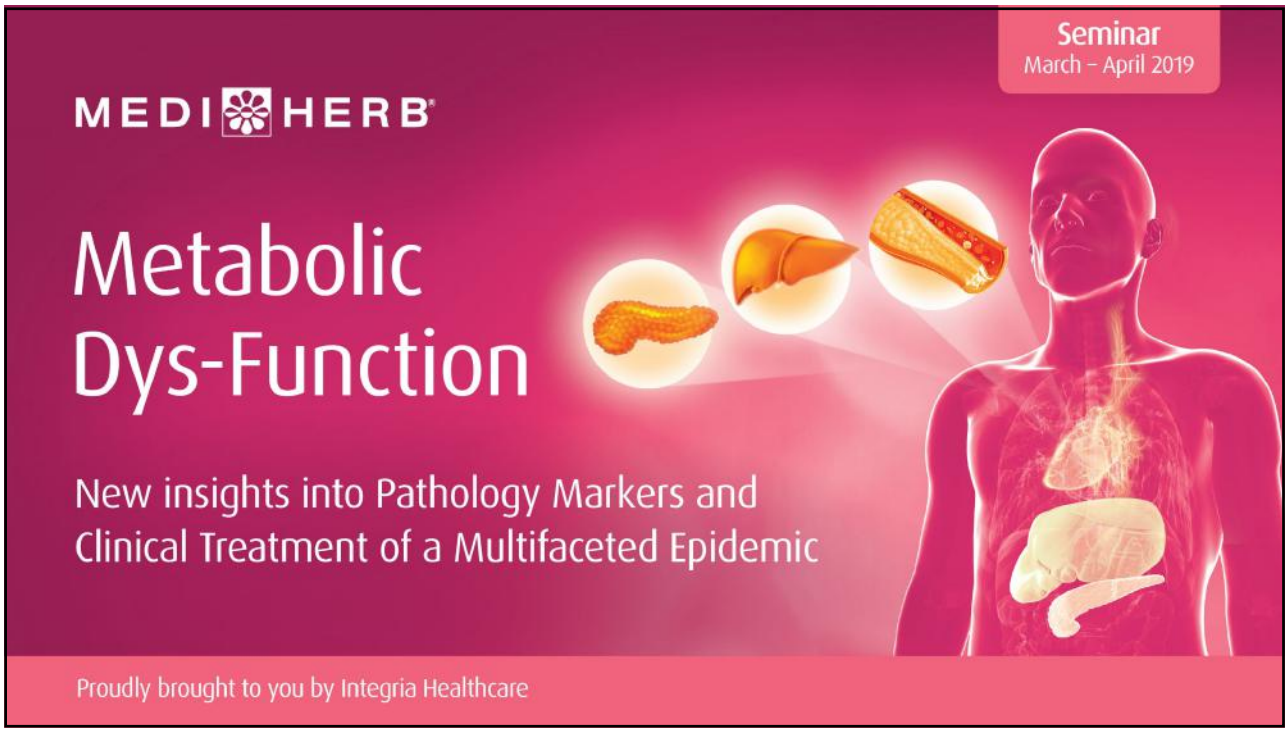
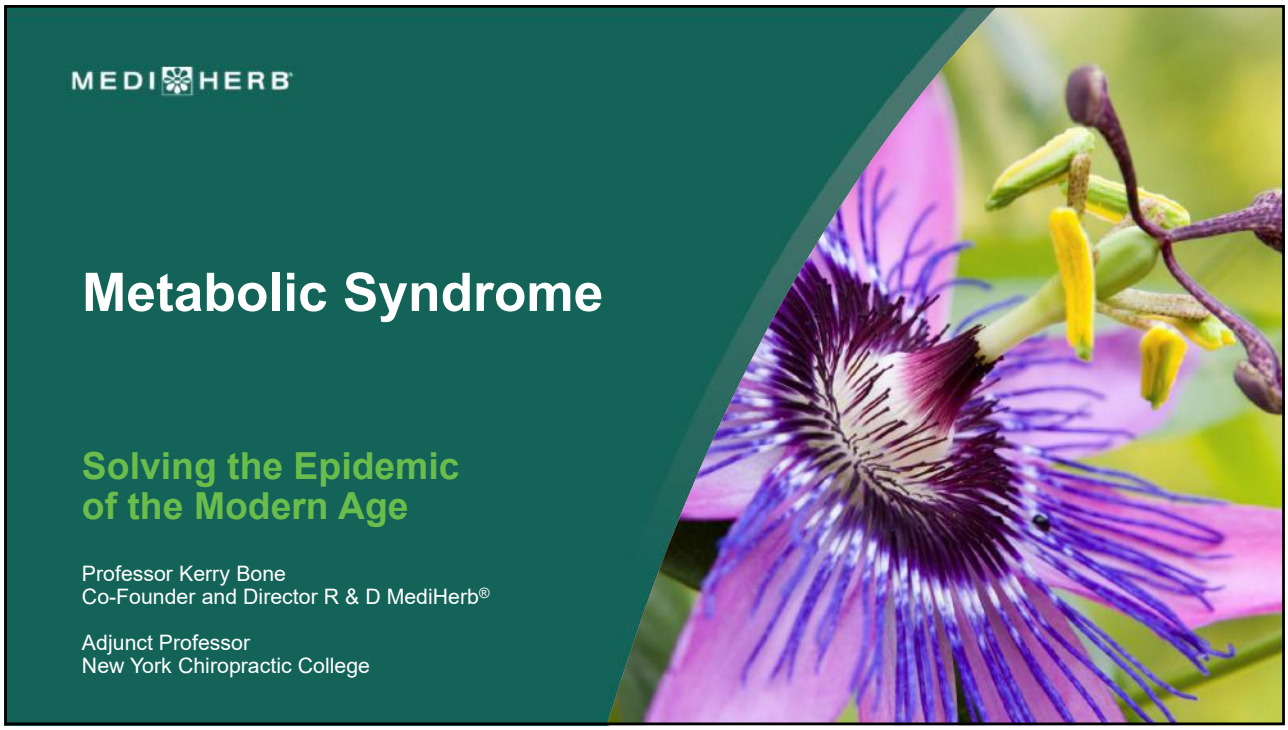




Our Topics

- Defining metabolic syndrome (MetS) and its comorbidities
- What causes insulin resistance (IR)?
- Cellular and systemic targets in MetS
- Managing MetS with diet, lifestyle and herbs: a close look at the evidence

MEDI HERB 3

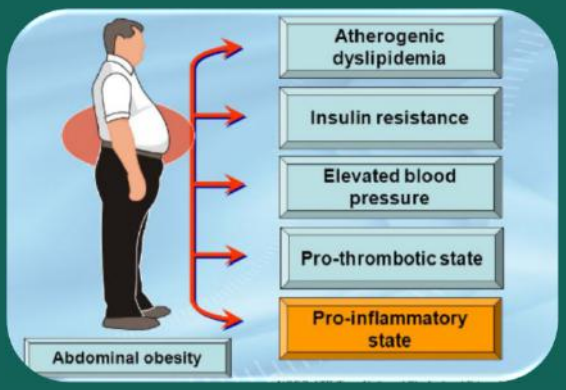
MEDI HERB

Defining Metabolic Syndrome

Defining MetS

Various definitions exist, but the commonality is:

1. Obesity, especially abdominal obesity as an indicator of visceral organ fat
2. Impaired glucose metabolism (IR)
3. Hypertension
4. Atherogenic dyslipidaemia



Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014; 43(1): 1-23. doi: 10.1016/j.ecl.2013.09.009. PMID: 24582089

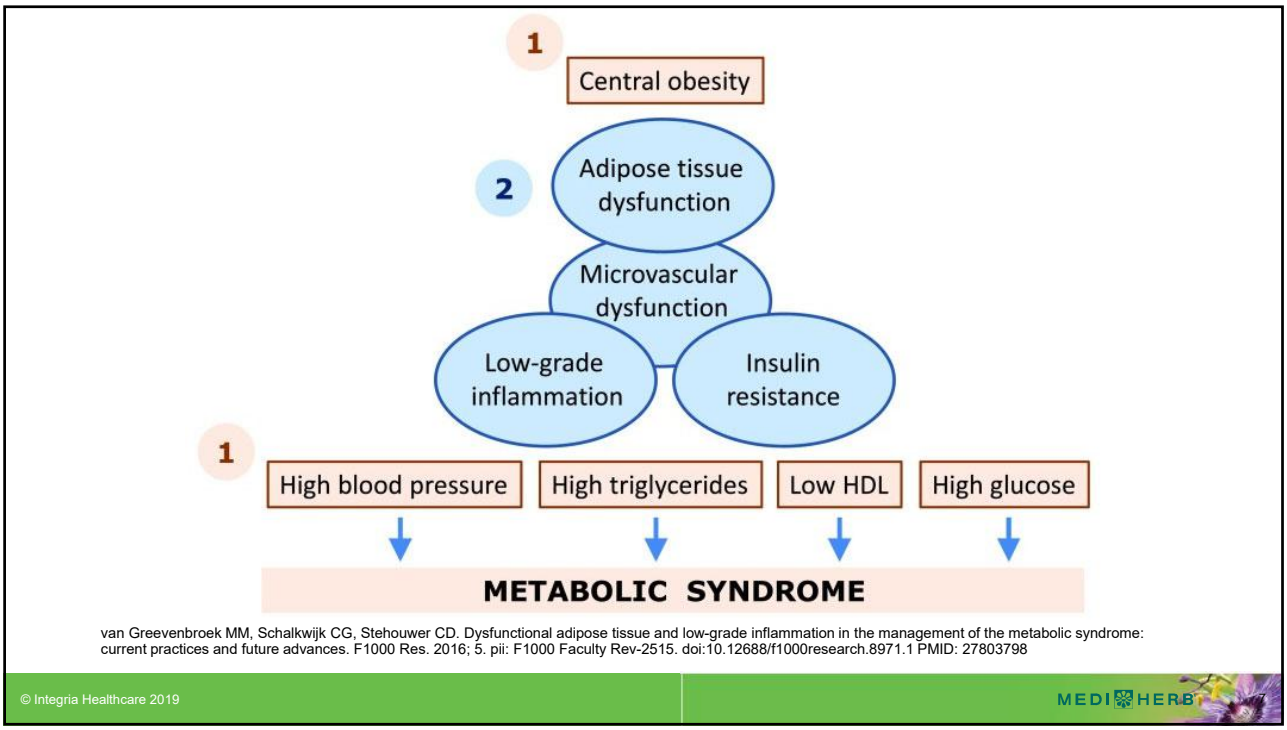
MEDI HERB 5

Defining MetS

- In 2009, 5 key groups arrived at a harmonised definition, which was 3 or more of:
  - Abdominal obesity: (≥ 102 cm male (M); 88 cm female (F) for USA/Canada, but varying with ethnicity)
  - Dyslipidaemia: HDL-C (< 1.0 mmol/L M; < 1.3 mmol/L F); triglycerides (≥ 1.7 mmol/L) or treated
  - Hyperglycaemia: fasting plasma glucose (≥ 5.6 mmol/L) or treated
  - Hypertension: systolic blood pressure (SBP) (≥ 130 mm Hg; diastolic blood pressure (DPB) ≥ 85 mm Hg) or treated

Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014; 43(1): 1-23. doi: 10.1016/j.ecl.2013.09.009. PMID: 24582089

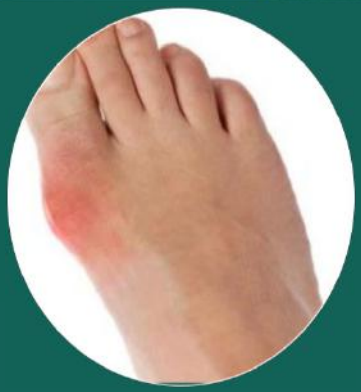
MEDI HERB 6



van Greevenbroek MM, Schalkwijk CG, Stehouwer CD. Dysfunctional adipose tissue and low-grade inflammation in the management of the metabolic syndrome: current practices and future advances. F1000 Res. 2016; 5. pii: F1000 Faculty Rev-2515. doi:10.12688/f1000research.8971.1 PMID: 27803798

Diseases Linked to MetS

- Twice the risk of large artery/cardiovascular disease (CVD)[1]
- Five times the risk of type 2 diabetes (T2D)[1]
- Non-alcoholic fatty liver disease (NAFLD)[2]
- Gout[3]



1. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014; 43(1): 1-23. doi: 10.1016/j.ecl.2013.09.009. PMID: 24582089
2. Tarantino G, Finelli C. What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome? World J Gastroenterol. 2013; 19(22): 33753384. doi: 10.3748/wjg.v19.i22.3375. PMID: 23801829
3. Thottam GE, Krasnokutsky S, Pillinger MH. Gout and metabolic syndrome: a tangled web. Curr Rheumatol Rep. 2017; 19(10): 60. doi: 10.1007/s11926-017-0688-y. PMID: 28844079

Diseases Linked to MetS

- Polycystic ovary syndrome (PCOS)[1]
- Microalbuminuria and chronic kidney disease[2]
- Cancer[3]
- Dementia[4]
- Ageing male disorders[5]

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1. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013; 6: 1-13. doi: 10.2147/CLEP.S375591.PMID: 24379699
2. Nistala R, Whaley-Connell A. Resistance to insulin and kidney disease in the cardiorenal metabolic syndrome; role for angiotensin II. Mol Cell Endocrinol. 2013; 378(1-2): 53-8. doi:10.1016/j.mce.2013.02.005. PMID: 23416840
3. Hursting SD. Obesity, energy balance, and cancer: a mechanistic perspective. Cancer Treat Res. 2014; 159: 21-33. doi:10.1007/978-3-642-38007-5_2. PMID: 24114472
4. Misiak B, Leszek J, Kiejna A. Metabolic syndrome, mild cognitive impairment and Alzheimer's disease-- the emerging role of systemic low-grade inflammation and adiposity. Brain Res Bull. 2012; 89(3-4): 144-149. doi: 10.1016/j.brainresbull.2012.08.003. PMID: 22921944
5. Sebastianelli A, Gacci M. Current status of the relationship between metabolic syndrome and lower urinary tract symptoms. Eur Urol Focus. 2018;4(1):25-27. doi: 10.1016/j.euf.2018.03.007. PMID: 29602736

MEDI HERB

What Causes Insulin Resistance?

What Causes MetS/IR?

Some key theories/contributing factors:

- Intermittent hypoxia (obstructive sleep apnoea)[1]
- The portal theory (visceral fat acting as an endocrine gland)[2]
- Microcirculatory dysfunction
- Unregulated nutrient flux, especially fructose
- Toxins: dietary, environmental and internal
- Dysbiosis or lack of “old friends”

1. Drager LF, Togeiro SM et al. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol. 2013; 62(7): 569-76, doi: 10.1016/j.jacc.2013.05.045. PMID: 23770180
2. Item F, Konrad D. Visceral fat and metabolic inflammation: the portal theory revisited. Obes Rev 2012; 13 Suppl 2: 30-39. doi: 10.1111/j.1467-789X.2012.01035.x. PMID: 23107257

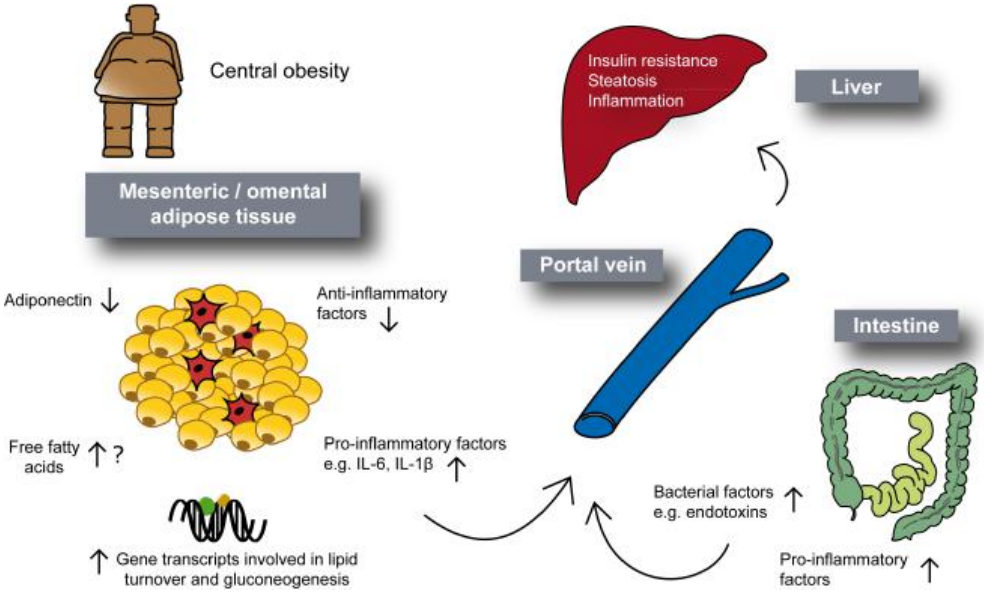
MEDI HERB 12

Adipokines

- These are adipose tissue hormones
- Leptin and adiponectin promote insulin sensitivity
- Tumour necrosis factor α (TNF-α), resistin, interleukin-6 (IL-6) are examples of adipokines that promote insulin resistance
- In central obesity, leptin levels rise and adiponectin levels fall but leptin resistance develops

Beale EG. Insulin signalling and insulin resistance. J Investig Med. 2013; 61(1): 11-14. doi: 10.2310/JIM.0b013e3182746f95. PMID: 23111650

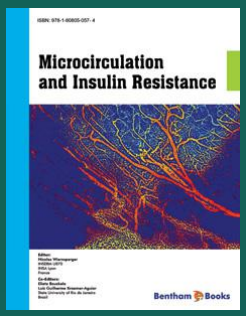
The Portal Theory



Item F, Konrad D. Visceral fat and metabolic inflammation: the portal theory revisited. Obes Rev 2012; 13 Suppl 2: 30-39. doi: 10.1111/j.1467-789X.2012.01035.x. PMID: 23107257

Microcirculation: Chicken or Egg?

- Type 2 diabetes (T2D) causes microvascular disease
- But a growing school of thought: microvascular dysfunction is the fundamental CAUSE of insulin resistance[1]
- "Prediabetes, T2DM, and measures of hyperglycemia are independently associated with impaired microvascular function in the retina and skin. These findings support the concept that microvascular dysfunction precedes and thus may contribute to … cardiovascular disease and other complications, which may in part have a microvascular origin such as impaired cognition and heart failure."[2]



1. Wiernsperger N, Rapin JR. Microvascular diseases: is a new era coming? Cardiovasc Hematol Agents Med Chem. 2012; 10(2): 167-183. doi: 10.2174/187152512800388885. PMID: 22480285
2. Sörensen BM, Houben AJ et al. Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: The Maastricht study. Circulation. 2016; 134(18): 1339-1352. doi: 10.1161/CIRCULATIONAHA.116.023446. PMID: 27678264

Unregulated Nutrient Flux

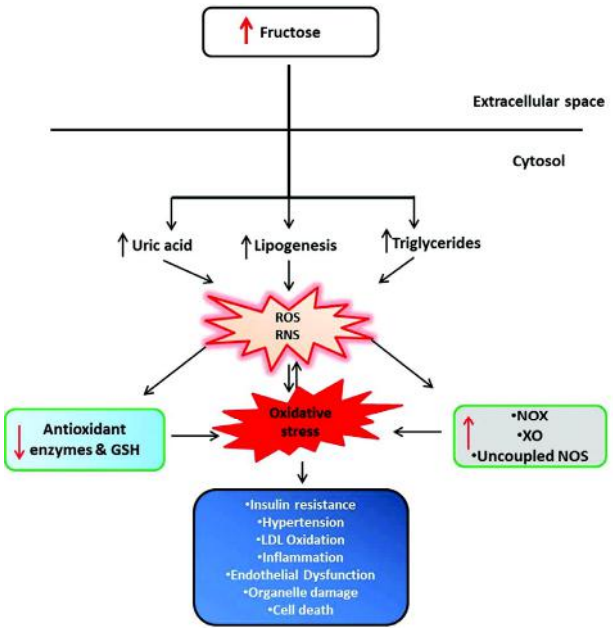
- Our liver is the primary metabolic clearing house for 4 specific nutrients that are:
  - not insulin-regulated
  - lack an appropriate turn off mechanism for excessive substrate
- Results in enhanced lipogenesis and ectopic adipose storage

Bremer AA, Mietus-Snyder M, Lustig RH. Toward a unifying hypothesis of metabolic syndrome. Pediatrics. 2012; 129(3):557-570. doi: 10.1542/peds.2011-2912. PMID: 22351884

Unregulated Nutrient Flux

- The four nutrients are:
  - trans-unsaturated fatty acids (trans-fats)
  - branched-chain amino acids (BCAAs: valine, leucine and isoleucine)
  - ethanol
  - fructose

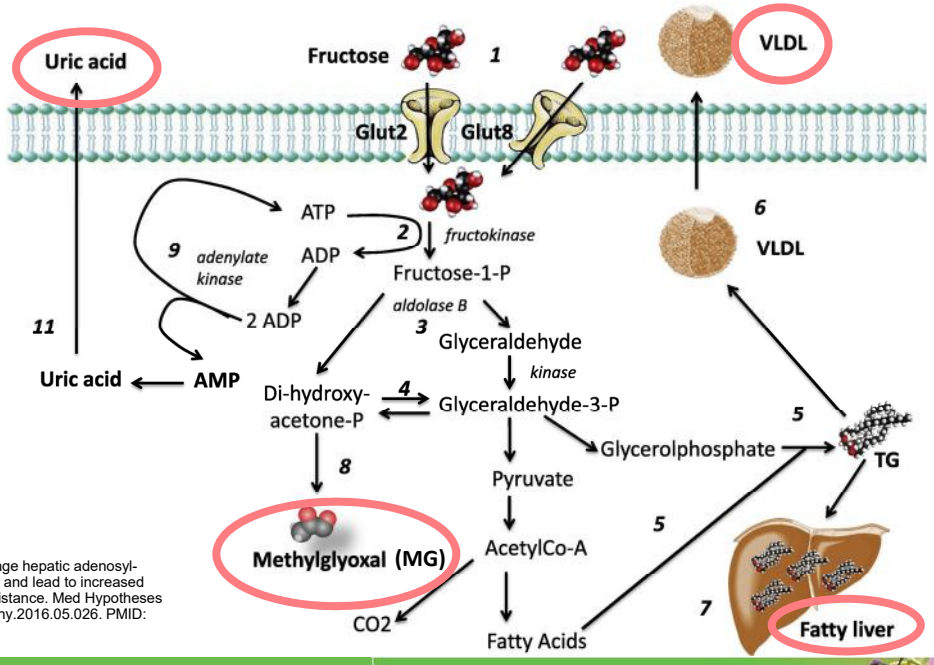
Bremer AA, Mietus-Snyder M, Lustig RH. Toward a unifying hypothesis of metabolic syndrome. Pediatrics. 2012; 129(3):557-570. doi: 10.1542/peds.2011-2912. PMID: 22351884



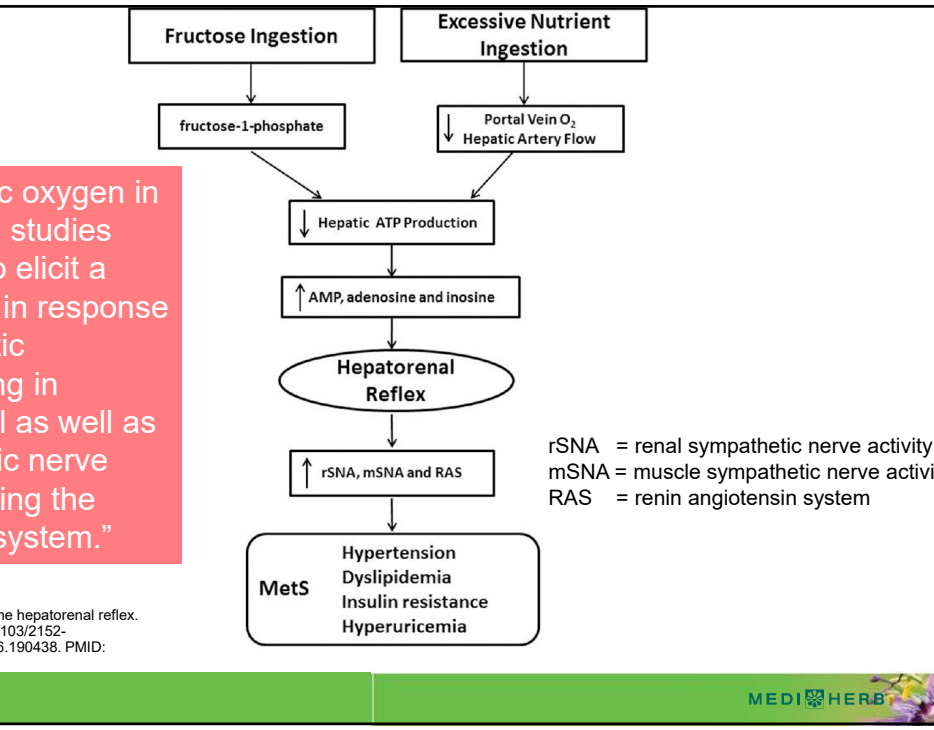
ROS = reactive oxygen species
RNS = reactive nitrogen species
GSH – glutathione
NOX = oxides of nitrogen
NOS = nitric oxide synthase

Bernardes N, Ayyappan P et al. Excessive consumption of fructose causes cardiometabolic dysfunctions through oxidative stress and inflammation. Can J Physiol Pharmacol. 2017; 95(10): 1078-1090. doi: 10.1139/cjpp-2016-0663. PMID: 28187269

Fructose, Uric Acid and MG



Gugliucci A. Fructose surges damage hepatic adenosyl-monophosphate-dependent kinase and lead to increased lipogenesis and hepatic insulin resistance. Med Hypotheses 2016; 93: 87-92. doi: 10.1016/j.mehy.2016.05.026. PMID: 27372863



"Insufficient hepatic oxygen in animal and human studies has been shown to elicit a hepatorenal reflex in response to increased hepatic adenosine, resulting in stimulation of renal as well as muscle sympathetic nerve activity and activating the renin angiotensin system."

rSNA = renal sympathetic nerve activity
mSNA = muscle sympathetic nerve activity
RAS = renin angiotensin system

Wider MD. Metabolic syndrome and the hepatorenal reflex. Surg Neurol Int. 2016; 7: 83. doi: 10.4103/2152-7806.190438. doi: 10.4103/2152-7806.190438. PMID: 27656314

Endocrine Disruptors and MetS

- A range of environmental chemicals can act as endocrine disruptors and obesogens[1]
- A meta-analysis of 9 studies compared highest versus lowest GGT levels and found a 63% increased risk of MetS (independent of alcohol intake)[2]
- Body levels of persistent organic pollutants (POPs) are linked to increased risks of T2D, IR and NAFLD, and appears to be causal[3]

1. Janesick A, Blumberg B. Obesogens, stem cells and the developmental programming of obesity. Int J Androl. 2012; 35(3): 437-448. doi: 10.1111/j.1365 2605.2012.01247.x.. PMID: 22372658
2. Liu CF, Zhou WN, Fang NY. Gamma-glutamyltransferase levels and risk of metabolic syndrome: a meta-analysis of prospective cohort studies. Int J Clin Pract. 2012; 66(7): 692-698. doi: 10.1111/j.1742-1241.2012.02959.x. PMID: 22698421
3. Ruzzin J, Lee DH, Carpenter DO, Jacobs DR Jr. Reconsidering metabolic diseases: the impacts of persistent organic pollutants. Atherosclerosis. 2012; 224(1): 1-3. doi: 10.1016/j.atherosclerosis.2012.02.039. PMID: 22472455

POPs and Insulin Resistance

- Polychlorinated biphenyls (PCBs) were positively associated with diabetes and prediabetes[1]
- Organochlorines are also implicated in T2D; and obesity was not linked to T2D with low serum POPs[2]
- PCBs, DDT metabolites and dioxin were linked to abdominal obesity[3]
- MetS was higher in more POP-polluted regions of the US[4]

References for Previous Slide

1. Gasull M, Pumarega J et al. Blood concentrations of persistent organic pollutants and prediabetes and diabetes in the general population of Catalonia. Environ Sci Technol. 2012; 46(14): 7799-7810. doi: 10.1021/es300712g. PMID: 22681243
2. Lee DH. Persistent organic pollutants and obesity-related metabolic dysfunction: focusing on type 2 diabetes. Epidemiol Health. 2012; 34: e2012002. doi: 10.4178/epih/e2012002. PMID: 22323980
3. Lee DH et al. Associations of persistent organic pollutants with abdominal obesity in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Environ Int. 2012; 40: 170-178. doi: 10.1016/j.envint.2011.07.010.PMID: 21835469
4. Sergeev AV, Carpenter DO. Increase in metabolic syndrome-related hospitalizations in relation to environmental sources of persistent organic pollutants. Int J Environ Res Public Health. 2011; 8(3): 762-776. doi: 10.3390/ijerph8030762. PMID: 21556177

Dietary Toxins

- Dietary advanced glycation end products (AGEs) are mainly formed from frying, grilling or roasting foods rich in protein and fat
- Human studies consistent: dietary AGEs increase inflammation, oxidative stress and endothelial dysfunction
- Trials in people with early MetS have shown ↓ IR, inflammation and lipids after low-AGE diets
- Dietary AGEs could add to the AGE load, accumulate in tissues and interact with the AGE receptor (RAGE)
- Hence, indirectly ↑ oxidation and inflammation, affect endothelial function, and promote IR

Luévano-Contreras C, Gómez-Ojeda A et al. Dietary advanced glycation end products and cardiometabolic risk. Curr Diab Rep. 2017; 17(8): 63. doi: 10.1007/s11892-017-0891-2. PMID: 28695383

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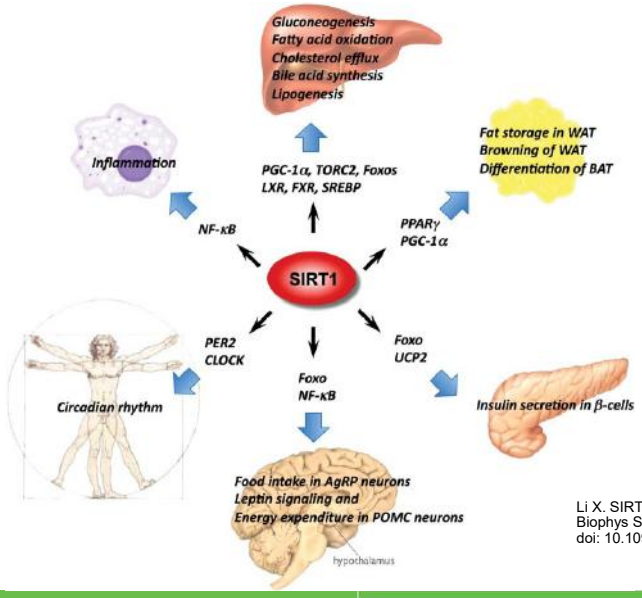
Cellular and Systemic Targets

Cellular Targets in MetS

- SIRT 1 (sirtuin 1) and Nrf2 (nuclear factor erythroid 2–related factor 2: detox, mitochondria)
- AMPK (adenosine monophosphate-activated protein kinase)
- NFκB (nuclear factor kappa B)
- GPRs (G protein coupled receptors) and incretins (see T2D presentation)
- 11βHSD-1 (11-beta-hydroxysteroid dehydrogenase type 1)
- Mitochondria
- Adipokines

MEDI HERB 26

SIRT1: The Master Metabolic Regulator



Li X. SIRT1 and energy metabolism. Acta Biochim Biophys Sin (Shanghai). 2013; 45(1): 51-60. doi: 10.1093/abbs/gms108. PMID: 23257294

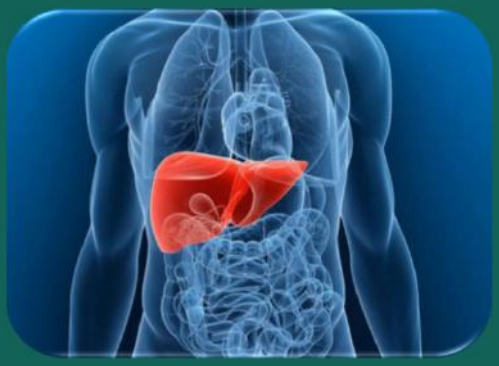
AMPK and MetS

- AMPK binds AMP and is antagonised by ATP[1]
- Hence it monitors and responds to nutrient and energy fluctuations[1]
- On activation, ↑ catabolism and ↓ anabolism[1]
- Its optimal functioning is central to cellular, tissue, organ and whole body health[2]
- "AMPK is a central regulator of processes that tend to mitigate against the metabolic syndrome"[2]

1. Fan W, Downes M et al. Nuclear receptors and AMPK: resetting metabolism. Cold Spring Harb Symp Quant Biol. 2011; **76**: 17-22. doi**:** 10.1101/sqb.2012.76.010470. PMID: 22411605
2. Thottam GE, Krasnokutsky S, Pillinger MH. Gout and metabolic syndrome: a tangled web. Curr Rheumatol Rep. 2017; 19(10): 60. doi:10.1007/s11926-017-0688-y. PMID: 28844079

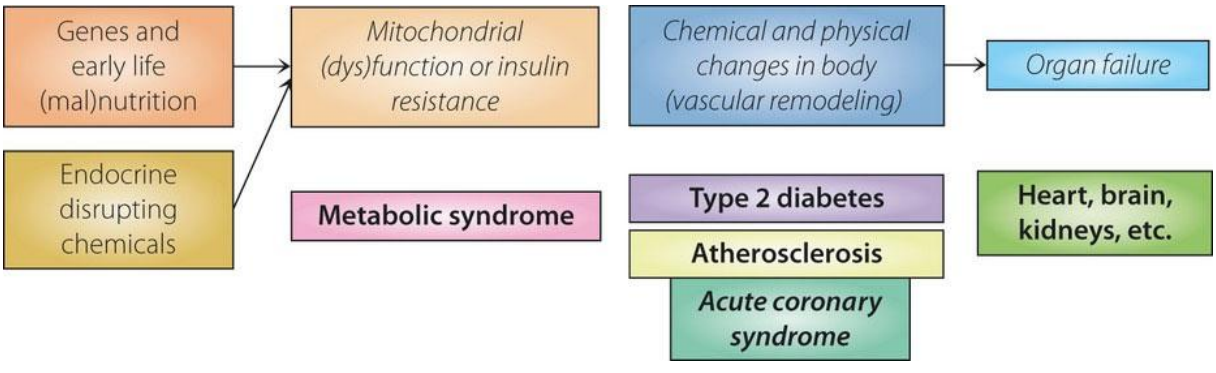
11βHSD-1 and MetS

"Growing evidence suggests that MetS and central obesity may result from an increased bioavailability of glucocorticoids at the tissue level (mainly liver and adipose tissue)"



Anagnostis P, Katsiki N et al. 11beta-Hydroxysteroid dehydrogenase type 1 inhibitors: novel agents for the treatment of metabolic syndrome and obesity-related disorders? Metabolism. 2013; 62(1): 21-33. doi: 10.1016/j.metabol.2012.05.002. PMID: 22652056

Mitochondria and MetS



Lee HK, Shim EB. Extension of the mitochondria dysfunction hypothesis of metabolic syndrome to atherosclerosis with emphasis on the endocrine-disrupting chemicals and biophysical laws. J Diabetes Investig. 2013; 4(1): 19-33. doi: 10.1111/jdi.12048. PMID: 24843625

Mfn = mitofusin

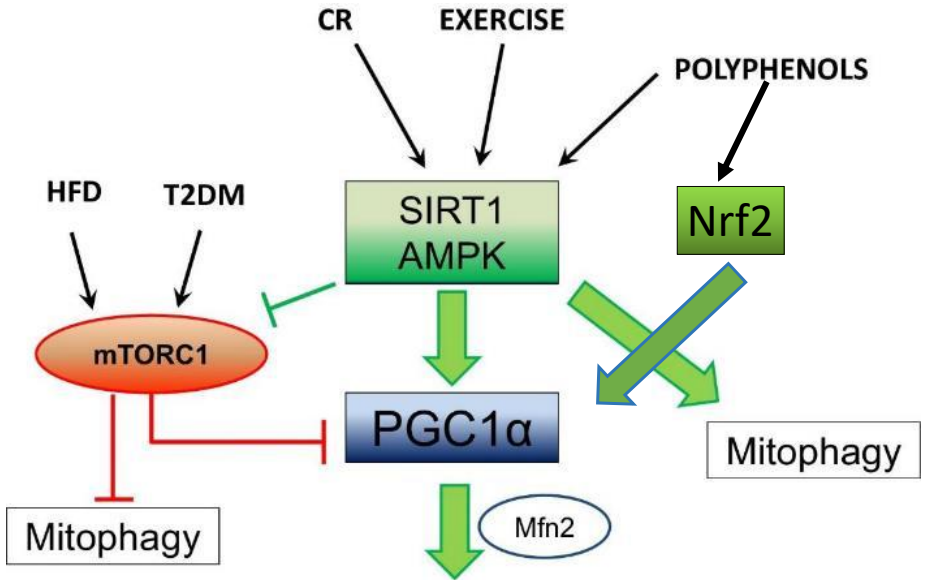
HFD = high fat diet

T2DM = type 2 diabetes

SIRT1 = sirtuin 1

PGC1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha

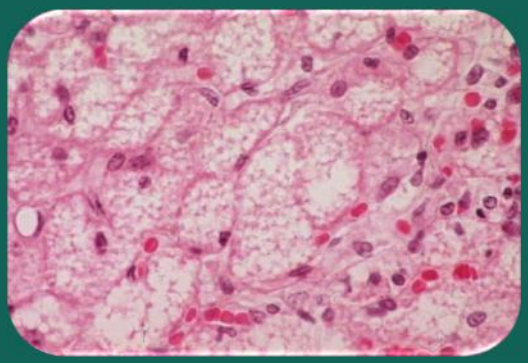
mTOR = mechanistic target of rapamycin



López-Lluch G. Mitochondrial activity and dynamics changes regarding metabolism in ageing and obesity. Mech Ageing Dev. 2017:162: 108-121. doi: 10.1016/j.mad.2016.12.005. PMID: 27993601

Systemic/Organ Targets in MetS

- Gut flora
- Environmental obesogens/endocrine disruptors/toxins
- Microcirculation
- Brown fat
- Visceral adiposity
- Stress responses/coping



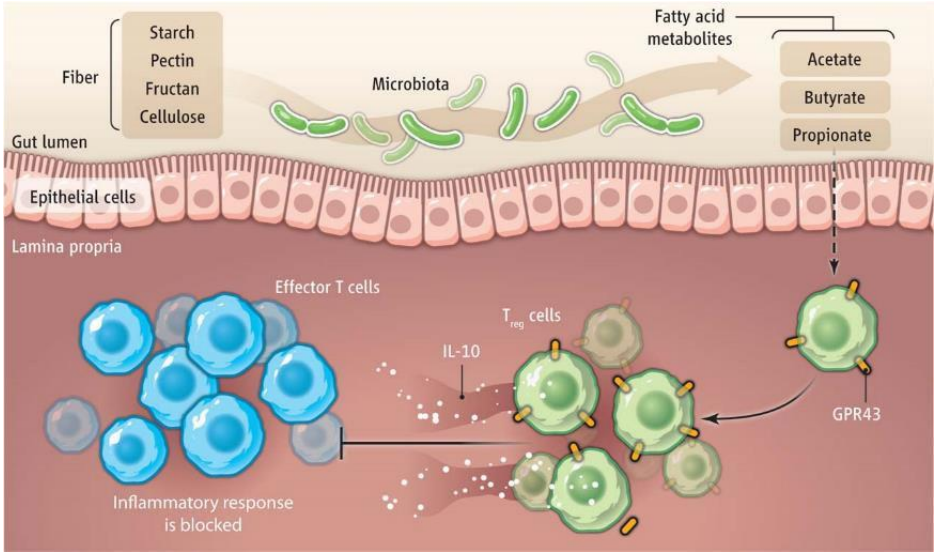
Gut Flora and MetS

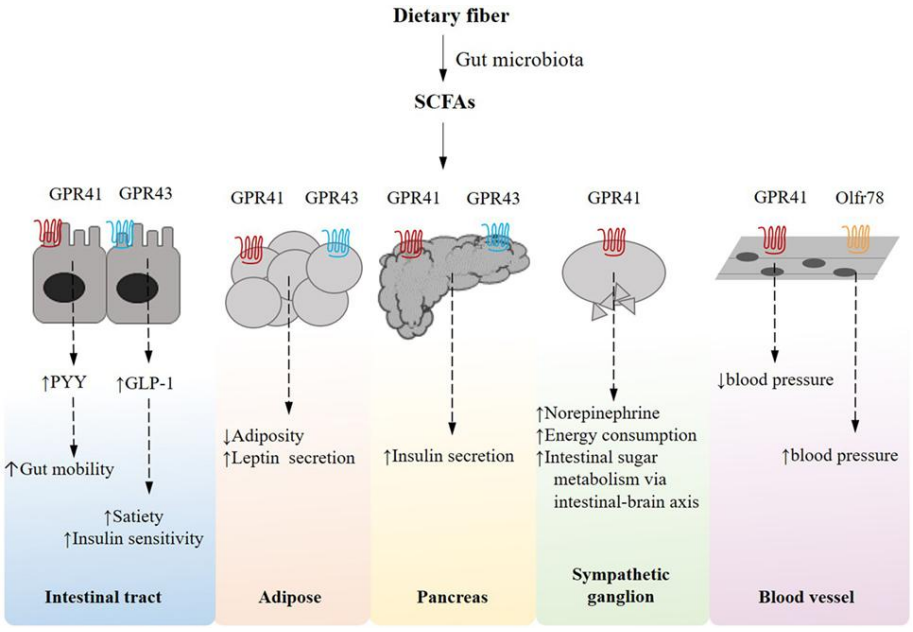
- Nutrient extraction
- Inflammatory overdrive via local (cross talk) and systemic (endotoxin) influences
- Metabolite-mediated mechanisms:
  - endocannabinoid release
  - incretin production
  - other: GPR regulation (GPR41 and 43)

References for Previous Slide

1. Piya MK, Harte AL, McTernan PG. Metabolic endotoxaemia: is it more than just a gut feeling? Curr Opin Lipidol. 2013; 24(1): 78-85. doi: 10.1097/MOL.0b013e32835b4431. PMID: 23298961
2. D'Aversa F, Tortora A et al. Gut microbiota and metabolic syndrome. Intern Emerg Med. 2013; 8 Suppl 1: S11-5 doi: 10.1007/s11739-013-0916-z. PMID: 23468402
3. Kovatcheva-Datchary P, Arora T. Nutrition, the gut microbiome and the metabolic syndrome. Best Pract Res Clin Gastroenterol. 2013; 27(1): 59-72. doi: 10.1016/j.bpg.2013.03.017. PMID: 23768553
4. Burcelin R, Garidou L, Pomié C. Immuno-microbiota cross and talk: the new paradigm of metabolic diseases.Semin Immunol 2012; 24(1): 67-74. doi: 10.1016/j.smim.2011.11.011. PMID: 22265028

Gut Bacteria, Fibre and MetS





Li X, Watanabe K, Kimura I. Gut microbiota dysbiosis drives and implies novel therapeutic strategies for diabetes mellitus and related metabolic diseases. Front Immunol 2017 Dec 20; 8: 1882. doi: 10.3389/fimmu.2017.01882. PMID: 29326727

Brown Fat

- "Until 2009 the question of whether adult humans had brown adipose tissue (BAT) and whether it could conceivably contribute to whole body energy usage in a meaningful way was a matter of vigorous debate. The publication of three papers...demonstrated adult humans do have BAT, that it can be activated and that this activation appears to be defective in obesity reframed the debate..."

Lockie SH, Stefanidis A et al. Brown adipose tissue thermogenesis in the resistance to and reversal of obesity: a potential new mechanism contributing to the metabolic benefits of proglucagon-derived peptides. Adipocyte 2013; 2(4): 196-200. doi: 10.4161/adip.25417. PMID: 24052894

Work stress and risk of death in men and women with and without cardiometabolic disease: a multicohort study

Mika Kivimäki, Jaana Pentti, Jane E Ferrie, G David Batty, Solja T Nyberg, Markus Jokela, Marianna Virtanen, Lars Alfredsson, Nico Dragano, Eleonor I Fransson, Marcel Goldberg, Anders Knutsson, Markku Koskenvuo, Aki Koskinen, Anne Kouvonen, Ritva Luukkonen, Tuula Oksanen, Reiner Rugulies, Johannes Siegrist, Archana Singh-Manoux, Sakari Suominen, Töres Theorell, Ari Väänänen, Jussi Vahtera, Peter J M Westerholm, Hugo Westerlund, Marie Zins, Timo Strandberg, Andrew Steptoe, John Deanfield, for the IPD-Work consortium

Summary

Background Although some cardiovascular disease prevention guidelines suggest a need to manage work stress in patients with established cardiometabolic disease, the evidence base for this recommendation is weak. We sought to clarify the status of stress as a risk factor in cardiometabolic disease by investigating the associations between work stress and mortality in

Methods In this multi
between 1985 and 2002
mortality. Work stress
data on prevalent card
diabetes type]) at baseli
and diastolic blood pres
also assessed at baseli
registries. We used Cox
men and women with and without cardiometabolic disease.

In men with cardiometabolic disease, the contribution of job strain to risk of death was clinically significant and independent of conventional risk factors and their treatment, and measured lifestyle factors. Standard care targeting conventional risk factors is therefore **unlikely to mitigate the mortality risk associated with job strain in this population.**

Lancet Diabetes Endocrinol 2018
Published Online
June 5, 2018
rg/10.1016/
8)30140-2
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ki FMedSci,
T Nyberg PhD,
hD,
erg MD), Institute
of Behavioural Sciences
(M Jokela PhD), Department of

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Managing Metabolic Syndrome

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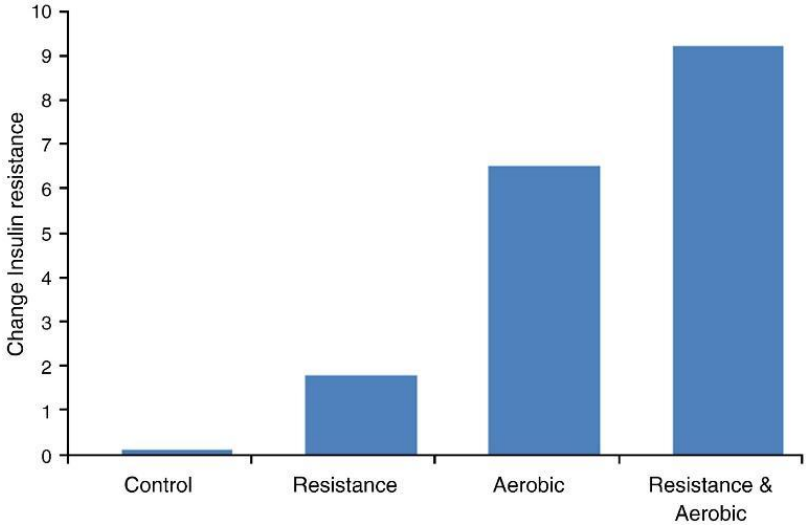
Diet and Lifestyle for MetS

Therapeutic Objectives in MetS/IR

- Reduce waist measurement (abdominal/visceral fat loss)
- Stress reduction with adequate sleep quality/quantity
- Adequate and appropriate exercise
- Appropriate dietary changes
- Carefully selected herbs & supplements

Exercise and MetS/IR



Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013; 97(3): 505-516. doi: 10.3945/ajcn.112.042457. PMID: 23364002

Exercise and MetS/IR

- Low-volume high-intensity interval training (HIIT, 51 min/week) was at least as effective as high-volume HIIT (114 min/week) and continuous training (150 min/week) in ameliorating MetS
- Participants in the HIIT groups trained 3 times a week (with at least a day between each session)
- Low-volume-HIIT sessions were preceded with a 10-min warm-up and concluded with a 3-min cool-down both at 60-70% peak heart rate
- The low-volume HIIT protocol only consisted of 1 bout of 4-min interval at 85%–95% peak heart rate

Ramos JS, Dalleck LC et al. Low-volume high-intensity interval training is sufficient to ameliorate the severity of metabolic syndrome. Metab Syndr Relat Disord. 2017; 15(7): 319-328. doi: 10.1089/met.2017.0042.PMID: 28846513

Diet and IR

- A review identified 20 randomised controlled trials (RCTs) lasting more than 6 months in people with T2D (n=3073)
- The 4 dietary patterns that showed the most benefit were low-carb (LC), low-GI (LGI), Mediterranean (Med), and high protein (HP)

Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013; 97(3): 505-516. doi: 10.3945/ajcn.112.042457. PMID: 23364002

Diet and IR

- All led to improved glycaemic control, but the strongest effect was for Med
- LC and Med led to greatest weight loss (relatively small)
- All diets except HP increased HDL

Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013; 97(3): 505-516. doi: 10.3945/ajcn.112.042457. PMID: 23364002

Other Dietary Considerations in MetS/IR

- Fibre from multiple plant sources
- No sugary drinks including juices
- Low fructose fruits
- Organic animal fat
- Low BCAA proteins

Other Dietary Considerations in MetS/IR

- Reduce haem iron (see T2D talk; MetS also linked to high ferritin)
- No synthetic trans-fats
- Minimal alcohol
- The 5-point microcirculation phytonutrient plan (low fructose version, see T2D talk)

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Managing MetS with Key Herbs

Herbs and Supplement Targets for MetS/IR

1. Reducing nutrient flux, altering glycaemic index of meals
2. Cellular targets
3. Systemic targets
4. Better glycaemic control (more important for T2D)
5. Standout disturbances, especially lipids, hypertension
6. Associated diseases/dysfunction eg gout, NAFLD, benign prostatic hyperplasia (BPH) etc

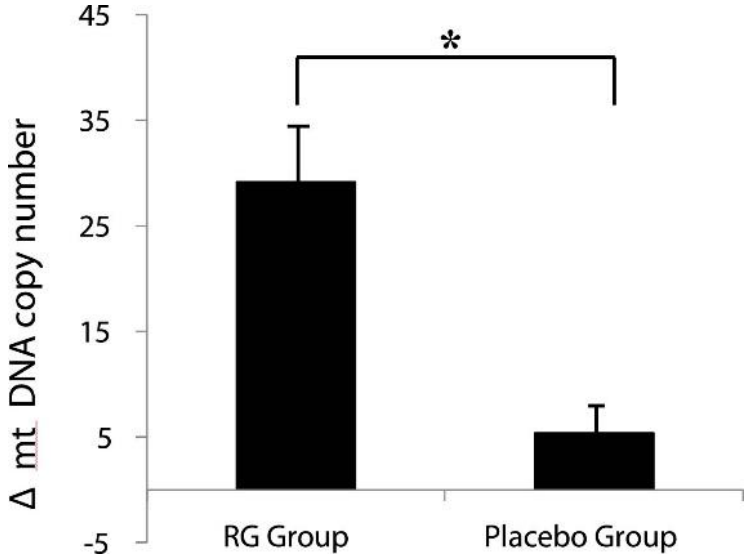
Reduce Nutrient Flux

Effectively by decreasing the glycaemic index of each meal with:

- Mucilage herbs: Slippery Elm, Linseed, Psyllium
- Tannins and other polyphenols: inhibit digestive enzymes, eg Grape Seed, Green Tea
- Gymnema: disrupts glucose transport

Kanetkar P, Singhal R, Kamat M. *Gymnema sylvestre*. A Memoir. J Clin Biochem Nutr .2007; 41(2): 77-81. doi: 10.3164/jcbn.2007010. PMID: 18193099

Korean Ginseng, Mitochondria and MetS



Jung DH, Lee YJ et al. Effects of ginseng on peripheral blood mitochondrial DNA copy number and hormones in men with metabolic syndrome: a randomized clinical and pilot study. Complement Ther Med 2016; 24: 40-46. doi: 10.1016/j.ctim.2015.12.001. PMID: 26860800

Berries for Vascular Health

Ref.	Type of study	Number of patients	Patients' characteristics	Age (years)	Intervention	Dose	Duration	Measured outcomes	Results
[92]	Placebo-controlled	48	Postmenopausal women with pre- and stage 1 hypertension	55–65	Blueberries	22 g/day powder	8 weeks	Blood pressure, arterial stiffness, CRP, nitric oxide, and superoxide dismutase	Decreased blood pressure and arterial stiffness and increased nitric oxide after blueberry intervention: no effects on CRP
[91]	Placebo-controlled	48	MetS	47–53	Blueberries	50 g/day powder	8 weeks	Blood pressure, lipid profile, HOMA index, oxidation, and inflammation parameters	Decreased blood pressure, no changes in body weight, HOMA index or lipid profile. Decreased oxLDL, MDA, and HNE. No changes in inflammatory biomarkers
[99]	Placebo-controlled	44	MetS	53–61	Blueberries	45 g/day powder	6 weeks	Blood pressure, endothelial function, and insulin sensitivity	Improved endothelial function. No changes in blood pressure or insulin sensitivity
[100]	Placebo-controlled	32	Obese, nondiabetic, and insulin-resistant	46–57	Blueberries	45 g/day powder	6 weeks	Insulin sensitivity, inflammatory biomarkers, and adiposity	Improved insulin sensitivity but no changes in adiposity or inflammatory biomarkers
[98]	Placebo-controlled	27	MetS	43–59	Bilberries	400 g fresh	8 weeks	Body weight, blood pressure, glucose, lipid profile, and inflammatory parameters	Decreased CRP, IL-6, IL-12, and LPS concentrations and decreased expression of MMD and CCR2 in monocytes. No changes in body weight, blood pressure, glucose, or lipid metabolism

Chiva-Blanch G, Badimon L. Effects of polyphenol intake on metabolic syndrome: current evidences from human trials. Oxid Med Cell Longev. 2017; 2017: 5812401. doi: 10.1155/2017/5812401. PMID: 28894509

Nigella and MetS

- RCT: Nigella seed (3 g/day) for 12 weeks in people at risk of MetS ⇒ lipid levels significantly improved from baseline ($p \leq 0.001$): HDL-cholesterol (+0.24 mmol/L), LDL-cholesterol (-0.22 mmol/L), triglycerides (-0.1 mmol/L), and versus placebo[1]
- RCT (n=30): Nigella seed (1 g/day for 2 months) in menopausal women with MetS ⇒ total cholesterol, LDL cholesterol and triglycerides ↓ significantly compared to baseline (16.1, 27.2 and 22.2%, respectively), and versus placebo (both $p < 0.05$)[2]

1. Al Dhaheri A. The effect of black seed powder on blood glycaemia, blood lipidemia and body composition on adults at risk for cardiovascular diseases. Dubai Nutrition Conference. Dubai, 2016. Available from: http://dubainutrition.ae/downloads/Ayesha%20al%20Dhaheri_Black%20Seed%20Project.pdf
2. Ibrahim R, Hamdan N et al. A randomised controlled trial on hypolipidemic effects of *Nigella Sativa* seeds powder in menopausal women. J Transl Med. 2014; 12: 82 doi: 10.1186/1479-5876-12-82. PMID: 24685020

Nigella: Recent Meta-analyses

- Meta-analysis of 11 RCTs (n=860): short-term treatment with Nigella significantly reduced SBP and DBP levels
- Preparations of Nigella in seed powder and oil demonstrated a different lowering effect (in favour of the former) on both SBP and DBP[1]
- Meta-analysis of 11 RCTs (n=783): Nigella exerted a moderate effect on reducing body weight, BMI and waist circumference[2]

1. Sahebkar A, Soranna D et al. A systematic review and meta-analysis of randomized controlled trials investigating the effects of supplementation with *Nigella sativa* (black seed) on blood pressure. J Hypertens. 2016; 34(11): 2127-2135. doi: 10.1097/ HJH.0000000000001049. PMID: 27512971
2. Namazi N, Larijani B et al. The effects of *Nigella sativa* L. on obesity: a systematic review and meta-analysis. J Ethnopharmacol. 2018; 219: 173-181. doi: 10.1016/j.jep.2018.03.001. PMID: 29559374

Bitter Melon and MetS

- Bitter melon is the fruit of *Momordica charantia*, a tropical vegetable and Ayurvedic herb
- Crossover acute study (n=10): a single dose of Bitter Melon extract ↓ postprandial glucose in half of the prediabetic participants[1]
- Crossover RCT (n=52 with prediabetes): Bitter Melon (2.5 g/day of dried fruit) for 8 weeks ⇒ ↓ fasting blood glucose compared to placebo (-0.28 mmol/L; p≤0.01)[2]

1. Boone CH, Stout JR et al. Acute effects of a beverage containing bitter melon extract (CARELA) on postprandial glycemia among prediabetic adults. Nutr Diabetes. 2017; 7(1): e241. doi: 10.1038/nutd.2016.51. PMID: 28092345
2. Krawinkel MB, Ludwig C et al. Bitter gourd reduces elevated fasting plasma glucose levels in an intervention study among prediabetics in Tanzania. J Ethnopharmacol. 2018; 216: 1-7. doi: 10.1016/j.jep.2018.01.016. PMID: 29339109

Cinnamon and Fenugreek in MetS

- RCT (n=116, MetS): Cinnamon (3 g/day for 16 weeks) significantly ↓ fasting blood glucose (p=0.001), HbA1c (2.6 units, p=0.023), waist circumference (4.8 cm, p=0.002) and BMI (1.3, p=0.001), compared to placebo[1]
- Prevalence of MetS was significantly reduced (34.5%) vs placebo (5.2%)[1]
- "Based on the beneficial metabolic properties that have been demonstrated, 4-hydroxyisoleucine, a simple, plant-derived amino acid (from Fenugreek), may represent an attractive new candidate for the treatment of… all key components of metabolic syndrome"[2]

1. Gupta Jain S, Puri S et al. Effect of oral cinnamon intervention on metabolic profile and body composition of Asian Indians with metabolic syndrome: a randomized double -blind control trial. Lipids Health Dis. 2017 Jun 12; 16(1): 113. doi: 10.1186/s12944-017-0504-8. PMID: 28606084
2. Jetté L, Harvey L et al. 4-Hydroxyisoleucine: a plant-derived treatment for metabolic syndrome. Curr Opin Investig Drugs. 2009; 10(4): 353-358. PMID: 19337956

Berberine and MetS

- A small RCT (n=24) patients with MetS (berberine 1500 mg/day)[1]
- Berberine resulted in a significant remission rate of 36%
- It also lowered SBP, triglycerides and IR

Pérez-Rubio KG, González-Ortiz M et al. Effect of berberine administration on metabolic syndrome, insulin sensitivity, and insulin secretion. Metab Syndr Relat Disord. 2013; 11(5): 366-369. doi: 10.1089/met.2012.0183. PMID: 23808999

MEDI HERB 57

Berberine and IR in PCOS

	Berberine		Metformin	
	Baseline	After treatment	Baseline	After treatment
Body Composition				
body mass index (kg/m²)	24.6	22.8	24.0	22.7
waist circumference (cm)	80.0	75.4	81.3	76.9
waist/hip ratio	0.88	0.82	0.90	0.85
Lipids				
total cholesterol (mmol/L)	5.7	4.4	5.8	5.3
LDL cholesterol (mmol/L)	4.3	3.5	4.2	4.0
Glucose Metabolism				
fasting blood glucose (mmol/L)	5.0	4.3	5.1	4.4
fasting insulin (mIU/mL)	20.5	10.2	19.9	12.0
HOMA-IR	4.9	2.6	4.7	2.8
Hormones				
total testosterone (nmol/L)	1.7	1.2	1.8	1.3
free androgen index (%)	6.7	3.2	7.0	3.2
SHBG (nmol/L)	33.7	58.3	34.2	59.5

Table 1. Results of treatment with berberine (1500 mg/day) and metformin in 128 women with PCOS completing the 3-month placebo-controlled trial prior to IVF.

Morgan M. [citing An Y, Sun Z et al. The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. Clin Endocrinol (Oxf). 2014;80(3):425-31.doi: 10.1111/cen.12294. PMID: 23869585] in; High-dose berberine: update of clinical research focus on metabolic syndrome & polycystic ovary syndrome. A Phytotherapist's Perspective. 2014; 171. Available from: www.mediherb.com.au

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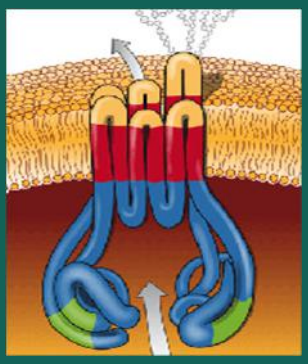
Augmenting Berberine's Activity

- Berberine has relatively low oral bioavailability (around 0.4%)
- This appears to be largely due to P-glycoprotein (P-gp) decreasing the amount of berberine able to cross the gut wall by a significant amount
- Silymarin from St Mary's Thistle is a clinically relevant P-gp inhibitor



Liu CS, Zheng YR et al. Research progress on berberine with a special focus on its oral bioavailability. Fitoterapia. 2016; 109: 274 282. doi: 10.1016/j.fitote.2016.02.001. PMID: 26851175

Green Tea and MetS

- Meta-analysis: 20 RCTs ⇒ green tea ↓ SBP and LDL-cholesterol[1]
- Pilot trial (n=15, healthy): green tea catechin with caffeine acutely ↑ energy expenditure associated with ↑ BAT activity and chronically ↑ non-shivering cold induced thermogenesis[2]
- RCT (n=35, MetS patients): green tea for 8 weeks ↑ whole blood glutathione (Nrf2 effect) and ↓ plasma iron[3]
- Meta-analysis: 5 RCTs in MetS ⇒ green tea ↓ BMI[4]

References for Previous Slide

1. Onakpoya I, Spencer E, Heneghan C. The effect of green tea on blood pressure and lipid profile: a systematic review and meta-analysis of randomized clinical trials. Nutr Metab Cardiovasc Dis. 2014; 24(8): 823-836. doi: 10.1016/j.numecd.2014.01.016. PMID: 24675010
2. Yoneshiro T, Matsushita M et al. Tea catechin and caffeine activate brown adipose tissue and increase cold-induced thermogenic capacity in humans. Am J Clin Nutr. 2017; 105(4): 873-881. doi: 10.3945/ajcn.116.144972. PMID: 28275131
3. Basu A, Betts NM et al.Green tea supplementation increases glutathione and plasma antioxidant capacity in adults with the metabolic syndrome. Nutr Res. 2013; 33(3): 180-187. doi: 10.1016/j.nutres.2012.12.010. PMID: 23507223
4. Zhong X, Zhang T et al. Short-term weight-centric effects of tea or tea extract in patients with metabolic syndrome: a meta-analysis of randomized controlled trials. Nutr Diabetes. 2015; 5: e160. doi: 10.1038/nutd.2015.10. PMID: 26075637

Gymnema and MetS

- Until recently Gymnema trials were all on T2D
- Last year a small randomised controlled trial (RCT, n=24) over 12 weeks in MetS patients
- Gymnema 600 mg/day or placebo
- Herb decreased body weight, BMI and VLDL levels (from baseline), but without changes in insulin secretion and insulin sensitivity
- No change in placebo group

Zuñiga LY, González-Ortiz M, Martínez-Abundis E. Effect of *Gymnema sylvestre* administration on metabolic syndrome, insulin sensitivity, and insulin secretion. J Med Food. 2017 Aug; 20(8):750-754. doi: 10.1089/jmf.2017.0001. PMID: 28459647

Resveratrol and MetS

- RCT (n=11, men with obesity but no other metabolic alteration) resveratrol (150 mg/day for 30 days) ⇒ activated AMPK in muscle and ↑ SIRT1 and PGC1alpha ⇒ higher lipolysis of adipose tissue. Also ↓ glucose, insulin and IR[1]
- Meta-analysis: 21 trials in overweight and obese people ⇒ resveratrol significantly lowered total cholesterol, BP and fasting glucose[2]
- But more is not better: 1000mg/day for 16 weeks (RCT, n=74) ⇒ resveratrol ↑ LDL-cholesterol and fructosamine[3]

References for Previous Slide

1. Timmers S, Konings E et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. 2011; 14(5): 612-622. doi: 10.1016/j.cmet.2011.10.002. PMID: 22055504
2. Huang H, Chen G et al. The effects of resveratrol intervention on risk markers of cardiovascular health in overweight and obese subjects: a pooled analysis of randomized controlled trials. Obes Rev. 2016; 17(12): 1329-1340. doi: 10.1111/obr.12458. PMID: 27456934
3. Kjær TN, Ornstrup MJ et al. No beneficial effects of resveratrol on the metabolic syndrome: a randomized placebo-controlled clinical trial. J Clin Endocrinol Metab. 2017; 102(5): 1642-1651. doi: 10.1210/jc.2016-2160. PMID: 28182820

Licorice and MetS

- Licorice is well documented to inhibit the activity of 11 beta-HSD type 2. This is responsible for its aldosterone-like side effects
- A group of Italian scientists found that Licorice taken for 2 months reduced body fat mass in 15 healthy volunteers without any change in calorie intake. BMI did not change
- The authors attributed this effect to inhibition of 11 beta-HSD type 1 at adipocytes

Armanini D, De Palo CB, Mattarello MJ et al. Effect of licorice on the reduction of body fat mass in healthy subjects. J Endocrinol Invest. 2003; 26(7): 646-650. doi: 10.1007/BF03347023. PMID: 14594116

11βHSD-1 and MetS

Table 1 – Non-selective 11β-HSD1 inhibitors.

Name	Action	References
Glycyrrhizic and glycyrrhetinic acid	- Reduction in body weight - Sodium retention, potassium loss, hypertension via inhibition of 11β-HSD2	[53–55]
Carbenoxolone	- Reduction in plasma glucose - Reduction in body weight (fat mass) - Decrease in hepatic triglyceride production - Inhibition of lipolysis - Increase in HDL-C levels - Sodium retention, potassium loss, hypertension via inhibition of 11β-HSD2	[57–62]
Vitamin A	- Inverse association between vitamin A and obesity - Reduction in body weight (fat mass) - *In vitro* inhibition of 11β-HSD2	[63–67]

Abbreviations: 11β-HSD1 and 11β-HSD2: 11β-hydroxysteroid dehydrogenase type 1 and type 2, HDL-C: high-density lipoprotein cholesterol.

Anagnostis P, Katsiki N et al. 11beta-Hydroxysteroid dehydrogenase type 1 inhibitors: novel agents for the treatment of metabolic syndrome and obesity-related disorders? Metabolism. 2013; 62(1): 21-33. doi: 10.1016/j.metabol.2012.05.002. PMID: 22652056

Other Herbs for MetS

- Pilot study (n=11 MetS patients) ⇒ ↓ hsCRP from 8.9 to 4.9 mg/L (-44.4%) (p<0.044) and IR from 3.1 to 2.60 (-15.3%) (p<0.012), as well as a beneficial changes in inflammatory and oxidative stress biomarkers after 2-months of Ginkgo[1]
- RCT (n=30) ⇒ Coleus extract (with 25 mg forskolin) for 12 weeks improved insulin concentration and IR (p=0.001 and 0.01, respectively) compared to placebo[2]
- RCT (n=44) ⇒ Saffron 100 mg/day for 12 weeks ↓ inflammatory cytokines, hsCRP, fasting blood glucose, cholesterol and triglycerides and ↑ HDL-cholesterol[3]

References for Previous Slide

1. Siegel G, Ermilov E et al. Combined lowering of low grade systemic inflammation and insulin resistance in metabolic syndrome patients treated with *Ginkgo biloba*. Atherosclerosis. 2014; 237(2): 584-588. doi: 10.1016/j.atherosclerosis.2014.10.023. PMID: 25463092
2. Loftus HL, Astell KJ.et al. *Coleus forskohlii* extract supplementation in conjunction with a hypocaloric diet reduces the risk factors of metabolic syndrome in overweight and obese subjects: a randomized controlled trial. Nutrients. 2015; 7(11): 9508-9522. doi: 10.3390/nu7115483. PMID: 26593941
3. Kermani T, Zebarjadi M et al. anti-inflammatory effect of *Crocus sativus* on serum cytokine levels in subjects with metabolic syndrome: a randomized, double-blind, placebo- controlled trial. Curr Clin Pharmacol. 2017; 12(2): 122-126. DOI: 10.2174/1574884712666170622082737. PMID: 28637418

Key Herbs and Why, by Target

Detox & intracellular antioxidant effects	Nrf2 herbs
Mitochondria	Rhodiola, Korean Ginseng, Ginkgo, Nrf2 herbs, AMPK herbs, SIRT1 herbs, Hawthorn
↑ adiponectin, ↓ leptin (see later in T2D)	Curcumin/Turmeric
Microcirculatory & general CV health (eg ↓BP)	Ginkgo, Gotu Kola, Grape Seed, Bilberry, Garlic, Phellodendron/berberine
↓ NFκB and inflammatory cytokines and markers	Curcumin/Turmeric, Ginkgo, Saffron
↑ brown fat and ↓ visceral fat	Green Tea, Ginger, Cinnamon

MEDI HERB 69

Key Herbs and Why, by Target

Abnormal lipids	Nigella, Curcumin/Turmeric, Garlic, Phellodendron/berberine
↑ SIRT1	Polygonum/resveratrol, St Mary's Thistle
↑ AMPK	Phellodendron/berberine, Gynostemma, Curcumin/Turmeric, Polygonum/resveratrol
↓ 11βHSD-1 at muscle and adipose tissue	Licorice (but watch for ↑ BP due to ↓ 11βHSD-2 at kidneys)
↑ incretins (see T2D presentation)	Bitter herbs (eg Feverfew, Gentian, Wormwood)
Prothrombotic state	Garlic, Ginger, Coleus
Fibre and GPRs	Bowel Flora Protocol with extra fibre

MEDI HERB 70

Herbs and Nutrients for Glycaemic Control

Key Herbs	Supporting Herbs
Nigella (black seed)	Fenugreek
Gymnema (long-term)	St Mary's Thistle (silymarin)
Bitters	Gynostemma
Polygonum/Raynoutria (resveratrol)	Sage
Bitter Melon	Curcumin/Turmeric
Green Tea	Korean Ginseng
Cinnamon	Coleus
Phellodendron (berberine)	Ginger
Key Nutrients	**Supporting Nutrients**
Chromium (Cr)	B vitamins
Magnesium (Mg)	Vitamin D
Zinc (Zn)	Fibre/probiotics

8-Point Dietary BP Plan

- The key elements of the DASH guidelines
- As a key part of this: berries
- Cocoa (85% chocolate, 20 g/day)
- Green tea and hibiscus tea - several cups per day of each
- Garlic as 1-2 fresh, crushed raw cloves/day
- Beetroot as juice or supplement plus sunlight
- Fibre, especially 30g/day of freshly milled linseeds
- Reduce salt to 3 g/day, increase potassium

DASH = dietary approaches to stop hypertension

Key Herbs and Why, by Herb

Nigella (Black Seed)	↓ blood glucose (BG), corrects lipids, ↓ BP
Ginkgo	Nrf2, mitochondria, ↓ inflammation, microcirculation (MC)
Curcumin/Turmeric	↑ adiponectin, ↓ leptin, ↓ inflammation Nrf2, MC, corrects lipids, ↓ IR, ↑ AMPK
Bitter Melon	incretin effect, ↓ BG, ↓ IR
Green Tea	↑ brown fat, ↓ visceral fat, ↓ BP, Nrf2
Reynoutria/Fallopia (Polygonum/resveratrol)	↑ AMPK, Nrf2, ↑ SIRT1
Cinnamon	↓ BG, weight loss and multiple other targets

Some Useful Combinations

Core:

1. Nigella, Bitter Melon, Cinnamon & Fenugreek **MetS Support**
2. **Bioavailable Curcumin**
3. **High Berberine Phellodendron Tablets**

But Don't Forget:

- Polygonum, Ginkgo, St Mary's Thistle, Korean Ginseng & Grape Seed **DNA Protection Support**
- Rosemary, Green Tea, Turmeric & Grape Seed **Herbal Antioxidant Tablets**
- Gentian, Wormwood, Feverfew, Ginger & Chen Pi **Bitter Digestive Formula**
- Gotu Kola, Ginkgo & Grape Seed **Connective Tissue & Microcirculation Formula**
- Rhodiola & Korean Ginseng **Vitality & Stamina Tablets**
- Gymnema
- **Allicin Releasing Garlic**

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Cinnamon Quality Issues

Cinnamon Quality

Two main quality concerns:

1. Safety – safe levels of coumarin
2. Identification – accurate ID is challenging

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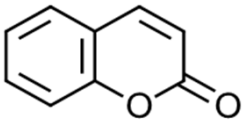
Cinnamon and Coumarin

- Coumarin is a naturally occurring substance in many plants including Cinnamon
- Scheduled S4 substance due to hepatotoxicity concerns. Banned as a food additive in the USA[1]
- Australian limit for coumarin in all Cinnamon products is no more than 0.001% (10ppm)



Coumarin

1. Wang, YH, Avula B et al. *Cassia cinnamon* as a source of coumarin in cinnamon-flavored food and food supplements in the United States. J Agric Food Chem. 2013; 61(18): 4470-4476. doi: 10.1021/jf4005862. PMID: 23627682

Coumarin: Should We be Worried?

- The main pathway of coumarin metabolism is 7-hydroxylation, leading to detoxification; but a minor pathway forms a coumarin 3,4-epoxide intermediate, which can lead to hepatotoxicity
- 7-hydroxylation needs CYP2A6
- Assumed that the cause of higher susceptibility to coumarin is genetic polymorphisms of CYP2A6 with deficient 7-hydroxylation

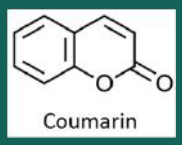
Iwata N, Kainuma M et al. The relation between hepatotoxicity and the total coumarin intake from traditional Japanese medicines containing cinnamon bark. Front Pharmacol. 2016 ; 7: 174. doi: 10.3389/fphar.2016.00174 PMID: 27378929

Cinnamon and Coumarin

- Around 250 species in the genus Cinnamomum
- 4 species below are most commonly used commercially, with wide variation in phytochemistry among species

Ceylon (True) Cinnamon (*C. verum*, syn. *C. zeylanicum*)	Low in coumarin
Cassia (*C. cassia*, syn. *C. aromaticum*)	High in coumarin
Indonesian (Korintji) Cinnamon (*C. burmanni*)	Very High in coumarin
Saigon Cinnamon (*C. loureiroi*)	High in coumarin

C. verum
Low in coumarin



Cinnamon ID is Challenging

- MediHerb's R&D team, partnering with Reading University, embarked on a research project to develop effective ID testing and ensure low levels of coumarin in our Cinnamon products
- Result is novel testing technique focussed on patterns of procyanidins unique to each species[1]

1. Leach D, Fryganas C, Harvey-Mueller I, Wohlmuth H. Phytoequivalence of therapeutic cinnamon barks and extracts with low coumarin levels. Planta Medica. 2017; 4(S 01): S1-S202. doi: 10.1055/s-0037-1608572.

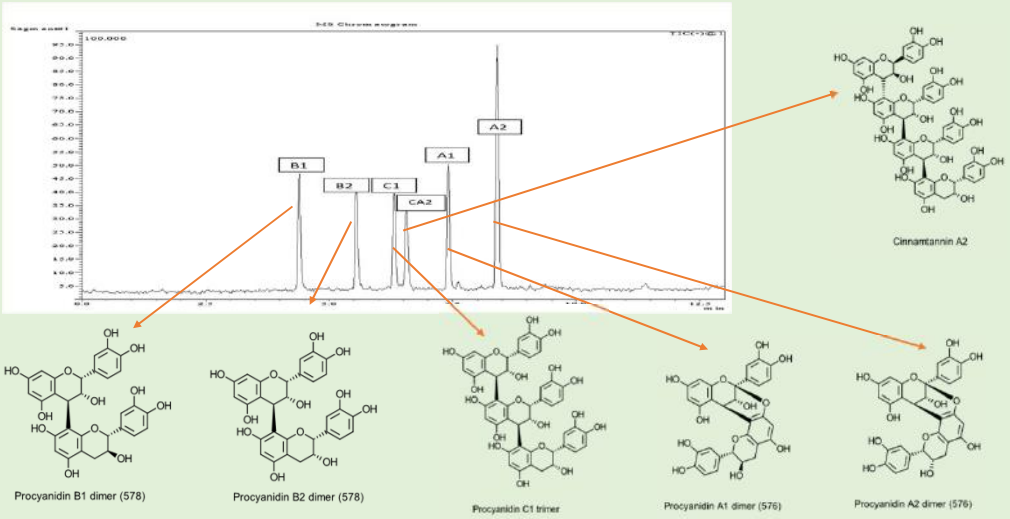
DNA Barcoding: Limited Potential for Cinnamon ID

Sample	Source	Identity by DNA
Bark NCNPR#5502	*C. verum*	No DNA
Bark NCNPR#5226	*C. cassia*	*C. cassia/loureiroi*
Bark NCNPR#5229	*C. loureiroi*	*C. loureiroi/cassia*
Bark NCNPR#5228	*C. burmannii*	*C. burmannii*
Bark	*C. verum*	*C. verum*
Bark	*C. cassia*	*C. cassia/loureiroi*
Bark	*C. verum*	*C. verum/osmophloem*
Extract #1	*C. verum*	No DNA
Tablet (Extract #1)	*C. verum*	No DNA
Extract #3	*C. verum*	No DNA

DNA not detected in any extract

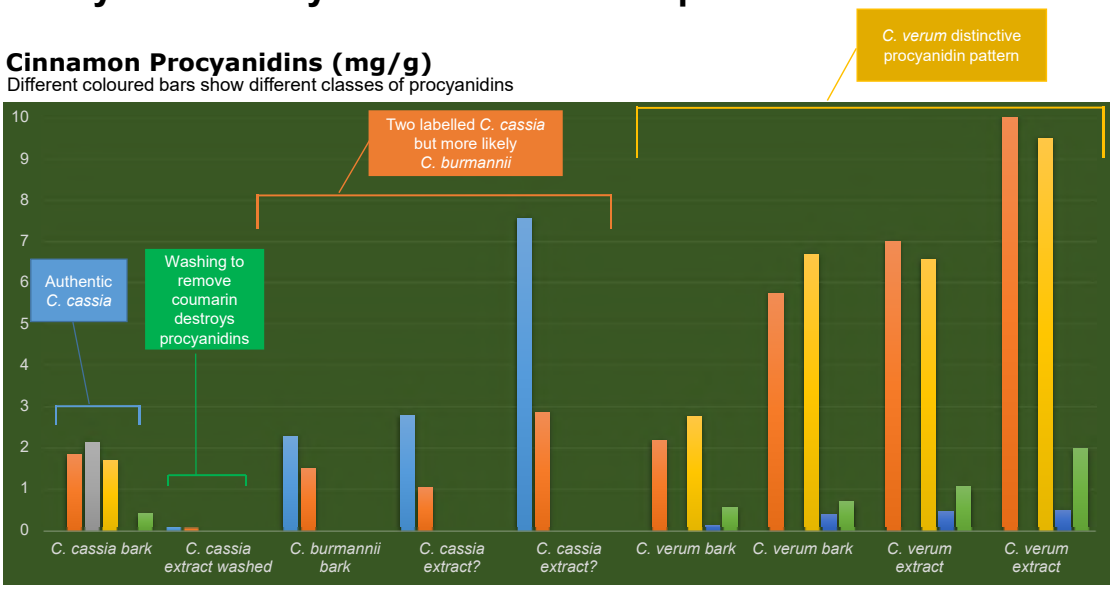
NCNPR: National Centre for Natural Products Research, University of Mississippi reference bark samples supplied by Prof Ikhlas Khan

Procyanidins May Assist Cinnamon Species Identification



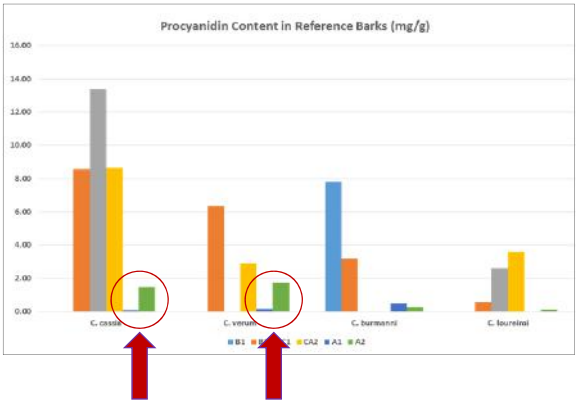
Procyanidins May Assist Cinnamon Species Identification

Cinnamon Procyanidins (mg/g)
Different coloured bars show different classes of procyanidins



Are Cinnamon Species Therapeutically Interchangeable?

- Most human data for blood glucose lowering activity cites *C. cassia*
- Veracity of authentication in research studies is questionable
- *In vitro* study of glucose metabolism
  - 4 species
  - no significant difference in activity
  - active compounds were type A procyanidin oligomers[1]



MediHerb's R&D work indicates that *C. verum* and *C. cassia* contain similar levels of active type A procyanidin dimers

1. Anderson RA, Broadhurst CL et al. Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem. 2004;52:65-70. doi:10.1021/jf034916b. PMID: 14709014

Are Cinnamon Species Medicinally Interchangeable?

Species	Origin	Condensed tannin content[1]	mDP[2]	Procyanidins[3]	cis[3]	trans[3]
C. cassia	China	5.60%	3.8	100	95.5	4.5
C. cassia	China	5.3%	5.0	100	95.0	5.0
C. cassia	China	7.1%	5.1	100	93.2	6.8
C. verum	Sri Lanka	4.8%	5.1	100	95.4	4.6
C. verum	India	6.1%	4.9	100	95.3	4.7
C. verum	India	5.3%	5.7	100	94.4	5.6
C. burmannii?[4]	Indonesia	8.6%	3.3	100	84.6	15.4

[1] HCl-butanol-acetone method; [2] mean degree of polymerization; [3] molar percentage; [4] sample labelled as *C. cassia*

MEDI HERB 85

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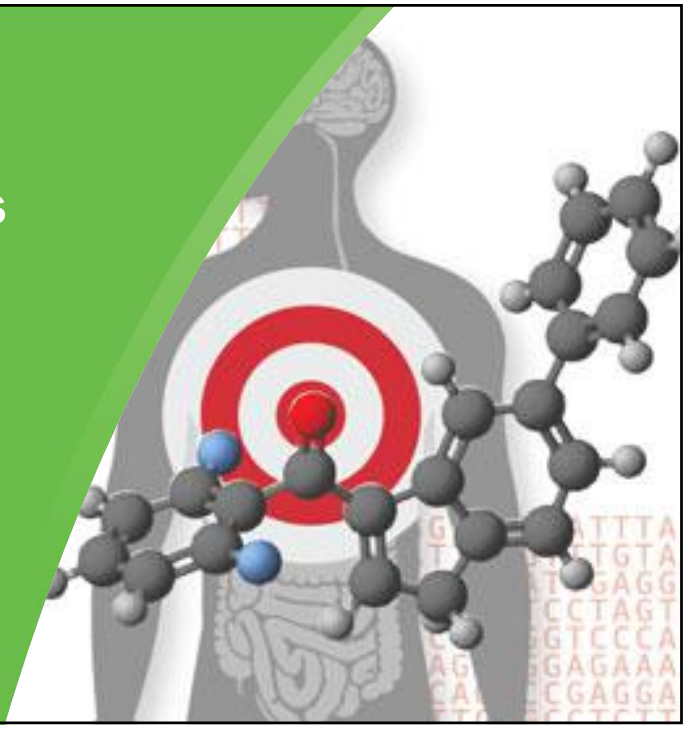
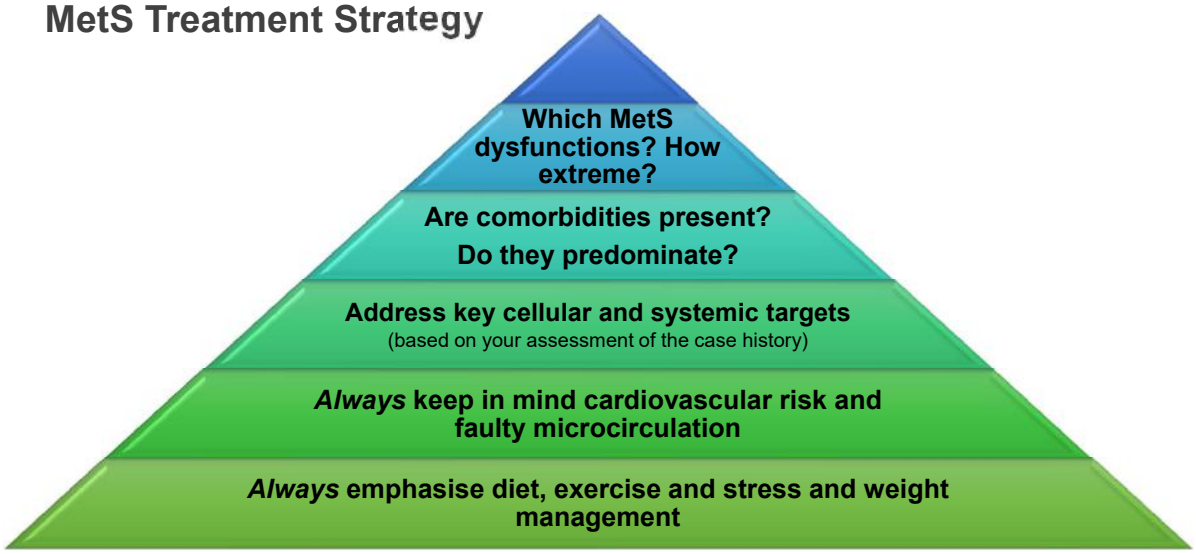
Treatment Strategies in MetS



MetS Treatment Strategy



Be guided by the clinical features of the case

MEDI HERB 87

MetS with Hypertension Predominating

- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **Allicin Releasing Garlic**
- **High Berberine Phellodendron Tablets**

And 8-Point dietary plan

- Key elements DASH guidelines (diet high in fruit, vegetables, whole grains, low-fat dairy products, fish, chicken and lean meats)

In addition include:

- Berries
- Cocoa (85% chocolate, 20 g/day)
- Green tea & hibiscus tea - several cups daily
- Garlic as 1-2 fresh, crushed raw cloves/day
- Beetroot as juice or supplement plus sunlight
- Fibre, especially 30g/day of freshly milled linseeds
- Reduce salt to 3 g/day, increase potassium

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MetS with High Triglycerides & LDL-cholesterol Predominating

- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **High Berberine Phellodendron Tablets**
- **Allicin Releasing Garlic**

MEDI HERB 89

MetS with Poor Appetite Control

- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **Bitter Digestive Formula** (Gentian, Wormwood, Feverfew, Ginger & Chen Pi)
- Gymnema

MEDI HERB 90

MetS with High Blood Glucose Predominating

- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **High Berberine Phellodendron Tablets**

And

- **DNA Protection Support** (Polygonum, Ginkgo, St Mary's Thistle, Korean Ginseng & Grape Seed)

Or

- **Bitter Digestive Formula** (Gentian, Wormwood, Feverfew, Ginger & Chen Pi)

Or

- Gymnema

MetS with Previous Heart Attack & Under Work/Life Stress

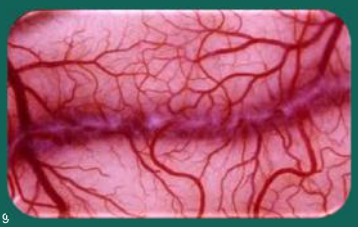
- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **Bioavailable Curcumin**
- **Connective Tissue & Microcirculation Formula** (Gotu Kola, Ginkgo, Grape Seed)

And

- Kava, Valerian
- Rehmannia etc

MetS with Clear Microvascular Issues

- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **Bioavailable Curcumin**
- **Connective Tissue & Microcirculation Formula** (Gotu Kola, Ginkgo & Grape Seed)



And 5-point dietary plan

- Boost dietary nitrate: green leafy vegetables, but especially beetroot as juice or a supplement
- Increase cocoa intake: 90% chocolate or cocoa 20 g/day
- Increase berry anthocyanin intake: 50 to 100 g/day of blueberries, strawberries, raspberries and blackberries
- Raw crushed Garlic: ½ to 1 clove/day
- Increase herbs and spices: especially Green Tea (3 to 4 cups/day with meals), Turmeric and Ginger

Older Male with MetS and Low Testosterone

- **MetS Support** (Nigella, Bitter Melon, Cinnamon & Fenugreek)
- **Bioavailable Curcumin**
- **Male Reproductive Support** (Tribulus Leaf)

And

- **DNA Protection Support** (Polygonum, Ginkgo, St Mary's Thistle, Korean Ginseng & Grape Seed)

Or

- **Vitality & Stamina Tablets** (Rhodiola & Korean Ginseng)

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Case Studies

Case Study 1

- Male patient aged 79 years with elevated body weight (95 Kg) and features of insulin resistance (mainly moderate hypertension 150/95 and FBG of 6.7 mmol/L)
- Also elevated cholesterol (7.4 mmol/L) and reduced kidney function (GFR 46)
- Had stopped all drug medication (was on 8 different drugs)
- The 8-point hypertension diet was recommended, together with more exercise and reduced carbs

MEDI HERB 96

Case Study 1

Herbal treatment

- **Allicin Releasing Garlic Tablets** containing *Allium sativum* (Garlic) extract equivalent to fresh bulb 3.6 g; standardized to alliin 12 mg (1 twice a day)
- Tablets containing *Gymnema sylvestre* (Gymnema) 4g (1 before each meal)
- **Bioavailable Curcumin Tablets** containing 100 mg bioavailable curcuminoids (2 twice a day)
- **St Mary's ThistleTablets** containing *Silybum marianum* extract equivalent to dry seed 14.7 g; standardized to contain flavonolignans calculated as silybin 168 mg (1 twice a day)

Case Study 1

- Also was taking **High Berberine Phellodendron Tablets** providing 800 mg of berberine per day
- After 12 months of treatment has lost 10 cm from waist and 11 Kg
- LDL-cholesterol was down by 10% after 6 months, awaiting another test, and also for GFR
- BP fluctuated, but averaged about 150/80; FBG was around 5.8 mmol/L
- He is now also taking **MetS Support** (Nigella, Cinnamon, Bitter Melon and Fenugreek), which has further reduced his BP to 138/77

Acknowledgments

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- Prof David Leach
- Billie O'Connor

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Appendix Slides

Will Berberine Imbalance Bowel Flora?

- Berberine has a broad-spectrum antimicrobial activity against protozoa, bacteria and fungi, so is less likely to induce a flora imbalance
- Tests have shown that it is LESS active against healthy bowel flora than pathogenic bacteria[1]
- A study in rats fed a high fat diet found berberine improved healthy bowel flora (short-chain fatty acid (SCFA) producers)[2]

1. Li GH, Wang DL et al. Berberine inhibits acute radiation intestinal syndrome in human with abdomen radiotherapy. Med Oncol. 2010; 27(3): 919-925. doi: 10.1007/s12032-009-9307-8. PMID: 19757213
2. Zhang X, Zhao Y et al. Structural changes of gut microbiota during berberine-mediated prevention of obesity and insulin resistance in high-fat diet-fed rats. PLoS One. 2012; 7(8): e42529. doi: 10.1371/journal.pone.0042529. PMID: 22880019

Case Study 2

- Male patient aged 59 years with elevated body weight (110 Kg) and features of insulin resistance (mainly moderate hypertension), mildly elevated cholesterol (6.4 mmol/L) and asthma
- Was on no drug medication
- Thyroid function and all other tests in normal ranges
- The 8-point hypertension diet was recommended, together with more exercise and reduced carbs

Case Study 2

Herbal treatment

- **Allicin Releasing Garlic Tablets** containing *Allium sativum* (Garlic) extract equivalent to fresh bulb 3.6 g; standardized to alliin 12 mg (1 twice a day)
- **DNA Protection Support** Tablets containing *Raynoutria japonica* (Polygonum/Giant Knotweed) root 8.0 g, *Vitis vinifera* (Grape Seed) 4.8 g, *Silybum marianum* (St Mary's Thistle) fruit 4.2 g, *Ginkgo biloba* (Ginkgo) leaf 1.5 g and *Panax ginseng* (Korean Ginseng) root 250 mg (2 before breakfast)

Case Study 2

Herbal treatment

- **Bioavailable Curcumin Tablets** containing 100 mg bioavailable curcuminoids (1 twice a day)
- **Coleus Tablets** containing *Coleus forskohlii* 5.61 g; standardized to contain forskolin 18.7 mg (1 twice a day)
- Over 12 months there has been a gradual reduction in body weight, waist measurement and blood pressure
- Recent readings: BP 130/85, waist down by 8 cm, body weight down 6 Kg