Isolated low high density lipoprotein-cholesterol (HDL-C): implications of global risk reduction. Case report and systematic scientific review

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Abstract

Background: The importance of low high-density lipoprotein cholesterol (HDL-C), elevated non HDL-C (as part of the metabolic syndrome, prediabetes, and type 2 diabetes mellitus), and an isolated low HDL-C is rapidly emerging. The antiatherosclerotic roles of reverse cholesterol transport and the pleiotropic antioxidant – anti-inflammatory mechanistic effects of HDL-C are undergoing rapid exponential growth.

Case presentation: In 1997 a 53-year-old Caucasian male presented with a lipoprotein profile of many years duration with an isolated low HDL-C and uric acid levels in the upper quintile of normal. He developed an acute myocardial infarction involving the right coronary artery and had percutaneous transluminal coronary angioplasty with stenting of this lesion. He also demonstrated a non-critical non-flow limiting lesion of the proximal left anterior descending coronary artery at the time of this evaluation.

Following a program of global risk reduction this patient has done well over the past 7 years and remains free of any clinical signs and symptoms of atherosclerosis. His HDL-C and uric acid levels are currently in the normal physiological range.

Conclusion: Low HDL-C and isolated low HDL-C constitute an important risk factor for atherosclerosis. Therapies that lead to a return to normal physiologic range of HDL-C may result in the delay of atherosclerotic progression.

Case presentation

MRH, a 53-year-old Caucasian male (physician) developed an acute inferior myocardial infarction (MI) associated with bradycardia and occasional PVCs. Emergency medication included aspirin, nitroglycerin and a bolus of TPA.

The cardiology team preformed PCTA at the site of near complete blockage of the right coronary artery with
successful stent placement. At this time a non-critical 40% lesion located in the proximal left anterior descending coronary artery was noted, which was not manipulated. The patient was discharged following 24 hours of stable monitoring.

**Past Medical History**
Relapsing fever 1971 full recovery, spontaneous left pneumothorax times two (1982–83), lumbar fusion back surgery 1985, and *Herpes Simplex* encephalitis 1989 with full recovery.

**Family History**
Mother with CVA (cerebellar) age 58 full recovery. Died of Hodgkin’s lymphoma 64. Brother with type 1 diabetes mellitus with onset at age 29 (known PAD and aorto-femoral bypass age 49) died in sleep age 51.

Father with CVA (vertebrobasilar) age 75 with full recovery, COPD, died in sleep while recovering from TIA and pneumonia age 84.

Grandparents lived to their 80s and died of old age.

**Social History**
High stress family physician who seldom drank alcohol and smoked a pipe occasionally. Blood pressure at times of high stress would elevate to 140/85–88 and return to 120–130/70–75 at times of non-stress in the office. He was physically active with no dedicated exercise program.

**Laboratory Values**
Five months prior to MI and reflective of numerous metabolic profiles over the preceding decades.

**Total cholesterol** 198 mg/dL
**Triglycerides** 154 mg/dL
**HDL-C** 34 mg/dL. HDL-C (1970–1973 32 mg/dL and 34 mg/dL)
**LDL-C calculated** 120 mg/dL
**Non HDL-C** = (198-34) = 164
**Total Chol/HDL ratio** = 6.2 > than 5 and is high
**Uric acid** 6.5 mg/dL
**Blood sugar non-fasting** 102 mg/dL
**Homocysteine first week post MI fasting**: 28 mc mol/L

Patient started a program reflecting the global risk reduction approach described in the RAAS acronym (table 1) and is currently taking an angiotensin receptor blocker, aspirin, beta blocker, folic acid, and a statin. Patient was intolerant of ACE inhibitor therapy due to cough and fatigue and has been unable to tolerate niacin on numerous attempts both pre and post MI due to incapacitating headaches.

**Current Laboratory Values 2004:**
**Total cholesterol**: 138 mg/dL
**Triglycerides**: 94 mg/dL
**HDL-C**: 45 mg/dL
**LDL-C calculated**: 74 mg/dL
**Non HDL-C**: (138-45) = 93
**Total Chol/HDL ratio** = 3.0
**Uric acid**: 6.5 mg/dL
**Blood sugar**: Fasting 80 mg/dL, 2 hour post prandial 118 mg/dL
**Homocysteine**: 7.2 mc mol/L
**Lp(a)**: 4.2 mg/dL in normal range immediate post MI and again at this time: 4.3 mg/dL
**hs-CRP**: 0.7 mg/L.

LFTs, electrolytes, calcium and phosphorus, serum iron, renal function, and CBC were all in normal range.

This patient has done well over the past seven years and remains free of any clinical signs and symptoms of cardiovascular disease. While this patient will always remain a CHD risk, his current laboratory values remain in a normal physiological range. As noted above his HDL-C and uric acid levels are currently in the normal physiological range and his hs-CRP remains in the second quartile.

**Comment**
According to Framingham risk scores associated with the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [1], few would have recommended any treatments other than therapeutic...
lifestyle changes (TLC) and possibly niacin, which our patient was intolerant both pre and post event in 1997.

If we score this patient according to the estimate of 10-year risk for men he gets 6 points for age 53, 2 points for total cholesterol 160–199 age 53, 3 points for being a pipe smoker, 2 points for HDL being < 40 mg/dL, and 1 point for systolic blood pressure 140–159 untreated. This totals 14 points and results in an estimated 10-year risk for men of 16%, which is less than the 20% recommended for more aggressive therapy.

Even if we apply the NCEP ATP III guidelines of having two plus risk factors: Male sex, hypertension, smoking, and low HDL-C with a 10 risk < or = to 20% we obtain the following recommendations: LDL-C goal < 130 mg/dL, initiation of TLC if LDL-C is = or > 130 mg/dL, consideration of drug therapy if LDL-C is > or = to 130 mg/dL after three months of TLC. It is important to note that our patient had a LDL-C of 120 mg/dL prior to his event. Even if we look at the non HDL-C levels, which are allowed to be 30 mg/dL higher than LDL-C goals we have a patient with a non HDL-C of only 164. MRH became a CHD risk patient within a short period of time of 5 months.

Discussion
The importance of low HDL-C and cardiovascular disease associated with the lipid triad (Low HDL-C, elevated triglycerides, and increased small dense LDL-C) found in the metabolic syndrome (metS) and overt type 2 diabetes mellitus (T2DM) and a contributing factor to the elevated non HDL-C discussed in the current NCEP ATP III guidelines or the patients with isolated low HDL-C is rapidly evolving.

The accelerated atherosclerosis (atheroscleropathy) associated with the metS and T2DM has been previously reviewed and is definitely a serious problem associated with the current epidemic of obesity – diabetes and T2DM [2-4].

Table 1: The RAAS acronym: global risk reduction

| R | Reductase inhibitors (HMG-CoA). Decreasing modified LDL-cholesterol, i.e. oxidized, acetylated LDL-cholesterol. Decreasing triglycerides and increasing HDL-cholesterol Improving endothelial cell dysfunction. Restoring the abnormal Lipoprotein fractions. Thus, decreasing the redox and oxidative stress to the arterial vessel wall and myocardium. **Redox stress reduction.** |
|---|---|
| A | AngII inhibition or blockade: ACEi-prils. ARBS-sartans. Both inhibiting the effect of angiotensin-II locally as well as systemically. Affecting hemodynamic stress through their antihypertensive effect as well as the deleterious effects of angiotensin II on cells at the local level – injurious stimuli - decreasing the stimulus for O2 production. Decreasing the A-FLIGHT toxicities. Plus the direct-indirect antioxidant effect within the arterial vessel wall and capillary. Antioxidant effects. Aspirin antiplatelet, anti-inflammatory effect. Adrenergic (non-selective blockade) in addition to its blockade of Prorenin→Renin Amlodipine with its calcium channel blocking antihypertensive effect, in addition to its direct antioxidant effects. **Redox stress reduction.** |
| A | Aggressive control of diabetes to HbA1c of less than 7. (This usually requires combination therapy with the use of: Insulin secretagogues, insulin sensitziers (thiazolidinediones), biguanides, alpha-glucosidase inhibitors, and ultimately exogenous insulin.) Decreasing modified LDL-cholesterol, i.e. glycated – glycoxidated LDL cholesterol. Improving endothelial cell dysfunction. Also decreasing glucotoxicity and the oxidative – redox stress to the intima and pancreatic islet. Aggressive control of blood pressure, which usually requires combination therapy, including thiazide diuretics to attain JNC 7 guidelines. Aggressive control of dyslipidemias, which frequently requires combination therapy (especially in the metabolic syndrome and T2DM), including TLC, statins, fibrates, selective cholesterol inhibitors such as ezetimibe, and niacin Aggressive control of Hcy with folic acid with its associated additional positive effect on re-coupling the eNOS reaction by restoring the activity of the BH4 cofactor to run the eNOS reaction and once again produce eNO. **Redox stress reduction.** |
| S | Statins. Improving plaque stability (pleiotropic effects) independent of cholesterol lowering. Improving endothelial cell dysfunction. Plus, the direct – indirect antioxidant anti-inflammatory effects within the islet and the arterial vessel wall promoting stabilization of the unstable, vulnerable islet and the arterial vessel wall. Style: Lifestyle modification: lose weight, exercise, and change eating habits. Stop Smoking **Redox stress reduction** |

Table 2: Effects of drugs on HDL-C levels

| DRUG | PERCENT INCREASE |
|------|------------------|
| Nicotinic acid (niacin) | 15% – 35% |
| Fibrates | 10% – 15% |
| Estrogens | 10% – 15% |
| Statins | 5% – 10% |
| Coupled Dual Effect Associated with potent LDL-C reduction, which make the statins "shine" | |
| Alpha blockers | 10% – 20% |
| Alcohol (in moderation) | 10% |
| Ezetimibe | 3% |
Both isolated low HDL-C and elevated non HDL-C (total cholesterol minus HDL-C) levels are difficult to get to known NCEP ATP III recommendations and this task usually requires combination therapy. These therapies consist of therapeutic lifestyle changes and pharmacotherapy including statins, fibrates, selective cholesterol inhibitors such as ezetimibe, and niacin in addition to a global risk reduction of all non HDL-C existing risk factors (table 2) [5].

In this case report a focus on isolated low HDL-C is appropriate. This case report demonstrates a marked improvement of all lipid parameters including his low HDL-C. However, this marked improvement is not always as simple as this case and therefore, both the patient and the clinician need to be very patient, as well as, creative in order to achieve global risk reduction [5].

**Isolated low HDL-C**

In 1977 the Tromso Heart Study demonstrated that CAD patients have HDL-C levels 35% lower than controls and those patients with low HDL-C are three times more likely to develop CAD than those with elevated LDL-C [6]. These early views certainly support the concept that an isolated low HDL-C is a common antecedent of clinical CHD, as well as being important in accelerating the progression of atherosclerosis.

The inverse relation of HDL-C to CHD events has been widely discussed since the original publication of data from the Framingham study (1986) [7,8]. Castelli WP et al. were able to show an inverse association of high HDL-C and low coronary risk was as statically as strong as the direct association of high LDL-C and high coronary risk in a cohort of men and women age 40–82 followed for 12 years who were free from CAD at study entry. At any level of cholesterol low HDL-C increases the rate of CHD [1].

The NCEP ATP III guidelines clearly defines a level < 40 mg/dL as an independent risk factor for CHD [1]. Raising HDL-C is not a target for either primary or secondary prevention at this time, however its importance as a tertiary target is rapidly emerging.

Michael Miller has stated: "Low HDL-C is the most common lipoprotein abnormality in patients with CHD and is predictive of CHD events, even when total cholesterol levels are normal" [9].

Goldbourt U et al., found that the prevalence of isolated low HDL-C as a risk factor for CHD mortality to be present in one out of six or 16.6 % while studying a 21-year follow up of 8000 men [10]. Furthermore, they found that an excess CHD risk associated with isolated low HDL-C appeared particularly increased in men with diabetes mellitus, whose death rate was 65% higher than in diabetics with HDL-C > 0.9 mmol/L or 36 mg/dL.

There are at least eight secondary causes for low HDL-C (table 3) and at least seven drugs that have a positive effect on raising HDL-C (table 2). As demonstrated in our case report, the beneficial effects of raising HDL-C with statin therapy and a program of global risk reduction have been positive in preventing the progression of atherosclerosis and recurrent acute coronary syndromes (table 4).

HDL-C is synthesized in the intestine and liver and is extremely important in reverse cholesterol transport from the tissues to the liver for disposal. It works in conjunction with the ABCA1 cholesterol transporter within the intimal macrophages (figure 1).

This important dual interaction of HDL-C and the ABCA1 transporter is of great importance and recently we have learned that certain gene polymorphism of ABCA1 transporter may have a profound effect on HDL-C in addition to the well known abnormality of Tangier disease [11].
Oxidative stress and the reductive stress (redox stress) associated with accelerated atherosclerosis may result in a greater than 4 mg/dL may be considered a red flag in those patients, such as our case report, with high risk for CHD. Although not a considered a risk factor or even an emerging, novel risk marker, uric acid may be a quite sensitive marker of underlying redox and oxidative stress. Uric acid levels greater than 4 mg/dL may be considered a red flag in those patients, such as our case report, with high risk for CHD [14].

The Atherosclerotic Kitchen Sink
When viewing the sources for atherosclerosis it is important to note that there are two routes for accumulation of atherogenic lipoproteins (input and outflow) within the arterial intima and subsequent remodeling of the arterial vessel wall.

The atherosclerosis equation: Lipoprotein Accumulation (retention) in the arterial vessel wall = Lipoprotein in - lipoprotein out. \[ \text{L-A avw} = \text{L-in} - \text{L-out} \]

L-in, would equal the net lipoproteins derived from the GI tract (absorption) plus that synthesized by the liver. Lipoprotein out is strictly via reverse cholesterol transport to the liver and secretion via bile into the gut. L-in is primarily the beta lipoproteins or apolipoprotein B containing lipoprotein particles, whereas L-out depends primarily on the alpha lipoproteins, apolipoprotein A or HDL-C. The beta lipoproteins are atherogenic and the alpha lipoproteins are antiatherogenic. From this analogy one can see why non HDL-C was so important in the recent NCEP ATP III guidelines: \[ \text{non HDL-C} = \text{total Cholesterol} - \text{HDL-C} \] (reflecting the total atherogenic burden).
This is also why the recent global (52 countries) INTERHART study found the ApoB/ApoA-1 ratio (the ratio of atherogenic lipoproteins to non atherogenic lipoproteins) to be the best predictor of CHD (odds ratio of 3.25 for top verses lowest quintile) as compared to the other eight other risk factors (table 5) [15].

L-Aavw = ApoB/ApoA-1 ratio of the INTERHART study

L-in, would be comparable to the faucet (GI tract and Liver) delivering the atherogenic apoB lipoproteins. While the kitchen sink would represent the accumulation of atherogenic lipoproteins within the arterial vessel wall or L-Aavw.
In a like manner, the DRAIN would represent \( L-out \) or HDL-C or apoA-1 lipoproteins. From this analogy it can easily be seen that if there is inadequate HDL-C or apoA-1 the atherogenic kitchen sink will overflow and result in acute coronary syndromes as happened in our case report (figure 2).

**Conclusion**

While the treatment of isolated HDL-C may seem overwhelming at times, it will be rewarding for both the clinician and the patient as demonstrated by the our case study. This patient has done well for seven years and it is anticipated he will continue to do well with his laboratory values now in a sustained, normal physiologic range.

Additional tests by nuclear magnetic resonance spectroscopy (NMR LipoProfile) would assist us in knowing the LDL particle number (LDL-P) and would assist us in even more aggressive therapy. In addition to his current goals he has met, he should have an LDL-P under 1000 micromol/L and small LDL-P under 700 micromol/L.

Even though we have discussed LDL-C from a quantity perspective, due to an isolated low HDL-C, we should additionally be aware that there exists and equally important role for the quality of HDL-C [12]. Recently, the *Apo A-1* \text{Milano} and *Apo A-1* \text{Paris} have resulted in a marked increase in research interest for the HDL-C lipoprotein particle and its future manipulation [16]. In the near future we may be utilizing gene transfer utilizing variations of the Milano and Paris forms, as well as the newer apoA-1 mimetics such as L-4F [17]. Recently there has been increased interest in CETP inhibitors and Phase II studies are underway with torcetrapib and the combination of torcetrapib and atorvastatin [18]. Additional attention to the PPAR agonists and atherosclerosis and the liver \( X \) receptor alpha (LXR alpha) agonists is being employed at the present and the positive dual effects on HDL-C and atherosclerosis is being actively investigated. This dual agonism of PPAR alpha, gamma, and possible delta, as well as the dual effects of PPAR alpha and LXR alpha are quite exciting and we will learn a great deal regarding their effects on atherosclerosis and HDL-C in the near future [19].

Recently John Snow, M.D. (1813–1858), a legendary figure in the field of epidemiology, of London, England was honored [20]. He hypothesized that Cholera was transmitted by water rather than miasma (bad air). He suspected the water from the Broad Street pump was the source of the disease and subsequently had the pump handle removed in 1854 (150 years ago) [21].

Could low HDL-C be the "pump handle" of atherosclerosis and CHD?

**List of abbreviations**

- ABCA-1: ATP binding cassette transporter A-1
- BMI: body mass index
- CHD: coronary heart disease
- CAD: coronary artery disease
- hs-CRP: highly sensitive C reactive protein
- T2DM: type 2 diabetes mellitus
- metS: metabolic syndrome
- HDL-C: high density lipoprotein cholesterol
- LDL-C: low density lipoprotein cholesterol
- LFTs: liver function tests
- PCTA: percutaneous transluminal coronary angioplasty

**Table 5: Nine risk factors account for up to 90 % of MIS worldwide in both sexes, all ages, and in all regions**

| RISK FACTOR | ODDS RATIO |
|-------------|------------|
| Abnormal lipids: ApoB/ApoA-1 | 3.25 |
| Smoking | 2.87 |
| Diabetes | 2.37 |
| Hypertension | 1.91 |
| Abdominal obesity | 1.12 |

Reason for such a high OR: This could aggravate smoking, diabetes, hypertension, obesity, alcohol abuse and even nutrition (eating aggressively)

| Psychosocial Factors | 2.67 |
| Alcohol use | 0.91 |
| Physical Activity | 0.86 |
| Consumption of fruits and vegetables | 0.70 |
**THE ATHEROSCLEROTIC KITCHEN SINK**

In order to prevent overflow
It may require **combination therapy**:
- STATINS
- Niacin
- Fenofibrate
- Ezetimibe
- Lifestyle

**Faucet Apo B**
(VLDL-C, IDL-C, LDL-C)

**Diet** + **Liver**

**Atherogenic Lipoproteins**

**Overflow**
Cardiac Events
ACS

APO B **non HDL-C**
L-Aavw
ApoB / ApoA-1 ratio
Atherogenic lipoproteins

**The HDL-C Drain**
Reverse Cholesterol Transport
+ **pleiotropic effects**
Anti-inflammatory - antioxidant

**The Atherosclerotic Kitchen Sink**. This image portrays the importance of the HDL-C drain in maintaining a certain level of atherogenic lipoproteins within the arterial vessel wall to prevent accumulation and the undesirable possibility of an acute event with overflow or acute coronary syndromes. This simple analogy of homeostasis points to an important concept: That being the frequent need for combination therapy in order to control the various components of the atherogenic lipoprotein profile. Isolated low HDL-C is certainly a red flag regarding the development of atherosclerosis and CHD and additionally the elevation of low HDL-C levels may have a DRANO-LIKE effect to open a clogged drain in an atherosclerotic arterial vessel wall.

**Author contribution**
MRH conceived the idea to write this manuscript. MRH and SCT wrote, and edited this manuscript together.

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VLDL-C: very low density lipoprotein cholesterol
TC: total cholesterol
TLC: therapeutic lifestyle changes
TPA: tissue plasminogen activator

**Competing interests**
The author(s) declare that they have no competing interests.
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