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Target Audience

This educational activity is designed for primary care physicians, endocrinologists, cardiologists, internists, and other healthcare professionals involved in the diagnosis and management of dyslipidemia and its comorbidities.

Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Recognize the association between fasting triglyceride (TG) level changes over time and coronary heart disease (CHD) risk in young adults.
- Identify the development of minor strokes with increased total serum cholesterol levels.
- Compare the effectiveness of two statins on CRP (<2 mg/L) and LDL-C (<70 mg/dL) among patients with type 2 diabetes.

Accreditation

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Grantor

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LIPIDManagement

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Study Examines TG Levels and Associated CHD Risk Over Time in Young Men

A majority of evidence suggests at least a moderate association between the levels of fasting triglycerides (TG) and the risk for coronary heart disease (CHD). But how often should TG be measured? Lifestyle modification, including aerobic exercise, has been demonstrated to reduce TG levels at least modestly; indeed, meta-analyses suggest that for every 10 lbs of weight reduction, TG levels decrease by at least 6 mg/dL. Thus, measurement of TG at a single time point may not be a reliable indicator of an individual's long-term triglyceridemia.

In a recent observational study, Tirosh and colleagues examined the association between changes in fasting TG levels over time and CHD risk in young adults, specifically young men already enrolled in the MELANY (Metabolic, Lifestyle, and Nutrition Assessment in Young Adults) trial. The MELANY study was designed to investigate risk factors for common diseases in young adults by evaluating service personnel of the Israeli Defense Forces every 5 years between the ages of 25 and 35 years, and then every 3 years thereafter until discharge. As part of the current study, Tirosh and colleagues measured TG levels and performed stress electrocardiography 5 years apart on young men (n=13,953) with TG levels <300 mg/dL; abnormal stress tests were followed by coronary angiography. Two TG measurements were obtained—one at enrollment and 5 years later. Lifestyle variables and incident cases of CHD (confirmed by angiography) were also measured.

Measurement of TG at a single time point may not be a reliable indicator of an individual's long-term triglyceridemia.

Within a 5.5-year period of follow-up, a total of 158 cases of CHD were identified. The investigators categorized TG levels according to low, intermediate, and high tertiles. The CHD risk for those men with an initially high-tertile TG level was dependent upon the tertile within which they resided following the second TG measurement. Among the participants with TG <300 mg/dL who were not receiving lipid-lowering therapy, changes in TG levels were significantly associated with alterations in body mass index, physical activity, and the habit of eating breakfast. However, a large proportion of the CHD risk remained attributable to changes in TG levels during the subsequent 5.5 years of follow-up independent of the lifestyle habits.

Compared to those individuals demonstrating low TG levels both at the enrollment and also at the 5-year measurement (low/low), those who were high at enrollment and remained high demonstrated a hazard ratio (HR) of 8.23 (95% confidence interval [CI], 2.5 to 27.13). Those who enrolled high and were categorized as having intermediate or low TG levels at the second measurement had an HR of 6.84 (95% CI, 1.95 to 23.98) or 4.90 (95% CI, 1.01 to 24.55), respectively, compared to the low/low group. The CHD risk for those men in the low tertile at enrollment also changed, based upon the tertile after 5 years. Compared to the low/low group, the low/intermediate and low/high groups had HR of 3.81 (95% CI, 0.96 to 15.31) and 6.76 (95% CI, 1.34 to 33.92), respectively.

Thus, a multivariate analysis of patient data from this study demonstrated that information on TG levels from two time points, 5 years apart are clinically relevant for assessing CHD risk. Further, the authors note that this study provides "compelling evidence" for targeting TG levels when trying to reduce CHD risk in young men.

Tirosh A, Rudich A, Shochat T, et al. Changes in triglyceride levels and risk for coronary heart disease in young men. *Ann Intern Med*. 2007;147(6):377-385.

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Post-Test Question 1

With respect to CHD risk assessment, which of the following statements reflects the findings of this study?

a. Monitoring TG levels over time further confuses assessment of CHD risk
b. Monitoring TG levels over time is clinically relevant to CHD risk assessment
c. Monitoring TG levels over time does not impact CHD risk assessment
d. Monitoring TG levels over time is only relevant to CHD risk assessment if the TG levels remain high

COMMENTARY

FRANK M. SACKS, MD, Professor of Medicine, Harvard Medical School; Professor of Cardiovascular Disease Prevention, Nutrition Department, Harvard School of Public Health; Senior Attending Physician, Hyperlipidemia Clinic, Cardiology Division, Brigham and Women's Hospital in Boston, Massachusetts.

In 2007, several articles substantially strengthened the evidence that triglyceride (TG) concentration is a clinically important risk factor for coronary heart disease (CHD). First, a meta-analysis that included more than 10,000 CHD cases in 29 prospective studies convincingly demonstrated that TG concentration predicts events independently of other risk factors, including low high-density lipoprotein cholesterol (HDL-C). This puts to rest concerns that a high TG level is merely secondary to low HDL-C to which it is moderately correlated. Second, a US study of women demonstrated that a high nonfasting TG concentration was even more predictive than a fasting concentration, and, especially so, when the blood sampling occurred at about the presumed peak of the postprandial TG rise (ie, 2-4 hours). Nonfasting TG >170 mg/dL defined the high-risk group. This overturns standard clinical practice to use only fasting TG values and even to discard nonfasting TG. Now, an Israeli research group addressed the clinical importance of persistence of high fasting TG and consistency of low TG. TG concentration is the most variable of the lipid risk factors since it is most affected by recent food and alcohol intake, and by fluctuations in body weight. Even on a constant weight-maintenance diet, TG level is more variable than low-density lipoprotein cholesterol or HDL-C. The researchers found that in relatively young men (mean age of 32 years), persistence over 5 years of a TG level of 131–299 mg/dL—the upper third of the distribution—was associated with higher CHD incidence compared to men whose TG levels decreased from this range. Such reduction in TG was associated with reduction in body mass index (BMI) and increase in physical activity. Conversely, an increase in TG level from a low level of <81 mg/dL to a high level of 131–299 mg/dL was associated with nearly a 7-fold higher CHD risk, compared to those whose TG levels stayed at <81 mg/dL, and was correlated with increased BMI and decreased exercise.

In conclusion, this group of papers give clinicians reasons to increase attention to their patients' TG concentration, whether fasting or nonfasting, and especially to changes. The good news is that maintaining a healthy body weight and exercising regularly helps to preserve or achieve a low TG level and reduce CHD risk. Medications such as fibrates, niacin, and high-dose statins are effective in lowering both fasting and postprandial TG.

Higher TC Level Favors Development of Less Severe Strokes

The link between cholesterol and stroke is rife with paradoxes. Although there are data to support total cholesterol as a risk factor for coronary disease, and evidence that cholesterol-lowering treatments reduce stroke risk, there is a paucity of direct evidence to support a link between cholesterol and the risk of stroke. There has been, however, a proposal that cholesterol may increase the risk of only a subset of stroke types. Expanding on this idea, Olsen and colleagues hypothesized that all the paradoxical observations could be explained if hypercholesterolemia was linked to minor, mainly small vessel stroke with a good prognosis.

To examine this hypothesis, the researchers performed a retrospective (10-year follow-up) study of 652 unselected patients with ischemic stroke who arrived at the hospital within 24 hours of stroke onset. Total cholesterol was obtained in 513 (79%) of these patients. Stroke severity was measured using the Scandinavian Stroke Scale (SSS; 0=worst, 58=best). A full cardiovascular risk profile was established for each patient. Data for death within 10 years of stroke onset were obtained from the Danish Registry of Persons.

Overall, the investigators discovered an inverse and almost linear independent relationship between total cholesterol concentrations and stroke severity. Results from a linear regression model demonstrated that an increase of 1 mmol/L (38.6 mg/dL) of cholesterol resulted in an average increase of 1.32 in the SSS (P=0.013), implying that higher cholesterol levels are associated with less severe stroke. Increasing age, history of previous stroke, diabetes, and atrial fibrillation all decreased SSS, meaning that the risk factors were all associated with more severe strokes. An inverse correlation between total cholesterol and infarct size was also noted. The mortality rates associated with 7 days, 30 days, 1 year, 5 years, and 10 years were 7.2%, 15.2%, 29.4%, 57.3%, and 80.7%, respectively. The majority (74%) of deaths during the 10-year follow-up were attributed to cardiac causes or cerebral stroke. Survival analyses, when adjusted for confounding factors, showed that increases of 1 mmol/L (38.6 mg/dL) in total cholesterol were associated with a hazard ratio of 0.89 (95% confidence interval, 0.82-0.97; P=0.01). Hence, consistent with the hypothesis that increased cholesterol levels were associated with smaller infarct size, smaller strokes, and a reduced risk of mortality. The authors concluded that the results of their study support the association between hypercholesterolemia and strokes as a result of small vessel occlusion. This is the first report of an inverse relation between stroke severity and cholesterol.

Olsen TS, Christensen RHB, Kammersgaard LP, Andersen KK. Higher total serum cholesterol levels are associated with less severe strokes and lower all-cause mortality: ten-year follow-up ischemic strokes in the Copenhagen Stroke Study. *Stroke*. 2007;38(10):2646-2651.

Post-Test Question 2

According to the study by Olsen et al, increasing total cholesterol levels are associated with which of the following?

a. Smaller infarct size
b. Strokes of lesser severity
c. Decreased risk of mortality from severe strokes
d. All of the above
e. None of the above

Comparison of Statins in Reducing LDL-C and CRP in Patients With Type 2 Diabetes

The use of statins to reduce low-density lipoprotein cholesterol (LDL-C) levels to a goal of <100 mg/dL in patients with type 2 diabetes (T2D) is recommended in guidelines; but additional data suggest that a goal of <70 mg/dL may provide additional benefits. In addition to their lipid-lowering ability, statins initiate anti-inflammatory activity, which may contribute to their protective vascular benefit. A commonly used marker for inflammation, C-reactive protein (CRP), has been closely linked to coronary heart disease (CHD) and these levels are significantly increased in patients with T2D. Previous studies demonstrated that lowering CRP to <2 mg/L with statin therapy decreased the risk of CHD and, when combined with an LDL-C <70 mg/dL, correlated with improved outcomes following myocardial infarction, subsequently lowering CHD risk in high-risk individuals.

In the ANDROMEDA trial, Betteridge and colleagues compared rosuvastatin and atorvastatin therapy in terms of their ability to achieve goals of <70 mg/dL LDL-C and <2 mg/L CRP during the treatment of 509 adults with T2D. ANDROMEDA was a randomized, double-blind, double-dummy, multicenter, Phase IIIb parallel-group study. Following discontinuation of lipid-lowering medications and a 4-week dietary lead-in, participants were randomized to receive rosuvastatin or atorvastatin at 10 mg/d. After 8 weeks, dosages were titrated up to 20 mg/d for 8 additional weeks (for a total of 16 weeks).

Rosuvastatin treatment resulted in greater mean reductions ($P<0.001$) in LDL-C, total cholesterol, non–high-density lipoprotein cholesterol, apolipoprotein B, and lipid ratios at both weeks 8 and 16 when compared with those of atorvastatin. Both agents elicited significant ($P<0.01$ and $P<0.001$ for atorvastatin and rosuvastatin, respectively) reductions in CRP from baseline. In subjects with baseline CRP ≥2 mg/L, rosuvastatin therapy resulted in a significantly greater ($P<0.05$) decrease in CRP levels when compared with those of atorvastatin. Furthermore, significantly more rosuvastatin-treated individuals (58%) attained the combined endpoint of CRP <2 mg/L and LDL-C <70 mg/dL when compared with the atorvastatin group (37%; $P<0.001$). These data show that both statins were able to effectively reduce CRP levels in patients with T2D and that rosuvastatin had more significant effects on LDL-C levels.

The authors call for long-term outcomes studies to clarify just what the role of CRP is in cardiovascular disease risk prediction, as well as how statin therapy can benefit those with elevated CRP and without signs of dyslipidemia.

Betteridge DJ, Gibson JM, Sager PT. Comparison of statins in reducing LDL-C and CRP in patients with type 2 diabetes. *Am J Cardiol*. 2007;100(8):1245-1248.

Post-Test Question 3

Considering the goals of LDL-C <70 mg/dL and CRP <2 mg/L, which of the following is true in this study?

a. Rosuvastatin and atorvastatin therapies were equally efficacious at attaining goal
b. Significantly more patients on atorvastatin therapy attained goal
c. Significantly more patients on rosuvastatin therapy attained goal
d. Neither therapy resulted in patients attaining goal