The Epidemiology of Triglyceride as a Coronary Artery Disease Risk Factor

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Summary: Triglyceride (TG) has long been associated as a risk factor for coronary artery disease. A recent meta-analysis of various epidemiologic studies has confirmed this link. An important issue is to assess further the appropriate cutpoints to classify desirable TG because recent data indicate that levels < 200 mg/dl confer elevated risk. The dietary habits of present hunter-gatherer populations reveal the impact of a Westernized diet on both TG and cholesterol and suggest that a desirable TG is < 100 mg/dl. The epidemiologic and observational data in support of this concept are explored.

Key words: coronary artery disease, high-density lipoprotein cholesterol, hypertriglyceridemia, risk factor, remnant lipoproteins, triglyceride

Introduction

The role of triglyceride (TG) as a risk factor for coronary artery disease (CAD) has received increased recognition in recent years. The evidence supporting this finding was initially reported in 1959 by Albrink and Mann.[1] Their case-control study compared TG and cholesterol levels in 100 subjects with established CAD with age-matched normal men and women. Significant differences were observed between the two groups as the mean TG in the CAD group (~180 mg/dl) was significantly higher than that in age-matched controls (~100 mg/dl). Epidemiologic data, notably from the Framingham Heart Study, observed that TG was an especially important predictor of CAD in women (Fig. 1).[2] These early endorsements were nullified by Hulley et al. who suggested that while TG ap-

peared to be an important CAD risk factor in univariate analysis, its predictive power was diminished following adjustment for other covariates such as high-density lipoprotein cholesterol (HDL-C).[3] In 1984, the National Institutes of Health adopted the following TG cutpoints based on a Consensus Conference. They included *desirable* (< 250 mg/dl), *borderline-high* (250–500 mg/dl), *high* (500–1,000 mg/dl), and *very high* TG (> 1,000 mg/dl).[4] Following release of the 1984 NIH guidelines, several other studies were published. Criqui et al. reviewed the Lipid Research Clinics' population study of approximately 7,500 individuals (4,000 men and 3,500 women).[5] While an association between plasma TG and mortality from CAD was observed in men and women, the effect was minimized after adjusting for body mass index (BMI) and HDL-C and abolished when fasting blood glucose was included. While the study concluded that TG was not an independent risk factor, 43% of the study cohort were hyperlipidemic, thereby limiting generalizability of the results. The Prospective Cardiovascular Munster Study (PROCAM) conducted by Assman et al. in Germany[6] demonstrated an early linear relationship between TG and CAD; however, once TG exceeded 800 mg/dl, event rates were lower and approximated those observed with TG between 200 and 399 mg/dl (Fig. 2). This contrasts with CAD rates and total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C); that is, as TC rises, CAD rates increase in a curvilinear fashion.[7] It is of interest that a similar distinction in CAD rates between serum cholesterol and TG-rich lipoproteins (S$_f$ 20–400) was observed in the Framingham Heart Study nearly 30 years ago (Fig. 3).[8] Thus, statistical models evaluating the impact of TG (as a continuous variable) on CAD events may be misleading. Further complicating this picture is that very high TG (> 1,000 mg/dl) may be associated with pancreatitis, resulting from environmental factors superimposed on genetic predispostion (e.g., excessive alcohol consumption) or inherited structural mutations in lipoprotein lipase (LPL) or apolipoprotein C-II, a cofactor for LPL. While it has been theorized that very high TG is less likely to lead to atherothrombosis because large uncatabolized TG-rich lipoproteins are inpenetrable through the vascular endothelium, recent data suggest that selected individuals with familial chylomicronemia may be at increased risk for premature atherothrombotic disease.[9] Moreover, elevated TG is associated with considerable heterogeneity of circulating TG-rich particles. They include less atherogenic very low-density

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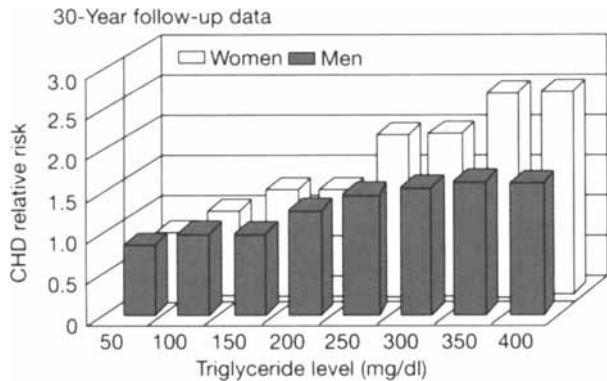Baltimore, MD 21201-1595, USA

FIG. 1   Relative risk of coronary heart disease (CHD) by triglyceride level in the Framingham Heart Study. Adapted from Ref. No. 2 with permission.

FIG. 2   Incidence rates of cardiovascular events in the Prospective Cardiovascular Munster (PROCAM) Study. Reprinted from Ref. No. 6 with permission.

lipoprotein cholesterol (VLDL-C) and, to a smaller extent, chylomicrons ($t_{1/2}$ is ~ 5 min in the absence of genetic deficiency states) to more atherogenic partially catabolized remnant particles. As CAD rates increase as TG exceeds 100 mg/dl (see also below), the atherogenic potential of TG-rich lipoproteins in an individual becomes exquisitively challenging when solely evaluating fasting plasma TG concentration.

Nevertheless, this challenge was overcome by the meta-analysis conducted by Hokanson and Austin.[10] They included the Lipid Research Clinics' Study and PROCAM. In univariate analysis, increases of 76% in women (n ~ 10,800) and 32% in men (n ~ 46,000) were observed for each mmol/l (88.5 mg/dl) increment in TG. Following adjustment for HDL-C, there
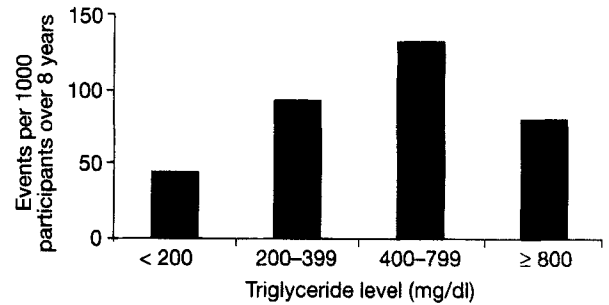
remained a 37% increased risk in women (n~ 6,300) and 14% enhanced risk in men (n~ 22,300). Two recently published studies, the Copenhagen Male Study[11] and the Physicians' Health Study[12] are consistent with the conclusions drawn from the meta-analysis.

In 1993, the National Cholesterol Education Program reassessed its classification of TG and lowered the cutpoints of desirable and borderline-high TG to < 200 mg/dl and 400 mg/dl, respectively.[7] Designation of high and very high TG remained unaltered. Despite a similar designation of desirable cutpoints for TC and TG, there are, however, important contrasts. For example, the cutpoint for TC is based on epidemiologic data from the Multiple Risk Factor Intervention Trial (MRFIT) which demonstrated that as levels of TC exceed 200 mg/dl, the risk of coronary events significantly increases.[13] Epidemiologic studies have not confirmed similar results for
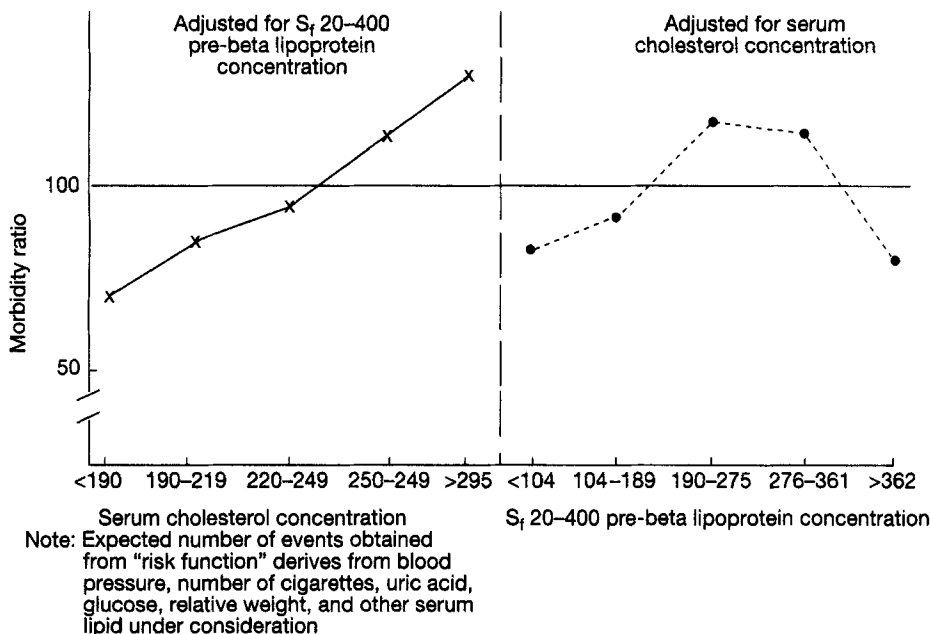

FIG. 3   Risk of coronary artery disease during a 14-year follow-up period according to serum lipid adjusted for associated variables: men, aged 38–69 years, The Framingham Study. Reprinted from Ref. No. 8 with permission.

TABLE I Normal plasma cholesterol and triglyceride concentrations from the Lipid Research Clinic's Population Study (U.S. and Canada)

	Plasma cholesterol (mg/dl)			Plasma triglyceride (mg/dl)		
	10	50	90	10	50	90
Males						
0–4	125	151	186	33	51	84
5–9	130	159	191	33	51	85
10–14	127	155	190	37	59	102
15–19	120	146	183	43	69	120
20–24	130	165	204	50	86	165
25–29	143	178	227	54	95	199
30–34	148	190	239	58	104	213
35–39	157	197	249	62	113	251
40–44	163	203	250	64	122	248
45–49	169	210	258	68	124	253
50–54	169	210	261	68	124	250
55–59	167	212	262	67	119	235
60–64	171	210	259	68	119	235
65–69	170	210	258	64	112	208
>70	162	205	252	67	111	212
Females						
0–4	120	156	189	38	59	96
5–9	134	163	195	36	55	90
10–14	131	158	190	44	70	114
15–19	126	154	190	44	66	107
20–24	130	160	203	41	64	112
25–29	136	168	209	42	65	116
30–34	139	172	213	44	69	123
35–39	147	182	225	46	73	137
40–44	154	191	235	51	82	155
45–49	161	199	247	53	87	171
50–54	172	215	268	59	97	186
55–59	183	228	282	63	106	204
60–64	186	228	280	64	105	202
65–69	183	229	280	66	112	204
>70	180	226	278	69	111	204

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TABLE II Coronary artery disease event rates in the COLTS study based on comparisons made between baseline TG and HDL levels

HDL	Triglyceride		p Value
	<100	>100	
<40	50% (29/58)	62% (109/176)	NS
>40	34% (19/56)	70% (42/60)	0.04

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Abbreviations: TG = triglyceride; HDL = high-density lipoprotein.

baseline TG > 100 mg/dl was associated with a 50% increased risk of new events.[15] Baseline TG and HDL-C were also studied in relationship to CAD event rate using cutpoints of 100 mg/dl and 40 mg/dl, respectively (Table II). As expected, the lowest number of CAD events occurred with TG < 100 mg/dl and HDL-C > 40 mg/dl. Of interest, however, was the finding that HDL-C did not confer protection if baseline TG exceeded 100 mg/dl. These results are consistent with the Copenhagen Male Study.[11]

Lipoproteins in Hunter-Gatherer Societies

Are there additional data supporting a lower cutpoint for "desirable" TG? Anthropologic research by Eaton and Konner has evaluated the dietary habits of societies that closely resemble our paleolithic ancestors.[16] For example, some modern day hunter-gatherer societies consume beans, nuts, and fruits as their most common nutrient sources, yielding a fiber intake of > 100 grams daily (compared with a fiber intake of ~25–30 g/day in the average American). Meat consumed in these societies is typically higher in protein and lower in total and saturated fat. For example, carcass fat in wild game is 3.9% with a small proportion contributed by omega-3 fatty acids (e.g., eicosapentanoic acid). In contrast, domesticated livestock contain ~ 30% fat with no detectable omega-3 fatty acids. Nutritional differences between the paleolithic diet and contemporary westernized diet are shown in Table III. Although a large amount of dietary cholesterol was consumed, the impact on raising serum cholesterol levels was considerably lower when viewed in the context of total and saturated fat intake. This is well illustrated in the cholesterol levels obtained in preliterate societies. Both TC and TG appear to be well within the physiologic range (Table IV).[17]

Does Dietary Perturbation Impact on Preliterate Societies ?

McMurray et al. examined the impact of a westernized diet in a group of Tarahumara Indians. Caloric intake was increased from 2700 to 4100 kcal/day, and they were switched from a low-fat (20%) diet to a highly saturated, high total fat (43%) diet. After consuming this diet for 4 to 5 weeks, TC rose from a mean 121 → 159 mg/dl with significant increases in

TG. In fact, in the Framingham Heart Study, increases in CAD events were observed as TG exceeded 100 mg/dl.[8] Second, whereas median TC in the Lipid Research Clinics' population was 200 mg/dl, median TG was only 100 mg/dl (Table I).[14] These data raise the possibility that a different cutpoint to designate a desirable TG may be more appropriate.

The Baltimore Coronary Observational Long-Term Study (COLTS) examined the relationship between TG levels and CAD events in patients with arteriographic CAD. Between 1977 and 1978, 740 consecutive patients underwent diagnostic coronary arteriography. Prior to the procedure, each patient completed an extensive questionnaire evaluating CAD risk factors and provided a fasting blood sample. The study included 350 patients with documented CAD at baseline. During the 18-year follow-up period, there were 199 new cardiovascular events. Cox regression analysis revealed that a

TABLE III   Composition analysis of late paleolithic and contemporary American diets compared with current dietary recommendations in the U.S.

	Late Paleolithic diet	Contemporary American diet	Current recommendations
Total dietary energy (%)			
Protein	33	12	12
Carbohydrate	46	46	58
Fat	21	42	30
Alcohol	~0	(7–10)[a]	—
P:S ratio	1.41	0.44	1.00
Cholesterol (mg)	520	300–500	300
Fiber (g)	100–150	19.7	30–60
Sodium (mg)	690	2,300–6,900	1,100–3,300
Calcium (mg)	1,500–2,000	740	800–1,600
Ascorbic acid (mg)	440	87.7	60

Updated from Ref. No. 4. Data base now includes 43 species of wild game and 153 types of wild plant food.

[a] Inclusion of calories from alcohol would require concomitant reduction in calories from other nutrients—mainly carbohydrate and fat.
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Abbreviation: P:S = polyunsaturated-to-saturated fat.

mean LDL-C (72 → 100 mg/dl) and TG (91 → 108 mg/dl).[18] Another study of 10 diabetic Australian Aborigines evaluated the impact of switching from a Western diet to a hunter-gatherer diet for a period of 7 weeks. Body mass index decreased from 27.2 kg/m² to 24.5 kg/m², while mean TC decreased from 219 → 193 mg/dl and TG was dramatically reduced (356 → 102 mg/dl).[19]

Normocholesterolemic Populations at Increased Risk for Coronary Artery Disease

Certain subgroups appear to be at exceptionally high risk of premature CAD even when there is no prominence of traditional cardiovascular risk factors. This is perhaps best exemplified by Asian Indians who have the highest rates of premature CAD. Typically, Asian Indians with CAD have similar TC but elevated TG and Lp(a) levels compared with their Caucasian counterparts.[20] These differences may be the result of alterations in certain candidate genes regulating lipid and lipoprotein metabolism or reflect the gene–environmental interactions.

TABLE IV   Comparison of cholesterol (TC) and triglyceride (TG) levels in selected preliterate societies

	TC (mg/dl)	TG (mg/dl)
New Guinea Melanesians	135	95
Rural Chinese	127	100
Tanzanian Villagers	114	81 (fish diet) - 116 (vegetarian diet)
Tarahumara Indians	125	120

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Sources: Am J Clin Nutr 1978;31:1131–1142 and 1990;52:1027–1036; Am J Epid 1996;44:1129–1142; Lancet 1996;348:784–788

Pathophysiology of Triglyceride Rich Lipoproteins and Coronary Artery Disease

There are both direct and indirect mechanisms that subserve the enhanced atherothrombogenicity proposed for TG-rich lipoproteins. The direct impact may be enhanced uptake of remnant lipoproteins by the TG-rich lipoprotein receptor (TGRLP) present in macrophages and selected tissues, as reported by Gianturco and Bradley (see Dr. Gianturco's manuscript). Indirect effects include the transfer of TG from chylomicrons and VLDL-C to HDL-C and LDL-C mediated by by cholesterol ester transfer protein (CETP). Triglyceride-rich HDL-C and LDL-C particles may be subsequently hydrolyzed by hepatic lipase to small, dense particles. Small LDL-C particles (also referred to as phenotype B—see below) are more susceptible to LDL-C oxidation and unregulated uptake by macrophages.[21] The relationship between TG concentration and LDL-C phenotype was described by Austin et al.[22] Phenotype A LDL-C particles are large, buoyant, and less susceptible to LDL-C oxidation than phenotype B. In general, individuals with low TG (e.g., 50 mg/dl) contain a preponderance of phenotype A subclass LDL-C particles, whereas subjects with borderline-high TG (e.g., 250 mg/dl) possess a significant proportion of LDL-C (80–90%) within the phenotype B subclass. It is noteworthy that the shift from phenotype A to B particles accelerates as TG concentration exceeds 100 mg/dl (Fig. 4).[22]

Conclusions

Triglyceride-rich lipoproteins enhance atherothrombotic risk and are underrecognized contributors to the elevated CAD rate observed in Westernized societies.

The genetic archictecture to which we have evolved suggests that a "desirable" TG may be considerably lower than the
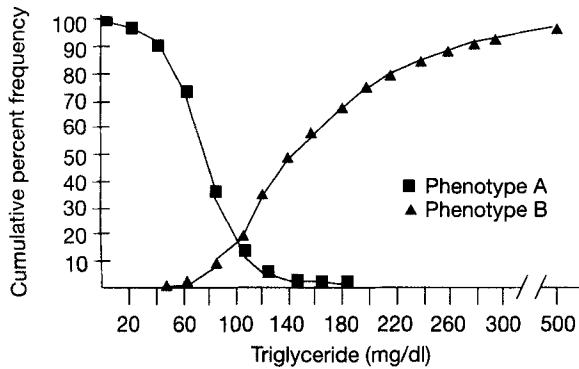
FIG. 4 Cumulative distribution of adjusted plasma triglyceride levels with corresponding prevalence of low-density lipoprotein (LDL) phenotypes A and B. Reprinted from Ref. No. 22 with permission.

present designate of 200 mg/dl. Indeed, present preliterate societies confirm that physiologic TC and TG are attainable.

It may be appropriate to consider lower cutpoints for TG that delineate enhanced CAD risk more accurately.

Discussion

Glueck: Hunter-gatherers were thin individuals with a much lower fasting insulin and insulin response to oral glucose tolerance. High fasting serum insulin (insulin resistance) is another risk factor for CAD. Insulin resistance is probably what stimulates plasminogen activator inhibitor (PAI-I). Part of the atherogenicity associated with a high TG level is the interaction of insulin resistance and hyperinsulinemia.

Miller: That's correct. However, the one exception to this rule are the Pima Indians who, for reasons not well understood, have a fairly low incidence of CAD despite elevated TG, adiposity, and insulin resistance.

Abrams: In terms of the risk from TG, it has been suggested that if one reduces LDL substantially, this risk is minimized or disappears. Is this true? If it is, perhaps the data need to be viewed in a different way since cholesterol levels were not factored into the analyses.

Miller: In the five randomized clinical trials using statins, LDL lowering was associated with marked reduction of primary or secondary CAD events. However, these studies did not assess the impact of TG lowering above and beyond LDL reduction. A study underway in Europe is investigating whether fenofibrate in combination with cerivastatin reduces CAD events in diabetics to a greater extent than either one alone. This study will help to answer the relative impact of TG reduction compared to LDL reduction in high-risk patients. In the U.S. and abroad, the TNT (treat to new targets) is examining whether aggressive LDL-C lowering with atorvastatin (e.g., to below 70 mg/dl) reduces the CAD event rate to a greater extent than reducing LDL-C to the NCEP goal of 100 mg/dl in men and women with preexisting CAD. The TNT study may help to answer your question, although high doses of atorvastatin

are also associated with TG reductions which may complicate such analyses.

Bachorik: There was a mention that, in the presence of high TG levels, higher concentrations of partially metabolized TG-rich lipoproteins are found. These become cholesterol-enriched lipoproteins more similar to LDL. There is also evidence that these particles are in fact atherogenic. The risk associated with TG goes up to some degree. Then, when the particles become much larger, they are apparently not as atherogenic. Viewed in this way, can TG, at least within certain concentration ranges, be viewed as surrogate measures of atherogenic particles that have yet to be reduced to the size of LDL (e.g., chylomicron remnants, VLDL remnants)?

Miller: One of the challenges is how to differentiate between atherogenic remnant lipoproteins and less atherogenic TG particles. Perhaps, Dr. Otvos will cover this area in his talk. Presently, I am not aware of any foolproof commercial method that can discriminate between these lipoproteins. Perhaps, maintaining TG levels below 100 mg/dl would circumvent this problem.

Criqui: The Copenhagen data confirm a finding found in the Lipid Research Clinics' Study and the PROCAM study. Above some level of TG, the risk drops, making it not a curvilinear or even a linear relationship, but rather an upside-down U. In the PROCAM study, the level was 800 g/dl, while in the Copenhagen Male Study, it was 222 mg/dl when the risk dropped rather sharply. When multivariate analysis was conducted by category in the Copenhagen Male Study, a very strong TG risk was shown at every level of HDL. This is consistent with the old observation that patients with Type I and Type V hyperlipidemia apparently do not have an increased risk of atherosclerosis even though their TG levels are very high. The Copenhagen and COLTS data show that, at high levels of HDL, TG continues to be a risk factor. In the Miller data, the risk was higher when the HDL was > 40 mg/dl than when the HDL was < 40 mg/dl and the TG was > 100 mg/dl. This is the direct opposite of all previous population studies, including the Lipid Research Clinics' Study, the Honolulu Heart Study, the PROCAM Study, and the Helsinki Subgroup Study. All of these showed that TG was the most potent as a risk factor when the HDL was low. If the HDL was high (> 40–50 mg/dl), there was no risk for TG. How can this inconsistency in the data be resolved?

Miller: With regard to your first comment, the upside-down U was also observed in Framingham (see Fig. 3). Both the Copenhagen Male Study, which evaluated initial CAD event rates, and the COLTS, which studied recurrent CAD events, showed that TG was important even at high HDL levels. These studies found significant risk at lower TG levels than previously considered. In Copenhagen, elevated risks were observed at lower TG levels; compared to the lowest tertile (< 97 mg/dl) levels between 97–140 mg/dl conferred a 50% increased risk of CAD while the highest tertile (> 140 mg/dl) more than doubled event rate. In COLTS, we observed a threshold effect with an increased rate of events observed as TG exceeded 100 mg/dl. It would be interesting to re-do the analyses of some of these earlier studies to determine whether

lower TG cutpoints also impact on the results. However, one must consider that some of the populations studied (e.g., Lipid Research Clinics') primarily evaluated hypercholesterolemic subjects. Thus, the impact of TG in this cohort may be very different.

Conti: Today, the life expectancy is 84 years for women and 78 for men. What would have been the speculated life span of a hunter- gatherer who did not succumb to an infectious disease or some other untimely death, such as being eaten by a dinosaur ?

Miller: It is difficult to speculate, although it is presumed they would have lived at least that long, perhaps longer. We have no way of knowing what type of lifespan we could achieve if cardiovascular disease (and cancer) was eliminated. Additional information from present hunter-gatherer societies may provide useful information in this regard.

Aknowledgment

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