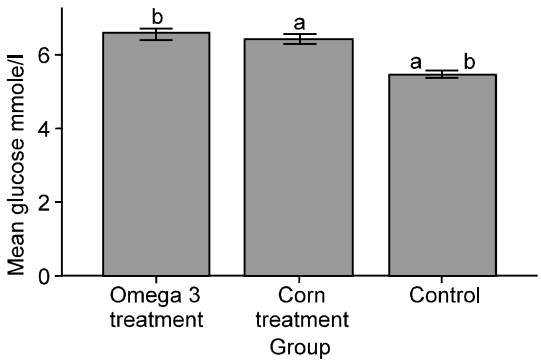

Fig. 5: Effects of dietary fat on plasma glucose in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means± standard error of the mean. Bars with different letters are significantly different from one another at p≤0.05 as determined by t-test. Error bars: +/- 1 SE

between the values of the two oil groups. The mean values of cholesterol in the three groups (HF-F, HF-C and Control) did not reach any statistical significance, being comparable (Fig. 7). The mean values of cholesterol also did not reach a statistically significant difference between the males and females in all three experimental groups (Fig. 8).

Histology

Liver: The histological examination (hematoxylin-eosin staining) showed mainly pronounced micro-

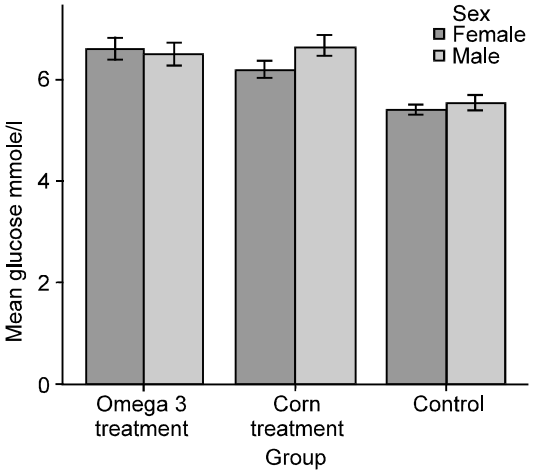

Fig. 6: A gender based comparison on the effects of dietary fat on plasma glucose in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means±standard error of the mean. Error bars: +/- 1 SE

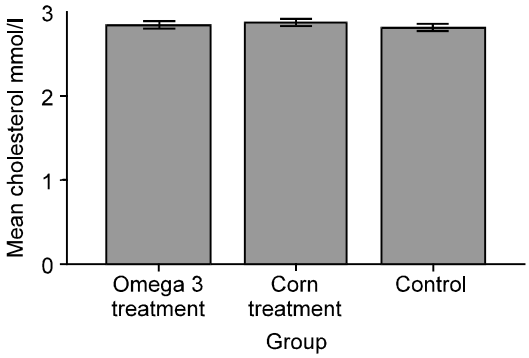

Fig. 7: Effects of dietary fat on plasma cholesterol in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means± standard error of the mean. Bars with different letters are significantly different from one another at p≤0.05 as determined by t-test. Error bars: +/- 1 SE

vacuolar steatosis and hyperplasia of Kupffer cells in the HF-F and HF-C fed rat livers in comparison with the control (Fig. 9 A, C, E). No signs of inflammation or fibrosis were detected in any group.

Kidney: Mild renal interstitial inflammation, albuminous cast deposition in lumen of the tubules and narrowing of the lumen tubules in addition to thickness of glomeruli capillaries was observed in the sections of kidneys hematoxylin-eosin staining) in the rats fed high fat diets (HF-C and HF-F) in comparison to the control, being more pronounced in the HF-C group (Fig. 9 B, D, F).

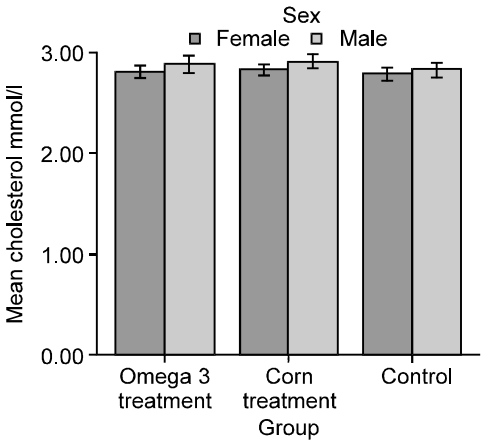

Fig. 8: A gender based comparison on the effects of dietary fat on plasma cholesterol in rats fed high fat and control diet during 8 weeks. Omega-3 treatment (HF-F), Corn treatment (HF-C) and Control. Values are means±standard error of the mean. Error bars: +/- 1 SE

Aorta: No histological abnormalities was noticeable in the wall of the aorta.

DISCUSSION

Feeding animal-or plant-derived fats for several weeks leads to hyperglycemia, hyperinsulinemia and hypertriglyceridemia resembling human obesity and insulin resistance in susceptible animals. It has been observed that the disorders achieved by high-fat feeding simulate the human metabolic syndrome (Aguila and Mandarim-de-Lacerda, 2003; Woods *et al*., 2003; Buettner *et al*., 2006) However, as evident from the literature the term 'high-fat diet' includes fats with different fatty acid composition which explains the variability in the results reported. Observations made in our study on the animal's phenotype and the parameters of body weight gain, plasma triglyceride, cholesterol and glucose levels, show that both the High-Fat (HF) oil based diets led to pronounced manifestations of obesity and insulin resistance. The animals in these groups gained more weight, had higher plasma triglyceride and glucose levels although the plasma cholesterol level was comparable to the control group fed a standard rat chow. These results are quite similar to the observations recorded in previous studies on the effects of high-fat-diet on Male Wistar rats. However the fat type used in these high-fat diets was mainly saturated fats (Buettner *et al*., 2000, 2004; Briaud *et al*., 2002; Gustafson *et al*., 2002; Yaspelkis *et al*., 2001) including a lard-based diet (Buettner *et al*., 2006). Available data on the effects of different types of PUFA on body adiposity are variable and controversial. Types of PUFA used, quantity of fat in the diets and time period of study are just a few of the factors that may affect the results. Diets high in omega-3 PUFAs such as those contained in fish oils, tend to reduce weight gain as well as fat accumulation relative to other types of fats/oils (Jen *et al*., 1989; Hill *et al*., 1993; Feskens *et al*., 1991; Hun *et al*., 1999) One of the possible mechanisms responsible for the differential effects of fatty acids on weight gain may be related to the rates of oxidation. Leyton *et al*. (1987) reported that rats fed fatty acids of different chain lengths and degrees of saturation showed variable oxidation rates, with saturated fatty acids showing lower oxidation rates than PUFAs. For PUFAs, linolenic acid (high in fish oil) is oxidized more efficiently than that of linoleic acid (DeLany *et al*., 2000). However, in our study we observed a higher weight gain in rats fed the HF diets containing PUFAs as compared to the control. Similar results were reported (Pellizzon *et al*., 2002; Gai´va *et al*., 2003) in Wistar rats fed with high fat diets containing fish oil, soyabean oil and palm oil. These rats recorded a higher body weight gain as compared to the control fed a standard chow. This has been attributed to the fact that the protective effect of fish oil is no longer effective when it was fed to animals for a long period of time and in high concentration.

It is well established that PUFAs are preferentially used for oxidation to produce energy (Simi *et al*., 1991) which explains a reduction in blood triglyceride levels in rats fed with PUFAs such as soybean oil and olive oil. It could also explain the fact that fatty acids in fish oil are known to reduce triglyceride synthesis and increase fatty acid oxidation in the liver relative to diets high in SFAs or n-6 PUFAs (Ide *et al*., 2000; Ikeda *et al*., 1998). However the triglyceride results in our study are complicated but interesting as the plasma triglyceride was highest in the rats fed the HF-F diet. Hepatic microvesicularsteaosis observed in rat fed HF-F diet could explain the dyslipidemia observed in these rats, which could be because of an impaired fat oxidation in the liver or an abnormal increase in the triglyceride synthesis. Hepatomegaly induced by fish oil has been consistently described in previous literature (Otto *et al*., 1991; Yaqoob *et al*., 1995; Nakatani *et al*., 2003) but the extent of hepatic fat deposition in fish oil-fed rats remains controversial. Some studies report an increase (Otto *et al*., 1991; Yaqoob *et al*., 1995). It has reported that an enrichment of the diet with omega-3 PUFAs produces hypolipidemia but may change liver metabolism in favor of lipid deposition (Gai´va *et al*., 2003). However a lowered liver lipid content is also reported in rats fed PUFAs (Levy *et al*., 2004). The variability of the results reflects either differences induced by the specific dietary source of fat or on the rat strain used. The effects of HF diets on cholesterol levels are inconsistent and definite statements about the putative induction of hypercholesterolemia by a pure HF diet, i.e., without addition of cholesterol, do not seem possible from the literature at present. The only exception is that it is clearly established that fish oil-based diets show a hypocholesterolemic effect (Garg *et al*., 1989; Otto *et al*., 1991; Luo *et al*., 1996; Kim *et al*., 1999). However in our

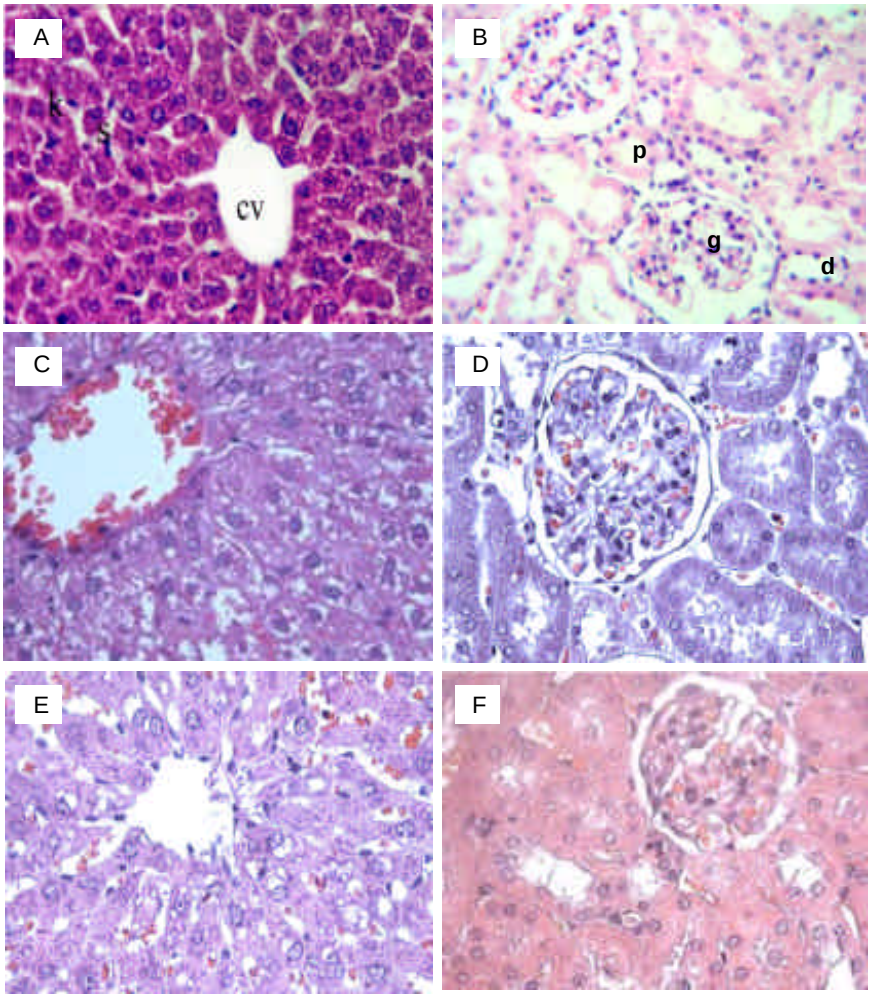

Fig. 9: Photomicrographs of liver and kidney sections. (A and B) control group showing normal architecture, central vein (CV), hepatocytes(H), blood sinusoids (S) and Kupffer cells (K), distal tubule (d), proximal tubule (p), glomerulus (g); (C and D) omega 3 group showing mild and hyperplasia of Kupffer cells and micro vacuolar and macro vacuolar steatosis in liver sections and mild renal interstitial inflammation, in addition to thickness of glomeruli capillaries in kidney section; (E and F) omega 6 group showing micro vacuolar and macro vacuolar steatosis in liver sections and albuminous cast deposition in lumen of the tubules and narrowing of the lumen tubules, in addition to thickness of glomeruli capillaries in kidney section (H&E 400x)

studies there was no hypocholesterolemia observed in rats fed fish oil based diet, HF-F. The cholesterol level was the same in all dietary groups. The hepatic steaosis observed causes a glucose intolerance that explains the moderate increase in blood glucose level in rats fed with the HF diets. Holness *et al*. (2003) demonstrated that omega-3 fatty acids decreased insulin and increased glucose concentration in Wister rats. Thus our results on blood glucose level are not surprising since the effects of fish oil on insulin and glucose levels have been inconsistent in the past also. It has been demonstrated recently that a high dietary fat intake using soybean oil as the fat source increases early kidney disease progression (Lu *et al*., 2003). Other studies reported that feeding flaxseed, enriched in 18:3(n-3), ameliorates early renal disease progression in Han:SPRD-cyrats (Ogborn *et al*., 1999). Whether these beneficial effects of dietary (n-3) fatty acids inflax seeds also occur with fish oil, however, is not known. InDBA/2FG-pcy/pcymice, feeding fish oil containing 20:5(n-3)and 22:6(n-3) was beneficial in a short-term early feeding study (Yamaguchi *et al*., 1990) but proved to be detrimental in a survival study (Aukema *et al*., 1992). Our study did not report any beneficial effect of fish oil (omega-3) as pronounced renal interstitial inflammation was observed in both the PUFA rich high fat diets. Hyperlipidemia is a contributing factor in the progression of many forms of chronic renal disease (Polat *et al*., 1998) which could be

a possible reason as we did observe an elevated lipid level in rats fed PUFA rich high fat diets. Hyperlipidemia is believed to be followed by lipid accumulation in the renal mesangium with resulting injurious effects such as foam cell formation, cell proliferation, matrix formation and alteration.

A pronounced gender based difference has been observed in the weight gain being more in males from all the three diets. This is in consensus with the established fact that there are sex-associated differences in rat Brown Adipose Tissue (BAT) thermogenesis mediated by Uncoupling Protein 1 (UCP1) in response to diet-induced obesity and general sex differences in body weight gain and lipolytic activity of White Adipose Tissue (WAT) (Roca *et al*., 1999; Llado *et al*., 2000; Rodriguez *et al*., 2001) Sex hormones are important factors in determining fat distribution and accumulation and in regulating energy balance (Wade *et al*., 1985). Further studies would however elucidate the higher weight gain observed in male rats fed omega fats.

A high quality systematic review published in BMJ in 2006 draws attention to uncertainties about some of the health benefits attributed to omega 3 fats (Hooper *et al*., 2006). The review shows that the evidence for a reduction in cardiovascular events and mortality is less conclusive than we believed. In a clinical trial including 3114 men with stable angina the hypothesis that the main benefit of omega 3 fat was tested. Surprisingly the study showed excess of sudden and total cardiac deaths. The highest number being in participants taking fish oil capsules rather than eating oily fish. The results of our study do support this as the rats fed the fish oil supplement based diet showed marked effects of dyslipidemia and obesity comparable to the omega-6 rich corn oil high fat diet, which are factors contributing to cardiovascular diseases. Future studies are however needed to directly address how high fat omega-3 diets could simulate the human metabolic syndrome in rodent models, by using defined high fat diets rather than a chow based diet.

Conclusion: Keeping in view the phenotypical, metabolic and histological data we obtained it is clear that in both male and female Wistar rats, a high fish oil and corn oil intake does not protect from high fat induced metabolic changes. High PUFA consumption appears to be less deleterious in terms of insulin resistance and hypercholesterolemia but it is associated with prominent hepatic steatosis, renal interstitial inflammation, hypertriglyceridemia and obesity. Further studies are however mandatory to compare the effects of plant based sources of omega-3 fats and fish oil using defined diets in rodent model studies.

Competing interests: The authors declare that they have no competing interests.

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Abbreviations: HF = High fat, PUFA = Polyunsaturated Fatty Acids, SFA = Saturated Fatty Acids, HF-F = High fat Fish oil, HF-C = High fat Corn oil, g = grams, mmol/l = millimolar/litre.

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