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REVIEW

Atherogenic Impact of Lecithin-Cholesterol Acyltransferase and Its Relation to Cholesterol Esterification Rate in HDL (FER_{HDL}) and AIP [log(TG/HDL-C)] Biomarkers: The Butterfly Effect?

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Summary

The atherogenic impact and functional capacity of LCAT was studied and discussed over a half century. This review aims to clarify the key points that may affect the final decision on whether LCAT is an anti-atherogenic or atherogenic factor. There are three main processes involving the efflux of free cholesterol from peripheral cells, LCAT action in intravascular pool where cholesterol esterification rate is under the control of HDL, LDL and VLDL subpopulations, and finally the destination of newly produced cholesteryl esters either to the catabolism in liver or to a futile cycle with apoB lipoproteins. The functionality of LCAT substantially depends on its mass together with the composition of the phospholipid bilayer as well as the saturation and the length of fatty acyls and other effectors about which we know yet nothing. Over the years, LCAT puzzle has been significantly supplemented but yet not so satisfactory as to enable how to manipulate LCAT in order to prevent cardiometabolic events. It reminds the butterfly effect when only a moderate change in the process of transformation free cholesterol to cholesteryl esters may cause a crucial turn in the intended target. On the other hand, two biomarkers – FER_{HDL} (fractional esterification rate in HDL) and AIP [log(TG/HDL-C)] can offer a benefit to identify the risk of cardiovascular disease (CVD). They both reflect the rate of cholesterol esterification by LCAT and the composition of lipoprotein subpopulations that controls this rate. In clinical practice, AIP can be calculated from the routine lipid profile with help of AIP calculator *www.biomed.cas.cz/fgu/aip/calculator.php*.

Key words

Lecithin-cholesterol acyltransferase (LCAT) • Atherosclerosis • FER_{HDL} (fractional esterification rate in HDL) • AIP (atherogenic index of plasma, log(TG/HDL-C) • Biomarkers of cardiometabolic risk • Lipoprotein particle size

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Introduction

> *The butterfly effect expresses the sensitive dependence of the development of a system on initial conditions whose small changes can result in large variations...*
> *WIKIPEDIA*

Lecithin cholesterol acyltransferase (LCAT, EC 2.3.1.43) is a plasma enzyme which catalyzes the transfer of fatty acids from 2n- lecithin to 3-hydroxy group of free cholesterol (FC) to form cholesteryl esters (CE) and lysolecithin (LPC). LCAT as the producer of a majority of cholesteryl esters in the human plasma has a unique role in the removal of unesterified cholesterol from peripheral cells, including macrophages into plasma lipoproteins in the pathway of reverse cholesterol transport (RCT) (Glomset *et al.* 1966, Glomset 1968). This was the basis for considering its role in the atherogenic process. There was a long-term attempt for finding the evidence that would support the manipulation of LCAT in the treatment of diseases of atherogenic

origin. Even more than 50 years of monitoring on pro- and anti-atherogenic LCAT impact did not provide a reliable answer. Since 1962, when the LCAT mechanism was first described (Glomset 1962), Google has monitored about 660 000 records of LCAT. Among them 86 000 records followed the relationship between LCAT and atherosclerosis or cardiovascular diseases (CVD). During this time thousands of details have been discovered that complement the pathway of FC from peripheral tissues to the intravascular pool, being transformed by the action of LCAT into cholesteryl esters which leave the pool. However, further knowledge about the characteristics and modus operandi of LCAT, it turned out that RCT pathway needs revising and supplementing with other data. Plenty of reviews have dealt with the issue of LCAT and its atherogenic aspects (Glomset 1968, Sodhi *et al*. 1980, Dobiášová 1983, Dobiášová and Frohlich 1999, Jonas 2000, Rousset *et al*. 2009, Rader 2009, Calabresi and Franceschini 2010, Vergeer *et al.* 2010, Rousset *et al*. 2011, Kunnen and Van Eck 2012, Ng 2012, Calabresi *et al.* 2012, Levinson and Wagner 2015, Ossoli *et al.* 2016). Some authors have found a protective effect of LCAT in patients with coronary heart disease (Solajic-Božičević *et al.* 1991, Solajic-Božičević *et al.* 1994, Hovingh *et al*. 2005, Sethi *et al.* 2010). Others, and probably majority of them, reported the increase in atherogenic risk by increasing the activity of LCAT or cholesterol esterification rate (Dobiášová *et al.* 1991, Takao *et al.* 2001, Guerin *et al.* 2001, Santos *et al.* 2003, Frohlich and Dobiášová 2003, Dullaart *et al.* 2008, Dullart *et al.* 2010, Hollebooom *et al.* 2010, Khera *et al*. 2011, Dobiášová *et al.* 2011, Li *et al.* 2013, Kim *et al*. 2014).

Free cholesterol meets the LCAT on the way from peripheral cells to the intravascular space and is transformed into CEs which leave this space in two ways. However, a number of small variations on this way may change atherogenic/anti-atherogenic impact of LCAT. Recently Philips (2014) reviewed four pathways for exporting free cholesterol from macrophages to extracellular HDL. The passive processes include simple diffusion *via* the aqueous phase and facilitated diffusion mediated by scavenger receptor class B, type I (SR-BI). The data about FC diffusion *via* aqueous phase were complemented by Czarnecka and Yokoyama (1995) in an earlier report on the regulation of cellular cholesterol efflux. SR-BI has also a significant role in the transfer of CE into the catabolic process in the liver (Acton *et al*. 1996, Hoekstra 2017). The active pathways are mediated by membrane lipid translocases such as the ATP-binding cassette (ABC) transporters ABCA1 and ABCG1. As stated by Philips (2014), both transporters mediate efflux of cholesterol from cells, but the reaction mechanisms are different. ABCG1 leads to redistribution of FC from cell interior into the plasma membranes. When activated pool of plasma membrane is created, it leads to the flux of cholesterol mass out of the cell by aqueous diffusion pathway, but not to lipid-free apoA. In contrast, the ABCA1 activity in the plasma membrane promotes efflux of phospholipids (with a preference of lecithin) and FC to lipid-free apoAI (plasma pre-β1/HDL).

When free cholesterol enters the intravascular space, it encounters the LCAT. As a relative small soluble glycoprotein (cca 67 kDa) LCAT operates in an aqueous plasma medium with less or more hydrophobic components. Therefore, the effectiveness of LCAT and cholesterol esterification rate will depend on many factors such as physicochemical nature of cholesterol-phospholipid bilayer (Yokoyama *et al*. 1980, Parks *et al*. 2000), the characteristics of the fatty acyls of lecithin, activator and inhibitor proteins – apoAI and apoAII (Fielding *et al.* 1972), apoC (Soutar *et al.* 1975), specific cholesterol ATP-binding cassette transporters ABCA1 and ABCG1 (Philips 2014) and the size of lipoproteins.

The size of HDL, LDL and VLDL particles and activity of LCAT probably represent the strongest connection with atherogenic plasma profile. The associations of high-density lipoprotein subclasses and apolipoproteins with ischemic heart disease and coronary atherosclerosis were found already in the eighties (Miller 1987). Barter *et al.* (1984, 1985) studied esterification of cholesterol by LCAT in two HDL subfractions, HDL-subfraction 3 (HDL3) and HDL-subfraction 2 (HDL2) and found that the two HDL subfractions may compete for interactions with the enzyme. HDL3 subfraction was highly effective substrate, while HDL2 subfraction function as an inhibitor of the cholesterol esterification reaction. Newer method of gradient gel electrophoresis in various gels (Nichols *et al.* 1986, Williams *et al.* 1990) enabled split subfractions HDL2 and HDL3 into smaller subpopulations, which confirmed that the smallest particles $HDL_{3b,c}$ are preferred substrate for LCAT, while the larger HDL_{2b} inhibit the reaction (Dobiášová *et al.* 1991, Dobiášová *et al.* 1992). The development of new methods has allowed to discover atherogenic potential of individual HDL subpopulations. The initial dichotomy of HDL2 and

HDL3 did not bring unambiguous view relative to the CVD, while the NMR spectroscopy is able to do it (Freedman *et al.* 1998, Jeyarajah *et al.* 2006, Movva and Rader 2008, Dobiášová *et al.* 2011, Hafiane and Genest 2015). These specific techniques confirmed that the best substrate for LCAT are only small HDL (HDL_{3bc}) particles from the whole population of HDL3. The HDL small particles are substantially correlated with the cardiovascular risk, similarly as small dense LDL particles (Austin *et al.* 1988) and large VLDL particles. Large LDLs and particularly large HDL have shown reduced CVD risk.

Moreover, the removal of highly hydrophobic cholesteryl esters out of the intravascular space is also subjected to the regulation by lipoproteins of different size. In the first case the efflux of cholesteryl esters associated with the HDL2 and SR-BI is directed into liver and steroidogenic tissues (Acton *et al.* 1996, Rigotti *et al*. 2003). In the second case, CETP transfers cholesteryl esters to exchange for triglycerides in VLDL and then they go through the lipolytic cascade to LDL (Barter *et al.* 1982, Guerin *et al.* 2001). The functionality of LCAT is thus linked not only to HDL but it is also regulated by particle size of VLDL and LDL (Tani *et al*. 2016). These two pathways differ in their impact on CVD risk: the HDL pathway into SR-BI is considered an anti-atherogenic because it aims to the catabolism in the liver, whereas the CETP pathway into VLDL appears to be atherogenic because it may share atherogenic VLDL-LDL fate.

The functionality of LCAT has been tested in many ways, which however did not avoid misunderstanding or technical errors in the methods. LCAT mass concentration and the activity of LCAT in a variety of substrates and the cholesterol esterification rate (CER) in the individual plasma samples were examined.

LCAT mass

The concentration of the LCAT has little effect on the rate of cholesterol esterification, being only 60 % (Albers *et al.* 1981). Even at low LCAT concentrations, which are found in heterozygotes for LCAT deficiency, the ratio of CE to FC in plasma remains within the normal range (Ohta *et al.* 1995). It was recently shown that LCAT mass correlates positively with HDL-cholesterol levels (HDLs are carriers of LCAT) and negatively with triglyceride levels in European individuals at high cardiovascular risk (Calabresi *et al*. 2011). This seemingly contradicts the fact that low LCAT does not represent an atherogenic risk, while low HDL and high triglycerides are the risk. A more likely explanation is simply that the mass of LCAT increases with the mass of HDL, which are the main carriers of plasma LCAT, but the resulting esterification is limited by the variability of HDL and LDL subpopulations.

LCAT activity

The purpose of determining the activity of LCAT is to establish the efficiency of autologous enzyme relative to the substrate which provides FC and which stimulates or limits its capacity. Many different substrates were used, such as liposomes, proteoliposomes (Vaisman and Remaley 2013) or plasma lipoproteins. The methods for measuring the activity of LCAT *in vitro* are focused on the direct measurement of a decrease of free cholesterol, on CE increase in a mixture of the enzyme and variety substrates, and on the fluorometric assay of LCAT phospholipase activity. The decrease of FC is measured by gas-liquid chromatography (Marcel and Vezina 1973) or by enzymatic methods (Patsch *et al.* 1976). The determination of the activity LCAT as CE production is carried out in countless variations of radioassays with ^{3}H-cholesterol based upon the original publication of Stokke and Norum (1971). However, in the recent years, fluorometric methods prevail (Parks *et al.* 2000, Homan *et al.* 2013). The differences in LCAT activity in a variety of substrates can be enormous. For example, using DMPC (dimyristylphosphatidylcholine)-cholesterol liposomes as the substrate (Manabe *et al.* 1987), LCAT activities in 120 human sera showed 4.4- to 5.4-fold higher values obtained by self-substrate radioassay method. Not only the specificity of different substrates determines values obtained but in radioassays it is essential how the radioactive label (^{3}H-cholesterol) is incorporated into the substrate (Dobiášová *et al.* 2000). Perfect equilibration of the cholesterol label with lipoproteins is the method of "cold labeled substrate" (Dobiášová and Schützová 1986, Dobiášová and Frohlich 1996) which allows the transfer of radioactive label from the small filter paper disc into a solution of lipoprotein in the cold without the intervention of chemicals, heat or non-standard emulsion with albumin.

CER – cholesterol esterification rate and FER_{HDL} – fractional cholesterol esterification rate in apoB-lipoprotein depleted plasma

The problem of a method for the determination

of cholesterol esterification rate **(**CER) is in the origin of free cholesterol that enters the LCAT reaction in the whole plasma. Since the esterification takes place mostly in HDL, a source of free cholesterol may be peripheral cells (including macrophages and foam cells), which are mostly not able to metabolize cholesterol. However, another source of free cholesterol for the esterification can be FC transported into HDL *via* aqueous diffusion from other lipoproteins. The paradox is that during the first five minutes of the process, only 5 % of cellular cholesterol is esterified in the pre-beta-3-HDL and alpha-HDL before it reaches LDL (Miida *et al.* 1990). As the remainder of free cholesterol first reaches other lipoproteins containing apoB and then it comes freely transferred into HDL subpopulations that specifically regulate the rate of its esterification, it was concluded that practically all free cholesterol substrate for the LCAT procedure originates from LDL and VLDL particles (Huang *et al.* 1993).

Plans for use of LCAT procedures in treatment of CVD

The measurement of LCAT mass, LCAT activity and LCAT esterification rate produced the hypothesis that by increasing the concentration of LCAT might be achieved a support of the RCT and the FC efflux from peripheral cells with resulting therapeutic effect in patients with atherosclerosis. However, this hypothesis in animal models has not proven. Over-expression of human LCAT in transgenic rabbits prevented diet-induced atherosclerosis (Hoeg *et al.* 1996, Brousseau *et al.* 1997). On the other hand, over-expression of human LCAT in mice did not prevent diet-induced atherosclerosis (Francone *et al.* 1997, Mehlum *et al.* 1997). On the contrary, high plasma HDL concentrations were associated with enhanced atherosclerosis in this animal model.

Not even 10 years later, large clinical trials found no protective effect of high concentration of HDL induced by the inhibition of cholesteryl ester transfer protein with torcetrapib (Nissen *et al.* 2007). Neither the further studies with torcetrapib derivatives have brought a clinical benefit (Eyvazian and Frishman 2017). These experiences support the idea that a moderate changes in the process of transformation free cholesterol to cholesteryl esters may cause a butterfly effect by a change of the intended target.

FER_{HDL} – fractional esterification rate in HDL

We have tried to compare LCAT esterification rate in normal population of men and women, in those with risks of cardiometabolic diseases and in those who already suffer of them. We studied that part of LCAT process (FER_{HDL}), which directly focuses on a change of free cholesterol into cholesteryl esters that takes place in HDL (Dobiášová and Frohlich 1996). The principle of the method is a radioassay of cholesterol esterification in the HDL labeled with ^{3}H-FC (Dobiášová *et al.* 1992) in plasma depleted of apoB containing lipoproteins. This depletion makes it possible to omit a secondary source of FC from LDL and VLDL. Thus, FER_{HDL} measures autologous capacity of LCAT and HDL in the natural plasma environment, which allows to eliminate the effect of other reaction products such as lysolecithin, whose increased concentration was observed in cardiovascular diseases and is able to inhibit the LCAT reaction *in vitro* (Wells *et al.* 1986). FER_{HDL} depends only slightly on the concentration of plasma total or LDL-cholesterol but considerably correlates with a rise of triglycerides and a fall in HDL-cholesterol. FER_{HDL} is controlled by a relative occurrence of large and small HDL particles in which LCAT reaction takes place. Surprisingly, there is also a highly positive correlation between FER_{HDL} and small-dense LDL particles and large VLDL particles, which had been removed prior to the reaction. This suggests an intimate relationship between apoA and apoB lipoproteins in the actual plasma (Ohta *et al.* 1995, Dobiášová *et al.* 2011). FER_{HDL} may therefore be regarded as a marker of plasma phenotype, since it reflects the distribution of differently-sized particles of lipoproteins.

It was shown that FER_{HDL} is significantly elevated in humans at risk of atherosclerosis, e.g. higher in men than in women (those before menopause), higher in hypertensives and diabetics type 2 or in patients with positive findings on coronary angiography (Frohlich and Dobiášová 2003, Dobiášová *et al.* 2011) and those with risk factors of CVD (Rašlová *et al.* 2011). Although FER_{HDL} can predict the particle size in HDL and LDL, which, in turn, predicts CVD risk, it is not applicable to routine clinical examinations.

AIP – atherogenic index of plasma [log(TG/HDL-C)]

We looked for a clinically available marker that could at least partially replace the FER_{HDL} test, which takes into account lipoprotein particle size distribution. Since Gaziano *et al.* (1997) reported that the ratio of triglycerides to HDL was a strong predictor of myocardial infarction, additional findings have been

made regarding the relationship between HDL-C and TGs. Although an independent, inverse relationship between HDL-C and cardiovascular risk was demonstrated beyond any doubt (Miller 1987), the contribution of triglycerides to cardiovascular risk was underestimated. However, triglycerides play a role in the regulation of lipoprotein interactions but they cannot serve convincingly as an independent marker of CVD. Among the first, who described the importance of linking triglycerides with HDL to predict CVD risk, was Treatment Panel III, referring this combination as an atherogenic dyslipidemia (Grundy *et al.* 2004). This claim is supported by the evidence that an increased plasma concentration of TGs is associated with increased populations of small dense LDL and large VLDL, with elevated cholesteryl ester transfer from HDL to apoB containing lipoproteins (Guerin *et al.* 2001) and also with an increased incidence of coronary artery disease (Hokanson and Austin 1996). Triglycerides have been proposed to be a major determinant of cholesterol esterification/transfer and HDL remodeling in human plasma (Murakami *et al.* 1995).

Increased ratio TG/HDL-C thus represents a cardiometabolic risk which is determined mainly by the increase in risk subpopulations – large VLDL and small LDL and small HDL. Higher concentrations of total HDL cholesterol contain more cardioprotective HDL_{2b} subpopulation and large LDL (Jeyarajah *et al.* 2006). For better expression of the relationship between triglycerides and HDL-C, we adopted the log-transformed molar ratio of TG/HDL-C, which we called atherogenic index of plasma (AIP). AIP is used as a logarithmically transformed value because in this form it produced better correlations and normal probability plots (Tan *et al.* 2004) and thus, it is more suitable from the statistical perspective than simple TG/HDL-C ratio (Urbina *et al.* 2011). The correlation plot between simple TG/HDL-C ratio and HDL and LDL particle sizes is curvilinear, while with log-transformed TG/HDL-C ratio is linear (Dobiášová *et al.* 2011).

Table 1. Atherogenic impact of LCAT, FER_{HDL} and AIP biomarkers: the correlation between AIP and the size of lipoprotein subpopulations (adapted from Dobiášová *et al.* 2011).

AIP	r	AIP	r	AIP	r
HDL large	-0.597[a]	*LDL large*	-0.670[a]	*VLDL large*	0.816[a]
HDL small	0.272[b]	*LDL small*	0.477[a]	*VLDL small*	-0.184[c]

The bivariate correlation coefficients (r) between AIP and size of lipoprotein subpopulations. [a] $p<0.0001$, [b] $p<0.002$, [c] $p<0.01$.

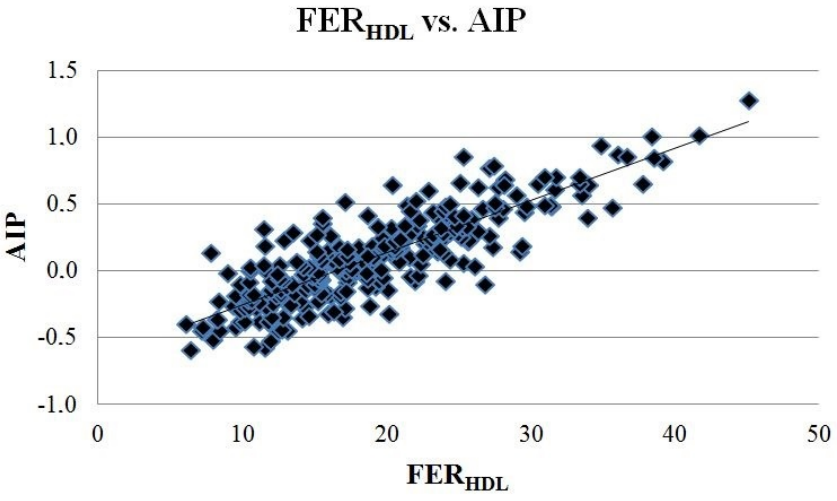

Fig. 1. Atherogenic impact of LCAT, FER_{HDL} and AIP biomarkers: the correlation between FER_{HDL} and AIP ($r^2 = 0.7112$, $y = 0.039x - 0.6446$).

We found that both tests – esterification rate in HDL (FER_{HDL}) as well as AIP – are controlled by the same size of the lipoproteins and highly correlate with each other (Fig. 1). The significance of lipoprotein particle size for determining AIP is shown also by the respective correlation coefficients *r* (Table 1) (Dobiášová *et al.* 2011). AIP correlates inversely with large HDLs and large LDL, which may be considered as anti-atherogenic effect, while AIP correlates positively with small dense LDLs and large VLDLs (atherogenic

effect). The values for both FER_{HDL} and AIP increased significantly with increasing atherogenic risk (Dobiášová and Frohlich 2001, Frohlich and Dobiášová 2003, Rašlová *et al.* 2011).

During the past years AIP was frequently used for the examination of different risk subjects (Dobiášová *et al.* 2001, Di Castelnuovo *et al.* 2007, Onat *et al*. 2010, Nwagha *et al.* 2010, Soška *et al.* 2011, Soška *et al.* 2012, Stefanović *et al.* 2012, Dos Santos-Weiss *et al*. 2013, Onyedum *et al.* 2014, Essiarab *et al*. 2014, Hermans *et al.* 2012, Akbas *et al*. 2014, Vrablík *et al.* 2014, Niroumand *et al.* 2015, Zhu *et al*. 2015, Nunes *et al.* 2015, Shen *et al*. 2017). When using readily available biochemical assays, AIP provides valuable information about the atherogenicity of plasma and may quantify the response to therapeutic intervention. The calculator of AIP, which sequesters investigated subjects into three categories of CVD risk (AIP Calculator on line), may be helpful in clinical practice.

Conclusions

The final atherogenic or antiatherogenic effects of LCAT depend on a balance between the efflux of free cholesterol from peripheral cells to the extracellular space, its esterification and destinations of CEs produced either into a futile excessive cycle together with apoB lipoproteins back to the plasma membranes or together with HDL_{2b} and SR-BI into the protective catabolism in the liver. Even if we comprehensively consider all LCAT activities when planning the therapy of cardiovascular diseases, it still remains a space for the butterfly effect when just a tiny deviation in a set of steps will change the sign of the impact. This does not detract from the importance of LCAT in maintaining the cholesterol metabolic balance and opens next possibilities for meaningful research. Biomarkers FER_{HDL} and AIP can help to reveal the risk of CVD having in mind that it reflects not only the lipid concentrations but also the interaction of LCAT with tiny changes in lipoprotein subpopulations.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

ABCA1 and ABCG1, ATP-binding cassette transporters; AIP, atherogenic index of plasma (log(TG/HDL-C); apoA, apoprotein A; apoB, apoprotein B; apoC, apoprotein C; C, cholesterol; CE, cholesteryl ester; CER, cholesterol esterification rate; CETP, cholesteryl ester transferring protein; CVD, cardiovascular disease; FER_{HDL}, fractional esterification rate in HDL; FC, free cholesterol; HDL, high density lipoprotein; HDL-C, HDL-cholesterol; LCAT, lecithin cholesterol acyltransferase; LDL, low density lipoprotein; LDL-C, LDL-cholesterol; NMR, nuclear magnetic resonance; RCT, reverse cholesterol transport; SR-BI, scavenger receptor class B type I; TG, triglycerides; VLDL, very low density lipoprotein; VLDL-C, VLDL-cholesterol.

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AIP CALCULATOR is available on *www.biomed.cas.cz/fgu/aip/calculator.php*

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