Clinical Cases in Cardiovascular Medicine

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Case 1 - Mrs SD. Age 57

- Presents to GP with palpitations on and off for 4 months
  - Hypertension (BP154/96)
  - Obesity – weight 120Kg, BMI 38
  - "Mild diabetic"
  - GORD
- Drugs:
  - Inhibace plus (5mg/12.5mg) one daily
  - Omeprazole 40mg daily

Case 1 - Mrs SD. Age 57

- What next?

Case 1 - Mrs SD. Age 57

- What next?
- Triggers - Other triggers or symptoms
  - ? Stimulants – caffeine, “energy” drinks
  - exercise
- What is the palpitation?
- ECG
- Investigations

Case 1 - Mrs SD. Age 57

- Palpitations – from the history

Patient Symptom/description	Probable dysrhythmia
Missed beats / bumps	Ectopics (atrial or ventricular)
Flutters (irregular)	PAF or salvoes of ectopics
Racing heart (> 130/min regular) – usually of sudden onset	SVT - AV re-entry tachycardia, atrial flutter with 2:1 block (150/min) or VT (especially if known IHD)
Thumping heart (regular <130/min)	Sinus tachycardia or slow VT

Case 1 - Mrs SD. Age 57

- Investigations
  - ECG – Sinus rhythm with frequent single and coupled supraventricular ectopics
- Additional tests?

Case 1 - Mrs SD. Age 57

TEST	RESULT	
FBC	Normal	
TFTs	TSH	3.2 (0.6-4.5)
U+E	K^+	3.2 mmol/l
	Na^+	130 mmol/l
	Urea	7.8 mmol/l
	Creatinine	118 mcmol/l
	Random glucose	9.8 mmol/l
	HBA1c	6.9%
Another test???		

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	HBA1c	6.9%
Magnesium		0.68 mmol/l (0.75-1.25mmol/l)

Case 1 – Treatment Plan

- What next?

Case 1 - Treatment

- Thiazide diuretic - ? stop
  - Hypokalaemia
  - Hypomagnesaemia
  - Worsening of IGT

- Reassess the need for PPI
  - Hypomagnesaemia
  - Impairment of absorption of Iron, Calcium and B_{12}

Hypomagnesaemia

- Associated with:
  - Hypertension
  - Impaired Glucose tolerance and diabetes
  - Muscle cramps
  - Arrhythmias – supraventricular and ventricular
  - Impaired muscle power
  - Impaired production of ATP (co-factor)
  - Impaired DNA and protein synthesis
  - Hypocalcaemia and reduced PTH production
  - Impaired Vitamin D utilisation
  - Prolonged PR, QT intervals, QRS duration, flat T waves
  - Digoxin toxicity

Hypomagnesaemia - Common but ignored

- Present in 12 % of hospitalized patients and 65% of ITU cases
  - Measurement – serum/plasma levels may be misleading
  - Intracellular ion; plasma level may be normal but the intracellular level low (RBC or mononuclear cell Mg^{++} expensive)

- Origins – Food (as long as it is in the soil)
  - Legumes, whole grains, nuts, green vegs, milk

Magnesium

- PPIs??
  - Reduced Absorption (orotic acid in small bowel)
  - pH dependant – needs acid environment
  - Gastric pH > 6-7 reduces absorption markedly

- Diuretics – both loop and thiazide
  - Increased losses

Magnesium supplements - Bioavailability

- NEED approx. 500mg elemental Mg per day
- Bioavailability:
  - Low < 10% absorbed:
    - Mg oxide and hydroxide (<10%)
  - Medium - approx. 40% absorbed
    - Mg chloride, citrate
    - Mg amino acid chelate
    - Mg aspartate, lactate
  - High > 60%
    - Mg orotate

Case 1 - Mrs SD

- Treatment:
  - Stopped diuretic and PPI
  - Corrected K with supplements
  - Added Mg supplements
  - Palpitations disappeared

- Other issues:
  - Added CCB for BP control
  - Diet
  - Metformin for diabetes
  - Statin for poor lipids

Case 2 – Mr JT age 68 Presents with:

- Continuing troublesome angina several times a day
- Muscle aches and pains especially the large muscles in the legs which he thinks is the statin

Case 2 – Mr JT age 68

- IHD
  - Anterior STEMI 2004
  - 4 x CABG 2004
  - NSTEMI 2008 – Angios:
    - Diffuse disease - stent to RCA
    - 2 x SVGs occluded. LIMA patent
  - NSTEMI 2010 Angios:
    - diffuse disease – for medical management
    - EF 30%

Case 2 – Mr JT age 68
Co-morbidities

- CCF – NYHA class II/III
- T2 Diabetes – HBA1c 9.6%
- Painful peripheral neuropathy in feet
- Hypertension
- Hyperlipdaemia
  - TC 4.6; HDL 0.8; LDL 2.4; TG 2.2
- Statin-induced myopathy with Simvastatin and struggling on with atorvastatin 10mg

Case 2 – Mr JT age 68
Current therapy:

- Betaloc CR 95mg daily
- Atorvastatin 10 mg daily (doesn't like it)
- Aspirin 100mg daily
- ISMN SR 90mg daily
- Inhibace 0.5 mg
- Metformin 850mg tds
- Pantoprazole 40mg daily
- Nortryptiline 25mg at night

- Allergies
  - CCBs cause oedema

Case 2 – Mr JT age 68
Problems:

- Continuing troublesome angina several times a day
- Muscle aches and pains especially the large muscles in the legs which he thinks is the statin
- Painful feet

Case 2 – Mr JT age 68
What next?

- Angina
- Myopathy
- Diabetic neuropathy

Case 2 – Mr JT age 68 What next?

- Chronic Stable Angina
  - Perhexiline (needs spec. Auth)
- Morphine?
- Spinal cord stimulator?

Case 2 – Mr JT age 68 What next?

- Chronic Stable Angina
  - Allopurinol (Noman et al. Lancet June 2010)
    - 600mg (titrated gradually) daily increased exercise capacity and walking time by 25% (p=0.0002)
    - Allopurinol protects heart from oxygen deprivation

Case 2 – Mr JT age 68
What next for Statin Myopathy

- ?

Case 2 – Mr JT age 68
What next for Statin Myopathy

- Ezetimibe
- Fibrates
- Nicotinic acid
- Co-enzyme Q10
- Red Yeast Rice

Case 2 – Mr JT age 68
What next for Statin Myopathy

- Ezetimibe:
  - Lowers LDL by 18% BUT No outcome evidence for benefit
- Nicotinic acid (Taylor et al. NEJM. November 2009)
  - Niacin LA (Niaspan) 2000mg + low dose statin caused significant reduction in carotid atheroma vs. Statin + ezetimibe (actually worsened)
- Fibrates
  - Can cause myopathy and much less effective than statins

Case 2 – Mr JT age 68
What next for Statin Myopathy

- Co-enzyme Q10
  - ? Helps to reduce myopathic symptoms
  - Conflicting reports from small studies
- Red Yeast Rice (Becker D et al. Annals Int Med. June 2009)
  - Lovastatin monocolins isolated
  - Patients with statin myopathy
  - 1800mg-2400 mg daily reduced LDL by 22% (similar to pravastatin 20mg)
  - No muscle problems

Case 2 – Mr JT age 68
What next for diabetic neuropathy?

- Anti-epileptic drugs
  - Carbamazepine / Gabapentin

- Alpha-lipoic acid – powerful thiol antioxidant – central to antioxidant defence of brain and nervous system
  - R-DB-PC trial in distal symmetrical neuropathy
  - 600mg daily $\rightarrow$ 62% reduction in total symptom score (pain, burning, numbness) score after 5 weeks ($p<0.05$). (Ziegler D et al. Diabetes Care. 2006;29:2365-70)

Case 3: The Hypertensive Middle Manager

- 43 yr old male middle manager in IT company
- Hypertension – BP average over 6 readings 162/90
- Father had MI at 66
- Overweight (BMI 30)
- GORD
- Alcohol approx. 30 units / week
- Non-smoker 6-months
- Exercise – plays squash once a week

Hypertensive Middle Manager

- What do you do next?

- Risk factor profiling:
  - Lipids
  - Fasting glucose
  - Renal function
  - Na/K/Mg
  - ECG

Hypertensive Middle Manager

- Risk factor profiling:
  - Lipids – TC 5.9; HDL 0.9; LDL 4.2; TG 2.6
  - Fasting glucose – 5.9mmol/l
  - Renal function – Urea 6.9; Creatinine 96
  - Na/K/Mg – 138/3.8/0.72
  - ECG – normal

Cardiovascular Risk Score

- 5 – year risk

Cardiovascular Risk Score: 5 – year risk

- 10-15%

- Recommendation:
  - Smoking cessation
  - Non-pharmacological treatment to reduce risk

Lifestyle and ? Nutraceuticals

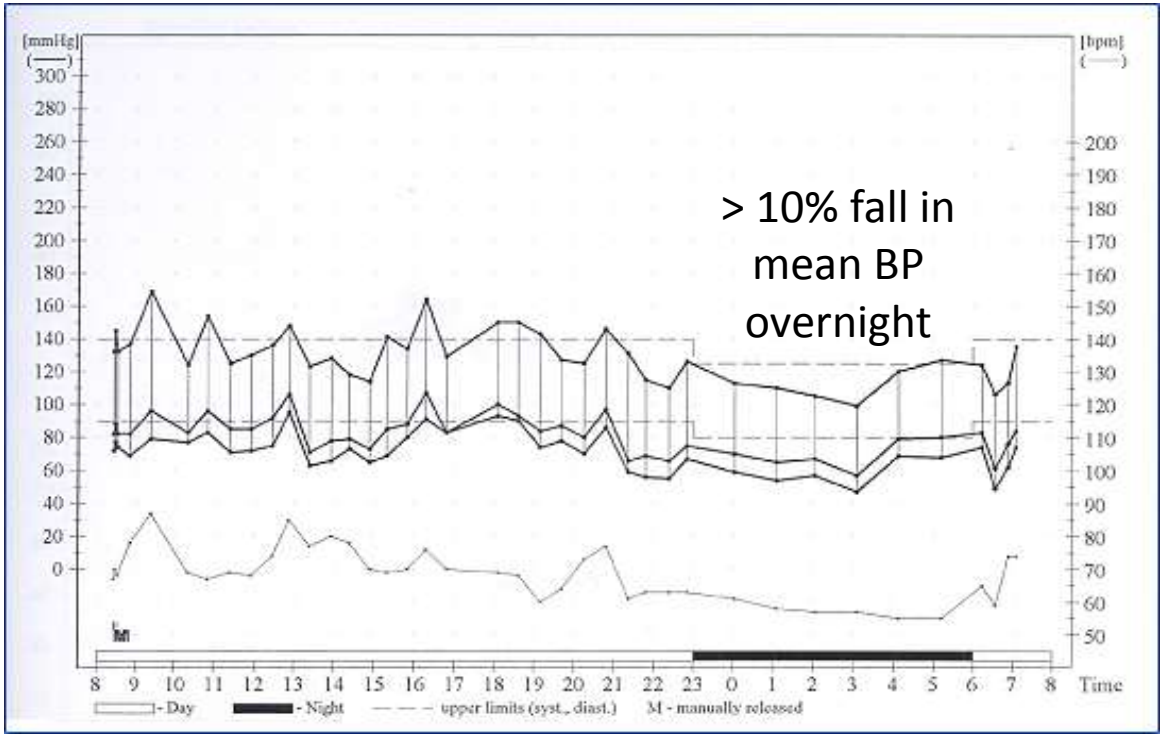
- Exercise
- Weight loss
- Nutrition and specific nutrients
- Vitamin D

Exercise and hypertension

- How much? (Whelton SP et al. Effect of aerobic exercise on BP – a metaanalysis of RCTs. Ann Intern Med 2002;136:493-503)
  - Moderate intensity (40-70% VO2 max) for 30-60 minutes 5-7 x weekly
  - > 70% VO2 max has no additional effect on BP

- 25% patients do not respond to exercise (Hagberg JM. The role of exercise training in the treatment of hypertension. Sports Med 2000;30:193-206)
  - ?? The non-dippers are the non-responders

24 hour Ambulatory BP measurement- Dippers vs. Non-Dippers



> 10% fall in mean BP overnight

Non-dippers – Increased target organ damage – heart and kidneys

When to exercise? (Park et al. Journal of Human Hypertension 2005;19(8):592-605

DIPPERS	Non-DIPPERS
Exercise anytime reduced average BP but not the mean nocturnal BP	Daytime exercise reduced mean BP
	Evening exercise reduced nocturnal BP very significantly

Message

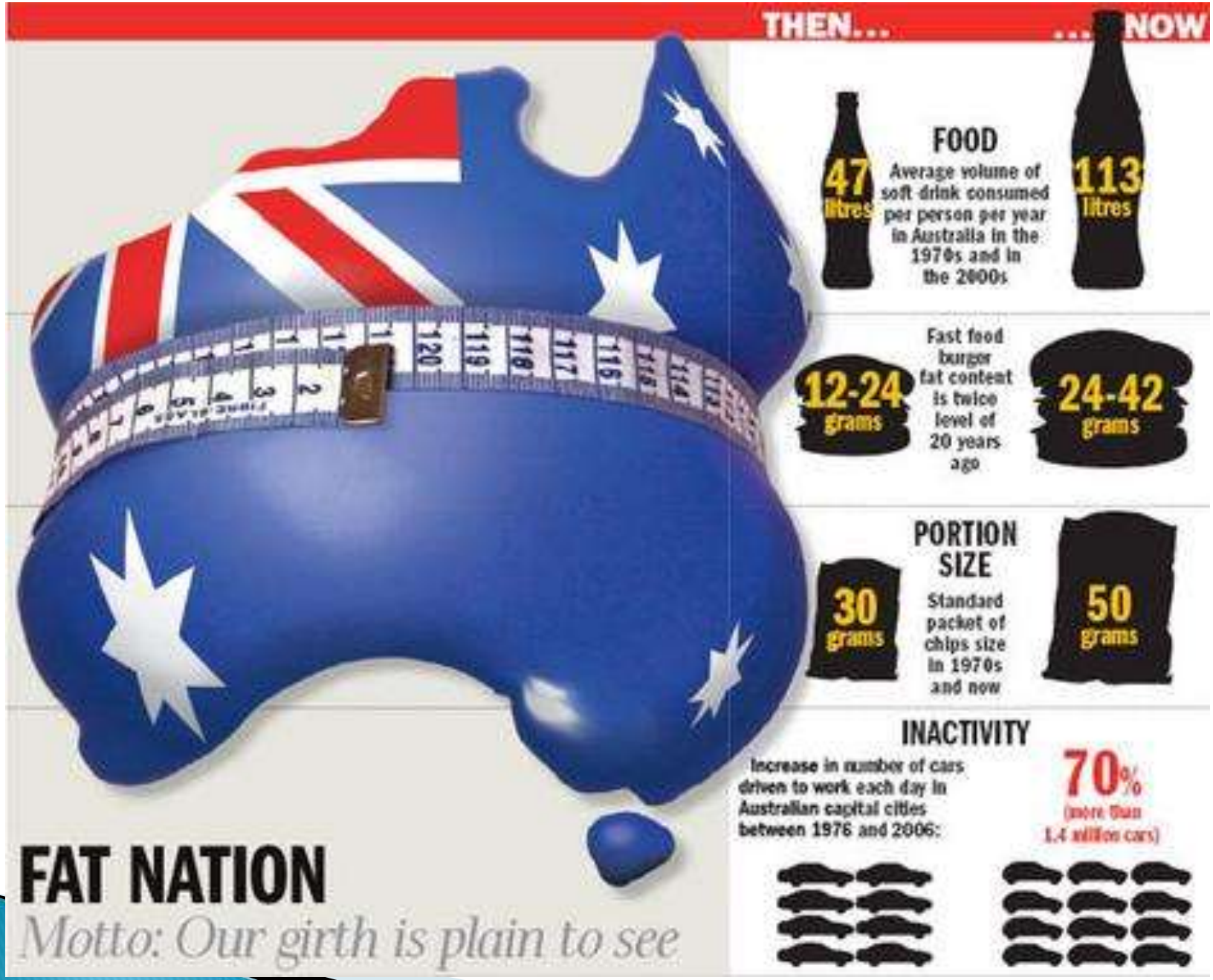
Non-dippers should exercise in the evenings

Dippers exercise anytime

Additional Benefits of Exercise

(Whelton SP et al. Effect of aerobic exercise on BP – a metaanalysis of RCTs. Ann Intern Med 2002;136:493-503)

Moderate Exercise (40-70% VO2 max)	Heavy Exercise (> 70% VO2 max)
Reduced platelet adhesiveness	Increased platelet aggregation Increased platelet count
Increased fibrinolysis Coagulability unchanged	Increased fibrinolysis Increased Coagulability
Reduction in LV hypertrophy Reduced oxidative stress Increased NO availability Improved metabolic profile Improved exercise capacity Improved QoL	


THEN...
...NOW
47 litres
FOOD
Average volume of soft drink consumed per person per year in Australia in the 1970s and in the 2000s
113 litres
12-24 grams
Fast food burger fat content is twice level of 20 years ago
24-42 grams
30 grams
PORTION SIZE
Standard packet of chips size in 1970s and now
50 grams
INACTIVITY
Increase in number of cars driven to work each day in Australian capital cities between 1976 and 2006:
70%
(more than 1.4 million cars)
FAT NATION
Motto: Our girth is plain to see

Weight Loss and Hypertension

- Framingham Study – Long-term effects of weight loss (Moore LL et al. Weight Loss in Overweight Adults and the long-term Risk of Hypertension. Arch Intern Med 2005;165(11):1298-1303)
  - Weight loss of > 6.8Kg reduced risk of developing hypertension by 21-29%
  - Sustained (>4 years) weight loss reduced hypertension risk by 22% in middle-aged and 26% in older adults
- Modest weight loss, particularly when sustained, substantially lowers the long-term risk of hypertension in overweight adults

Weight loss facts

- Every 1% Weight ↓ = 1 mmHg ↓ BP.

- Weight-reducing diets:
  - 3–9% decrease in body weight
    - reduces SBP + DBP by 3 mmHg.
  - Losing 4.5 kg
    - reduces blood pressure or prevents hypertension in a large proportion of overweight people
  - Losing 10 kg
    - can reduce systolic blood pressure by 6–10 mmHg.

Weight Loss and Hypertension

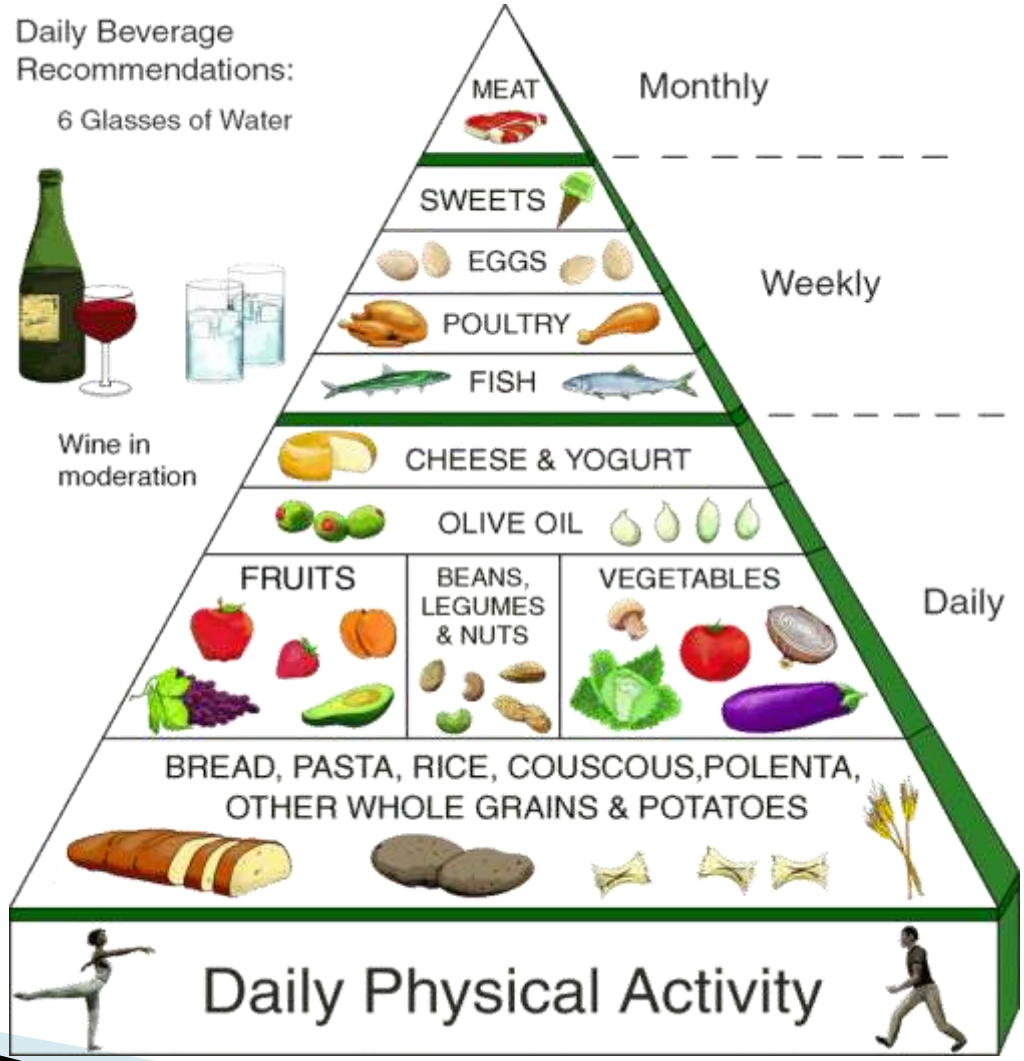
- Obesity, Diabetes, Hypertension and the metabolic syndrome are associated with **elevated levels of inflammatory cytokines and Excess Free Radicals**

- Weight loss by however achieved:
  - Dramatically reduces inflammation as measured by CRP

What diet is best, Doc?

- Low fat / high carb? – Worsens cardiovascular risk factors
- High protein / low carb? – Atkins-type
  - Improves lipid profile but difficult to sustain
- Palaeolithic – not studied in depth
- Mediterranean
  - Improves insulin sensitivity
  - Improves lipid profiles
  - Reduces BP
  - Reduces cardiovascular risk

The Mediterranean diet



Olive oil, the Mediterranean Diet and arterial BP.
Am J Clin Nutr. 2004;80(4):1012-18

- 20,343 participants in the Greek EPIC Study (European Prospective Investigation into Cancer and Nutrition)
- 10-point score of adherence to MD
  - Effect of individual components and Olive oil
- Diet score significant inverse association with both systolic and diastolic BP
  - Olive oil, vegetables and fruit – inverse risk
  - Cereals, meat and meat products positive correlation with risk
- Olive oil had dominant effect overall on BP

Mediterranean Diet and Incidence of Hypertension

(Hypertension 2009;54:1143-1150)

- 9,408 men and women enrolled 1999-2005 in prospective cohort study
- 9-point MD score
- Median follow up 4.2 years
  - Systolic BP reduced by 2.4mmHg in moderate adherence and 3.1 in high adherence
  - Diastolic BP reduced 1.3mmHg in moderate and 1.9mmHg in high adherence after 6 years follow up

Olive oil and reduced need for antihypertensive medications

Arch Intern Med. 2000 Mar 27;160(6):837-42

- 23 Hypertensive patients - Randomised double blind crossover study
  - Extra Virgin Olive oil (MUFA) vs. Sunflower (PUFA)
- Resting BP was significantly lower at the end of the MUFA diet compared with the PUFA diet (P = 0.05 for systolic BP; P = 0.01 for diastolic BP)

Olive oil and reduced need for antihypertensive medications

Arch Intern Med. 2000 Mar 27;160(6):837-42

- Daily drug dosage was significantly reduced during the MUFA but not the PUFA diet (-48% vs. - 4%, $P<0.005$).
- All patients receiving the PUFA diet required antihypertensive treatment,
- 8 of those receiving the MUFA diet needed no drug therapy.

Endothelial Dysfunction and Hypertension (Wong WT. J Cardiovasc Pharmacol. 2010;55(4):300-7)

- Key role in vascular complications of diabetes and hypertension.
  - ↓ Endothelium-derived NO synthesis
- Exaggerated production of vasoconstrictors
  - Angiotensin II, endothelin-1, reactive oxygen species, cyclooxygenase-derived metabolites of arachidonic acid
- Specific therapies:
  - target Renin-angiotensin system
  - Increase NO synthesis
  - Antioxidants vs. Reactive oxygen species

Specific Nutritional components and Hypertension

- Magnesium – the forgotten mineral
  - Epidemiologically inverse relationship with Mg intake and BP
  - Cellular depletion contributes to LVH, insulin resistance, obesity and Type 2 diabetes, arrythmias
  - Intracellular Magnesium deficit (NMR spectroscopy) in human hypertension

Effects of Magnesium supplementation in Hypertension.

***Hypertension* 1998;32:260-265Kawano et al.**

- 34 male and 26 female Japanese hypertensives
- 8 weeks supplementation Mg oxide 480mg

- Systolic and diastolic BPs fell significantly
- Those with highest BP had greatest falls

- Other trials give a mixed picture

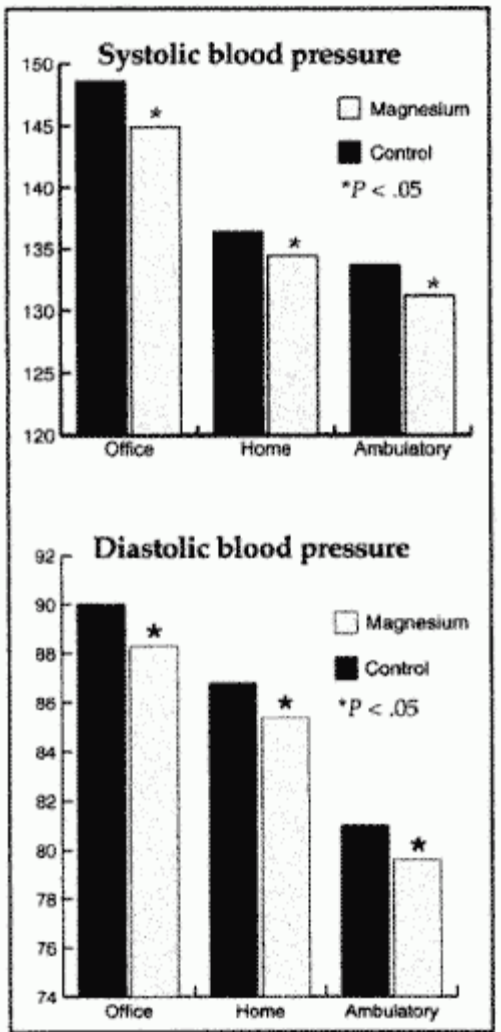
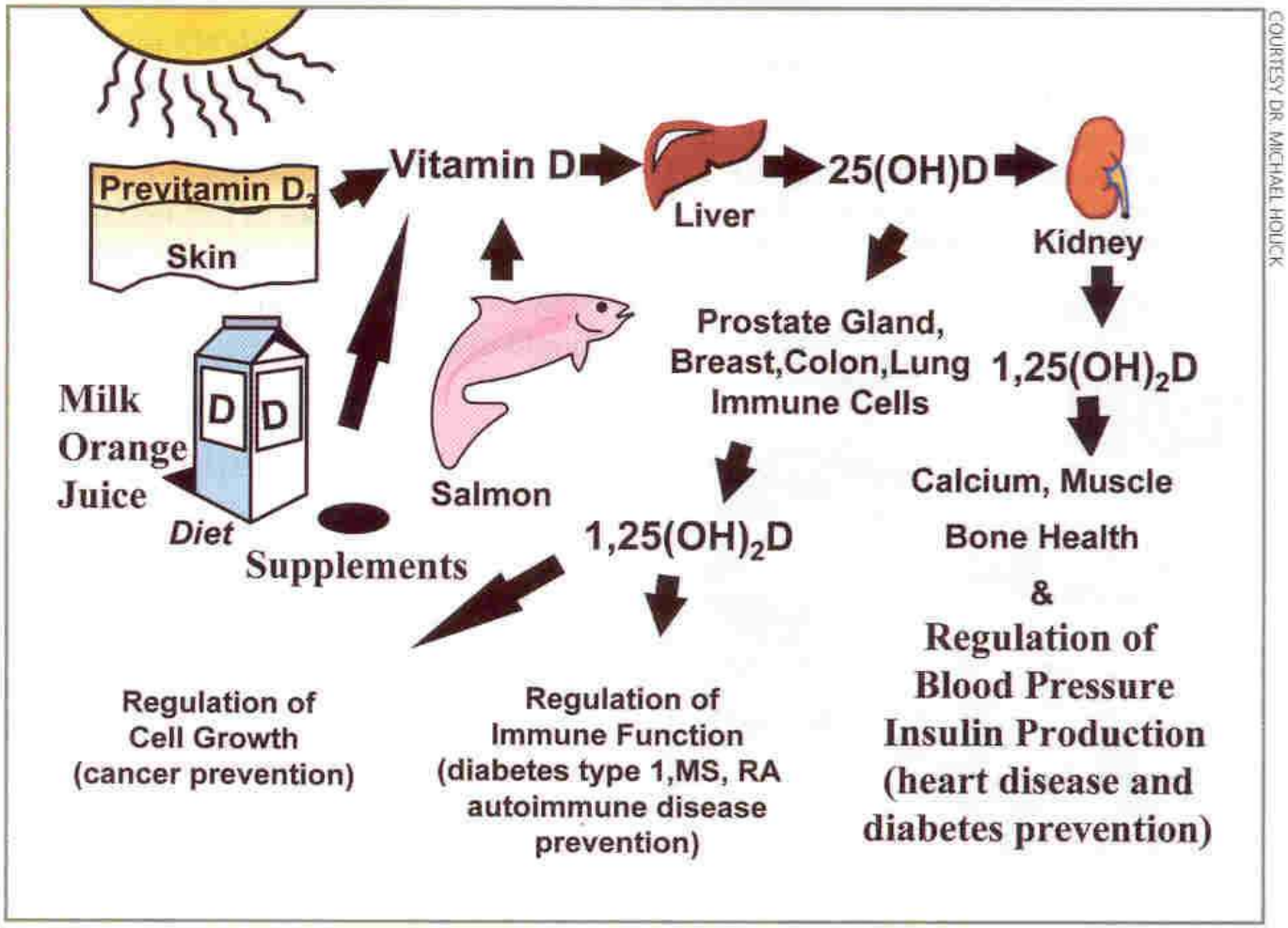


Figure. Oral magnesium oxide supplementation lowered systolic and diastolic blood pressure measured in the office, at home, and when ambulatory (data from Kawano, Matsuoka, Takishita, and Omae).

Magnesium and Hypertension Points of interest

- Universal intracellular deficit of Mg
- Serum Mg values can be within the normal range
- Proper patient selection
  - Patients with high or normal Renin have low intracellular and serum magnesium levels
  - Normal or High Renin predicts response to Mg

Vitamin D and Hypertension



COURTESY DR. MICHAEL HOLICK

Vitamin D and Hypertension

Nat Rev Cardiol. 2009 Oct;6(10):621-30. Epub 2009 Aug 18

- Vitamin D
  - renoprotective effects
  - suppression of the renin-angiotensin-aldosterone system
  - direct effects on vascular cells
  - effects on calcium metabolism, including prevention of secondary hyperparathyroidism

Plasma 25-Hydroxyvitamin D Levels and Risk of Incident Hypertension Among Young Women

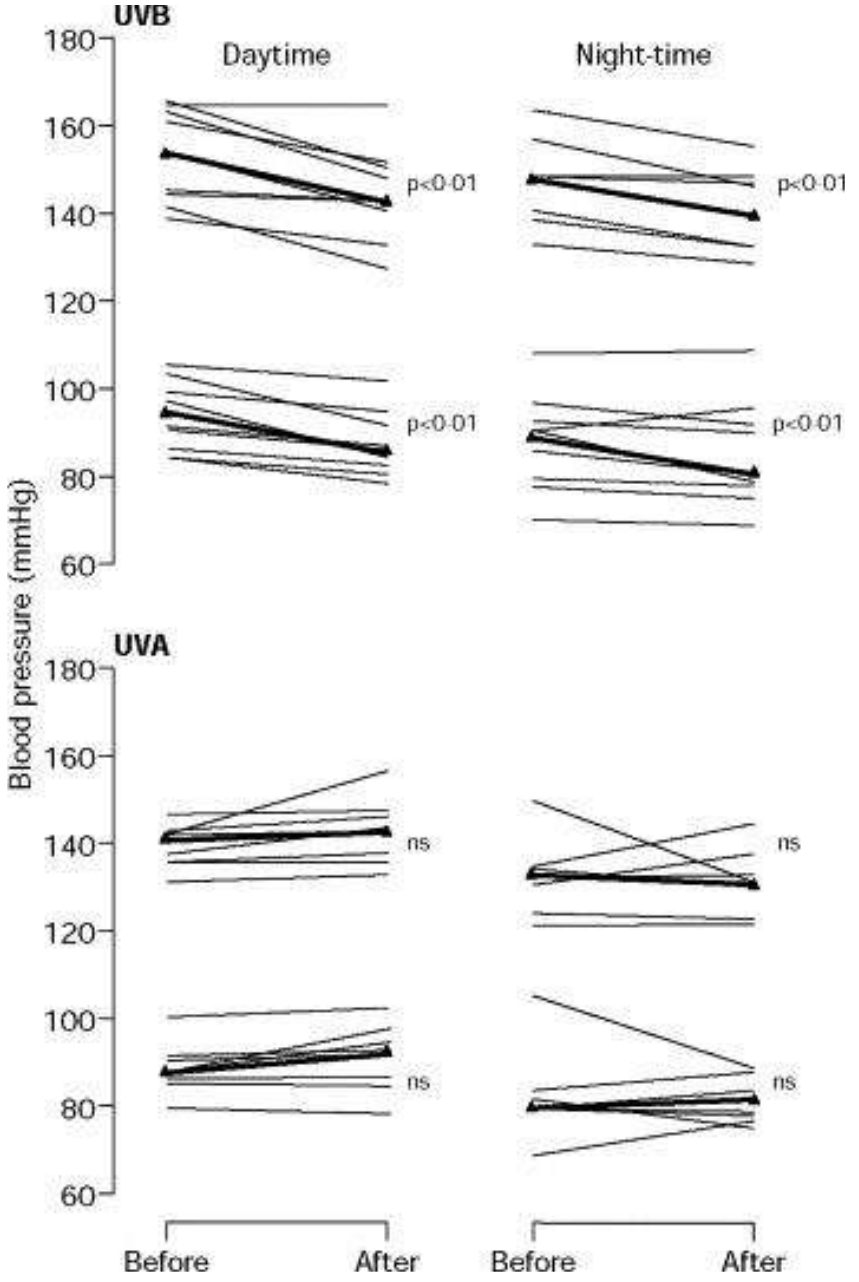
Hypertension. 2008;52:828-832

- 1484 women aged 32-52 yrs without hypertension
  - Nested case-control study
- Median 25OH-D level 64nmol/l (controls 68nmol/l)
- Lowest vs.highest quartile of Vitamin D - OR of developing hypertension **1.66** (1.11-2.48)
- Vitamin D level < 75nmol/l had multivariable OR **1.47** for developing hypertension

UVB and hypertension

•18 patient with mild untreated hypertension (age 26-66)
•UVB vs. UVA 3 x weekly for 6 weeks
•162% increase in Vitamin D (UVB)
•Significant fall in both systolic and diastolic day and night-time BP

The Lancet 1998; 352:709-710



Can Vitamin D supplementation treat or prevent hypertension?

- Trials are conflicting
- Levels of supplementation were low and the levels of plasma Vitamin D achieved barely reached the minimum level now regarded as indicating sufficiency (75nmol/l)

- Big interventional trials needed aiming to achieve levels > 75 nmol/l

Nutraceuticals and Hypertension

- Co-Enzyme Q 10 – conflicting results
- Hawthorn – unclear. Does help in heart failure
- Pycnogenol
- Grape seed extract – (works in rats)
- Tomato Extract
- Melatonin

Nutraceuticals and BP

- ***Pycnogenol*** ® (French Maritime Pine Bark extract) D-B PCT trial (Liu X et al. Life Sci. 2004;74(7):855-62)
  - 58 pts with mild hypertension – 100mg daily over 12 weeks
  - Significant reduction in Nifedipine dosage achieved
  - Significant decrease in endothelin-1 level

Tomato Extract - R-PCT, double-blind crossover (Paran E et al. Cardiovasc Drugs Ther. 2009;23:)

- 50 poorly controlled hypertensive patients already on variety of drugs
  - Automatic BP measurements
  - Lyc-O-Mato 250mg daily
  - Reduction of **13/4** mmHg vs. Placebo
  - Reduced lipid peroxidation products

- Flavonoids - Lycopene, quercetin, rutin
  - Antioxidants
    - Protects NO from degradation by oxygen free radicals
- Polyphenols
  - Increases l-arginine availability (rate-limiting factor in production of NO)

Melatonin in Hypertension

- Significantly reduces night blood pressure in patients with nocturnal hypertension
  (Grossman E et al. Am J Med 2006;119(10):898-902)

- 38 treated hypertensives (non-dippers)
- RDBPCT
- SBP reduced (p=0.01)
- DBP reduced (p=0.002)
- Most prominent between 2.00 AM and 5.00AM

Summary and thoughts

- The use of current drug therapies
  - What adverse effects are we ignoring?
    - Magnesium and potassium deficiency in diuretic use
    - Magnesium deficiency with PPIs
- Many unanswered questions and need for interventional trials:
  - Adequate Vitamin D – an exciting prospect in many facets of Medicine
  - Antioxidants – a target for new drugs?