

Fasting and Nonfasting Triglycerides in Cardiovascular and Other Diseases

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Received September 21, 2015

Accepted October 5, 2015

Summary

Moderately elevated plasma/serum triglycerides (2-10 mmol/l) signalize increased risk for cardiovascular disease or presence of non-alcoholic steatohepatitis. Extremely elevated triglycerides (more than 10 mmol/l) signalize increased risk for pancreatitis and lipemia retinalis. The concentration of triglycerides is regulated by many genetic and nongenetic factors. Extremely elevated triglycerides not provoked by nutritional factors, especially inappropriate alcohol intake are more likely to have a monogenic cause. On the contrary, mildly to moderately elevated triglycerides are often caused by polygenic disorders; these could be also associated with central obesity, insulin resistance, and diabetes mellitus. Concentration of triglycerides is also closely interconnected with presence of atherogenic remnant lipoproteins, impaired reverse cholesterol transport and more atherogenic small LDL particles. In general, there is tight association between triglycerides and many other metabolic factors including intermediate products of lipoprotein metabolism which are frequently atherogenic. Therefore, reliable evaluation of the independent role of triglycerides especially in atherosclerosis and cardiovascular disease is difficult. In individual cases values of HDL cholesterol, non-HDL cholesterol (total minus HDL cholesterol), non-HDL/nonLDL cholesterol (total minus HDL minus LDL cholesterol, especially in nonfasting status), atherogenic index of plasma and/or apolipoprotein B could help in decisions regarding aggressiveness of treatment.

Key words

Fasting triglycerides • Nonfasting triglycerides • Cardiovascular disease • Lipoproteins

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Introduction

As hunter and a gatherers humans developed several mechanisms for energy storage and expenditure. One of the key players in these processes are triglycerides. Their storage and circulation in blood is kept under control by several enzymes, which are regulated by many genes and they reflect the nutritional needs of organism including fasting and nonfasting status (White 2010, Havel 1994). In addition, triglycerides are closely associated with many other lipid factors. They are positively associated with atherogenic LDL cholesterol, presence of small LDL particles, remnant lipoproteins, apolipoprotein C-III (Apo C-III) and negatively with atheroprotective HDL cholesterol and apolipoprotein C-II (Apo C-II). This implicates that reliable assessment of the real and independent role of circulating triglycerides in the process of atherosclerosis and other diseases in epidemiological and clinical studies is difficult and that robustness of their association with cardiovascular disease depends more on the extent of statistical standardization for other risk and lipid factors than on their real biological role. Epidemiological evidence and evidence from clinical trials must be therefore also supported by some physiological evidence. This review is focused on the role of triglycerides mainly in atherosclerosis and cardiovascular disease and presents

data from epidemiological and physiological studies and offers some implications for clinical practice. The impact of alcohol and particularly the treatment of hypertriglyceridemia are in detail discussed elsewhere in this supplement (Kovar and Zemankova 2015, Vrablik and Ceska 2015).

Epidemiology and definitions

In several prospective population-based studies triglycerides for a long time has been found to be significant and independent risk factor for cardiovascular disease with recently renewed interest (Austin 1999, Bansal *et al.* 2007, Libby 2015, Nordestgaard *et al.* 2007, Nordestgaard and Varbo 2014, Tirosh *et al.* 2007).

According to already classic metaanalysis of population based prospective studies, this effect was rather modest in men (response rate per 1 mmol/l – increase 1.14), but stronger in women (response rate per 1 mmol/l – increase 1.37) (Hokanson and Austin 1996). In more recent study in women, the strongest effect was observed when nonfasting levels of triglycerides were analyzed (Bansal *et al.* 2007). Similar findings were found in non-European – Asian and Pacific population (Patel *et al.* 2004). Most patients manifesting cardiovascular disease have elevated triglycerides accompanied by low HDL cholesterol. This pattern is also most frequently found in patients with peripheral artery disease (Valdivielso *et al.* 2014a).

Table 1. Definition of hypertriglyceridemia (modified Hegele *et al.* 2014).

	Value of triglycerides	Risk factor for
<i>Normal values</i>	Less than 1.7 mmol/l	–
<i>Mild-to-moderate hypertriglyceridemia</i>	1.7-10.0 mmol/l	Cardiovascular disease Non-alcoholic steatohepatitis Pancreatitis
<i>Severe hypertriglyceridemia</i>	More than 10.0 mmol/l	Lipemia retinalis

Hypertriglyceridemia is accordingly to recent recommendations categorized as mild, moderate and extreme (Table 1) (Hegele *et al.* 2014). Mild to moderate values are most often associated with cardiovascular events and non-alcoholic steatohepatitis while extremely elevated values are most often associated with pancreatitis and lipemia retinalis. On the contrary, low levels especially of nonfasting triglycerides associated with relatively common mutations in lipoprotein lipase (LPL) have positive effect on mortality as found in recent work, in which stepwise reduced risk of mortality by decreasing concentrations of nonfasting plasma triglycerides was detected. In this study age and sex adjusted hazard ratios were 0.84 (95 % CI 0.73-0.96) for 2.00-2.99 mmol/l, 0.67 (95 % CI 0.60-0.76) for 1.00-1.99 mmol/l, and 0.51 (95 % CI 0.44-0.58) for individuals with nonfasting triglycerides less than 1.00 mmol/l. Similar results were found using multivariably adjusted hazard ratios (Thomsen *et al.* 2014). This work also confirmed that genetic studies could be in general free from confounding and that they might offer reliable results. Another evidence supporting this finding comes

from study focused on morphological signs of atherosclerosis and which proved, that lifelong low triglycerides resulting from genetic polymorphisms are associated with a decreased burden of atherosclerosis expressed as coronary artery calcification (Polin *et al.* 2008). This study using a genome-wide association approach found that heterozygous carriers (population of Lancaster Amish) of a null mutation in the gene encoding Apo C-III, which inhibits triglyceride hydrolysis express half the amount of Apo C-III present in noncarriers. Mutation carriers had lower fasting and postprandial serum triglycerides, higher levels of HDL-cholesterol and lower levels of LDL-cholesterol. In addition, subclinical atherosclerosis, as measured by coronary artery calcification, was less common in carriers than noncarriers. This suggests that lifelong deficiency of Apo C-III has a cardioprotective effect. On the other hand in prospective observational study of Israeli soldier men increase of triglycerides during 5 years was significantly associated with cardiovascular events (Tirosh *et al.* 2007). In this study association between changes over time in fasting triglyceride levels and coronary heart

disease risk was studied. Follow-up was more than 5.5 years after two measurements of fasting triglycerides 5 years apart. In approximately 14,000 healthy, untreated and young men with triglyceride levels less than 3.39 mmol/l the multivariate model adjusted for age, family history, fasting glucose, high-density lipoprotein cholesterol, blood pressure, body mass index, and changes between time 1 and time 2 in body mass index, physical activity, smoking status, and habit of eating breakfast revealed that triglyceride levels according to low, intermediate, and high tertiles (as measured at time 1 and time 2), the risk for coronary heart disease in men with high-tertile triglyceride levels at time 1 changed depending on the tertile at time 2 (hazard ratios, 8.23 [95 % CI, 2.50 to 27.13] for high/high, 6.84 [CI, 1.95 to 23.98] for high/intermediate, and 4.90 [CI, 1.01 to 24.55] for high/low, compared with the stable low/low group). The risk in men with low-tertile levels at time 1 also changed depending on the tertile at time 2 (hazard ratios, 3.81 [CI, 0.96 to 15.31] for low/intermediate and 6.76 [CI, 1.34 to 33.92] for low/high, compared with the stable low/low group). On the contrary, a decrease in initially elevated triglyceride levels was associated with a decreased risk compared with stable high triglyceride levels. However, still this risk remained higher than in those with persistently low triglyceride levels. Therefore, there is strong epidemiological evidence for the association between fasting and even more for nonfasting triglycerides and cardiovascular disease. The robustness of this association depends on design of the study and statistical standardization.

Most frequently encountered and discussed disorders associated with hypertriglyceridemia

Moderately elevated plasma/serum triglycerides signalize increased risk for cardiovascular disease, extremely elevated triglycerides signalize increased risk for pancreatitis and lipemia retinalis. Several genetic and non-genetic factors are included in regulation of triglycerides levels. Extremely elevated triglycerides (concentration more than 10 mmol/l) not provoked by dietary factors, especially by high alcohol intake are more likely to have a monogenic cause. On the contrary, mildly to moderately elevated triglycerides (concentration 2 to 10 mmol/l) have mostly polygenic origin and often coexist with other metabolic disturbances, mainly with central obesity, insulin resistance and diabetes mellitus.

However, changes of circulating triglycerides are rather marker for changes in several metabolic pathways, some of them definitely associated with so called cardiometabolic risk. Most recently discussed is the role of Apo C-III which inhibits triglyceride hydrolysis and has been implicated in coronary artery disease (Boren *et al.* 2015, Wyller von Ballmoos *et al.* 2015).

In particular, the increase in circulating triglycerides could signalize several entities and is associated with several diseases. The most frequently discussed ones are listed below and in Table 2.

From the point of view of atherosclerosis and cardiovascular disease there are three main areas where increased triglycerides indirectly indicate increased risk. First, increased triglycerides in fasting and even more in nonfasting status could be marker for increased levels of remnant lipoprotein particles, which could be directly atherogenic, they could penetrate into the vessel wall and cause inflammation. In contrast to LDL particles, they do not need to be modified/oxidized to become atherogenic (Varbo *et al.* 2014). They could be more important in women (McNamara *et al.* 2001) especially in women changing reproductive status from premenopause to menopause (Pitha *et al.* 2015). Their reliable measurement was based on sophisticated and not widely available methods (Nakajima *et al.* 1996, Nakano *et al.* 2011). Recent studies used so called nonHDL/nonLDL cholesterol obtained mainly from nonfasting blood and calculated as total cholesterol minus LDL cholesterol minus HDL cholesterol. This parameter could rather reliably reflect cholesterol content in remnant lipoprotein particles and is strongly associated with cardiovascular events (Varbo *et al.* 2014).

Second and already mentioned is the inappropriate impact of Apo C-III on metabolism of lipids, which often leads to hypertriglyceridemia. Recent study focused on factors that predict the kinetics of VLDL1 triglycerides in 50 subjects with abdominal obesity and additional cardiometabolic risk factors. It showed that plasma triglyceride concentrations were dependent on both the secretion rate and fractional catabolism of VLDL1-triglycerides and VLDL1-apoB. Liver fat mass was independently and directly associated with secretion rates of VLDL1-triglycerides and VLDL1-apoB. Also plasma Apo C-III concentration was independently and inversely associated with the fractional catabolisms of VLDL1-triglycerides and VLDL1-apoB. These results indicated that plasma triglyceride concentrations in abdominal obesity were determined by

the kinetics of VLDL1 subspecies, catabolism being mainly dependent on Apo C-III concentration and secretion on liver fat content. Therefore, reduction in liver fat and targeting Apo C-III may be an effective approach for correcting triglyceride metabolism atherogenic dyslipidemia in obesity (Boren *et al.* 2015). The atherogenic process in general could be described in general as follows. Triglyceride-rich lipoprotein metabolism shifts from an apolipoprotein E system in normotriglyceridemic participants characterized by rapid clearance from circulation of very low density lipoproteins to an Apo C-III system in hypertriglyceridemic subjects, which is characterized by reduced clearance of triglyceride-rich lipoproteins and the formation of increased number the dense LDL particles more prone to modification/oxidation and therefore more atherogenic (Stavek *et al.* 1998, Sacks 2015).

Third, increased triglycerides could also indicate malfunctioning reverse cholesterol transport, namely malfunctioning of fraction cholesterol esterification rate of HDL as a causative factor of increased cardiovascular risk. The fraction esterification rate could be measured by rather sophisticated laboratory methods, but can be also reliably assessed by simple calculation from standard lipid profile as a logarithmically transformed ratio of molar concentrations of triglycerides to HDL-cholesterol. This parameter was named atherogenic index of plasma (AIP) (Dobiasova *et al.* 2006, Frohlich *et al.* 2001). The close association of fraction esterification rate of HDL with AIP can be explained by triglyceride participation in the production of large VLDL and small dense LDLs and have also been proposed to be the major determinants of cholesterol esterification/transfer and HDL remodeling in particles that regulate the esterification rate. The strong correlation of AIP with HDL lipoprotein particle size may also explain its high predictive value. It was proved, that AIP values significantly increase with increasing cardiovascular risk. Based on data from young children, healthy women, men and subjects with hypertension, diabetes mellitus, and mainly hypetriglyceridemia it was suggested that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high cardiovascular risk. In the population study men had higher AIP values than women. In patients undergoing coronary angiography, in statistical model that included age, body mass index, waist circumference, diabetes mellitus type 2, blood pressure, smoking, triglycerides, total, LDL, HDL cholesterol, ratio of total to HDL cholesterol and apolipoprotein B, AIP was the best

predictor of positive findings (Dobiasova *et al.* 2011). AIP was also a highly sensitive marker of differences in lipoprotein profiles in families of patients with premature myocardial infarction and in control families. As a marker of lipoprotein particle size it adds predictive value beyond that of the individual lipids including total/HDL cholesterol ratio. However, the changes of these risk biomarkers with different therapies and their relation to treatment outcomes have not been studied.

Another recently discussed entity is microvascular disease in patients with diabetes mellitus type 2 and its reduction by treatment by fenofibrate, drug reducing triglycerides (Rajamani *et al.* 2009). The mechanism is not clear but according to studies of renal diseases in diabetes mellitus it seems possible that causative factor might be stimulation of transforming growth factor beta by triglyceride-rich lipoproteins and inducing the production of reactive oxygen species causing damage to the glomeruli and glomerular glycocalyx and it could be speculated that these processes could also affect basal membranes in small vessels not only in kidneys. This hypothesis is supported by findings from experimental and clinical studies which strongly suggest that excess amounts of a triglyceride-rich lipoproteins worsens diabetes-associated microvascular and macrovascular disease, increases glomerular injury, increases tubulointerstitial fibrosis, and accelerates the progression of diabetic nephropathy (Rutledge *et al.* 2010).

Frequently discussed disorder associated with hypertriglyceridemia is non-alcoholic steatohepatitis. Liver inadequate triglyceride accumulation is probably one of the most frequent pathology in industrialized populations caused by an excess of energy intake for prevailing energy expenditure and/or higher alcohol intake and is probably also influenced by composition of diet, when high intake of saturated fatty acids or fructose could play an additional role (Jacome-Sosa 2014, Zimmermann *et al.* 2009). Therefore, reduction in liver fat and targeting of already discussed Apo C-III may be an effective approach for correcting triglyceride metabolism atherogenic dyslipidemia in obesity (Boren *et al.* 2015).

Extreme hypertriglyceridemia could be also strong risk factors of pancreatitis. The mechanisms are still not well understood but there is still permanently discussed hypothesis initially raised by Havel (1969) which focuses on the excess of triglycerides hydrolyzed by high levels of pancreatic lipase released in the vascular

bed of the pancreas. Subsequently, free fatty acids are formed in high concentrations, which overwhelm the binding capacity of albumin and they self-aggregate to micellar structures with detergent properties and then acinar cell and pancreatic capillary injury is promoted. The resultant ischemia creates an acidic environment, which further triggers free fatty acids toxicity.

Additionally, the elevated levels of chylomicrons increase the viscosity of blood and therefore impair the blood flow in the pancreas causing ischemia and acidosis within the pancreas. Furthermore, endoplasmic reticulum stress is also discussed as a causative factor (Havel 1969, Valdivielso *et al.* 2014).

Table 2. Role of elevated triglycerides in cardiovascular and other diseases.

	Triglycerides signalize	Mechanism(s)	Detected by
<i>Cardiovascular disease</i>	Elevated remnant lipoproteins	Direct atherogenic effect (inflammation of the vessel wall)	Non-HDL cholesterol Non-HDL/non-LDL cholesterol (nonfasting)
	Presence of increased number of small LDL particles	Proatherogenic effect (increased modification/oxidation of LDL)	Apolipoprotein B
	Impaired reverse cholesterol transport	Impaired esterification rate of HDL cholesterol	Low HDL cholesterol, Decreased level of apolipoprotein AI, Increased atherogenic index of plasma (log (tg/HDL))
	Increased level of apolipoprotein C-III	Lipoprotein lipase activity inhibited by apolipoprotein C-III	Hypertriglyceridemia
<i>Microvascular disease</i>	Not well controlled diabetes mellitus	Activation of transforming growth factor beta by triglyceride-rich lipoproteins	Hypertriglyceridemia Clinical findings
<i>Pancreatitis</i>	Increased FFA in circulation	Not exactly known, might be activation of pancreatic enzymes by increased FFA	Clinical findings: elevated urine amylases
<i>Steatohepatitis</i>	Triglycerides marker of impaired lipoprotein transport from liver	Liver inadequate triglyceride accumulation	Moderate hypertriglyceridemia and elevated liver tests and often C-reactive protein
<i>Lipemia retinalis</i>	Triglyceride rich particles - chylomicrons in substantially increased concentration	Dispersion of light caused by chylomicrons	Imaging of optic fundi Extreme hypertriglyceridemia

* FFA – free fatty acids.

Rather rare consequence of hypertriglyceridemia is lipemia retinalis which is a rare and asymptomatic condition which occurs when high levels of triglycerides and chylomicrons are present in blood. Creamy white appearance of retinal vessels occurs when triglyceride value reaches more than 20-30 mmol/l. Fundus changes are probably caused by dispersion of light caused by

chylomicrons, which are presented in substantially increased numbers/concentrations. These findings most commonly occur in familial hyperchylomicronemia, an autosomal recessive disorder associated with lipoprotein lipase or apolipoprotein C-II deficiency (Fred and Accad 1999).

Assessment of atherogenicity associated with triglycerides in clinical practice

The main task in clinical practice is to assess if hypertriglyceridemia is atherogenic. Several simple rules could help in such assessment. First, mild hypertriglyceridemia is most frequently associated with increased cardiovascular risk. If hypertriglyceridemia is more than 5-10 mmol/l its atherogenic potential could be decreased. In mild hypertriglyceridemia, non-HDL cholesterol (total minus HDL cholesterol) and/or apolipoprotein B could be reliable markers of atherogenic lipid profile as shown in Table 3 (Vaverkova *et al.* 2007). Recently, as already mentioned, simple method is used for assessment of cholesterol content of remnant lipoprotein particles by formula: total cholesterol minus LDL cholesterol minus HDL cholesterol (Varbo *et al.* 2014). However, in this case no recommended/target values are available and future studies are needed. The status of reverse cholesterol transport potentially affected by hypertriglyceridemia could be assessed by atherogenic index of plasma, where safe values are approximately 0 and less (Dobiasova *et al.* 2011).

Table 3. Target values of atherogenic plasma lipids in patients at very high risk (Vaverkova *et al.* 2007).

LDL-cholesterol	Lower than 2.0 mmol/l
Non-HDL-cholesterol	Lower than 2.8 mmol/l*
Apolipoprotein B	Lower than 0.8 g/l*

* recommended if the concentration of triglycerides exceeds 2.3 mmol/l.

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Conclusions

Hypertriglyceridemia is rather marker than causative factor for several disease entities, but mainly for cardiovascular disease. For prediction of cardiovascular events nonfasting triglycerides were stronger indicator, but this parameter is not yet well standardized, but promising for future clinical use. Triglycerides especially nonfasting are stronger indicator for future cardiovascular events in women and could reflect increased sensitivity of this population to increased levels of remnant lipoprotein particles. In individual cases values of HDL cholesterol, non-HDL cholesterol, non-HDL/nonLDL cholesterol, atherogenic index of plasma and/or apolipoprotein B could help in decisions regarding aggressiveness of treatment. These factors are better indicators for diagnosis and successful treatment, especially in patients with moderate to severe hypertriglyceridemia, but this is discussed in detail elsewhere in this supplement (Vrablik and Ceska 2015).

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This project was supported through the Internal Grant Agency of the Ministry of Health, Czech Republic (NT 14008-3/2013 and NT 13151-3/2013) and by the research project MH CZ – DRO (Institute for Clinical and Experimental Medicine – IKEM, IN 00023001) of the Ministry of Health of the Czech Republic.

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