
The Ketogenic Diet for Health

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2013-09-03

The Ketogenic Diet Reverses Indicators of Heart Disease

Cardiovascular disease (CVD) is the leading cause of death worldwide ¹. Because of its prevalence and life-threatening nature, and because it appears that a keto diet is likely to reverse it, we consider it one of the most important conditions to discuss here.

In our last post, we argued that [CVD, being a disease strongly associated with metabolic syndrome, is likely to be best treated with a ketogenic diet](#). In this post we will present more evidence that ketogenic diets do improve heart disease risk factors.

Unfortunately, there is much confusion and misinformation about the impact of nutrition on CVD among scientists and non-scientists alike. ***Not only does a high fat, keto diet not worsen heart disease risk — as would commonly be assumed — it actually improves it.*** This confusion about dietary fat is probably the reason that we do not yet have clinical trials directly testing the effects of ketogenic diets on CVD outcomes.

However, we already have many trials of ketogenic diets that measured known CVD risk factors, especially cholesterol profiles. It turns out that these trials show a powerful heart disease risk reduction in those following a ketogenic diet. It is powerful both in absolute terms, and in comparison with low-fat diets, which tend to improve some weakly predictive factors while worsening stronger predictors.

As such, a high-fat ketogenic diet is currently the best known non-drug intervention for heart disease, as defined by mainstream measures of risk. It is arguably better than drug interventions, too.

In brief:

- Total cholesterol and LDL cholesterol are only weak predictors of CVD.
- Triglycerides, HDL, LDL particle size, and the HDL-to-triglyceride ratio are much stronger predictors of CVD.

- Keto diets improve triglyceride levels, HDL, and LDL particle size — precisely those measures that strongly indicate risk.

Total cholesterol and LDL cholesterol are only weakly associated with CVD

The connection between blood cholesterol levels and the development of heart disease began to be explored in the last century. Over the last several decades, our understanding of the predictive power of various blood lipids has gone through many refinements as our ability to measure finer and finer detail has advanced.

In the early years, it appeared that high levels of total cholesterol carried some risk of heart disease in many cases. However, it is now well established that total cholesterol by itself is a weak predictor [2](#), [3](#), [4](#).

The reason is quite simple. The different subtypes of cholesterol work together in an intricately balanced system. There is a wide range of total cholesterol levels that are perfectly healthy, so long as the proportions of the subtypes are healthy ones. By the same token, a given level of total cholesterol, even if it is perfectly normal, could be pathological when examined by subtype. Strong evidence from recent decades suggests that the best known blood lipid measures for predicting future risk of CVD are HDL, triglycerides, and related ratios (see below).

Similarly, while LDL cholesterol is probably important, it appears that it does not have good predictive power when looking at its magnitude alone [5](#), [6](#), [7](#), [8](#).

One reason for this is that like total cholesterol, LDL is not uniform. Just as we distinguish between HDL and LDL, the so-called “good” and “bad” cholesterol, LDL itself is now known to have two important subtypes with opposite risk implications. Having more large, light LDL particles (also called Pattern A), does not indicate high CVD risk, but having more small, dense particles (Pattern B) does [9](#), [10](#), [11](#), [12](#), [13](#). Therefore high LDL by itself is not necessarily indicative of CVD.

Low HDL cholesterol is strongly associated with CVD

Having high blood levels of HDL is now widely recognized as predicting lower levels of heart disease. The proportion of total cholesterol that is HDL cholesterol is a particularly strong predictor. In 2007, a meta-analysis was published in the *Lancet* that examined information from 61 prospective observational studies, consisting of almost 900,000 adults. Information about HDL was available for about 150,000 of them, among whom there were 5000 vascular deaths. According to the authors, “the ratio of total to HDL cholesterol is a substantially more informative predictor of IHD mortality than are total cholesterol, HDL cholesterol, or

non-HDL cholesterol." ¹⁴

This is consistent with many other studies, for example this very recent analysis from the COURAGE trial ¹⁵.

High triglycerides are strongly associated with CVD

There has been drawn out controversy in the medical community as to the relationship of triglyceride levels to CVD. There are two parts to the controversy: whether or not triglycerides are an *independent* predictor of CVD, and whether or not triglycerides play a *causative* role in CVD.

In both cases, however, it doesn't matter in which way the controversy is resolved! Whether or not triglycerides *independently* predict CVD (and there is at least some evidence that they do), and whether or not they *cause* CVD, there is no controversy about whether they predict CVD. The association between triglyceride levels and CVD still holds and is strongly predictive ^{16, 17, 18}. In fact it is so predictive that those who argue that triglyceride levels are not an independent risk factor, call it instead a "biomarker" for CVD ¹⁹. In other words, seeing high triglycerides is tantamount to seeing the progression of heart disease.

HDL-to-Triglycerides Ratio: compounding evidence

Triglycerides and HDL levels statistically interact. That means it is a mistake to treat one as redundant with respect to the other. If you do, you will miss the fact that the effect of one on your outcome of interest changes depending on the value of the other. Despite the fact that most heart disease researchers who study risk factors have not used methods tuned to find interactions between triglycerides and HDL, many studies have at least measured both. This has allowed others to do the appropriate analysis. When triglycerides and HDL have been examined with respect to each other, that is, when the effect of triglycerides is measured under the condition of low HDL, or when the effect of HDL is measured under the condition of high triglycerides, this combination of factors turns out to be even more indicative of CVD ^{20, 21, 22, 23}.

One of the most interesting aspects of this finding from our perspective, is that the ratio of triglyceride levels to HDL is considered to be a surrogate marker of insulin resistance (See [The Ketogenic Diet as a Treatment for Metabolic Syndrome](#).) In other words, the best lipid predictors of CVD are also those that indicate insulin resistance.

Ketogenic Diets improve risk factors for CVD

There is now ample evidence that a low carbohydrate, ketogenic diet improves lipid profiles, particularly with respect to the risk factors outlined above: triglycerides, HDL, and their ratio ^{24, 25, 26, 27, 28, 29, 30, 31}.

Although a ketogenic diet typically raises LDL levels, which has been traditionally seen as a risk factor, it has also been shown to improve LDL particle size. In other words, although the absolute amount of LDL goes up, it is the "good" LDL that goes up, whereas the "bad" LDL goes down ^{31, 32}. This is hardly surprising, since LDL particle size is also strongly predicted by triglycerides ^{33, 34, 35}.

Although there have not yet been intervention studies testing the effect of a ketogenic diet on the rate of actual CVD incidents (e.g. heart attacks), the evidence about lipid profiles is strong enough to make ketogenic diets more likely to reduce heart disease than any other known intervention.

Summary:

- Current medical practice uses blood lipid measurements to assess the risk of heart disease.
- Despite the continuing tradition of measuring total cholesterol and LDL, we have known for decades that triglycerides, HDL, and the ratio of the two, are much better predictors of heart disease. LDL particle size is also considered strongly predictive.
- A ketogenic diet has a very favourable impact on these risk factors, and thus should be considered the diet of choice for those at risk of CVD.

In their 2011 paper, "Low-carbohydrate diet review: shifting the paradigm", Hite et al. display the following graph (VLCKD stands for Very Low Carbohydrate Ketogenic Diet, and LFD for Low Fat Diet) ³⁶ based on data from ³¹:

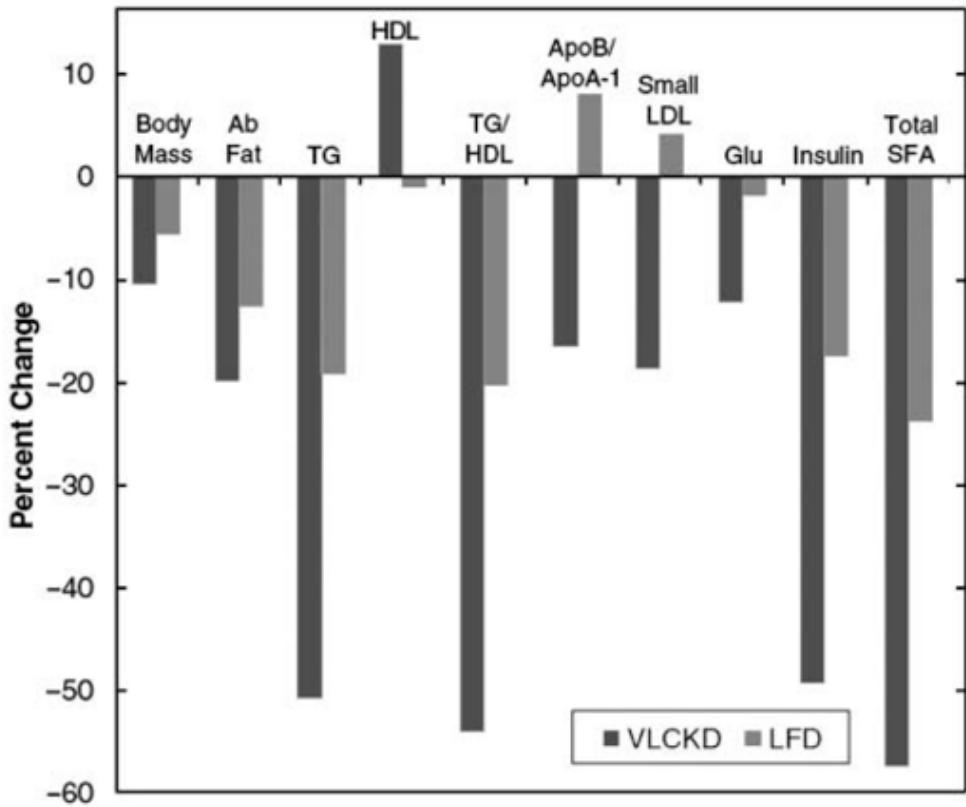


Figure 1. Comparison of low- and high-carbohydrate diets at 12 weeks. Results from trial in which 40 subjects with atherogenic dyslipidemia were randomly assigned to either diet²². Ab, abdominal; ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; Glu, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SFA, saturated fatty acids; TG, triglycerides. LFD, low-fat diet.

It makes an excellent visualization of the factors at stake, and how powerful a ketogenic diet is. It also shows quite clearly that not only is restricting carbohydrate more effective for this purpose than a low fat diet, but that a low fat diet is detrimental for some important risk factors — apolipoprotein ratios, LDL particle size, and HDL — but a low carb diet is not. The ketogenic diet resulted in a significant improvement in every measure.

References:

¹ Evidence type: observational

[World Health Organization Fact sheet N°317: Cardiovascular diseases \(CVDs\) September 2011](#)

- CVDs are the number one cause of death globally: more people die annually from CVDs than from any

other cause.

- An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke.
- Low- and middle-income countries are disproportionately affected: over 80% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women.
- By 2030, almost 23.6 million people will die from CVDs, mainly from heart disease and stroke. These are projected to remain the single leading causes of death.

² Evidence type: observational

[Role of lipid and lipoprotein profiles in risk assessment and therapy.](#)

[Ballantyne CM, Hoogeveen RC. Am Heart J. 2003 Aug;146\(2\):227-33.](#)

Despite a strong and consistent association within populations, elevated TC [(total cholesterol)] alone is not a useful test to discriminate between individuals who will have CHD [(coronary heart disease)] events and those who will not.

³ Evidence type: observational

[Relation of serum lipoprotein cholesterol levels to presence and severity of angiographic coronary artery disease. Philip A. Romm, MD, Curtis E. Green, MD, Kathleen Reagan, MD, Charles E. Rackley, MD. The American Journal of Cardiology Volume 67, Issue 6, 1 March 1991, Pages 479–483](#)

Most CAD [(coronary artery disease)] occurs in persons who have only mild or moderate elevations in cholesterol levels. Total cholesterol level alone is a poor predictor of CAD, particularly in older patients in whom the major lipid risk factor is the HDL cholesterol level.

⁴ Evidence type: observational

[Lipids, risk factors and ischaemic heart disease. Atherosclerosis. 1996 Jul;124 Suppl:S1-9. Castelli WP.](#)

Those individuals who had TC [(total cholesterol)] levels of 150-300 mg/dl (3.9-7.8 mmol/l) fell into the overlapping area (Fig. 1), demonstrating that 90% of the TC levels

measured were useless (by themselves) for predicting risk of CHD [(coronary heart disease)] in a general population. Indeed, twice as many individuals who had a lifetime TC level of less than 200 mg/dl (5.2 mmol/l) had CHD compared with those who had a TC level greater than 300 mg/dl (7.8 mmol/l) (Fig. 1).

⁵ Evidence type: observational

Range of Serum Cholesterol Values in the Population Developing Coronary Artery Disease. William B. Kannel, MD, MPH. The American Journal of Cardiology, Volume 76, Issue 9, Supplement 1, 28 September 1995, Pages 69C–77C

The ranges of serum cholesterol and LDL cholesterol levels varied widely both in the general population and in patients who had already manifested CAD (Figures 1 and 2). Because of the extensive overlap between levels, it was impossible to differentiate the patients with CAD from the control subjects.

⁶ Evidence type: observational

Lipoprotein cholesterol, apolipoprotein A-I and B and lipoprotein (a) abnormalities in men with premature coronary artery disease. Jacques Genest Jr., MD,FACC, Judith R. McNamara, MT, Jose M. Ordovas, PhD, Jennifer L. Jenner, BSc, Steven R. Silberman, PhD, Keaven M. Anderson, PhD, Peter W.F. Wilson, MD, Deeb N. Salem, MD, FACC, Ernst J. Schaefer, MD. Journal of the American College of Cardiology Volume 19, Issue 4, 15 March 1992, Pages 792–802.

Our data suggest that total and LDL cholesterol may not be the best discriminants for the presence of coronary artery disease despite the strong association between elevated cholesterol and the development of coronary artery disease in cross-sectional population studies and prospective epidemiologic studies.

⁷ Evidence type: observational

Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. Walldius, G. and Jungner, I. (2004), Journal of Internal Medicine, 255: 188–205. doi: 10.1046/j.1365-2796.2003.01276.x

(Emphasis ours.)

For over three decades it has been recognized that a high level of total blood cholesterol, particularly in the form of LDL cholesterol (LDL-C), is a major risk factor for developing coronary heart disease (CHD) [1–4]. However, as more recent research has expanded our understanding of lipoprotein

function and metabolism, it has become apparent that LDL-C is not the only lipoprotein species involved in atherogenesis. **A considerable proportion of patients with atherosclerotic disease have levels of LDL-C and total cholesterol (TC) within the recommended range [5, 6], and some patients who achieve significant LDL-C reduction with lipid-lowering therapy still develop CHD [7].**

Other lipid parameters are also associated with elevated cardiovascular risk, and **it has been suggested that LDL-C and TC may not be the best discriminants for the presence of coronary artery disease (CAD) [5].**

⁸ Evidence type: observational

[Plasma Lipoprotein Levels as Predictors of Cardiovascular Death in Women. Katherine Miller Bass, MD, MHS; Craig J. Newschaffer, MS; Michael J. Klag, MD, MPH; Trudy L. Bush, PhD, MHS. Arch Intern Med. 1993;153\(19\):2209-2216.](#)

Using a sample of 1405 women aged 50 to 69 years from the Lipid Research Clinics' Follow-up Study, age-adjusted CVD death rates and summary relative risk (RR) estimates by categories of lipid and lipoprotein levels were calculated. Multivariate analysis was performed to provide RR estimates adjusted for other CVD risk factors.

RESULTS: Average follow-up was 14 years. High-density lipoprotein and triglyceride levels were strong predictors of CVD death in age-adjusted and multivariate analyses. Low-density lipoprotein and total cholesterol levels were poorer predictors of CVD mortality. After adjustment for other CVD risk factors, HDL levels less than 1.30 mmol/L (50 mg/dL) were strongly associated with cardiovascular mortality (RR = 1.74; 95% confidence interval [CI], 1.10 to 2.75). Triglyceride levels were associated with increased CVD mortality at levels of 2.25 to 4.49 mmol/L (200 to 399 mg/dL) (RR = 1.65; 95% CI, 0.99 to 2.77) and 4.50 mmol/L (400 mg/dL) or greater (RR = 3.44; 95% CI, 1.65 to 7.20). At total cholesterol levels of 5.20 mmol/L (200 mg/dL) or greater and at all levels of LDL and triglycerides, women with HDL levels of less than 1.30 mmol/L (< 50 mg/dL) had CVD death rates that were higher than those of women with HDL levels of 1.30 mmol/L (50 mg/dL) or greater.

⁹ Evidence type: plausible mechanism and observational review

[Particle size: the key to the atherogenic lipoprotein? Rajman I, Maxwell S, Cramb R, Kendall M. QJM. 1994 Dec;87\(12\):709-20.](#)

Using different analytical methods, up to 12 low-density lipoprotein (LDL) subfractions can be separated. LDL particle size decreases with increasing density. Smaller, denser LDL particles seem more atherogenic than the larger, lighter particles, based on the experimental findings that smaller LDL particles are more susceptible for oxidation in vitro, have lower binding affinity for the LDL receptors and lower catabolic rate, have a higher concentration of polyunsaturated fatty acids, and potentially interact more easily with proteoglycans of the arterial wall. Clinical studies have shown that a smaller LDL subfraction profile is associated with an increased risk of heart disease, even when total cholesterol level is only slightly raised. There is a strong inverse association between LDL particle size and triglyceride concentrations. Although LDL particle size is genetically determined, its phenotypic expression may also be affected by environmental factors such as drugs, diet, obesity, exercise or disease. Factors that shift the LDL subfractions profile towards larger particles may reduce the risk of heart disease.

¹⁰ Evidence type: nested case-control study

[Association of Small Low-Density Lipoprotein Particles With the Incidence of Coronary Artery Disease in Men and Women. Christopher D. Gardner, PhD; Stephen P. Fortmann, MD; Ronald M. Krauss, MD JAMA. 1996;276\(11\):875-881. doi:10.1001/jama.1996.03540110029028.](#)

Incident CAD cases were identified through FCP surveillance between 1979 and 1992. Controls were matched by sex, 5-year age groups, survey time point, ethnicity, and FCP treatment condition. The sample included 124 matched pairs: 90 pairs of men and 34 pairs of women.

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LDL size was smaller among CAD cases than controls (mean \pm SD) ($26.17 \pm 1.00 \text{ nm}$ vs $26.68 \pm 0.90 \text{ nm}$; $P < .001$). The association was graded across control quintiles of LDL size. The significant case-control difference in LDL size was independent of levels of high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (non-HDL-C), triglyceride, smoking, systolic blood pressure, and body mass index, but was not significant after adjusting for the ratio of total cholesterol (TC) to HDL-C (TC:HDL-C). Among all the physiological risk factors, LDL size was the best differentiator of CAD status in conditional logistic regression. However, when added to the physiological parameters above, the TC:HDL-C ratio was found to be a stronger independent

predictor of CAD status.

¹¹ Evidence type: review

The small, dense LDL phenotype and the risk of coronary heart disease: epidemiology, patho-physiology and therapeutic aspects. Lamarche B, Lemieux I, Després JP. *Diabetes Metab.* 1999 Sep;25(3):199-211.

More than decade ago, several cross-sectional studies have reported differences in LDL particle size, density and composition between coronary heart disease (CHD) patients and healthy controls. Three recent prospective, nested case-control studies have since confirmed that the presence of small, dense LDL particles was associated with more than a three-fold increase in the risk of CHD. The small, dense LDL phenotype rarely occurs as an isolated disorder. It is most frequently accompanied by hypertriglyceridemia, reduced HDL cholesterol levels, abdominal obesity, insulin resistance and by a series of other metabolic alterations predictive of an impaired endothelial function and increased susceptibility to thrombosis.

²⁸ Evidence type: prospective

A prospective, population-based study of low density lipoprotein particle size as a risk factor for ischemic heart disease in men. Lamarche B, St-Pierre AC, Ruel IL, Cantin B, Dagenais GR, Després JP. *Can J Cardiol.* 2001 Aug;17(8):859-65.

Analyses were conducted in a cohort of 2057 men who were all initially free of IHD, and who were followed up over a five-year period, during which 108 first IHD events (myocardial infarction, angina or coronary death) were recorded. LDL particle size was measured by nondenaturing gradient gel electrophoresis.

RESULTS: Cox proportional hazards analysis indicated that the relationship between LDL particle size and the risk of future IHD events was not linear. Men with an LDL particle size less than 256.0 Å had a significant 2.2-fold increase in the five-year rate of IHD ($P < 0.001$) compared with men having an LDL particle size greater than 256.0 Å. Multivariate and subgroup analyses indicated that small, dense LDL particles predicted the rate of IHD independent of LDL cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, apolipoprotein B and the total cholesterol to HDL cholesterol ratio. Finally, the magnitude of the increase in IHD risk attributed to lipid risk factors was modulated to a significant extent by variations in LDL particle size.

¹³ Evidence type: review

Small, dense low-density-lipoproteins and the metabolic syndrome. Rizzo M, Berneis K. *Diabetes Metab Res Rev.* 2007 Jan;23(1):14-20.

Small, dense low-density-lipoproteins (LDL) are associated with increased risk for cardiovascular diseases and diabetes mellitus and a reduction in LDL size has been reported in patients with coronary and non-coronary forms of atherosclerosis. LDL size has been accepted as an important predictor of cardiovascular events and progression of coronary artery disease as well as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III. Small, dense LDL, with elevated triglyceride levels and low HDL-cholesterol concentrations, constitute the 'atherogenic lipoprotein phenotype (ALP)', a form of atherogenic dyslipidemia that is a feature of type 2 diabetes and the metabolic syndrome.

¹⁴ Evidence type: meta-analysis of prospective studies

Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. *Lancet.* 2007 Dec 1;370(9602):1829-39.

Of various simple indices involving HDL cholesterol, the ratio total/HDL cholesterol was the strongest predictor of IHD mortality (40% more informative than non-HDL cholesterol and more than twice as informative as total cholesterol). Total cholesterol was weakly positively related to ischaemic and total stroke mortality in early middle age (40-59 years), but this finding could be largely or wholly accounted for by the association of cholesterol with blood pressure. Moreover, a positive relation was seen only in middle age and only in those with below-average blood pressure; at older ages (70-89 years) and, particularly, for those with systolic blood pressure over about 145 mm Hg, total cholesterol was negatively related to haemorrhagic and total stroke mortality.

¹⁵ Evidence type: post-hoc analysis

Low Levels of High Density Lipoprotein Cholesterol and Increased Risk of Cardiovascular Events in Stable Ischemic Heart Disease Patients: A Post Hoc Analysis from the COURAGE Trial. Acharjee S, Boden WE, Hartigan PM, Teo KK, Maron DJ, Sedlis SP, Kostuk W, Spertus JA, Dada M, Chaitman BR, Mancini GB, Weintraub WS. *J Am Coll Cardiol.* 2013 Aug 8. pii: S0735-1097(13)03082-9. doi: 10.1016/j.jacc.2013.07.051. [Epub ahead of print]

Abstract:

OBJECTIVES: The aim of this study was to assess the independent effect of high-density lipoprotein cholesterol (HDL-C) level on cardiovascular risk in patients with stable ischemic heart disease (SIHD) while on optimal medical therapy (OMT).

BACKGROUND: While low HDL-C level is a powerful and independent predictor of cardiovascular risk, recent data suggest that this may not apply when low-density lipoprotein cholesterol (LDL-C) is reduced to optimal levels using intensive statin therapy.

METHODS: We performed a post hoc analysis in 2,193 men and women with stable ischemic heart disease (SIHD) from the COURAGE trial. The primary outcome measure was the composite of death from any cause or nonfatal myocardial infarction (MI). The independent association between HDL-C levels measured after 6 months on optimal medical therapy (OMT) and the rate of cardiovascular events after 4 years was assessed. Similar analyses were performed separately in subjects with LDL-C levels below 70 mg/dL (1.8 mmol/L).

RESULTS: In the overall population, the rate of death/MI was 33% lower in the highest HDL-C quartile as compared with the lowest quartile, with quartile of HDL-C being a significant, independent predictor of death/MI ($P = 0.05$), but with no interaction for LDL-C category ($P=0.40$). Among subjects with LDL-C levels < 70 mg/dL, those in the highest quintile of HDL-C had a 65% relative risk reduction in death or MI as compared to the lowest quintile, with HDL-C quintile demonstrating a significant, inverse predictive effect ($P=0.02$).

CONCLUSIONS: In this post hoc analysis, patients with SIHD continued to experience incremental cardiovascular risk associated with low HDL-C levels despite OMT during long-term follow-up. This relationship persisted and appeared more prominent even when LDL-C was reduced to optimal levels with intensive dyslipidemic therapy.

¹⁶ Evidence type: meta-analysis of prospective studies

Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. Hokanson JE, Austin MA. *J Cardiovasc Risk*. 1996 Apr;3(2):213-9.

Seventeen studies were selected for the analysis based on published reports of population-based, prospective studies, including 46413 men and 10864 women. To insure comparability, only studies reporting the association between fasting triglyceride levels and incident cardiovascular endpoints were included. Using standard meta-analysis calculations, relative risks (RR) and 95% confidence intervals (CI) were calculated and standardized with respect to a 1 mmol/l increase in triglyceride. Multivariable-adjusted RRs were determined for the six studies in men and two studies in women that reported adjustments for HDL cholesterol.

RESULTS: For men and women, the univariate RRs for triglyceride were 1.32 (95% CI 1.26-1.39) and 1.76 (95% CI 1.50-2.07), respectively, indicating an approximately 30% increased risk in men and a 75% increase in women. Adjustment of HDL cholesterol and other risk factors attenuated these RRs to 1.14 (95% CI 1.05-1.28) and 1.37 (95% CI 1.13-1.66), respectively, which were still statistically significant values.

CONCLUSION: Based on combined data from prospective studies, triglyceride is a risk factor for cardiovascular disease for both men and women in the general population, independent of HDL cholesterol. These findings demonstrate the necessity for clinical trials to evaluate whether lowering plasma triglyceride decreases the risk of cardiovascular disease.

<http://www.ncbi.nlm.nih.gov/pubmed/8782637>

¹⁷ Evidence type: prospective cohort study

A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, Hennekens CH. JAMA. 1996 Sep 18;276(11):882-8.

RESULTS: Cases (n=266) had a significantly smaller LDL diameter (mean [SD], 25.6 [0.9] nm) than did controls (n=308) matched on age and smoking (mean [SD], 25.9 [0.8] nm; P<.001). Cases also had higher median triglyceride levels (1.90 vs 1.49 mmol/L [168 vs 132 mg/dL]; P<.001). The LDL diameter had a high inverse correlation with triglyceride level (r=-0.71), and a high direct correlation with high-density lipoprotein cholesterol (HDL-C) level (r=0.60). We observed a significant multiplicative interaction between triglyceride and total cholesterol (TC) levels (P=.01). After simultaneous adjustment for lipids and a variety of coronary

risk factors, LDL particle diameter was no longer a statistically significant risk indicator, with a relative risk (RR) of 1.09 (95% confidence interval [CI], 0.85-1.40) per 0.8-nm decrease. However, triglyceride level remained significant with an RR of 1.40 (95% CI, 1.10-1.77) per 1.13 mmol/L (100-mg/dL) increase. The association between triglyceride level and MI risk appeared linear across the distribution; men in the highest quintile had a risk about 2.5 times that of those in the lowest quintile. The TC level, but not HDL-C level, also remained significant, with an RR of 1.80 (95% CI, 1.44-2.26) per 1.03-mmol/L (40-mg/dL) increase.

CONCLUSIONS: These findings indicate that nonfasting triglyceride levels appear to be a strong and independent predictor of future risk of MI, particularly when the total cholesterol level is also elevated. In contrast, LDL particle diameter is associated with risk of MI, but not after adjustment for triglyceride level. Increased triglyceride level, small LDL particle diameter, and decreased HDL-C levels appear to reflect underlying metabolic perturbations with adverse consequences for risk of MI; elevated triglyceride levels may help identify high-risk individuals.

¹⁸ Evidence type: prospective study

The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Assmann G, Schulte H, Funke H, von Eckardstein A. *Eur Heart J.* 1998 Oct;19 Suppl M:M8-14.

The Prospective Cardiovascular Münster (PROCAM) study involved 4849 middle-aged men who were followed up for 8 years to record the incidence of coronary heart disease (CHD) events according to the risk factors present at study entry. The study showed that fasting levels of triglycerides were an independent risk factor for CHD events, irrespective of serum levels of high density lipoprotein cholesterol (HDL-C) or low density lipoprotein cholesterol (LDL-C). Other independent predictors of CHD included serum levels of LDL-C and HDL-C, age, systolic blood pressure, cigarette smoking, diabetes mellitus, a family history of myocardial infarction and angina pectoris, but did not include total serum cholesterol levels. Individuals with an LDL-C/HDL-C ratio > 5 had a 19.2% chance of experiencing a CHD event in the next 8 years. Furthermore, if an LDL-C/HDL-C ratio > 5 was combined with hypertriglyceridaemia (> or = 2.3 mmol. l⁻¹), the risk of CHD increased to 26.9%. The association between hypertriglyceridaemia and CHD events may be related to the presence of atherogenic, triglyceride-rich

particles in plasma, such as LDL and very low density lipoproteins. High triglyceride levels may also predispose to thrombosis.

¹⁹ Evidence type: observation

[The role of triglycerides in cardiovascular risk. Gandotra P, Miller M. Curr Cardiol Rep. 2008 Nov;10\(6\):505-11.](#)

Triglycerides' role in coronary heart disease (CHD) risk assessment has long been debated. Although meta-analyses have suggested that triglycerides are an independent risk factor for CHD, a consensus has emerged that triglycerides more appropriately represent a biomarker of CHD risk rather than an independent risk factor. Ongoing studies will determine whether triglyceride lowering confers additional CHD benefit beyond that attained via low-density lipoprotein (LDL) cholesterol reduction. The American Diabetes Association presently recommends lowering elevated triglycerides as a secondary therapeutic target after LDL cholesterol, whereas other organizations, such as the National Cholesterol Education Program, recommend non-high-density lipoprotein cholesterol as the second priority after attaining the LDL cholesterol goal. However, reducing very high triglycerides (ie, > 500 mg/dL) remains a sufficiently high priority in affected individuals.

²⁰ Evidence type: analysis of observational results from a randomized controlled trial

[The Triglyceride Issue Revisited Findings From the Helsinki Heart Study Leena Tenkanen, PhD; Kati Pietilä; Vesa Manninen, MD; Matti Mänttari, MD Arch Intern Med. 1994;154\(23\):2714-2720. doi:10.1001/archinte.1994.00420230107012.](#)

Results: Triglycerides occupied a central role in the pattern of associations of the factors studied; in particular, the associations with HDL-C level, blood pressure, and blood glucose level were without threshold values. The prevalence of high triglyceride level plus low HDL-C level was strongly associated with blood pressure and blood glucose level, while the prevalence of low HDL-C level alone was not. Only the subgroup with both high triglyceride and low HDL-C levels showed a substantial CHD risk, while those with low HDL-C levels alone or high triglyceride levels alone showed a marginal risk.

Conclusions: Our results suggest that triglycerides play a central mediating role in the occurrence of several CHD risk factors, especially those related to the insulin resistance

syndrome. Because of these interdependencies, the question of an independent effect of triglycerides is not relevant, and when assessing CHD risk, triglycerides should be considered jointly with HDL-C

²¹ Evidence type: prospective analysis

[Relation of High TG–Low HDL Cholesterol and LDL Cholesterol to the Incidence of Ischemic Heart Disease: An 8-Year Follow-up in the Copenhagen Male Study. Jørgen Jeppesen, Hans Ole Hein, Poul Suadicani, Finn Gyntelberg. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1997; 17: 1114-1120](#)

High triglyceride (TG) and low HDL cholesterol (HDL-C) is the characteristic dyslipidemia seen in insulin-resistant subjects. We examined the role of this dyslipidemia as a risk factor of ischemic heart disease (IHD) compared with that of high LDL cholesterol (LDL-C) in the Copenhagen Male Study. In total 2910 white men, aged 53 to 74 years, free of cardiovascular disease at baseline, were subdivided into four groups on the basis of fasting concentrations of serum TG, HDL-C, and LDL-C. “High TG–low HDL-C” was defined as belonging to both the highest third of TG and the lowest third of HDL-C; this group encompassed one fifth of the population. “High LDL-C” was defined as belonging to the highest fifth of LDL-C. A control group was defined as not belonging to either of these two groups. “Combined dyslipidemia” was defined as belonging to both dyslipidemic groups. Age-adjusted incidence of IHD during 8 years of follow-up was 11.4% in high TG–low HDL-C, 8.2% in high LDL-C, 6.6% in the control group, and 17.5% in combined dyslipidemia.

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At both low and high levels of total cholesterol and LDL-C, the presence of high TG–low HDL-C approximately doubled the risk of IHD, and individuals with high TG–low HDL-C in the lowest fifth of LDL-C (≤ 3.6 mmol/L) had a similar risk of IHD to subjects without high TG–low HDL-C in the highest fifth of LDL-C (≥ 5.3 mmol/L). High TG–low HDL-C thus clearly identified a group at high risk of IHD, though they had LDL-C levels considered to be safe or borderline (< 3.4 mmol/L).

²² Evidence type: observational

[Fasting Triglycerides, High-Density Lipoprotein, and Risk of Myocardial Infarction. J. Michael Gaziano, MD, MPH; Charles H. Hennekens, MD, DrPH; Christopher J. O’Donnell, MD, MPH; Jan L. Breslow, MD; Julie E. Buring, ScD. *Circulation*. 1997; 96: 2520-2525 doi: 10.1161/01.CIR.96.8.2520](#)

We examined the interrelationships of fasting triglycerides, other lipid parameters, and nonlipid risk factors with risk of myocardial infarction among 340 cases and an equal number of age-, sex-, and community-matched control subjects. Cases were men or women of <76 years of age with no prior history of coronary disease who were discharged from one of six Boston area hospitals with the diagnosis of a confirmed myocardial infarction. In crude analyses, we observed a significant association of elevated fasting triglycerides with risk of myocardial infarction (relative risk [RR] in the highest compared with the lowest quartile=6.8; 95% confidence interval [CI]=3.8 to 12.1; P for trend <.001). Results were not materially altered after control for nonlipid coronary risk factors. As expected, the relationship was attenuated after adjustment for HDL but remained statistically significant (RR in the highest quartile=2.7; 95% confidence interval [CI]=1.4 to 5.5; P for trend=.016). Furthermore, the ratio of triglycerides to HDL was a strong predictor of myocardial infarction (RR in the highest compared with the lowest quartile=16.0; 95% CI=7.7 to 33.1; P for trend <.001).

²³ Evidence type: observational

[High Ratio of Triglycerides to HDL-Cholesterol Predicts Extensive Coronary Disease. Protasio Lemos da Luz, Desiderio Favarato, Jose Rocha Faria-Neto Junior, Pedro Lemos, and Antonio Carlos Palandri Chagas. Clinics. 2008 August; 63\(4\): 427-432. doi: 10.1590/S1807-59322008000400003 PMID: PMC2664115](#)

High-risk patients (n = 374) submitted for coronary angiography had their lipid variables measured and coronary disease extent scored by the Friesinger index.

RESULTS: The subjects consisted of 220 males and 154 females, age 57.2 ± 11.1 years, with total cholesterol of 210 ± 50.3 mg/dL, triglycerides of 173.8 ± 169.8 mg/dL, HDL-cholesterol (HDL-c) of 40.1 ± 12.8 mg/dL, LDL-cholesterol (LDL-c) of 137.3 ± 46.2 mg/dL, TG/HDL-c of 5.1 ± 5.3 , and a Friesinger index of 6.6 ± 4.7 . The relationship between the extent of coronary disease (dichotomized by a Friesinger index of 5 and lipid levels (normal vs. abnormal) was statistically significant for the following: triglycerides, odds ratio of 2.02 (1.31-3.1; p = 0.0018); HDL-c, odds ratio of 2.21 (1.42-3.43; p = 0.0005); and TG/HDL-c, odds ratio of 2.01 (1.30-3.09; p = 0.0018). However, the relationship was not significant between extent of coronary disease and total cholesterol [1.25 (0.82-1.91; p = 0.33)] or LDL-c [1.47 (0.96-2.25; p = 0.0842)]. The chi-square for linear trends for

Friesinger > 4 and lipid quartiles was statistically significant for triglycerides ($p = 0.0017$), HDL-c ($p = 0.0001$), and TG/HDL-c ($p = 0.0018$), but not for total cholesterol ($p = 0.393$) or LDL-c ($p = 0.0568$). The multivariate analysis by logistic regression OR gave 1.3 ± 0.79 ($p = .0001$) for TG/HDL-c, 0.779 ± 0.074 ($p = .0001$) for HDL-c, and 1.234 ± 0.097 ($p = 0.03$) for LDL. Analysis of receiver operating characteristic curves showed that only TG/HDL-c and HDL-c were useful for detecting extensive coronary disease, with the former more strongly associated with disease.

CONCLUSIONS: Although some lipid variables were associated with the extent of coronary disease, the ratio of triglycerides to HDL-cholesterol showed the strongest association with extent.

²⁴ Evidence type: non-randomized experiment

[A Ketogenic Diet Favorably Affects Serum Biomarkers for Cardiovascular Disease in Normal-Weight Men. Matthew J. Sharman, William J. Kraemer, Dawn M. Love, Neva G. Avery, Ana L. Gómez, Timothy P. Scheett, and Jeff S. Volek. J. Nutr. July 1, 2002 vol. 132 no. 7 1879-1885](#)

The primary objective of this study was to examine how healthy normolipidemic, normal-weight men respond to a ketogenic diet in terms of fasting and postprandial CVD biomarkers. Ketogenic diets have been criticized on the grounds they jeopardize health (8); however, very few studies have directly evaluated the effects of a ketogenic diet on fasting and postprandial risk factors for CVD. Subjects consumed a diet that consisted of 8% carbohydrate (<50 g/d), 61% fat, and 30% protein. Adaptation to this ketogenic diet resulted in significant reductions in fasting TAG (−33%), postprandial lipemia after a fat-rich meal (−29%), and fasting insulin concentrations (−34%). There were significant increases in LDL particle size, and no change in the oxidative LDL concentrations. There was a significant increase in HDL cholesterol at wk 3 after the ketogenic diet. Collectively, the responses in serum lipids, insulin and lipid subclasses to the ketogenic diet were favorable in terms of overall CVD risk profile.

²⁵ Evidence type: review of experiments

[Cardiovascular and hormonal aspects of very-low-carbohydrate ketogenic diets. Volek JS, Sharman MJ. Obes Res. 2004 Nov;12 Suppl 2:115S-23S.](#)

Compared with low-fat diets, short-term VLCKDs [very low carb diets] consistently result in improvements in fat loss,

fasting and postprandial triacylglycerols, high-density lipoprotein-cholesterol, the distribution of low-density lipoprotein-cholesterol subclasses, and insulin resistance.

²⁶ Evidence type: randomized controlled trial

Long-term effects of a ketogenic diet in obese patients. Dashti HM, Mathew TC, Hussein T, Asfar SK, Behbahani A, Khoursheed MA, Al-Sayer HM, Bo-Abbas YY, Al-Zaid NS. *Exp Clin Cardiol.* 2004 Fall;9(3):200-5.

The level of total cholesterol showed a significant decrease from week 1 to week 24 (Figure 3). The level of HDL cholesterol significantly increased (Figure 4), whereas LDL cholesterol levels significantly decreased with treatment (Figure 5). The level of triglycerides decreased significantly after 24 weeks of treatment. The initial level of triglycerides was 2.75 ± 0.23 mmol/L, whereas at week 24, the level decreased to 1.09 ± 0.08 mmol/L (Figure 6).

²⁷ Evidence type: randomized controlled trial

Very Low-Carbohydrate and Low-Fat Diets Affect Fasting Lipids and Postprandial Lipemia Differently in Overweight Men. Matthew J. Sharman, Ana L. Gómez, William J. Kraemer, and Jeff S. Volek. *J. Nutr.* April 1, 2004 vol. 134 no. 4 880-885

The primary purpose of this study was to compare the effects of a very low-carbohydrate and a low-fat diet on fasting blood lipids and postprandial lipemia in overweight men. In a balanced, randomized, crossover design, overweight men ($n = 15$; body fat $>25\%$; BMI, 34 kg/m^2) consumed 2 experimental diets for 2 consecutive 6-wk periods. One was a very low-carbohydrate ($<10\%$ energy as carbohydrate) diet and the other a low-fat ($<30\%$ energy as fat) diet. Blood was drawn from fasting subjects on separate days and an oral fat tolerance test was performed at baseline, after the very low-carbohydrate diet period, and after the low-fat diet period. Both diets had the same effect on serum total cholesterol, serum insulin, and homeostasis model analysis-insulin resistance (HOMA-IR). Neither diet affected serum HDL cholesterol (HDL-C) or oxidized LDL (oxLDL) concentrations. Serum LDL cholesterol (LDL-C) was reduced ($P < 0.05$) only by the low-fat diet (-18%). Fasting serum triacylglycerol (TAG), the TAG/HDL-C ratio, and glucose were significantly reduced only by the very low-carbohydrate diet (-44 , -42 , and -6% , respectively). Postprandial lipemia was significantly reduced when the men consumed both diets compared with baseline, but the reduction was significantly greater after intake of the very low-carbohydrate diet. Mean and peak LDL particle size increased only after the very low-

carbohydrate diet. The short-term hypoenergetic low-fat diet was more effective at lowering serum LDL-C, but the very low-carbohydrate diet was more effective at improving characteristics of the metabolic syndrome as shown by a decrease in fasting serum TAG, the TAG/HDL-C ratio, postprandial lipemia, serum glucose, an increase in LDL particle size, and also greater weight loss ($P < 0.05$).

²⁸ Evidence type: uncontrolled trial

Long term effects of ketogenic diet in obese subjects with high cholesterol level. Dashti HM, Al-Zaid NS, Mathew TC, Al-Mousawi M, Talib H, Asfar SK, Behbahani AI. *Mol Cell Biochem.* 2006 Jun;286(1-2):1-9. Epub 2006 Apr 21.

In this study, 66 healthy obese subjects with body mass index (BMI) greater than 30, having high cholesterol level (Group I; $n = 35$) and those subjects with normal cholesterol level (Group II; $n = 31$) were selected. The body weight, body mass index, total cholesterol, LDL-cholesterol, HDL-cholesterol, urea, creatinine, glucose and triglycerides were determined before and after the administration of the ketogenic diet. Changes in these parameters were monitored at 8, 16, 24, 32, 40, 48 and 56 weeks of the treatment.

RESULTS: The body weight and body mass index of both groups decreased significantly ($P < 0.0001$). The level of total cholesterol, LDL cholesterol, triglycerides and blood glucose level decreased significantly ($P < 0.0001$), whereas HDL cholesterol increased significantly ($P < 0.0001$) after the treatment in both groups.

CONCLUSION: This study shows the beneficial effects of ketogenic diet following its long term administration in obese subjects with a high level of total cholesterol. Moreover, this study demonstrates that low carbohydrate diet is safe to use for a longer period of time in obese subjects with a high total cholesterol level and those with normocholesterolemia.

²⁹ Evidence type: randomized controlled trial

Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, Golan R, Fraser D, Bolotin A, Vardi H, Tangi-Rozental O, Zuk-Ramot R, Sarusi B, Brickner D, Schwartz Z, Sheiner E, Marko R, Katorza E, Thiery J, Fiedler GM, Blüher M, Stumvoll M, Stampfer MJ; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. *N Engl J Med.* 2008 Jul 17;359(3):229-41. doi: 10.1056/NEJMoa0708681.

Changes in lipid profiles during the weight-loss and

maintenance phases are shown in Figure 3. HDL cholesterol (Figure 3A) increased during the weight-loss and maintenance phases in all groups, with the greatest increase in the low-carbohydrate group (8.4 mg per deciliter [0.22 mmol per liter], $P < 0.01$ for the interaction between diet group and time), as compared with the low-fat group (6.3 mg per deciliter [0.16 mmol per liter]). Triglyceride levels (Figure 3B) decreased significantly in the low-carbohydrate group (23.7 mg per deciliter [0.27 mmol per liter], $P = 0.03$ for the interaction between diet group and time), as compared with the low-fat group (2.7 mg per deciliter [0.03 mmol per liter]). LDL cholesterol levels (Figure 3C) did not change significantly within groups, and there were no significant differences between the groups in the amount of change. Overall, the ratio of total cholesterol to HDL cholesterol (Figure 3D) decreased during both the weight-loss and the maintenance phases. The low-carbohydrate group had the greatest improvement, with a relative decrease of 20% ($P = 0.01$ for the interaction between diet group and time), as compared with a decrease of 12% in the low-fat group.

³⁰ Evidence type: review

[Influence of dietary carbohydrate and fat on LDL and HDL particle distributions. Siri PW, Krauss RM. Curr Atheroscler Rep. 2005 Nov;7\(6\):455-9.](#)

Variations in the size and density distributions of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles have been related to risk for cardiovascular disease. In particular, increased levels of small, dense LDL particles, together with reduced levels of large HDL and increases in small HDL, are integral features of the atherogenic dyslipidemia found in patients with insulin resistance, obesity, and metabolic syndrome. Increased dietary carbohydrates, particularly simple sugars and starches with high glycemic index, can increase levels of small, dense LDL and HDL, primarily by mechanisms that involve increasing plasma triglyceride concentrations. Low-carbohydrate diets may have the opposite effects. Diets with differing fatty acid composition can also influence LDL and HDL particle distributions.

³¹ Evidence type: controlled experiment

[Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, Kraemer WJ, Bibus DM, Fernandez ML, Feinman RD. Lipids. 2009 Apr;44\(4\):297-309. doi:](#)

Abstract

We recently proposed that the biological markers improved by carbohydrate restriction were precisely those that define the metabolic syndrome (MetS), and that the common thread was regulation of insulin as a control element. We specifically tested the idea with a 12-week study comparing two hypocaloric diets (approximately 1,500 kcal): a carbohydrate-restricted diet (CRD) (%carbohydrate:fat:protein = 12:59:28) and a low-fat diet (LFD) (56:24:20) in 40 subjects with atherogenic dyslipidemia. Both interventions led to improvements in several metabolic markers, but subjects following the CRD had consistently reduced glucose (-12%) and insulin (-50%) concentrations, insulin sensitivity (-55%), weight loss (-10%), decreased adiposity (-14%), and more favorable triacylglycerol (TAG) (-51%), HDL-C (13%) and total cholesterol/HDL-C ratio (-14%) responses. In addition to these markers for MetS, the CRD subjects showed more favorable responses to alternative indicators of cardiovascular risk: postprandial lipemia (-47%), the Apo B/Apo A-1 ratio (-16%), and LDL particle distribution. Despite a threefold higher intake of dietary saturated fat during the CRD, saturated fatty acids in TAG and cholesteryl ester were significantly decreased, as was palmitoleic acid (16:1n-7), an endogenous marker of lipogenesis, compared to subjects consuming the LFD. Serum retinol binding protein 4 has been linked to insulin-resistant states, and only the CRD decreased this marker (-20%). The findings provide support for unifying the disparate markers of MetS and for the proposed intimate connection with dietary carbohydrate. The results support the use of dietary carbohydrate restriction as an effective approach to improve features of MetS and cardiovascular risk.

³² Evidence type: randomized controlled trial

Effect of a low-carbohydrate, ketogenic diet program compared to a low-fat diet on fasting lipoprotein subclasses. Westman EC, Yancy WS Jr, Olsen MK, Dudley T, Guyton JR. *Int J Cardiol.* 2006 Jun 16;110(2):212-6. Epub 2005 Nov 16.

Comparing baseline to 6 months, the LCKD [low carb ketogenic diet] group had significant changes in large VLDL (-78%), medium VLDL (-60%), small VLDL (-57%), LDL particle size (+2%), large LDL (+54%), medium LDL (-42%), small LDL (-78%), HDL particle size (+5%), large HDL

(+21%), and LDL particle concentration (-11%).

...

CONCLUSIONS: The LCKD with nutritional supplementation led to beneficial changes in serum lipid subclasses during weight loss. While the LCKD did not lower total LDL cholesterol, it did result in a shift from small, dense LDL to large, buoyant LDL, which could lower cardiovascular disease risk.

³³ Evidence type: longitudinal analysis

[Change in LDL particle size is associated with change in plasma triglyceride concentration. McNamara JR, Jenner JL, Li Z, Wilson PW, Schaefer EJ. Arterioscler Thromb. 1992 Nov;12\(11\):1284-90.](#)

Low density lipoprotein (LDL) particle size is inversely associated with plasma triglyceride concentration in cross-sectional analyses. In the present study, changes in the LDL particle size of 227 participants of the Framingham Offspring Study were analyzed longitudinally by non-denaturing gradient gel electrophoresis at two examinations that were separated by 3-4 years. All subjects had triglyceride concentrations < 400 mg/dl at both exams. Using laser scanning densitometry to assess mean LDL particle size, 56% of samples displayed a change in size: 41% had a one-band size change, 13% had a two-band change, and 2% had a three-band change. These changes in size corresponded to a 15% change in pattern type, based on pattern A and B terminology. There was a significant inverse association between change in LDL size and change in triglyceride ($p < 0.0001$) and glucose ($p < 0.004$) concentrations, body weight ($p < 0.02$), and age ($p < 0.03$). There was also a significant positive association with change in high density lipoprotein (HDL) cholesterol concentration ($p < 0.0001$).

³⁴ Evidence type: observational

[Ratio of triglycerides to HDL cholesterol is an indicator of LDL particle size in patients with type 2 diabetes and normal HDL cholesterol levels. Boizel R, Benhamou PY, Lardy B, Laporte F, Foulon T, Halimi S. Diabetes Care. 2000 Nov;23\(11\):1679-85.](#)

LDL size correlated negatively with plasma triglycerides (TGs) ($R^2 = 0.52$) and positively with HDL cholesterol ($R^2 = 0.14$). However, an inverse correlation between the TG-to-HDL cholesterol molar ratio and LDL size was even stronger ($R^2 = 0.59$). The ratio was > 1.33 in 90% of the patients with small LDL particles (95% CI 79.3-100) and 16.5% of those with

larger LDL particles. A cutoff point of 1.33 for the TG-to-HDL cholesterol ratio distinguishes between patients having small LDL values better than TG cutoff of 1.70 and 1.45 mmol/l.

CONCLUSIONS: The TG-to-HDL cholesterol ratio may be related to the processes involved in LDL size pathophysiology and relevant with regard to the risk of clinical vascular disease. It may be suitable for the selection of patients needing an earlier and aggressive treatment of lipid abnormalities.

³⁵ Evidence type: observational

[Assessment of LDL particle size by triglyceride/HDL-cholesterol ratio in non-diabetic, healthy subjects without prominent hyperlipidemia. Maruyama C, Imamura K, Teramoto T. J Atheroscler Thromb. 2003;10\(3\):186-91.](#)

Abstract

Small, dense low-density lipoprotein (LDL) is an atherogenic lipoprotein because of its susceptibility to oxidative modification. However, evaluating LDL size requires highly sophisticated techniques. We investigated potentially convenient biochemical parameters for assessing the presence of small, dense LDL. Thirty-nine male subjects, who had been involved in a work-site health promotion program, were recruited. Subjects were divided into two groups: normal LDL size (> 25.5 nm, Normal LDL group) and small LDL (≤ 25.5 nm, Small LDL group). Significant negative correlations were observed between LDL size and both triglyceride (TG) ($p < 0.001$) and remnant-like particle cholesterol concentrations ($p < 0.01$), while there was a significant positive correlation between LDL size and the high density lipoprotein cholesterol (HDL-C) concentration ($p < 0.01$). The TG concentration was a negative and the HDL-C concentration a positive independent variable predicting LDL size in multiple regression analysis ($p < 0.0001$). Seventy-five percent of the Small LDL group had TG/HDL-C ratios higher than 0.9 using mmol/L or 2.0 using mg/dL, while only 25% of the normal LDL group had ratios above the levels ($p = 0.0013$). A combined parameter, the TG/HDL-C ratio, is beneficial for assessing the presence of small LDL.

³⁶ Evidence type: review of experiments

[Low-carbohydrate diet review: shifting the paradigm. Hite AH, Berkowitz VG, Berkowitz K. Nutr Clin Pract. 2011 Jun;26\(3\):300-8. doi: 10.1177/0884533611405791.](#)

Note that there is an error in the text accompanying this figure (not visible in our image). The data is attributed to a study by Jakobsen et al., but it comes from the study in ³¹, by Volek et al.

L. Amber O'Hearn at 1:27 PM

Share



19 comments:



Evelyn Mitchell September 3, 2013 at 6:00 PM

Thanks for the article, this is important work.

I have a suggestion about formatting/presentation. Examine.com in their Human Effect Matrix, illustrates very clearly the different weights to assign to different studies:

<http://examine.com/supplements/Beta-Alanine/>

I have a hard time remembering things like Prospective is better than Observational, so this sort of visual presentation is helpful to me.

[Reply](#)

▼ Replies



L. Amber Wilcox-O'Hearn September 3, 2013 at 6:13 PM

Ah, yes, we have been thinking about this issue. We had been planning to have some kind of little icon/graphic to put next to each study or claim. I like the graded approach on that site you mention, because, as you say, it incorporates not just type, but "goodness". Thank you for the feedback!

[Reply](#)



Patrick Snook September 9, 2013 at 8:50 PM

Hello Amber,

First, my compliments on your site and your approach and commitment to evidence-based blogging

I found and enjoyed your blog by following a link you posted in a comment on Peter Attia's blog a few months ago.

His series of postings on cholesterol, as I'm sure you have read, emphasizes LDL-P (= particle number) as the only reliable and valid predictor of risk for atherosclerosis. I recall he mentions more than a half dozen recent studies in support of that.

He dismisses LDL particle size as a reliable and valid predictor. (I'm hurriedly summarizing, rather coarsely. It's a fine-grained series of articles, worth multiple readings.)

How do you reconcile that data with the studies you cite?

Thanks,

Patrick

[Reply](#)



L. Amber Wilcox-O'Hearn September 10, 2013 at 1:26 AM

Patrick, that's an excellent point. The post that goes into detail on that is [The straight dope on cholesterol – Part V](#). I agree that Peter Attia's blog is worth reading multiple times.

Attia reports two relevant observations. The first is that *if you adjust for particle number*, the effect of size goes away. However, this part is only an argument that particle size doesn't give you more information than particle number. So that's not particularly condemning. It's similar to arguments about whether or not trig are an independent risk factor.

The second observation is that if you adjust only for small particles, you see that having more large particles still indicates more risk than fewer large particles. That's an interesting refinement of what we have reported here.

However, it can be seen as simply a continuation of the pattern of getting better estimates as we get more refined measurements. When all we could measure was total cholesterol, then that was what we use to approximate risk. When we figured out how to measure LDL, triglycerides, and HDL, we were able to refine our assessments of risk. When we were able to measure particle size, again we got a clearer picture. This is no different.

According to Attia, particle number is better than particle size for differentiating CVD risk. We already know that according to HDL,

triglycerides, and LDL particle size, a keto diet reverses risk factors. So now we would like to see if a ketogenic diet also affects particle number.

This was measured in [Carbohydrate Restriction Alters Lipoprotein Metabolism by Modifying VLDL, LDL, and HDL Subfraction Distribution and Size in Overweight Men](#), by Wood et al. in *J. Nutr.* February 2006 vol. 136 no. 2 384-389 where LDL particle number decreased in their subjects:

"LDL particle size increased ($P < 0.001$) and particle number decreased ($P < 0.05$) from baseline to wk 12 (Table 3). The increase in particle size was reflected by a 35% increase in large LDL particles ($P < 0.001$) and a 24.7% reduction in very small LDL particles ($P < 0.001$). The number of medium and small LDL particles was also reduced by 27 and 30% ($P < 0.01$), respectively, over time."

So, if particle number is an even better predictor than the ones we detailed here, we can be glad to know that there is at least one experiment that shows that a keto diet is helping by that measure too. There are, of course other measures, such as oxidized LDL, markers of inflammation, flow mediated dilation, etc. I hope to go into those things in another post.

[Reply](#)



Patrick Snook September 10, 2013 at 3:00 PM

Amber--many thanks for taking the time to reply so generously and clearly. You really have the knack for summarizing research and enlightening your readers. I can't imagine how you find the time, but I'm really grateful you do!

(A nice reminder: I should return and read again those sections at least in which Peter Attia addresses LDL particle size.)

I'm particularly sensitized to this because I just had my first LDL-P test and I'm thinking (and reading) about the several measures of risk for CVD or atherosclerosis (by the way, they are not necessarily synonyms--or are they?).

Specifically, I recall Peter Attia's posting on discordance and concordance, and I'm struck by my own lipid panel, which reports extremely low risk for CVD/atherosclerosis, according to TG levels, HDL-C and HDL-P numbers, insulin resistance score, and (if I apply what I learn from your post), LDL particle sizes. Not to bore you, or distract you with any request for a diagnosis, if I look at only my LDL-P, I have more like average risk, at least as I judge from the evidence drawn from available studies, whose subjects apparently ate (SAD) quite differently

from me (LCHF).

So my relaxed curiosity about this focusses on this mixed message from my scores: genuinely excellent low risk, as indicated by several (well supported, evidence based) measures; only average risk, as supported by one (ditto) measure.

I can imagine several possibilities to explain this discordance (if I understand that term). Perhaps LCHF, keto-adapted biochemistry benefits from a higher LDL-P level. Or perhaps the large-particle LDL, which I have in abundance, confer some biochemical benefit (after all, cholesterol is an essential chemical!). Or, can it be that something elsewhere in the body has required a higher than optimal (lowest risk) LDL-P number? In other words, are those particles doing good (whether or not they thereby raise my risk for CVD or atherosclerosis) by fixing something else that's out of whack? Or perhaps the LDL particles are neutralized anyway by the action of HDL, as I have read somewhere (although in which case why am I making so many LDL particles in the first place?--it seems oddly redundant or inefficient, when so much about my lipid chemistry appears to work so well). Or perhaps even, as Peter Attia commented (he suspects, and hopes to find out) for LCHF and keto-adapted individuals, LDL-P does not matter (perhaps because of some other as yet poorly understood mechanical action involving LDL in the arteries underway during ketosis).

It could be that some good evidence for or against these possible explanations already exists, although I think Peter Attia would have already shouted it from the hill tops by now. I'm looking and listening, albeit non-systematically, while enjoying so much the more I learn from you and others like you who so thoughtfully discuss this fascinating, delightfully geeky (and, oh yes, possibly life-enriching, not to say life-saving) area of biochemistry.

In sum, while I try to remind myself of the pitfalls of the confirmation bias, I do draw some encouragement from what you write here and elsewhere on your two blogs. Thank you!

Patrick

[Reply](#)

▼ [Replies](#)



L. Amber Wilcox-O'Hearn September 10, 2013 at 6:54 PM

😊 I am enjoying the delightful geekiness, too.

Yes, we're getting into unknown territory. I'm sure the epidemiology data did not have strong representation of keto

dieters, and of course the whole risk factor approach has potential problems. I suppose a calcium score would tell you much more directly what's going on. Have you looked into that?

I very recently gave blood samples to get a more elaborate panel that should include LDL particle size and number. I'll post the details to empiri.ca when they come in.

Thank you so much for your words of encouragement and support. I don't know how I find the time, either, but to hear genuine interest and appreciation of what I'm writing makes it feel worth it.

[Reply](#)



Greg September 11, 2013 at 2:57 AM

Hi, thanks Amber for all of your work on this and all of the detail you put into the backup evidence.

One point about the Yancy controlled trial which I believe is the same one you cite above as Westman et al 2006 (I think it was first reported in May 18, 2004 *Annals of Internal Medicine* as Yancy et al, "A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia"). It is worth pointing out that a substantial minority of the participants on the ketogenic diet experienced an increase in LDL cholesterol. 30% of participants had LDL increase by 10% or more in the ketogenic arm, vs. 16% on the low fat diet. Two ketogenic diet participants dropped out because of increases in LDL, and one ketogenic diet participant had LDL go from 184 to 283 in 3 months.

Based on this it is probably more prudent to say that ketogenic diets do not cause adverse changes in cardiovascular risk factors on average, but that individuals may experience a meaningful increase in non-HDL cholesterol (I don't think it is at all useful to calculate LDL, but non-HDL is a cheap proxy for apoB aka particle number in most people -- see Dayspring re this). While it is not absolutely certain what this means from the standpoint of actual risk of heart disease in those eating ketogenic diets, I think caution is warranted if non-HDL rises catastrophically on the diet even while triglycerides and HDL may be improving.

[Reply](#)

▼ [Replies](#)



L. Amber Wilcox-O'Hearn September 11, 2013 at 4:59 PM

Hi Greg,

Thanks for the comments and reference.

I do agree that when we are looking at risk factors like this, we are making indirect inferences, and ought to be cautious about conclusions. That's true of the arguments here, and it's also true of the older arguments condemning high LDL in the first place.

It is true that subjects in both groups in the study you cite had substantial increases in LDL, and that this happened twice as often for the keto dieters. However, given the whole of the argument I have detailed above, I don't find it necessarily alarming.

LDL by itself is a weak predictor of CVD. So my contention is that an LDL measure even of 283 is unlikely to indicate high risk of CVD *if* it is in the context of low triglycerides and high HDL.

The evidence implies something much stronger than a keto diet is "not adverse on average", because averaging would be weighing a weak predictor with the same weight as a strong predictor.

There is another line of complexity here that I decided not to discuss in this post but to save for a subsequent one, and that is statistical interactions. However, it's relevant here. There is [a very nice paper by Manninen et al. called Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment.](#) that illustrates some of the concepts.

Table 4 on page 42 compares risk of cardiac events for people with high or low triglycerides (meaning above or below 204) under the conditions of high or low LDL (meaning above or below 193). The bottom part shows a drug trial condition which we can ignore for this purpose -- we are looking at the placebo group who had no intervention.

The table shows that when triglycerides are low (and 204 is a very high cutoff point!), the cardiac events were similarly low whether LDL was high or low. **With 1 corresponding to having**

low triggs and low LDL, the relative risk if LDL is high and triggs are still low was only 1.06, whereas having high triggs gave a relative risk of 1.61 if LDL was still low, and 2.37 if LDL was also high.

It would be nice to see more stratification of these interactions, and of course

there is more experimentation we'd like to see before saying with certainty that a keto diet is reversing CVD, but I think the claim that it is improving known risk factors holds up quite well, even in light of higher LDL.

Caution is always warranted. If I personally had a cholesterol profile that made me feel doubtful, I would probably go for a calcium scan.



L. Amber Wilcox-O'Hearn September 11, 2013 at 5:11 PM

Greg, I forgot to respond to your apoB /particle number point, which is a good point. It does make things less clear cut (although see the particle number discussion above).



Greg September 12, 2013 at 1:07 PM

Amber, thanks for the detailed response. I took a quick look at the Manninen paper -- it is an interesting result but I'm curious to know the mean and SD for LDL in that placebo group (maybe it is in the original Helsinki study report -- probably Frick 1987 in NEJM but I can't get the full text). I'm doubtful there is enough coverage in their population to say much about LDLs in the high 200s even if they had done a more detailed analysis. I'm not prepared to assume the relationships can be linearly extrapolated out that far, especially given research suggesting the risk curve is u-shaped (see e.g. Petursson 2012 on the Norwegian HUNT-2 study). We don't know how triglyceride levels interact with the shape of that curve. A u-shaped curve would be consistent with what we know about familial hypercholesterolemia -- lots of (large) LDL, and lots of heart disease. Not saying this is the answer, but it is suggestive. As you say, caution is warranted.

Sadly a definitive answer would require a study that will never pass an IRB -- putting people on a diet that dramatically raises their non-HDL (because we're interested in the subset whose non-HDL goes up on a ketogenic diet) while withholding statins and waiting long enough for them to get (or not get) heart disease.



L. Amber Wilcox-O'Hearn September 12, 2013 at 6:51 PM

Sure. Not only is their population not likely to have many with LDLs in the high 200s, but it's not likely to have a high proportion of keto dieters either.

I wouldn't draw conclusions about what happens to other people with high LDL from a group that has a defect in the LDL receptor system.

It also occurs to me to wonder whether Yancy et al. were using calculated LDL (as almost everyone does), which is known to overestimate LDL when triglycerides are low (see [The impact of low serum triglyceride on LDL-cholesterol estimation. Ahmadi et al.](#)).

In your proposed experiment, there are other things that could be done besides waiting to see who dies. I don't have the time to get into it in depth today, but, other more direct measures of CVD could be looked at in those people. For example, [carbohydrate restriction has been shown to improve postprandial vascular function](#). It could be interesting to look at those high LDL responders as a subgroup and see what their other measures look like.

By the way, since everything I have researched suggests that a low carb diet is healthier than any other diet on several parameters, when I say caution is warranted, that implies that it would be imprudent in my opinion, to follow any other diet than a ketogenic one, particularly if you have a life-threatening disease. If the alternative lowers my LDL but raises markers of metS, I would consider that much more risky.



Greg September 13, 2013 at 2:16 PM

"It also occurs to me to wonder whether Yancy et al. were using calculated LDL..."

They were. More evidence of mass delusion in the biomed research field :)

"...other more direct measures of CVD could be looked at in those people."

I've been wondering if the BodyMetrix personal ultrasound can measure carotid artery IMT.

"If the alternative lowers my LDL but raises markers of metS, I would consider that much more risky."

Absolutely agree, tangible health improvements should trump biometric risk factors any day. MetS seems to be a clear indication for low carb and/or ketogenic diet.

[Reply](#)



Patrick Snook September 11, 2013 at 6:30 PM

Hi Greg and Amber,

See my earlier comments expressing my quandary about the importance of rising "non-HDL" cholesterol. There are some data (cited and addressed by the blog Health Correlator) that show an inverse correlation between total cholesterol and mortality, i.e. the lower the cholesterol, the higher the mortality. So it does not hold true that an increase in non-HDL--whether or not it can be positively correlated with a ketogenic diet--should always be "catastrophic".

And about the phrase "reversing CVD". Is it possible to reverse, as in, repair damage already done? I had assumed that the build-up of arterial plaque was a permanent accretion, and the best that could be hoped for was a reduction (or even prevention) of further calcification. Alternatively, in the absence of actual damage, we could hope to reduce the risk of damage occurring, as far as possible (again which does not "reverse" the disease; merely it reduces the risk).

As you suggest, Amber, I might look further in to the calcium scan idea. It raises other questions, however; in the absence of some baseline measure and then later measures (say three years ago, and then two-and-a-half years ago, and then two years ago, in my case) about the link between any LDL-C or LDL-P measure and the *current* condition of my arteries, and the part that diet (then and now) might have played in all this, what am I to make of a calcium score?

Did you ever see that movie "Sliding Doors"? I often think of it, when I read about nutrition and n=1 experimentation. If only we could change *one* initial condition, and run both experiments on ourselves, in a forking path of our two clones (I suppose we should call our plural self).

Cheers!

Patrick

Reply



Patrick Snook September 11, 2013 at 6:36 PM

Amber,

I note your original does refer to reversing "indicators" of CVD (by "indicators" I take it you mean "risk factors"). My question arises because I'm curious about the assumption that, as you say in your second sentence, the disease can likely be reversed.

I'm not sure the distinction is often made, unless it's superfluous to do so.

Patrick

Reply

▼ Replies



L. Amber Wilcox-O'Hearn September 11, 2013 at 10:01 PM

Yes, "indicators" was meant to express exactly that we are talking about risk factors.

[Macrophages, dendritic cells, and regression of atherosclerosis](#) is a very interesting review of the initial controversy and current research into factors that contribute to regression in animal models. One of them is HDL.

Reply



Spunk October 9, 2013 at 1:14 AM

There is a mention in one of the studies that 30% of the population is affected and something later about people with LDL receptor dysfunction. The population that fits this characteristic also produces high non-HDL linked to ApO-B being higher and in some cases poor

thyroid function which can resolve this. The identified group are gene carrier of ApO-E4's

The research was cited in a Berkeley Labs report which I cannot locate on their website but a similar chart summary is here.

<http://www.gdx.net/core/interpretive-guides/CVHealth-Genomic-Interp-Guide.pdf>

This also has been noted on Dr W Davis trackyourplaque

<http://blog.trackyourplaque.com/2011/07/the-exception-to-low-carb.html>

we are also aware of it at www.heartlifetalk.com and we do indeed believe that a rising LDL-P# is a risk factor not to be ignored and calcified plaque can be reversed.

Your blog is shows excellent research.

[Reply](#)



Wieslaw Kruczala June 28, 2014 at 5:28 PM

Part 2

Maybe you think the medicines did not work properly. They did. The “bad” LDL level was as low as it can only be possible in healthy people, but my “good” HDL cholesterol was twice bigger than the upper limit observed in such people. It means that in the eyes of doctors my blood results were extremely good. Extremely good! So why was I again about to die?

I came to the conclusion that my life would stop soon and the doctors not help me. The cardiac surgeons told me that as I was very slim my chances to overcome are extremely low. However their comprehension of the disease was limited. There are so many theories on the reasons of the atherosclerosis! Fortunately I remembered about Eskimos. I started reading about them to get knowledge of their way of eating. But how could I follow it?

From that time I almost removed not fat but carbs from my diet. A ate only one or two tomatoes a day, a cucumber, lettuce, natural yoghurt, some bran, a piece of smoked fish (mainly mackerel). No bread, cereals, soup, potatoes. Instead I ate 150 g of butter a day.

And a mirracle happened. The arrythmia was slowly diminishing day by day. After three weeks of the diet I stopped taking aspirin. There was no need to use it, for the arrythmia disappeared at all.

I have only a stethoscope to monitor my heart. No doctors are interested in the results of my diet. Ordinary people do not believe me or treat the diet as too demanding for them. I have no money for accurate medical examinations. I know that it will take about half a year for my organism to clean my vessels completely. I am still taking atorvastatine for night to help my body in it. Then I will ask a cardiologist to examine me with a ECG holter device. That's all what I am able to do.

In order to control how my organism reacts to the frequency and

contents of my meals I have bought kitchen scales and count the calories, proteins, carbohydrates in all products I consume. With Keto-Diastix test I measure the level of ketones in my urine.

My understanding of the coronary disease is the following. Too much glucose in blood seriously make harm not only to red cells by the Maillard reaction. Also the lining layer of the vessels is injured. Macrophages settle in the damaged places, as their aim is to fight bacteria which can enter the body through wounds. They gather and gather in great numbers because the damages don't stop. Many of them die. In this way the plaque is formed. But when glucose is almost absent from the blood, organism can clean the vessels. I am surprised how quickly it can happen.

And the disease has had a serious impact on my mind. As I said my problem originated from my attempt to be good so it forced me to examine my life and everything I knew about God. Can you imagine that I am still a Christian although I do not believe in God any longer? After all these events I realized that it seems that he created us to be killers, as we are genetically prepared for eating fat, a lot of fat, and meat. It was only Jesus who tried to make us sympathetic to all people, no matter who they are, and to other creatures.

[Reply](#)



Wieslaw Kruczala June 28, 2014 at 5:29 PM

Part1

My name is Wieslaw Kruczala. I am Polish and live in Poland, so excuse me for language mistakes. I feel I should write some words about the Eskimo diet, because it saved my life.

I was always interested rather in science than physical activities. I am weakly built, not a macho. I am 170 cm tall, and for many years I have never weighed more than 66 kg. Because I am a physics and science teacher, I spend many hours sitting at the computer. As the result of this style of living I always had some kilograms of fat on my belly. About six years ago I decided to loose them to have a perfect figure, so that my abdominal muscles could be seen. I started to exercise a lot and eat less, especially I removed almost all fat from my diet. Fat has twice more calories than proteins than carbs have. I consumed only milk fat contained in my breakfast milk soup. The milk was with cornflakes or oats flakes. I ate a tea spoon of flaxseed oil once a day, because I ate fish very seldom. As a vegetarian I ate lots of apples or other fruit, usually a kilogram or more during a day. I loved them. I ate a lot of fruit yoghurt, but I never sweetened my tea. I preferred whole-meal bread to white bread. I ate very little margarine and no butter. To my vegetarian soups I added canola oil. I fried food only with oil. To deliver all necessary amino-acids I often ate peas, beans, lentil. I was very

pleased that I do not harm animals. I expected that God would give me good health for my good behaviour, for my sensitivity to sufferings of other creatures.

About four years ago I started to notice strong heart beats a few times a day. I did not expect coronary disease because I was really thin, exercised quite a lot, had never smoked or drink alcohol. In my blood there was quite a lot of bilirubin due to Gilbert syndrome. As I read the bilirubin should in some degree protect me from atherosclerosis.

First I went to an immunologist, as my TSH level was a bit too high. After a year my thyroid gland became all right somehow and the doctor said that it could not be the reason of the arrhythmia. At that time I had an additional heart beat once in some minutes.

So I went to a cardiologist. A USG examination revealed that the interventricular septum was not contracting sufficiently, then a day long Holter monitoring showed that I had up to 380 VE events (strong irregular beats) per hour, finally a cardiac stress test showed the left bundle branch blocking. The doctor decided to send me to a coronarography check, but in fact she did not expect the coronary disease, because in me there were no factors of risk.

During the coronarography it turned out that I was about to have a heart stroke which for sure would kill me. It would be so strong, because my heart arteries supplying blood to the left ventricle were at the beginning and in some other places blocked up to 90%. The doctors put a stent in the most important place. I started to take medicines containing aspirin and atorwasatine. I started to exercise over an hour each day.

For a month the arrhythmia was really small, yet it was growing. As I read more and more on the Internet I understood that there was something in my food what caused it. I realised that I had eaten too much carbs, especially starch and fructose and oil containing omega-6 fatty acids. So I started to eat butter (but not more than average people), use lard for frying, avoid fruit. However it was not a strict diet. Half a year passed. The arrhythmia became as big as when I did not have the stent yet, did not use medicines, did not exercise so much . I must explain that I should have had two stents. The other was missing in a less important place (diagonal artery). The lack of the stent gave me the opportunity to observe the condition of my circulatory system. With a stethoscope I listened to my heart for many minutes some times a day. I observed that my health was getting worse and worse. Again there occurred some hundreds of bad beats per hour.

[Reply](#)



Zooko Wilcox-O'Hearn March 25, 2015 at 10:34 PM

A fun recent blog post about this same topic:

<http://hopefulgeranium.blogspot.com/2015/03/tghdl-ratio-trumps-ldl-in-treated-and.html>

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