Orthomolecular Cardiology:
Unmasking the magnesium link to multiple cardiovascular risk factors

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The growing burden of heart disease

- In Canada cardiovascular disease is the most common chronic degenerative disease
  - affects 11.6% of the population
- It is also the most costly disease to treat
  - $21.2 billion in direct and indirect costs annually
- For comparison, musculoskeletal diseases are 2nd at $18.8 billion, and cancer comes 3rd at $16.3 billion

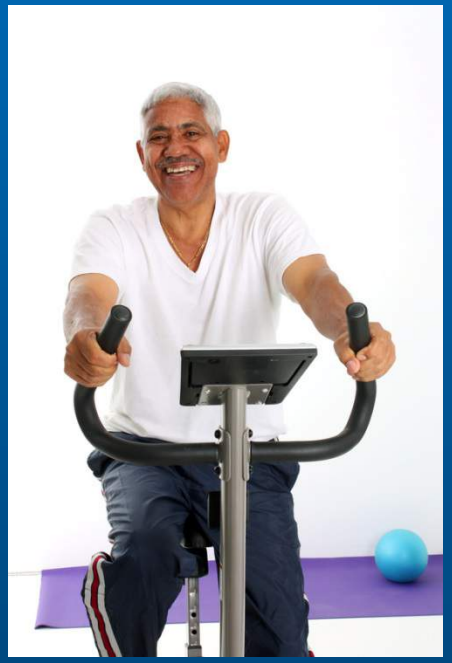
Coronary Heart Disease Statistics

by country *(www.worldlifeexpectancy.com)*

Country	Death rate (per 100,000)	Ranking (out of 192 countries)
Ukraine	399.8	2
Russia	296.7	9
USA	80.5	135
Ireland	79.2	138
Canada	66.2	159
Japan	31.2	190
France	29.2	191

Risk factors for cardiovascular disease

- Non-modifiable risk factors
  - Family history, age, sex and ethnicity
- Modifiable risk factors
  - Dysregulated cholesterol
  - High blood pressure
  - Obesity
  - Unhealthy diets
  - Inactivity
  - Excess alcohol
  - Smoking



Low-risk diet and lifestyle habits in the primary prevention of myocardial infarction in men

Åkesson, A et al. J Am Coll 2014;64(13):1299-1306

- Study: 45-79 yr-old Swedish men (n=20,071) followed for 12 years
  - No history of cancer, diabetes, cardiovascular disease, ↑BP or cholesterol
- Results: Adherence to 5 "lifestyle" habits reduced the incidence of heart attacks **by 79%**
  - Exercise; Not smoking; Healthy diets, Low abdominal fat
  - Modest alcohol intake (1-2½ drinks a day)

Women and Heart Disease
The estrogen advantage?

- CVD used to considered mainly a man's disease
  - However its the #1 killer of women in Canada and worldwide
  - Women are x 10 times more likely to die from CVD than from any other disease
- Premenopausal women have a lower risk of CVD than age-matched men
  - This advantage disappears after menopause

Primary prevention of coronary heart disease in women through diet and lifestyle

Stampfer MJ et al. N Engl J Med 2000;343(1):16-2

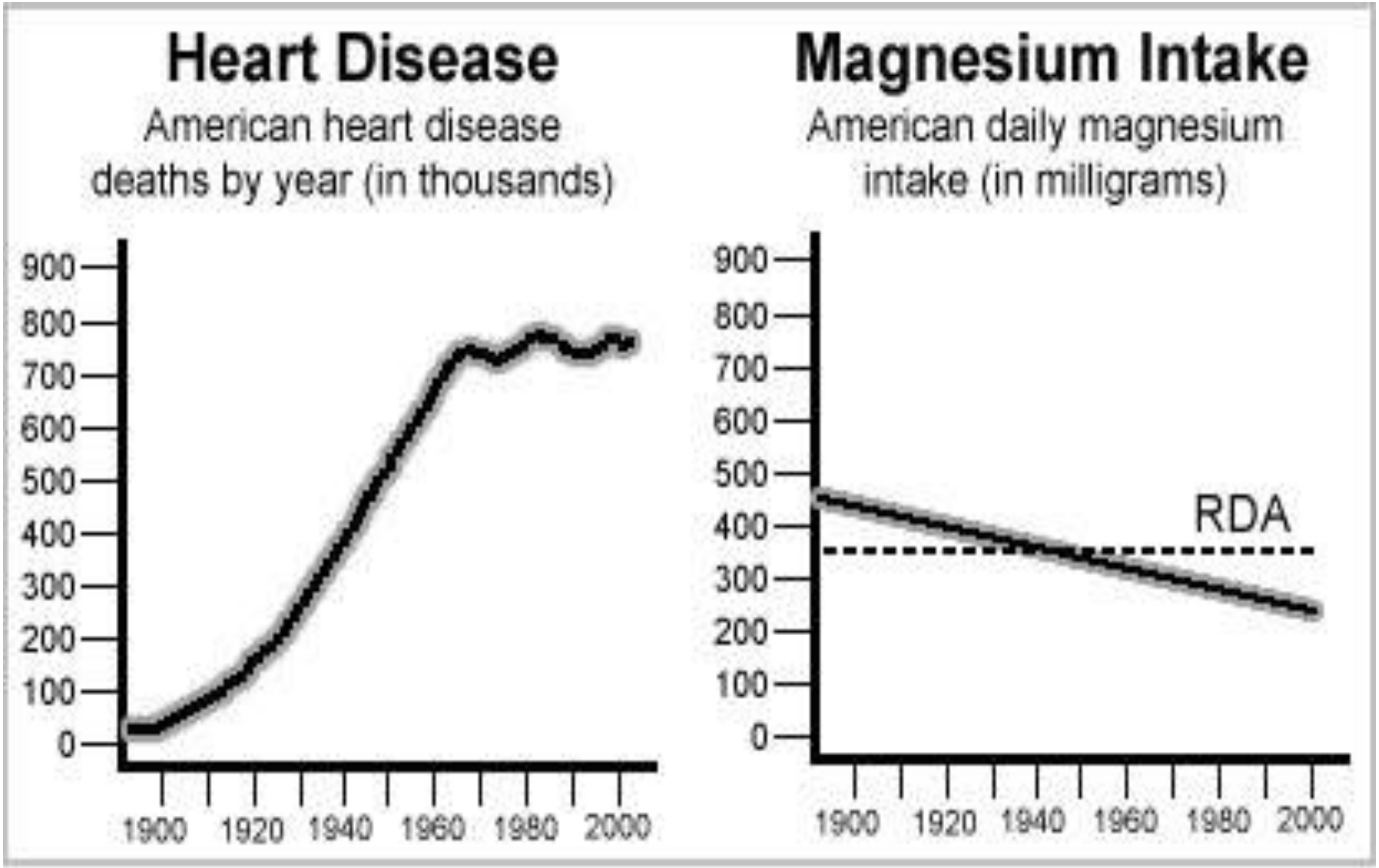
- Study: 84,129 women (Nurses' Health Study) aged 30 to 55 years followed for 14 yrs
  - Initially free from CVD, cancer or diabetes
- Lower risk of developing CHD associated with
  - BMI < 25
  - Moderate alcohol consumption (~ ½ drink a day)
  - Non smoking
  - Physical activity for 30 minutes/day
  - Healthy diet:
    - ↑ omega 3 fats, ↑ cereal fiber, ↑ folate,
    - ↑ low trans fats, low GL
    - ↑ high ratio of polyunsaturated to saturated fats

Magnesium and CVD

Magnesium deficiency and CVD

Deficiency of magnesium is linked to multiple aspects of heart disease

- Dysregulation of cholesterol
- Increased blood pressure
  - *NOTE: Most drugs used to treat ↑ BP deplete magnesium*
- Arterial calcification
- Imbalance of calcium with magnesium linked to increased risk of
  - arrhythmias, tachycardia, atrial fibrillation, sudden cardiac arrest



Source: American Heart Association 2000 Heart and Stroke Statistical Update, "Quantitative Factors Regarding Magnesium Status in the Modern-Day World," Magnesium 1 (1982):3-15.

Magnesium – How much do we need?

- Daily adult requirement (DRI) 300-450mg
  - Average intake in North America ~ 200mg
- Foods richest in magnesium
  - Dark green leafy vegetables
  - Nuts, seeds and legumes
  - Whole grains
  - Seafood and meat
  - Chocolate (350mg per 8 oz bar!)

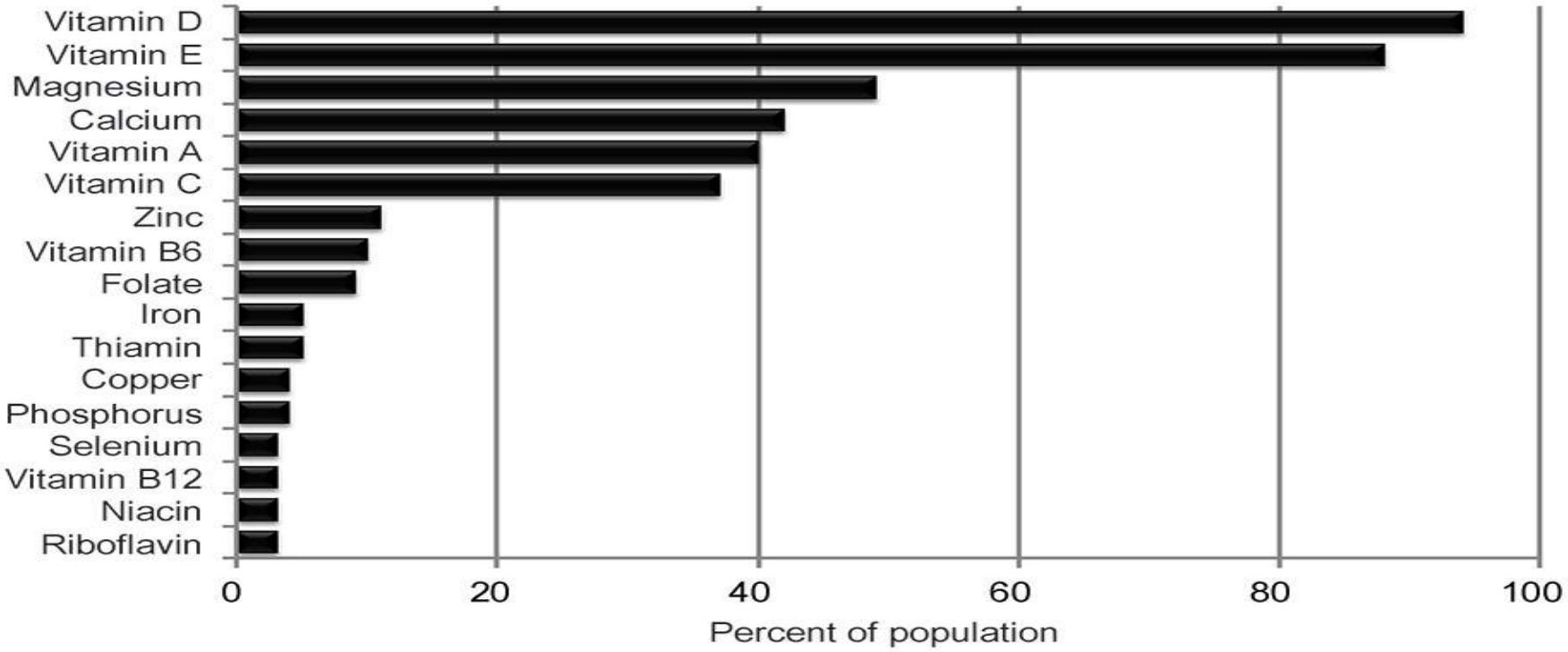
- Note: refining of grains removes magnesium which is *not replaced* with fortification

Magnesium, chocolate and cardiovascular disease

- Consumption of dark chocolate shown to have several benefits for heart health *[Curr Hypertens Rep. 2012;14(4):279-84]*
  - reduces blood pressure
  - improves vascular endothelial function
  - improves glucose metabolism
  - reduces platelet aggregation and adhesion
- Researchers usually assume benefits are due solely to chocolate's antioxidant properties
  - contribution to enhancing magnesium status rarely mentioned or considered

Scientific Report of the 2015 Dietary Advisory Committee

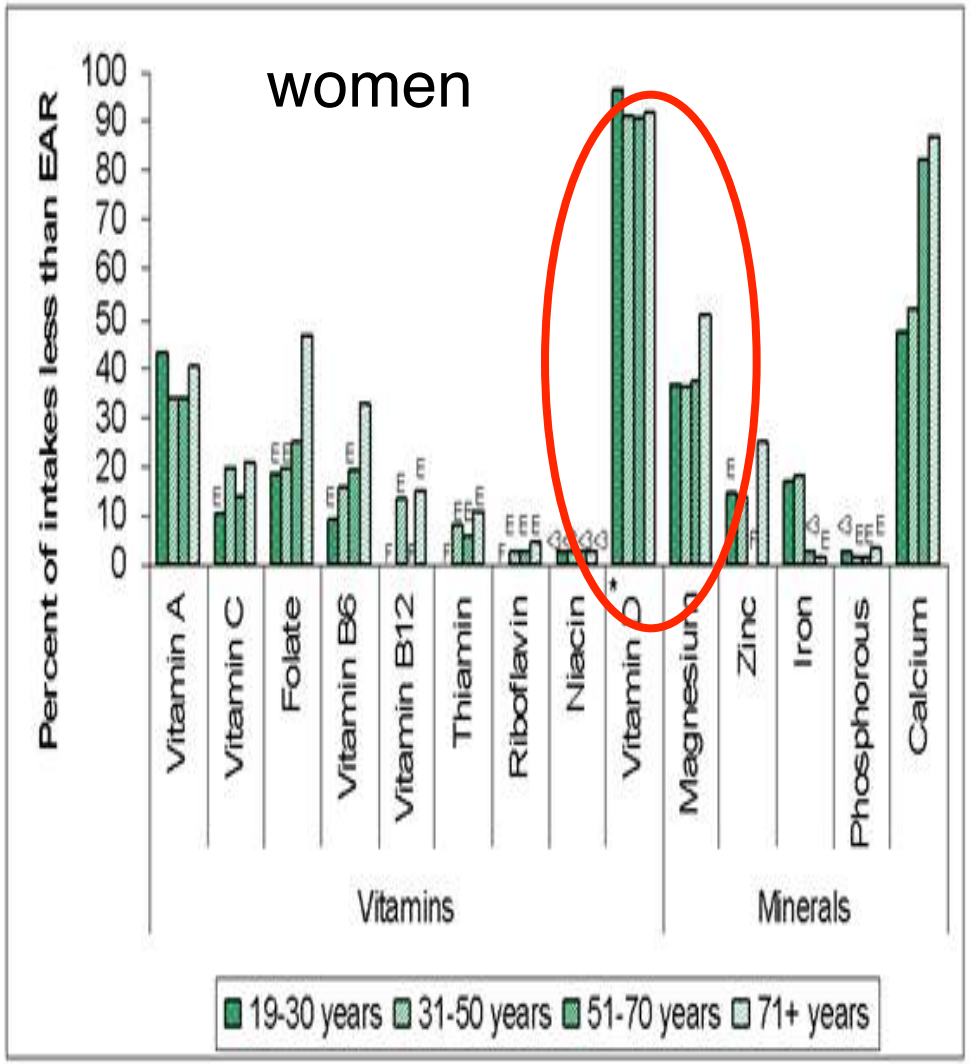
http://www.health.gov/dietaryguidelines/2015-scientific-report

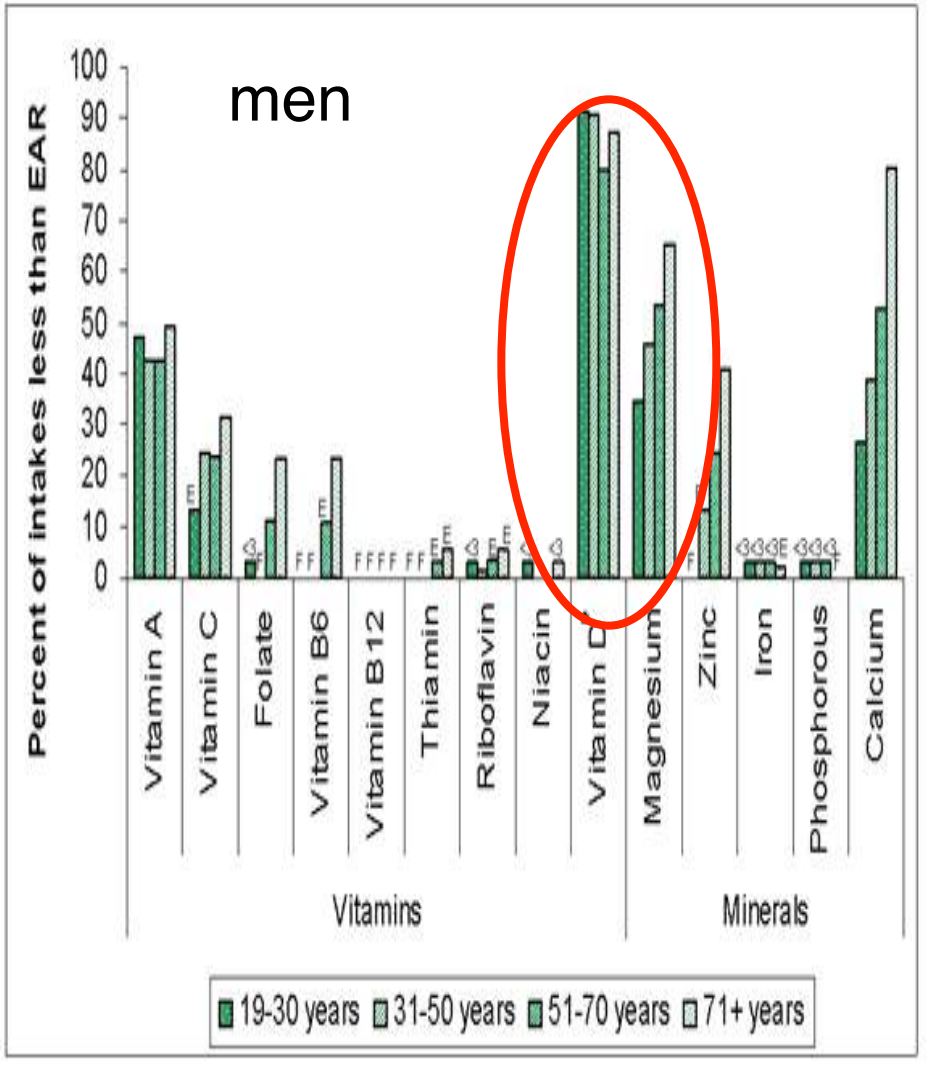


Percentage of US population with intakes below the Estimated Average Requirement (EAR). *Note: the EAR is the amount of a nutrient that will meet the needs of half the population – the other half being assumed to be deficient*

Canadian Community Health Survey Cycle 2.2, Nutrition (2004) (accessed 28-03-15)

http://www.hc-sc.gc.ca/fn-an/surveill/nutrition/commun/art-nutr-adult-eng.php#a33





Calcium to magnesium ratio: Relevance to CVD

Ca/Mg ratio and muscle function

- Intracellular calcium regulates muscle contraction
  - Rising calcium in muscle cells causes contraction
- Removal of calcium into intracellular storage sites or out of cells is needed for muscle fibres to depolarize and relax again
  - This requires magnesium
- Deficiency of magnesium relative to calcium therefore causes sustained contraction of muscle
  - Indicates a functional magnesium deficit

Annual death rates from CVD in relation to calcium/magnesium ratios by country

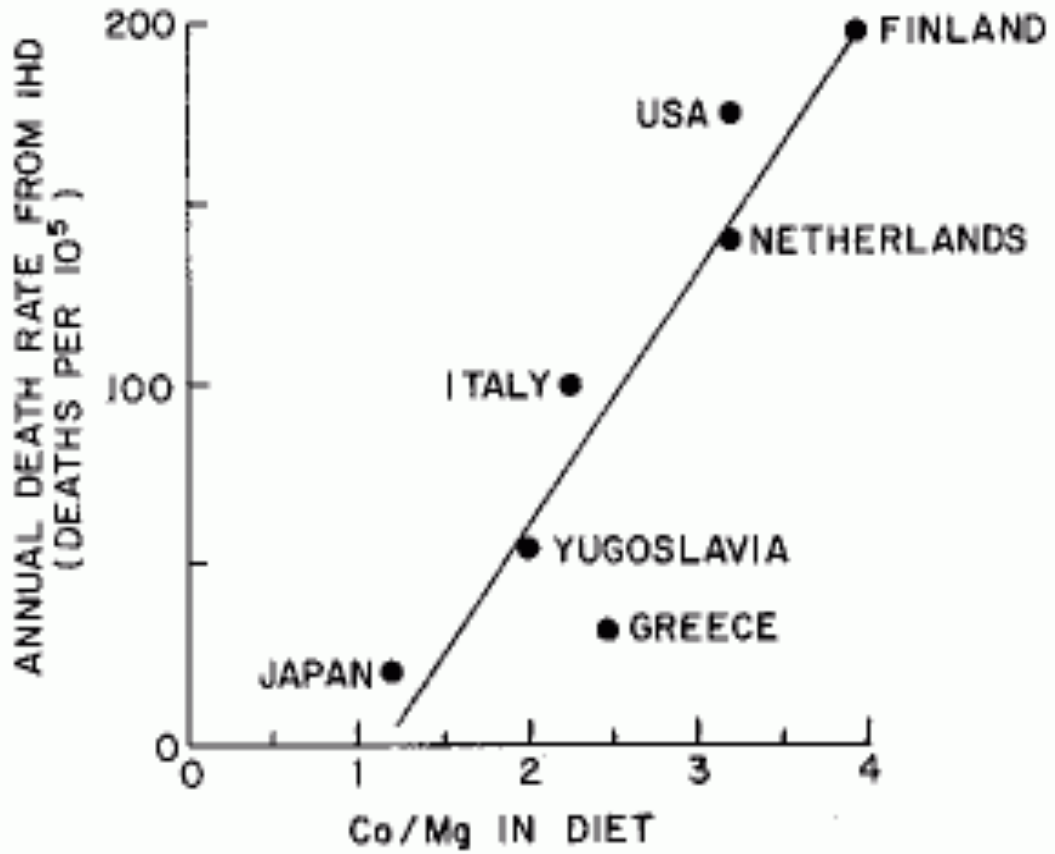


FIGURE 1-10. Ischemic heart disease rates correlated with dietary calcium/magnesium ratios. [From H Karppanen *et al.: Advances in Cardiology*. V Manninen and PI Halonen (Eds), S Karger, Basel, 1978, pp 9–24.]

Current Ca/Mg Balance in N. America

- Dietary surveys show that ~ 90% North Americans get less than RDA for magnesium
  - But diets are often rich in calcium, esp. if dairy or calcium-fortified products consumed
- Women often encouraged to increase supplemental and dietary calcium intake to avoid osteoporosis
  - Many women still take supplements containing 1000-1500mg calcium per day
- The calcium/magnesium ratio has therefore shifted dramatically from physiological norms

Ratio of Calcium to Magnesium: Ancestral Diets

Burford-Mason AP. Magnesium. In: Scientific Evidence for Musculoskeletal, Bariatric and Sports Nutrition. CRC Press 2006

Whole wheat	0.4:1	Venison	0.3:1
Oats	0.4:1	Pheasant	0.6:1
Wild rice	0.2:1	Salmon	0.4:1
Blueberries	1.2:1	Trout	1.9:1
Cranberries	1.4:1	Oysters	0.8:1
Apples	1.6:1	Shrimp	1.4:1
Hazelnuts	1.1:1	Spinach	1.4:1
Walnuts	0.8:1	Turnip	2.0:1
Eggs	4.6:1	Average	1.3:1

Ratio of Calcium to Magnesium: Modern Diets

Burford-Mason AP. Magnesium. In: Scientific Evidence for Musculoskeletal, Bariatric and Sports Nutrition. CRC Press 2006

Bagel (white)	2:1	Hamburger	0.5:1
Pancakes	4:1	French fries	0.2:1
Doughnut	1.8:1	Onions	2.5:1
Cookies	13:1	Orange juice	1:1
Blueberry muffin	3.1:1	Ice cream	4:1
White rice	3.6:1	Milk	7:1
Macaroni	0.4:1	Yogurt (plain)	11:1
Beef steak	0.5:1	Cheese (hard)	26:1
Chicken breast	0.5:1	Average	4.8:1

Calcium:Magnesium Ratio in Local Groundwater and Incidence of Acute Myocardial Infarction among Males in Rural Finland

Kausa A et al. Environ Health Perspect. 2006;114(5):730–734

- Study: relationship between acute MI risk and mineral content in local groundwater
  - Divided rural areas into 10 km × 10 km grids
  - Ground water sampled and related to MI incidence
- Results: Median Ca:Mg ratio was 5.39
  - Each 1 mg/L increase in Mg reduced MI risk by 4.9%
  - A one unit increment in the Ca:Mg ratio increased the risk by 3.1%

Calcium and magnesium imbalance and physical symptoms of Mg deficits

Skeletal:
leg cramps
muscle tension
fasciculations
myalgia
restless legs

Smooth muscle:
shortness of breath
vascular headache
wheezing after exercise
frequency of urination
constipation

Cardiovascular:
arrhythmias/
atrial fibrillation
palpitations
↑ blood pressure

Other:
hot flashes
night sweats
excess mucous production
excess salivation

Effects of dietary magnesium deficiency in the rat with special reference to ultrastructural examination

Ikeda T et al. Kokuritsu Iyakuhin Shokuhin Eisei Kenkyysho Hokoku 1997;115:112-118

- Rats fed either:
  - Group 1: Normal diet
  - Group 2: Magnesium deficient diet
  - Group 3: Calcium doubled diet
  - Group 4: Magnesium deficient and calcium doubled diet
- Results:
  - Degeneration of mitochondria of heart, liver and kidney cells seen in groups 2-4 compared to group 1
  - Severe degeneration most evident in group 4

Effects of dietary magnesium deficiency in the rat with special reference to ultrastructural examination

Ikeda T et al. Kokuritsu Iyakuhin Shokuhin Eisei Kenkyysho Hokoku 1997;115:112-118

"Our results show that dietary magnesium deficiency gives rise to retrogressive changes in some organs, including the heart, and that concurrent calcium over intake synergistically enhances the myocardial injury due to magnesium deficiency."

Women, CVD and the estrogen effect

Magnesium and Estrogen

- When present in normal physiologic amounts, estrogen enhances Mg utilization
  - favours magnesium uptake and deposition in storage sites (muscles and bones)
- This may explain why premenopausal women are protected from heart disease and osteoporosis *(Biol Trace Elem Res. 2007; 118(1): 1-9.)*
- Loss of estrogen after menopause reduces magnesium uptake by bone and muscle
  - explains ↑ in BP; arrhythmia; osteoporosis

Cardiovascular disease and symptoms of menopause

- Hot flashes indicate on-going vascular changes and subclinical CVD (*Circulation. 2008;118:1234–40*)
- Hot flashes are associated with
  - Increased aortic calcification *(Thurston RC et al. Menopause. 2010;17:256–261)*
  - Poor sleep (*Kravitz HM et al. Menopause. 2003;10:19–28)*
  - Depression *(Bromberger JT et al. Psychol Med. 2009;39:55–64)*
  - Increased risk of poor bone health *(Crandall CJ et al. J Bone Miner Res 2011;26(4):840-9)*

Hot flashes, night sweats

Pathognomonic of magnesium deficiency?

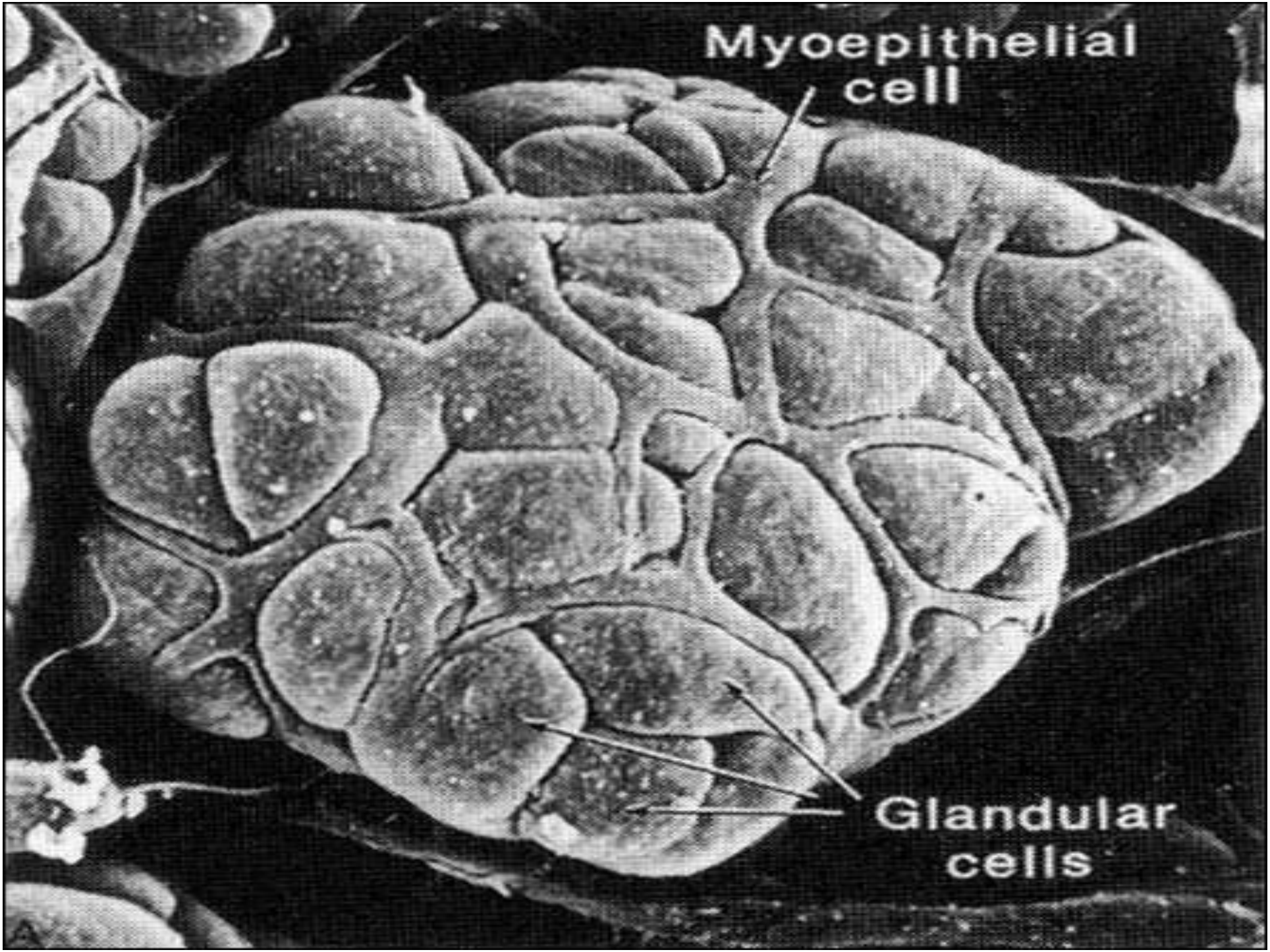
Physiology of hot flashes

Freedman RR. Am J Hum Biol. 2001 Jul-Aug;13(4):453-64

- Review: Hot flashes (HF) are characterised by an inappropriate heat-dissipation response
  - Sweating (face, neck, chest) and vasodilation
- Thermoneutral zone non-existent in women who are symptomatic
  - Tiny changes in ambient temperature ↑ HFs
- Estrogen administration will abolish HFs but estrogen deficiency alone not causal. Why?
  - No difference in estrogen levels between women with/without menopausal symptoms

Magnesium and hot flashes

- Sweat is produced in the secretory cells that line the coils of sweat glands
  - Sweating occurs when the myoepithelial cells surrounding the secretory cells contract
- Myoepithelial cells are activated to contract by the hormone/neurotransmitter oxytocin
  - Contractions are promoted by calcium and inhibited by magnesium *(Clin Exp Obstet Gynecol. 2007;34(4):223-7*
- Mechanism applies to all glands: salivary, sweat, mucus, tear ducts, milk glands, etc.


Myoepithelial cell
Glandular cells

Consequences of magnesium deficiency on the enhancement of stress reactions; preventative and therapeutic implications

Seelig MS. *J Am Coll Nutr 13 (5): 1429-446; 1994*

- 70% of the body's enzymes require magnesium to function. Deficiency results in
  - Failure to utilize B vitamins (esp. B1)
  - Depression and anxiety
  - Sleep disturbance
  - Insulin resistance and diabetes
  - ↑ blood pressure
- Excess dietary calcium can intensify Mg inadequacy, especially under conditions of stress

Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial.

Boland MJ et al. BMJ. 2008;336(7638):262-6.

- Study: influence of calcium intake on risk of myocardial infarction (MI), stroke, and sudden death
  - 5 yr RCT of 1471 postmenopausal women (mean age 74) given calcium citrate 1000mg or placebo
- Results: MI more common in the Ca group (P=0.01)
  - Composite endpoint of MI, stroke, or sudden death also ↑ in the calcium group (P=0.008)

Duration of Menopausal Hot Flushes and Associated Risk Factors

Freeman EW et al. Obstet Gynecol. 2011 May; 117(5): 1095–1104.

- Duration of hot flushes longer than previously assumed
  - > 11.57 years if they began before entry into menopause transition
  - 7.35 years if they started in the early transition stage
  - 3.84 years if they began in late transition stage
- *"…while hot flushes appear to originate in the central nervous system… …their pathophysiology is not well understood."*

A pilot phase II trial of magnesium supplements to reduce menopausal hot flashes in breast cancer patients

Park H et al Support Care Cancer. 2011;19(6):859-863.

- Study: Breast cancer patients with hot flashes (≥ 14/week) given 400 mg magnesium oxide for 4 weeks
  - dose increased to 800 mg/day **if needed**
- Results: Magnesium reduced frequency of hot flashes from 52/week to 28/week - a 41% reduction
  - Fatigue, sweating, and distress were also significantly reduced

FDA Warns GERD Drugs May Deplete Magnesium. *www.medpagetoday.com 3/03/2011*

- New warnings from FDA about depletion of magnesium by PPIs
  - Low magnesium can lead to complications such as muscle spasms, irregular heartbeat and seizures
- Approx 4 dozen cases of low serum magnesium have been reported in patients on PPIs
  - Most low-magnesium cases occurred after 1y but some as early as 3m after starting drugs
- In 25% of users who developed low serum magnesium, magnesium supplements did not help
  - Patients had to stop taking the drugs

Mg and modifiable CVD risk factors 1.Cholesterol

USA rethinks warnings against cholesterol *(Globe and Mail 9th February 2015)*

- The 2015 USDA panel reviewing national dietary guidelines has decided to drop its caution against foods rich in cholesterol
  - Cholesterol in food will no longer be considered a "nutrient of concern"
  - Saturated fat *per se* not a problem. Just excess
- The Committee did not reverse its warnings on high blood levels of "bad" (LDL) cholesterol


I HAVE A PHOBIA OF PEOPLE WITH PHOBIAS
(C) 2001 - RICK LONDON / JOEL COUGHLIN

Magnesium and cholesterol regulation (1)

- The amount of available magnesium determines cholesterol synthesis
  - When optimal amounts are present HMG-CoA reductase is turned off when necessary
- When magnesium is deficient insufficient Mg-ATP is available to deactivate HMG-CoA reductase
  - The result is sustained cholesterol production

(J Am Coll Nutr. 2004 Oct;23(5):501S-505S)

Magnesium and cholesterol regulation (2)

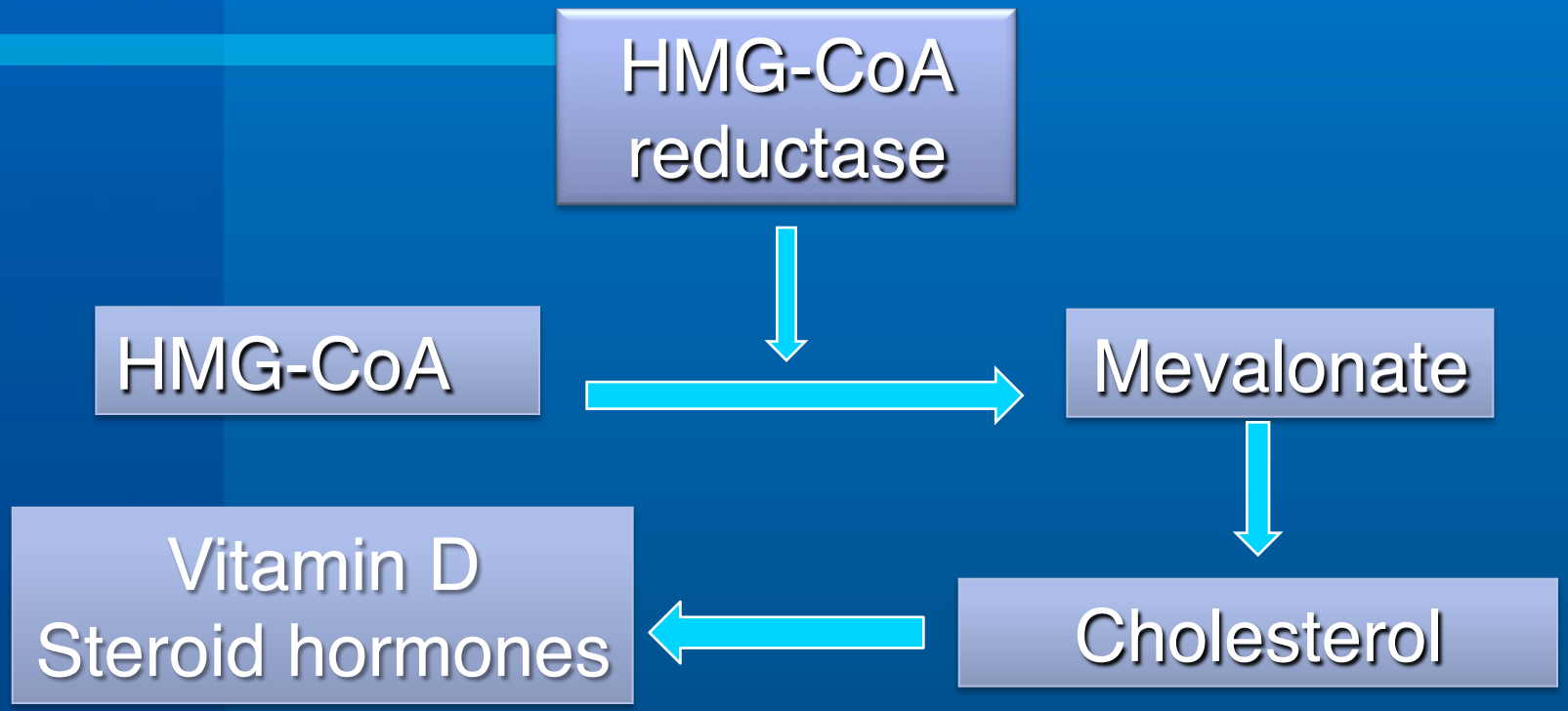
- Magnesium supplementation can reduce total and LDL-C and apolipoprotein B and increase HDL-C *(South Med J. 2001 Dec;94(12):1195-201)*
- Experimental magnesium deficiency in animals has been shown to
  - ↑ triglycerides, total cholesterol, VLDL and LDL and apolipoprotein B *(Nutr Res. 2009 May;29(5):343-9)*
  - Reduce HDL and apolipoprotein A1 *(ibid)*

Comparison of mechanism and functional effects of magnesium and statin pharmaceuticals

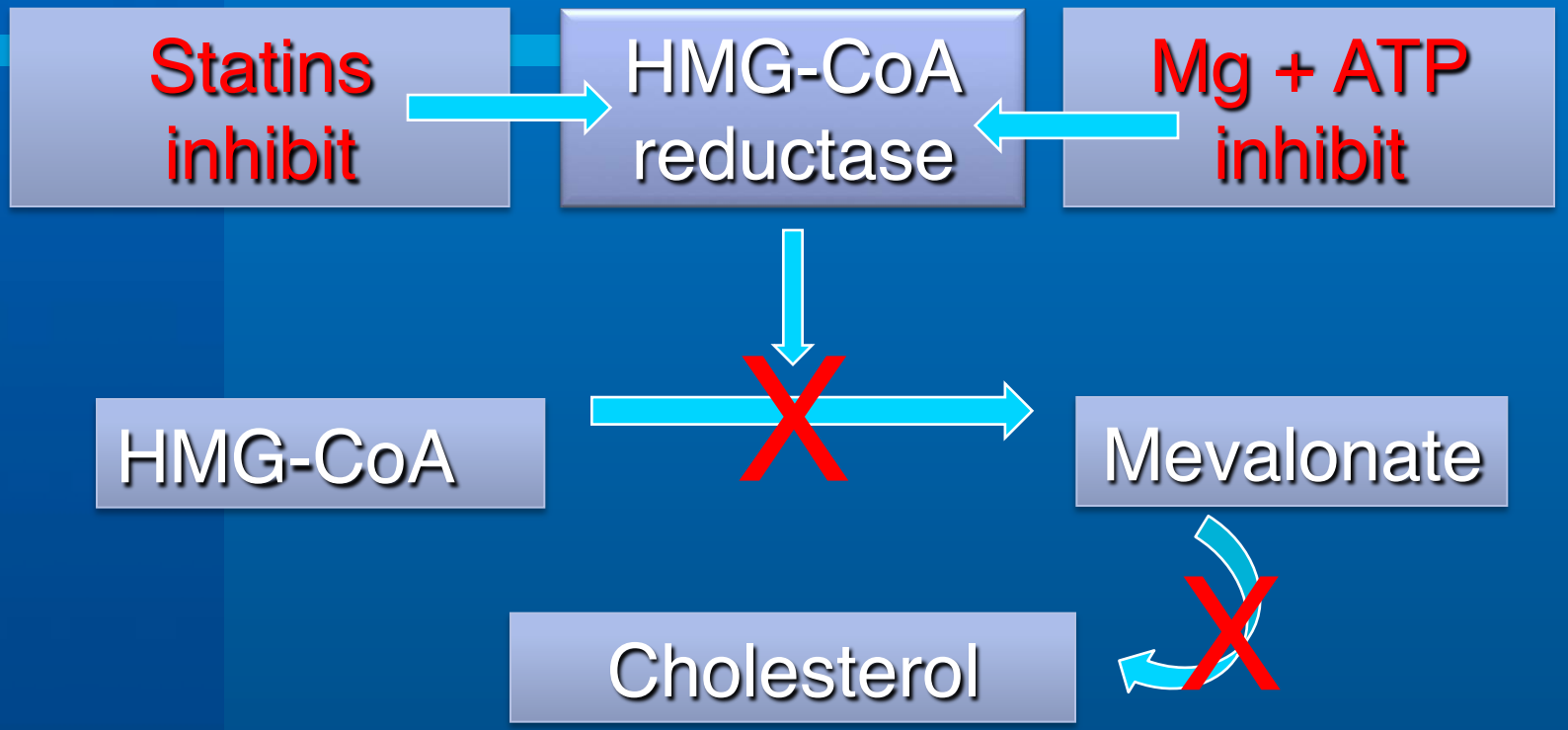
Rosanoff A, Seelig MS. J Am Coll Nutr. 2004 Oct;23(5):501S-505S

- Review: Mode of action of statin drugs compared with magnesium
- Statin drugs work because they block one of the final steps in cholesterol synthesis
  - conversion of HMG-CoA to cholesterol
- Magnesium controls HMG-CoA synthesis
  - Magnesium is needed at *optimal cellular concentrations* to regulate cholesterol production

Cholesterol Synthesis



Inhibition of cholesterol synthesis



Note: familial hypercholesterolemia does not respond to magnesium supplementation

Mg and modifiable CVD risk factors
2. Calcification

Vascular calcifications seen on mammography: an independent factor indicating coronary artery disease. *Oliveira EL et al. Clinics (Sao Paulo). 2009;64(8):763-7*

- Study: Case-control.
  - Investigated relationship between vascular calcification and other risk factors for coronary artery disease (CAD)
  - 40 women with CAD compared with 40 age matched controls without CAD
- Results: Vascular calcification seen via mammography was an independent risk factor for CAD as was hypertension and a family history of coronary artery disease

Magnesium Intake Is Inversely Associated With Coronary Artery Calcification: The Framingham Heart Study. *Hruby A et al. JACC Cardiovasc Imaging. 2014; 7(1): 59–69*

- Study: Participants in the Framingham Heart Study (n = 2,695; 53 ± 11 yrs)
  - Calcification of coronary artery (CAC) and abdominal aorta (ACC) checked in relation to Mg intake at time of study
- Results: Comparing highest [>427.4mg] vs. lowest [<258.8mg] magnesium intake
  - Odds of any CAC was ↓ 58% and AAC ↓ 34%
  - Stronger inverse associations were observed in women than in men.

Mg and modifiable CVD risk factors
3. Blood Pressure

Effect of magnesium supplementation on blood pressure: a meta-analysis

Kass L et al. Eur J Clin Nutr. 2012 Apr;66(4):411-8.

- Meta-analysis: 22 trials. Follow-up 3 to 24w
  - magnesium dose range 120-973 mg (m = 410 mg)
- Results: Not all individual trials showed significant BP reduction
- However, combining all trials showed
  - ↓ SBP of 3-4 mm Hg and ↓ DBP of 2-3 mm Hg
  - Intake >370 mg/day showed greatest reductions
- Conclusion: Mg supplements appear to have a small but clinically significant effect on BP

CVD, Magnesium and Vitamin D:
Interdependent?

Vitamin D and Heart Disease

- Low vitamin D status increases the risk of MI, congestive heart failure and all-cause mortality
  - Some studies have shown effect of D levels on CVD to be more pronounced for women than men *[Eur J Clin Invest. 2014 Jul;44(7):634-42]*
- Studies suggest that serum 25-(OH)D is modified by magnesium status
  - Magnesium plays an essential role in both the synthesis and metabolism of vitamin D *[J Clin Endocrinol Metab. 1985;61:933-40]*

The association between serum 25-hydroxyvitamin D3 concentration and risk of disease death in men: modification by magnesium intake

Mursu J et al. Eur J Epidemiol.2015 Mar 12. [Epub ahead of print]

- Finnish Study: Does Mg intake modify serum 25(OH)D3 and its association with mortality in middle-aged and older men?
- Results: Serum 25(OH)D_3 < 32.1 nmol/l was associated with 31% ↑ risk of death
  - Mainly in those with lowest Mg intake
- Average magnesium intake was 422mg
  - Lowest quartile < 373mg/day
  - Highest quartile > 458mg/day

Case Study
Interaction of vitamin D with magnesium

- Subject: Male, Caucasian, 55 years
- Medical doctor. Had been testing his personal 25-hydroxy D3 for several years
- Became aware that magnesium was needed to optimize 25-(OH) D blood levels
  - D3 conversion to 25-hydroxy D3 is magnesium dependent
- Started on magnesium glycinate 200mg b.i.d. and rechecked 25-(OH)D

Case Study
Vitamin D and magnesium

Date	**D3 dose** IU/day	**25-(OH)D** nmol/L	**Mg dose** (elemental)	**Serum Mg** mmol/L	**Red cell Mg Mmol/L**
Oct 2012	2600	79	None	N/A	N/A
July 2013	2600	91	None	N/A	N/A
Mar 2014	**3600**	110	None	N/A	N/A
Nov 2014	**3600**	N/A	None	0.73	1.78
Dec 2014	**3600**	N/A	200 mg b.i.d.	0.86	2.00
Feb 2015	**3600**	127 (161; 164)	200 mg b.i.d.	N/A	N/A

Supplementing with magnesium

Testing for magnesium deficiency

- Serum Magnesium
  - Not a true indicator of tissue stores
  - Only 1% total body Mg present in serum
  - This is tightly controlled
- Red cell magnesium
  - Hypomagnesemia can occur when red cell magnesium is normal
  - Low cellular levels may co-exist with normal serum levels
- Best method
  - Functional signs of magnesium deficiency

Assessment of magnesium status for diagnosis and therapy

Elin RH. Magnes Res. 2010 Dec;23(4):S194-8

- Only 1% of total body Mg is present in blood
  - However, serum Mg is the predominant test used to assess magnesium status in patients
- Reference range for serum Hg is flawed
  - Intake of magnesium has been steadily dropping
  - Now many "normal" individuals on whom the reference range is based are chronically Mg deficient
- Need to establish a new lower limit
  - Based on current literature this should be ~ 0.85 mmol/L

Effects of serum calcium and magnesium on heart rate variability in adult women

Kim YH et al. Biol Trace Elem Res. 2012;150(1-3):116-22.

- Study: Examined link between serum Ca and Mg and Ca/Mg ratio and heart rate variability
- Results: Mean heart rate increased from lowest to highest tertile of Ca levels but decreased significantly with higher Mg levels ($p = 0.026$)
  - HRV decreased significantly from the lowest to the highest tertile of Ca/Mg ratio ($p = 0.03$)
- Conclusion: Low serum Mg and high Ca/Mg ratio may be one factor in risk of CVD

Correcting the Ca:Mg balance

– Critical for heart health –

Identifying magnesium deficiency:
Questions to ask Patients

- Do you get leg or foot cramps?
- Are your shoulders frequently tight or tense ?
- Does your back ever go into spasm?
- Do you get muscle twitches, esp. around the eye?
- Do you suffer from wheezing or asthma?
- Are you short of breath, for example, climbing stairs?
- Do you sigh frequently?
- Do you get palpitations or arrhythmias?
- Do you need to urinate frequently, especially at night?
- **Are you ever constipated?**

Titrating magnesium to bowel tolerance (1)
– correcting the Ca/Mg balance –

- Start with 100mg magnesium glycinate at night before bed
- Increase dose gradually (every 3 days) in 50mg increments, alternating each new addition between morning and evening
  - Continue increasing until 2-3 soft bowel movements per day are obtained
- Avoid diarrhea - this will cause magnesium wasting

Titrating magnesium to bowel tolerance (2)
– correcting the Ca/Mg balance –

- Important: keep calcium intake from diet and supplements steady from day to day
  - Most people can get 1000-1200mg calcium from diet, especially if they consume dairy products or calcium fortified foods
  - Make sure they avoid excess dietary calcium
- Note: Stress depletes magnesium but not calcium *(Magnes Res. 2006 Jun;19(2):102-6)*
  - This can affect the Ca:Mg balance
  - Instruct patients to take 50mg magnesium extra at bedtime any day bowels are sluggish

www.osteoporosis.ca/osteoporosis-and-you/calculate-my-calcium