Hypertriglyceridemia

How low to go and how to go low?

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INTRODUCTION

ATHEROSCLEROSIS is the most common underlying cause of cardiovascular disease. It is due a complex interplay between lipoproteins, white blood cells (macrophages), the immune system and the natural elements of the arterial wall.
LIPOPROTIENS

- Lipoproteins are the particles that transport cholesterol and triglycerides in the blood stream.

- Lipoproteins that are directly involved in atherosclerosis are termed **atherogenic**.

- Most of these lipoproteins carry cholesterol and other types of fats such as triglycerides.

- **Low Density Lipoprotein Cholesterol** (LDL-C) has become a primary goal of therapy in cardiovascular treatment and prevention. Recommendations regarding diet and drug therapy to lower cholesterol are most often based on the LDL-C number.

  However, LDL is not the only lipoprotein involved in atherosclerotic heart disease.
* Triglyceride-rich very low-density lipoprotein (VLDL) and the so-called remnant lipoproteins are also atherogenic.

* This is of particular importance when the LDL level is not elevated and Triglyceride level are high .. which is quite common, among people with:

  * abdominal obesity or metabolic syndrome.
  * Who are at high risk of CVD

Hypertriglyceridemia
TG Levels ... What Is Considered High?

<table>
<thead>
<tr>
<th></th>
<th>NCEP ATP III*</th>
<th>The Endocrine Society 2010b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 150 mg/dl</td>
<td>Normal &lt; 150 mg/dl</td>
</tr>
<tr>
<td>Borderline-high TGs</td>
<td>150-199 mg/dl</td>
<td>Mild hypertriglyceridemia</td>
</tr>
<tr>
<td>High TGs</td>
<td>200-499 mg/dl</td>
<td>Moderate hypertriglyceridemia</td>
</tr>
<tr>
<td>Very high TGs</td>
<td>≥ 500 mg/dl</td>
<td>Severe hypertriglyceridemia</td>
</tr>
<tr>
<td>Very severe TGs</td>
<td>≥ 2000 mg/dl</td>
<td>Very severe hypertriglyceridemia</td>
</tr>
</tbody>
</table>

- Risk of pancreatitis:
  - Risk is greater when TG ≥ 1000 mg/dL
  - Caution with TG 500 mg/dL owing to wide variances in daily TG levels

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

1. Overproduction of VLDL by the liver in response to an increase in free fatty acids flowing to this organ

2. Defect in the lysis of VLDL triglycerides and chylomicrons by lipoprotein lipase

Remnants

When lipoprotein lipase activity is deficient, triglycerides cannot be converted, hydrolyzed, or broken down, and the metabolism of chylomicron and VLDL remnants may be delayed

Development of Hypertriglyceridemia
Three Atherogenic Consequences of Hypertriglyceridemia

1. ↑TG/VLDL-C
2. SD LDL/↑LDL-P
3. ↓HDL-C

“Athero Dyslip”

Liver

FFA/TG

↑Central Adiposity

CETP = cholesterol ester transfer protein

Hepatic Lipase

Kidney

Rapid Degradation Apo A-I

HDL

LDL size

LDL-P

Possible Atherogenic Changes Accompanying Hypertriglyceridemia

Increased VLDL cholesterol-rich remnants

Low HDL

Small, dense LDL

Coagulation changes

Increased chylomicron remnants

Hypertriglyceridemia

Courtesy of Christie Ballantyne.

Risk of CHD by Triglyceride Level
(The Framingham Heart Study)

N=5127

Castelli WP. Am J Cardiol. 1992;70: 3H-9H.

Meta-analysis of 61 Studies
TGs Associated With CVD, All-cause Mortality

- Median follow-up of 12 y
- Excluded studies in patients with cancer, diabetes, CVD, dyslipidemia

<table>
<thead>
<tr>
<th>TG Level, mg/dL</th>
<th>CVD Mortality RR (95% CI)</th>
<th>P Value</th>
<th>All-cause Mortality RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 90</td>
<td>0.83 (0.75-0.93)</td>
<td>.001</td>
<td>0.94 (0.85-1.03)</td>
<td>.15</td>
</tr>
<tr>
<td>90-150</td>
<td>1.00 [referent]</td>
<td>.001</td>
<td>1.00 [referent]</td>
<td>.015</td>
</tr>
<tr>
<td>&gt; 150-200</td>
<td>1.15 (1.03-1.29)</td>
<td>.015</td>
<td>1.09 (1.02-1.17)</td>
<td>.011</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>1.25 (1.05-1.50)</td>
<td>.013</td>
<td>1.20 (1.04-1.38)</td>
<td>.011</td>
</tr>
</tbody>
</table>

CI = confidence interval; CVD = cardiovascular disease; RR = risk ratio; TG = triglyceride.
Secondary Causes of HTG

- Increase Dietary Carbohydrates and Fats
- Obesity
- Uncontrolled diabetes
- Hypothyroidism
- Nephrotic syndrome
- Various medications: antiretroviral regimens, some phenothiazines and second-generation antipsychotics, nonselective β-blockers, thiazide diuretics, oral estrogens, glucocorticosteroids, tamoxifen, isotretinoin
- Excessive alcohol consumption
- Pregnancy

Autoimmune Disease (SLE, )


Beyond CV Risk

ACUTE PANCRITIS
Mechanism of HTG-Induced Pancreatitis

AP develops when intracellular mechanisms to inhibit trypsin activation are overwhelmed by biochemical/structural injury. Pancreatitis induction depends on a cascade of events.

↑ Intracellular Ca^{2+}  ↓ Intracellular pH  Cathepsin B activation  Acinar cell cytoskeleton disruption

NF-κB activation

Increases production of:

- AP-1
- TNFα
- MCP-1
- Interleukins
- Adhesion molecules
- Selectins

Drive and sustain the inflammatory mediator "storm."


MANGEMENT
Managing Hypertriglyceridemia
Lifestyle Interventions


Effects of Nutrition Practices on TG Lowering

TG Lowering, %

- Weight loss (5%-10% of body weight) - 20%
- Implement a Mediterranean-style diet - 15%
- Add omega-3 fatty acids (per gram) - 10%
- Decrease carbohydrate - 1% Energy replacement with omega fatty acids - 2%
- Eliminate trans fats - 1% Energy replacement with omega fatty acids - 1%

• 2016 ESC/EAS Guidelines for the management of dyslipidaemias

The Task Force of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)
Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Task Force Members: A L. Catapano* (Chairperson) (Italy), J Graham* (Chairperson) (Ireland), G De Backer (Belgium), O Wiklund (Sweden), M. J Chapman (France), H Drexel (Austria), A W. Hoes (The Netherlands), C S. Jennings (UK), U Landmesser (Germany), T R. Pedersen (Norway), Ž Reiner (Croatia), G Riccardi (Italy), M-R Taskinen (Finland), L Tokgozoglu (Turkey), W. M. M Verschuren (The Netherlands), Ch Vlachopoulos (Greece), D A. Wood (UK), J L Zamorano (Spain).
Additional Contributor: M T Cooney (Ireland)
Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.

If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.
Triglyceride Target Level

• The target for triglyceride level is related to the degree of CV risk.

• Treatment for high triglyceride should take into account other cholesterol levels and weather triglyceride level consistently high, where the cause must be considered.

• Triglycerides add information about the risk, and is indicated for the diagnosis and the choice of treatment.

THANK U