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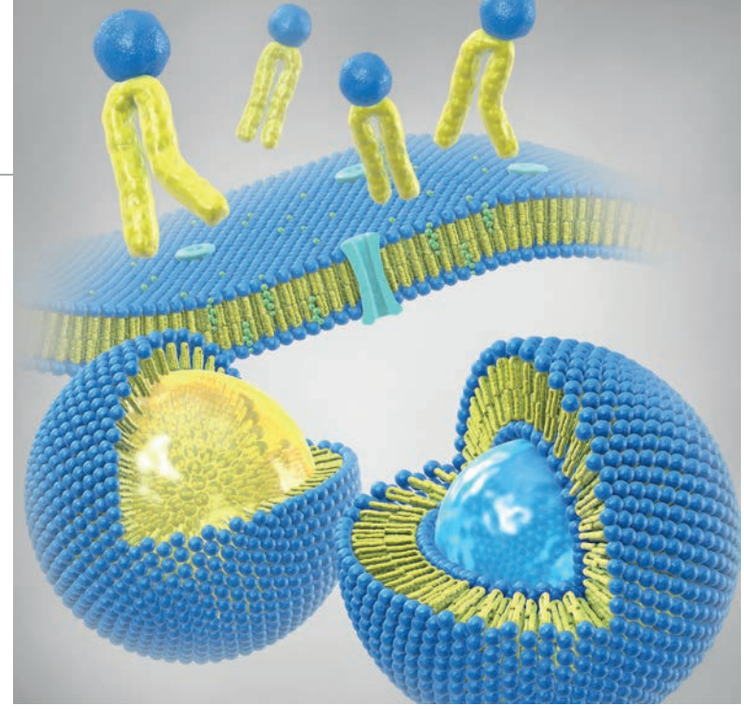

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Phosphatidylcholine: The active substance from lecithin for liver and vascular health

Philipp Gebhardt

Fatty liver is caused by a disorder of the lipid metabolism of the liver and affects about a quarter of the population, with increasing incidence. Due to its mediating effect between water and fat, the phospholipid phosphatidylcholine, contained in lecithin, plays a key role in the body's fat metabolism. Since adequate intakes also contribute to normal homocysteine levels, phosphatidylcholine also beneficially affects vascular health. As part of the cellular membranes of all living organisms, phosphatidylcholine is contained in the diet, but the ingested amounts are often below those recommended by the EFSA.

Fatty liver – a disease with increasing relevance

Fatty liver disease is characterized by a, usually reversible storage of fats (triglycerides) in the liver cells. It is the most common liver disease in the world and is caused by a disturbance in the fatty acid and triglyceride metabolism of the hepatocytes. Mostly, the non-alcoholic form of the disease (*Non-alcoholic fatty liver disease*, NAFLD) is attributed to a mismatch between energy intake (overeating) and energy expenditure (sedentary lifestyle). Excess energy is stored as fat also in the liver, so that obesity, caused by malnutrition and overeating is one of the main risk factors of the disease. On the other hand, alcoholic fatty liver disease (AFLD) is the result of the excessive production of acetyl-CoA ("activated acetic acid"), which is formed during the degradation of alcohol and is increasingly stored in the form of fatty acids and triglycerides in the liver cells when alcohol is consumed in excess.

The alcoholic fatty liver disease can be differentiated from the non-alcoholic form by the assessment of drinking habits. However, the amount of alcohol consumed is not always traceable, and mixed forms of both causes of the disease are probably common.

Over the past 10 years, the prevalence of overweight has increased significantly, especially in the Western world. Also in Germany, there is a trend towards obesity, affecting 21.5 % of the male, and 24.5 % of the female adult population[2]. According to a meta-analysis published in 2016, the proportion of people with fatty liver disease increased from 15 % to 25 % in the period 2005-2010, worldwide. In Europe, the frequency of NAFLD is given as 24 %, so that about one in four is affected.[3] Globally, the proportion of obese children and adolescents has increased from 0.8 % in 1975 to 6.8 % in 2016, so that NAFLD is increas-

ingly being diagnosed even in adolescence[4]. On the other hand, obesity is not a prerequisite for the development of NAFLD, as prevalence in normal-weight and lean individuals is also rising[5]. The epidemiological extent is reflected by an English investigation that depicted an increase in hospital admissions due to fatty liver disease by a factor of 26 between 2001 and 2016 (Fig. 1).

With the onset of inflammation and fibrosis (scarred tissue remodelling), the alcoholic fatty liver, as well as the non-alcoholic form can progress to steatohepatitis and liver cirrhosis. A prerequisite for both forms of the disease is an accumulation of fat in the liver due to a disproportion of fat inflow or fat synthesis compared to the amount of fat oxidized or discharged from the organ.

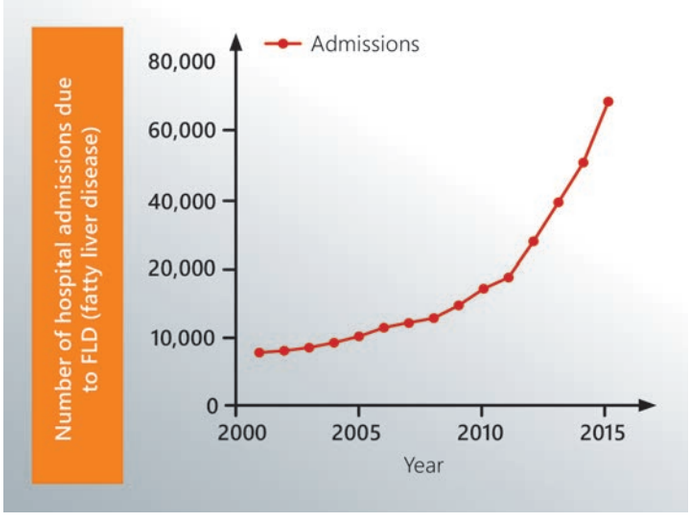

Fig. 1: Rise in hospital admissions due to fatty liver disease in England between 2001 and 2016 (modified from [1]).

Phosphatidylcholine – The physiologic phospholipid from lecithin

The transport of the water-insoluble lipids to the cells of the body is established by certain transport molecules called lipoproteins (VLDL), which are formed in the liver. Lipoproteins are largely composed of phospholipids (Fig. 2). These amphiphilic ("both loving") molecules consist of a water-friendly, as well as a fat-friendly moiety. They can combine with fats, so that the water-friendly head groups form a shell, which encloses a fat droplet and allows for the transport in the blood. With a proportion of about 70 %, phosphatidylcholine is the most important phospholipid for the function of the various lipoproteins.[6]

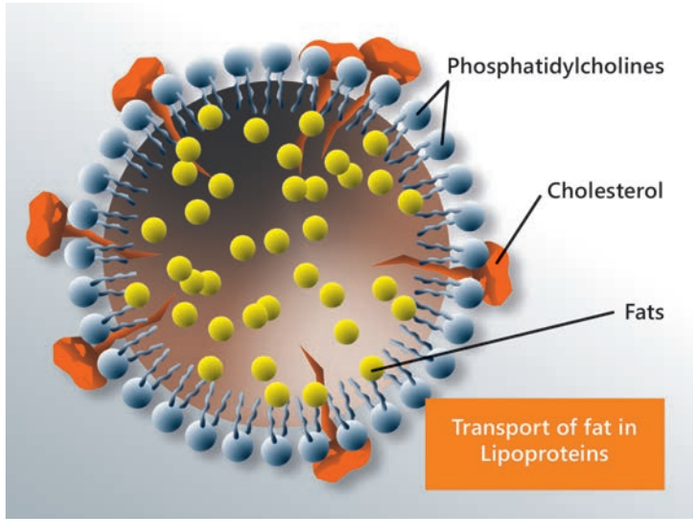

Fig. 2: Fats are packaged in the liver into lipoproteins to allow for their transport in the blood. Because of its ability to mediate between water and fat, phosphatidylcholine is essential for the formation of lipoproteins.

For the production of sufficient amounts of phosphatidylcholine, the body relies on the supply of its precursor choline. Choline can be produced in the liver, but the capacity of this endogenous synthesis is limited, so that additional supply is required. As part of the cellular membranes of every living cell, phosphatidylcholine is also the most important, natural source of choline, which is supplied in different amounts through the diet. Many of the choline-rich foods are also higher in fat and cholesterol, so reducing fat intake is often associated with inadequate choline uptake and limitation of the body's ability to synthesize phosphatidylcholine. In the absence of phosphatidylcholine, fatty acids produced in the liver, which are normally transported into the blood in conjunction with the phospholipid, cannot be packaged and released in lipoproteins into the blood. The accumulation of fats then leads to an increasing steatosis of the liver. Due to the lack of phosphatidylcholine, an inadequate supply of choline leads to the clinical manifestation of a fatty liver and ultimately to dysfunction and damage of the organ[7] (Fig. 3).

The consequences of phosphatidylcholine deficiency could be simulated in a clinical setting with 57 healthy adults receiving a controlled, choline deficient diet. Under the experimental conditions, 77 % of men, 80 % of postmenopausal women and 44 % of premenopausal women developed fatty liver, liver damage and/or muscle damage. Symptoms were completely reversible after choline was reintroduced to the diet.[8] Against this background, the European Food Safety Authority (EFSA) has set adequate daily intake levels for choline as 400 mg for adults, 480 mg for pregnant women, and 520 mg for lactating women (EFSA 2016)[9]. In contrast, the average intake among adults in Europe is stated to be only in the range of 291–468 mg[10]. In view of the limited endogenous synthesis capacity and fluctuating

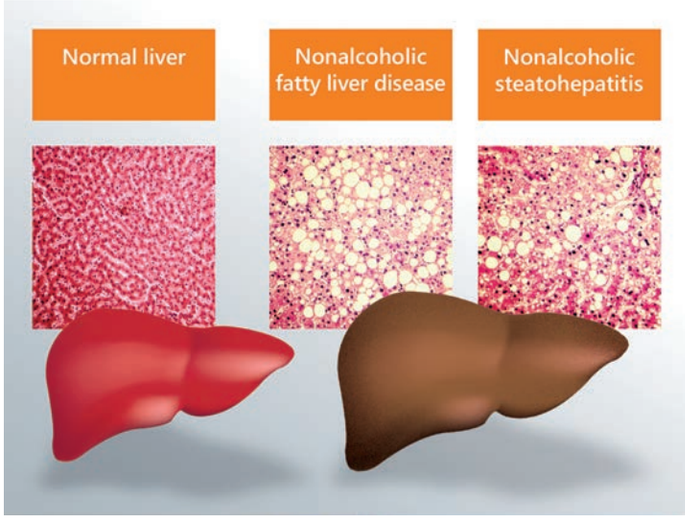

Fig. 3: Fatty liver disease is characterized by an increasing storage of fats in the liver cells (hepatocytes). The disease can progress to an inflammatory form (steatohepatitis).

intakes with food, an additional supply of phosphatidylcholine-rich lecithin is therefore beneficial to ensure vascular, as well as liver health.

Sensitivity to phosphatidylcholine deficiency is dependent on several factors and less pronounced in premenopausal women, compared to postmenopausal women and men[11]. This difference is attributed to correspondingly higher levels of the hormone oestrogen, which stimulates endogenous phosphatidylcholine production by activating the enzyme phosphatidylethanolamine methyltransferase (PEMT). By transferring methyl groups to phosphatidylethanolamine, PEMT serves to produce phosphatidylcholine in the liver. Reduced PEMT activity thus results in lower phosphatidylcholine synthesis in postmenopausal women and increases the risk of deficiency. In addition, it is reported that nearly half of women in the US (and probably also in Europe) carry one or more single nucleotide polymorphisms (SNPs) in the PEMT gene. These are inherited genetic variations that prevent the gene from being activated by oestrogen[12]. Under choline deficiency in a clinical setting, these women were at particularly high risk for developing liver dysfunction, which could be reversed by the supplementation with choline[13]. Although the underlying mechanisms have been scientifically elucidated, only a few epidemiological studies have addressed the risk of liver disease associated with insufficient choline supply. A study with 664 NAFLD patients found a clear association of the degree of fibrosis with low nutritional choline in postmenopausal women[14]. However, due to the increasing incidence of the disease and a mutual influence between obesity and fatty liver[15], adequate supply of phosphatidylcholine is of paramount importance for health.

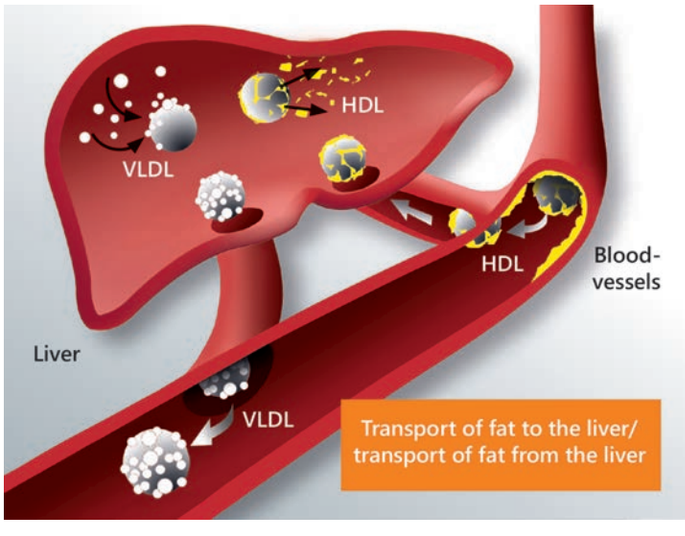

Fig. 4: The liver represents the central organ for lipid metabolism. Lipoproteins synthesized in the liver are transported into the body in form of very low density lipoproteins (VLDL). On the other hand, high density lipoproteins (HDL) transport fat from the body to the liver, thereby reducing accumulation of fats in the blood vessels.

In addition to very low density lipoproteins (VLDLs), which promote the removal of fat from the liver, phosphatidylcholine is also of essential importance for the formation and function of high density lipoproteins (HDLs). The main task of HDLs is to transport excess ch olesterol from the peripheral tissues, such as the blood vessel walls, back to the liver, where it can be eliminated via the bile. HDL is also referred to as "good cholesterol" because higher blood levels are associated with a lower risk of cardiovascular diseases (Fig. 4).

Homocysteine – An important factor in vascular health

Another contributing factor for vascular health is phosphatidylcholine also as an alternative source of methyl groups, needed for the reduction of homocysteine levels. Elevated homocysteine is considered an independent risk factor for arteriosclerosis. Homocysteine is thought to promote the disease by reducing the flexibility of vessels and exerting a direct damaging effect on endothelial cells[16]. However, with sufficient availability of methyl groups, homocysteine can be recycled to the amino acid methio-

nine, thereby avoiding an increase to critical levels. The inverse association of elevated homocysteine levels with dietary choline intake has clearly been demonstrated by analysis of data from a broad epidemiological study involving more than 3,700 participants[17].

Table 1: Phosphatidylcholine and Choline content of lecithins with increasing grades of purification.

Lecithin-Type	Phosphatidyl-choline, PC content [g/100g]	Choline content [g/100g]
Liquid Lecithin	12	1,56
Deoiled Lecithin Powder	20	2,6
Refined Lecithin	50	6,5
Refined Phosphatidyl-choline	90	11,7

Regulatory

Phosphatidylcholine is a major constituent of lecithins classified as GRAS (Generally Recognized As Safe) by the US Food and Drug Administration (FDA)[18]. Also, the European Food Safety Authority (EFSA) considers lecithin as safe and has consequently not set an upper limit for consumption[19].

Conclusion

In addition to dietary interventions and increased exercise, supplementation with natural, lipotropic substances such as phosphatidylcholine is a promising, side-effect-free option for the treatment and prevention of fatty liver disease. As a function-determining component of lipoproteins, the phospholipid is of essential importance for lipid metabolism and contributes as a source of methyl groups to the reduction of elevated homocysteine levels.

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