Addressing HDL Dysfunction Through Functional Nutrition

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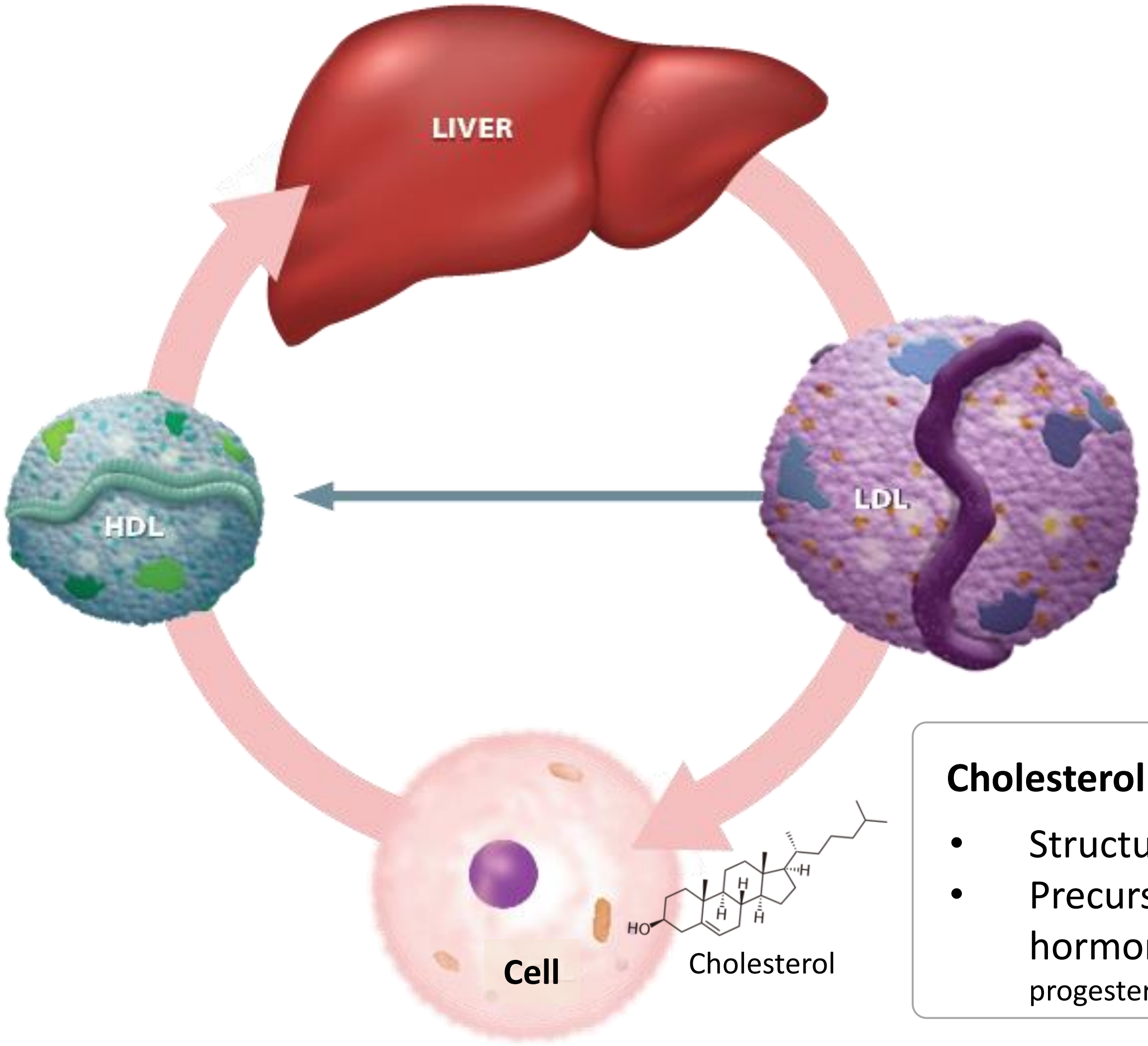
Cholesterol Transport Cycle



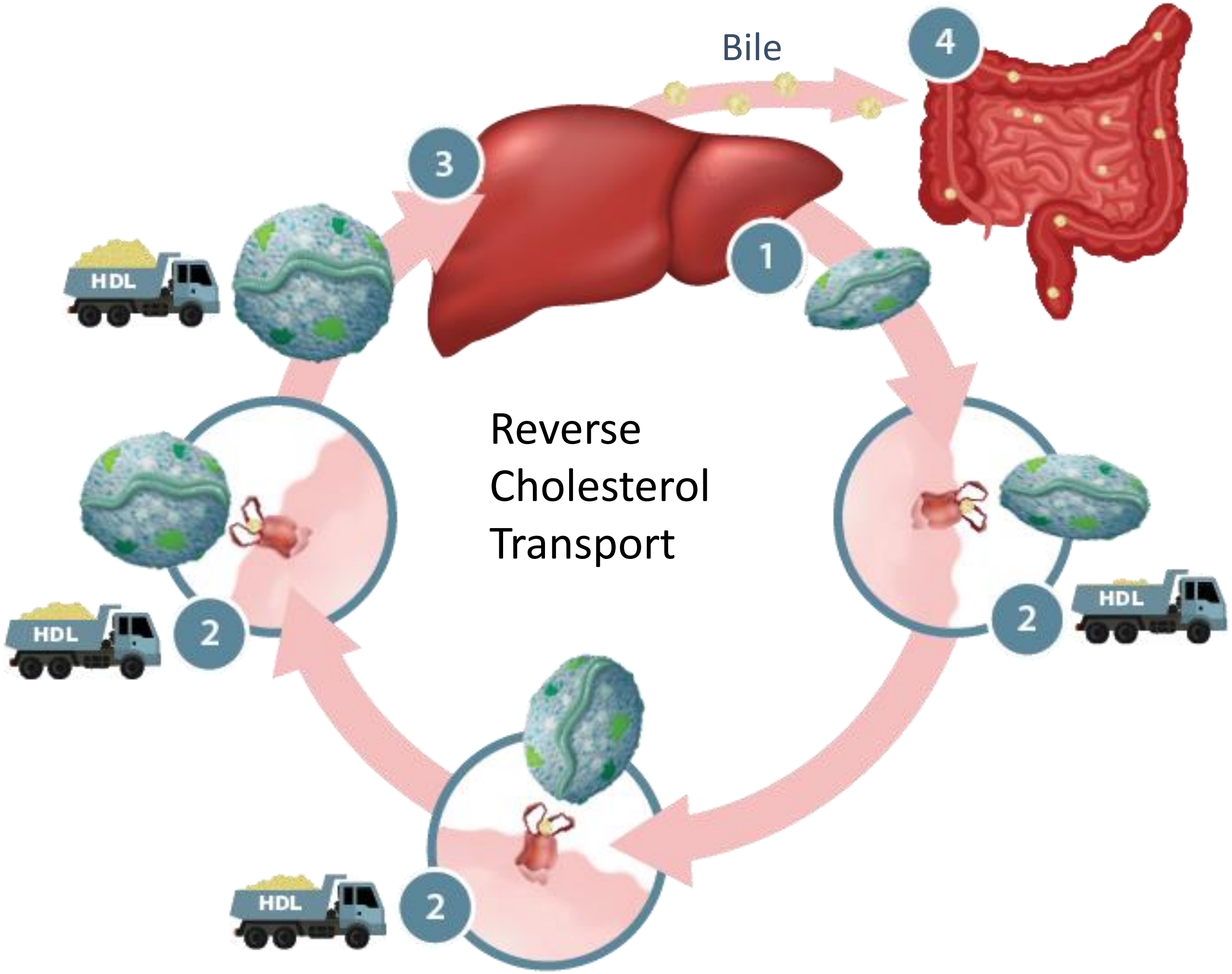
High-Density Lipoprotein
- Collects and removes excess cholesterol
- Returns to liver

Low-Density Lipoprotein
- Delivers essential cholesterol to the body

Cholesterol
- Structural support
- Precursor to vitamin D and other hormones e.g. estrogen, androgens, progesterone, cortisol

Feingold KR, Grunfeld C. Introduction to Lipids and Lipoproteins. [Updated 2018 Feb 2]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305896/.

Reverse Cholesterol Transport: Key Function of HDL



1. HDL forms in liver

2. Collects cholesterol from peripheral cells e.g. macrophage

3. Returns cholesterol to liver

4. Cholesterol leaves the body through bile or is recycled

Feingold KR, Grunfeld C. Introduction to Lipids and Lipoproteins. [Updated 2018 Feb 2]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305896/.

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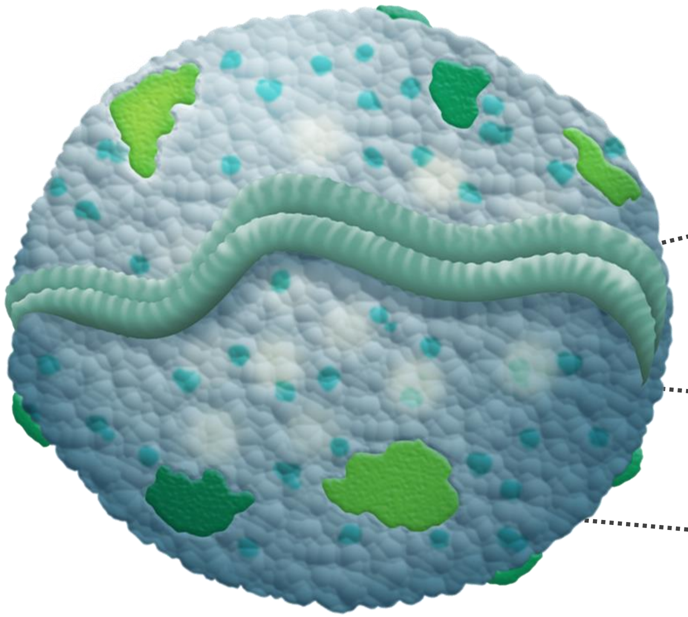
HDL Particle Overview



HDL particle consists of a phospholipid shell with a core of lipids
There are >80 proteins on HDL that impact its function

Apolipoprotein A-I (apoA-I): A structural HDL protein and the main protein on HDL, is secreted by the intestine and liver is required to accept cholesterol from cells and integrate it into HDL

Paraoxonase (PON): Protein on HDL important for function. PON has anti-oxidant capacity and protects LDL from oxidation

Lecithin Transfer Acyltransferase (LCAT): Enzyme involved in packaging cholesterol tightly within HDL, which is essential for the maturation of the HDL particle

Kajani S et al. *Int J Mol Sci.* 2018;19(7).pii:E1971.

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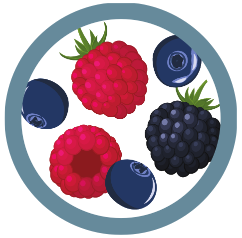
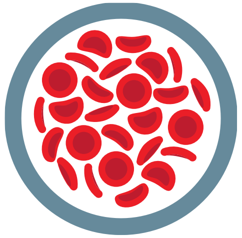
Cardioprotective actions of functional HDL[1-3]

Reverse Cholesterol Transport: ↓ Excess cholesterol

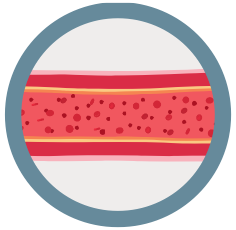


Anti-oxidant: ↓ Reactive oxygen species, ↓LDL oxidation

Anti-inflammatory: ↓ Vascular inflammation, Sequesters LPS



Anti-thrombotic: ↑ Prostacyclin



Endothelial function: ↑ expression of eNOS and NO

LPS, lipopolysaccharide: Component of bacteria
ENOS, endothelial nitric oxide synthase: Enzyme involved in synthesis of nitric oxide
NO, nitric oxide: Vasodilator and important for endothelial function

1. Kajani S et al. *Int J Mol Sci.* 2018;19(7). pii: E1971.
2. Rosenson RS et al. *Nat Rev Cardiol.* 2016;13(1):48-60.
3. Garcia C et al. *J Thromb Haemost*. 2018;16(5):933-945.

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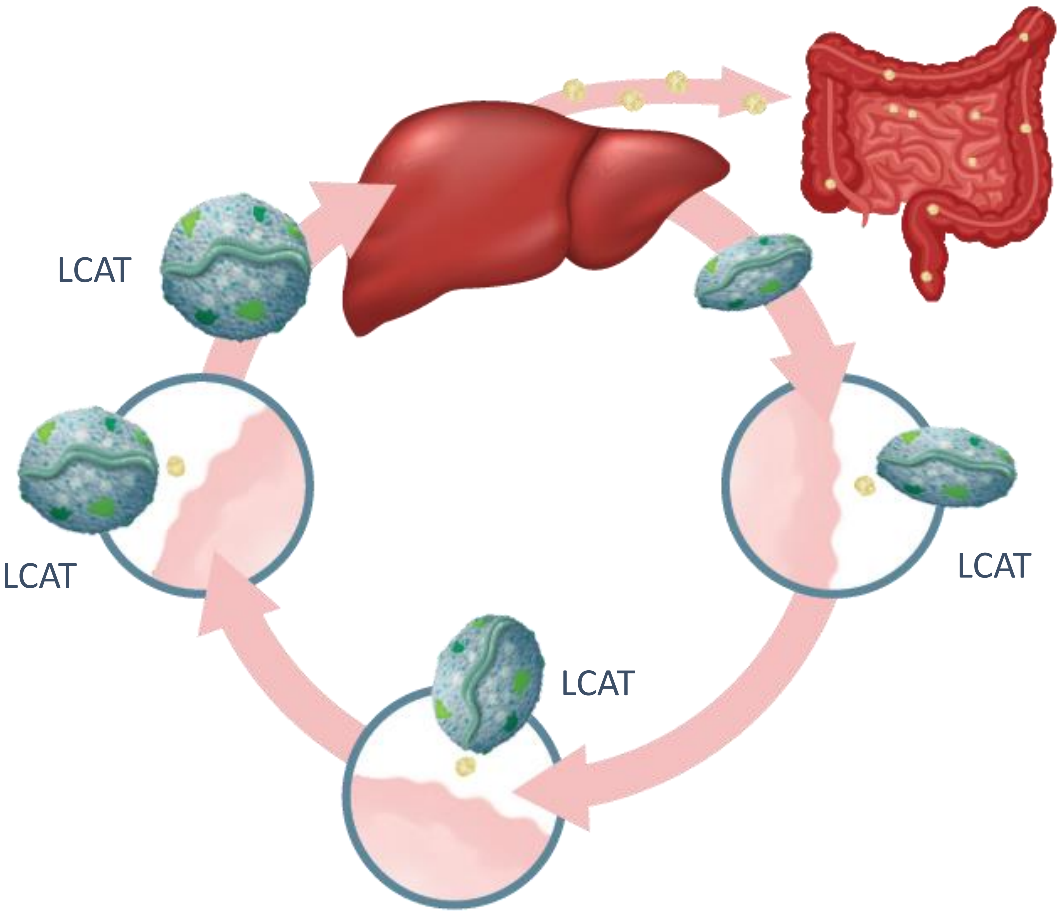
HDL Metabolism

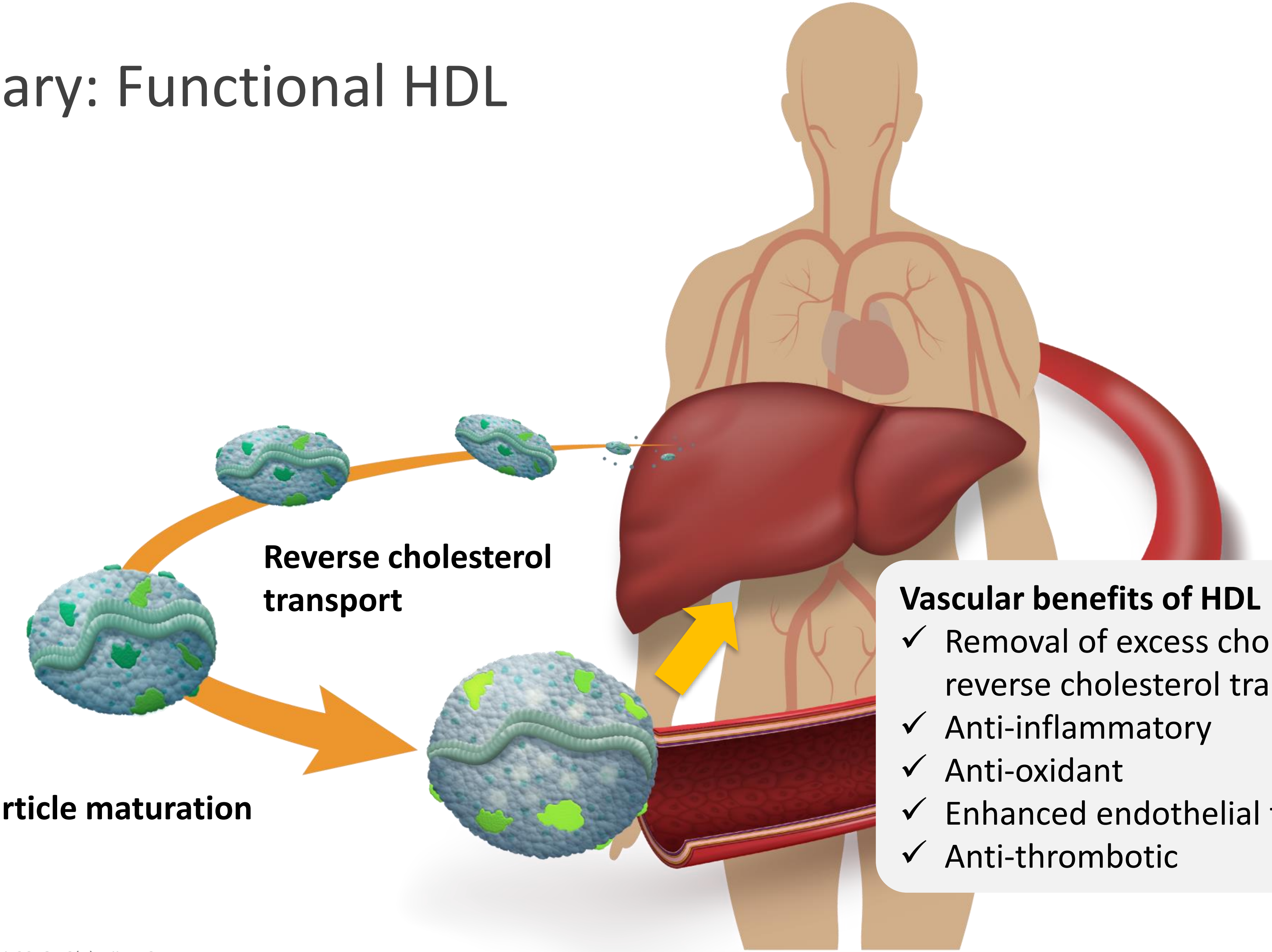


- HDL particles grow more spherical and increase in size as they collect cholesterol. The enzyme LCAT helps package cholesterol tightly within HDL, allowing it to grow and mature
- Larger particles are more effective at delivering cholesterol to the liver
- Smaller particles are more effective at accepting cholesterol from cells expressing certain receptors.
- A representation of all particle sizes is important and indicates appropriate HDL maturation.

LCAT, lecithin cholesterol acyltransferase: Enzyme that packages cholesterol tightly within HDL , allowing the particle to develop

Feingold KR, Grunfeld C. Introduction to Lipids and Lipoproteins. [Updated 2018 Feb 2]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305896.

Summary: Functional HDL



Vascular benefits of HDL

- ✓ Removal of excess cholesterol through reverse cholesterol transport
- ✓ Anti-inflammatory
- ✓ Anti-oxidant
- ✓ Enhanced endothelial function
- ✓ Anti-thrombotic

Kajani S et al. *Int J Mol Sci.* 2018;19(7). pii: E1971.
Rosenson RS et al. *Nat Rev Cardiol.* 2016;13(1):48-60.
Garcia C et al. *J Thromb Haemost*. 2018;16(5):933-945.
Landmesser U. *Nat Rev Cardiol* 2014;11:559–560.

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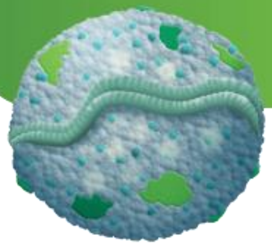
Dysfunctional HDL: A Wolf in Sheep's Clothing

HDL Stressors
(oxidative stress, inflammation, high glucose)

Function | **Loss of function** | **Gain of *dys*function**



- HDL is cardioprotective

- ↓ Reverse Cholesterol Transport
- ↓ anti-oxidative, anti-thrombotic and anti-inflammatory benefit

- Gain of pro-oxidant and pro-inflammatory properties

Kajani S et al. *Int J Mol Sci.* 2018;19(7).pii:E1971.

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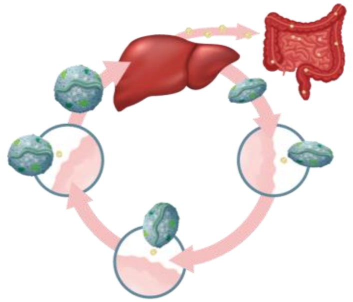
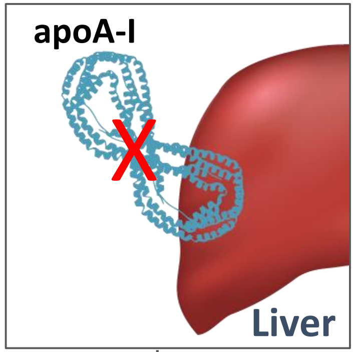
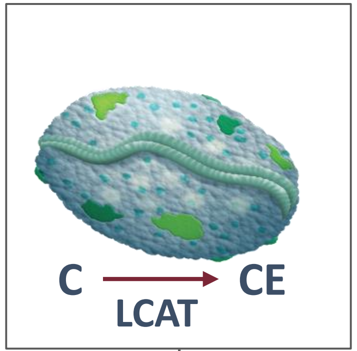


Inflammation Drives HDL Dysfunction[1-3]

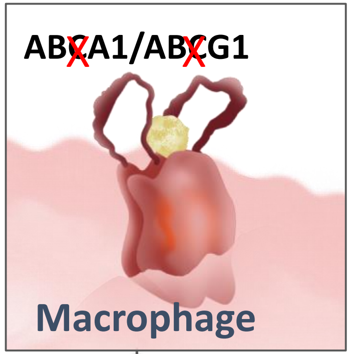
Reduced synthesis of apoA-I

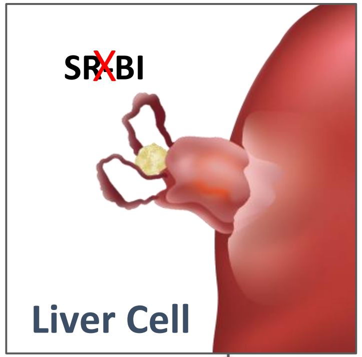


Suppression of LCAT

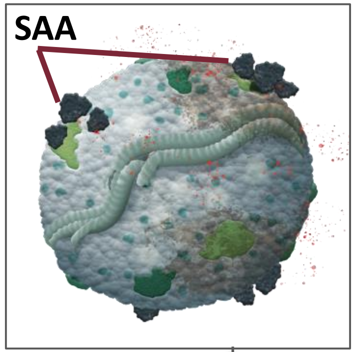


Reduced expression and activity of enzymes involved in the transport of cholesterol to and from HDL





Accumulation of inflammatory molecules such as Serum Amyloid A (SAA)



Inflammation drives dysfunction at all stages of HDL metabolism

ApoA-I, apolipoproteinA-I. Key protein involved in transport of cholesterol into HDL particle
LCAT, lecitin cholesterol acyltransferase. Enzyme responsible for packaging of cholesterol tightly within the HDL particle as cholesterol esters, which is important for HDL particle maturation
ABCA1, ATP Binding Cassette Subfamily A, Member 1. Protein on cells involved in transport of cholesterol into HDL
ABCG1, ATP Binding Cassette Subfamily G, Member 1. Protein on cells involved in transport of cholesterol into HDL
SR-BI, Scavenger Receptor, Class B, Type I. Protein on cells involved in transport of cholesterol into cells. On the liver, can be involved in transport of cholesterol from HDL into the liver.

1. Feingold KR, Grunfeld C, 2019 Available from: https://www.ncbi.nlm.nih.gov/books/NBK326741.
2. Ronsein GE et al. *Curr Opin Lipidol*. 2017;28(1):52-59.
3. de la Llera Moya M et al. *Atherosclerosis*. 2012;222(2):390-394.

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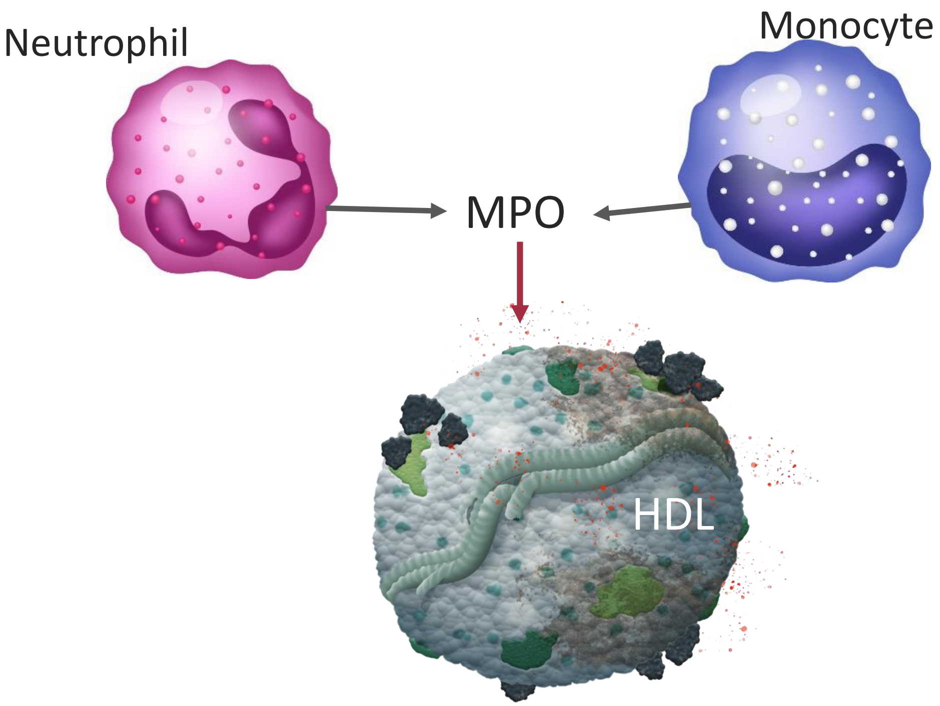
Oxidation Drives HDL Dysfunction[1-8]

Immune Dysregulation



- Myeloperoxidase (MPO) is a prooxidant secreted by proinflammatory immune cells
- MPO oxidizes apoA-I and PON, which impairs HDL function

1. Teng N et al. *Redox Rep.* 2017;22(2):51-73.
2. Meuwese MC et al. *J Am Coll Cardiol.* 2007;50(2):159-165.
3. Brennan ML et al. *N Engl J Med.* 2003;349(17):1595-1604.
4. Dullaart RP et al. *Atherosclerosis.* 2014;234(1):185-192.
5. Tietge UJF. *Curr Opin Endocrinol Diabetes Obes.* 2018;25(2):137-142.
6. Huang Y et al. *Nat Med.* 2014;20(2):193-203.
7. Anderson JL et al. *Sci Rep.* 2017;7:41481.
8. Undurti A et al. *J Biol Chem.* 2009;284(45):30825-30835.

- **ApoA-I,** apolipoproteinA-I. Key protein involved in transport of cholesterol into HDL particle
- **PON,** paroxonase. Anti-oxidant protein critical for HDL function

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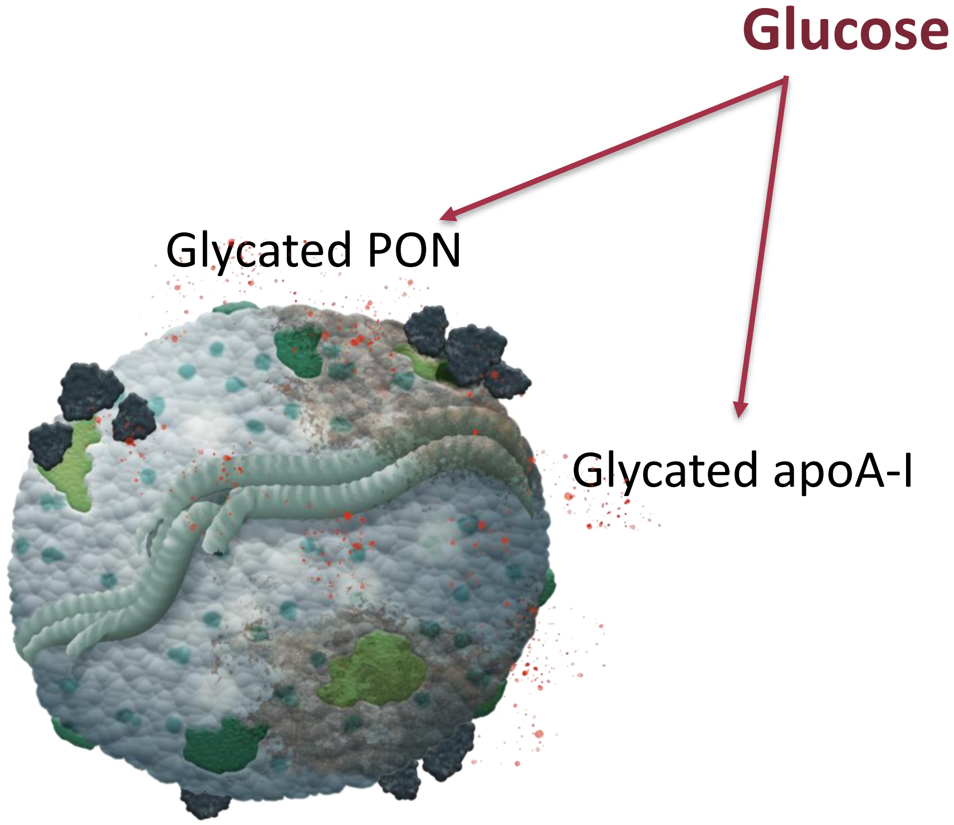
Glucose and Insulin Dysregulation Drives HDL Dysfunction[1-4]



- Glycated apoA-I has a 3x shorter half life
- Glycated PON has reduced activity and impairs HDL function
- In animal models, glycated PON was shown to induce endothelial dysfunction

- **ApoA-I,** apolipoproteinA-I. Key protein involved in transport of cholesterol into HDL particle
- **PON,** paroxonase. Anti-oxidant protein critical for HDL function

1. Kashyap SR et al. *J Clin Endocrinol Metab*. 2018;103(2):388-396.
2. Yu W et al. *Sci Rep*. 2017;7:45827.
3. Mastorikou M et al. *Diabet Med*. 2008;25(9):1049-1055.
4. Yu W et al. *Sci Rep*. 2017;7:45827.

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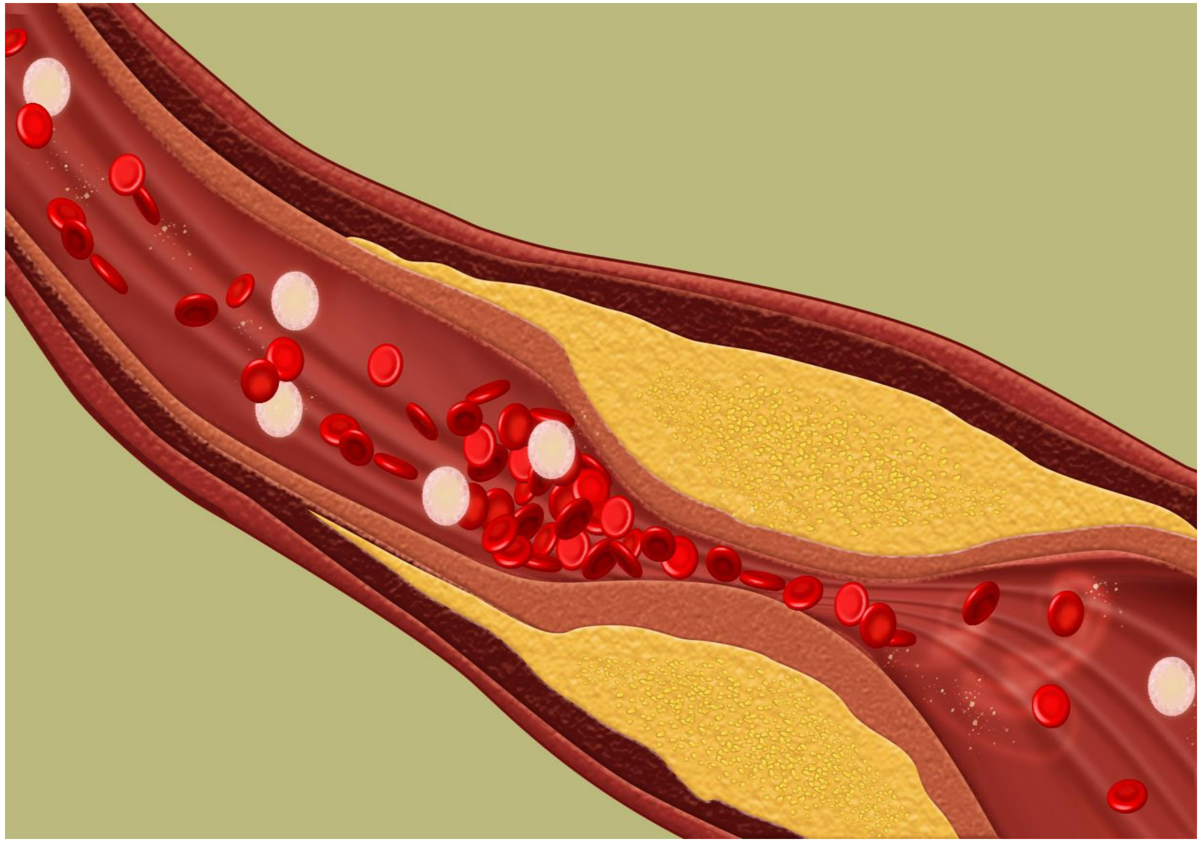
Dysfunctional HDL is atherogenic



- **Dysfunctional HDL**, and a reduced ability to effectively remove cholesterol from cells in the blood vessel, always **contributes to plaque growth**[1-2]
- **Following an MI, greater HDL function** (measured by cholesterol efflux capacity) **predicts survival**[3]

1. Ebtehaj S et al. *Arterioscler Thromb Vasc Biol.* 2019;39(9):1874-1883.
2. Cahill LE et al. *J Lipid Res.* 2019;60(8):1457-1464.
3. Guerin M et al. *J Am Coll Cardiol.* 2018;72(25):3259-3269.

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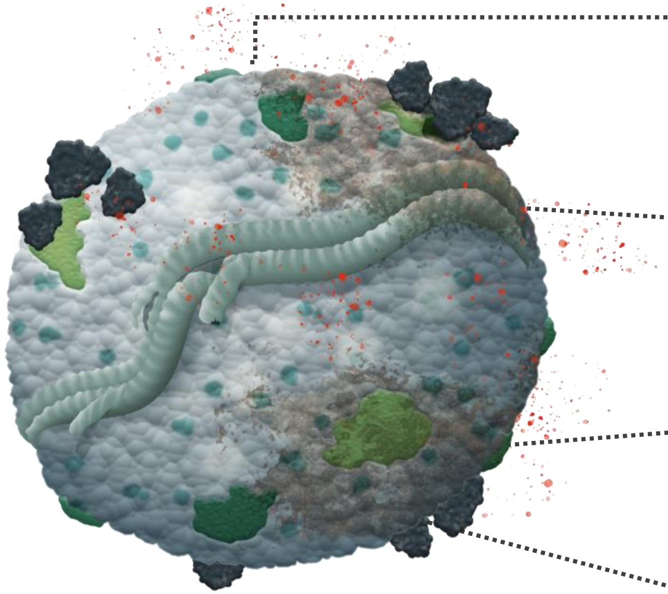
Summary – Dysfunctional HDL



HDL Stressors such as inflammation, oxidative stress, and high glucose damage the HDL particle

Apo-AI can become oxidized or displaced.

Serum amyloid A (SAA), a pro-inflammatory marker can accumulate on HDL, displacing other important proteins and causing dysfunction.

PON can become oxidized by the pro-oxidant myeloperoxidase (MPO) leading it to become less active.

- **ApoA-I,** apolipoproteinA-I. Key protein involved in transport of cholesterol into HDL particle
- **PON,** paroxonase. Anti-oxidant protein critical for HDL function

Kajani S et al. *Int J Mol Sci.* 2018;19(7).pii:E1971.

Who is at risk?

Cardiovascular disease
- Coronary heart disease
- Coronary artery disease
- Acute coronary syndrome
- Hypertension

Metabolic disease
- Obesity
- Metabolic syndrome
- Type 2 diabetes
- Non-alcoholic fatty liver disease
- Polycystic ovary syndrome

Chronic inflammatory and autoimmune disease
- Type 1 diabetes
- Rheumatoid arthritis
- Systemic lupus Erythematosus
- Psoriasis
- Periodontitis

Kidney disease
- Chronic kidney disease
- End-stage renal disease

Other conditions
- Cardiac surgery
- Obstructive sleep apnea
- Hyper-homocysteinemia
- Hyper-alphalipoproteinemia
- HIV infection

For references, see Slide 28

Limitations of measuring and tracking HDL-C alone[1-5]

- HDL-C ≠ HDL function

- Normal HDL-C levels can provide a false sense of security

- Higher HDL-C is not necessarily better

1. Davidson WS et al. *Clin Chem*. 2014;60(11):e1-3.
2. de la Llera-Moya M et al. *Arterioscler Thromb Vasc Biol*. 2010;30(4):796–801.
3. Wilkins JT et al. *J Am Heart Assoc.* 2014;3(2):e000519.
4. Hirata A et al. *J Clin Lipidol.* 2018;12(3):674-684 e675.
5. Madsen CM et al. *Eur Heart J.* 2017;38(32):2478-2486.

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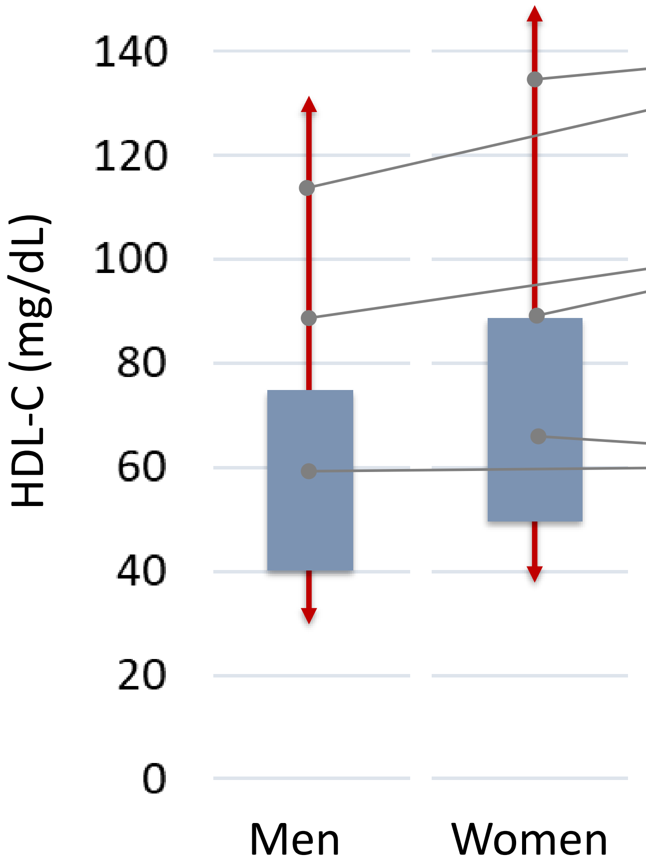
HDL-C: Higher not always better[1-3]



HDL-C >114mg/dL for men and >135mg/dL in women: ↑ CVD risk
- Northern European cohorts (n= 116,508 men and women) followed for ~6 years (median; range 0-23 years)[1]

HDL-C >90mg/dL for men and women: ↑ CVD risk
- Japanese cohorts (n= 43,407 men and women) followed for ~12.1 years[2]

HDL-C >75mg/dL for men and 90mg/dL for women: no added benefit
- US cohorts (n= 24,510 men and women) followed for up to 20 years[3]

'Normal Reference Range' [Men: 40-75mg/dL; Women; 50-90mg/dL]

Undesirable Range [Men: <40mg/dL >75/dL; Women: <50mg/L >90mg/dL]

1. Wilkins JT et al. *J Am Heart Assoc.* 2014;3(2):e000519.
2. Hirata A et al. *J Clin Lipidol.* 2018;12(3):674-684 e675.
3. Madsen CM et al. *Eur Heart J.* 2017;38(32):2478-2486.

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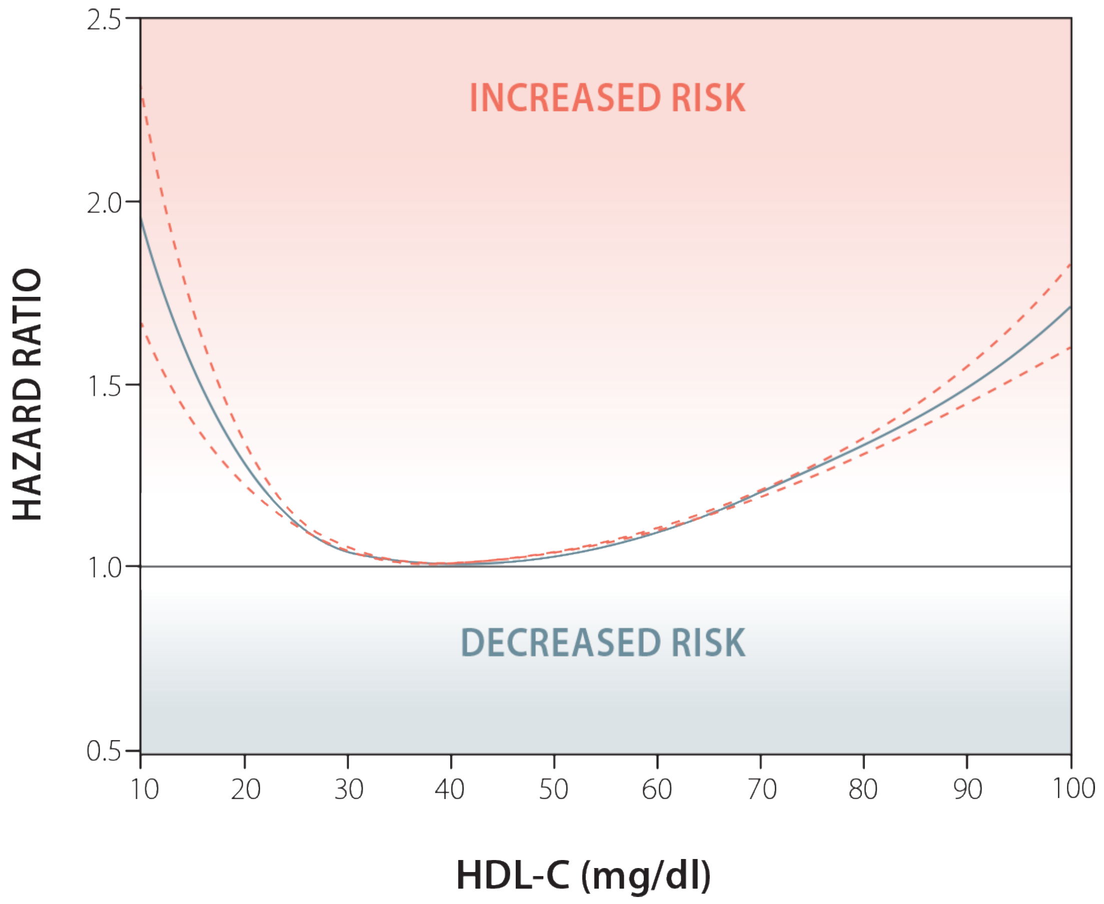
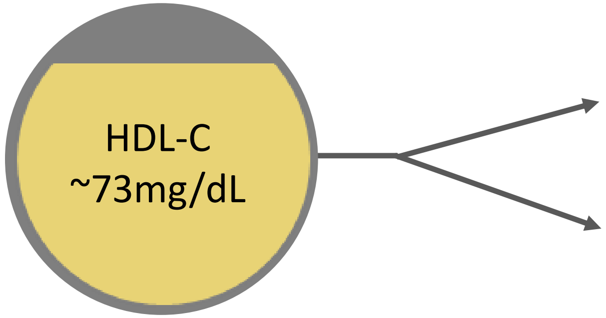
HDL-C U-Shaped Curve: Very low and high HDL-C associated with increased risk of all-cause mortality



Study Population
Cohort of 1,764,986 men who were United States veterans followed for ~10 years

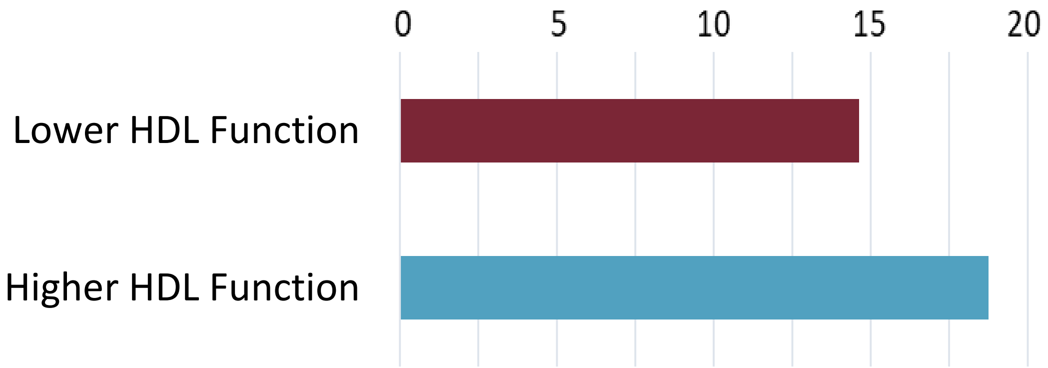
Bowe B et al. *Clin J Am Soc Nephrol*. 2016;11(10):1784-1793.

Quality versus quantity: HDL-C ≠ Function

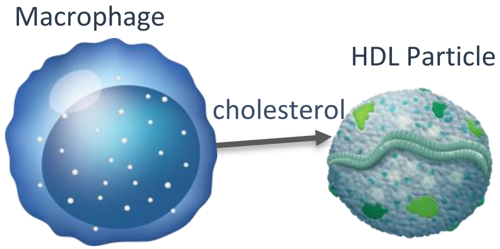


HDL-C of group (n=18 women) within the ‘normal range’

Macrophage Cholesterol Efflux Capacity* (%) at 4hours



Additional testing for HDL function showed two clear groups, one group with higher function and one with lower function



* Test for Macrophage Cholesterol Efflux Capacity measures the capacity of cholesterol to move from cells (e.g. macrophages) into the HDL particle

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de la Llera-Moya M et al. *Arterioscler Thromb Vasc Biol*. 2010;30(4):796–801.

How do you investigate HDL dysfunction clinically?

Clinically Available Biomarkers	Reference Range*
Low HDL-Particle Number (HDL-P)[1,2] Does not provide direct information about HDL function but has been associated with HDL function in clinical studies. Better predictor of cardiovascular risk than HDL-C.	>7000 nmol/L
Other markers indicative of HDL stressors in the environment	
Elevated Myeloperoxidase (MPO)[3-5] A marker of pro-oxidant environment and a surrogate marker of HDL function. MPO can oxidize proteins on HDL, leading to dysfunction.	<470 pmol/L
Elevated High Sensitivity C-Reactive Protein (hsCRP)[6] Pro-inflammatory marker. Provides information about environment that promotes HDL dysfunction.	<1.0 mg/L

*Reference range may vary slightly across different clinical labs

1. Schwartz GG et al. *N Engl J Med.* 2012;367(22):2089-2099.
2. Barter PJ et al. *N Engl J Med.* 2007;357(21):2109-2122.
3. Huang Y et al. *Nat Med.* 2014;20(2):193-203.
4. Tietge UJF. *Curr Opin Endocrinol Diabetes Obes.* 2018;25(2):137-142.
5. Undurti A et al. *J Biol Chem.* 2009;284(45):30825-30835.
6. Ebtehaj S et al. *Arterioscler Thromb Vasc Biol.* 2019;39(9):1874-1883.

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Mediterranean Dietary Patterns Support HDL Function

In a subsample from the PREDIMED study (n=296), a **Mediterranean diet** enriched in virgin olive oil or nuts for **1 year significantly increased cholesterol efflux capacity, increased PON activity and enhanced the vasodilatory capacity of HDL**[1]

- Increases of virgin olive oil (+10g/day) and whole grains (+25g/day) were associated with increased cholesterol efflux capacity.
- Increases in nut consumption (+30g/day), legumes (+25g/day), and fish (+25g/day) were linked with increased PON activity[2]

PON, paroxonase. Anti-oxidant protein critical for HDL function
PREDIMED, Prevencion con Dieta Mediterranea

1. Hernáez Á et al. *Circulation*. 2017;135(7):633-643.
2. Hernáez Á et al. *Mol Nutr Food Res*. 2019;63(6):e1800847.

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Diet and lifestyle interventions support HDL function

In patients with type 2 diabetes (n=80) consumption of ≥6 portions of fruits and vegetables for 8 weeks increased PON activity[1]

In people with central obesity and dyslipidemia (n=113), 1 year of increased physical activity (160 minutes moderate intensity aerobic per week) in combination with a reduced kcal diet (-500kcal/day) significantly increased HDL cholesterol efflux capacity[2]

1. Daniels JA et al. *Cardiovasc Diabetol*. 2014;13:16.
2. Boyer M et al. *Am J Physiol Endocrinol Metab*. 2018;315(4):E460-E468.

Smoking cessation improves HDL function[1]

In men and women (n=32) enrolled in a 12-week smoking cessation program, **smoking cessation improved cholesterol efflux capacity and HDL inflammation index** (the ability of HDL to prevent the formation of the inactive oxidized phospholipids).

HDL, apoA-I, and HDL subfractions did not change over the course of the study.[1]

- **ApoA-I,** apolipoproteinA-I. Key protein involved in transport of cholesterol into HDL particle

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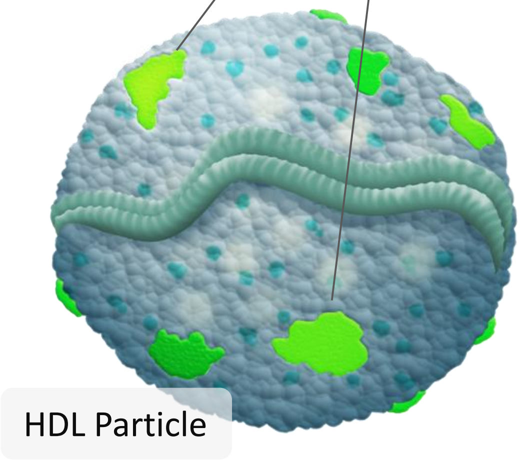
1. Takata K et al. *Circ J.* 2014;78(12):2955-2962.

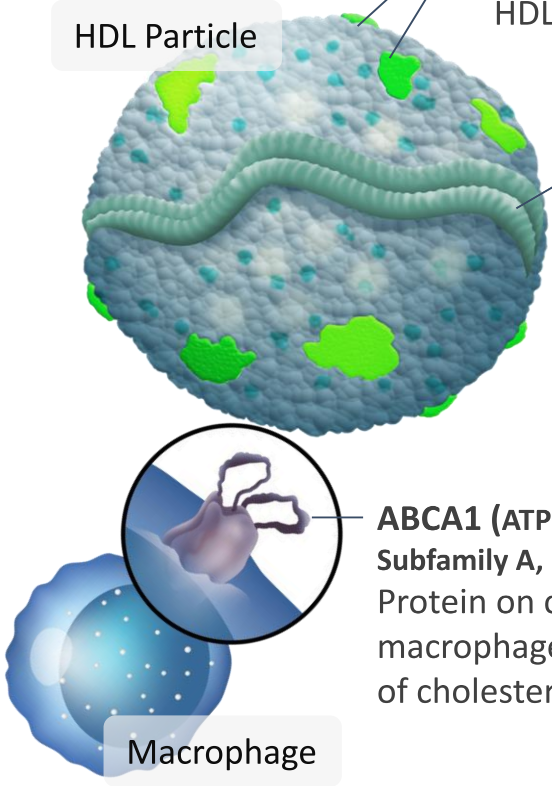
Pomegranate: Targeted nutrition for HDL function



Study Design	Main Findings
• **Subjects with T2DM (n=6) supplemented with juice containing 130mg pomegranate polyphenols for 4 weeks[1]**	• Increased PON binding to HDL via reduction in oxidative stress
• **Subjects with T2DM (n=30) supplemented with pomegranate polyphenols (130mg and 650 mg/day)[2]**	• Increased PON activity vs. baseline • Increased PON protein binding to HDL vs. baseline • Decreased serum oxidative stress vs. baseline
• **Subjects with T2D (n=50) supplemented with pomegranate juice for 6 weeks[3]**	• Increased PON activity vs. baseline • Decreased serum MDA vs. baseline • Improved serum fasting glucose, total cholesterol and LDL cholesterol vs. baseline

1. Fuhrman B et al. *Nutrition.* 2010;26:359-366.
2. Rock W et al. *J Agric Food Chem.* 2008;56:8704-8713.
3. Parsaeyan N et al. *J Diabetes Metab Disord.* 2012;11:11.

Lycopene: Targeted nutrition for HDL function



PON (paroxonase) Anti-oxidant protein critical for HDL function

ApoA-I (apolipoproteinA-I) Key protein involved in transport of cholesterol into HDL particle

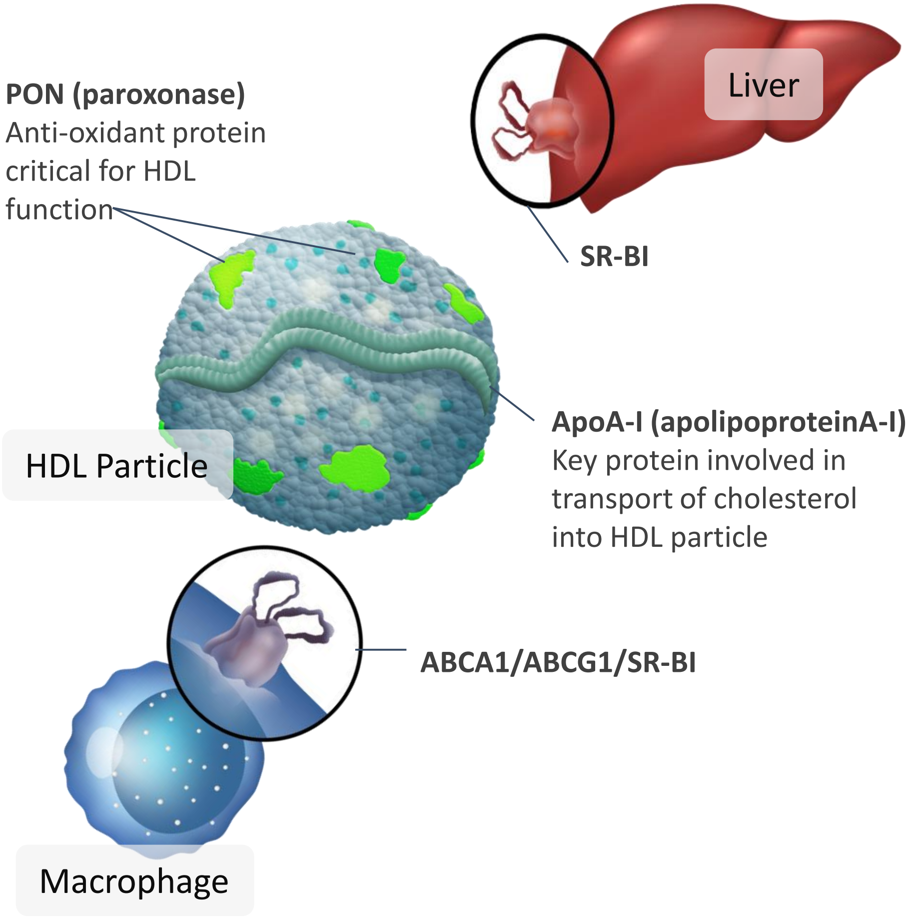
ABCA1 (ATP Binding Cassette Subfamily A, Member 1) Protein on cells such as macrophages involved in transport of cholesterol into HDL

Study Design	Main Finding
Subjects with overweight (n=54) consuming lycopene supplement (70 mg/week) or lycopene-rich diet[1]	• Increased serum HDL2 and HDL3 • Decreased SAA levels in serum and HDL3 • Increased PON activity in serum, HDL2 and HDL3 • Increased LCAT activity in serum and HDL3 • Decreased CETP activity in serum
Subjects with type 2 diabetes (n=32) consuming 200 g/day tomato for 8 weeks[2]	• Increased apoA-I vs. baseline • Decreased systolic and diastolic blood pressure vs. baseline
In vitro models treated with lycopene[3,4]	• Increased expression of ABCA1
Animal model treatment with lycopene[5]	• Increased HDL Function

HDL2, larger more buoyant high density lipoprotein particles
HDL3, smaller less buoyant high density lipoprotein particles
LCAT, Lecithin cholesterol acyltransferase. Enzyme responsible for packaging of cholesterol tightly within the HDL particle.
CETP, Cholesterol ester transfer protein. Enzyme involved in transfer of cholesterol and triglycerides between lipoproteins.

1. McEneney J et al. *J Nutr Biochem.* 2013;24(1):163-168.
2. Shidfar F et al. *Int J Food Sci Nutr*. 2011;62(3):289-294.
3. Yang CM et al. *J Nutr Biochem.* 2012;23(1):8-17.
4. Yang CM et al. *J Nutr Biochem.* 2012;23:1155-1162.
5. Vilahur G et al. *Trans Res.* 2015;166(1):44-56.

Quercetin: Targeted nutrition for HDL function



Study Design	Main Finding
Animal model of atherosclerosis (LDLR-/- mice)[1] and rats[2] supplemented with quercetin	• Increased liver and serum PON activity[1,2]
Animal model of atherosclerosis (ApoE-/-) mice supplemented with quercetin[3] and *in vitro* models[4-6]	• Increased ABCA1 expression in aorta and liver tissue,[3] macrophages[4,5] and foam cells[6]
Liver cells (HepG2 human cell line) and intestinal cells (Caco-2 human cell line) treated with *in vitro* quercetin[7]	• Increased apoA-I synthesis[7]
Animal model of atherosclerosis (ApoE-/- mice) supplemented with quercetin.[8]	• Increased reverse cholesterol transport[8]
Rats supplemented with quercetin.[9]	• Increased expression of bile synthesis pathways (final step of reverse cholesterol transport)[9]
Liver cell line (HepG2 cells) treated *in vitro* with quercetin[10]	• Promotes SR-BI expression in liver cells[10]

ABCA1, ATP Binding Cassette Subfamily A, Member 1. Protein on cells involved in transport of cholesterol into HDL
ABCG1, ATP Binding Cassette Subfamily G, Member 1. Protein on cells involved in transport of cholesterol into HDL
SR-BI, Scavenger Receptor, Class B, Type I. Protein on cells involved in transport of cholesterol into cells. On the liver, can be involved in transport of cholesterol from HDL into the liver.

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Summary

- Even at normal levels of HDL-C, HDL can be dysfunctional
- Oxidative stress, high glucose, and a pro-inflammatory environment can lead to HDL dysfunction
- Dysfunctional HDL lacks the cardioprotective benefits normally associated with HDL
- Dysfunctional HDL has been identified in many patient groups including those with cardiometabolic and renal conditions, and those with chronic inflammatory conditions such as autoimmune diseases
- Dietary interventions as well as smoking cessation can lay the foundation for functional HDL
- Targeted nutraceutical ingredients have been shown to support multiple facets of HDL and protect its function

Glossary of Terms

	What is it?	What does it do?
ABCA1	*ATP Binding Cassette Subfamily A, Member 1*	A protein on cells involved in transport of cholesterol to the HDL particle
ABCG1	*ATP Binding Cassette Subfamily G, Member 1*	A protein on cells involved in transport of cholesterol to the HDL particle
ApoA-I	*Apolipoprotein A-I*	The main protein in the HDL particle, is secreted by the intestine and liver and is required to accept cholesterol from cells and integrate it into HDL
CEC	*Cholesterol Efflux Capacity*	Describes the capacity of cholesterol to move from cells (e.g. macrophages) into the HDL particle
HDL	*High-Density Lipoprotein*	The HDL particle is central in reverse cholesterol transport, as well as having other important cardioprotective benefits
LCAT	*Lecithin cholesterol acyltransferase*	Enzyme responsible for packaging of cholesterol tightly within the HDL particle as cholesterol esters. This packaging of cholesterol is important for the development of the HDL particle
LDL	*Low-Density Lipoprotein*	The LDL particle circulates in the blood stream and delivers cholesterol to cells throughout the body
PON	*Paraoxonase*	HDL particle-associated enzyme with anti-oxidant capacity. Supports function of the HDL particle including protection of LDL from oxidation
RCT	*Reverse Cholesterol Transport*	A multi-step process resulting in the movement of cholesterol from cells around the body back to the liver for secretion into bile and removal from the body through the intestine
SAA	*Serum Amyloid A*	Acute phase inflammatory marker that can associate with HDL in circulation
SR-BI	*Scavenger receptor, class B type 1*	A protein on cells involved in transport of cholesterol to the HDL particle. Also present on liver cells where it is involved in transport of cholesterol from cells to liver

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References for Slide 18: Patient Types

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