“The role of GI problems and microbes in cardiovascular disease.”

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Aims of this session

• Evidence-based summary of associations between GI function, microbes and cardiovascular disease.
• Possible mechanisms.
• Spotlight on *H. pylori* as a prime example.
• Identifying possible triggers from symptoms and lab testing.
Aims of this session

• This is a vast area to try and cover in 60min.
• It’s incredibly interesting.
• It offers huge potential for CVD prevention and possibly treatment.
• Some labs (e.g. Cleveland Heart Lab) are already offering important markers).
Background

• In researching *H. pylori*, I found a lot of research associating infections with CVD.
• I wrote a book to force me to understand things in more detail.
• It’s not just about *H. pylori*. 
Background

- Medical system recognizes a selection of risk factors (as you know); they are called *traditional* risk factors:
  - Age
  - Diabetes
  - Hypertension
  - Dyslipidemia (cholesterol, triglycerides)
  - Smoking
  - Lack of exercise
  - Obesity
  - [ApoE genotype]
Background

• Obviously these factors are important.
  – But *what causes* hypertension, diabetes, cholesterol issues, etc.?
    • Could the GI system & microbiome be involved?
  – AND... 50% people who have heart attacks do NOT have any of these risk factors!
The other 50%

“If cholesterol were the omnikiller, then everyone with heart disease would have high cholesterol. Yet half of all heart attacks occur in individuals with normal cholesterol.”

Page 4.
The other 50%

“Life-threatening plaque is now regarded as an inflammatory injury – a lesion – that develops almost like a boil, along the inner surface of the arterial walls where vital biological functions take place as blood rushes by.”
The other 50%

“The walls become damaged by the inflammation — a process influenced by lifestyle, environment and genetics. In some cases, the process unfolds slowly, stifling arterial wall chemistry and causing vessels to narrow. In other cases, deterioration occurs surprisingly fast, leading to vessel closure, stroke or sudden death.”
What is atherosclerosis?
How does atherosclerosis develop?

• We’re not here to discuss the atherosclerotic process but here are some links:
  – http://www.uofmhealth.org/health-library/zp3082abc
  – http://www.healio.com/cardiology/learn-the-heart/cardiology-review/topic-reviews/atherosclerosis
  – http://watchlearnlive.heart.org/CVML_Player.php?module Select=athero (nice animations)
How early does atherosclerosis develop?

- 3% men 15-19 years had 40% narrowing in at least one coronary vessel.
- 20% in 30-34 year olds.
- 40% narrowing not found in women ‘til 25 years.
- 8% women 30-34 years.

“These numbers show that millions already have significant coronary disease at an early age.”
How does it all begin?

“Exactly how atherosclerosis begins or what causes it isn't known, but some theories have been proposed. Many scientists believe plaque begins to form because the **inner lining of the artery, called the endothelium, becomes damaged**. 3 possible causes of damage to the arterial wall are (...HBP, cholesterol, smoking).”

http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Atherosclerosis_is_UCM_305564_Article.jsp#.WMiN_0IFhA
How does it all begin?

“The delicate endothelium can become damaged from a variety of elements, including cigarette smoke, toxic chemicals and metals, bad fats, poor diet, elevated insulin, bacteria, high blood pressure, and excess stress.”
How does it all begin?

- Too much insulin
- High blood pressure
- Homocysteine
- Lipoprotein(a)
- C-Reactive protein
- Fibrinogen
- Ferritin
- Oxidative stress
- Poor bioenergetics

- Gum disease
- Nanobacteria
- Heavy metals
- Emotional stress
- Gender factors
- Trans fatty acids
- Genetics
- Radiation
The GI environment

• Can the GI environment or microbes contribute to these risk factors?
  – Infection?
  – Dysbiosis?
  – Inflammation?
  – Malabsorption?
  – Let’s take a look!
H. pylori and CVD

“Since the discovery that gastric mucosa could be colonized by bacteria, evidence of greater than 50 extragastric manifestations has been reported, linking H. pylori infection and the development of diseases associated with cardiology, dermatology, endocrinology, obstetrics and gynecology, hematology, pneumology, neurology, odontology, ophthalmology, otorhinolaryngology, and pediatrics.”

*Helicobacter pylori* and Hematologic Diseases Germán Campuzano-Mayá. [http://dx.doi.org/10.5772/62971](http://dx.doi.org/10.5772/62971)
H. pylori & CVD

Traditional Risk Factors
- Age (Menopause)
- Diabetes
- Smoking
- Hypertension
- Dyslipidaemia
- Obesity/ Lack of exercise
- Premature Family History of CAD

Non-Traditional Risk Factors
- Abnormal Ankle Brachial Index
- Chronic Inflammation
- Homocysteine
- Microproteinuria Albumin/ Creatine
- Metabolic Syndrome
- Left Ventricular Hypertrophy
- Renal Disease
- Calcium Score
- Oxidative Stress

Major Risk Factors for Coronary Artery Disease

Figure 8 - Traditional and Non-Traditional Heart Disease Risk Factors as listed at http://emedicine.medscape.com/article/164163-overview
**H. pylori & CVD**

**Traditional Risk Factors**
- Age (Menopause)
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- Smoking
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**Non-Traditional Risk Factors**
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- Renal Disease
- Calcium Score
- Oxidative Stress
- CRP
- Fibrinogen
- Lipoprotein a
- HIV
- BNP

**Major Risk Factors for Coronary Artery Disease**

*Figure 9 - Traditional and Non-Traditional Heart Disease Risk Factors Influenced by H. pylori. The factors influenced by H. pylori are shaded red*
H. pylori & CVD

• In a nutshell, *H. pylori* (esp. CagA) appears to:
  – Accelerate/worsen atherosclerosis
  – Increase risk of heart attack and stroke
  – Increase risk and severity of angina
  – Cause/worsen dyslipidemia [including Lp(a)]
  – Increase insulin resistance
  – Increase blood pressure
  – Increase CRP (inflammation)
  – Increase oxidative stress
  – Increase homocysteine
  – Increase fibrinogen
  – Result in nutritional deficiencies
Possible mechanisms

1. Specific location of bacteria (arteries?)
2. Gut-brain axis (sympathetic / parasympathetic)
3. Systemic inflammation
4. Microbiome perturbation
5. LPS and leaky gut
6. Nutrient deficiencies - B12, folate, Mg, antioxidants?
7. Stress response - HPA, HPT, HPG axes
8. Hypothyroidism (?)
   - We won’t discuss these today – see my *H. pylori* presentation
Microbiome and metabolism

• We know that the microbiome affects metabolism in general.
  – It’s really just common sense.
• LPS from gram negative bacteria.
• Inflammation spreading from GI tract > systemic.
• Easily measured by organic acids that appear in urine
  – some research has been done in this area.
Microbiome and metabolism

“Because of the complex interactions between the huge quantities and diverse range of microbes found in the gut and the human body while we know that gut microbiota do interact with a diverse range of disease, we still don't understand the underlying mechanisms.”

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4333723/
Microbiome and metabolism

Microbiome and metabolism

Firmicutes / Bacteroidetes

“Gut bacteria is an important determinant of susceptibility to obesity and related metabolic diseases. The ratio of Firmicutes to Bacteroides has been found to be correlated to body weight, with the ratio being higher in obese people. Gut bacteria could also affect obesity by promoting chronic inflammatory status.”

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425030/
CLA / obesity

“Lactobacillus rhamnosus PL60 is a human originated bacterium that produces t10, c12-CLA. A study showed that after eight weeks of feeding, L. rhamnosus PL60 reduced the body weight of diet-induced obese mice without reducing energy intake, and caused a significant, specific reduction of white adipose tissue, including epididymal and perirenal.”

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425030/
SIBO

- 923 patients between 2006 and 2014.
- The rates of metabolic syndrome were evaluated.
- R81 (54.7%) of SIBO-positive patients with 67 (45.3%) SIBO-negative patients.
- Patients with SIBO had an overwhelmingly higher frequency of arteries affected by CAD.
- 80.2 percent vs. 38.8 percent.
- In addition, SIBO-positive patients had more coronary arteries affected than non-SIBO patients.

“We postulate that there is a poorly understood gut-heart axis in which there is a bidirectional relationship: SIBO, through the increased production of bacterial byproducts, may predispose a patient to CAD. On the other hand, CAD and atherosclerosis may be related to proinflammatory cytokines that lead to changes in the gut microbiota equilibrium.”

“What our research adds is that patients with SIBO may be considered high risk for CAD and may need to have other CAD risk factors, such as hypertension, hyperlipidemia or diabetes, more aggressively controlled to decrease their chances of worsening coronary artery disease, leading to serious event like a heart attack.”

TMAO

• Phosphatidylcholine, choline, and L-carnitine in animal-derived products.
• Processed by gut bacteria resulting in the release of various metabolites including TMA (trimethylamine) into the blood.
• TMA is transported to the liver where it is converted into TMAO (trimethylamine N-oxide).
• TMAO is involved in atherosclerosis.
“Cardiometabolic diseases (CMDs) have been associated with changes in the composition of the gut microbiota, with links between the host environment and microbiota identified in preclinical models... patients with CMDs frequently exhibit enrichment or depletion of certain bacterial groups in their resident microbiota compared to healthy individuals.”

Conventional mice

1. High-fat diet

Obesity
- Insulin resistance
- Steatosis
- Intestinal permeability
- Endotoxaemia
- Adipose tissue inflammation

Obese conventional mice

Obese transplanted mice

Clinical outcomes depend on the diet

Faecal transfer

Less obese germ-free mice

Minimal weight gain

Germ-free mice
"In our current study, we found that resveratrol can remodel the gut microbiota including increasing the Bacteroidetes-to-Firmicutes ratios, significantly inhibiting the growth of Prevotella, and increasing the relative abundance of Bacteroides, Lactobacillus, Bifidobacterium, and Akkermansia in mice...Resveratrol reduces TMAO levels by inhibiting the gut microbial TMA formation via remodeling gut microbiota.”

Beyond the gut

• What about other infections?
• Could other bugs increase the risk of cardiovascular diseases?

“Organisms such as the spirochetes Borrelia burgdorferi (Lyme disease) and Treponema pallidum (syphilis), and flagellated bacteria such as the streptococci have well-recognized atherosclerotic potential.”

Chlamydia pneumoniae

• Association first suggested in 1988.
• Evidence is quite strong.
• Common bacterial respiratory pathogen.
• About 50% of adults in the United States have been infected with *C. pneumoniae* by age 20.
• The germ causes 10% of community-acquired pneumonia cases in adults.
• Reinfection is common, as the organism is ubiquitous
Viruses

• Several viruses have been shown to affect the heart.
• Adenoviruses, Coxsackie viruses, hepatitis A virus, and herpes simplex viruses.
• Marek's disease virus (MDV) has been recognized for some time as a causal agent for atherosclerosis in chickens.
Viruses

• In a study of 391 patients referred for chest pain or other evidence of myocardial ischemia, Zhu et al found that 52% of the patients had IgG antibodies for hepatitis A virus (HAV).

• The association remained significant after controlling for other cardiovascular risk factors, including other infectious agents.

• The authors concluded that HAV might contribute to CAD by eliciting a chronic inflammatory response.
Viruses

- *Herpes simplex* virus 1 (HSV1) and herpes simplex virus 2 (HSV2) have been found in human atherosclerotic plaque.
- *Cytomegalovirus* (CMV), a member of the herpes virus family, can infect individuals but does not cause signs and symptoms.
- Studies have shown both positive and negative associations of CMV with coronary artery disease.
Autoimmune & CVD

“Patients with autoimmune diseases characterized by chronic systemic inflammation, such as rheumatoid arthritis (RA) and systemic lupus erythematosis (SLE), demonstrate a significantly increased risk of CVD.”

Secondary and tertiary effects

• Infection > autoimmune > inflammation > CVD…
• *H. pylori* infection > PPI > malabsorption > CVD…
• Rheumatoid arthritis > methotrexate > low folate > low nitric oxide > high blood pressure > CVD…
• Infection > GI inflammation > increased toxin (e.g. mercury) retention > CVD…
Musculoskeletal inflammation

- *Entamoeba histolytica*
- *Endolimax nana*
- *Giardia*
- *Blastocystis hominis*
- *Klebsiella pneumoniae*
- *Citrobacter freundii*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Streptococcus*
- *Candida*

- These organisms may trigger an intense or chronic inflammatory response on an individual basis.
- Perhaps the inflammation might open
Periodontal disease

- Association has been suspected for over 20 years.
- Early studies indicated that patients with poor dental health were 1.3 to 1.7 times more likely to experience myocardial infarction than patients with good dental health.
“Years ago periodontists were divided into two camps: the localists and the generalists. The localists claimed that periodontal diseases were a result of local irritational and occlusal circumstances. The generalists said that systemic conditions were the immediate cause of periodontal disturbances. There is a tendency today to consider systemic (intrinsic) influences of minor importance because of our inability to pinpoint them.”

Philippe P. Hujoel
Periodontal disease

Generalists

Diabetes

- CHD
- Stroke
- Blindness
- Renal Failure
- Adverse Pregnancy outcome
- Periodontitis
- Limb Amputation
Periodontal disease

Localists

Periodontitis

- CHD
- Stroke
- Blindness
- Renal Failure
- Limb Amputation
- Adverse Pregnancy outcome
Periodontal disease

• Periodontal disease involves inflammation and infection of the supportive structures for the teeth, including soft tissue and bone.
• Periodontal disease becomes established when plaque accumulation on the teeth causes an inflammatory response, resulting in detachment from the gums.
• Many people have at least a mild form of periodontal disease, or a more severe form.
Periodontal disease

Periodontal disease

• Mechanism postulated is that chronic local infection characteristic of periodontitis increases systemic inflammatory chemicals.
• The increased inflammatory mediators promote atherosclerosis.
• Several periodontal pathogens have been found in atherosclerotic plaques in carotid arteries.
  – E.g. *Porphyromonas gingivalis*
Nanobacteria?

- *Nanobacterium sanguineum*
- One hundreth the size of normal bacteria
- Form biofilms
- Burrow into healthy cells and cause death
- Stimulate CRP
- Detected in up to 60% atherosclerotic plaques
Candida, fungi and oxalates

- Dr. William Shaw’s work, and others.
- There is a correlation between oxalates, *Candida* and *Aspergillus* overgrowth
Candida, fungi and oxalates

- *Candida* produces collagenase that can break down collagen in the gut and urinary tract walls.
- Collagen is broken down via a series of steps to glyoxylate and then into oxalate.
- In addition to high oxalate foods (e.g. spinach, soy), *Candida* can increase oxalate levels.
Oxalate crystals

- According to Shaw, oxalate crystals can form in any or every tissue, even the heart tissue.
- The image shows oxalate crystals in the heart.
Oxalate crystals

• These stones can literally tear the heart apart microscopically as it contracts.
• They may trigger atherosclerosis.
• Crystals cause inflammation – recall this is step one in atherosclerotic plaque formation.
• Some people have atherosclerotic plaque containing oxalates but no typical oxalate issues (e.g. kidney stones).
Oxalate crystals

• Levin et al 1990: high urinary oxalic acid suppressed endothelial cell migration, potentially increasing atherosclerosis:

“We conclude that sodium oxalate acts as a uremic toxin, inhibiting endothelial cell replication and migration, functions which may be important for constitutive inhibition of atherosclerosis.”

http://atvb.ahajournals.org/content/10/2/198
Cardiovascular risk assessment

• Must go beyond smoking, obesity, activity levels, etc.
• Must go beyond cholesterol and the LDL/HDL ratio idea (which is mostly defunct).
• Must go beyond blood pressure and diabetes.
  – These are good starting points, but they are woefully incomplete and inadequate.
Cardiovascular risk assessment

• Remember: 50% people who have a heart attack don’t have high cholesterol.
• Many patients are blissfully unaware that other markers can be helpful.
• Many patients are blissfully unaware that these markers can be obtained in just a few days from private labs.
Cardiovascular risk assessment

• High sensitivity C-reactive protein
• Homocysteine & methylation status
  – MTHFR and associated genes
• Ferritin and iron status
  – haemochromatosis – genetic iron overload
    • 1 in 200-250 Caucasians homozygous (HFE gene)
    • 1 in 67 African Americans

• Why are these markers elevated?
Cardiovascular risk assessment

• *H. pylori* CagA (!)
• Other microbes from this presentation
• Oral and dental health
• *Candida* - oxalates
• Gut inflammation – from any trigger (e.g. gluten)
• Nutritional deficiency – vitamin D, Mg, vitamin C, other antioxidants
• Glutathione (vascular endothelium can’t make GSH))
• Thyroid and adrenal status
• Sex hormone balance
Cardiovascular risk assessment

- Challenges:
  - Doctors are stuck in the old cholesterol paradigm
  - May test CRP, vitamin D
  - Possibly B12, folate in some cases
  - The only way patients can get state of the art testing is through people like you and I, thanks to forward-thinking labs and people like Don and Humphrey.
  - It must begin with education
Myeloperoxidase
Lp-PLA₂ activity
hsCRP
Microalbumin
ADMA/SDMA
Oxidized LDL
F₂- Isoprostanes
ApoB and ApoA1
sdLDL
Lp(a)
HDL2b

TMAO
Adiponectin
Omega 3/6
CoQ10
Vitamin D, 25 OH
AspirinWorks
Galectin-3
NT-proBNP
CYP2C19
Apolipoprotein E
MTHFR
A note on cancer

How important are infectious causes of cancer?

“To date, there is no unambiguous evidence that any class of human cancers is regularly caused by a virus. Some cancers have been shown to be associated with elevated levels of antibody to certain viruses or viral components . . . However, no direct evidence exists that the viruses and the cancers are causally linked.” *Cecil Textbook of Medicine 15th Edn.* 1979. p. 1910

“One-fifth of cancers worldwide are due to chronic infections.” *W.H.O. Media Centre. February 2006*
How long will it be before people get to know the truth about heart disease from their physician and/or the media?
Thanks and questions!
We look forward to connecting and collaborating with fellow clinicians for the advancement of knowledge in Gastro-Intestinal Health, for best patient outcomes.

https://www.facebook.com/groups/invivosupportgi/