

‘Triglyceride effect’ on the dynamics of plasma lipoproteins and its possible link to atherogenesis

To the Editor,

The metabolic link between cholesterol and atherogenesis is a fundamental premise on which scientific literature abound with results and publications. Apart from cholesterol, many other analytes are now considered to act as the driving force behind cholesterol uptake by the arterial intima. Among them plasma triglycerides have gained significant importance as atherogenic accelerator, by driving cholesterol into arterial intima. It is appropriate to evaluate and understand the role of ‘triglyceride effect’ on lipid metabolism and its clinical outcome (1–4).

Table 1 shows the changing perspectives on changing pattern of risk factors associated with atherosclerosis.

Lipoproteins are a transportable form of lipid components enclosed in a phospholipid membrane with apoproteins to guide their transport and utilization. The lipid components are mainly triglycerides [in very low-density lipoproteins (VLDL) and chylomicrons] and cholesterol esters [in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol] (Fig. 1) (5).

Lipoproteins are divided into groups according to their physical characteristics such as density or mobility in an electrophoretic field. Lipoproteins are synthesized in the liver where dysfunction can lead to the production of abnormal lipoprotein subtypes.

Dynamic equilibrium

Definitive subdivision of lipoproteins has long been a bone of contention, and it was felt that in reality the particles are reportedly in dynamic equilibrium, with frequent interactions and transfer of lipids between different subclasses. Triglyceride levels are reported to

have direct influence on this equilibrium and also on the shape, size, and atherogenicity of the lipoproteins. This effect is reported to be mediated through a protein called ‘cholesterol ester transport protein’ (CETP) which transports triglycerides from VLDL and chylomicrons to LDL and HDL lipoproteins in hypertriglyceridemic conditions. Consequently, cholesterol esters are transported in the opposite direction, altering the physical characteristics of the lipoproteins (Fig. 2) (6, 7).

Triglyceride effect

It is now suggested that triglyceride exerts its effect by altering the physical characteristics of lipoprotein particles which also alters their atherogenic potential. CETP plays a vital role, enabling rapid transfer of triglycerides and cholesterol esters between lipoprotein subclasses.

In hypertriglyceridemia excess triglycerides are transferred to LDL and HDL through CETP in an attempt to establish equilibrium. This concept has led to the introduction of several subclasses of lipoproteins, with variations in physical characteristics and reactivity. Many LDL subfractions have been described, which are reported to be most dense and most atherogenic. Triglycerides alter the properties of both HDL and LDL cholesterol making them small and dense (Fig. 2) (8).

In view of these findings it is now believed that it is important to measure LDL subfractions to accurately assess the level of cardiac risk in such patients. LDL subtype identification and measurement are very difficult to carry out as a routine procedure in the clinical chemistry laboratory. However, the strong relationship between plasma triglyceride and LDL may be used to

Table 1. Old, old/new, and new risk factors for atherosclerosis (3)

Old	Old/new	New
Sex (men > women)	High-normal blood pressure	Apolipoprotein B; apolipoprotein A-I
Age	Metabolic syndrome	Triglycerides; triglyceride-rich lipoprotein remnants
Family history of premature cardiovascular disease	Diabetes mellitus; impaired glucose tolerance; impaired fasting glucose	Small, dense LDL; oxidized LDL; antibodies against oxidized LDL
Total cholesterol; LDL cholesterol; HDL cholesterol (negative risk factor)		Lipoprotein(a)
Hypertension		Homocysteine
Smoking		High-sensitivity C-reactive protein

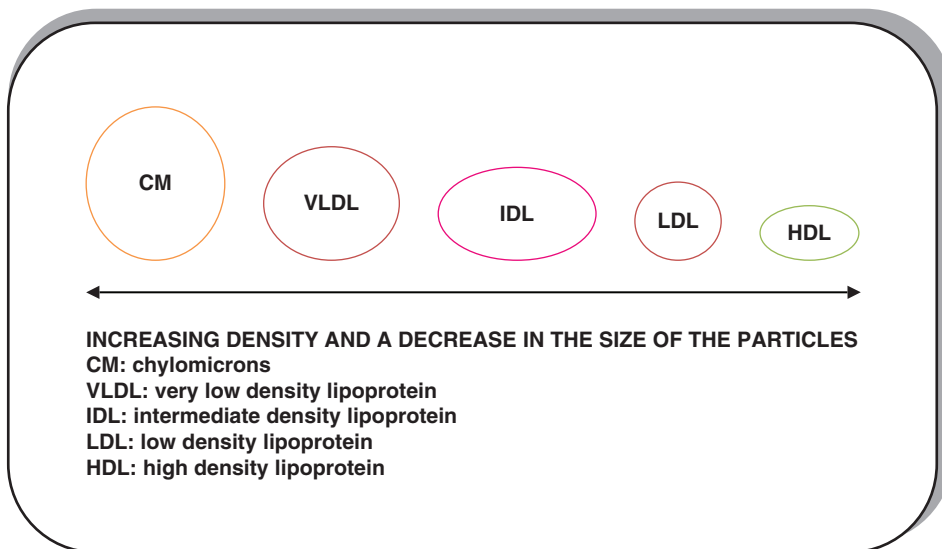


Fig. 1. Lipoprotein classification.

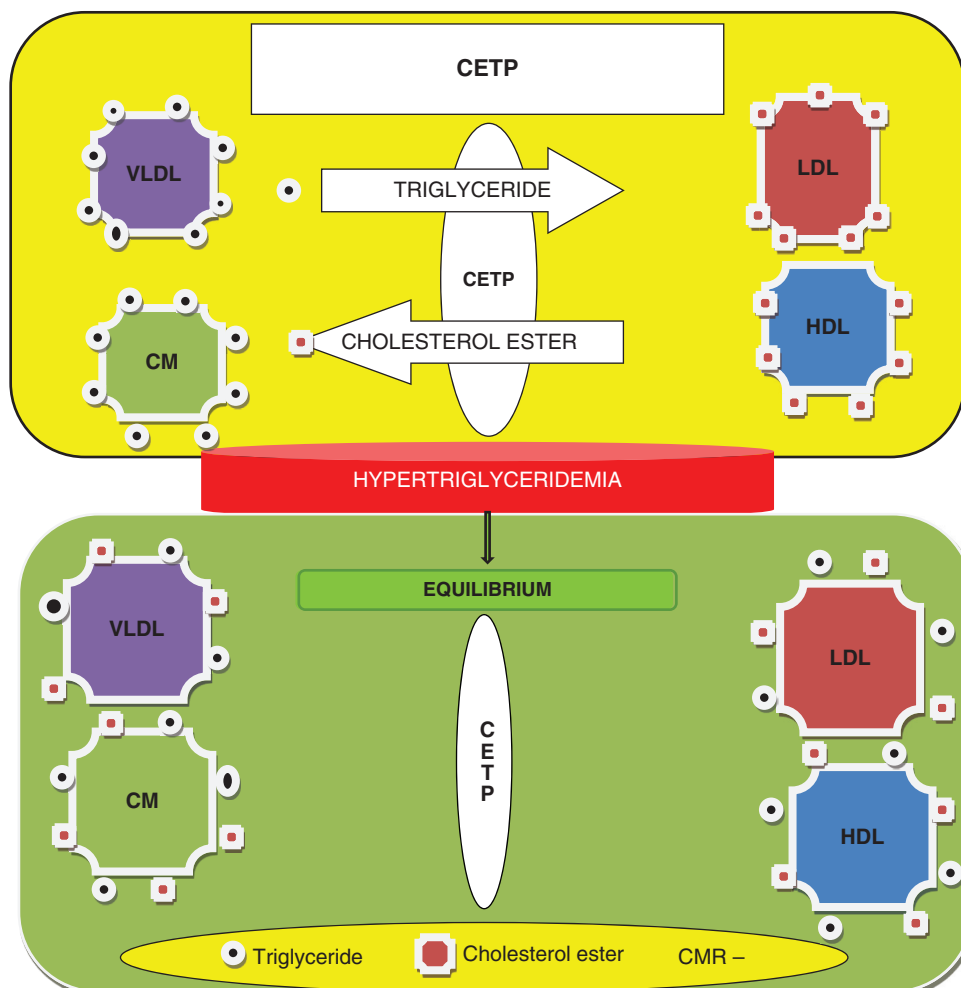


Fig. 2. Cholesterol ester transfer protein.

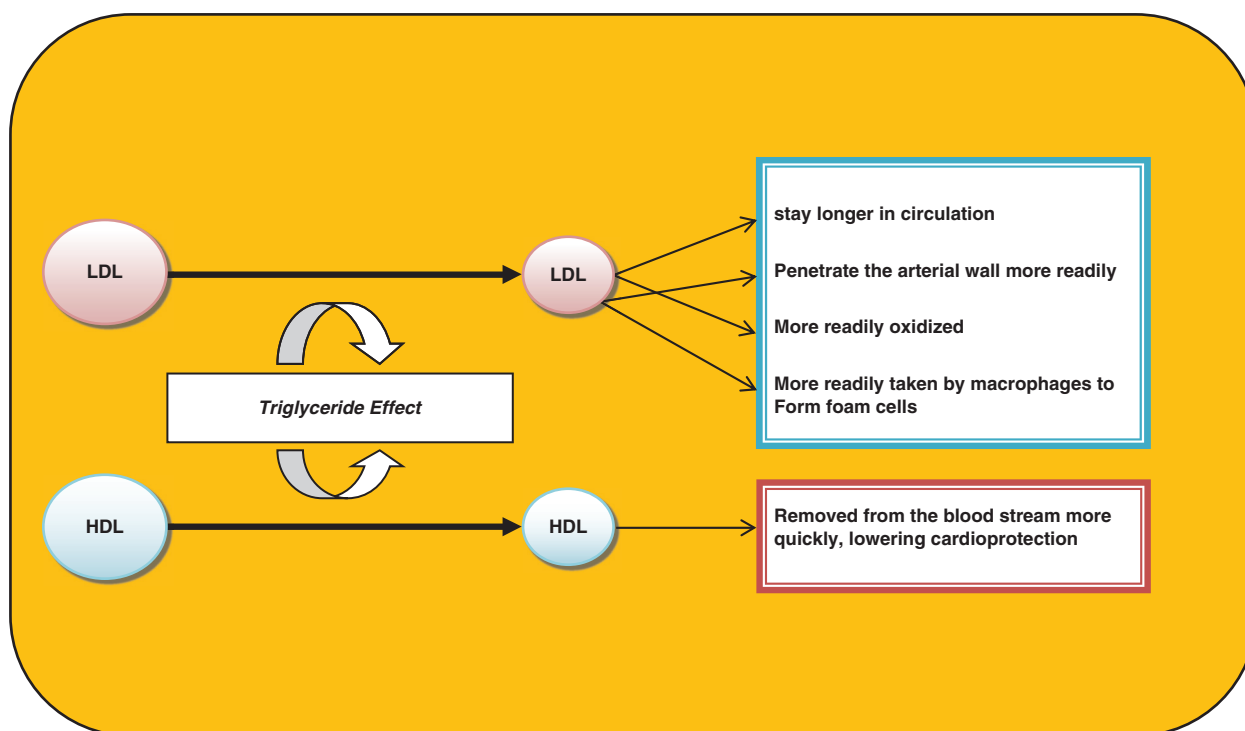


Fig. 3. The triglyceride effect.

assess the distribution of lipoproteins in subfractions. Elevated triglyceride levels accelerate the CETP-induced lipid shift, resulting in smaller and more atherogenic LDL (Fig. 3). Plasma triglyceride level is the major determinant of LDL size (9, 10).

Small, dense lipoproteins have been strongly associated with cardiovascular risk in many studies.

- 1) Patients with higher risk of premature coronary heart disease (CHD) have predominantly small, dense LDL.
- 2) The level of small, dense LDL particles was significantly correlated with reduced number diameter in coronary artery segments.
- 3) The level of plasma triglycerides (hypertriglyceridemia) is a reliable indicator of small, dense LDL (11).

Cholesterol alone is not the answer

Many still rely on plasma cholesterol level to assess cardiac risk in such patients in spite of numerous studies indicating that triglycerides are another important risk factor to be considered.

A few studies that emphasized a fall in plasma cholesterol level which associated with a reduction of coronary artery disease did not take the triglyceride effect into consideration. This led to overestimation of cholesterol reduction as the major concern in patients with

coronary artery disease and resulted in giving more importance to hypocholesterolemic agents (11, 12). However, the focus is now shifted to other therapeutic methods such as raising HDL cholesterol levels through administration of CETP inhibitors. But the findings of studies related to CETP inhibitors seem to suggest that it is more important to restore HDL cholesterol functionality than merely increasing HDL cholesterol levels (13), prompting more studies to evaluate the dynamics of lipoprotein metabolism in health and disease in general.

Particularly, there is a real need for reevaluation and serious reconsideration to study the triglyceride effect on the dynamics of lipoprotein cholesterol and triglyceride in the pathophysiology of atherogenesis.

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