Casual Friday Series

# Functional Blood Chemistry Series
# Pt. VIII: Lipids (1)

A Biogenetix Clinical Presentation

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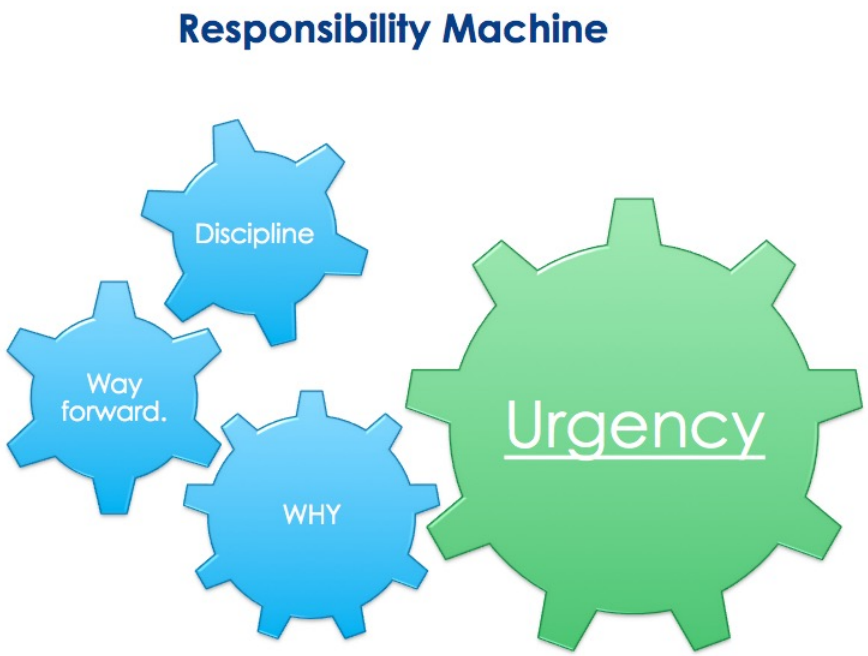
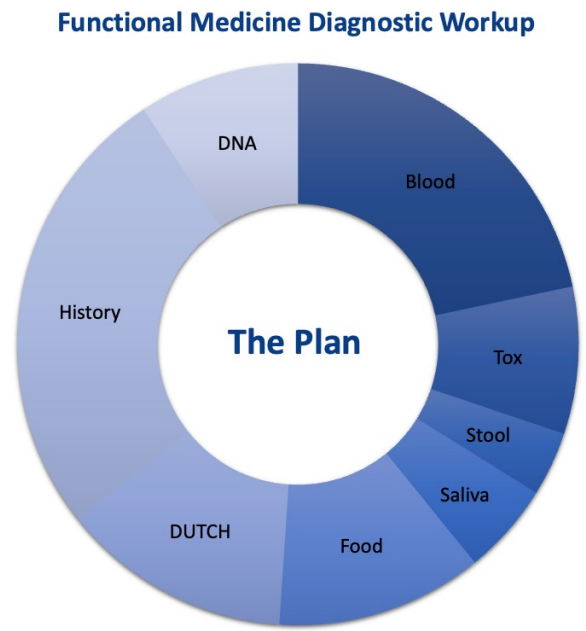
# Disclaimer

- *Information in this presentation is not intended to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

# Applied FM




**Progress.**

# Lipids

- Cholesterol, HDL-C, LDL-C, triglycerides
- Not valuable for identifying cardiovascular risk
- Low cholesterol is not associated with sex hormone levels
- Elevated cholesterol
  - Insulin, glucose dysregulation, low thyroid hormone

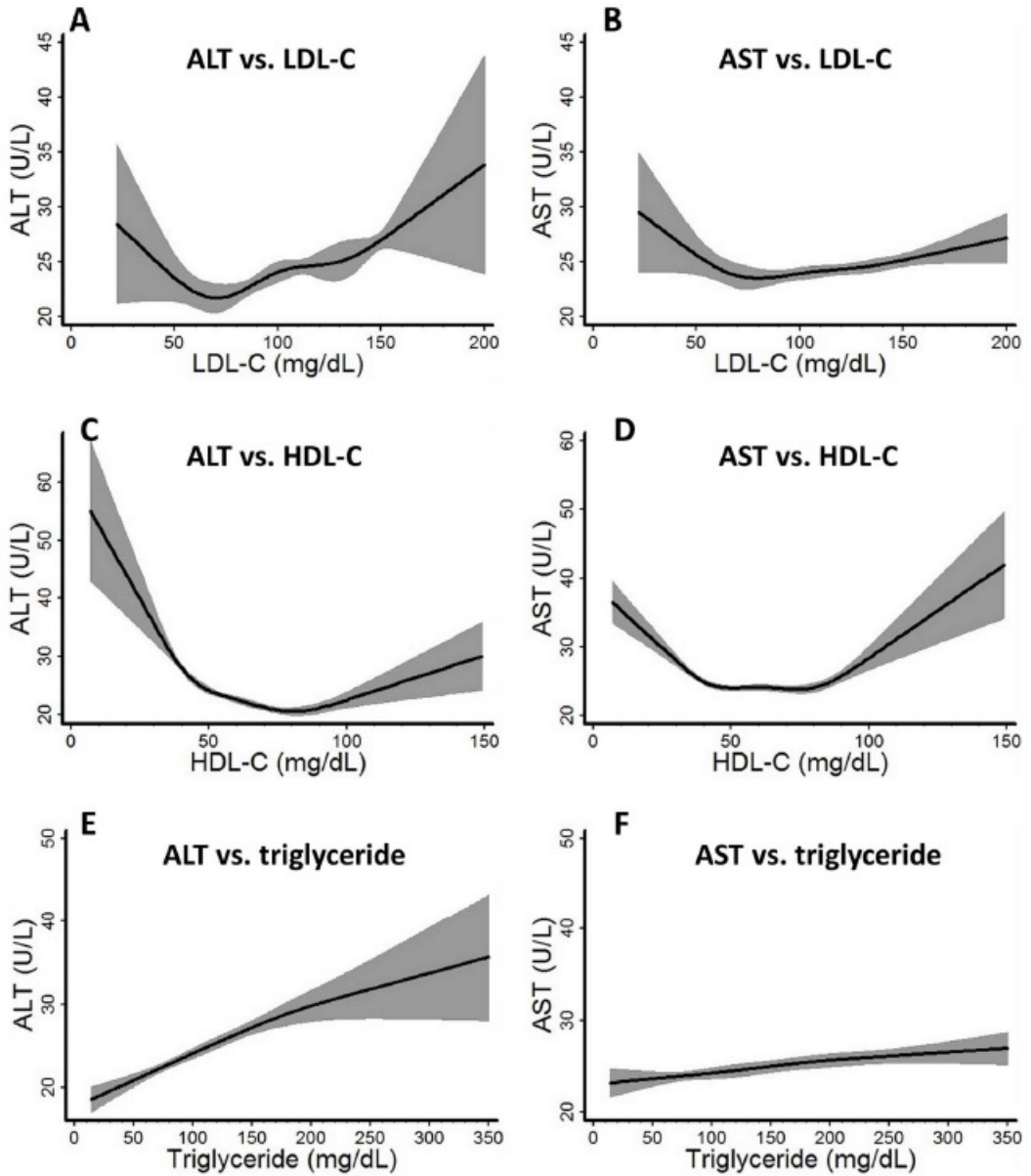
# Lipids

| Ratio | Range | Consideration |
|---|---|---|
| **Cholesterol/ Triglyceride** | >2 | Insulin resistance |
| **Cholesterol/HDL** | < 3.0 | Cardiovascular disease risk |
| **Triglyceride/HDL** | < 3.8 | LDL Particle size |
| **LDL/HDL** | > 2.0 | Inflammation, liver dysfunction |

OPEN ACCESS Freely available online

PLOS ONE

# Low LDL-C and High HDL-C Levels Are Associated with Elevated Serum Transaminases amongst Adults in the United States: A Cross-sectional Study



# High Density Lipoprotein-Lipopolysaccharide Binding Lowers HDL's Basal Antioxidant Capacity

- It has been established that HDL has a role in the innate immune system through its ability to sequester lipopolysaccharide (LPS) or lipoteichoic acid (LTA) in the blood. This sequestering prevents the endotoxins from binding to their respective toll-like receptors and subsequently stimulating the transcription of pro-inflammatory cytokines. Elevated HDL levels are seen to attenuate sepsis by rapidly removing LPS molecules from the blood.

# High Density Lipoprotein-Lipopolysaccharide Binding Lowers HDL's Basal Antioxidant Capacity

- The anti-oxidative capacity of HDL was not observed in the presence of LPS and elicited greater oxidative stress, possibly due to increased LPS-HDL binding. This data suggest that the anti-inflammatory effect of HDL may come at the cost of its other biological functions. It also suggests that chronic low-grade endotoxemia may counter the clinical significance of HDL as a negative risk factor for cardiovascular and metabolic disease disease.

Science is moving toward particle number and size, rather than cholesterol numbers for heart disease and insulin resistance risk assessments.

(Heads will explode)

LDL-P is the measurement of lipoprotein particles. (carriers)

LDL-C is the measurement of cholesterol mass within the LDL particles.

Cholesterol is transported by lipoproteins in the blood
Cholesterol carried by low density lipoprotein (LDL) is associated with increased risk of heart disease

The trucks represent LDL particles.

The yellow sand represents cholesterol carried by LDL particles

Each truck (LDL) carries one ton of sand (cholesterol)

LDL cholesterol (LDL-C) is the number of tons of cholesterol carried by all the trucks

LDL particle number (LDL-P) is the number of trucks

LDL-C is 5 (tons of sand) and LDL-P is 5 (number of trucks)

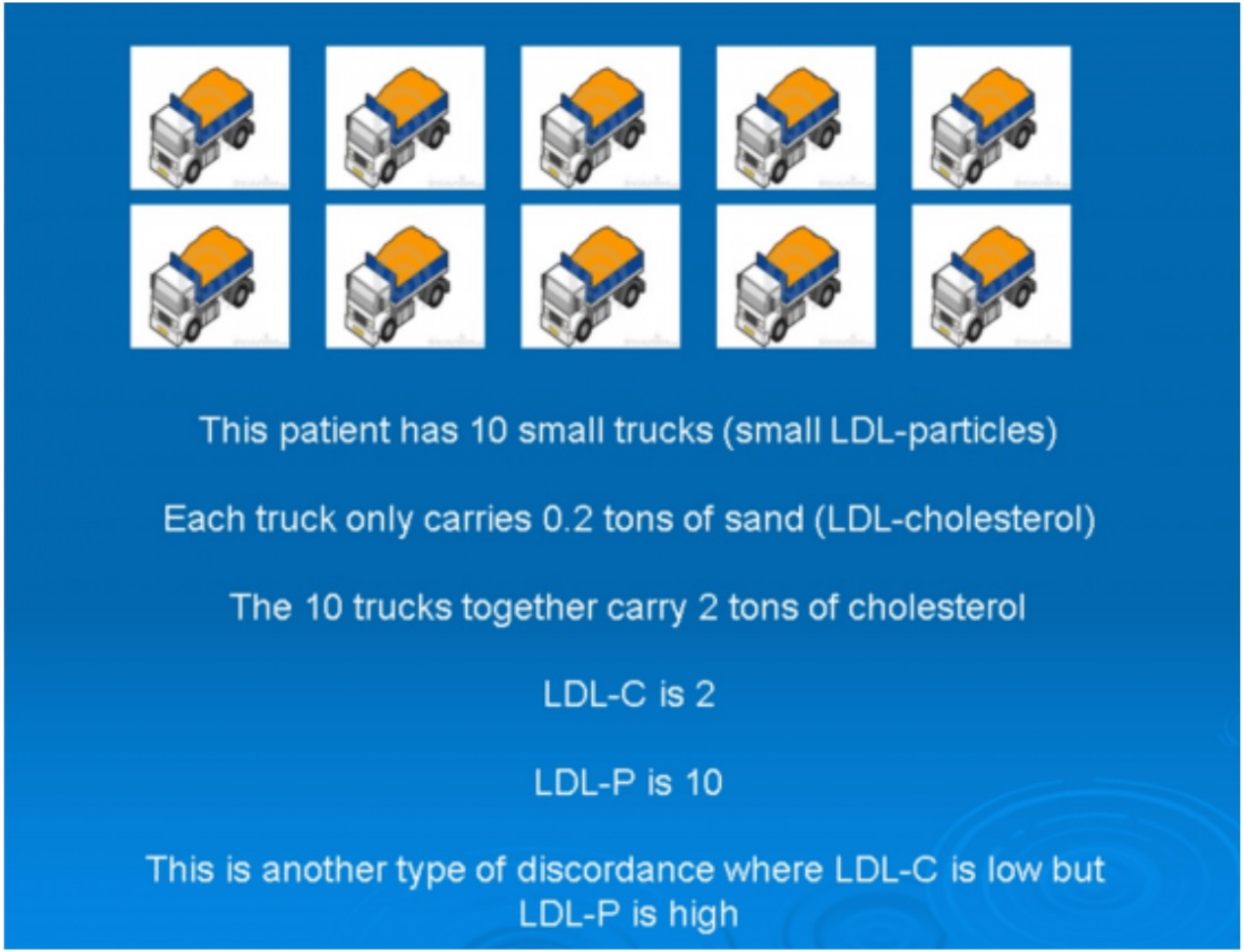
https://www.docsopinion.com/2013/10/20/ldl-cholesterol-particle-number-particle-size-made-easy/

Here are bigger trucks (larger LDL particles)
Each truck is carrying more sand (LDL cholesterol)

Each truck is carrying 5 tons of cholesterol
The total amount of cholesterol carried by the three trucks is 15
LDL-P (number of trucks) is 3

This is an example of discordance
LDL-C is high but LDL-P is low

https://www.docsopinion.com/2013/10/20/ldl-cholesterol-particle-number-particle-size-made-easy/

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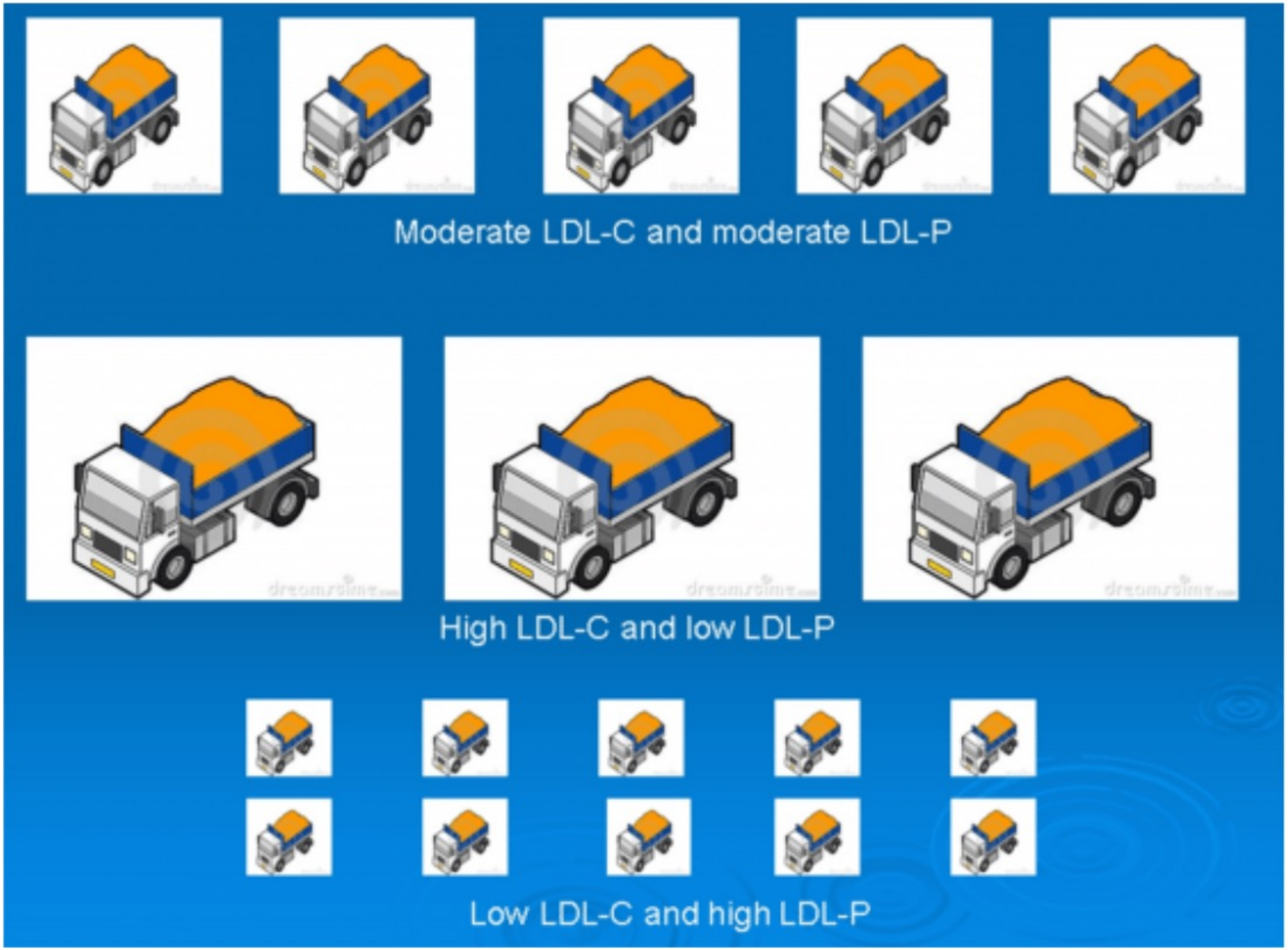


https://www.docsopinion.com/2013/10/20/ldl-cholesterol-particle-number-particle-size-made-easy/

**NMR LipoProf wSubCls+Graph**

| | | | | | |
|---|---|---|---|---|---|
| LDL Particle Number | | | | | 01 |
| **LDL-P** | **1200** | **High** | nmol/L | <1000 | 01 |
| | | | **Low** | **< 1000** | |
| | | | **Moderate** | **1000 - 1299** | |
| | | | **Borderline-High** | **1300 - 1599** | |
| | | | **High** | **1600 - 2000** | |
| | | | **Very High** | **> 2000** | |
| Lipids | | | | | 01 |
| LDL-C | 92 | | mg/dL | 0 - 99 | |
| | | | Optimal | < 100 | |
| | | | Above optimal | 100 - 129 | |
| | | | Borderline | 130 - 159 | |
| | | | High | 160 - 189 | |
| | | | Very high | > 189 | |
| Comment: | | | | | 01 |
| LDL-C is inaccurate if patient is non-fasting. | | | | | |
| HDL-C | 57 | | mg/dL | >39 | 01 |
| Triglycerides | 51 | | mg/dL | 0 - 149 | 01 |
| Cholesterol, Total | 159 | | mg/dL | 100 - 199 | 01 |
| LDL and HDL Particles | | | | | 01 |
| HDL-P (Total) | 36.6 | | umol/L | >=30.5 | 01 |

| | | | | |
|---|---|---|---|---|
| Small LDL-P | 362 | nmol/L | <=527 | 01 |
| LDL Size | 20.8 | nm | >20.5 | 01 |

** INTERPRETATIVE INFORMATION**
PARTICLE CONCENTRATION AND SIZE

| LDL AND HDL PARTICLES | <--Lower CVD Risk Percentile in Reference Population--> | | | | |
|---|---|---|---|---|---|
| HDL-P (total) | High | 75th | 50th | 25th | Low |
| | >34.9 | 34.9 | 30.5 | 26.7 | <26.7 |
| Small LDL-P | Low | 25th | 50th | 75th | High |
| | <117 | 117 | 527 | 839 | >839 |
| LDL Size | <-Large (Pattern A)-> | | <-Small (Pattern B)-> | | |
| | 23.0 | 20.6 | 20.5 | 19.0 | |

Comment: 01

Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account.
These assays were developed and their performance characteristics determined by LipoScience. These assays have not been cleared by the US Food and Drug Administration. The clinical utility of these laboratory values have not been fully established.

| | | | | |
|---|---|---|---|---|
| Insulin Resistance/Diab. Risk | | | | 01 |
| Large VLDL-P | 1.0 | nmol/L | <=2.7 | 01 |
| Small LDL-P | 362 | nmol/L | <=527 | 01 |
| Large HDL-P | 8.1 | umol/L | >=4.8 | 01 |
| VLDL Size | 40.8 | nm | <=46.6 | 01 |
| LDL Size | 20.8 | nm | >=20.8 | 01 |
| HDL Size | 9.4 | nm | >=9.2 | 01 |
| Insulin Resistance Score | | | | 01 |
| LP-IR Score | <25 | | <=45 | 01 |

INSULIN RESISTANCE / DIABETES RISK MARKERS

<--Insulin Sensitive  Insulin Resistant-->

Percentile in Reference Population

| | | | | | |
|---|---|---|---|---|---|
| Large VLDL-P | Low | 25th | 50th | 75th | High |
| | <0.9 | 0.9 | 2.7 | 6.9 | >6.9 |
| Small LDL-P | Low | 25th | 50th | 75th | High |
| | <117 | 117 | 527 | 839 | >839 |
| Large HDL-P | High | 75th | 50th | 25th | Low |
| | >7.3 | 7.3 | 4.8 | 3.1 | <3.1 |
| VLDL Size | Small | 25th | 50th | 75th | Large |
| | <42.4 | 42.4 | 46.6 | 52.5 | >52.5 |
| LDL Size | Large | 75th | 50th | 25th | Small |
| | >21.2 | 21.2 | 20.8 | 20.4 | <20.4 |
| HDL Size | Large | 75th | 50th | 25th | Small |
| | >9.6 | 9.6 | 9.2 | 8.9 | <8.9 |
| Insulin Resistance Score | | | | | |
| LP-IR SCORE | Low | 25th | 50th | 75th | High |
| | <27 | 27 | 45 | 63 | >63 |

# Lipid Lab Ranges

| | Range | |
|---|---|---|
| **Cholesterol** | 145-199 | Be Smart. |
| **HDL** | 45-59 | What happens when its too high? |
| **Trigs** | 50-99 | Particle size will skew. |
| **LDL** | 50-99 | |

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PMCID: PMC8540246
PMID: 34677405

# Apolipoprotein B and Cardiovascular Disease: Biomarker and Potential Therapeutic Target

Jennifer Behbodikhah, Saba Ahmed, Ailin Elyasi, Lora J. Kasselman, Joshua De Leon, Amy D. Glass, and Allison B. Reiss*

Apolipoprotein (apo) B, the critical structural protein of the atherogenic lipoproteins, has two major isoforms: apoB48 and apoB100. ApoB48 is found in chylomicrons and chylomicron remnants with one apoB48 molecule per chylomicron particle. Similarly, a single apoB100 molecule is contained per particle of very-low-density lipoprotein (VLDL), intermediate density lipoprotein, LDL and lipoprotein(a). This unique one apoB per particle ratio makes plasma apoB concentration a direct measure of the number of circulating atherogenic lipoproteins. ApoB levels indicate the atherogenic particle concentration independent of the particle cholesterol content, which is variable. While LDL, the major cholesterol-carrying serum lipoprotein, is the primary therapeutic target for management and prevention of atherosclerotic cardiovascular disease, there is strong evidence that apoB is a more accurate indicator of cardiovascular risk than either total cholesterol or LDL cholesterol. This review examines multiple aspects of apoB structure and function, with a focus on the controversy over use of apoB as a therapeutic target in clinical practice. Ongoing coronary artery disease residual risk, despite lipid-lowering treatment, has left patients and clinicians with unsatisfactory options for monitoring cardiovascular health. At the present time, the substitution of apoB for LDL-C in cardiovascular disease prevention guidelines has been deemed unjustified, but discussions continue.

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Traditionally, LDL cholesterol has been used to assess the risk associated with CVD and is a frequently used surrogate CVD risk marker in clinical trials [86,87,88,89]. However, LDL-C is an imperfect predictor and many individuals with normal LDL-C levels develop CVD [90].

Moreover, in individuals with diabetes and metabolic syndrome, although LDL-C levels are normal, the overall lipid profile is pro-atherogenic with high triglycerides and low HDL-C. An added atherogenic factor in those with diabetes and metabolic syndrome is a significant increase in small dense LDL particles. These unique lipid abnormalities pose an increased risk for cardiovascular events, but the normal LDL-C levels can mislead clinicians, who then may not initiate lipid-lowering therapy [92]. A new biomarker may more accurately represent CVD risk and improved management in these patients.

Current guidelines suggest lowering LDL-C as much as possible, as stated by the American Heart Association and the American College of Cardiology [8]. Analysis of data from the Treating to New Targets (TNT) study, a clinical trial in which stable CAD patients with LDL-C above 130 were randomized to 10 mg or 80 mg of atorvastatin per day for about 5 years, has shown that the predictive power of LDL-C is less significant than that of other potential biomarkers such as apoB and non-HDL-C [96]. However, these levels are still not generally suggested as a first-line target for medical therapies.

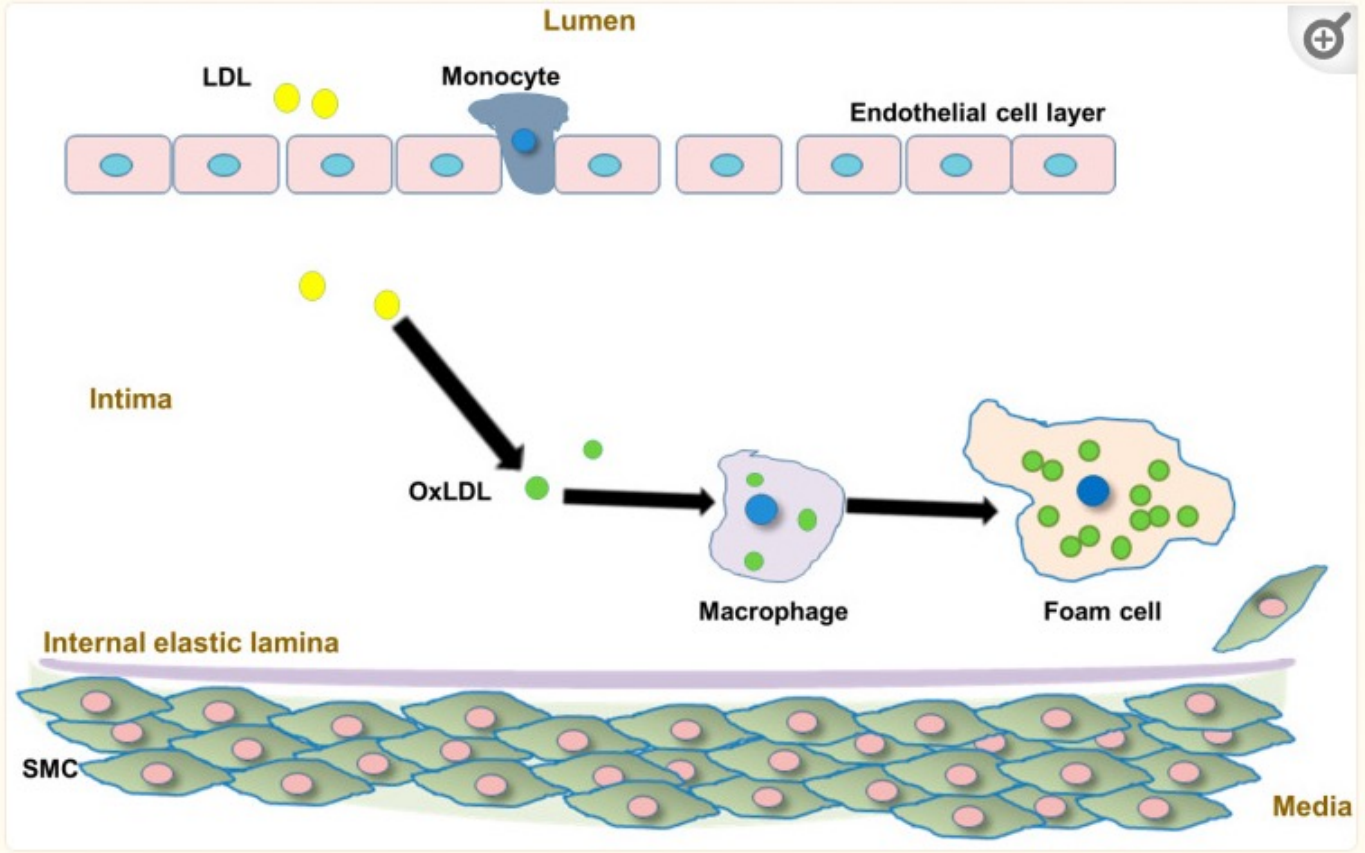


Figure 1

Atherosclerosis involves apoB-containing lipoproteins. The atherosclerotic process begins with compromise of the endothelial barrier, allowing apoB-containing LDL cholesterol to migrate into the arterial intima. Activated endothelium fosters attachment, migration and proliferation of vascular smooth muscle cells (SMC) and macrophages. Retained apoB-containing lipoproteins are oxidatively modified within the vascular intima. Oxidized (ox)LDL contains protein components, creating a net negative charge, making the particles highly attractive to macrophages. Phagocytosis allows for the accumulation of lipids within macrophages, producing foam cells. OxLDL-laden foam cells amass and form the fatty streak and eventually the lumen-narrowing atheromatous plaque that restricts blood flow. Additionally, inflammatory signaling pathways are activated, leading to increased cell migration and LDL modification.

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Approximately half of all patients with recurrent coronary syndrome have normal cholesterol levels on standard lipid profiles, and despite having achieved the recommended LDL-C levels, these patients are still at high risk of cardiovascular-related events [117,118,119]. At the forefront of promising biomarkers lie apoB and non-HDL-C [117,120].

A single molecule of apoB is present in every atherogenic particle; therefore, it has been proposed as a better predictor of cardiovascular events. Standard LDL-C, on the other hand, is a measurement of lipid concentration in lipoprotein particles that are heterogeneous and vary in size, density and lipid content [121]. Over 90% of total apoB is normally found in LDL particles [122,123]. However, since the lipid composition differs between LDL particles, these values do not strongly correlate with LDL cholesterol levels [113,124,125]. Recent studies have shown that apoB has a higher sensitivity and specificity than LDL-C in predicting cardiovascular events, such as myocardial infarction (MI) in both men and women, independent of age [126]. In a population of Japanese patients with established stable CAD documented by coronary artery stenosis exceeding 75% on coronary angiography, a virtual-histology intravascular ultrasound of the culprit lesions demonstrated greater lesion length and higher plaque volume and percentage of necrotic core volume in patients with high plasma apoB levels when compared to patients with low plasma apoB levels. No correlation was found between apoA1 and the percentage of necrotic core volume of the target coronary artery lesion. In this population, the apoB level was a very good indicator of the size of necrotic core and a potential biomarker for unstable plaque with an advantage over LDL-C

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# Apolipoprotein B and Cardiovascular Disease: Biomarker and Potential Therapeutic Target

Cardiovascular disease remains the leading cause of death worldwide [264]. Recent data have shown a decline in mortality from CHD in the United States of America, but the rate of decline is decelerating and, in younger adults under age 45, there is a lack of progress in reducing cardiovascular deaths [265,266]. In this younger group, a rise in diabetes mellitus and obesity may be hindering improvement in cardiovascular mortality [267]. It has been predicted that by the year 2035, over half of the US population will suffer from some form of cardiovascular disease and projected annual costs may exceed 1 trillion dollars [268]. Pharmacotherapy based on cholesterol management and lipid profile is the cornerstone of treatment and prevention. However, even with lipid-lowering therapy, the absolute risk of cardiovascular-related events remains elevated, and many patients do not achieve lipid goals, most frequently those at high cardiovascular risk [269,270]. Current American guidelines focus on LDL-C-targeted therapy; however, as shown in this review, there is a preponderance of data supporting a role for apoB in cardiovascular risk prediction. ApoB has been proposed as a better predictor of MCVE because a single molecule is found in every atherogenic particle and LDL-C levels alone can miss elevated particle numbers [271].

The wide acceptance of LDL-C coupled with the added expense and complication of measuring apoB has thus far prevented a major shift toward clinical application of plasma apoB at the point-of-care [275,276]. This may change as standardization of apoB measurement improves and as data supporting the benefits of apoB in cardiovascular health assessment accumulate [277,278].

P1: 39 yo male

## NMR LipoProfile+Lipids+Graph

| Test | Current Result and Flag | | Previous Result and Date | Units | Reference Interval |
|---|---|---|---|---|---|
| LDL Particle Number[01] | | | | | |
| ▲ **LDL-P**[A,01] | **1296** | **High** | | nmol/L | <1000 |
| | | | Low | < 1000 | |
| | | | Moderate | 1000 - 1299 | |
| | | | Borderline-High | 1300 - 1599 | |
| | | | High | 1600 - 2000 | |
| | | | Very High | > 2000 | |
| Lipids[01] | | | | | |
| ▲ **LDL-C (NIH Calc)**[01] | **168** | **High** | | mg/dL | 0-99 |
| | | | Optimal | < 100 | |
| | | | Above optimal | 100 - 129 | |
| | | | Borderline | 130 - 159 | |
| | | | High | 160 - 189 | |
| | | | Very high | > 189 | |
| HDL-C[A,01] | 80 | | | mg/dL | >39 |
| Triglycerides[A,01] | 58 | | | mg/dL | 0-149 |
| ▲ **Cholesterol, Total**[A,01] | **257** | **High** | | mg/dL | 100-199 |
| LDL and HDL Particles[01] | | | | | |
| HDL-P (Total)[A,01] | 39.2 | | | umol/L | >=30.5 |
| Small LDL-P[A,01] | 279 | | | nmol/L | <=527 |
| LDL Size[A,01] | 21.8 | | | nm | >20.5 |

```
------------------------------------------------------------
                ** INTERPRETATIVE INFORMATION**
                PARTICLE CONCENTRATION AND SIZE
                   <--Lower CVD Risk   Higher CVD Risk-->
 LDL AND HDL PARTICLES   Percentile in Reference Population
 HDL-P (total)        High     75th    50th    25th    Low
                      >34.9    34.9    30.5    26.7    <26.7
 Small LDL-P          Low      25th    50th    75th    High
                      <117     117     527     839     >839
 LDL Size   <-Large (Pattern A)->    <-Small (Pattern B)->
                    23.0    20.6          20.5      19.0
------------------------------------------------------------
```

| | | |
|---|---|---|
| Comment:[01] | Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account. | |
| Insulin Resistance Score[01] | | |
| LP-IR Score[A,01] | <25 | <=45 |

```
INSULIN RESISTANCE MARKER
    <--Insulin Sensitive    Insulin Resistant-->
          Percentile in Reference Population
```

P2: 37 yo male

## NMR LipoProfile+Lipids+Graph

| Test | Current Result and Flag | | Previous Result and Date | Units | Reference Interval |
|---|---|---|---|---|---|
| LDL Particle Number[01] | | | | | |
| ▲ **LDL-P**[A,01] | **1296** | **High** | | nmol/L | <1000 |
| | | | Low | < 1000 | |
| | | | Moderate | 1000 - 1299 | |
| | | | Borderline-High | 1300 - 1599 | |
| | | | High | 1600 - 2000 | |
| | | | Very High | > 2000 | |
| Lipids[01] | | | | | |
| ▲ **LDL-C (NIH Calc)**[01] | **168** | **High** | | mg/dL | 0-99 |
| | | | Optimal | < 100 | |
| | | | Above optimal | 100 - 129 | |
| | | | Borderline | 130 - 159 | |
| | | | High | 160 - 189 | |
| | | | Very high | > 189 | |
| HDL-C[A,01] | 80 | | | mg/dL | >39 |
| Triglycerides[A,01] | 58 | | | mg/dL | 0-149 |
| ▲ **Cholesterol, Total**[A,01] | **257** | **High** | | mg/dL | 100-199 |
| LDL and HDL Particles[01] | | | | | |
| HDL-P (Total)[A,01] | 39.2 | | | umol/L | >=30.5 |
| Small LDL-P[A,01] | 279 | | | nmol/L | <=527 |
| LDL Size[A,01] | 21.8 | | | nm | >20.5 |

```
------------------------------------------------------------
               ** INTERPRETATIVE INFORMATION**
               PARTICLE CONCENTRATION AND SIZE
                 <--Lower CVD Risk   Higher CVD Risk-->
 LDL AND HDL PARTICLES   Percentile in Reference Population
 HDL-P (total)        High     75th    50th    25th   Low
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 Small LDL-P          Low      25th    50th    75th   High
                      <117     117     527     839    >839
 LDL Size   <-Large (Pattern A)->    <-Small (Pattern B)->
                  23.0    20.6          20.5      19.0
------------------------------------------------------------
```

| | | |
|---|---|---|
| Comment:[01] | Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account. | |
| Insulin Resistance Score[01] | | |
| LP-IR Score[A,01] | <25 | <=45 |

```
INSULIN RESISTANCE MARKER
    <--Insulin Sensitive    Insulin Resistant-->
          Percentile in Reference Population
```

P3: 42 yo male

## NMR LipoProfile+Lipids+Graph

| Test | Current Result and Flag | Previous Result and Date | Units | Reference Interval |
|---|---|---|---|---|
| LDL Particle Number[01] | | | | |
| LDL-P[A,01] | 657 | | nmol/L | <1000 |
| | | Low | < 1000 | |
| | | Moderate | 1000 - 1299 | |
| | | Borderline-High | 1300 - 1599 | |
| | | High | 1600 - 2000 | |
| | | Very High | > 2000 | |
| Lipids[01] | | | | |
| LDL-C (NIH Calc)[01] | 66 | | mg/dL | 0-99 |
| | | Optimal | < 100 | |
| | | Above optimal | 100 - 129 | |
| | | Borderline | 130 - 159 | |
| | | High | 160 - 189 | |
| | | Very high | > 189 | |
| HDL-C[A,01] | 59 | | mg/dL | >39 |
| Triglycerides[A,01] | 37 | | mg/dL | 0-149 |
| Cholesterol, Total[A,01] | 134 | | mg/dL | 100-199 |
| LDL and HDL Particles[01] | | | | |
| HDL-P (Total)[A,01] | 36.3 | | umol/L | >=30.5 |
| Small LDL-P[A,01] | 222 | | nmol/L | <=527 |
| LDL Size[A,01] | 20.9 | | nm | >20.5 |

** INTERPRETATIVE INFORMATION**
PARTICLE CONCENTRATION AND SIZE

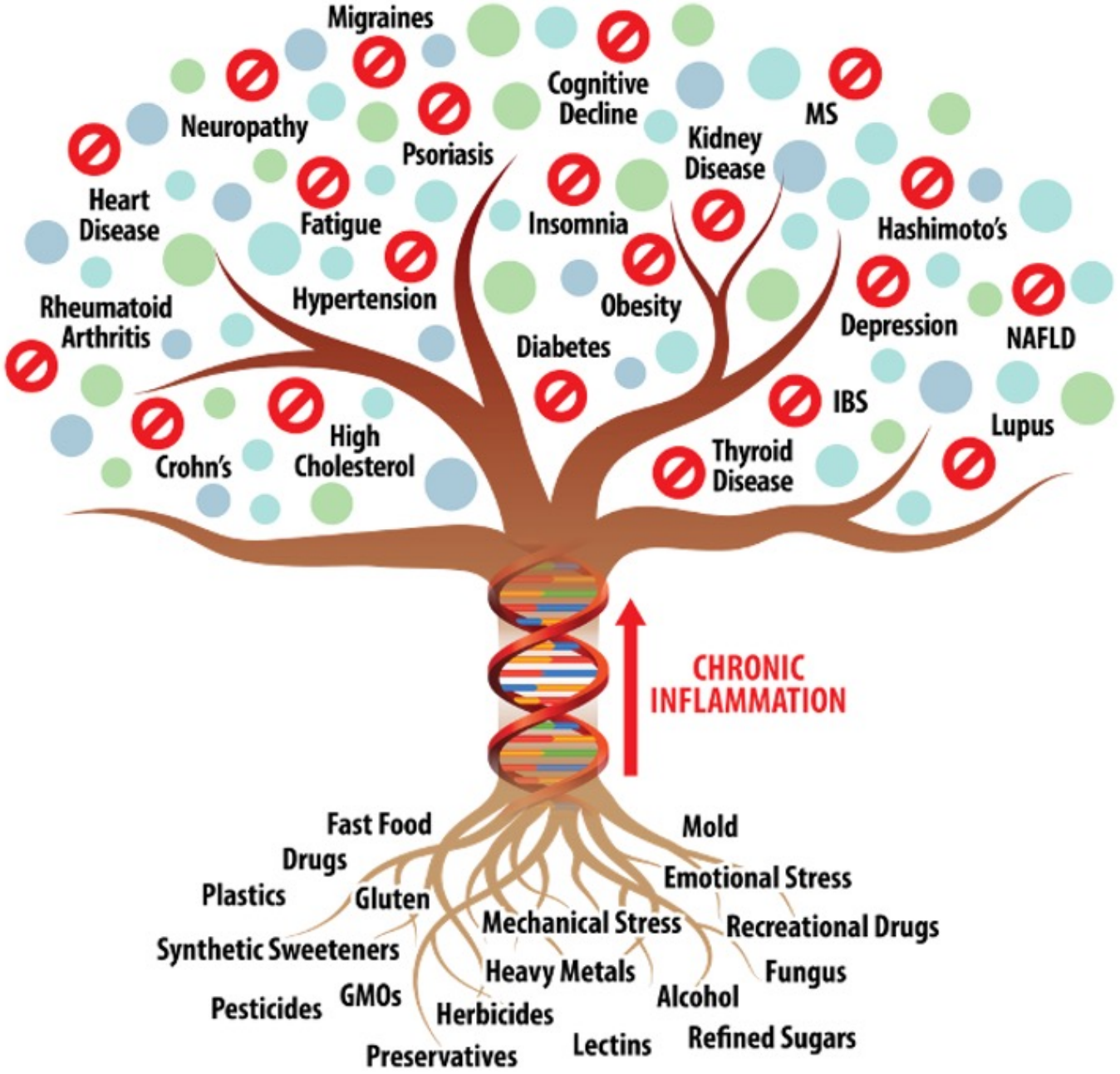
| | <--Lower CVD Risk | | Higher CVD Risk--> | |
|---|---|---|---|---|
| LDL AND HDL PARTICLES | Percentile in Reference Population | | | |
| HDL-P (total) | High | 75th | 50th | 25th | Low |
| | >34.9 | 34.9 | 30.5 | 26.7 | <26.7 |
| Small LDL-P | Low | 25th | 50th | 75th | High |
| | <117 | 117 | 527 | 839 | >839 |

| LDL Size | <-Large (Pattern A)-> | | <-Small (Pattern B)-> | |
|---|---|---|---|---|
| | 23.0 | 20.6 | 20.5 | 19.0 |

| | | |
|---|---|---|
| Comment:[01] | Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account. | |
| Insulin Resistance Score[01] | | |
| LP-IR Score[A,01] | <25 | <=45 |

INSULIN RESISTANCE MARKER

| <--Insulin Sensitive | | Insulin Resistant--> | |
|---|---|---|---|
| Percentile in Reference Population | | | |


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Preservatives
Lectins
Refined Sugars

# The Wedge Protocol