The pathways of Insulin Resistance
Exposure and Implications

Ivor Cummins, BE(Chem) CEng MIEI

...with special thanks to
Gabor Erdosi MSc Molecular Biology / Molecular Genetics
Disclosure

1. My work is supported by David Bobbett and the Irish Heart Disease Awareness (http://www.ihda.ie/)

2. David Bobbett and the IHDA are funding myself and Dr. Gerber’s new book which includes the content in this presentation

3. No financial ties to the heart imaging industry (!)
Content

1. The Exposure
2. Paths to Hyperinsulinemia / IR
3. The Power of the CAC Score
   & a word on LDL, the ‘bad cholesterol’
4. Wrapup
Skeletal Muscle Insulin Resistance in Normoglycemic Subjects With a Strong Family History of Type 2 Diabetes Is Associated With Decreased Insulin-Stimulated Insulin Receptor Substrate-1 Tyrosine Phosphorylation

* Diabetes, Vol. 50, November 2001
HYPERINSULINEMIA

IN THE LIVER

INSULIN

RECEPTOR

GRB2 / SOS

RAS

RAF

MEK

ERK 1,2

PI3K - C2γ

PDPK 1

AKT/PKB pT308 pS473

PI(3,4,5)P3

PI3K - C1

GSK3β

TSC2

RHEB

mTORC1

S6K1

Srebp1c

mRNA

De-novo Lipogenesis

S6K1

mTORC2

SULF2

PRAS40

FOXO1

PI(3,4)P2

LIVER

IN THE LIVER

GLUT transloc'n

Peptcd

mRNA

Glucose uptake

Gluconeogenesis

Remains ACTIVE

Remains ACTIVE

GetS SUPPRESSED

Gluconeogenesis

Syndecan-1

HSPG

Extracellular H2O2

NADPH

O2-

AQP3

PTEN PTPases

Intracellular H2O2

PTEN PTPases

Intracellular H2O2

PTEN PTPases

Intracellular H2O2

PTEN PTPases
PART 1

THE EXPOSURE
Dr. Joseph R. Kraft, MD, MS, FCAP
1922 – 2017
Chairman, Department of Clinical Pathology and Nuclear Medicine,
St. Joseph’s Hospital 1962-1990 (appointed Chairman Emeritus on retirement)
Dr. Joseph R. Kraft, MD, MS, FCAP
1922 – 2017

Chairman, Department of Clinical Pathology and Nuclear Medicine, St. Joseph’s Hospital 1962-1990 (appointed Chairman Emeritus on retirement)
Hyperinsulinemia and Insulin Resistance:
“They are not combatants. They are one and the same.”
The Kraft “Diabetes In Situ” Test
The Kraft “Diabetes In Situ” Test

Kraft Patterns - The Earliest Diagnosis of Diabetes

1. Drink 75g Glucose…
2. Measure the Insulin Response over time…
Kraft Pattern I - Euinsulinemia (Non-Diabetic)

Kraft Patterns - The Earliest Diagnosis of Diabetes

Pattern 1 = Healthy
Kraft Pattern 2, 3, 4 - Hyperinsulinemia (Diabetes in Situ)
Kraft Pattern 2, 3, 4 - Hyperinsulinemia (Diabetes in Situ)

"The Earliest Laboratory Diagnosis for Diabetes" - Dr. Joseph R. Kraft
Kraft predicts Full-blown T2D...2013 Study

Patterns of Insulin Concentration During the OGTT Predict the Risk of Type 2 Diabetes in Japanese Americans

DIABETES CARE, VOLUME 36, MAY 2013
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DIABETES CARE, VOLUME 36, MAY 2013
Patterns of Insulin Concentration During the OGTT Predict the Risk of Type 2 Diabetes in Japanese Americans

**Table: DIABETES INCIDENCE 11 Years Later**

<table>
<thead>
<tr>
<th>Pattern 1</th>
<th>Pattern 2</th>
<th>Pattern 3</th>
<th>Pattern 4</th>
<th>Pattern 5</th>
</tr>
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<tbody>
<tr>
<td>3%</td>
<td>10%</td>
<td>15%</td>
<td>48%</td>
<td>38%</td>
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**Graph A: Fasting plasma insulin**

Patterns of insulin concentration during the OGTT predict the risk of Type 2 Diabetes in Japanese Americans.
And did you know…

That 49%-52% in the US are now…

pre-Diabetic or Diabetic.

Pre-Diabetic ≈ Diabetic ≈ Insulin Resistant ≈ Hyperinsulinemic

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That 49%-52% in the US are now…

pre-Diabetic or Diabetic.

Pre-Diabetic ≈ Diabetic ≈ Insulin Resistant ≈ Hyperinsulinemic

Using Kraft’s test, probably >65% would have

Hyperinsulinemia / Diabetes In Situ

And did you know...

“Those with cardiovascular disease not identified with diabetes... are simply undiagnosed” - Dr. Joseph R. Kraft

Using Kraft’s test, many more would have Hyperinsulinemia / Diabetes In Situ

Latest Data... 2015 Study

Diabetes and Heart Disease – Terrible Twins

Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV -- a survey from the European Society of Cardiology

European Heart Journal, 02/12/2015 Evidence Based Medicine Clinical Article

- In EUROASPIRE IV, a cross-sectional survey of patients aged 18–80 years with coronary artery disease in 24 European countries, 4004 patients with no reported history of diabetes had FPG, 2hPG, and HbA1c measured.
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Using all screening tests together, 1158 (29%) had undetected diabetes.
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- Screening according to the ADA criteria for FPG + HbA1c identified 2643 (66%) as having a ‘high risk for diabetes’

I’d be surprised if many of the remaining 34% would pass a Kraft Test…!
Cardiology

CVD Burden in U.S. Expanding Faster Than Expected
— 2015 saw levels once projected for 2030, report says

The growth in cardiovascular disease has outpaced expectations, reaching a prevalence of 41.5% in 2015 -- 15 years ahead of schedule, according to a report from the American Heart Association (AHA).

"So in short, the burden of CVD is growing faster than our ability to combat it," he said -- and the projections suggested it will get worse.
What about Hyperinsulinemia/IR versus Cholesterol ...as cause of CVD?
What do Leading-Edge Experts Say?

- ‘Cholesterol and Disease’ Experts are called ‘Lipidologists’

- One of the USA’s foremost is Thomas Dayspring, MD, FACP, FNLA, NCMP
  - Clinical Assistant Professor of Medicine, Director of Cardiovascular Education

In reply to Ivor Cummins

Thomas Dayspring @Drlipid · 11 Nov 2014
@FatEmperor Current NHANES data: majority of MI are explained by IR. But real message is unless >200 mg/dL - LDLc is terrible biomarker
What do Leading-Edge Experts Say?

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My translation:

1) In reality, the majority of Heart Attacks are due to **INSULIN RESISTANCE**
What do Leading-Edge Experts Say?

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My translation:

1) *In reality, the majority of Heart Attacks are due to INSULIN RESISTANCE*

2) *LDL is a near-worthless predictor for cardiovascular issues*

*(people with LDLc above 200mg/dL, or 5.3mmol/L are rare…)*
So what is this ‘**Insulin Resistance**’ thing then?

Well, if this is ‘LDL’ as a causal driver of Coronary Vascular Disease...
So what is this ‘Insulin Resistance’ thing then?

...then this is **INSULIN RESISTANCE**!

Well, if this is ‘LDL’ as a causal driver of Coronary Vascular Disease...
PART 2

Paths to Hyperinsulinemia / IR
Pathway to Hyperinsulinemia/IR

"The Gut is Ground Zero"
The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions
www.thelancet.com/diabetes-endocrinology Published online February 11, 2016
Intestinal Imperatives – and the Incretin Effect

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Intestinal Imperatives – and the Incretin Effect

What drives up GIP?
1. Carbohydrate (glucose)
   - especially refined
2. Fat + glucose combo

↑↑ INSULIN
↑↑ Adipose Storage

↑ Pancreatic Function
↑ Satiety

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Intestinal Imperatives – and the Incretin Effect

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1. Carbohydrate (glucose)
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2. Fat + glucose combo
   …but not Fat on its own

↑↑ INSULIN
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The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions
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What can Gastric Bypass Surgery outcomes tell us?
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Effect of Modified Roux-en-Y Gastric Bypass Surgery on GLP-1, GIP in Patients with Type 2 Diabetes Mellitus
Gastroenterology Research and Practice Volume 2015
What can Gastric Bypass Surgery outcomes tell us?

- GIP, GLP-I & PYY resolve Blood Glucose control – **way ahead of weight loss**
- The “Diabetic” GIP to GLP-I & PYY ratio is reversed – **signaling is restored**

Effect of Modified Roux-en-Y Gastric Bypass Surgery on GLP-I, GIP in Patients with Type 2 Diabetes Mellitus

*Gastroenterology Research and Practice Volume 2015*
So surgery does the trick - but what can **Diet** do?

Plant-rich mixed meals based on Palaeolithic diet principles have a dramatic impact on incretin, peptide YY and satiety response, but show little effect on glucose and insulin homeostasis: an acute-effects randomised study *British Journal of Nutrition (2015), 113, 574–584*
So surgery does the trick - but what can Diet do?

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So surgery does the trick - but what can Diet do?

Other studies show that cellular structure of food is key.

Plant-rich mixed meals based on Palaeolithic diet principles have a dramatic impact on incretin, peptide YY and satiety response, but show little effect on glucose and insulin homeostasis: an acute-effects randomised study. British Journal of Nutrition (2015), 113, 574–584
Refined Food makes Refined Mice? Or does it make **FAT** Mice?
Diet-induced obesity in ad libitum-fed mice: Food texture overrides the effect of macronutrient composition. The British journal of nutrition · August 2012
Diet-induced obesity in ad libitum-fed mice: Food texture overrides the effect of macronutrient composition. The British journal of nutrition · August 2012

Refined Food makes Refined Mice? Or does it make FAT Mice?

Grind up each diet?
Refined Food makes Refined Mice? Or does it make FAT Mice?

Diet-induced obesity in ad libitum-fed mice: Food texture overrides the effect of macronutrient composition

The British journal of nutrition · August 2012
Refined Grains make FAT Humans?

It wasn’t the “fiber”.
It wasn’t the “gastric emptying” effect.

It wasn’t the “fiber”.
It wasn’t the “gastric emptying” effect.
It was simply the cellular structure of the food particles.

The Insulin Resistance / Hyperinsulinemia Journey

Pancreas

Adipose Tissue

Liver
The Insulin Resistance / Hyperinsulinemia Journey
The Insulin Resistance / Hyperinsulinemia Journey
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose)

Pancreas

Glucagon

Insulin

Adipose Tissue

GLUT4

DNL

Liver

"Lipokines"
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose) "Too Much"

Adipose Tissue

↑GLUT4

↑DNL

"Lipolysis"

Liver
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose)

"Too Much"

Pancreas

Insulin

Liver

GLUT4

DNL

"Lipokinesis"

Adipose Tissue

"Too Much"

Insulin...
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose) → “Too Much”

Pancreas

Adipose Tissue

Liver

Insulin... Insulin

GLUT4 DNL

Too Much

“Lipokines”
CARBOHYDRATES (i.e. Glucose)...

“Too Much”

Pancreas

Liver

Adipose Tissue

GLUT4

DNL

The Insulin Resistance / Hyperinsulinemia Journey
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose) "Too Much"

Pancreas

Insulin...

Insulin

Liver

Adipose Tissue

GLUT4

DNL

"Lipokines"

FRUCTOSE
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose) “Too Much”

Pancreas

Insulin...

Insulin

Liver

Insulin

Adipose Tissue

GLUT4

DNL

“Lipokines”

FRUCTOSE “Too Much”
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose) → Insulin → Adipose Tissue

Pancreas → Insulin

Liver → Insulin

Too Much

Too Much

GLUT4

DNL

“Lipokines”

FRUCTOSE
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose)

“Too Much”

CARBOHYDRATES

Adipose Tissue

Pancreas

Insulin...

Insulin

Liver

Smoking

Genetic Tendency

Stress

Omega 6 Seed Oils

Low Sleep / Exercise

Low Omega 3

Sedentary Behaviour

Low Sun / Vitamin D

The Insulin Resistance / Hyperinsulinemia Journey
CARBOHYDRATES (i.e. Glucose)

Too Much

Adipose Tissue

Pancreas

Insulin...

Liver

Smoking
Genetic Tendency
Low Sleep / Exercise
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Low Sun / Vitamin D
Low Omega 3
Stress

The Insulin Resistance / Hyperinsulinemia Journey
CARBOHYDRATES (i.e. Glucose)

"Too Much"

Insulin…

Adipose Tissue

Pancreas

Liver

Smoking

Genetic Tendency

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Stress

The Insulin Resistance / Hyperinsulinemia Journey
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES
(i.e. Glucose)
“Too Much”

Pancreas

Adipose Tissue

Liver

FRUCTOSE
‘Too Much’
CARBOHYDRATES (i.e. Glucose)

"Too Much"

“Too Much”

The Insulin Resistance / Hyperinsulinemia Journey

Pancreas

Adipose Tissue

Adipose Macrophage (Inflammation)

Liver

FRUCTOSE

‘Too Much’
But Blood Glucose is still under control...

...so how do you get into Endgame?
CARBOHYDRATES (i.e. Glucose)

"Too Much"

Adipose Tissue

Insulin

Liver

Adipose Macrophage (Inflammation)

The Insulin Resistance / Hyperinsulinemia Journey
The Insulin Resistance / Hyperinsulinemia Journey

1. "Too Much" CARBOHYDRATES (i.e. Glucose)
2. Fructose

- Insulin Resistance
- Brake Failure
- Adipose Macrophage (Inflammation)

Liver

- Adipose Tissue
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose)

“Too Much”

Pancreas

Adipose Tissue

Free Fatty Acids

Glycerol

Liver

Fructose

Too Much

Insulin Resistance

Brake Failure

Adipose Macrophage (Inflammation)
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose)

Too Much

Pancreas

Brake Failure

Insulin... Insulin

Liver

LIVER GLUCOSE OUTPUT

Too Much

Free Fatty Acids

Glycerol

Adipose Tissue

Adipose Macrophage (Inflammation)

FRUCTOSE
The Insulin Resistance / Hyperinsulinemia Journey

CARBOHYDRATES (i.e. Glucose)

Too Much

Pancreas

Adipose Tissue

Insulin...

Insulin

Macrophage (Inflammation)

Free Fatty Acids

Glycerol

Brake Failure

INSERT INSULIN TO CONTINUE
PART 3
The Power of the CAC Score

The Ultimate Test for CVD Presence
“We Stand on the Shoulder’s of Giants…”

Bruce Brundage
Cardiologist
Former Professor David Geffan
School of Medicine UCLA

Doug Boyd
Physicist, Inventor of CAC Technology
Former Professor of Radiology (Physics)
UCSF

Harvey S. Hecht
Cardiologist
Professor Mount Sinai Medical Centre New York

John A. Rumberger
Cardiologist
Princeton Longevity Centre

Arthur Agatston
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Associate Professor of Medicine
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On Vimeo & iTunes
watch this film... it could save your life
THE WIDOWMAKER

www.widowmakerthemovie.com
The CT Scan – and the CAC Score
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<th>AND WITH YOUR CAC SCORE?</th>
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# Framingham Versus Calcium Scoring & CAC

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0 | 1-80 | 81-400 | 401-600 | >600 |

AND WITH YOUR CAC SCORE?
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AND WITH YOUR CAC SCORE?

- 0
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- Framingham Risk Score:
  - 10% with CAC Score:
    - 0: 2.4%
    - 1-80: 5.4%
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    - 401-600: 25%
    - >600: 36%

- CAC Score:
  - 0: Happy
  - 1-80: Happy
  - 81-400: Sad
  - 401-600: Sad
  - >600: Sad
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**Muddy Framingham Takes A Guess...**
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The calcium scan **sees** the disease.

---

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**Muddy Framingham Takes A Guess...**

The calcium scan **SEES** the disease.
Always the best test, across all the studies….

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<th>Study</th>
<th>Screening Power of CAC Scoring</th>
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<td>2005 St Francis Heart</td>
<td>Predicted ~10x Risk with CAC &gt; 100 Vs CAC &lt; 100 (after RF adjustment, and CRP failed)</td>
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<td>2008 MESA</td>
<td>Predicted ~8x Risk with CAC &gt; 100 Vs CAC &lt; 100 (after RF adjustment)</td>
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<td>Predicted ~7x Risk with CAC &gt; 170 Vs CAC &lt; 170 (after RF adjustment)</td>
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<td>2005 Taylor et al</td>
<td>Predicted ~12x Risk with CAC &gt; 0 Vs CAC &lt; 0 (after RF adjustment, and CRP failed)</td>
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<td>2005 Yeboah et al</td>
<td>CAC beat all predictors as always (CIMT, brachial flow dilation etc. failed again).</td>
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<td>2008/2010/2012</td>
<td>CAC re-classified ~60% of Middle-Risk people…20% became High-Risk, 39% became Low-Risk</td>
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<td>Pencina/Polonsky et al</td>
<td>(CAC blew away CIMT and other predictors by a full order of magnitude)</td>
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<td>Budoff et al 2009</td>
<td>CAC = 1 to 10 showed 20x more first-year events vs. CAC = 0 (note factor changes over time…!)</td>
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<td>Raggi/Greenland et al</td>
<td>CAC &gt; 400 had 4.8% cardiac events per year, versus 0.1% for CAC = 0.</td>
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<td>2000/2010</td>
<td>Greenland et al verified CAC = 0 had 0.1% events over 3-5 years, independent of Risk Factors...</td>
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**Screening Power of CAC Scoring**

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<td>Budoff et al 2009</td>
<td>CAC = 1 to 10 showed 20x more first-year events vs. CAC = 0 (note factor changes over time…!)</td>
</tr>
<tr>
<td>Raggi/Greenland et al 2000/2010</td>
<td>CAC &gt; 400 had 4.8% cardiac events per year, versus 0.1% for CAC = 0. Greenland et al verified CAC = 0 had 0.1% events over 3-5 years, independent of Risk Factors…</td>
</tr>
</tbody>
</table>

Coronary Calcium is not a ‘Risk Factor’

**CALCIUM SEES THE DISEASE PROCESS ITSELF**
And what about CAC Score progression??
And what about CAC Score progression??

Yearly CAC Score Increase High (more than 15%)

Starting Score 100-1000
3.5 Years Pass by…
And what about CAC Score progression??

Yearly CAC Score Increase High (more than 15%)

Starting Score 100-1000

3.5 Years Pass by…

“Progression of Coronary Artery Calcium and Risk of First Myocardial Infarction in Patients Receiving Cholesterol-Lowering Therapy”
And what about CAC Score progression??

Yearly CAC Score Increase High (more than 15%)

Starting Score 100-1000 3.5 Years Pass by…

Yearly CAC Score Increase Low (less than 15%)

Starting Score 100-1000 6 Years Pass by…

“Progression of Coronary Artery Calcium and Risk of First Myocardial Infarction in Patients Receiving Cholesterol-Lowering Therapy”
And what about CAC Score progression??

Yearly CAC Score Increase High (more than 15%)

Starting Score 100-1000

3.5 Years Pass by…

Yearly CAC Score Increase Low (less than 15%)

Starting Score 100-1000

6 Years Pass by…

“Progression of Coronary Artery Calcium and Risk of First Myocardial Infarction in Patients Receiving Cholesterol-Lowering Therapy”
“Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death”

*JAMA Cardiol.* doi:10.1001/jamacardio.2016.5493

Published online February 8, 2017.

- Adults aged 32 to 46 followed
- Mean event follow-up 12.5 years
- CAC score makes a farce of “risk factors”…
- …because it ain’t guessing.
CAC Score is now obligatory for all US presidents and all Astronauts
BUT... If CAC Score Obliterates the “Risk Factors”...

...which it does

The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression.

Then WHY doesn’t LDLc correlate with it?

**Why do studies that looked for a correlation between TC or LDL and the progression of atherosclerosis find no statistically significant association [12,16–24]?** All 10 studies involved EBT/CAC.

- Why do autopsy studies of the correlation between the extent of coronary atherosclerosis and serum cholesterol yield null results? The answer that the blood samples, mostly from accidents, were drawn from asymptomatic individuals judged free of CHD (Spearman’s coefficient = 0.07 and 0.08, respectively). Even the correlation coefficients were near zero. Multivariate analysis gave an odds ratio of 1.005 for LDL [9].

- Why did Kronmal et al. [12] find among approximately 2900 individuals that the relative risk of incident coronary calcium associated with LDL was only 1.03 per 10 mg/dL and barely reached statistical significance (lower CI 1.01) whereas both HDL and triglycerides exhibited much stronger associations?

- Why were Takamiya et al. [15] unable to find any association between LDL and plaque extension in asymptomatic individuals and why did only LDL and not TC show associations with progression of coronary artery calcium? (CAC).

- Why did Hecht et al. [7] fail to find no correlation between LDL and the coronary calcium percentile (correlation coefficient 0.06 with a scatter plot showing no visible correlation) for 304 asymptomatic individuals?

- Why do adults with familial hypercholesterolemia, did Jensen et al. [11] find that age-adjusted coronary calcium scores were not associated with cholesterol levels as assessed by either scatter plots or correlation coefficients?

- Why did Arad et al. [10] in the St. Francis Heart Study find no correlation (r = 0.03, p = 0.15) between LDL levels and coronary calcium scores in 4903 asymptomatic individuals?
The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression. Why doesn’t LDLc correlate with it?

DIABETIC PHYSIOLOGY is the most powerful predictor of CAC Score.

- Why do autopsy studies of the correlation between the extent of coronary atherosclerosis and serum cholesterol yield mixed results? The answer that the correlation is spurious is not consistent with the clincher described in the imaging of coronary artery plaques.

- Why did Kronmal et al. [12] find among approximately 2900 individuals with a relative risk of 1.5 per 10 mg/dL and LDL was only 1.2 per 10 mg/dL and barely statistically significant associations? What explains the failure to find any association between TC or LDL and the extent of coronary artery calcium scores in asymptomatic individuals judged free of CHD (Spearman’s coefficient = 0.07 and 0.08, respectively). Even the correlation coefficients in diabetic individuals are far from statistically significant [12,16–24]? An 10 studies involved EBT/CAC.

- Why in a study of 177 asymptomatic patients of intermediate risk of CHD did Ramadan et al. [14] find a null result (OR = 1.022, $p = 0.361$) for the odds of positive coronary calcification outcome and LDL in a multivariate model? The group studied had a wide range of both LDL levels and calcium scores.

- Why for adults with familial hypercholesterolemia, did Jensen et al. [11] find that age-adjusted coronary calcium scores were not associated with cholesterol levels as assessed by either scatter plots or correlation coefficients?

- Why did Arad et al. [10] in the St. Francis Heart Study find no correlation ($r = 0.03$, $p = 0.15$) between LDL levels and coronary calcium scores in 4903 asymptomatic individuals?

Medical Hypotheses 73 (2009) 596–600
Then WHY doesn’t LDLc correlate with it?

- Why do autopsy studies of the correlation between the extent of coronary atherosclerosis and plasma cholesterol levels yield conflicting results? The answer that the mainstream hypothesis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression.
- Why did Kronmal et al. find among approximately 2900 individuals a 33% relative risk of incident coronary artery calcification with LDL was only 0.5 mg/dL over 10 mg/dL and barely reached statistical significance (CI 1.01)?
- Why didn’t we find any association between TC or LDL and the coronary calcium score? All 10 studies involved EBT/CAC scans, each with a significant association [12,16–24]? An odds ratio of 1.005 for LDL [9].

Why in a study of 177 asymptomatic individuals judged free of CHD (Spearman’s correlation coefficient = 0.07 and 0.11, respectively)? Even the correlation coefficient for the association between fasting lipids and coronary calcium scores were not significantly different by either scatter plots. Between the Framingham Heart Study find no correlation (r = 0.03, p = 0.15) between LDL levels and coronary calcium scores in 4903 asymptomatic individuals?

DIABETIC PHYSIOLOGY is the most powerful predictor of CAC Score…LDL Cholesterol doesn’t even show up

The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression.

Medical Hypotheses 73 (2009) 596–600
WRAPUP

“Striking at the Root”

What would I personally prioritise?
“There are a thousand hacking at the branches of evil - to one who is striking at the root (causes).”
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