

Dietary phospholipids, hepatic lipid metabolism and cardiovascular disease

Jeffrey S. Cohn, Elaine Wat, Alvin Kamili and Sally Tandy

Nutrition and Metabolism Group, Heart Research Institute, Sydney, Australia

Correspondence to Dr Jeffrey S. Cohn, Group Leader, Nutrition and Metabolism Group, Heart Research Institute, 114 Pyrmont Bridge Road, Camperdown, NSW 2050, Australia
Tel: +612 8208 8906; fax: +612 9565 5584;
e-mail: cohnj@hri.org.au

Current Opinion in Lipidology 2008, 19:257–262

Purpose of review

An increasing number of studies in experimental animals suggest that dietary phospholipids might be of benefit in the treatment of fatty liver disease. This raises the possibility that synthetic or naturally occurring phospholipid isolates could be used as hepatoprotective nutraceuticals or functional foods. The aim of the present article is to review published data describing the beneficial effects of dietary phospholipids on hepatic lipid metabolism and their potential to affect atherosclerosis and cardiovascular disease.

Recent findings

Consistent results have been obtained supporting the concept that phospholipid from various sources (i.e., soybean, safflower, egg and fish roe) can reduce liver lipid levels. The primary site of action for this effect appears to be in the intestinal lumen, where dietary phospholipids are able to interfere with neutral sterol absorption. Results have also been obtained suggesting that dietary phospholipids can stimulate bile acid and cholesterol secretion. Additional work suggests that dietary phospholipids can have a beneficial effect on plasma lipid and lipoprotein levels.

Summary

The concept of using naturally occurring compounds such as phospholipid to treat or prevent hepatic steatosis is very attractive. Controlled human trials are, however, required to verify the efficacy of this approach. It is also important that additional research be conducted to determine the extent to which certain phospholipids have the ability to increase plasma HDL levels and potentially affect the onset or development of cardiovascular disease.

Keywords

cholesterol, high-density lipoprotein, liver, phosphatidylcholine, steatosis, triglyceride

Curr Opin Lipidol 19:257–262
© 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins
0957-9672

Introduction

Increasing evidence suggests that lipid accumulation in the liver plays an important role in the pathogenesis of obesity, diabetes and cardiovascular disease [1]. In addition, fatty liver (i.e., hepatic steatosis) gives rise to more severe forms of nonalcoholic fatty liver disease (NAFLD), including steatohepatitis, fibrosis or hepatic cirrhosis [2]. NAFLD is an escalating health concern, and its prevalence is in the range of 15–30% in the general population. Its prevalence is as high as 70% in type 2 diabetic patients, in whom NAFLD is a risk factor for cardiovascular disease, independent of the metabolic syndrome and other classical risk factors [3^{*}]. There is thus considerable interest in nutritional and pharmacological agents that are able to reduce hepatic lipid accumulation. One approach that has considerable promise is the oral administration of phospholipid either as a nutraceutical or as a functional food. An increasing number of studies in experimental animals suggest that

either synthetic phospholipids or naturally occurring phospholipid isolates might be of significant benefit. The aim of the present article is to review studies that describe the beneficial effects of dietary phospholipid on hepatic lipid metabolism and their potential to affect atherosclerosis and cardiovascular disease.

Phospholipid intake and digestion in humans

The normal dietary intake of phospholipid is 2–8 g per day, which represents 1–10% of total daily fat intake. The most common phospholipid in the diet is phosphatidylcholine (i.e., lecithin). Dietary phosphatidylcholine is almost completely absorbed (>90%) by the human intestine, and rapidly appears in the phosphatidylcholine of plasma lipoproteins and red blood cells [4]. Other phospholipids, such as phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol are also ingested, but in much smaller amounts. Sphingomyelin, better classified as a sphingolipid, but still a phosphorus-containing

0957-9672 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

lipid, is ingested at a level of 0.3–0.4 g per day, being present in eggs, milk, meat and fish. Phosphatidylcholine in these foods usually contains palmitic, stearic, oleic, or linoleic acid. The fatty acid composition of phosphatidylcholine in the intestinal lumen is, however, different from dietary phosphatidylcholine, since the majority of luminal phosphatidylcholine is derived from the bile. The biliary pathway delivers approximately 12 g of phospholipid and 1.5 g of cholesterol to the intestinal lumen per day, which is at least four times more than that supplied by the diet.

Pancreatic phospholipase A2 (PLA2) is largely responsible for phosphatidylcholine hydrolysis, yielding fatty acid and lysophosphatidylcholine (lysoPC). Pancreatic PLA2 is secreted as an anionic zymogen and is activated in the small intestine by tryptic cleavage of an N-terminal heptapeptide. It has a molecular weight of approximately 14 kDa and requires calcium for activation and the presence of bile salts for its activity. As described in an excellent review [5[•]], dietary sphingomyelin is hydrolyzed by intestinal alkaline sphingomyelinase and neutral ceramidase to sphingosine, which is absorbed and converted to palmitic acid. Once absorbed by the intestinal epithelium, lysoPC is reacylated to form phosphatidylcholine or alternatively hydrolyzed to form glycerol-3-phosphorylcholine. Liberated fatty acids are used for triglyceride synthesis. This triglyceride, together with reacylated phosphatidylcholine, is then incorporated into chylomicrons for transport via the lymph into the blood circulation. It is possible that some dietary phospholipid is also incorporated directly into HDL by the intestine, based on evidence that human intestinal CaCo-2 cells secrete apoA-I-containing HDL-sized lipoproteins [6], fat feeding stimulates rat intestinal HDL production [7], and jejunal apoA-I synthesis can be regulated by dietary phosphatidylcholine in newborn swine [8]. Thus, either by direct or indirect means, a major proportion of dietary phosphatidylcholine finds its way quite rapidly into plasma HDL [4].

Hepatoprotective effects of dietary phospholipids

A number of informative studies by Lieber *et al.* (reviewed in [9,10]) have provided evidence that dilinoleoylphosphatidylcholine (DLPC), the major phospholipid species (43–50%) in polyenylphosphatidylcholine (PPC) extracted from soybeans, is able to protect against liver damage associated with excessive alcohol intake. *In vitro*, DLPC has a number of hepatoprotective properties including the ability to reduce alcohol-induced hepatocyte apoptosis, cytochrome P450IIE1 (CYP2E1) induction, mitochondrial respiratory dysfunction, and TNF- α generation by Kupffer cells. In addition to reducing lipid peroxidation and oxidative stress, DLPC inhibits hepatic fibrosis, by affecting hepatic stellate cell proliferation and collagen accumu-

lation [9,10]. Soybean PPC also reduces hyperlipidemia and fatty liver in rats given excess alcohol, an effect associated with improved hepatic fatty acid oxidation [11].

Several investigators have described the effect of dietary phospholipid on hepatic steatosis in animals with non-alcoholic liver disease (as summarized in Table 1 [12–19,20[•]]). Different manipulations have been used to induce steatosis in these experiments, such as administering a high-fat diet or supplementing diets with orotic acid. In some studies, animals with relatively normal livers were investigated, while in one study [20[•]], rats with a genetic predisposition to obesity and fatty liver disease were used. In all of these studies, dietary phospholipids (derived from safflowers, soybeans, egg or fish roe) were found to consistently lower plasma or hepatic lipid levels. The magnitude of reduction in hepatic lipid levels has been quite striking. For example, in hypercholesterolemic rabbits, dietary PPC reduced total liver cholesterol by 42% and liver triglyceride by 28% [17]. In orotic acid-fed rats, dietary phosphatidylcholine reduced hepatic triglyceride by 45% [19]. In hyperlipidemic rats with alcohol-induced fatty liver, PPC reduced liver triglyceride and cholesterol by 40% and 45%, respectively [11]. Hepatic lipid-lowering has generally been achieved with phospholipid added to the diet at levels varying from 2 to 6% by weight (Table 1).

Mechanisms responsible for the reduction in hepatic lipid by dietary phospholipid

The antisteatotic effect of dietary phospholipid has often been found to be associated with a decrease in hepatic fatty acid synthesis and in some cases an increase in fatty acid oxidation (Table 1). In addition, an increase in faecal neutral steroid excretion has been observed, providing a mechanistic explanation for the reduction of cholesterol ester in the liver of phospholipid-supplemented animals. Egg phosphatidylcholine and egg sphingomyelin have both been shown to inhibit the intestinal absorption of cholesterol [21,22]. At first glance, this might seem a little paradoxical, considering that phosphatidylcholine plays an important role in intestinal lipid absorption by enhancing micellar lipid solubility and providing surface material for the formation of intestinal lipoproteins (i.e., chylomicrons and HDL). One can speculate, however, that an excess of phospholipid in the gut lumen may lead to the formation of oversized or inappropriately formed lipid micelles that are not optimally processed by luminal enzymes or that are impeded from crossing the unstirred water layer. Reduced absorption of dietary lipids or reduced reabsorption of biliary lipids would thus lead to a reduction in liver lipid levels and amelioration of steatosis.

Interestingly, Duivenvoorden *et al.* [23[•]] recently demonstrated that egg sphingomyelin (at dietary concentrations

Table 1 Studies in different animal species demonstrating the effect of dietary phospholipid on hepatic lipid metabolism

Phospholipid	Dose	Species	Concomitant treatment	Effect	Reference
Soybean PC Synthetic PE	2 g per 100 g diet 2 g per 100 g diet	Wistar rats (male)	Semi-purified diet (8% soybean oil)	PE-diet lowered plasma cholesterol more than PC-diet PE and PC-diets lowered hepatic cholesterol; PC-diet lowered hepatic TG PE and PC-diets increased faecal neutral steroid excretion	Imaizumi <i>et al.</i> 1983 [12]
Soybean PL Safflower PL	6 g per 100 g diet	Sprague-Dawley rats (male)	Commercial nonpurified diet 0.5% cholesterol 0.25% cholic acid	Compared to 6% safflower and palm oil: Reduced liver weight in both soy-PL and safflower-PL groups Reduced plasma cholesterol due to lower chylomicron- and VLDL-cholesterol Reduced liver cholesterol and TG Increased faecal neutral steroid Increased plasma LCAT activity	Iwata <i>et al.</i> 1992 [13]
Soybean PL	3% of dietary fatty acid	Rats	Coconut oil diet (12% fatty acid)	Reduced serum lipids Reduced liver TG and CHOL Reduced activity of enzymes mediating hepatic fatty acid synthesis	Kabir and Ide, 1995 [14]
Semipurified lecithin (23% PC) Pure soyabean lecithin (93% PC) Crude or purified Safflower PL	20% lecithin (4.6 g PC per 100 g diet) 20% lecithin (18.6 g PC per 100 g diet) 5% crude PL (2.5 g PL per 100 g diet) 5% purified PL (5.0 g PL per 100 g diet)	Wistar rats (male) White laying hens	High-fat diet (20% sunflower-seed oil) Barley-soybean meal-based diet (5% fat)	Reduced plasma and HDL cholesterol Increased levels of bile PC, bile salts and cholesterol Reduced serum cholesterol Reduced liver cholesterol and triglyceride Increased faecal neutral steroid	Polichetti <i>et al.</i> 1996 [15] An <i>et al.</i> 1997 [16]
Soybean lecithin (93% PPC)	5 g per 100 g diet (4.65 g PPC/100 g diet)	New Zealand White Rabbits (male)	High-fat/cholesterol diet (cholesterol, 0.2% by weight) (fat, 7.7% by weight)	Reduced plasma concentration of β -VLDL TG and CHOL Reduced liver TG and CHOL Histological evidence for reduced hepatic lipid Stimulation of bile sterol secretion	Polichetti <i>et al.</i> 2000 [17]
Soybean lecithin (containing 22% PL)	20 g per 100 g diet (4.4 g PL per 100 g diet)	Sprague-Dawley rats (male)	TG-enriched semi-purified diet (16% by weight PUFA margarine)	Reduced hepatic lipid content Stimulation in biliary lipid secretion Reduced hepatic ACAT activity	LeBlanc <i>et al.</i> , 2003 [18]
Egg PC	2 g per 100 g diet	Sprague-Dawley rats (male)	Orotic acid (1% by weight)	Reduced hepatomegaly Reduced liver TG Reduced hepatic fatty acid synthesis and increase in fatty acid oxidation	Buang <i>et al.</i> 2005 [19]
w-3-FA-PC (from fish roe)	2 g per 100 g diet	Otsuka LETF obese rats	5% corn oil diet	Compared to 2% egg PC: Reduction in liver weight and hepatic lipids Suppression of fatty acid synthesis enzymes Enhancement of fatty acid β -oxidation	Shirouchi <i>et al.</i> 2007 [20*]

ACAT, acyl-CoA cholesterol acyltransferase; CHOL, cholesterol; FA, fatty acid; LCAT, lecithin-cholesterol acyltransferase; LETF, Long-Evans Tokushima fatty; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PL, phospholipid; PPC, polyenylphosphatidylcholine; PUFA, polyunsaturated fatty acid; TG, triglyceride.

of 0.2% and 0.4% by weight) can dose-dependently lower plasma cholesterol and triglyceride levels in APOE*3 Leiden mice fed a Western-type diet. Other sphingolipids, which were not phospholipids, such as phytosphingosine, sphingosine, sphinganine, ceramide and cerebroside, also lowered plasma lipid levels. Dietary phytosphingosine (1% by weight) reduced hepatic steatosis by 50–60%. Dietary sphingolipids and phospholipids may or may not affect hepatic lipid metabolism by the same mechanism, but it is interesting to note that dietary phytosphingosine can also inhibit the intestinal absorption of both cholesterol and triglyceride [23*].

Other work has suggested that dietary phospholipid can stimulate biliary lipid secretion. In a recent study, Lamireau *et al.* [24*], investigated mice with homozygous disruption of the *ABCB4* gene. These animals (given dietary supplementation with cholic acid), are a model for human *Acb4* deficiency, a hereditary cholestatic liver disease that leads to hepatic fibrosis and cirrhosis. Mice lacking *Acb4* are unable to transfer phosphatidylcholine from the inner to the outer leaflet of the canalicular membrane and are unable to secrete phospholipids into bile. When fed diets containing 20% by weight lecithin granules (i.e., 4.4% phospholipid-containing diets), cholic acid-supplemented animals were protected against hepatic fibrosis and cholestatic disease. Phospholipid-feeding in control and *Acb4*^{-/-} animals was associated with increased bile flow and increased secretion of bile acids and cholesterol, providing evidence of hepatoprotection through stimulation of biliary lipid output.

Phospholipid structure and hepatoprotection

An important question that remains to be answered regarding the hepatoprotective effects of dietary phospholipids is the extent to which their lipid-lowering activity is dependent on their chemical structure. In other words, to what extent is their hypolipidemic activity a function of the type of fatty acids attached at the 1 and 2 positions of the glycerol backbone or to what extent is it dependent on the type of charged head-group. Evidence to date seems to suggest that both fatty acid composition and head-group arrangement play an important role. For example, Shirouchi *et al.* [20*] recently carried out experiments in Otsuka Long-Evans Tokushima fatty (OLETF) rats. These animals are hyperphagic, due to a lack of cholecystokinin receptors, and therefore become obese, with concomitant hyperlipidemia, diabetes and fatty liver. OLETF rats were fed 5% corn oil-containing semisynthetic diets, which also contained either 2% (by weight) egg phosphatidylcholine or 2% ω 3-phosphatidylcholine (derived from fish roe). The egg phosphatidylcholine contained 29.9% palmitic acid (16:0), 17.5% stearic acid (18:0), 21.0% oleic acid (18:1) and 15.4% linoleic acid (18:2), in comparison to the ω 3-phosphatidylcholine which contained

15.0%, 13.9%, 10.5% and 0.7% respectively. The ω 3-phosphatidylcholine also contained 12.0%, 5.2% and 28.1% of 20:5 ω 3, 22:5 ω 3 22:6 ω 3, which were not detected in the egg-phosphatidylcholine. After 4 weeks of feeding, the ω 3-phosphatidylcholine diet significantly reduced liver weight and hepatic triglyceride levels compared with the egg-phosphatidylcholine diet. The ω 3-phosphatidylcholine diet also lowered serum cholesterol and glucose levels, and increased serum adiponectin. These results clearly demonstrate that the fatty acid composition of dietary phosphatidylcholine is an important determinant of its ability to lower plasma and liver lipid levels.

Other studies, however, point to the fact that lipid-lowering effects are independent of fatty acid composition. For example, in the work of Navder *et al.* [11], rats with alcohol-induced fatty liver and hyperlipidemia were given PPC. They were compared with control animals given the same amount of linoleate (as safflower oil) and choline (as bitartrate salt). Beneficial effects were observed on hepatomegaly and hepatic lipid accumulation in PPC-fed rather than control animals, supporting the concept that choline structurally attached to the dietary phospholipid is an important factor. A second example is provided by the work of Buang *et al.* [19]. In these experiments, carried out in Sprague–Dawley rats with orotic acid-induced fatty liver, the effect of dietary phosphatidylcholine was compared with that of dietary triglyceride having a very similar fatty acid profile. The S:M:P ratio was 16:19:63 for the phosphatidylcholine diet and 15:20:64 for the triglyceride diet. The phosphatidylcholine diet attenuated liver triglyceride accumulation by 45% compared to the triglyceride diet, providing evidence of a fatty acid-independent effect of the dietary phosphatidylcholine. At the same time, the lipid-lowering effect of phospholipid in the diet is not simply a function of the amount of phosphatidylcholine present, as supported by the early work of Imaizumi *et al.* [12], in which synthetically prepared phosphatidylethanolamine at a level of 2% in the diet of Wistar rats had both plasma and liver lipid-lowering activity. Phosphatidylcholine and phosphatidylethanolamine are asymmetrically distributed in the plasma membrane, with the majority of phosphatidylcholine being associated with the outer leaflet and the majority of phosphatidylethanolamine being in the inner leaflet. Li *et al.* [25*] have provided very interesting evidence that manipulation of phosphatidylcholine/phosphatidylethanolamine levels in mice leads to significant changes in cell membrane integrity, which in turn affects the progression of steatosis into steatohepatitis.

Dietary phospholipid and atherosclerosis

The aforementioned studies provide indirect evidence that dietary phospholipid, through beneficial effects on plasma and liver lipid metabolism, may protect against

the development of atherosclerosis. Only a few studies, however, have drawn a direct link between dietary phospholipid and the inhibition of atherogenesis. In the first of these, O'Brien and Corrigan [26] fed soybean and egg lecithin (7.5% for 6 weeks) to guinea pigs with diet-induced hypercholesterolemia (i.e., 15% lard and 0.5% cholesterol diet). Soybean lecithin decreased total plasma cholesterol by 51% without decreasing HDL-cholesterol, while egg lecithin increased HDL-cholesterol by 177% without increasing total plasma cholesterol. Aortic cholesterol was significantly reduced (by 41%) in soybean lecithin-fed animals. A similar reduction was not observed, however, in the egg lecithin-fed animals.

Wilson *et al.* [27] fed three modified nonpurified diets to hamsters for 8 weeks: a hypercholesterolemic diet (HCD; 10% coconut oil + 0.05% cholesterol), a soy lecithin HCD (HCD+SL, 3.4% soy lecithin containing 40% phosphatidylcholine, 35% phosphatidylethanolamine and 25% phosphatidylinositol), and an HCD with added linoleate and choline (HCD-SL). The HCD-SL diet reduced plasma triglyceride, cholesterol and non-HDL-cholesterol by 43, 37 and 47%, while the HCD+SL diet reduced these parameters to a significantly greater extent, 54, 58 and 73%, respectively. Aortic fatty streak area was in turn significantly lower in HCD+SL compared with HCD-SL-fed animals (−90% versus −49%, $P < 0.001$). These results show that a mixture of soy phospholipids added to the diet of hypercholesterolemic hamsters can reduce atherosclerosis, and this effect is not entirely dependent on the presence of linoleate or choline.

More recently, Navab *et al.* [28] carried out experiments in apoE-deficient mice, which were given either soy or egg lecithin in their drinking water (1.0 mg/ml), or alternatively, a similar concentration of the synthetic phospholipid, dimyristoylphosphatidylcholine (DMPC). Animals given DMPC (though not soy or egg lecithin) had significantly increased levels of plasma HDL-cholesterol and apoA-I, increased levels of jejunal apoA-I synthesis, and significantly reduced aortic sinus lesion area and en face whole aortic lesion area. Although it is unclear why DMPC, but not the other two natural phospholipid preparations, had antiatherogenic effects, these data suggest that certain types of phospholipid can inhibit atherosclerosis in animals with genetically dependent cardiovascular disease.

Dietary phospholipids in humans

Increasing evidence exists (as reviewed above) to support the concept that dietary phospholipid has beneficial effects on liver and plasma lipid metabolism in experimental animals. Only limited evidence is available, however, to suggest that dietary phospholipid supplementation is of benefit in humans. Several years ago, Knuiman *et al.* [29] scrutinized 24 studies on the effect of dietary lecithin

(ranging from 1 to 54 g per day), in order to establish whether the consumption of lecithin had a more beneficial effect on serum cholesterol levels than equivalent amounts of polyunsaturated triglyceride. They concluded that there was no evidence for a specific effect of lecithin on serum cholesterol levels independent of its linoleic acid content.

More recently, there has been a focus on the ability of oral phospholipid to affect plasma HDL levels. Klimov *et al.* [30] treated 50 combined hyperlipidemic patients with purified phospholipid from soybeans (Lipostabil 300 forte, 1.8 g/day for 6 months). In this nonplacebo-controlled trial, phospholipid treatment resulted in significant reductions in total cholesterol, triglyceride and LDL-cholesterol, in association with a significant 12% increase in plasma HDL-cholesterol. Bunca *et al.* [31] investigated the effect of krill oil (1–3 g/day for 3 months) on plasma lipids in patients with hyperlipidemia. Krill oil is extracted from Antarctic krill and is rich in phospholipids containing long-chain ω -3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid). It also contains various antioxidants including vitamin A, vitamin E, and the carotenoid, astaxanthin. A remarkable dose-dependent 44–60% increase was observed in HDL-cholesterol levels, in association with favourable reductions in plasma cholesterol, triglyceride and LDL-cholesterol [31]. In a much smaller study, Burgess *et al.* treated 16 normolipidemic individuals with phosphatidylinositol at a dose of either 2.8 or 5.6 g per day. The low dose resulted in a 13% increase in HDL-cholesterol, whereas the higher dose caused an increase of 18% over the 2-week treatment period [32]. Together, these results are interesting, but larger and better-controlled studies are clearly needed in order to define the extent to which different phospholipid preparations are able to beneficially affect plasma lipid and lipoprotein levels. It also remains to be seen whether dietary or dose-administered phospholipid can reduce hepatic lipid levels in human subjects.

Conclusion

In view of recent problems with drugs designed to treat the metabolic syndrome and prevent cardiovascular disease [33], the concept of using naturally occurring compounds as cardioprotective or hepatoprotective agents is very attractive. Targeting nutraceutical therapy against the accumulation of fat in the liver is a sound strategy, which has the potential to beneficially affect plasma lipid levels and insulin sensitivity. As reviewed above, there is consistent experimental evidence to suggest that phospholipids from different sources have the potential to reduce hepatic lipid levels. Carefully controlled human trials are, however, required to substantiate the efficacy of this approach. It is also important that additional research be conducted to determine the extent to which certain phospholipids have the ability to affect plasma HDL

levels and the development of cardiovascular disease. Future experiments will need to address such questions as which type of phospholipid (phosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylserine or phosphatidylinositol) and what fatty acid composition (degree of saturation and chain length) is optimal for providing hepatoprotection? Do all phospholipids affect liver lipid metabolism in the same way and can this mode of action be targeted by synthetic phospholipids? To what extent do different dietary phospholipids affect plasma lipid and lipoprotein levels, particularly HDL? Which subject/patient groups are most likely to benefit from phospholipid therapy? What is the optimal dose and optimal route of administration of dietary phospholipid (i.e., as a nutraceutical in capsule form or as a functional food incorporated into food products)? And finally, should phospholipids be added to other active nutraceutical ingredients (e.g., flavonoids) to provide optimal benefit?

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 314–315).

- 1 Tarantino G, Saldamacia G, Conca P, Arena A. Nonalcoholic fatty liver disease: further expression of the metabolic syndrome. *J Gastroenterol Hepatol* 2007; 22:293–303.
- 2 Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; 43:S99–S112.
- 3 Targher G, Bertolini L, Rodella S, *et al.* Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetes Care* 2007; 30:2119–2121. This important study provided evidence that NAFLD is an independent risk factor for cardiovascular disease in diabetic subjects.
- 4 Zierenberg O, Grundy SM. Intestinal absorption of polyenephosphatidylcholine in man. *J Lipid Res* 1982; 23:1136–1142.
- 5 Nilsson A, Duan RD. Absorption and lipoprotein transport of sphingomyelin. *J Lipid Res* 2006; 47:154–171. This is a timely and very informative review on the metabolism of sphingomyelin.
- 6 Krimbou L, Hajj Hassan H, Blain S, *et al.* Biogenesis and speciation of nascent apoA-I-containing particles in various cell lines. *J Lipid Res* 2005; 46:1668–1677.
- 7 Magun AM, Mish B, Glickman RM. Intracellular apoA-I and apoB distribution in rat intestine is altered by lipid feeding. *J Lipid Res* 1988; 29:1107–1116.
- 8 Wang H, Du J, Lu S, Yao Y, *et al.* Regulation of intestinal apolipoprotein A-I synthesis by dietary phosphatidylcholine in newborn swine. *Lipids* 2001; 36:683–687.
- 9 Lieber CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol* 2004; 34:9–19.
- 10 Lieber CS. New concepts of the pathogenesis of alcoholic liver disease lead to novel treatments. *Curr Gastroenterol Rep* 2004; 6:60–65.
- 11 Navder KP, Baraona E, Lieber CS. Polyenylphosphatidylcholine attenuates alcohol-induced fatty liver and hyperlipidemia in rats. *J Nutr* 1997; 127:1800–1806.
- 12 Imaizumi K, Mawatari K, Murata M, *et al.* The contrasting effect of dietary phosphatidylethanolamine and phosphatidylcholine on serum lipoproteins and liver lipids in rats. *J Nutr* 1983; 113:2403–2411.
- 13 Iwata T, Hoshi S, Takehisa F, *et al.* The effect of dietary safflower phospholipid and soybean phospholipid on plasma and liver lipids in rats fed a hypercholesterolemic diet. *J Nutr Sci Vitaminol* 1992; 38:471–479.
- 14 Kabir Y, Ide T. Effect of dietary soybean phospholipids and fats differing in the degree of unsaturation on fatty acid synthesis and oxidation in rat liver. *J Nutr Sci Vitaminol (Tokyo)* 1995; 41:635–645.
- 15 Polichetti E, Diaconescu N, De La Porte PL, *et al.* Cholesterol-lowering effect of soybean lecithin in normolipidaemic rats by stimulation of biliary lipid secretion. *Br J Nutr* 1996; 75:471–478.
- 16 An BK, Nishiyama H, Tanaka K, *et al.* Dietary safflower phospholipid reduces liver lipids in laying hens. *Poult Sci* 1997; 76:689–695.
- 17 Polichetti E, Janisson A, de la Porte PL, *et al.* Dietary polyenylphosphatidylcholine decreases cholesterolemia in hypercholesterolemic rabbits: role of the hepato-biliary axis. *Life Sci* 2000; 67:2563–2576.
- 18 LeBlanc MJ, Brunet S, Bouchard G, *et al.* Effects of dietary soybean lecithin on plasma lipid transport and hepatic cholesterol metabolism in rats. *J Nutr Biochem* 2003; 14:40–48.
- 19 Buang Y, Wang YM, Cha JY, *et al.* Dietary phosphatidylcholine alleviates fatty liver induced by orotic acid. *Nutrition* 2005; 21:867–873.
- 20 Shirouchi B, Nagao K, Inoue N, *et al.* Effect of dietary omega 3 phosphatidylcholine on obesity-related disorders in obese Otsuka Long-Evans Tokushima fatty rats. *J Agric Food Chem* 2007; 55:7170–7176. Recent evidence describes the protective effects of dietary phospholipid containing omega-3 fatty acids. Unfortunately, a control group not given dietary phospholipid was not included in this study.
- 21 Jiang Y, Noh SK, Koo SI. Egg phosphatidylcholine decreases the lymphatic absorption of cholesterol in rats. *J Nutr* 2001; 131:2358–2363.
- 22 Noh SK, Koo SI. Egg sphingomyelin lowers the lymphatic absorption of cholesterol and alpha-tocopherol in rats. *J Nutr* 2003; 133:3571–3576.
- 23 Duivenvoorden I, Voshol PJ, Rensen PC, *et al.* Dietary sphingolipids lower plasma cholesterol and triacylglycerol and prevent liver steatosis in APOE*3Leiden mice. *Am J Clin Nutr* 2006; 84:312–321. Very interesting work provides evidence that dietary sphingolipids can be hepatoprotective. Whether all sphingolipids are equally protective and whether they all have the same mechanism of action requires further investigation.
- 24 Lamireau T, Bouchard G, Yousef IM, *et al.* Dietary lecithin protects against cholestatic liver disease in cholic acid-fed Abcb4-deficient mice. *Pediatr Res* 2007; 61:185–190. A recent study supported the concept that dietary lecithin can beneficially affect cholestatic liver disease.
- 25 Li Z, Agellon LB, Allen TM, *et al.* The ratio of phosphatidylcholine to phosphatidylethanolamine influences membrane integrity and steatohepatitis. *Cell Metab* 2007; 3:321–331. Original work demonstrates that liver failure in CD-Pem1–/– mice is due to loss of membrane integrity caused by a decreased phosphatidylcholine to phosphatidylethanolamine (PC/PE) ratio. These data suggest that additional experiments are needed to investigate the importance of membrane PC/PE ratio in maintaining normal liver function.
- 26 O'Brien BC, Corrigan SM. Influence of dietary soybean and egg lecithins on lipid responses in cholesterol-fed guinea pigs. *Lipids* 1988; 23:647–650.
- 27 Wilson TA, Meservey CM, Nicolosi RJ. Soy lecithin reduces plasma lipoprotein cholesterol and early atherogenesis in hypercholesterolemic monkeys and hamsters: beyond linoleate. *Atherosclerosis* 1998; 140:147–153.
- 28 Navab M, Hama S, Hough G, Fogelman AM. Oral synthetic phospholipid (DMPC) raises high-density lipoprotein cholesterol levels, improves high-density lipoprotein function, and markedly reduces atherosclerosis in apo-lipoprotein E-null mice. *Circulation* 2003; 108:1735–1739.
- 29 Knuiman JT, Beynen AC, Katan MB. Lecithin intake and serum cholesterol. *Am J Clin Nutr* 1989; 49:266–268.
- 30 Klimov AN, Konstantinov VO, Lipovetsky BM, *et al.* "Essential" phospholipids versus nicotinic acid in the treatment of patients with type IIb hyperlipoproteinemia and ischemic heart disease. *Cardiovasc Drugs Ther* 1995; 9:779–784.
- 31 Bunea R, El Farrah K, Deutsch L. Evaluation of the effects of Neptune Krill Oil on the clinical course of hyperlipidemia. *Altern Med Rev* 2004; 9:420–428.
- 32 Burgess JW, Neville TA, Rouillard P, *et al.* Phosphatidylinositol increases HDL-C levels in humans. *J Lipid Res* 2005; 46:350–355.
- 33 Cohn JS. Lipid metabolism and metabolic disease: defining new targets. *Curr Opin Lipidol* 2007; 18:237–239.