Atherogenic Index of Plasma [Log(Triglycerides/HDL-Cholesterol)]: Theoretical and Practical Implications

In individuals with type 2 diabetes, metabolic syndrome, and the combined dyslipidemia, cardiovascular risk is increased by a clustering of risk factors such as abdominal obesity, impaired fasting glucose, increased blood pressure, low HDL-cholesterol (HDL-C), increased triglycerides (TGs), and an increase in small, dense LDL particles. The current increase in the incidence of type 2 diabetes in the population perhaps poses the most urgent cardiovascular risk *(1)*. Although insulin resistance is crucial to the pathogenesis of the disease, the associated atherogenic lipoprotein phenotype considerably enhances the risk. Hence there is an ongoing intense search for a medication capable of modifying the atherogenic lipid profile as well as lowering glucose. Medications of the thiazolidinedione class traditionally used for glycemic control in patients with type 2 diabetes seem to hold promise in this respect.

In this issue of *Clinical Chemistry*, Tan et al. *(2)* studied the effect of pioglitazone, a thiazolidinedione that reduces insulin resistance, on the atherogenic lipoprotein profile in individuals with type 2 diabetes. Data were obtained from four randomized, placebo-controlled dose–response clinical trials examining the efficacy of therapy with pioglitazone when added to sulfonylurea, metformin, or insulin therapy. To evaluate changes in the lipoprotein profile induced by their therapy, Tan et al. *(2)* used the atherogenic index of plasma (AIP), calculated as log(TG/HDL-C), with TG and HDL-C expressed in molar concentrations *(3)*. Changes in the AIP of pioglitazone-treated patients were evaluated by a statistical model of single-slope analysis of covariance, and each of the pioglitazone treatments was compared with placebo. All pioglitazone treatment groups had a high AIP at baseline, and pioglitazone treatment significantly decreased the AIP in each study group. Pioglitazone treatment groups had significantly lower AIP than did their respective placebo controls. AIP correlated inversely with insulin sensitivity measures, i.e., the homeostasis model measurement (HOMA-S) and the quantitative insulin sensitivity check index (QUICKI). The study also showed differences between pioglitazone and placebo groups in mean percentage change from baseline. Tan et al. *(2)* compared the results of AIP analysis with those of a TG/HDL-C ratio analysis used in another study *(4)*. The *P* values for AIP were consistently lower than those for TG/HDL-C. In addition, normal probability plots showing the relationship of residual error to expected residuals from a gaussian distribution showed a higher correlation for AIP in each study than for TG/HDL-C.

The authors should be complimented for evaluating this atherogenicity index to test its significance and statistical reliability in a large study with 1669 diabetic patients. They found AIP to be suitable and statistically reliable.

AIP may be an important tool for analyzing the results of clinical trials. The association of TGs and HDL-C in this simple ratio theoretically reflects the balance between risk and protective lipoprotein forces, and both TGs and HDL-C are widely measured and available.

Since Gaziano et al. reported that "the ratio of triglycerides to HDL was a strong predictor of myocardial infarction" *(5)*, additional findings have been made regarding the relationship between HDL-C and TGs.

Although an independent, inverse relationship between HDL-C and cardiovascular risk has been demonstrated beyond any doubt, the contribution of TGs to cardiovascular risk has been underestimated. This may have been attributable to the high variability of plasma TG concentrations (which decreases the statistical significance of assessments), the lack of information on the role of TGs in biochemical mechanisms, or the incessant efforts to find an atherogenic marker independent of other lipids. In reality, any therapeutic hypolipidemic intervention leads to bigger or smaller changes in the spectrum of plasma lipids and apoproteins, including changes in lipoprotein particle sizes and changes in cholesterol esterification and lipolytic rates. Thus, TGs play the role of a regulator of lipoprotein interactions and not the role of an independent risk marker. This claim is supported by evidence that an increased plasma concentration of TGs is associated with (*a*) an increased incidence of coronary artery disease (CAD) *(6)*, (*b*) an increased population of small, dense LDLs, and (*c*) enhanced cholesteryl ester (CE) mass transfer from HDL to apolipoprotein B (apoB)-containing lipoproteins *(7)*. TGs have also been proposed to be a major determinant of cholesterol esterification/transfer and HDL remodeling in human plasma *(8)*.

It is difficult to fully appreciate the complexity of the lipoprotein phenotype or changes in the lipoprotein profile induced by therapeutic interventions. Perhaps changes in the rate of enzyme reactions such as cholesterol esterification may help us better to understand this complexity. The principle of this test is measurement of the rate of cholesterol esterification (FER_{HDL}) by lecithin cholesterol acyltransferase (LCAT) in plasma containing only HDLs *(9)*.

Because most human CEs are produced in plasma by the action of LCAT, this process, which takes place only in HDLs, is exceptionally important for intravascular cholesterol transport. Cholesterol esterification is a substantial part of the process called reverse cholesterol transport, representing the chain of consecutive steps starting with

efflux of cell free cholesterol (FC) to apoA-I, forming nascent HDL particles with consecutive FC esterification by LCAT *(10)*. Part of the newly produced CE is then transported by means of CE transfer protein (CETP) to VLDL in exchange for TGs and, through the lipolytic cascade, to LDL *(11)*. Another part of the CE remaining on HDLs is transferred to the cell-surface scavenger receptor class B type I (SR-BI), which mediates selective HDL-CE uptake into cells *(12)*. These two destinations differ in their impact on risk: the HDL pathway into SR-BI is considered an antiatherogenic pathway, whereas the CETP pathway into VLDL appears to be proatherogenic.

Although LCAT does not affect the first part of reverse cholesterol transport, i.e., the efflux of FC from cells, its key role lies in the interaction with HDL particles. FC esterification proceeds most effectively on the smallest HDL particles, whereas large HDL particles inhibit the reaction. Thus, the ratio of the smallest HDL particles to large HDL particles regulates the esterification rate, expressed as FER_{HDL}. A significant inverse correlation has been observed between FER_{HDL} and the size of HDL particles *(13)*. Thus, FER_{HDL} predicts particle size in HDL.

An even more striking finding was that FER_{HDL} can also predict LDL particle size [$r = -0.82$ *(3)*], and this is despite the fact that LDLs are actually removed from the reaction as a source of additional FC (FER_{HDL} is measured in plasma-depleted apoB lipoproteins). This provides evidence that LDL and HDL particle patterns are closely synchronized with respect to the associations with TG and HDL-C concentrations.

The cholesterol esterification rate and HDL particle size are the points at which TGs interact with HDL-C. Low HDL-C and high TG concentrations induce both an increase in the proportion of small HDL particles and an increase in small, dense LDL particles; FER_{HDL} also increases. The CETP rate transferring CE to VLDLs also increases in this scenario.

This mechanism is supported by findings of significant correlations between FER_{HDL} and HDL-C (inverse) and TGs (positive) in any cohort of healthy or diseased individuals with normal or abnormal plasma lipid profiles *(3, 13–15)*.

The highly significant association between FER_{HDL} and AIP was found in all 35 cohorts (a total of 1433 individuals) with various risks of atherosclerosis (newborns; children; healthy men and women; pre- and postmenopausal women; patients with hypertension, type 2 diabetes, or dyslipidemia; and those with angiographically documented CAD). The values for both FER_{HDL} and AIP increased significantly with increasing atherogenic risk (AIP from −0.24 to 0.51). In patients with type 2 diabetes, FER_{HDL} and AIP were among the highest values *(3)*.

These results suggest that AIP reflects the delicate metabolic interactions within the whole lipoprotein complex.

The clinical impact of FER_{HDL} and AIP was seen in a recent study assessing the predictive value of various clinical and biochemical markers for angiographically defined CAD (aCAD) *(15)*. Patients (788 men and 320 women) undergoing coronary angiography were classified into groups with positive and negative CAD findings. A large number of variables were assessed, including alcohol intake and exercise habits, and numerous lipids were measured, including plasma HDL unesterified cholesterol, apoB, AIP, and the ratio TC/HDL-C. In a multivariate logistic model, significant predictors of the presence of aCAD were FER_{HDL}, age, smoking, and diabetes. When FER_{HDL}, a nonclassic lipoprotein marker, was omitted from this model, the significant predictors were AIP, age, smoking, waist circumference, and diabetes. If only laboratory tests were included in the multivariate model, FER_{HDL} appeared to be the sole predictor of aCAD.

In summary, Tan et al. *(2)* have shown the practical use of AIP for assessing changes in the lipoprotein profile during pioglitazone clinical trials. When using the results of well-standardized assays, AIP provides information about the atherogenicity of plasma and quantifies the response to therapeutic intervention. Application of AIP to data from earlier trials may offer new insights.

Supported by research grants from the Grant Agency of the Czech Republic (Grant 306/96/K220) and from the Ministry of Health of the Czech Republic (Grant NA/6590-3).

References

1. Gilling L, Suwattee P, DeSouza C, Asnani S, Fonseca V. Effects of the thiazolidinediones on vascular risk factors. Am J Cardiovasc Drugs 2002;2:149–56.
2. Tan MH, Johns D, Glazer NB. Pioglitazone reduces atherogenic index of plasma in patients with type 2 diabetes. Clin Chem 2004;50:1184–8.
3. Dobiášová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER_{HDL}). Clin Biochem 2001;34:583–8.
4. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Cardiovascular risk factors clustering with endogenous hyperinsulinaemia predict death from coronary heart disease in patients with type II diabetes. Diabetologia 2000;43:148–55.
5. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. Circulation 1997;96:2520–5.
6. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor to cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population based prospective studies. J Cardiovasc Risk 1996;3:213–9.
7. Guérin M, Le Goff W, Lassel TS, Van Tol A, Steiner G, Chapman MJ. Proatherogenic role of elevated CE transfer from HDL to $VLDL_1$ and dense LDL in type 2 diabetes. Arterioscler Thromb Vasc Biol 2001;21:282–9.
8. Murakami T, Michelagnoli S, Longhi R, Gianfranceschini G, Pazzucconi F, Calabresi L, et al. Triglycerides are major determinants of cholesterol esterification/transfer and HDL remodeling in human plasma. Arterioscler Thromb Vasc Biol 1995;15:1819–28.
9. Dobiášová M, Frohlich J. Assays of lecithin cholesterol acyltransferase (LCAT). In: Ordovas JM, ed. Methods in molecular biology. Lipoprotein protocols. Totowa, NJ: Humana Press, 1998:217–30.
10. Rader DJ. High-density lipoprotein and atherosclerosis. Am J Cardiol 2002;92:62i–72i.
11. Barter PJ, Hopkins GJ, Calvert GD. Transfers and exchanges of esterified cholesterol between plasma lipoproteins. Biochem J 1982;208:1–7.
12. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M. Identification of scavenger receptor SR-BI as a high-density lipoprotein receptor. Science 196;271:518–20.

13. Dobiášová M, Stříbrná J, Pritchard PH, Frohlich J. Cholesterol esterification rate in plasma depleted of very low and low density lipoproteins is controlled by the proportion of HDL2 and HDL3 subclasses: study in hypertensive and normal middle-aged and septuagenarian men. J Lipid Res 1992;33: 1411–8.

14. Dobiášová M, Rašlová K, Rauchová H, Vohnout B, Ptáčková K, Frohlich J. Atherogenic lipoprotein profile in families with and without history of early myocardial infarction; fractional esterification rate of cholesterol in plasma depleted of apoB lipoproteins (FER_{HDL}) and logarithmically transformed ratio of triglycerides to HDL-cholesterol. Physiol Res 2001;50:1–8.

15. Frohlich J, Dobiášová M. Fractional esterification rate of cholesterol and ratio of triglycerides to HDL-cholesterol are powerful predictors of positive findings on coronary angiography. Clin Chem 2003;49:1873–80.

Milada Dobiášová

Vídenská 1083
Krc
PRAHA 4, NA 142 20 Czech Republic
Fax 420-2-41062488
E-mail dobias@biomed.cas.cz

DOI: 10.1373/clinchem.2004.033175