FUNCTIONAL MEDICINE
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Food-Based & Nutraceutical Interventions in Cardiometabolic Conditions

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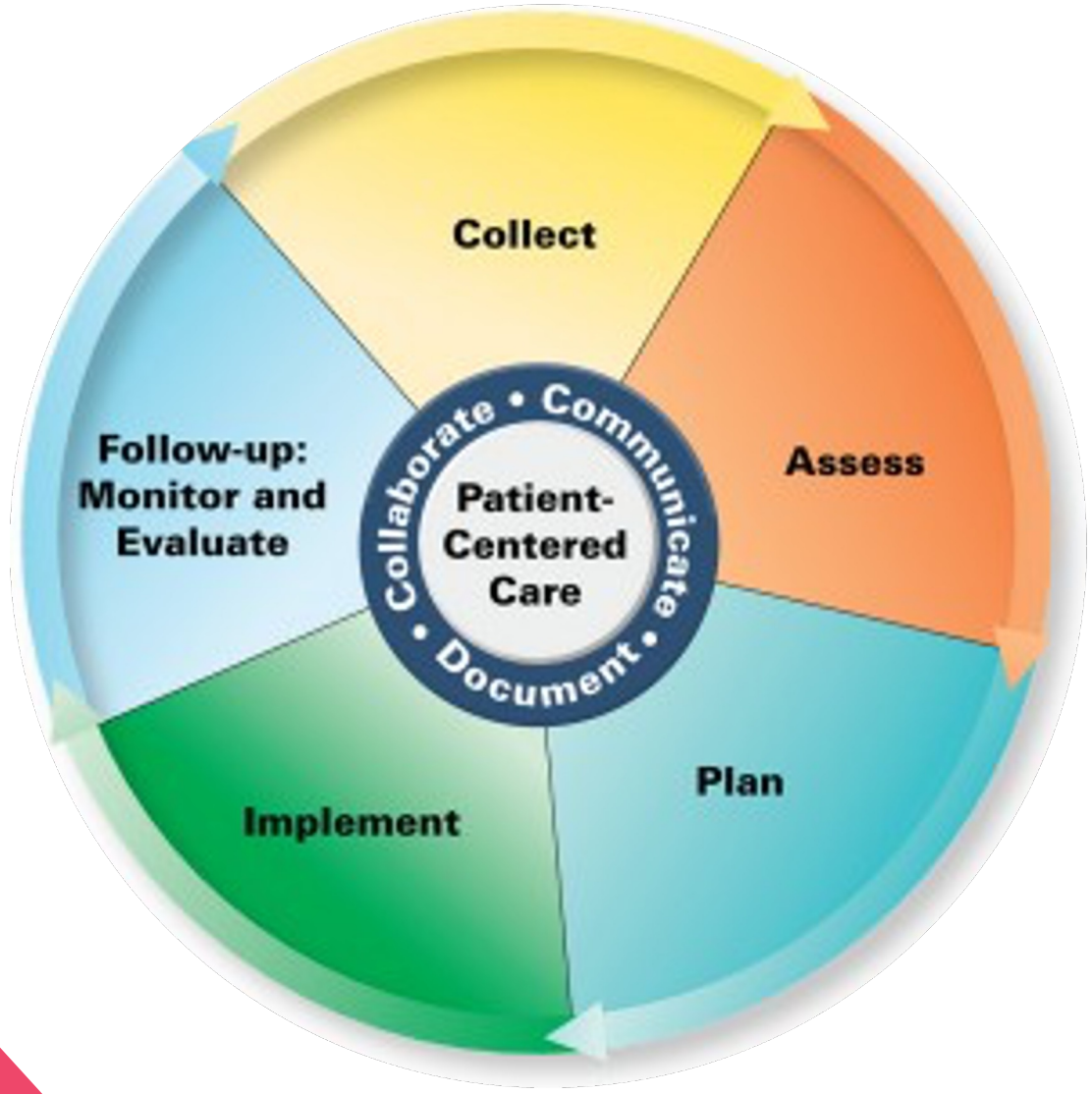
Disclosures

- Lara Zakaria does not report any actual or potential conflicts of interest in relation to this continuing pharmacy education course.

Objectives

1. Discuss the role of the Standard American Diet in the development of cardiometabolic conditions.
2. Provide the Food Rx for reducing inflammation and decreasing cardiometabolic risk
3. Recommend nutritional supplementation for cardiometabolic conditions



Pharmacists' Patient Care Process

Pharmacists use a patient-centered approach in collaboration with other providers on the health care team to optimize patient health and medication outcomes.

Using principles of evidence-based practice, pharmacists:

Collect
The pharmacist assures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient.

Assess
The pharmacist assesses the information collected and analyzes the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize problems and achieve optimal care.

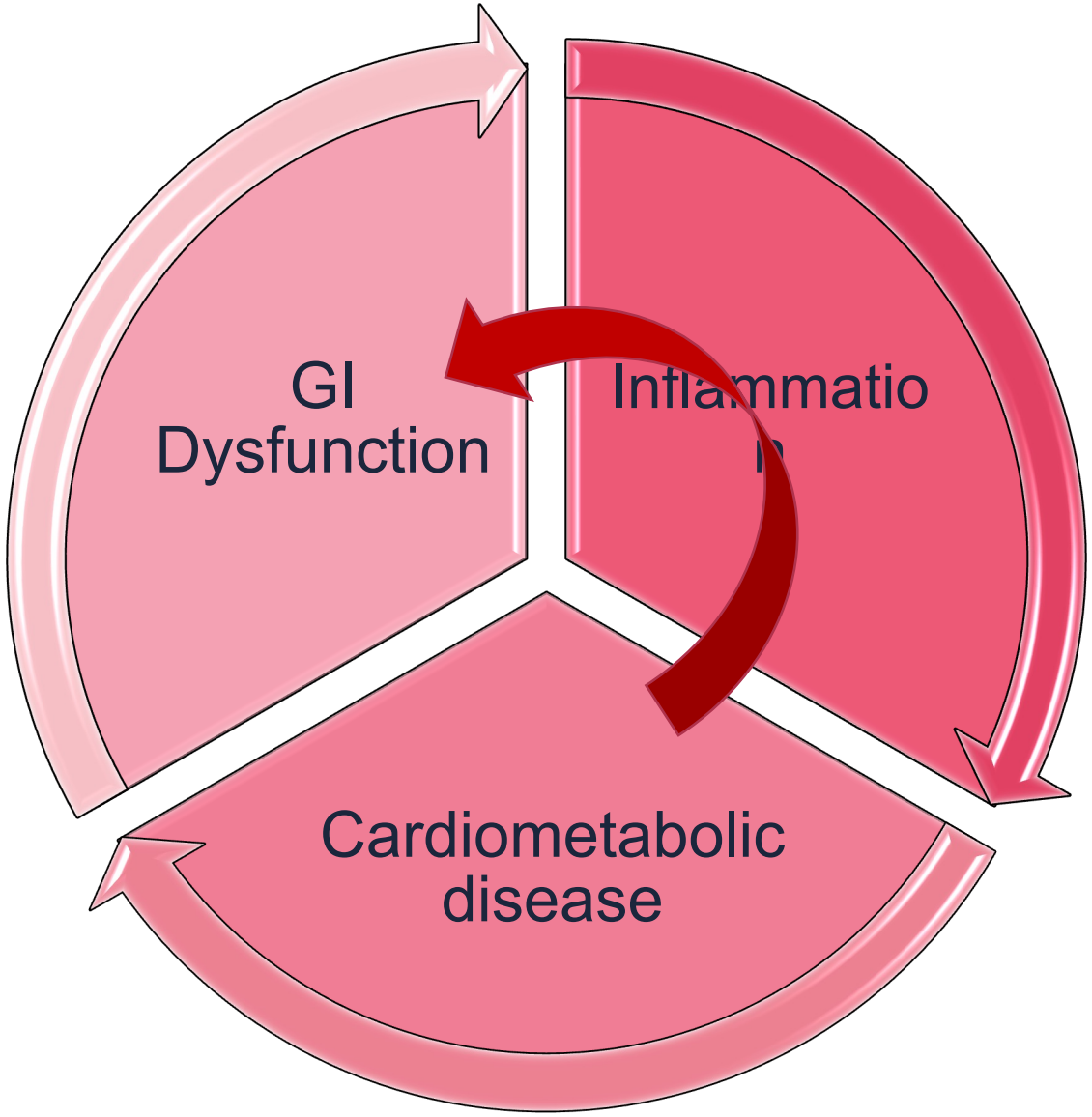
Plan
The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective.

Implement
The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver.

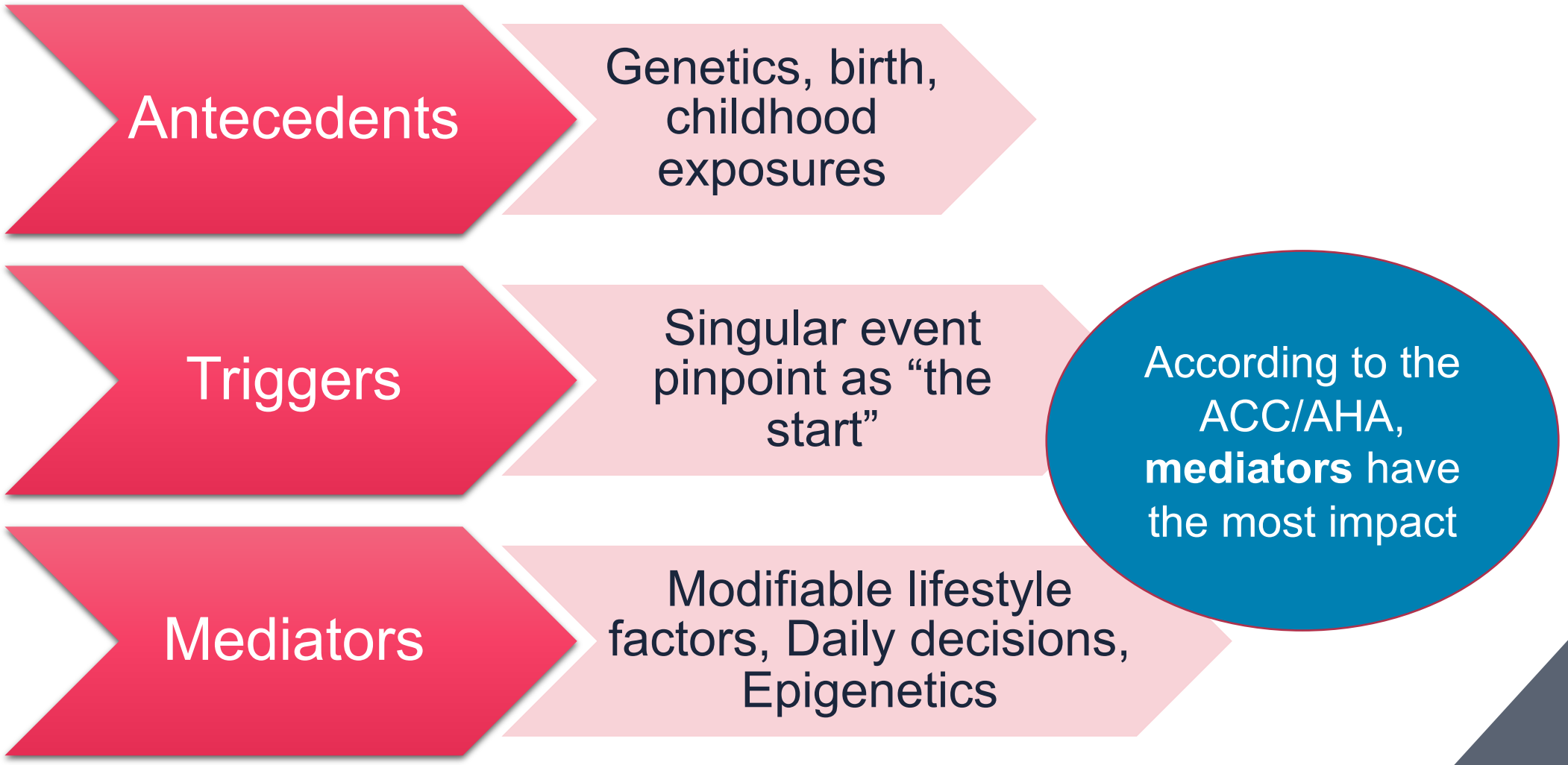
Follow-up: Monitor and Evaluate
The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed.

Joint Commission of Pharmacy Practitioners (JCPP) https://jcpp.net/patient-care-process/

The Gut, Inflammation & Cardiometabolic Disease



Functional Medicine: ATMs



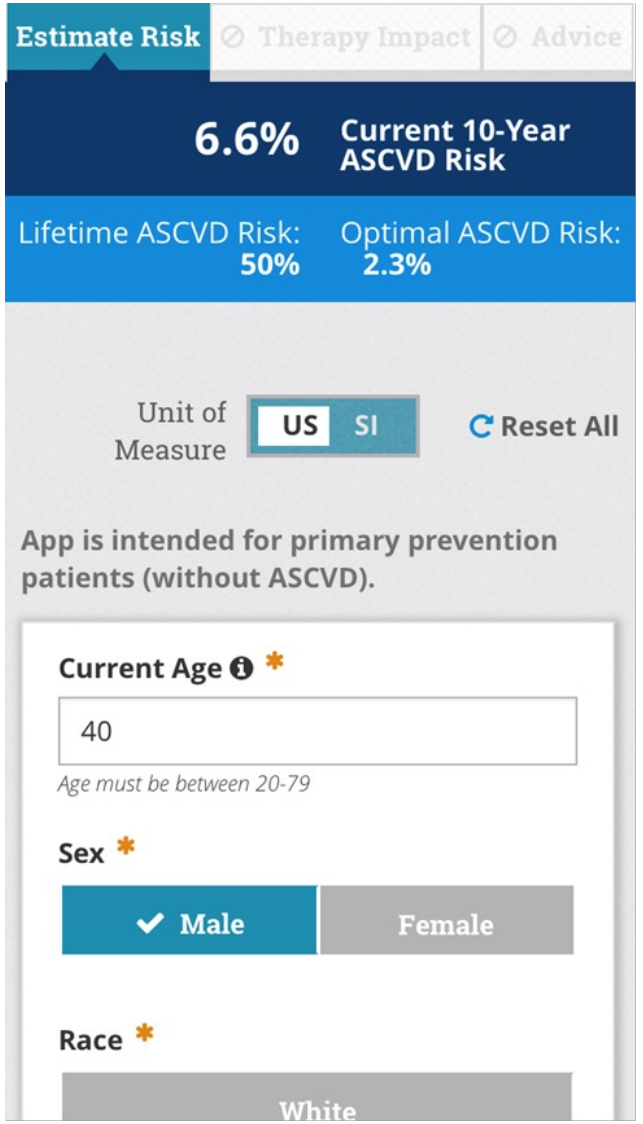
2018 AHA/ACC Guidelines

Assess “lifetime risk” using ACC/AHA ASCVD risk estimation tool (younger adults)

Identify and address metabolic syndrome

- Cluster of risk factors associated w/ increased risk of ASCVD
- 1/3 of US adults meet criteria for metabolic syndrome

Lifestyle is the primary intervention for metabolic syndrome



http://tools.acc.org/LDL/ascvd_risk_estimator/index.html#!/calulate/estimator/

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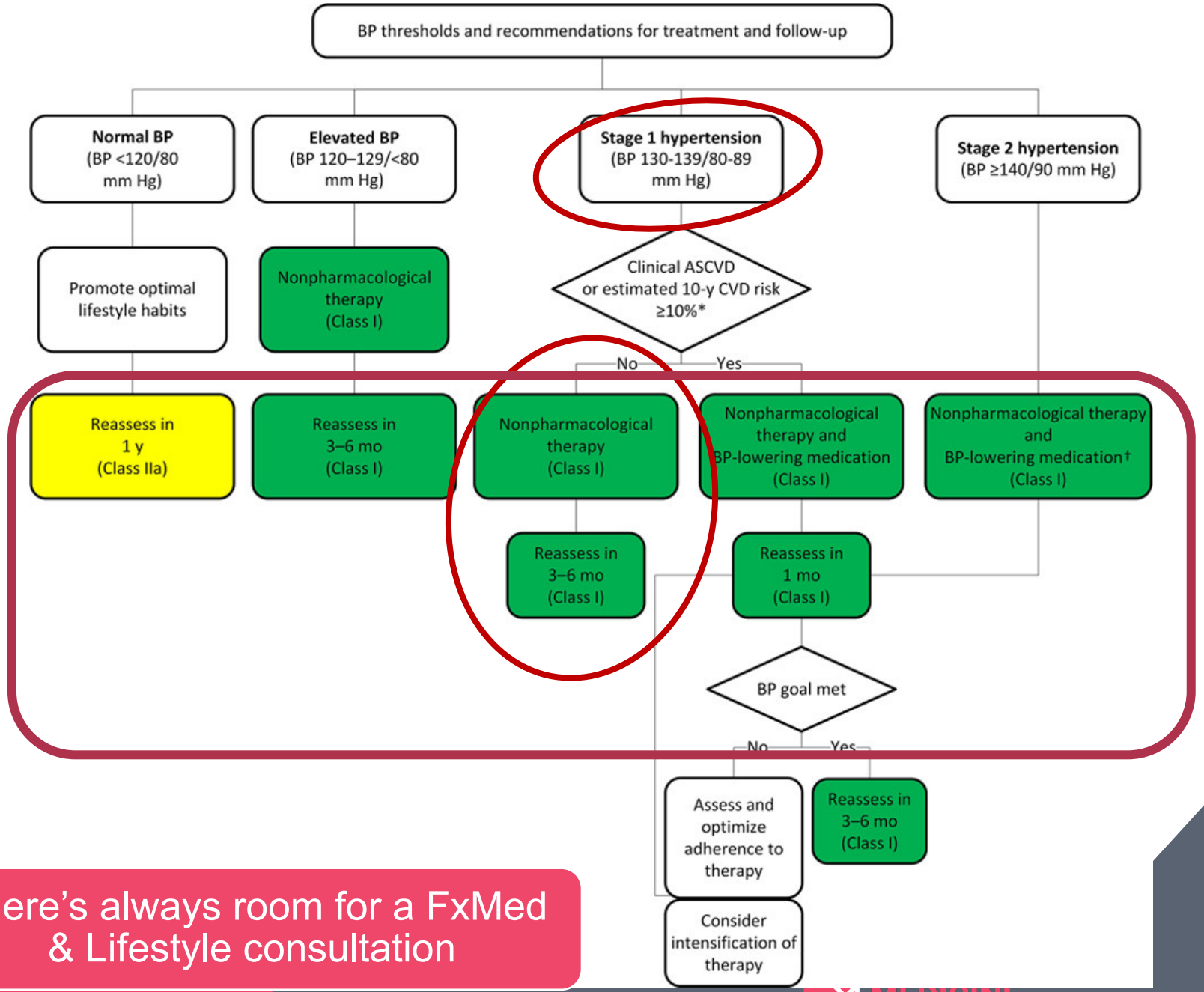
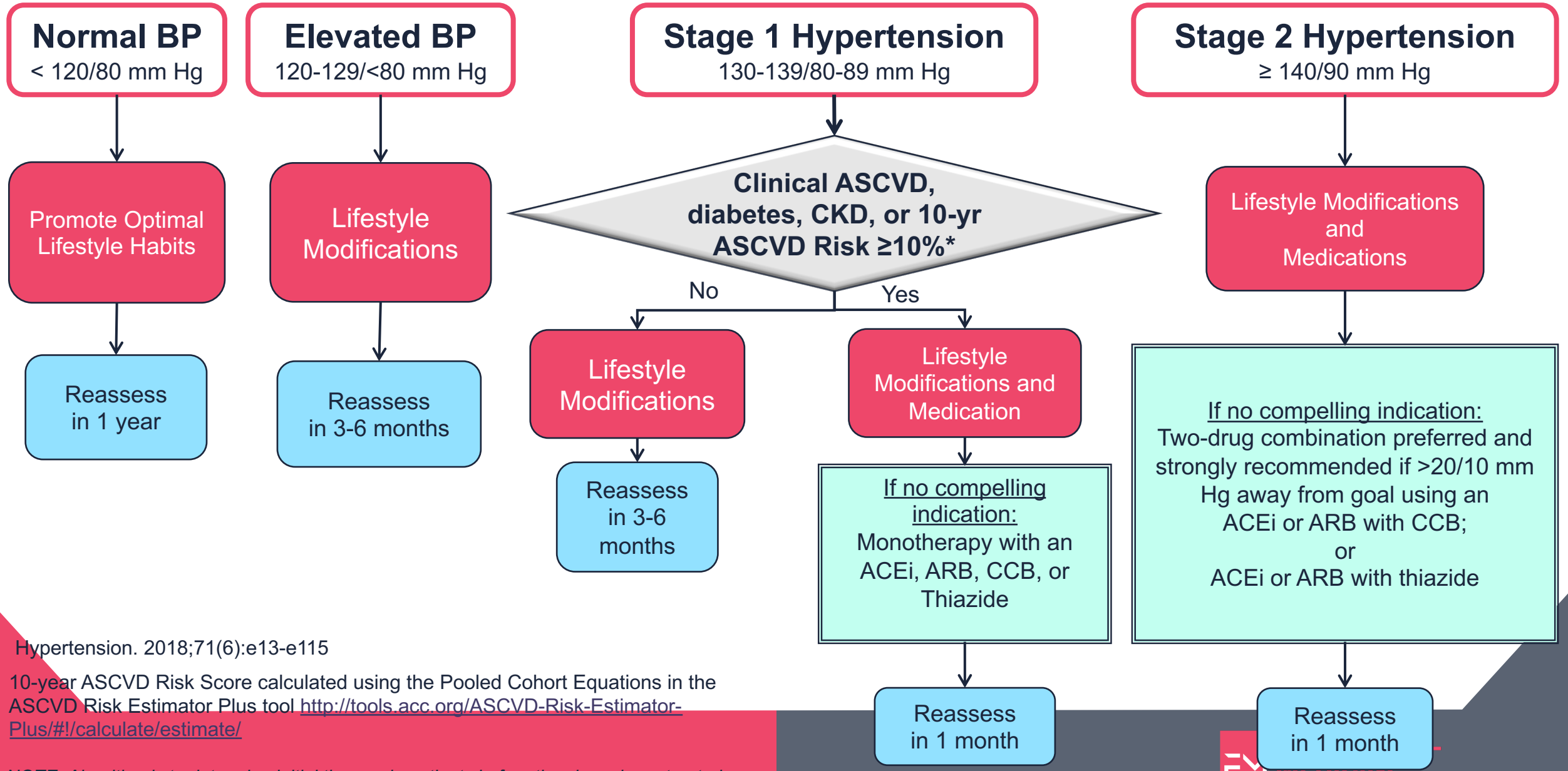
ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults



There's always room for a FxMed & Lifestyle consultation

Hypertension. 2018;71(6):e13-e115

Initial HTN Therapy Treatment Algorithm per ACC-AHA 2017 guideline

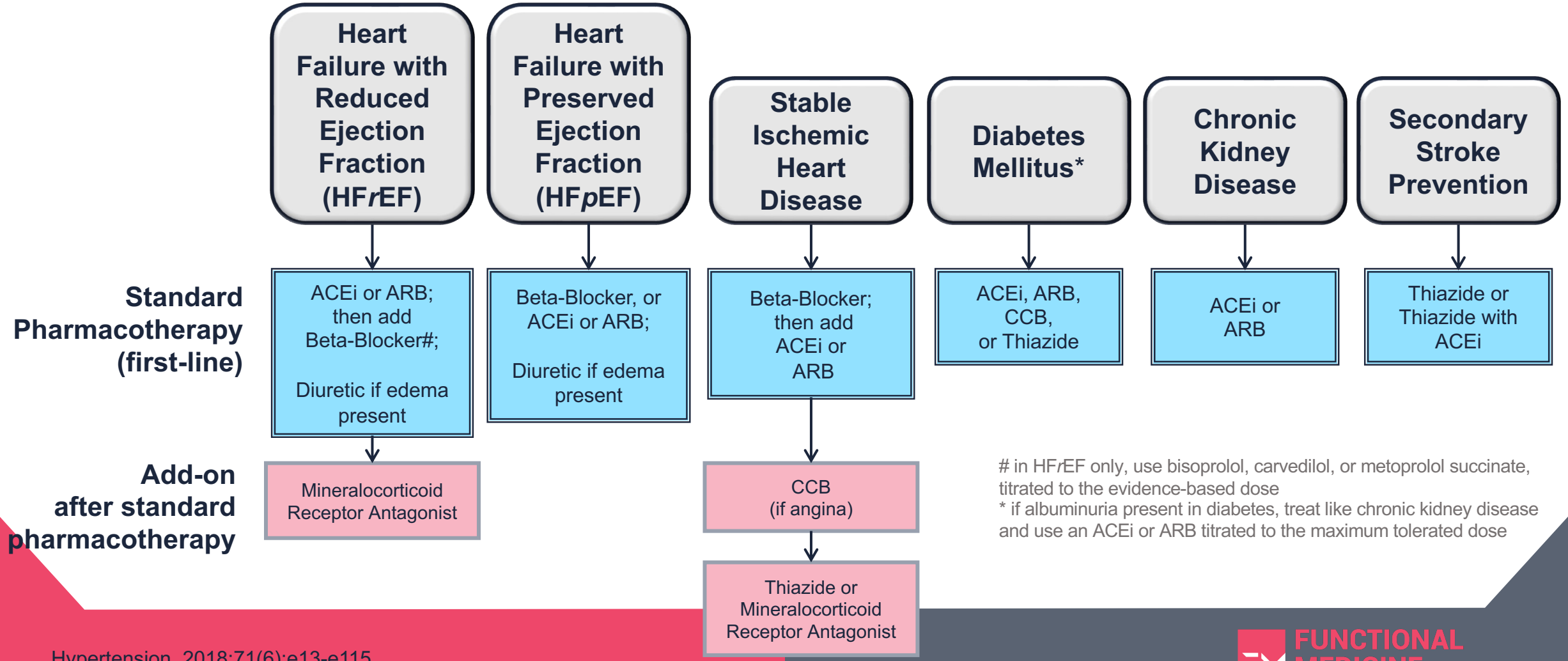


Hypertension. 2018;71(6):e13-e115

- 10-year ASCVD Risk Score calculated using the Pooled Cohort Equations in the ASCVD Risk Estimator Plus tool http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

NOTE: Algorithm is to determine initial therapy in patients before they have been treated.

Comorbid conditions with specific Medication recommendations to reduce risk of ASCVD events



in HF*r*EF only, use bisoprolol, carvedilol, or metoprolol succinate, titrated to the evidence-based dose
* if albuminuria present in diabetes, treat like chronic kidney disease and use an ACEi or ARB titrated to the maximum tolerated dose

Hypertension. 2018;71(6):e13-e115

Non-Pharmacological Interventions Per ACC/AHA 2017 Guidelines

Table 15. Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension* (Table view)

	Nonpharmacological Intervention	Dose	Approximate Impact on SBP		
			Hypertension	Normotension	Reference
Weight loss	Weight/body fat	Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	−5 mm Hg	−2/3 mm Hg	S6.2-1
Healthy diet	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	−11 mm Hg	−3 mm Hg	S6.2-6,S6.2-7
Reduced intake of dietary sodium	Dietary sodium	Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.	−5/6 mm Hg	−2/3 mm Hg	S6.2-9,S6.2-10
Enhanced intake of dietary potassium	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	−4/5 mm Hg	−2 mm Hg	S6.2-13
Physical activity	Aerobic	90–150 min/wk65%–75% heart rate reserve	−5/8 mm Hg	−2/4 mm Hg	S6.2-18,S6.2-22
	Dynamic resistance	90–150 min/wk50%–80% 1 rep maximum6 exercises, 3 sets/exercise, 10 repetitions/set	−4 mm Hg	−2 mm Hg	S6.2-18
	Isometric resistance	4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk8–10 wk	−5 mm Hg	−4 mm Hg	S6.2-19,S6.2-31
Moderation in alcohol intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol† to: Men: ≤2 drinks daily Women: ≤1 drink daily	−4 mm Hg	−3 mm Hg	S6.2-22—S6.2-24

Hypertension. 2018;71(6):e13-e115

Common Cardiovascular Drug Induced Nutrient Depletion (DIND)

Statins	Beta Blockers	Diuretics	Metformin	ACEi & ARBs	Calcium channel blockers
• CoQ10 • Selenium • Omega 3 • Fat soluble vitamins • Carnitine • Free T3	• Melatonin	• Potassium • Magnesium • Folate • B6 • B12 • B1 • Iodine • Selenium	• Folate • B12	• Zinc	• Potassium • Zinc

HMG-CoA Reductase Inhibitors "statins"

MOA:

- Competitively inhibit the hepatic enzyme HMGCR the rate limiting step in conversion of HMG-CoA to mevalonate, a precursor to cholesterol
- Compensatory mechanisms increase the synthesis of hepatic LDL-C receptors

Pharmacologic differences exist amongst members of this class

- Drug Interactions (e.g. CYP3A4 inhibitors, OATP1B1 inhibitors, P-gp inhibitors)
- Dose adjustments for renal function (does not apply to atorvastatin)
- Dose adjustments for ethnicity (e.g. Asian ancestry)

Robust clinical outcomes data in both primary and secondary prevention of ASCVD make statins the first line therapy for treatment of dyslipidemia and ASCVD risk reduction

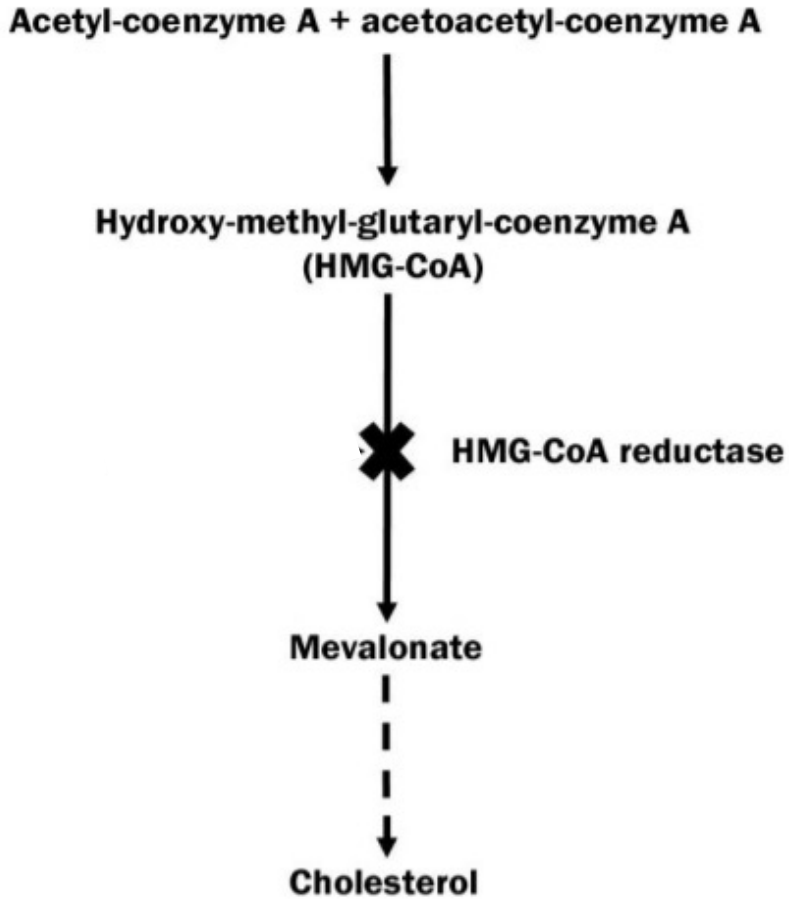


Figure 1.
Main cholesterol-lowering mechanism of action of red yeast rice.

Methodist Debakey Cardiovasc J. 2019;15(3):192-199

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Statins are associated with nutrient depletions

- CoQ10
- Carnitine
- Vitamin E
- Vitamin D
- Omega-3 fatty acids
- Selenium

Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms.
https://doi.org/10.1586/17512433.2015.1011125

The full list?

CoQ10	Tocopherols and tocotrienols	Essential fatty acids	Vitamin D
Vitamin K2	Vitamin A	Heme A	Selenoproteins and selenium
Carnitine	Copper	Zinc	Creatine

Okuyama H, Langsjoen PH, Hamazaki T, Ogushi Y, Hama R, Kobayashi T, Uchino H. Expert Rev Clin Pharmacol. 2015 Mar;8(2):189-99. doi: 10.1586/17512433.2015.1011125. Epub 2015 Feb 6.

The Gut

Implications on CM Health

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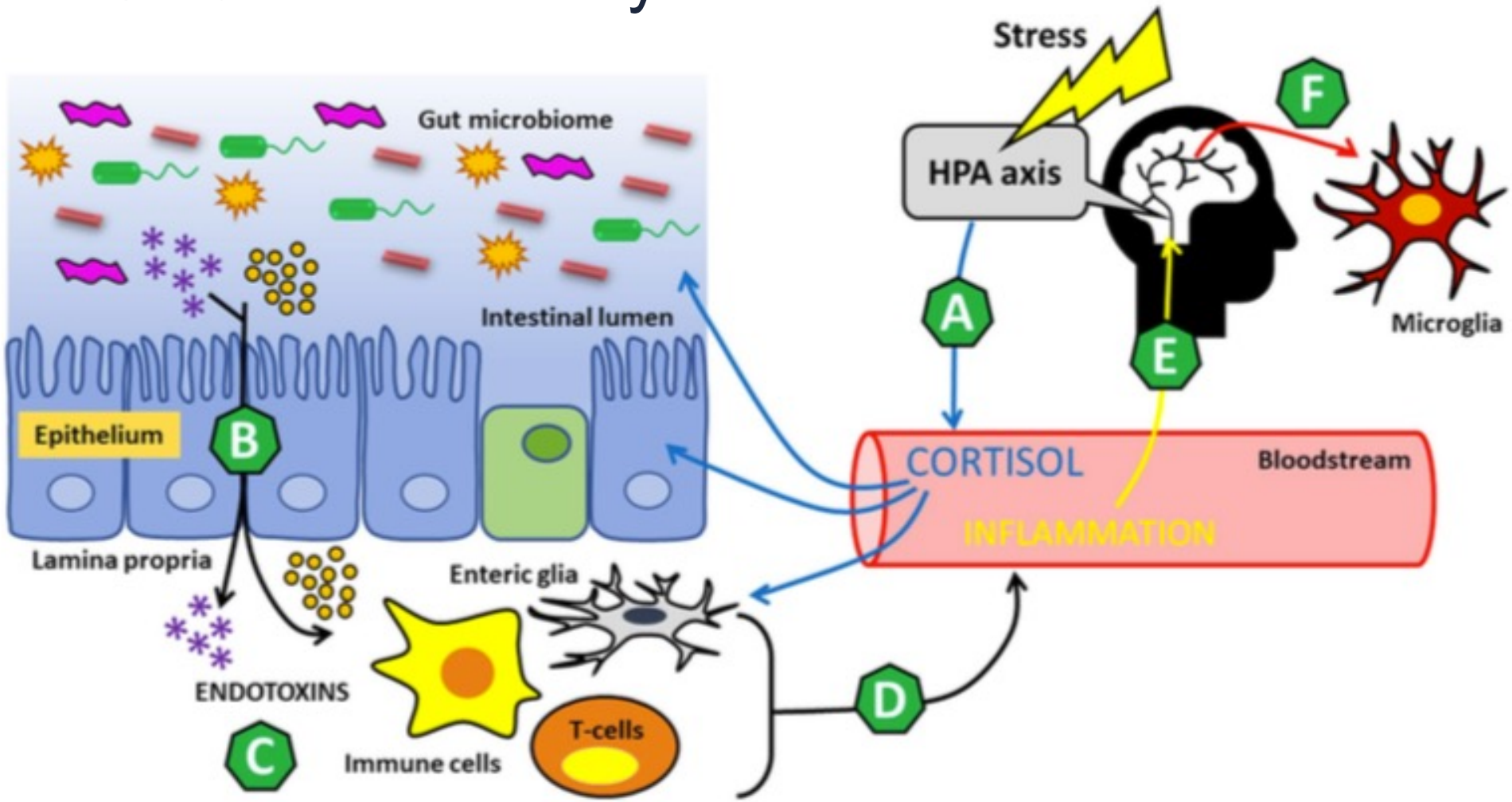
Bidirectional communication between the gut microbiome and the CNS is affected by stress



J Neuro Res. 2019;97:1223–1241.

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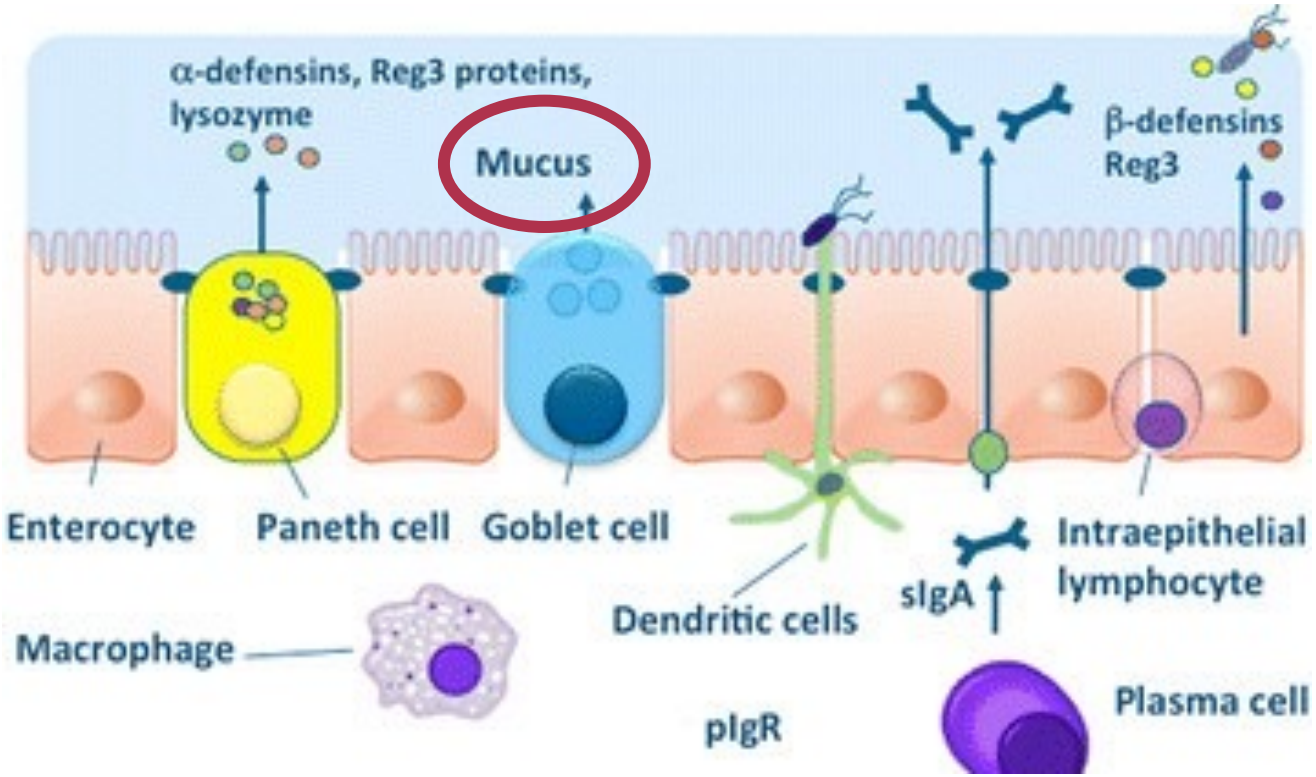
The gut-immune interface



- Significance of the connection between GI and immune function (70-80% of host immune cells)
- Major site of host defense (mechanical, chemical, immunological)
- Increased intestinal permeability linked with CM disease (endotoxemia)

BMC Gastroenterol 2014

Metabolic Endotoxemia and Diabetes Mellitus

Epithelial barrier provides an important protection from environmental assaults, allowing healthy passage of water, nutrients, bioactive compounds, and blocking the passage f dietary antigens, microbes and endotoxins.

Increased intestinal permeability contributes to insulin resistance and DM

Translocation of Endotoxins and LPS (major component of the outer membrane of G- bacteria) and trigger inflammatory response (via TLR and NF-κβ)

Antidiabetic medications decrease fasting LPS concentrations. Among these medications, rosiglitazone and insulin present higher and lower effects, respectively, compared with other treatments.

confounders such as diet, age, medication, smoking and obesity influence both diabetes and endotoxemia manifestation. A better understanding of the interaction of these factors is still needed

Metabolism. 2017;68:133-144

Metabolic Endotoxemia and Diabetes Mellitus

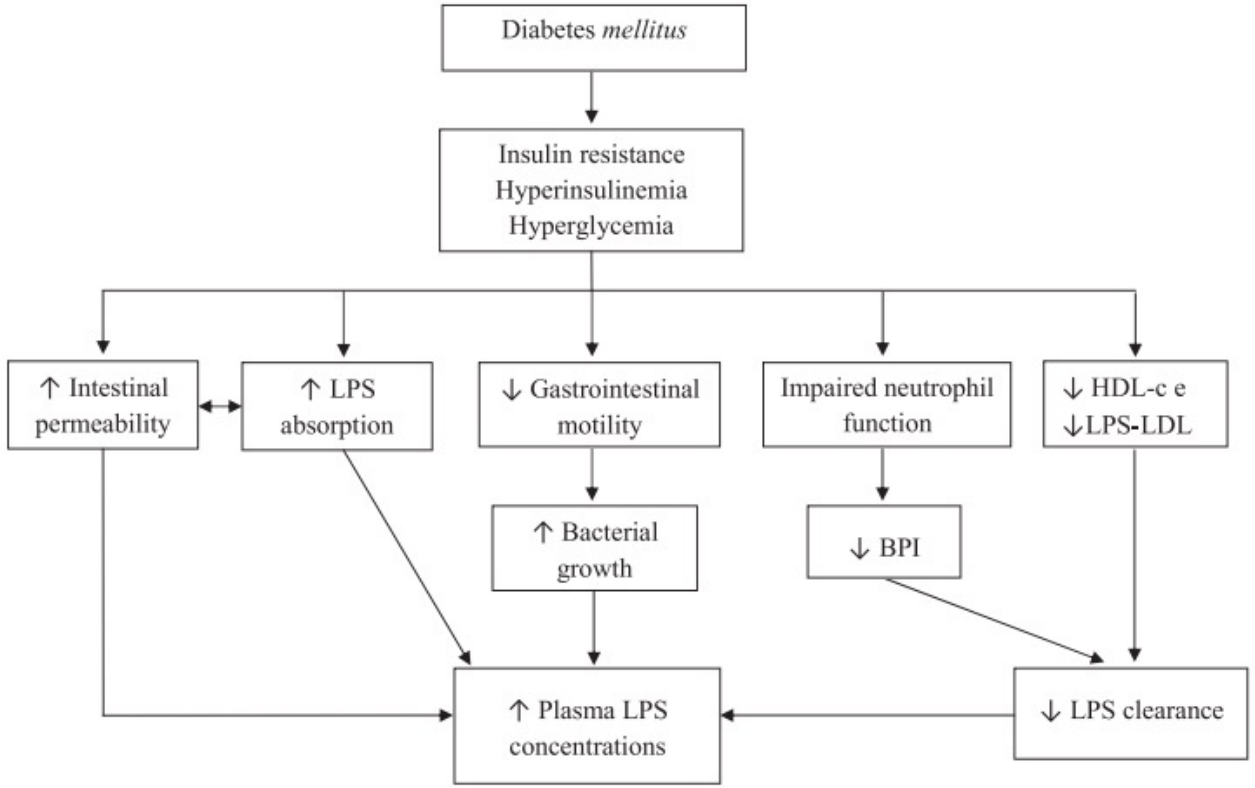


Fig. 2 – Possible mechanisms explaining high-LPS concentrations in diabetic subjects. LPS, lipopolysaccharide; BPI, bactericidal/permeability-increasing protein; HDL-c, high-density lipoprotein cholesterol.

Metabolism. 2017;68:133-144

JOURNAL OF MEDICAL MICROBIOLOGY

REVIEW

Hasani *et al.*, *Journal of Medical Microbiology* 2021;70:001435

DOI 10.1099/jmm.0.001435

MICROBIOLOGY SOCIETY

The role of *Akkermansia muciniphila* in obesity, diabetes and atherosclerosis

Alka Hasani[1,2], Saba Ebrahimzadeh[3], Fatemeh Hemmati[2], Aytak Khabbaz[1,4], Akbar Hasani[5] and Pourya Gholizadeh[2,6,*]

Abstract

Alteration in the composition of the gut microbiota can lead to a n
is an anaerobic bacteria constituting 3–5% of the gut microbial co
degenerating mucin in the gut; its scarcity leads to diverse clinical
in diabetes, obesity and atherosclerosis, as well as the use of this
and diabetes, human and animal trials have shown that *A. mucinip*
energy metabolism. However, the underlying mechanisms by whi
betes and atherosclerosis are unclear. At the same time, its abund
bolic endotoxemia, adiposity insulin resistance and glucose tolerance.
lesions and atherosclerosis. Well-characterized virulence factors, antigens and cell wall extracts of *A. muciniphila* may act as effector molecules in these diseases. These molecules may provide novel mechanisms and strategies by which this bacterium could be used as a probiotic for the treatment of obesity, diabetes and atherosclerosis.

The role of Akkermansia muciniphila is implicated in declining aortic lesions and atherosclerosis. Well-characterized virulence factors, antigens and cell wall extracts of A. muciniphila may act as effector molecules in these diseases. These molecules may provide novel mechanisms and strategies by which this bacterium could be used as a probiotic for the treatment of obesity, diabetes and atherosclerosis.

Published in final edited form as:
J Funct Foods. 2017 June ; 33: 194–201. doi:10.1016/j.jff.2017.03.045.

Strategies to promote abundance of *Akkermansia muciniphila*, an emerging probiotics in the gut, evidence from dietary intervention studies

Kequan Zhou
Department of Nutrition & Food Science, Wayne State University, Detroit, MI 48202, USA

Abstract

Akkermansia muciniphila is a mucin-degrading bacterium *muciniphila* has been inversely associated with obesity, diabetes, inflammation, and metabolic disorders. Due to its highly promising probiotic activities against obesity *muciniphila* has drawn intensive interest for research and development of human and animal studies have shown that the abundance of *A. muciniphila* enhanced through dietary interventions. The present review focuses on strategies of improving *A. muciniphila* abundance in the gut by critically available human and animal intervention studies on *A. muciniphila* and risk factors of obesity and diabetes. Their potential mechanisms in promoting *A. muciniphila* are also discussed along with the discussions of mechanism of action for *A. muciniphila* to exert probiotic functions.

Mechanisms impacting Akkermansia muciniphila abundance

- Supplement with A mucophilia
- Other probiotics (Lactobacillus rhamnosus LMG S-28148 and Bifidobacterium animalis subsp. lactis LMG P-28149 for 14 weeks (5 days/week, 5 × 108 CFU of each strain in PBS) increased A. muciniphila abundance)
- FODMAP in diet promoted A. muciniphila
- dietary polyphenols
- Metformin consistently increased A. muciniphila abundance
- Rhubarb** extract promoted A. muciniphila abundance
- Caloric restriction (CR): inconsistent results from human and animal studies
- Selective antibiotic treatment remarkably promoted A. muciniphila abundance in humans and mice (by reducing abundance of firmicutes and bacteroides)
- High fat diet and alcohol could reduce abundance of A. muciniphila

microbial biotechnology

Open Access

Minireview

Akkermansia muciniphila is a promising probiotic

Ting Zhang,[1,2] Qianqian Li,[1,2] Lei Cheng,[3,4] Heena Buch[1] and Faming Zhang[1,2,*]

[1]*Medical Center for Digestive Diseases, the Second Affiliated Hospital of Nanjing Medical University, Nanjing 210011, China.*

[2]*Key Lab of Holistic Integrative Enterology, Nanjing Medical University, Nanjing 210011, China.*

[3]*Biogas Institute of Ministry of Agriculture and Rural Affairs, Chengdu 610041, China.*

[4]*Center for Anaerobic Microbial Resources of Sichuan Province, Chengdu 610041, China.*

Summary

***Akkermansia muciniphila* (*A. muciniphila*), an intestinal symbiont colonizing in the mucosal layer, is considered to be a promising candidate as probiotics. *A. muciniphila* is known to have an important value in improving the host metabolic functions and immune responses. Moreover, *A. muciniphila* may have a value in modifying cancer treatment. However, most of the current researches focus on the correlation between *A. muciniphila* and diseases, and little is known about the causal relationship between them. Few intervention studies on *A. muciniphila* are limited to animal experiments, and limited studies have explored its safety and effi-**

Introduction

Several microbial species are getting increasing attention for their role in modulating the gut microbiota. At present, many diseases and conditions have been reported to be closely related to gut microbiota (de Vos and de Vos, 2012), so it is of great interest to improve the host health by modulating the intestinal bacteria. *Akkermansia muci-*

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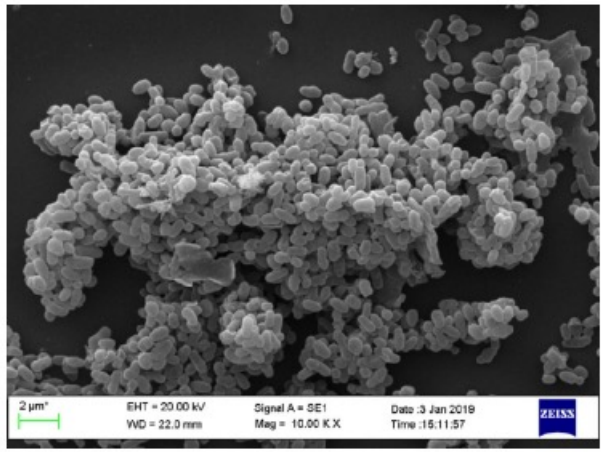
firmed *A. muciniphila* can degrade mucin and exert competitive inhibition on other pathogenic bacteria that degrade the mucin (Belzer and de Vos, 2012). These findings provide a rationale for *A. muciniphila* to become



Akkermansia muciniphila, as a potential probiotic that can make good use of gastrointestinal mucin, is inextricably linked to host metabolism and immune response. It promises to be a therapeutic target in the microbiota-related diseases, such as colitis, metabolic syndrome, immune diseases and cancer. Preliminary human data suggest oral administration of A. muciniphila is safe, but its effect needs to be further verified in more human clinical trials in the near future.

Review > Clin Res Hepatol Gastroenterol. 2018 Apr;42(2):110-117.
doi: 10.1016/j.clinre.2017.09.006. Epub 2017 Nov 1.

Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies

Yongbo Kang [1], Yue Cai [2]

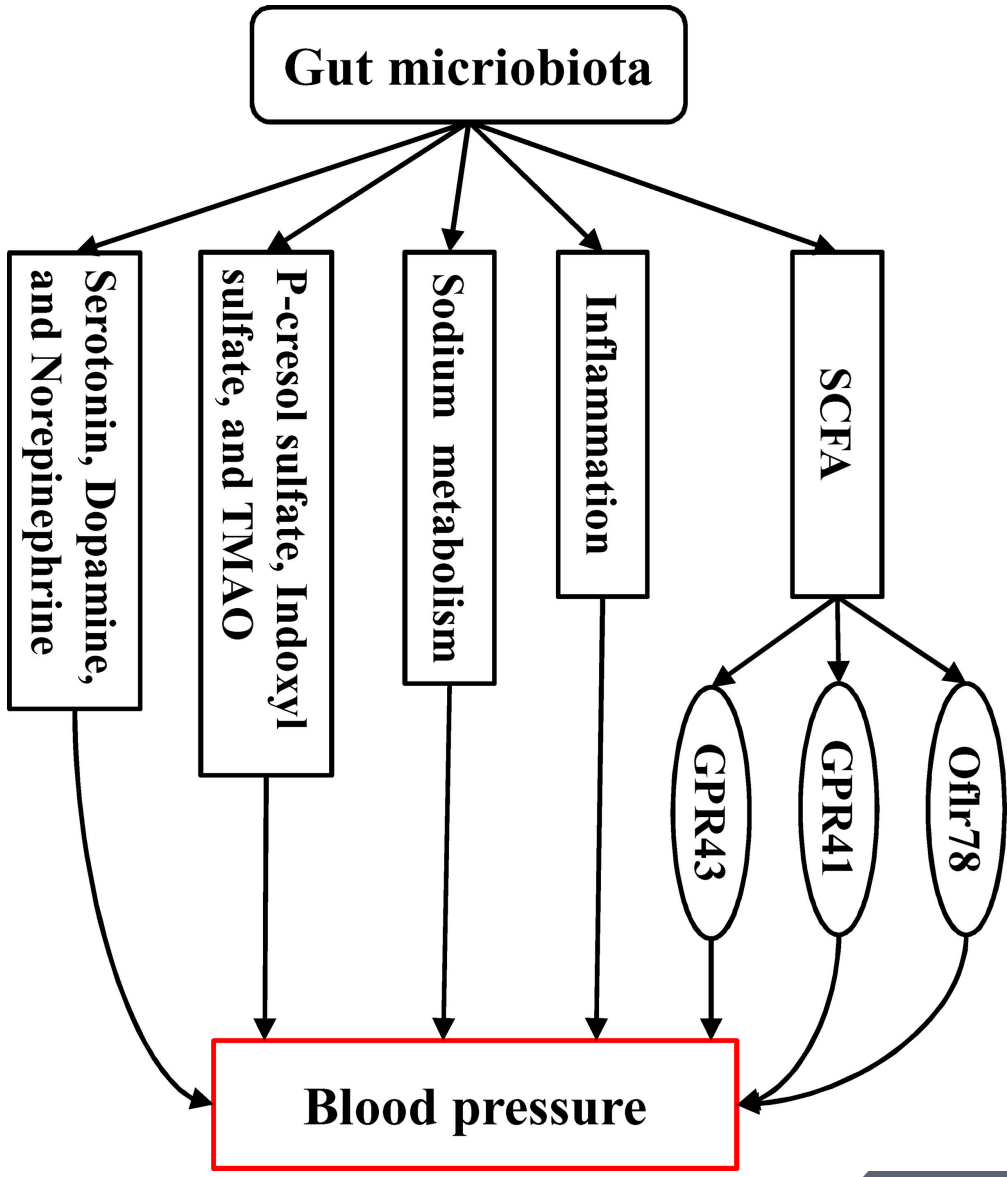
Affiliations + expand

PMID: 29102544 DOI: 10.1016/j.clinre.2017.09.006

Abstract

Hypertension (HTN) has become a global public health concern and a major risk factor for cardiovascular, cerebrovascular, and kidney diseases. The complex interplay of genetic and environmental influences is important for the development of the disease. Accumulating evidence has illustrated the association of dysbiosis of gut microbiota with hypertension. Certain gut microbial strains may play either a pathogenic or a protective role in the development of hypertension. Oral probiotics can therefore represent a therapeutic approach for hypertension treatment. However, the relevant scientific work has only just begun, and the available data in this field remain limited. Fortunately, recent technological developments that permit identification of microbes and their products using culture-independent molecular detection techniques. In this review, we summarize the role of gut microbiota in hypertension progression, and probiotics in the treatment of hypertension.

Keywords: Gut microbiota dysbiosis; Hypertension; Metabolic disorders; Metagenomics; Probiotic therapy.



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nutrients

MDPI

Nutrients. 2018 Jun; 10(6): 773.
Published online 2018 Jun 15. doi: 10.3390/nu10060773

PMCID: PMC6024794
PMID: 29914095

Dose-Dependent Effects of Multispecies Probiotic Supplementation on the Lipopolysaccharide (LPS) Level and Cardiometabolic Profile in Obese Postmenopausal Women: A 12-Week Randomized Clinical Trial

Monika Szulińska,[1] Igor Łoniewski,[2,*] Saskia van Hemert,[3] Magdalena Sobieska,[4] and Paweł Bogdański[1]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Post hoc tests revealed significant differences in the mean changes (mostly medium effects) between the HD and LD groups for uric acid, glucose, insulin, and HOMA-IR. In the 12-week randomized, placebo-controlled, double-blind intervention, we observed that supplementation with the multispecies probiotic Ecologic® Barrier favorably affected the risk factors in a dose-dependent manner, showing beneficial effects on the cardiometabolic parameters and gut permeability of the patients. Our results suggest that this product can be effective in the prevention and treatment of cardiovascular diseases in obese postmenopausal women

Inflammation

Various causes of inflammaging

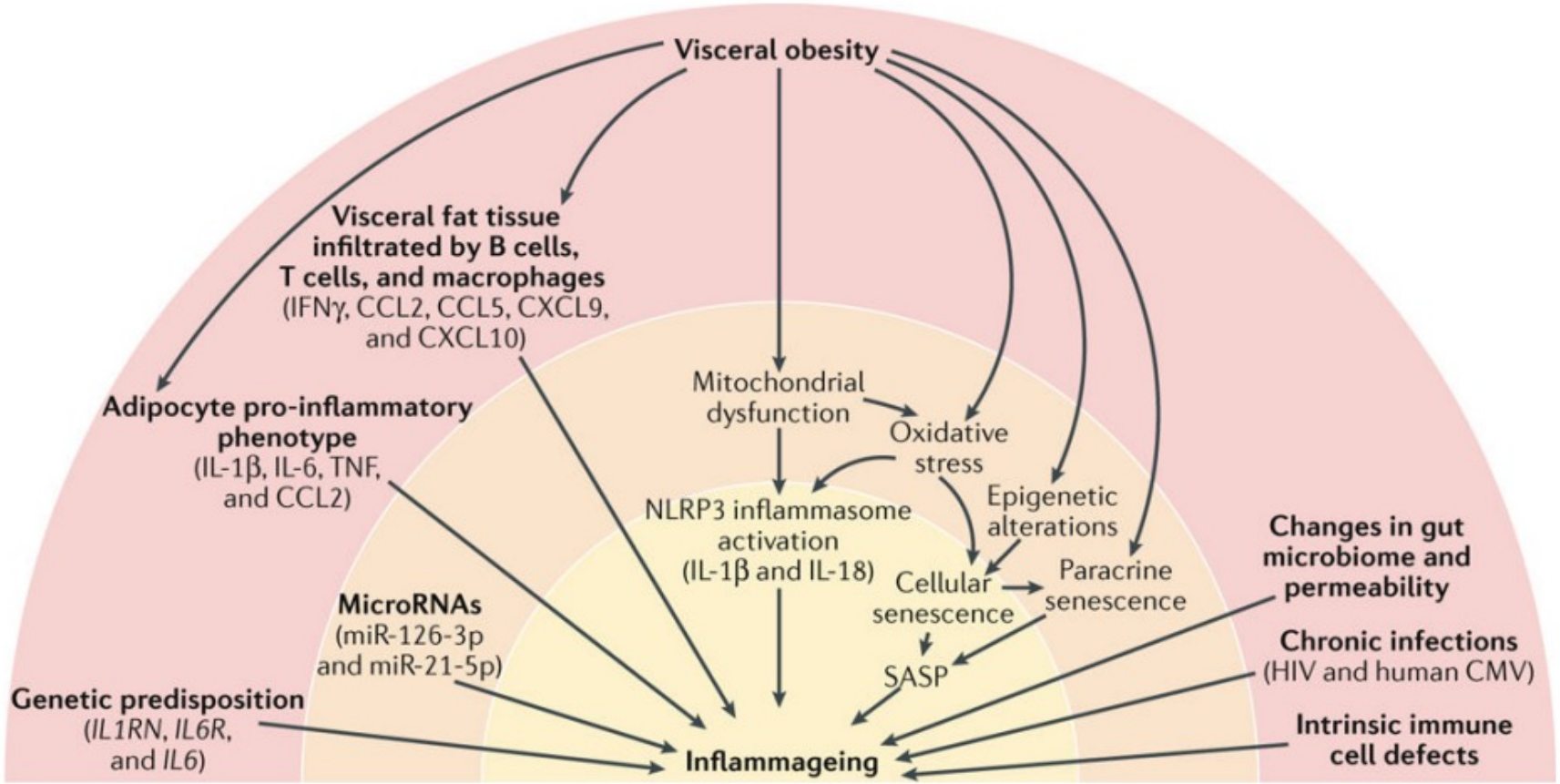

Fig. 1 |. Potential causes of inflammageing.

Nat Rev Cardiol. 2018;15(9):505-522

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Inflammaging is a cause of chronic disease

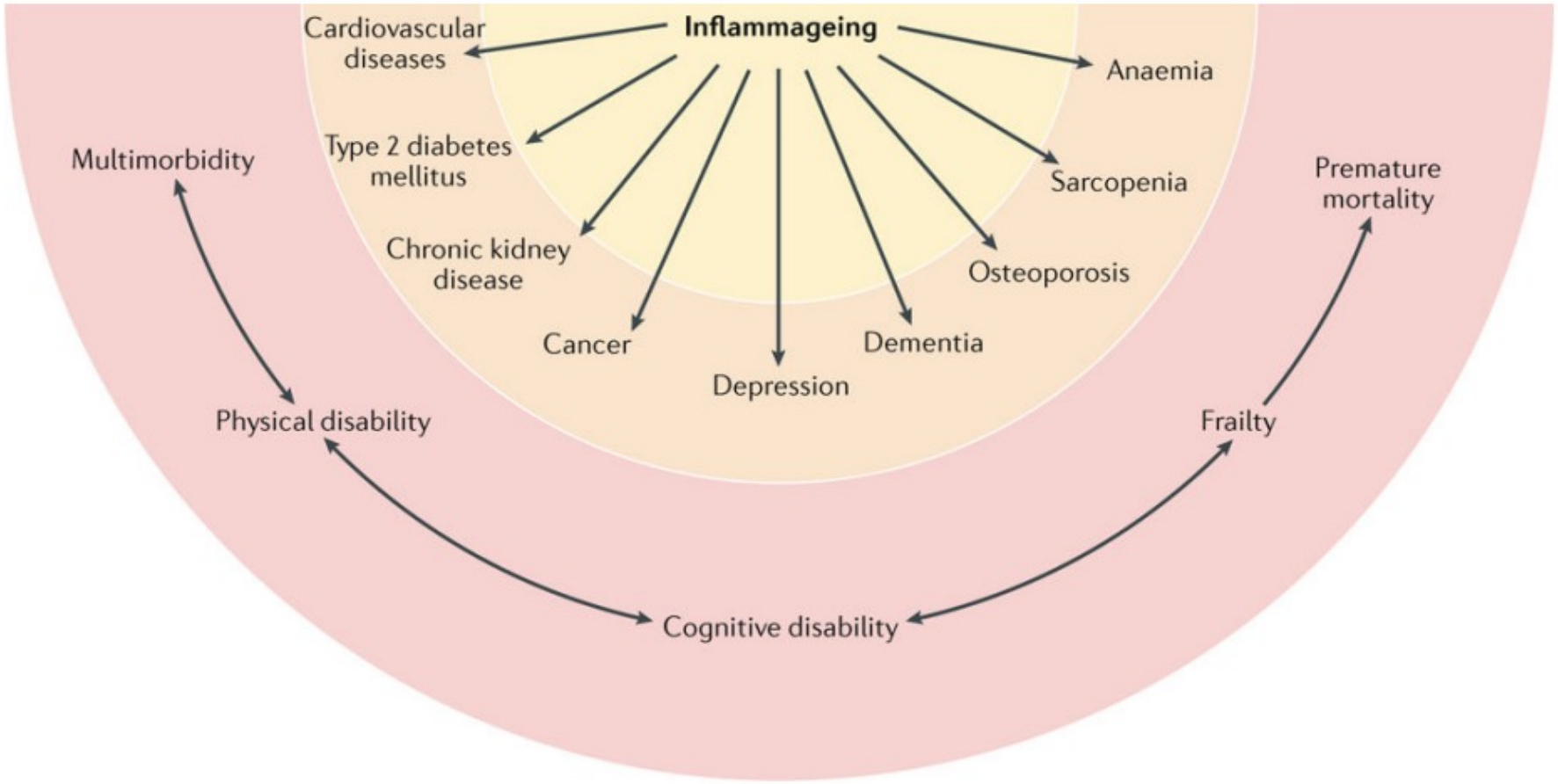


Fig. 2 |. Inflammageing is a risk factor for multiple chronic diseases.

Nat Rev Cardiol. 2018;15(9):505-522

Therapeutic Advances in Cardiovascular Disease *Review*

The role of noninvasive cardiovascular testing, applied clinical nutrition and nutritional supplements in the prevention and treatment of coronary heart disease

Ther Adv Cardiovasc Dis
2018, Vol. 12(3) 85–108
DOI: 10.1177/1753944717743920

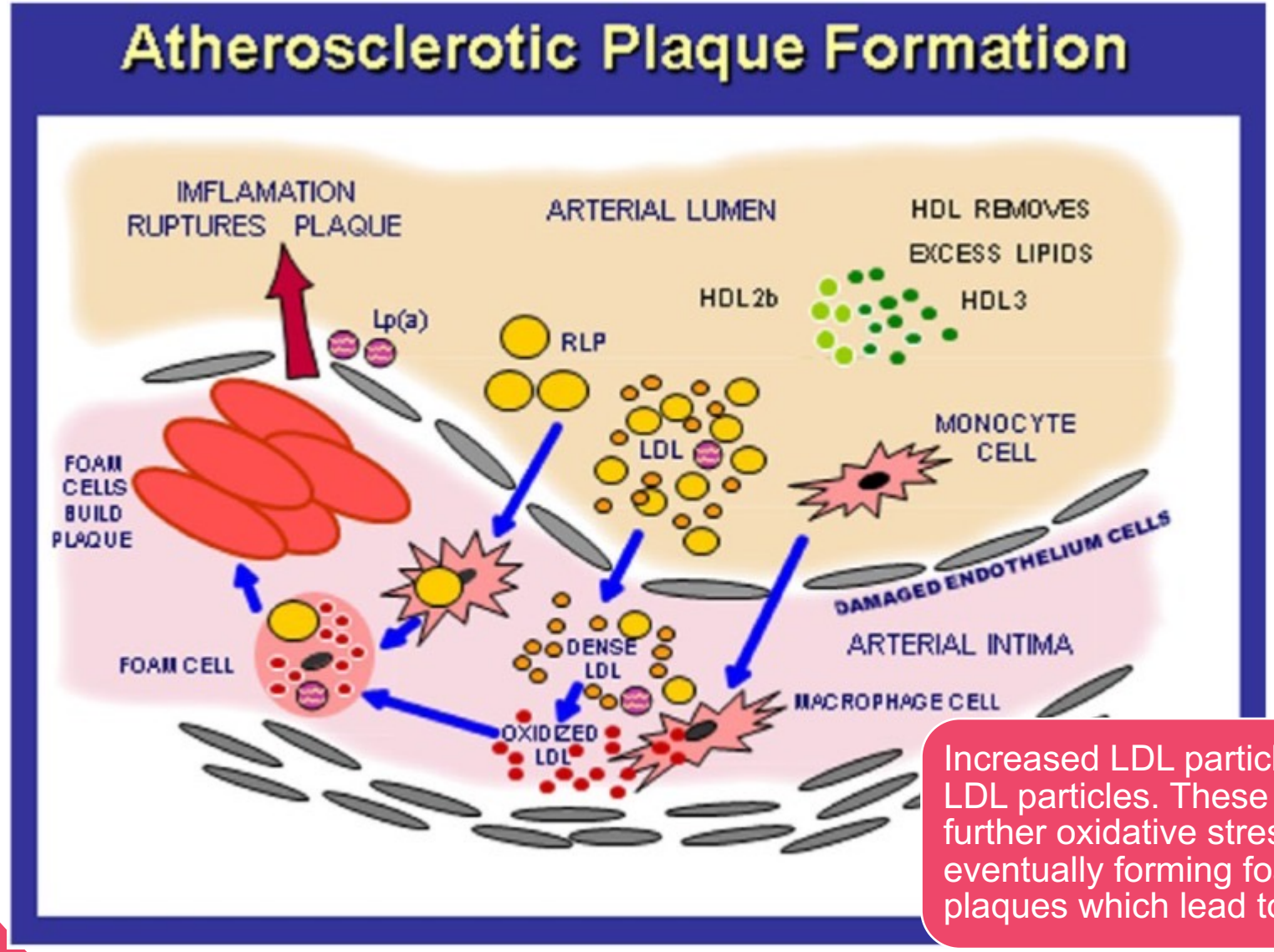
Mark Houston

Abstract: Numerous clinical trials suggest that we have reached a limit in our ability to decrease the incidence of coronary heart disease (CHD) and cardiovascular disease (CVD) utilizing the traditional diagnostic evaluation, prevention and treatment strategies for the top five cardiovascular risk factors of hypertension, diabetes mellitus, dyslipidemia, obesity and smoking.

About 80% of heart disease (heart attacks, angina, coronary heart disease and congestive heart failure) can be prevented by optimal nutrition, optimal exercise, optimal weight and body composition, mild alcohol intake and avoiding smoking. Statistics show that approximately 50% of patients continue to have CHD or myocardial infarction (MI) despite presently defined 'normal' levels of the five risk factors listed above. This is often referred to as the 'CHD gap'. Novel and more accurate definitions and evaluations of these top five risk factors are required, such as 24 h ambulatory blood pressure (ABM) results, advanced lipid profiles, redefined fasting and 2 h dysglycemia parameters, a focus on visceral obesity and body composition and the effects of adipokines on cardiovascular risk. There are numerous traumatic insults from the environment that damage the cardiovascular system but there are only three finite vascular endothelial responses, which are inflammation, oxidative stress and immune vascular dysfunction. In addition, the concept of translational cardiovascular medicine is mandatory in order to correlate the myriad of CHD risk factors to the presence or absence of functional or structural damage to the vascular system, preclinical and clinical CHD. This can be accomplished by utilizing advanced and updated CV risk scoring systems, new and redefined CV risk factors and biomarkers, micronutrient testing, cardiovascular genetics, nutrigenomics, metabolomics, genetic expression testing and noninvasive cardiovascular testing.

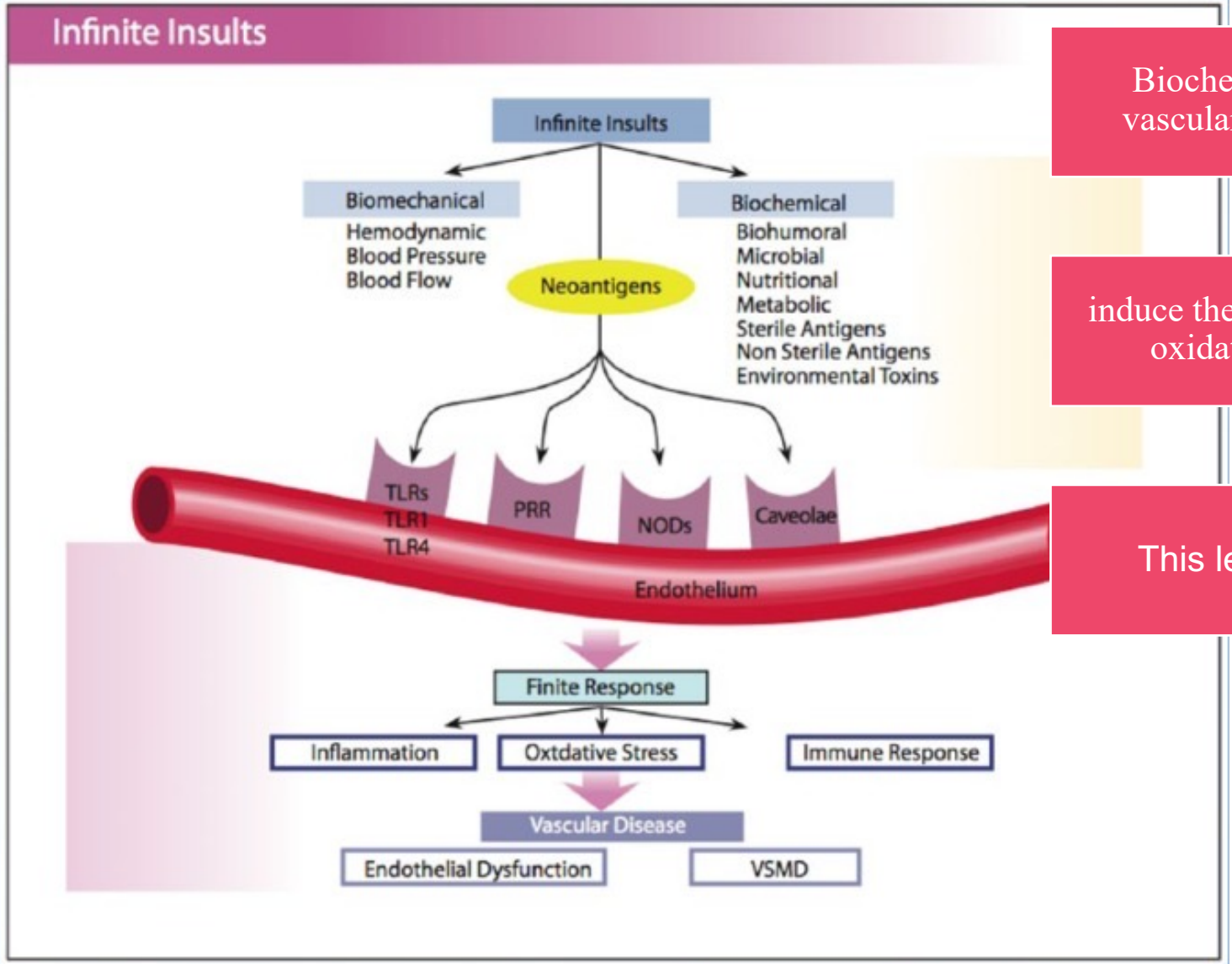
The top five CV risk factors, as presently defined, are not an adequate explanation for the current limited reduction in CHD or the 'CHD gap' […] downstream mediators should be included with measurement of the three finite responses of inflammation, oxidative stress and vascular immune dysfunction, micronutrient testing, CV genetics, nutrigenomics, metabolomics, gene expression testing and noninvasive vascular testing. Early detection coupled with aggressive prevention and treatment of all CV risk factors will diminish the progression of functional CV abnormalities, CV structural problems and clinical CVD.

Approximately 80% of CHD can be prevented with this approach.



Increased LDL particle number leads to increased oxidation of LDL particles. These are taken up by macrophages and induce further oxidative stress, inflammation, immune dysfunction – eventually forming foam cells, fatty streaks and coronary artery plaques which lead to cardiovascular events.

Ther Adv Cardiovasc Dis. 2018;12(3):85-108.



Biochemical and biomechanical insults interact with vascular receptors (PRRs, NLRs, TLRs and caveolae)

induce the three finite responses of vascular inflammation, oxidative stress and vascular immune dysfunction

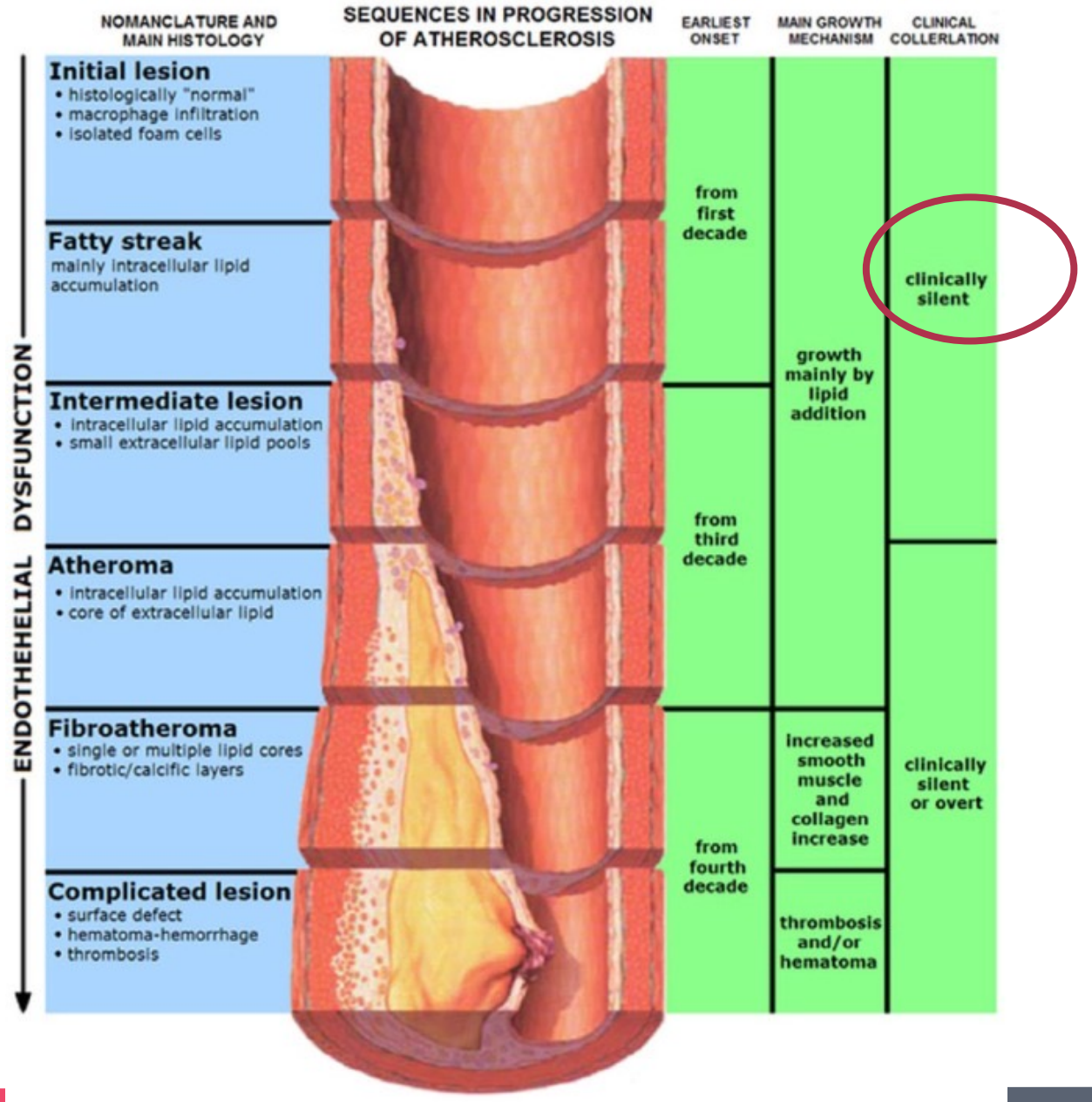
This leads to complications and cardiac events

Ther Adv Cardiovasc Dis. 2018;12(3):85-108.

The earliest abnormality is endothelial dysfunction and loss of nitric oxide bioavailability

Then the intimal medial thickness (IMT)

Eventually followed by fatty streaks, atheroma, fibroatheroma and lesion development contributing to MI and other CV events



Ther Adv Cardiovasc Dis. 2018;12(3):85-108.

Lifestyle Modification

The Diet and nutraceutical prescription

Basic nutrition:

- Macronutrients
  - Carbohydrates, fiber, fats, and protein
- Micronutrients
  - Vitamins, minerals
  - Some antioxidants
- Phytonutrients
  - Pigments and bioactive compounds
  - Antioxidant function

Setting the record straight

- Research suggests dietary cholesterol intake will not alter serum cholesterol or cardiovascular disease significantly
- Saturated fats have a minimal influence on serum lipids and CHD risk
- Monounsaturated and PUFAs have a positive effect on serum lipids and CHD risk.

The American Journal of
CLINICAL NUTRITION
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Changes in blood lipid concentrations associated with changes in intake of dietary saturated fat in the context of a healthy low-carbohydrate weight-loss diet: a secondary analysis of the Diet Intervention Examining The Factors Interacting with Treatment Success (DIETFITS) trial

Cynthia W Shih,[1] Michelle E Hauser,[2] Lucia Aronica,[2] Joseph Rigdon,[3] and Christopher D Gardner[2]

[1]Department of Health Research & Policy; [2]Stanford Prevention Research Center; and [3]Quantitative Sciences Unit, Stanford Univ
Stanford, CA

ABSTRACT

Background: For low-carbohydrate diets, a public health approach has focused on the replacement of carbohydrates with unsaturated fats. However, little research exists on the impacts of saturated fat intake on the lipid profile in the context of whole-food-based low-carbohydrate weight-loss diets.

Objectives: The primary aim of this secondary analysis of the DIETFITS weight loss trial was to evaluate the associations between changes in percentage of dietary saturated fatty acid intake (%SFA) and changes in low-density lipoproteins, high-density lipoproteins, and triglyceride concentrations for those following a healthy low-carbohydrate (HLC) diet. The secondary aim was to examine these associations specifically for HLC dieters who had the highest 12-month increases in %SFA.

Methods: In the DIETFITS trial, 609 generally healthy adults, aged 18–50 years, with body mass indices of 28–40 kg/m^2 were randomly assigned to a healthy low-fat (HLF) or HLC diet for 12 months. In this analysis, linear regression, both without and with adjustment for potential confounders, was used to measure the association between 12-month change in %SFA and blood lipids in 208 HLC participants with complete diet and blood lipid data.

Results: Participants consumed an average of 12–18% of calories from SFA. An increase of %SFA, without significant changes in absolute saturated fat intake, over 12 months was associated with

Keywords: saturated fat, low carbohydrate, cholesterol, triglycerides, human study, w adults, diet quality

Introduction

The 2015 Dietary Guidelines for Americans (DGA) recommend consuming less than 10% of daily calories from saturated fats, but more than 70% of Americans exceed this limit (1). This emphasis on limiting saturated fat intake has continued for decades based on the scientific understanding that dietary intake of saturated fatty acids (SFAs) increases plasma LDL cholesterol, whereas substituting mono- and poly-unsaturated fatty acids for SFAs reduces LDL cholesterol concentrations (2–5). However, evidence on the impact of SFAs on cardiovascular disease (CVD) risk is more nuanced than guidelines suggest. Although replacing dietary saturated fats with unsaturated fats is associated

The study received support from The European Union's Horizon 2020 Research and Innovation Programme (grant/award number 701,944). This investigation was supported by the National Institute of Diabetes and Digestive and Kidney Diseases NIH 1R01DK091831, the Nutrition Science Initiative, the National Heart, Lung, and Blood Institute NIH T32HL007034,

Conclusion: Those on a **low-carbohydrate** weight-loss diet who **increase** their percentage intake of dietary saturated fat may improve their overall lipid profile provided they focus on a high-quality diet and lower their intakes of both calories and refined carbohydrates.

Am J Clin Nutr. 2019;109(2):433-441. doi:10.1093/ajcn/nqy305

Impact of carbohydrates

Increased refined carbohydrate intake has a more important impact in changing serum lipids and lipid sub-fractions

Refined carbohydrates contribute to:

- Insulin resistance
- Artherogenic LDL
- LDL particle number
- VLDL production
- Triglycerides number
- Total HDL and HDL sub-fractions

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Why are phytochemicals important?

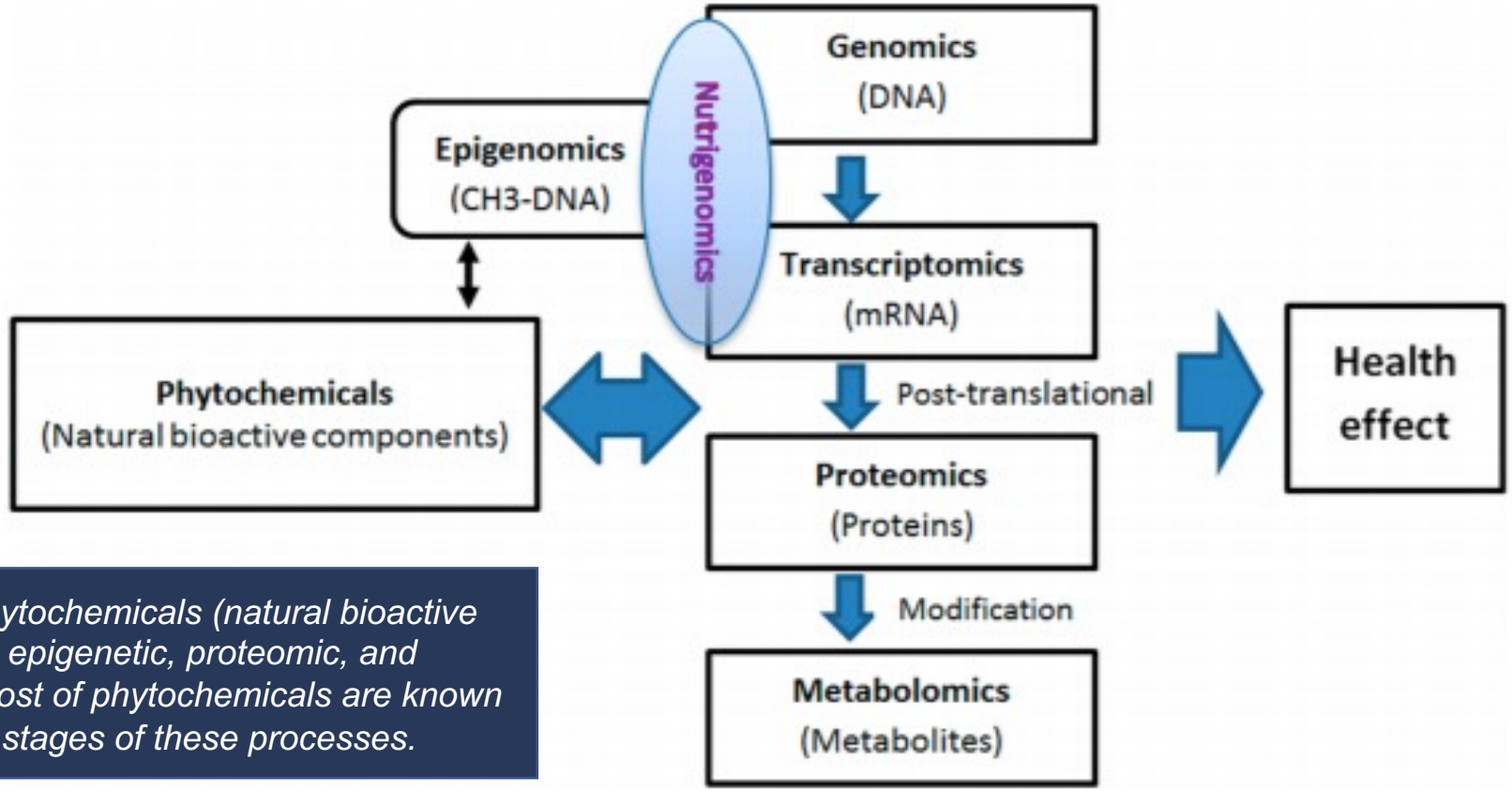


Figure 1. *Influence of phytochemicals (natural bioactive components) on genetic, epigenetic, proteomic, and metabolomic events. A host of phytochemicals are known to influence one or more stages of these processes.*

J Proteome Res. 2013

Phytochemicals sit at the interface of the microbiome, genetics, environment, lifestyle and health outcomes

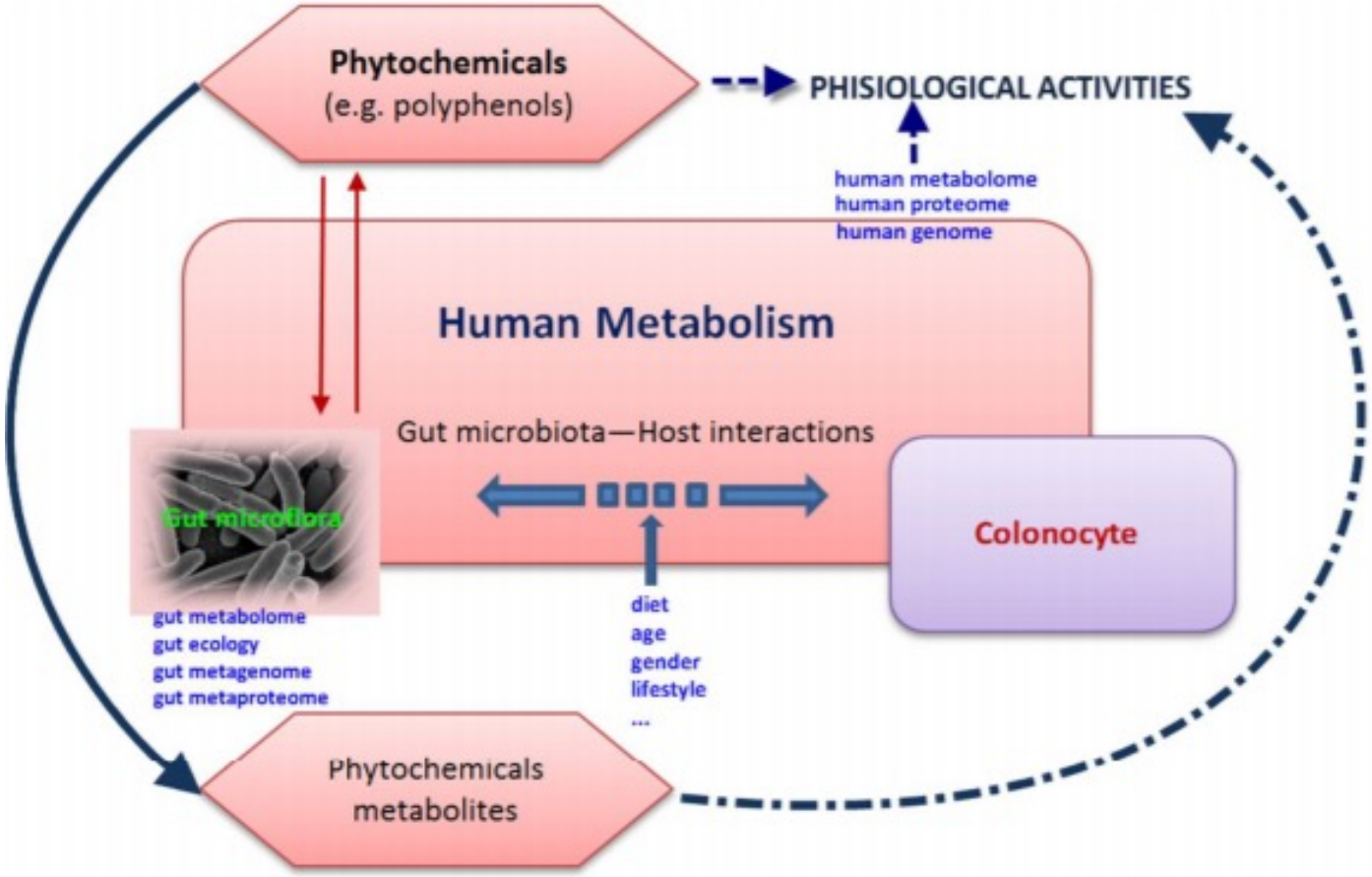


Figure 3. *Interactions between phytochemicals, gut microbiota and host as a combined contribution to human metabolism. The interplay between gut microbiota and host, and its modulation by nutrition, will benefit from the integration of information on a systems biology-wide approach.*

J Proteome Res. 2013

Biological associations

Inflammaging and metabolic factors

- Low Vit D
- Insulin resistance
- Low omega 3 index
- Altered body composition
- Elevated homocysteine/altered methylation function
- Elevated hsCRP (inflammatory marker)

Oxidative stress

- Antioxidant reserve depletion

Increased Advanced Glycation Endproducts (AGE)

- Increasing HgA1C

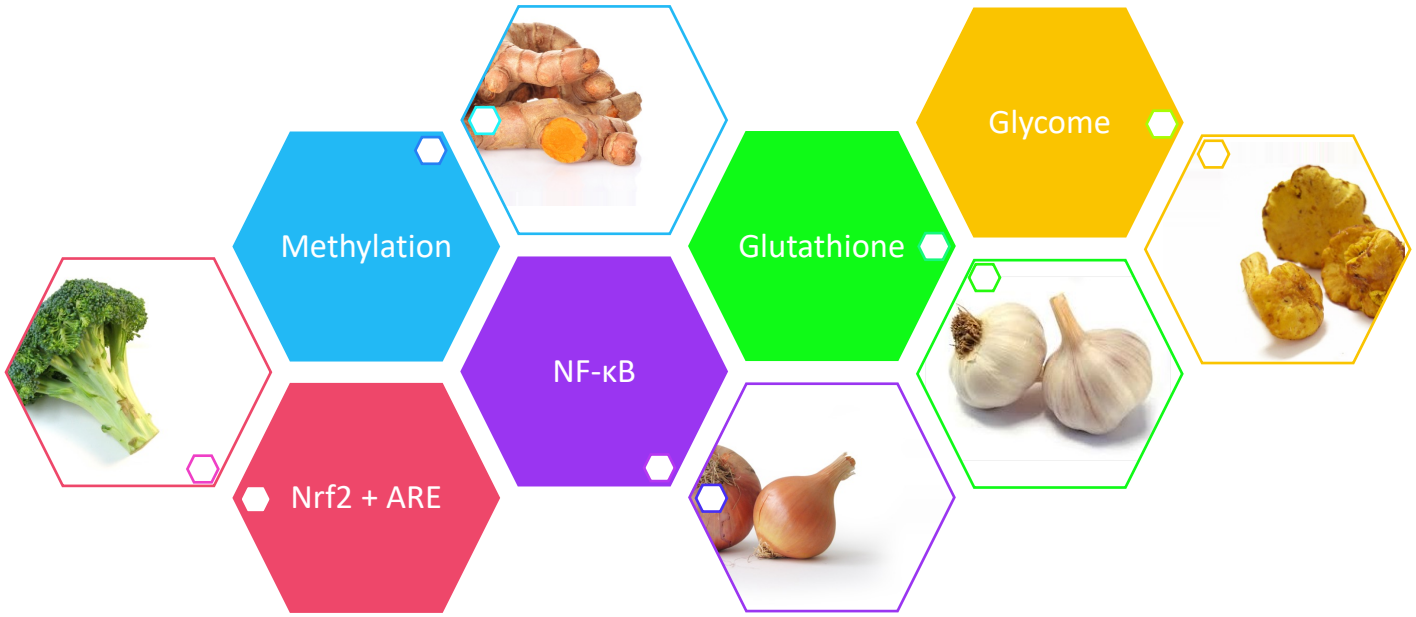
Increased production of autoantibodies

- ANA and various autoimmune process activation

Reduced immune performance

- Reduced WBC count

Targets



Enhance antioxidant reserve

Upregulate capacity to neutralize ROS

Modulate inflammation/immune response

Dietary Phytochemicals & Nrf2

Sulforophane (cruciferous veggies)

EGCG (Catechins, green tea)

Grape seed

Resveratrol

Curcumin (turmeric)

Pomegranate (ellagitannins)

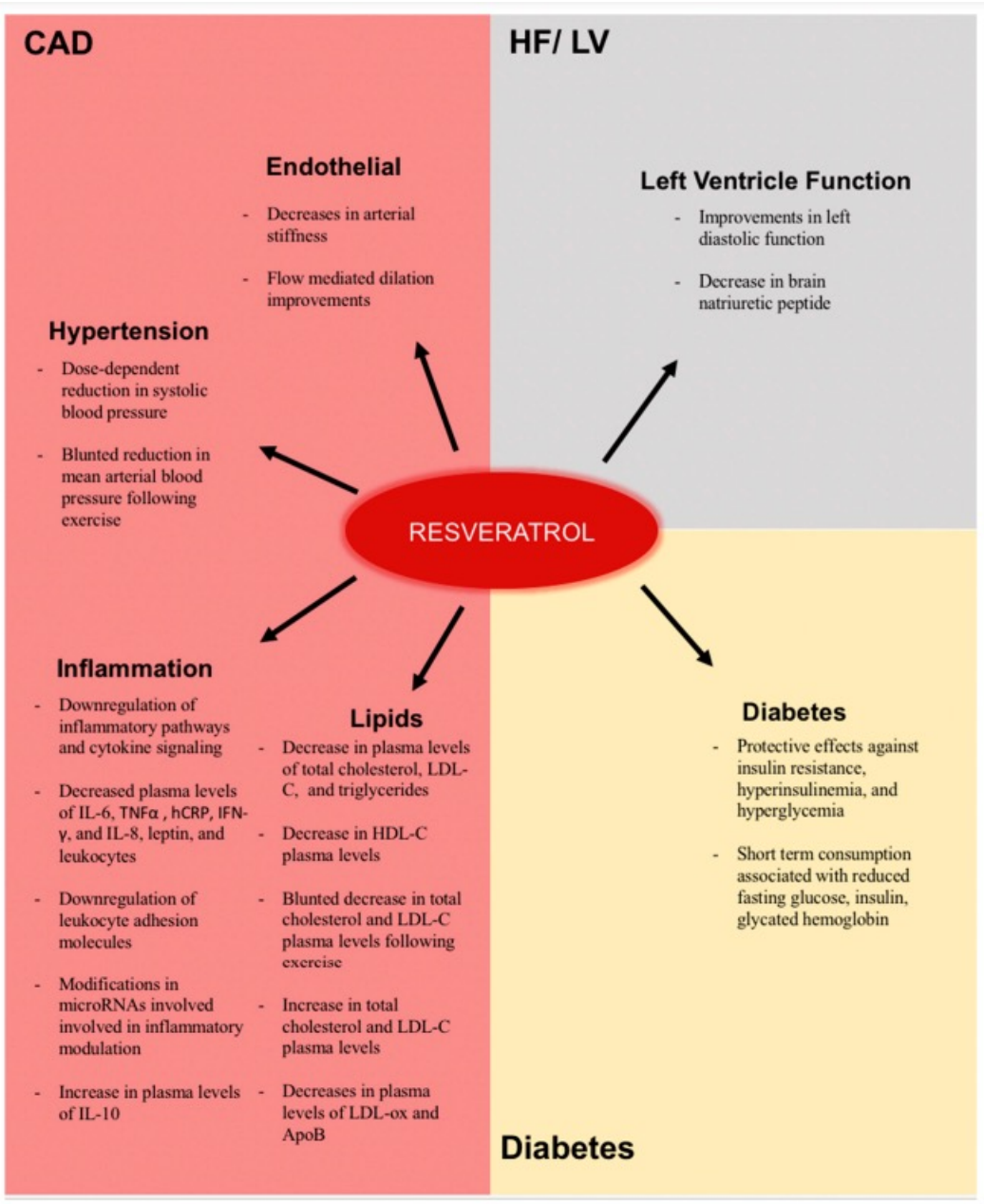
Cacao (polyphenols)

Quercetin (onions, watercress, apple and others)

Alkyl catechols (Traditionally fermented “ancient” and wood-fire smoked foods)

Crit Rev Food Sci Nutr. 2018;58(8):1260-1270

Resveratrol



Int J Mol Sci. 2019;20(4):904
Front Immunol. 2018 Dec 20;9:2992
Acta Virol. 2020;64(3):276-280

Epigallocatechin gallate (EGCG)

EGCG was found to exhibit a wide range of therapeutic properties including:

- Anti-atherosclerosis
- Anti-cardiac hypertrophy
- Anti-myocardial infarction
- Anti-diabetes
- Anti-inflammatory and antioxidant.

These therapeutic effects are mainly associated with:

- The inhibition of LDL cholesterol (anti-atherosclerosis)
- Inhibition of NF-κB (anti-cardiac hypertrophy),
- Inhibition of MPO activity (anti-myocardial infarction)
- Reduction in plasma glucose and glycated haemoglobin level (anti-diabetes)
- Reduction of inflammatory markers (anti-inflammatory)
- Inhibition of ROS generation (antioxidant).

J Ethnopharmacol. 2018;210:296-310

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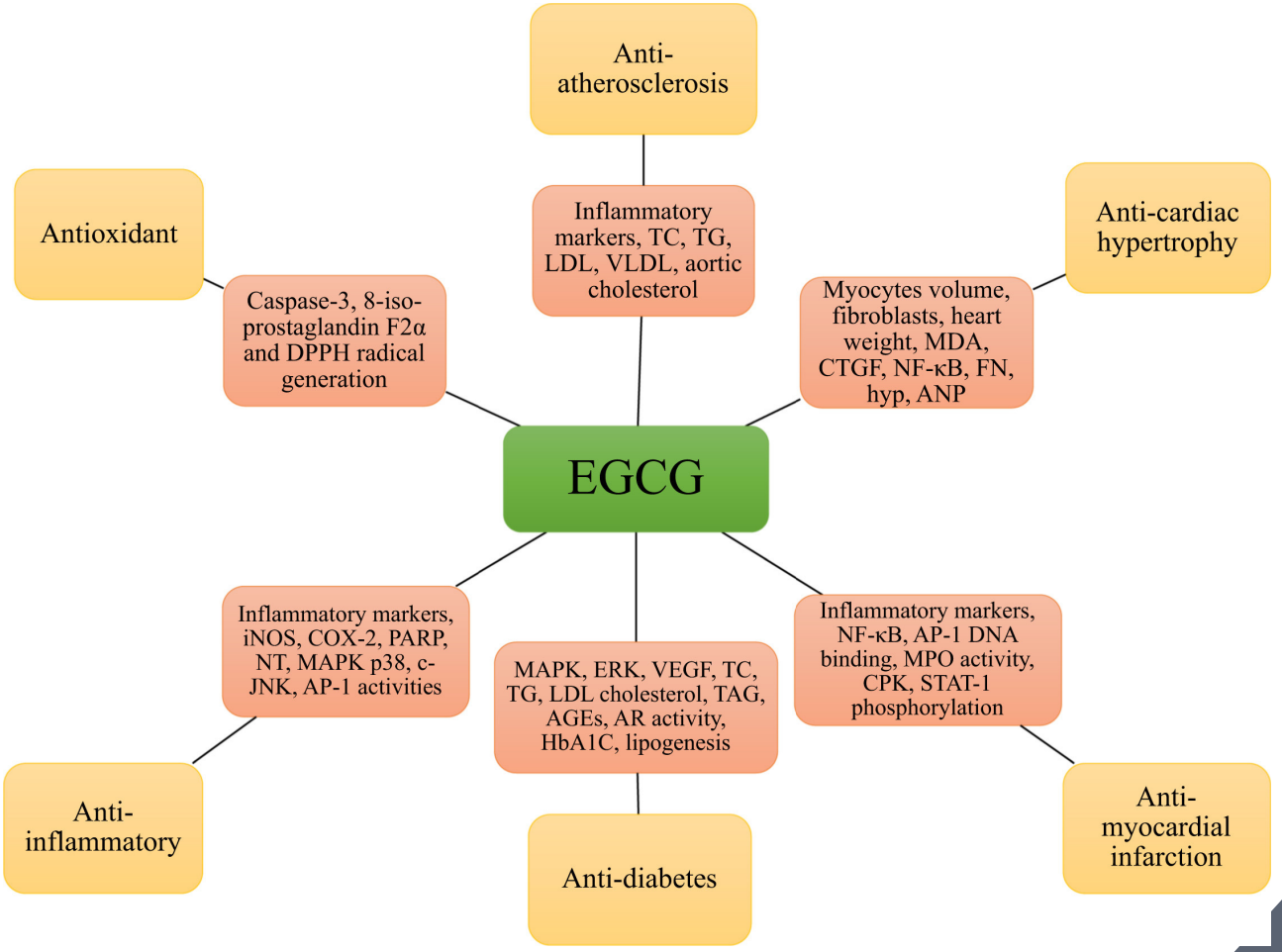
Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

Molecular understanding of Epigallocatechin gallate (EGCG) in cardiovascular and metabolic diseases

Qian Yi Eng[1], Punniyakoti Veeraveedu Thanikachalam[1], Srinivasan Ramamurthy*



J Ethnopharmacol. 2018;210:296-310

Therapeutic Diets

Dietary Recommendations

Dietary approaches to stop hypertension (DASH) diets

DASH 1 (restricting salt intake to 2300mg/day) and 2 (restricting salt intake to 1500mg/day)

- Include fruit, vegetables, whole grains, beans, fiber, low-fat dairy products, poultry, fish, seeds and nuts. Focus on intake of potassium, magnesium, and calcium sources.
- Limit red meat, sweets, and sugar-containing beverages; variable restriction in dietary sodium.

Both DASH diets reduced blood pressure within 4 weeks by 10/5 mm Hg or more, which is at least as effective as one antihypertensive medication.

The American Journal of CLINICAL NUTRITION

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Am J Clin Nutr. 2016 Feb; 103(2): 341–347.
Published online 2015 Dec 30. doi: 10.3945/ajcn.115.123281

PMCID: PMC4733264
PMID: 26718414

Comparison of the DASH (Dietary Approaches to Stop Hypertension) diet and a higher-fat DASH diet on blood pressure and lipids and lipoproteins: a randomized controlled trial[1,2,3]

Sally Chiu,[4] Nathalie Bergeron,[4,5] Paul T Williams,[4] George A Bray,[4] Barbara Sutherland,[4] and Ronald M Krauss[4,*]

HF-DASH diet significantly reduced triglycerides and large and medium very-low-density lipoprotein (VLDL) particle concentrations and increased LDL peak particle diameter compared with the DASH diet.

The DASH diet, but not the HF-DASH diet, significantly reduced LDL cholesterol, HDL cholesterol, apolipoprotein A-I, intermediate-density lipoprotein and large LDL particles, and LDL peak diameter compared with the control diet

Conclusion: The HF-DASH diet lowered blood pressure to the same extent as the DASH diet but also reduced plasma triglyceride and VLDL concentrations without significantly increasing LDL cholesterol

Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(1): 036
http://doi.org/10.31083/j.rcm2301036

Review

Overview of salt restriction in the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean diet for blood pressure reduction

Christina Filippou[1], Fotis Tatakis[1], Dimitrios Polyzos[1], Eleni Manta[1], Costas Thomopoulos[2], Petros Nihoyannopoulos[1], Dimitrios Tou

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*Correspondence: ktsioufis@hippocratio.gr (Konstantinos Tsiouf
Academic Editors: Tzung-Dau Wang, Demosthenes B Panagiotak
Submitted: 23 November 2021 Revised: 5 January 2022 Ac

Abstract

Despite considerable advances in pharmacological treatme
worldwide since elevated blood pressure (BP) adversely
pertension guidelines recommend the adoption of dietary
include salt intake reduction and a healthy diet, such as the
diet (MedDiet), independently of the underlying antihype
adults with prehypertension or hypertension are usually e
with other dietary changes. The purpose of the present rev
in the context of the DASH diet and the MedDiet. We also
when they are applied as the only intervention for BP red
mechanisms underlying their beneficial effects on BP leve

[A]lthough BP-lowering by drugs should be reserved for patients with hypertension or high cardiovascular risk and high normal BP, non-pharmacological measures, including appropriate dietary and lifestyle changes, should be implemented to all individuals irrespectively of BP levels

[…] may increase the net clinical benefit, contribute to BP control with fewer antihypertensive drugs, and exert properties independent of BP reduction, decreasing CVD risk more than expected.

[…] the DASH diet, salt restriction produces a less pronounced reduction in BP, which could be because of the overlapping mechanisms of action, resulting in a reduced capacity to lower BP with salt reduction further, when accounting for the effects of the DASH diet.

Evidence about the contribution of salt reduction in the context of the MedDiet is yet insufficient

Dietary Rx for HTN

Ensure adequate amounts of pure, filtered water everyday

Increase

- Garlic intake
- Dietary fiber
- Lycopene-rich foods
- Polyphenol-rich sources
- Flax seeds 40g/day
- Omega-3 fatty acids
- Sea vegetables

Consider avoiding caffeine (slow metabolizers CYP1A2)

- Slow metabolizers of caffeine have higher BP 8.1/5.7 mm Hg, lasting >3 hrs after consumption, tachycardia, increased aortic stiffness, higher pulse wave velocity, vascular inflammation and increased catecholamines.

Mediterranean Diet for CVD is the Gold Standard

The 4.8-year primary prevention trial (PREDIMED) demonstrated significant reductions in the rate of major CV events from MI, CVA or total CV deaths were reduced, as were onset of T2DM and hypertension.

Improvements were associated with decreases in hsCRP and interleukin-6 (IL-6) (inflammation driver)

Benefits associated with EVOO, and increased amount of omega 3 fatty acids (FAs), good omega 6 Fas, and polyphenols (such as quercetin, resveratrol and catechins)

Summary of Benefits of the MedD on CV Risk

- Lowers BP
- Improves serum lipids: lowers total cholesterol (TC), LDL, TG, increases HDL, lowers oxLDL and Lp(a), improves LDL size and lowers LDL-P to a less atherogenic profile
- Improves T2DM and dysglycemia
- Improves oxidative defense and reduces oxidative stress: F-2 isoprostanes and 8 hydroxy guanosine
- Reduces inflammation: lowers hsCRP, IL-6, soluble vascular adhesion molecule, soluble intercellular adhesion molecule
- Reduces thrombosis and factor VII after meals
- Improves BNP
- Increases nitrates/nitrites
- Improves membrane fluidity
- Reduces MI, CHD and CVA
- Reduces homocysteine

Ther Adv Cardiovasc Dis. 2018;12(3):85-108.

nutrients

MDPI

Article

Impact of a Mediterranean Dietary Pattern and Its Components on Cardiovascular Risk Factors, Glucose Control, and Body Weight in People with Type 2 Diabetes: A Real-Life Study

Marilena Vitale [1], Maria Masulli [1], Ilaria Calabrese [1], Angela Albarosa Rivellese [1], Enzo Bonora [2], Stefano Signorini [3], Gabriele Perriello [4], Sebastiano Squatrito [5], Raffaella Buzzetti [6], Giovanni Sartore [7], Anna Carla Babini [8], Giovanna Gregori [9], Carla Giordano [10], Gennaro Clemente [11], Sara Grioni [12], Pasquale Dolce [13], Gabriele Riccardi [1], Olga Vaccaro [1,*] and on behalf of the TOSCA.IT Study Group [†]

…] associated with more favorable cardiovascular risk factors profile, better glucose control and lower BMI […]

[…] emphasize the need to reinforce the importance of higher fiber, low glycemic index foods such as legumes, fruit and vegetables, wholegrain cereals, and the substitution of monounsaturated for saturated fat sources […]

Nutrients. 2018;10(8):1067.

Table 1. Spices in different culture diets.

Diet Category	Spices	Prevalence of CVD	Reference
Western diet	Spice-free with salt and sugar	11–15%	[21]
Mediterranean diet	Anise, basil, bay, cardamom, cinnamon, chervil, chilis, chives, cloves, cumin, coriander, dill, fennel, fenugreek, garlic, mace, marjoram, mint, nutmeg, oregano, peppers, rosemary, saffron, sage, savoury, sumac, tarragon and thyme.	1.5–3.2%	[3–6,22–24]
Chinese diet	Cardamom, cinnamon, cumin, cloves, peppers, nutmeg, peppercorns, fennel, star anise, garlic, ginger, peppers and chili peppers.	5%	[7,8,21]
Indian diet	Cardamom, clove, cassia, peppers, cumin, coriander, nutmeg, mustard seed, fenugreek, turmeric, saffron and garlic.	7–11%	[9,21]
Arabic diet	Saffron, peppers, allspice, turmeric, garlic, cumin, cinnamon, parsley, and coriander.	7–12%	[10,21]

The Journal of Nutrition
Nutritional Epidemiology

Paleolithic and Mediterranean Diet Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Balance in Adults[1–3]

Kristine A Whalen,[4] Marjorie L McCullough,[7] W Dana Flanders,[4–6] Terryl J Hartman,[4,6] Suzanne Judd,[8] and Roberd M Bostick[4,6]*

[4]Department of Epidemiology and [5]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, and [6]Winship Cancer Institute, Emory University, Atlanta, GA; [7]Epidemiology Research Program, American Cancer Society, Atlanta, GA; and [8]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL

Abstract

Background: Chronic inflammation and oxidative balance are associated with poor diet quality and risk of cancer and other chronic diseases. A diet–inflammation/oxidative balance association may relate to evolutionary discordance.

Objective: We investigated associations between 2 diet pattern scores, the Paleolithic and the Mediterranean, and circulating concentrations of 2 related biomarkers, high-sensitivity C-reactive protein (hsCRP), an acute inflammatory protein, and F_2-isoprostane, a reliable marker of in vivo lipid peroxidation.

Methods: In a pooled cross-sectional study of 30- to 74-y-old men and women i
population (n = 646), we created diet scores from responses on Willett food-freq
plasma hsCRP and F_2-isoprostane concentrations by ELISA and gas chromatograp
Both diet scores were calculated and categorized into quintiles, and their associations
estimated with the use of general linear models to calculate and compare adjusted ge
ordinal logistic regression.

Results: There were statistically significant trends for decreasing geometric mean plasma hsCRP and F_2-isoprostane concentrations with increasing quintiles of the Paleolithic and Mediterranean diet scores. The multivariable-adjusted ORs comparing those in the highest with those in the lowest quintiles of the Paleolithic and Mediterranean diet scores were 0.61 (95% CI: 0.36, 1.05; P-trend = 0.06) and 0.71 (95% CI: 0.42, 1.20; P-trend = 0.01), respectively, for a higher hsCRP concentration, and 0.51 (95% CI: 0.27, 0.95; P-trend 0.01) and 0.39 (95% CI: 0.21, 0.73; P-trend = 0.01), respectively, for a higher F_2-isoprostane concentration.

Conclusion: These findings suggest that diets that are more Paleolithic- or Mediterranean-like may be associated with lower levels of systemic inflammation and oxidative stress in humans. *J Nutr* 2016;146:1217–26.

CONCLUSION: These findings suggest that diets that are more Paleolithic- or Mediterranean-like may be associated with lower levels of systemic inflammation and oxidative stress in humans.

J Nutr 2016;146:1217-26
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4877627/

Circulation

ORIGINAL RESEARCH ARTICLE

Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile

CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet)

Editorial, see p 1114

BACKGROUND: Only a few randomized dietary intervention studies that investigated the effects of lacto-ovo vegetarian diet (VD) in clinically healthy omnivorous subjects are available.

METHODS: We randomly assigned to overweight omnivores with a low-to-moderate cardiovascular risk profile a low-calorie VD compared with a low-calorie Mediterranean diet (MD), each lasting 3 months, with a crossover design. The primary outcome was the difference in body weight, body mass index, and fat mass changes between the 2 groups. Secondary outcomes were differences in circulating cardiovascular disease risk parameters changes between the 2 groups.

Francesco Sofi, MD, PhD
Monica Dinu, MSc, PhD
Giuditta Pagliai, MSc
Francesca Cesari, MSc, PhD
Anna Maria Gori, MSc
Alice Sereni, MSc
Matteo Becatti, MSc, PhD
Claudia Fiorillo, MSc, PhD
Rossella Marcucci, MD, PhD
Alessandro Casini, MD

Clinical Perspective

What Is New?

- To date, this randomized controlled trial is the first study assessing the effects of a lacto-ovo vegetarian diet (VD) compared with a Mediterranean diet (MD) in the same cohort of omnivorous subjects living in a low-risk country for cardiovascular disease.
- After 3 months of dietary intervention, both VD and MD were effective in reducing body weight, body mass index, and fat mass, with no significant differences between them.
- The VD significantly reduced low-density lipoprotein cholesterol, vitamin B_{12}, and uric acid levels, whereas only the MD showed the potential to improve triglycerides and interleukin-17 levels.

What Are the Clinical Implications?

- Our findings suggest that in the context of behavioral counseling that promotes a reduced caloric intake, VD and MD determine similar reduction in body weight and fat mass.
- The present results suggest that following a VD leads to a significant reduction in low-density lipoprotein cholesterol, whereas the MD could be more effective in reducing triglyceride levels.
- This work could improve the awareness of the general population that both VD and MD may help in reducing cardiovascular disease risk factors.

Circulation. 2018;137(11):1103-1113

Calorie Restriction and Fasting

Calorie Restriction (CR)

- Control/limit the number of calories consumed on a daily basis

Time Restricted Eating (TRE)

- Limiting the time range during which food is consumed to 6–12 h
- Goal to optimize nutrient utilization and storage, and minimize the potentially harmful byproducts of biological reactions

Intermittent Fasting (IF)

- Regular cycles of fasting for 48 hrs or less.
- There are several different IF methods, all of which split the day or week into eating periods and fasting periods.
- Consists of water fasting or eating a severely calorie-restricted diet for 1–2 days/week, ex 5:2 diet, consisting of 5 days/week of normal eating and 2 days/week of caloric restriction (500– 600 kcal intake/day)

Alternate day fasting (ADF)

- A sub-category of IF, in which days of low-calorie consumption or complete fasting alternate with days of *feasting* (> 100% of necessary caloric intake)

Periodic water-only fasting (PF)

- **C**onsists of total food restriction for several days (only water)

Fasting-mimicking diets (FMDs)

- Developed to match or surpass the effects of PF while reducing side effects.
- Low protein, high in healthy fats, and containing complex carbohydrates, as well as essential vitamins and minerals—mimic the effects of fasting in part by decreasing insulin and glucose and increasing IGFBP1 and ketone bodies

Curr Diab Rep. 2020;20(12):83

nutrients

MDPI

Review

Intermittent Fasting in Cardiovascular Disorders—An Overview

Bartosz Malinowski [1,*], Klaudia Zalewska [1], Anna Węsierska [1], Maya M. Sok
Maciej Socha [2], Grzegorz Liczner [1], Katarzyna Pawlak-Osińska [3] and Michał

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Received: 12 February 2019; Accepted: 18 March 2019; Published: 20 March 2019

Abstract: Intermittent fasting is a form of time restricted eating (typically 16 h f
which has gained popularity in recent years and shows promise as a possible
approach to weight loss and the reduction of inflammation, and has many pote
benefits. In this review, the authors will incorporate many aspects of fasting,
its effects on the cardiovascular system, involving atherosclerosis progression, benefits for diabetes mellitus type 2, lowering of blood pressure, and exploring other cardiovascular risk factors (such as lipid profile and inflammation).

metabolic switch to of glucose to ketone as fuel, improving body composition and has a positive influence on lipid profile parameters (reduces total cholesterol, triglycerides, and LDL cholesterol)

reducing the concentration of inflammatory markers, such as IL-6, homocysteine, and CRP

increase of BDNF factor, which results in lowering the systolic and diastolic blood pressure by activating the parasympathetic system

improves glucose metabolism and increases the sensitivity of tissues to insulin by increasing the B cells of the pancreatic islets

Fasting is not recommended for people with hormonal imbalances, pregnant and breastfeeding women, and some uncontrolled diabetics. Avoid in eating disorders, when BMI < 18.5.

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Current Diabetes Reports (2020) 20: 83
https://doi.org/10.1007/s11892-020-01362-4

MACROVASCULAR COMPLICATIONS IN DIABETES (VS ARODA AND L-S CHANG, SECTION EDITORS)

Periodic and Intermittent Fasting in Diabetes and Cardiovascular Disease

Annunziata Nancy Crupi[1] · Jonathan Haase[1] · Sebastian Brandhorst[1] · Valter D Longo[1,2]

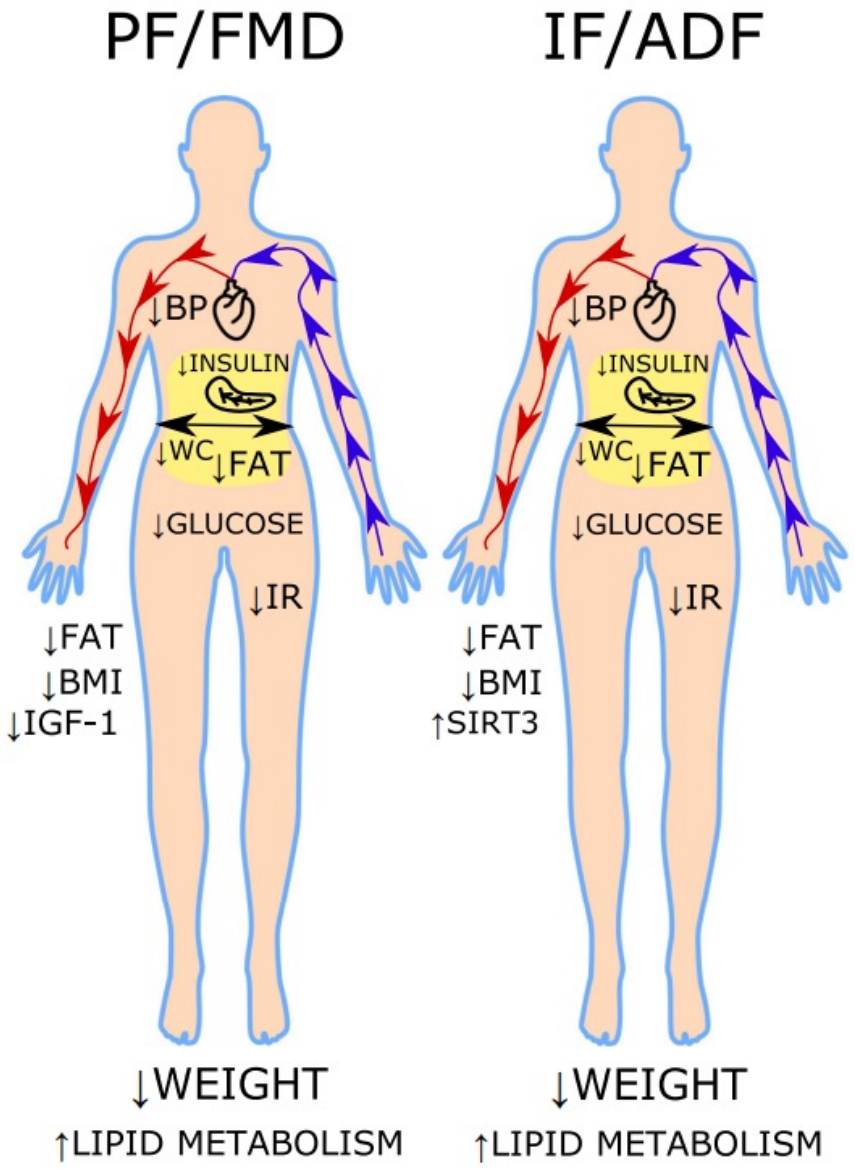
Accepted: 26 October 2020 / Published online: 10 December 2020

Abstract

Purpose of Review Cardiovascular disease (CVD) is one of the leading causes of death globally. Nutrition plays a central role in CVD risk by affecting aging, adiposity, glycemia, blood pressure, cholesterol, inflammation, and other risk factors and can affect CVD risk not only based on calorie intake and dietary composition but also the timing and range of meals. This review evaluates the effects of fasting, fasting-mimicking diets, and time-restricted eating on the reduction of CVD risk factors and provides initial data on their potential to serve as CVD prevention and treatment therapies.

Recent Findings Intermittent fasting (IF), time-restricted eating (TRE), prolonged fasting (PF), and fasting-mimicking diets (FMD) show promise in the reduction of CVD risk factors.

Summary Results on IF, TRE, PF, and FMD on CVD risk factors are significant and often independent of weight loss, yet long-term studies on their effect on CVD are still lacking. Coupling periodic and prolonged, or intermittent and more frequent cycles of fasting or fasting-mimicking diets, designed to maximize compliance and minimize side effects, has the potential to play a central role in the prevention and treatment of CVD and metabolic syndrome.



Which diet do you choose?

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General dietary & lifestyle recommendations to reduce CV Risk

Dietary Recommendations

- Reduce or eliminate refined carbohydrate intake, increase fiber
- Avoid sugar substitutes
- Avoid hydrogenated vegetable oils, focus on anti-inflammatory fats
- Include sources of high-quality protein
- Focus on EVOO, nuts/seeds, garlic, “eat the rainbow”, herbs & spices, green tea, red wine (in moderation) and fermented foods
- Practice cooking techniques that reduce AGE (“slow & wet”)

Lifestyle Recommendations

- Improve body composition (muscle mass)
- Exercise/movement
- Practice stress reduction techniques
- Reduce or eliminate alcohol
- Focus on sleep hygiene (and consistency)
- Reduce exposure to toxins (especially heavy metals, endocrine disruptors, glyphosate)
- Avoid tobacco (including e-cigs)

Cardiometabolic Nutritional focus

Macronutrients

- Protein 30% of total calories
- Fat 30% of total calories
  - MUFAs, PUFAs O3/O6/O9
  - Modest saturated fats
- Carbs 40% of total calories
  - Beta-glucans and psyllium

Micronutrients

- Sodium restriction
- Potassium
- Magnesium
- Zinc
- B6
- Vit C
- Vit D3
- Vit E (mixed tocopherols)

Active Compounds (nutraceutical targets)

- AA
  - Arginine, carnitine, taurine
- ALA
- CoQ10
- Melatonin
- Transresveratrol
- Grape seed extract

Nutraceutical Options

The CM Workhorses

Berberine

Fish oil

Magnesium

Efficacy of Berberine Alone and in Combination for the Treatment of Hyperlipidemia: A Systematic Review

Journal of Evidence-Based Complementary & Alternative Medicine
2017, Vol. 22(4) 956-968

DOI: 10.1177/2156587216687695
journals.sagepub.com/home/cam
SAGE

Laura M. Koppen, PharmD[1], Andrea Whitaker, PharmD[2], Audrey Rosene, PharmD[3], and Robert D. Beckett, PharmD, BCPS[4]

Abstract

The objective of this review is to identify, summarize, and evaluate clinical trials of berberine for the treatment of hyperlipidemia and other dyslipidemias. A literature search for randomized, controlled trials of berberine that assessed at least 2 lipid values as endpoints resulted in identification of 12 articles that met criteria. The majority of evaluated articles consistently suggest that berberine has a beneficial effect on low-density lipoprotein (reduct
triglycerides (reductions ranging from approximately 25 to 55 mg/dL)
precision in their endpoints, description of blinding, transparency in
medications. Berberine could serve as an alternative for patients who a
therapy but who are open to alternative treatments, and for low-risk

Keywords

berberine, hyperlipidemia, low-density lipoprotein, triglycerides

Received May 23, 2015. Accepted for publication December 9, 2016.

Berberine could serve as an alternative for patients who are intolerant to statins, patients resistant to starting statin therapy but who are open to alternative treatments, and for low-risk patients not indicated for statin therapy.

Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 285–292
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression

Hao Zhang[a,1], Jing Wei[b,1], Rong Xue[c,1], Jin-Dan Wu[b], Wei Zhao[c], Zi-Zheng Wang[b], Shu-Kui Wang[b], Zheng-Xian Zhou[c], Dan-Qing Song[a], Yue-Ming Wang[a], Huai-Ning Pan[b], Wei-Jia Kong[a,*], Jian-Dong Jiang[a,*]

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Received 23 March 2009; accepted 28 July 2009

Abstract

Our previous work demonstrated that berberine (BBR) increases insulin recepto
vitro and in animal models. Here, we study the InsR–up-regulating and glucose-lo
that BBR increased InsR messenger RNA and protein expression in a variety of
HT1080, 293T, and hepatitis B virus–transfected human liver cells. Accordingly
and Akt were increased after BBR treatment in cultured cells. In the clinical st
(FBG), hemoglobin A_{1c}, triglyceride, and insulin levels in patients with type 2 diab
lowering efficacies of BBR were similar to those of metformin and rosiglitazone. In the BBR-treated patients, the percentages of peripheral blood lymphocytes that express InsR were significantly elevated after therapy. Berberine also lowered FBG effectively in chronic hepatitis B and hepatitis C patients with T2DM or impaired fasting glucose. Liver function was improved greatly in these patients by showing reduction of liver enzymes. Our results confirmed the activity of BBR on InsR in humans and its relationship with the glucose-lowering effect. Together with our previous report, we strongly suggest BBR as an ideal medicine for T2DM with a mechanism different from metformin and rosiglitazone.

Berberine upregulates GLUT4 transporters it increases Insulin receptor expression and improves glucose lowering effects

Metabolism. 2010;59(2):285-292

Berberine Summary

Benefit on blood sugar control related to multiple mechanism including improved insulin sensitivity

Established efficacy in addressing dyslipidemia

Useful in patients with high cholesterol in the absence or presence of elevated BS, A1C, insulin

Other CV risk reduction agents: Icosapent Ethyl

Icosapent Ethyl (REDUCE-IT trial)

Prior AHA guidelines suggested 1g of EFA for all CV risk patients, later deemed “unnecessary” with other advancements in interventional and pharmaceutical therapy (and mixed data results)

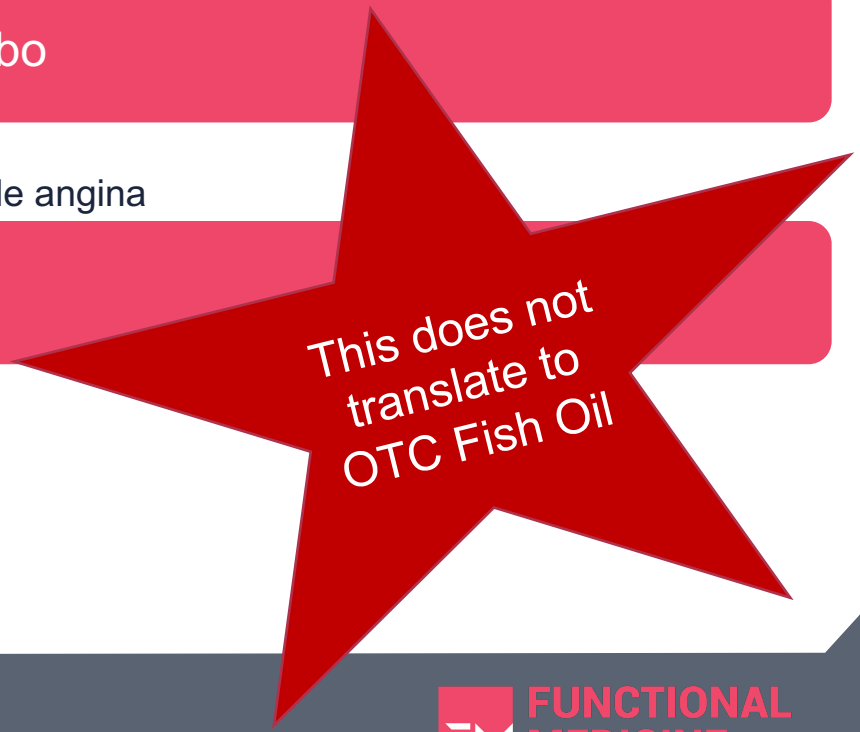
REDUCE-IT trial published in 2019 demonstrated potential efficacy (might be time to revaluate)

Omega-3 (in the form of icosapent ethyl) 4 grams daily vs placebo

- 8179 patients (age ≥ 45 w/ CVD or ≥ 50 w/ DM + RF)
- Primary endpoint: CV death, MI, stroke, coronary revascularization, or unstable angina

Inclusion Criteria

- ~70% were secondary prevention of ASCVD
- TG 200-499* mg/dL
- LDL 41- 100 mg/dL
- Stable dose statin x 4 weeks



Bhatt DL, et al. N Engl J Med 2019;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10

REDUCE-IT Primary Endpoint Outcomes

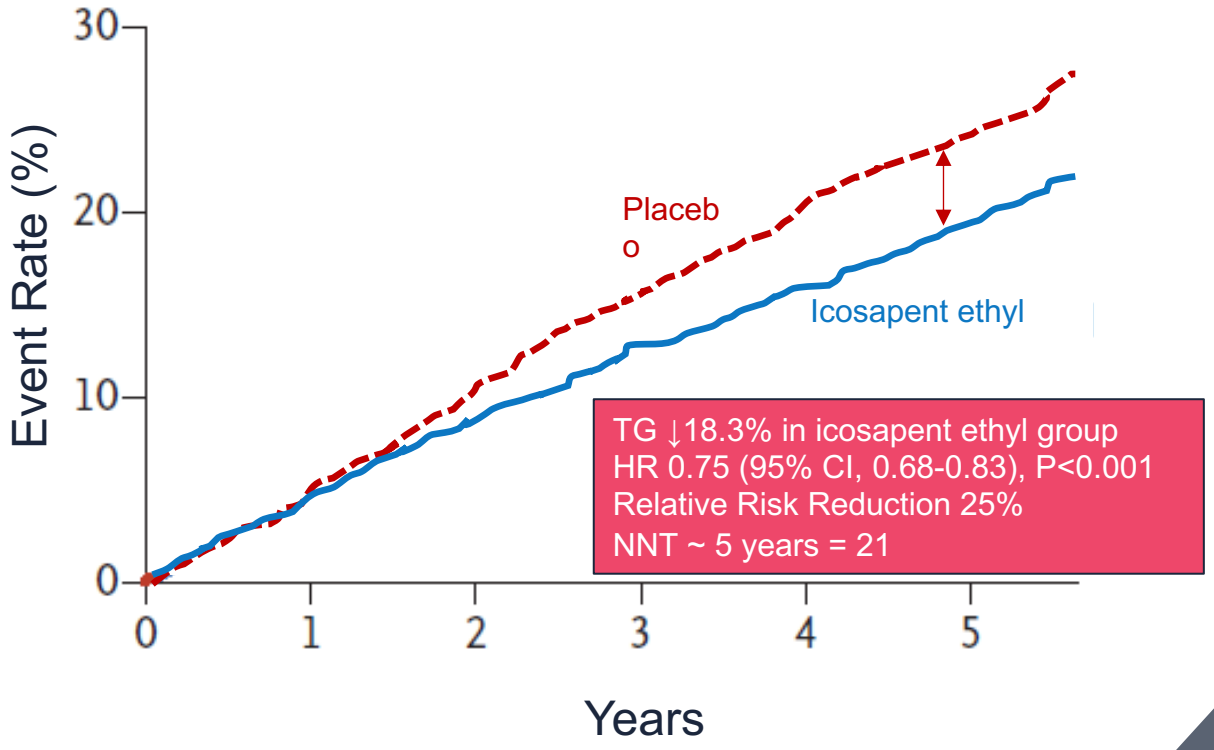
Statistically significant improvement in primary endpoint:

- 17.2% on omega-3 vs 22.0% on placebo
- Absolute Risk Reduction: 4.8% (better some of the PSK9 trials)
- Relative RR: 25%
- Number Needed to Treat for 4.9 yrs = 21 (excellent)

Challenges

- Cost

Can OTC EFAs be useful in the same capacity?



Bhatt DL, et al. N Engl J Med 2019;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10

American Journal of Therapeutics 23, e905–e910 (2016)

Eicosapentaenoic Acid Versus Docosahexaenoic Acid as Options for Vascular Risk Prevention: A Fish Story

Sarabjeet Singh, MD, PA-C, RDMS,[1]* Rohit R. Arora, MD, FACC,[2]
Mukesh Singh, MD,[3] and Sandeep Khosla, MD, FACC[3]

Vascular inflammation is a key component involved in the process of arthrosclerosis, which in turn increases the risk for cardiovascular injury. In the last 10 years, there have been many trials that looked at omega-3 fatty acids as a way to reduce cardiovascular risk. These trials observed the effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the traditional lipid panel and found that both EPA and DHA reduce triglyceride (TG) level and increase high-density lipoprotein cholesterol (HDL-C) levels but also increase the low-density lipoprotein cholesterol (LDL-C) levels. In the 2 more recent trials, the MARINE and ANCHOR, EPA was given as an adjunct therapy to high-ri
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these 2 trials not only showed reduction in cardiovascular risk because of
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acid is superior to the other. Data search for omega-3 fatty acids and cardi
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on the effect seen in the lipid panel. The first 7 studies looked at the effects
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The benefit might not be as strong on the surrogate markers of CV risk (LDL, TG, etc..) however it **impacts inflammatory markers, improves lipid QUALITY, and addresses the underlying risk factor of glycemic control**

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Review > Curr Pharm Biotechnol. 2006 Dec;7(6):467-82. doi: 10.2174/138920106779116856.

Essential Fatty acids – a review

Undurti N Das [1]

Affiliations + expand

PMID: 17168664 DOI: 10.2174/138920106779116856

EFAs and their metabolites may function as endogenous angiotensin converting enzyme and HMG-CoA reductase inhibitors, nitric oxide enhancers, anti-hypertensives, and anti-atherosclerotic molecules.

EFAs react with nitric oxide (NO) to yield respective nitroalkene derivatives that have cell-signaling actions via ligation and activation of peroxisome proliferator-activated receptors (PPARs).

Abstract

Essential fatty acids (EFAs): cis-linoleic acid (LA) and alpha-linole
humans and their deficiency is rare in humans due to their easy availability in diet. EFAs are metabolized to their respective long-chain metabolites: dihomo-gamma-linolenic acid (DGLA), and arachidonic acid (AA) from LA; and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA. Some of these long-chain metabolites form precursors to respective prostaglandins (PGs), thromboxanes (TXs), and leukotrienes (LTs), lipoxins (LXs) and resolvins. EFAs and their metabolites may function as endogenous angiotensin converting enzyme and HMG-CoA reductase inhibitors, nitric oxide enhancers, anti-hypertensives, and anti-atherosclerotic molecules. EFAs react with nitric oxide (NO) to yield respective nitroalkene derivatives that have cell-signaling actions via ligation and activation of peroxisome proliferator-activated receptors (PPARs). In several diseases such as obesity, hypertension, diabetes mellitus, coronary heart disease, alcoholism, schizophrenia, Alzheimer's disease, atherosclerosis, and cancer the metabolism of EFAs is altered. Thus, EFAs and their derivatives have significant clinical implications.

Original research

Omega-3 for the prevention of cardiovascular diseases: meta-analysis and trial-sequential analysis

Maria Francesca Cabiddu[1], Alberto Russi[2], Lucia Appolloni[3], Daniele Mengato[4], Marco Chiumente[5]

Author affiliations +

Abstract

Objectives The effectiveness of omega-3 fatty acids (PUFAs) in cardiovascular diseases (CVD) remains a matter of debate. The aim of this work was to evaluate PUFAs in the reduction of cardiovascular mortality in primary and secondary prevention of CVD to determine if further original studies are needed or the available data can be considered conclusive.

Methods A meta-analysis was performed according to a dichotomous endpoint followed by a trial-sequential analysis (TSA). Clinical data were identified through a PubMed search based on the following keywords: omega-3 fatty acids; cardiovascular disease; death; and cardiovascular risk. The clinical trials identified by this procedure were subjected to standard meta-analysis and TSA.

Results and conclusions A total of 11 randomised studies for 100 609 patients were analysed. Our meta-analysis showed a statistically significant reduction in mortality due to cardiovascular issues (RR=0.937; 95% CI: 0.88 to 0.98; P=0.018). The TSA indicated that no further trials are needed to better evaluate the efficacy of PUFAs in preventing death related to CVD.

European Journal of Hospital Pharmacy Published Online First: 16 June 2020.
https://ejhp.bmj.com/content/early/2020/06/15/ejhpharm-2020-002207

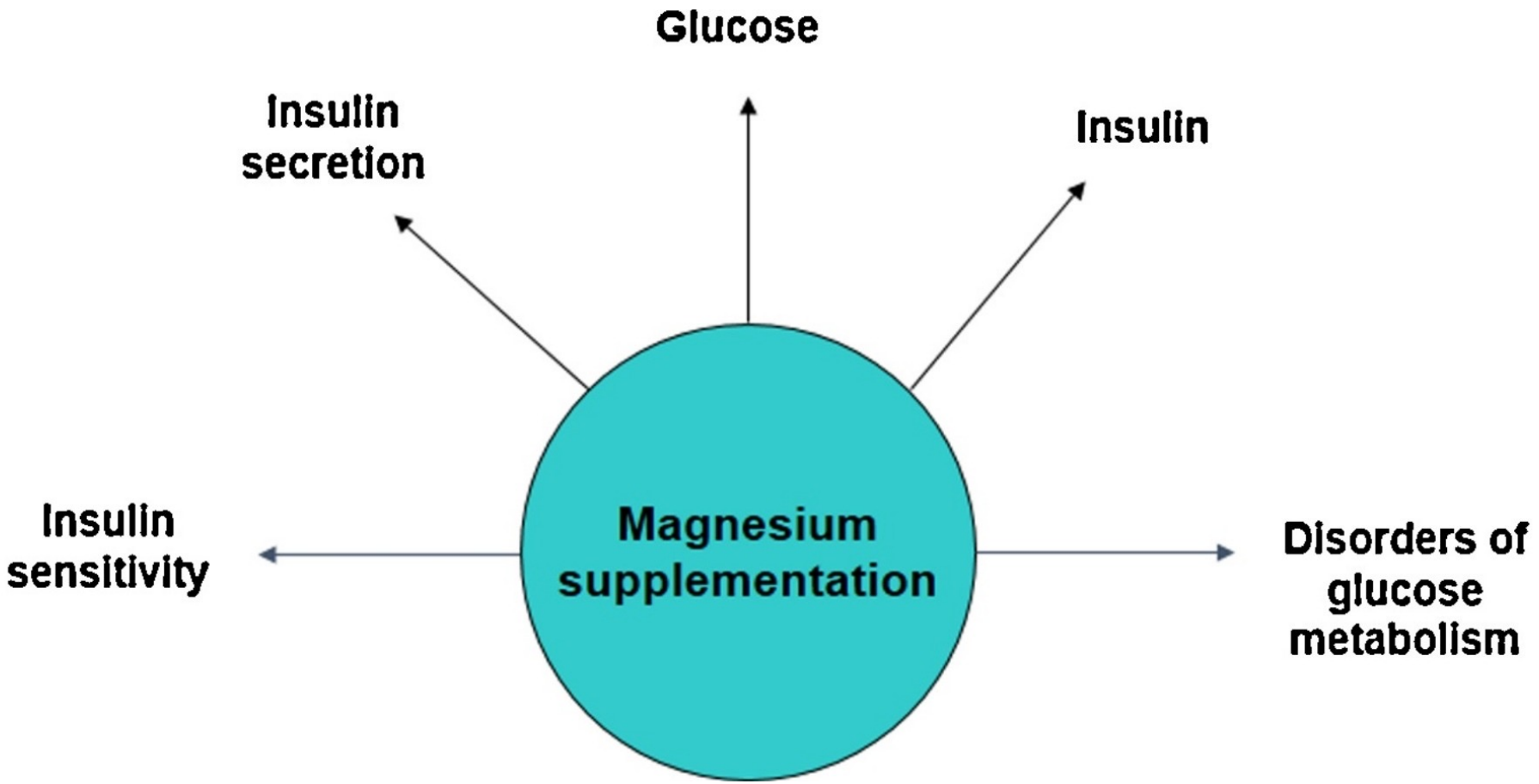
Omega-3 Fatty Acids

Benefit might be the synergistic benefit on various CV end-points, including inflammation, blood sugar control, endothelial functions/stability, and obesity

Target dosage 2 – 3 grams/d and Omega-3 index of 8% or higher

PLoS One. 2015;10(11):e0142652
BMC Cardiovasc Disord. 2012;12:77
PLoS One. 2012;7(9):e46028

Magnesium supplementation and BS control



Nutrients. 2018;11(1):44.
Pharmacol Res. 2016;111:272-282. doi:10.1016/j.phrs.2016.06.019

Magnesium in HTN

Mechanism

- Diuretic
- Vasodilator
- Calcium channel blocker

Dietary intake:

- A high dietary intake of 500 – 1000 mg per day reduces blood pressure (demonstrated by clinical trials)

Dose

- Oral 240 mg to 600 mg/day safely reduces BP in medicated and unmedicated hypertensives

Monitoring

- RBC magnesium is more accurate in assessing total body magnesium

Taurine

- Enhance by adding 1000 – 2000 mg/d of taurine

Nutrients. 2021;13(1):195
I Kohlstadt. *Advancing Medicine with Food and Nutrients*, 2nd Edition. 2011.

Other Nutraceutical Considerations

(besides EFA, Mg & berberine)

Dyslipidemia

- Bergamot
- Niacin (250mg/day +)
- Phytosterols
- Red Yeast Rice (2400-4800 mg/day)
- Tocotrienols (250mg/day)
- Resveratrol
- CoQ10

Hypertension

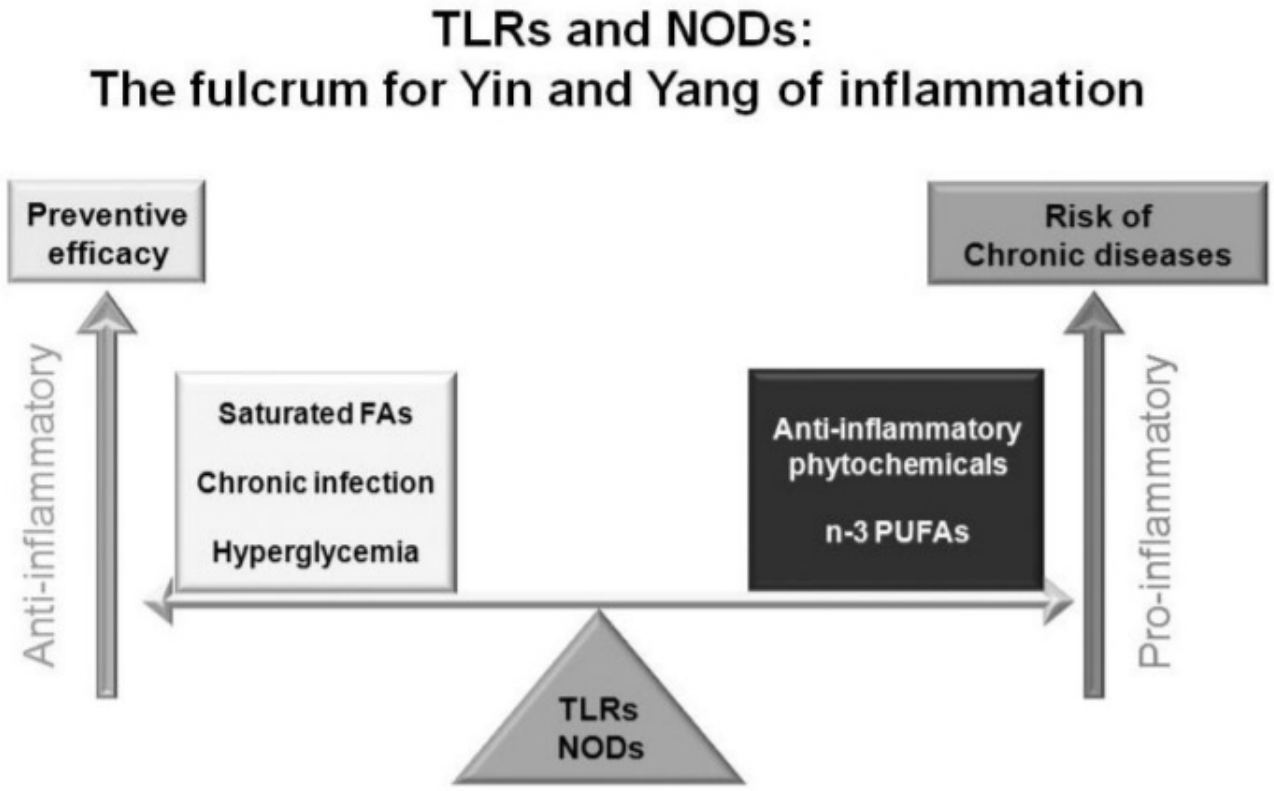
- Potassium
- Amino acids (Arg, Cit, Tau)
- Vitamin B6
- Vitamin D
- Zinc
- CoQ10
- Hawthorn berry
- Garlic extract

Dysglycemia

- Pro/pre-biotics
- Vitamin D
- ALA
- American ginseng *(Panax quinquefolius)*
- Chromium
- Cinnamon

Several dietary and nutritional components have been shown to interrupt the inflammatory vascular receptors (PRRs, NLRs and TLRs)

- Curcurmin (turmeric)
- Cinnamaldehyde (cinnamon)
- Sulforaphane
- Resveratrol
- Epigallocatechin gallate (EGCG)
- Luteolin
- Quercetin



Ther Adv Cardiovasc Dis. 2018;12(3):85-108
Nutr Rev. 2011;69(6):310-320

Lifestyle Modification Counseling Recommendations

Exercise

- Aerobic training
- Resistance training

Weigh reduction

- Target BMI <25
- Weight circumference W <35 inches M < 40 inches
- Total body fat W < 22% and M < 16%

Sleep

- Rule out sleep apnea
- Refer for sleep oral appliance or CPAP
- https://my.clevelandclinic.org/health/treatments/21129-oral-appliance-therapy-for-sleep-apnea

Alcohol restriction/reduction

Caffeine restriction, tobacco cessation, and other stimulants

What’s our role in patient management?

FUNCTIONAL MEDICINE
Continuing Education

In Summary

1. Pharmacists can play an integral role in improving patient outcomes using an evidenced-based Functional approach CM management
2. ACC/AHA guidelines include lifestyle modification as first line therapy in addition to high intensity statin therapy. A comprehensive approach involves addressing oxidative stress, inflammation, and insulin resistance
3. Evidence-based recommendations for diet and nutraceuticals can improve CV outcomes especially in the medication hesitant
4. Various nutrient and herbal interventions have proven efficacy in CM disease due to synergistic properties of the pathophysiology
5. MedD and the DASH diet have the most substantial evidence for improving dyslipidemia and CVD end points

Thank you!

Lara Zakaria PharmD MS CNS CDN IFMCP

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lara zakaria

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FUNCTIONAL MEDICINE
Continuing Education