Nutrition and Chronic Disease in Transition Countries

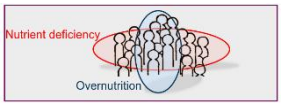
- *What characterizes a transition country and how this leads to a problem*
- *How overweight and obesity can influence iron status*
- *How other micronutrients, such as zinc and iodine may also be affected by weight status*

Characteristics of a transition country

- Increasing industrialization (often rapid), economic growth
  - Agriculture → urbanization (shift)
  - Growing gaps: poor/rich; rural/urban
- Rapid changes in diet and lifestyle in large parts of the population such as:
  - Migration from rural to urban areas
  - Reduced physical activity (also consequences of migration to urban areas)
  - Increasingly sedentary lifestyle
  - Reduced consumption of traditional foods
  - Availability of western food (fast food chains)

<u>Consequences of the transition</u>**:** overnutrition and nutrient deficiencies coexist within one country and even within one person!

→ "Double Burden of Malnutrition"



The multiple burdens of malnutrition

- No malnutrition
- Adult obesity
- Child stunting
- Child MN deficiency

Burdens overlap in some countries, some countries are only affected by one, some by none.

Definitions

- disability-adjusted life years (DALYs): measure to quantify disease related morbidity and mortality.
  1 DALY = 1 lost healthy year of life. Measured to measure overall disease burdens, expressed as the cumulative number of years lost due to ill-health, disability, or early death. Can also be used to compare countries, etc.
  DALY = YLD (years lived with Disability) + YLL (Years of life lost)
- BMI definition in children: Changes in body composition as a result of growth and developments → needs to be adapted to the age of the child. Use of percentiles: overweight: > 85th, obese: >95th, underweight: < 5th
  Graph!!

Global burden of disease Study 2017

Risk assessment of 84 behavioural, environmental, and occupational, and metabolic risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. → <u>Calculated the DALYs attributable to 84 risk factors.</u>

Leading risk factors in 2017 were high blood pressure, tobacco smoking, high fasting plasma glucose

Leading risk factors in 1990: childhood underweight; household air pollution, from solid fuels, tobacco smoking

Shift from communicable diseases in children to non-communicable disease in adults. Related to: population growth, aging population and changes in risk exposures. But, in some regions, e.g. sub-Saharan Africa, the leading risks are still those associated with poverty!

Global burden of disease study 2016

Decrease in death rate since 1990 for most causes was not matched by decline in age-standardized years lived with disability (YLD) (see graphs, remained stable, did not decrease like death rates, explanation in second graph, increase in total life years lived with disability when not age adjusted)

Aging population → steep increase in disabling disease → increasing demand for costly health service. (Burden for overall community)

Micronutrient deficiency

Examples: Anaemia prevalence in Mexico, South Africa, India and China.

<u>China</u>

- Shift in population: rural → urban
- Demographic aging:
  - Higher percentage of over 65 year olds(7% vs. 4.7%), higher percentage of 15-64 year olds (70.2% vs. 59.8%), lower percentage of 0-14 year olds (22.9% vs. 35.5%)
- Dietary changes: more fat, less carbohydrates. Less cereal consumption (overall), more meat

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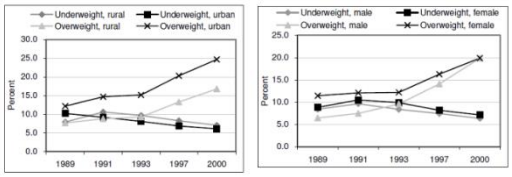
consumption (more in medium and high social economic groups)

- Changes in nutritional status



- anaemia prevalence: Decrease in urban areas (rural similar)

	1992	2002	1992	2002
	males		females	
rural	17.8	18.0	23.3	24.9
urban	15.2	12.0	25.8	20.1

Mexico

- Less childhood undernutrition
- More adult/childhood overweight/obesity
- Increase in cardiovascular disease, diabetes
- Vitamin A and iron deficiency still common
- Differences in childhood overweight in different regions: higher prevalence in the north, higher prevalence in urban areas, higher prevalence with high school or more maternal education.

➔ Changes in transition countries allows new lifestyles

Difference Mexico and USA: about the same percentage of adult obesity, but childhood stunting, and childhood anaemia is very different, i.e., much higher in Mexico.

- Prevalence of obesity:
  - Women: 25.3%, Children: 3.5%
- Higher risk for iron deficiency in obesity
  - Odds ratio for obese women: 1.92
  - Odds ratio for obese children: 3.96
- In women: similar iron intakes but lower serum iron in obesity
- Inflammation (CRP) correlates with Obesity and Iron Status

Iron deficiency efforts in Mexico may be hampered by increasing rates of adiposity in women and children!

India

- Undernutrition in certain regions
- Increased rate of overweight (mainly in urban areas)
- Increase in CVDs and diabetes
- Micronutrient deficiencies still common (iodine, vit A, iron, folic acid)
- Big difference of prevalence of diabetes between urban and rural areas (Urban has almost double the rate)
- BMI change in children (1989 to 2007):
  - Both studies conducted in wealthy urban areas. Clear shift towards higher BMI/age in both genders and for 50th and 85th percentile.

➔ But! Using the old percentiles to define prevalence's in the new population would lead to higher prevalence! (Big differences in results with different weight charts used in the studies)

South Africa

- Reduction in childhood undernutrition
- Increase in adult overweight/obesity
- Increase in CVD, diabetes, cancer
- Micronutrient deficiencies (vit A, Iron)
- Specific concern : physical activity, 58% of population reported to be never physically active → promotion of physical activity important, Solution: "Getting the nation to play".
  - Goals: improve access to sports infrastructure, especially for disadvantaged population groups, provide professional training for everybody in their strongest disciplines

Overweight impairs the effect of iron supplementation

- Does weight status predict the response to oral iron supplements?

➔ 8.5 mt placebo-controlled intervention in schoolchildren

➔ At endpoint: overweight children have lower iron status.

➔ South African children with high BAZ had a 2-fold higher risk of remaining ID after iron supplements

→ The rapid increase in overweight in transition countries may interfere with efforts to control Iron deficiency and anemia!

Fighting overnutrition in transition countries

What is important in the fight against overnutrition?

- Increasing population's knowledge. Consider local circumstances
  - Fruit and vegetable consumption
  - Energy intake
  - Physical activity
  - Overweight/obesity as a status symbol
  - High proportion of population with low education level

Obesity - micronutrient interactions

Iron

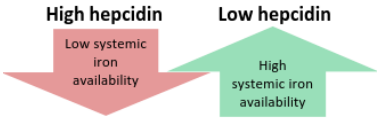
Epidemiological examples

Increased risk for iron deficiency in obese people. Possible reasons for the interaction→ Originally 3 hypotheses:

- Poor dietary choices → lower dietary iron intake?
  - No convincing evidence! Iron uptake was shown to be similar in both groups
- Higher iron requirements as a result of larger blood volume
  - Can explain part, but not the entire problem!
- Reduced iron absorption as a result of chronic low grade inflammation?

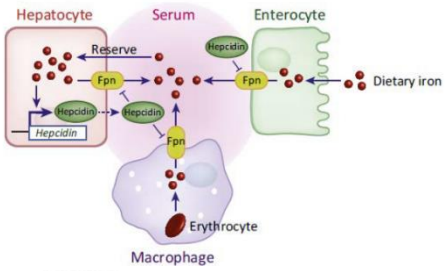
Hepcidin → regulator of body iron

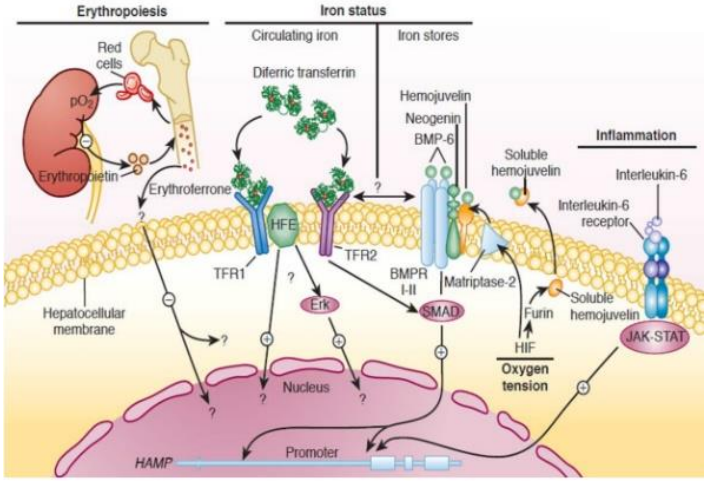
Peptide hormone that play a key role in iron regulation. Hepcidin production is mainly in the liver, and small amounts in the adipose tissue



Hepcidin binds to ferroportin which leads to internalization and degradation and reduces iron release into circulation.

High amounts of adipose tissue, together with chronic low grade inflammation may reduce iron absorption in overweight/obese persons!





Reduced iron absorption in obesity: first observation

Findings in Thai women:

- Higher BMI → lower iron absorption
- Higher BMI → higher CRP
- Higher CRP → lower iron absorption

Findings in schoolchildren in Morocco and India:

- Higher BMI → lower iron stores, poorer iron status
- Higher BMI → decreased response to iron fortification

→ The current surge in overweight in transition countries may impair efforts to control iron deficiency in these target groups!

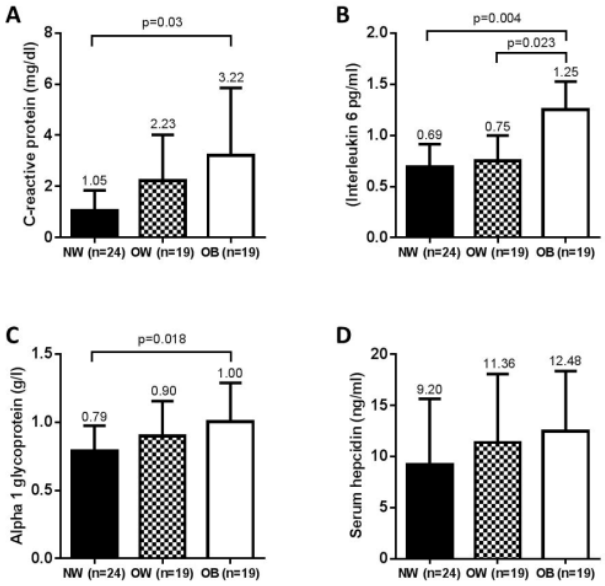
Iron absorption by weight status

Hypothesis:

- Iron absorption is reduced in OW and OB women compared to NW women.
- The effect of vitamin C is blunted in OW/OB

Study design:

- Iron absorption study using stable isotopes (fe 57/FE 58)
- 24 NW, 19 OW and 19 OB women in Zurich
- Body composition (DXA)
- Blood volume (CO re-breathing method)
- Iron status, inflammation, hepcidin

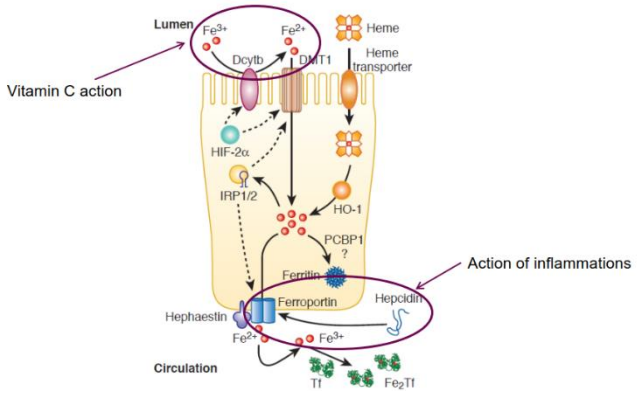


Clearly increased inflammatory markers with increasing BMI but only small change in hepcidin!

Significantly higher iron absorption from standard meal in NW compared to OW/OB subjects

Absorption enhancement by ascorbic acid significantly better in NW compared to OW/OB subjects.

Iron absorption



Hepcidin binds to ferroportin and restricts iron from sites. Vitamin C works at ?? site of enterocytes → fe to anderes fe ??????? (Wichtig!?) ????

Effect of weight loss on hepcidin

Looked at Subjects undergoing bariatric surgery, with a BMI at baseline of 47.6 kg/m^2

BMI was reduced a little bit, hepcidin a lot, IL-6 went down some. Dietary iron about the same. Serum ferritin the same, but transferrin receptor went down (increase in iron status).

Effect of weight loss on iron absorption

Looked at 38 obese subjects undergoing Sleeve gastrectomy, with timepoints at 5 weeks after surgery and again 6 months later. They looked at Iron absorption, body composition and inflammation.

Body fat, C-reactive protein, IL-6 and Hepcidin went down (some more, some less). Significant improvement of iron absorption only in subjects with low iron stats!

→ The body's iron needs seems to be able to overrule the effect of inflammation and increased hepcidin at least to a certain extent!

Obesity, iron deficiency and cognition

- Adults/adolescents: lower educational achievement associated with obesity
- Obesity = direct cause or surrogate for other risk factors? → Not well studied
- Childhood obesity has been associated with psychological outcomes: low self-esteem, depression → Effect on academic performance?

Is there a psychologic reason, why childhood obesity might independently impair cognitive development?

Lower cognitive function in obesity and hypertension

Objective: to determine independent effects of obesity and hypertension on cognitive functioning.

Looked at 551 men and 872 women from the Framingham Heart study.

→ Results: Obesity and hypertension are independent and cumulative predictors of cognitive deficit in men but not in women!

Effect of obesity on cognition

- Overweight children show lower performance on cognitive control tasks and impaired underlying brain activity during task performance
- Insulin resistance and central adiposity are associated with lower cognitive control in children
- Causal relationship between obesity and academic achievement still inconclusive in prospective studies, but cross-sectional evidence for negative association between obesity and academic achievement

Study on the Effect of early onset obesity on cerebellar development showed decrease in Cerebral and cerebellar volume, as well as decreased GIA.

These results raise the possibility, that early childhood obesity retards both cerebellar and cognitive development

Impact of iron deficiency and obesity on cognition

Summary:

- Obesity → poor cognitive performance: some evidence
- Iron deficiency → psychological and neurobiological outcome

Taken together the increase in obesity in transition countries with high prevalence's of iron deficiency may aggravate the situation of already disadvantaged children and possibly also adults

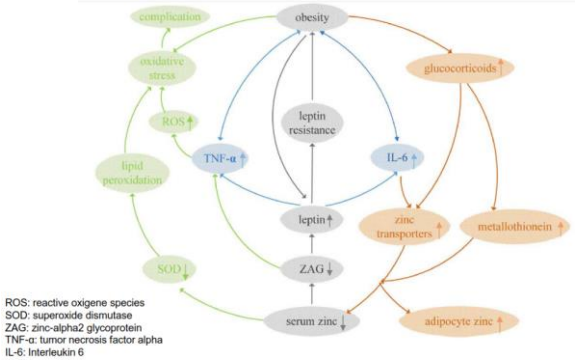
Zinc

Obesity and zinc deficiency: epidemiological data

- Brazil (children): lower zinc in plasma and erythrocytes in obese children, higher zinc excretion and higher insulin concentration
- Egypt (children): lower serum zinc and SOD and higher IL-6 and leptin in obese children
- UK (adults): lower serum zinc concentration in obesity specifically in males
- Taiwan (adults): serum and hair zinc inversely associated with BMI and lower in obesity
- India (men): zinc deficiency as a risk factor for central obesity and high body fat

Lower Zinc status related to higher BMI/body fat!

Zinc - obesity interactions



Obesity and zinc deficiency: Effect of intake

Effect of zinc intake in obese subjects on metabolic outcomes:

- Zinc intake </> RDA (women: 7 mg/d; men: 9.5 md/d)

	Low Zn	High Zn
CRP	0.80	0.20
Insulin	10.11	8.58
LDL cholesterol	148.79	117.42
HDL cholesterol	60.24	73.63

➔ Clearly worse metabolic profile in subjects with lower zinc intakes! (all obese BMI)

Obesity and zinc deficiency: Effect of supplements

Zinc supplementation (20 mg/d, 8wk) in obese Iranian children:

	Zinc	Placebo
Weight	↘	↗
BMI	↘	↗
Serum zinc	↗	→
LDL cholesterol	↘	→
Insulin	↘	↗
CRP	↘	↗

→ Should Zinc supplementation be considered as a treatment of obesity related metabolic disorders?

Iodine

Iodine and the metabolic syndrome

- Overweight, dyslipidemia and insulin resistance are all associated with elevated TSH
- T4 substitution in adults with subclinical hypothyroidism can reduce the cardiovascular risk
- Iodine deficiency leads to elevated TSH
- Iodine supplementation can normalize TSH

➔ Can iodine supplementation in an iodine deficient area with a high obesity prevalence reduce cardiovascular risk?

Iodine supplementation in children

- Secondary data analysis on iodine supplementation studies
- 262 5-14 year old children in Morocco, Albania and South Africa
- TSH > 2.5 mU/l
- 5-6 months iodized oil or iodized salt

Results: more Urinary Iodine conc. In subjects with iodine supplementation. Median TSH decreased, mean TT4 increased, total cholesterol decreased, LDL cholesterol decreased, C-peptide decreased.

- Correcting hypothyroidism can improve insulin metabolism and lipid status and therefore potentially reduce the risk for cardiovascular disease!
- But: The study population was at a relatively low risk (children, low OW prevalence, relatively good baseline values)

➔ What would be the situation in a population group with increased risk?

Iodine supplementation in overweight women

- Randomized, controlled, double blind trial
- 163 overweight women in Morocco
- 200 microgram iodine/d for 6 months

Results: Supplemented group show increased UIC.

- Iodine deficiency in OW women leads to elevated TSH and an unfavorable lipid profile
- Iodine supplementation significantly reduces the prevalence of hypercholesterolemia

➔ Iodine prophylaxis in countries with a high obesity rate may help reduce the cardiovascular risk of the population!

Food and diseases of the gastrointestinal tract

Food may act as a pathogenic factor, a preventative/protective factor or as treatment ("functional food", Pre-biotics, Pro-biotics). It may act:

- Locally (in the mucosa, e.g. of the stomach) → Intoxication, Allergy, Intolerance, "Infection"
- Systemic → resorption, systemic circulation, gastrointestinal organs (can also affect other organs)

There is acute effect/disease such as Intoxication and allergic reaction, and chronic disease/protection, such as colon cancer and obesity.

Most frequent reason for liver transplantation → NASH

NAFLD and Obesity

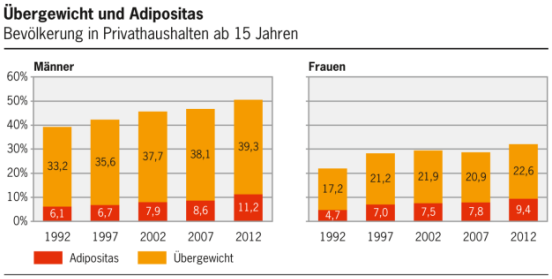
NAFLD as a complex Disease trait: Genetic and Environmental modifiers

Influenced by: Environment, sedentary lifestyle, snacking, fast food, saturated fats, trans fat and processed red meat can all contribute to development of the Disease.

Widespread → A quarter of the population in a lot of countries have NAFLD. Global prevalence: 25%.

Why do people die from NAFLD? The answer is Cirrhosis → hepatocellular carcinoma (HCC). Development: First Liver steatosis + genetic steatosis, then NASH, then Cirrhosis. Can be affected by chronic food intake (e.g. Coffee)

Obesity

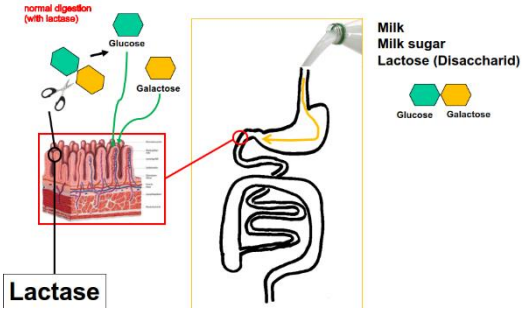


Acute/local effect: lactose intolerance

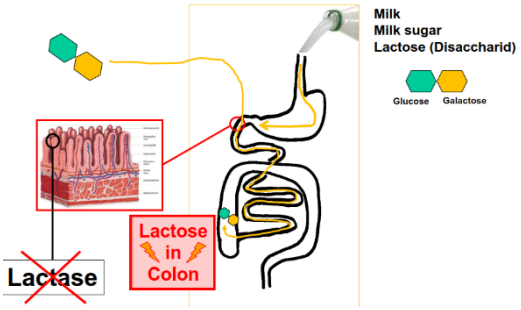
- Gas Bloating
- Pain, cramps (also just discomfort (reflux))
- Diarrhea

→ Lack of the enzyme Lactase

Physology of Lactose digestion



Lactase deficiency



How do the symptoms develop?

- Bacteria digest Lactose: Gas develops → leads to bloating and cramps
- Increased liquid in the colon → osmotic diarrhea

Sympzoms of lactase deficiency are dose dependent! Symptoms start >50 g Lactose/day

Reasons for Lactase deficiency:

1. Primary or ethnic lactose intolerance: mutation in gen for Lactase production (most frequent: 13910 C/T and 22018 G/A). Autosomal recessive, Lactase diappears after the 4. Year of life. White population: 30-40 %.Asian, african, southamerican: 90 %
2. Secondary Lactose-intolerance (rare): diseases of the small bowel, e.g. Mb. Crohn.
3. Congential lactase deficiency (CLD) (very rare): Autosomal recessive, no lactase at all

How to test for lactoseintolerance

- Mutation in blood
- Breathtest: assumption that everyone has some bacteria in the large bowel: bacteria produce hydrogen (gas → bloating) which goes from blood to lung and is measureable in breath.

Treatment

1. Diet (avoid all products containing lactose)
2. Enzyme replacement

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Irritable bowel syndrome (IBS)

- 15-25 % of the general population has IBS. 2-3 % of all general practitioner consultation are because of IBS. 40 % of all Gastroenterologist consultation are because of IBS

➔ High costs

Definition: Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

Other diseases with the same symptom profile: **Lactose intolerance**, Fructose intolerance, Celiac disease, colon cancer, Lymphoma, etc.

Lactose intolerance and IBS

There is a high correlation between Lactose intolerance and IBS, since their symptoms are identical. in 122 Patient, 33 (27%) have lactose intolerance. Treated with Diet.

→ about 10% of all IBS patients get better if they just avoid lactose

Treatment with FODMAPs Diet

FODMAPs = fermentable oligosaccharides, disaccharides, monosaccharides and polyols (sugar free gums and some fruits and vegetables, wheat, onion, garlic, legumes and Dependent on results of breath test: Fructose and/or Lactose)

➔ Diet with low FODMAP for IBS treatment

Results: decrease in in overall symptoms (VAS), bloating, abdominal pain, passage of wind.

➔ Diets as a therapy for irritable bowel syndrome
➔ More people pick elimination diets to discover food sensitivities
➔ For IBS consider: dairy, wheat, high fructose corn syrup, sorbitol (chewing gums), eggs, nuts, shellfish, soybeans, beef, pork, lamb

IBS and Glutamate

- Glutamate MSG: enhance other taste-active compounds
- 75 patients with IBS, 4 weeks diet without Glutamate and aspartate
- 73 patients (84 %) with > 30 % symptom improvement
- With MSG: re-appearance of symptoms and worsening of IBS

Lin seeds and IBS

40 patients with IBS, treated with 2 spoons lin seeds or 2 spoons grounded lin seeds or nothing (control). Results: no effect compared to control. May be useful in IBS symptoms butfurther research is needed.

Probiotics effect on diseases

• Pouchitis	➢ YES	clear effect of improvement
• Antibiotic use	➢ YES	
• Preterm, low birth-weight infants	➢ YES	
• IBS	➢ Only in clinical trials	not really any proven effects and not really recommended
• Crohn's disease	➢ Only in clinical trials	
• Ulcerative colitis	➢ Only in clinical trials	
• C.difficile colitis	➢ Only in clinical trials	
• Infectious gastroenteritis (children)	➢ Not recommended	

→ in 2015: 3.9 million American adults used probiotics or prebiotics → 4 times increase since 2007. Its extremely industry driven, and very expensive.

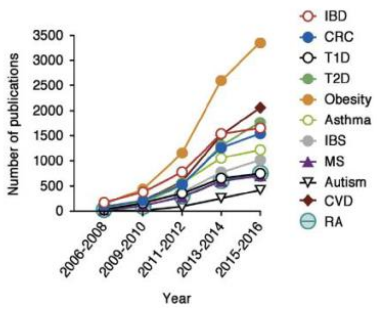
Microbiome and Mikrobiome

Microbiome(Aminoacids and Vitamin → products of Mikrobiome) != Mikrobiome (Bacteria, Fungi, Virus, Protozoa)

Bacteria

- 80 % are not culturable
- More than 1500 species
- GI tract: more than 1500 genomes sequenced. Classification of microbiome through mRNA and not because of culture
- 1.5 kg bowel microbiome
- Number of microbes in the bowel: 10'000 x earth population

Microbiomes in various diseases



Fecal transplantation: fecal microbiota transfer (FMT)

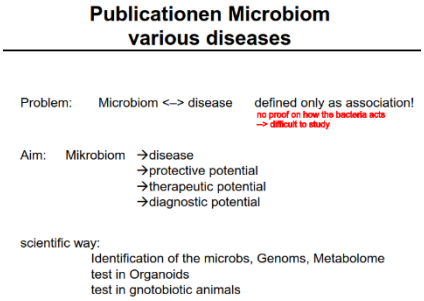
Example: fecal transfer after infection with C. diff.:

Results: Percentage of Patients cured without relapse is almost 100%

→ proves importance of microbiome

Mikrobiome : Obesity

Mikrobiome of an obese patient causes obesity in a healthy patient



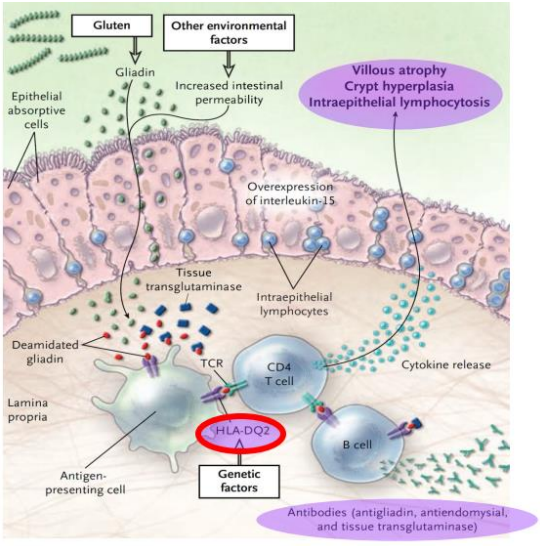
Evidence mikrobiome could be related to IBS: treatment of IBS with an Antibiotic - Rifaximin shows improvement of symptoms and also bloating. Bloating lasted for up to 3 months after antibiotic treatment.

Celiac disease

- Disease of the small bowl caused by gliadin, a gluten protein in wheat etc.
- Activation of the immune system (autoimmune disorder)
- Inflammatory reaction of the small bowl mucosa
- Destruction of the villi
- Genetic predisposition (depending on HLA system)

Prevalence: 1:150 (CH), 1:266 (Blood screening), 1:3345 (Prevalence Clinical)

Pathogenesis:



Typical clinical symptoms are chronic diarrhea, abdominal distension, failure to thrive.

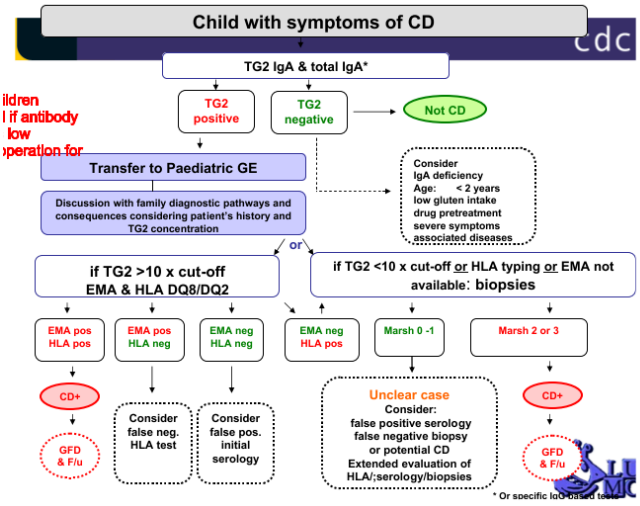
Cancer, IBS, and celiac disease → all affect the intestine, always have the same symptoms.

→ Gluten free diet in IBS also can improve symptoms!

Diagnosis celiac disease: Serology

Test	Sensitivity	Spezifity
AGA IgG	57-100	42-98
AGA IgA	53-100	65-100
AEA IgA	75-98	96-100
tTG IgG+IgA	76-100	95-100

Diagnostic procedure celiac disease



Diagnostic in children is sometimes hard if antibody concentration is low.

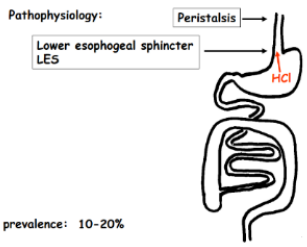
"Unhealthy food" or "healthy food" as a pathogenetic factor for gastrointestinal diseases

- Heartburn, Reflux esophagitis, Gastric ulcer, Duodenal ulcer, non-ulcer-dyspepsie, gastric cancer, gallstones, obstipation, irritable bowel syndrome, Hemorrhoids, Colon diverticula, colon cancer

→ Basically no GI disease where food does not have an association.

Heartburn, Reflux esophagitis, Gastric ulcer, Duodenal ulcer, Non-ulcer-dyspepsie, Gastric cancer → Acid secretion of the stomach

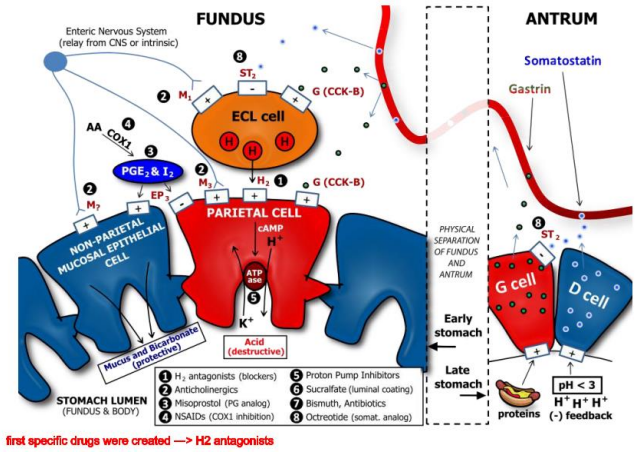
Heartburn, reflux esophagitis causes esophageal cancer (cancer goes up the digestive tract instead of down).



Effect of food:

- Fat, Chocolat, Alcohol, Coffee: lower pressure of lower esophageal sphincter
- Obesity: increased pressure in the abdomen
- Chewing gum: increased peristalsis

Treatment: Acid inhibition, H2-Antagonists, Proton pump inhibitor.



Ulcer

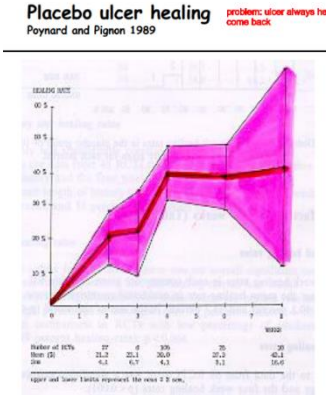
Ulkuskur: treatment with milk to neutralize the acid → no acid, no ulcer

Low fiber diet results in lower percentage against relapse after cure compared to high fiber diet.

High salt intake = high number of gastric ulcer

There is also ulcer healing under complete acid inhibition with proton pump inhibitors (PPI).

Problem: ulcer always heals after certain time, but they come back.



Continuation of acid inhibition → treatment with Ranitidine → ulcer seem not to come back (study by the industry → ulcer did come back eventually)

H.pylori Epidemiology:

- Very common infection, age-dependent
- Africa and southern Asia: 100% of population is H.p. positive but only 5% develop ulcers!

H.p. and ulcers: Ulcer relapse probability higher if the bacteria is present.

Colon Cancer

→ First there was an association with food intake found, then: counterinformation → no one was sure

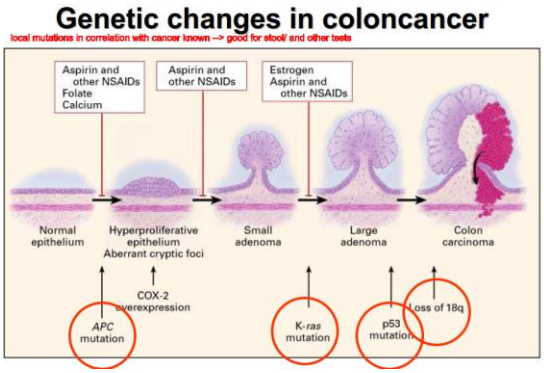
Risk factors are Meat, Job type and Marriage! Also Obesity is a 50 % increase of the risk for colorectal cancer.

Primary prophylaxis of colon cancer:

food:	Micronutrients:	Drugs:
• Vegetables • Fruits • Fibre • Meat • Meat preparation • Fish	• Calcium • Magnesium • Iron • Selen • Vitamin A • Vitamin C • Vitamin D • Vitamin E • Folic acid •	• NSAID (Aspirin) • Contrazeptiva • Ursodeoxycholacid • H_2 Antagonists • Statins • ....

Vitamin intake correlated with colon cancer risk reduction:

15 yrs multi vitamins	-60%
600 g fruits/d	-15%
No read meat	-30%
Stressful office job	+50%
Total	-55%



Screening colon cancer: Endoscopy

Colonoscopy is very importan, because colon cancer grows from polyps, and they take 5-10 years to develop and it is therefore detectable ealry on! It can reduce the incidence up tp 32%. But the problem is a lot of endoscopied are necessary to prevent cancer! Idea: select the patients with more risk and screen those more regularly!

Summary

- Food affects gastrointestinal function and well-being
- Few real food-related diseases (celiac disease, Lactose intolerance)
- Food (and lifestyle) is an important factor for primary prophylaxis for many diseases (i.e. colon cancer) (direct relation not possible, changing lifestyle will not definitely prevent cancer dev.)

Micronutrient Interactions in Health and Disease

Over ½ billion children lack vitamins and minerals that are essential - in minute quantities - for health. Micronutrient deficiencies, often called hidden hunger, lead to mental impairment, poor health, and even death.

It is often children and women in developing countries who suffer most

➔ Probably no other technology today offers as large an opportunity to improve lives and accelerate development at such low cost and in such a short time. Fortifying food with essential vitamins and minerals is both essential and affordable.

Important interactions: Iodine and Iron. Iron and Lead. Vitamin A and Iodine

Iodine deficiency

Every day, about 120'000 babies worldwide are born iodine deficient and at risk for mental and physical retardation.

2/3rds of them in South Asia and Sub Saharan Asia

What is Iodine deficiency?

Iodine is a trace element found in soil. In a perfect world, crops absorb iodine through their roots, and humans take in iodine through foods they eat. In vast regions of the world however, land doesn't contain enough, and crops and livestock in these areas are deficient in iodine. Iodine is needed to produce thyroid hormone (by the thyroid)

The amount of iodine needed by the human body is extremely small, just a teaspoon over the course of a whole lifetime. But it must be provided on a daily basis. → If not: Goiter (enlargement of the thyroid gland) and hyperthyroidism reduces IQ.

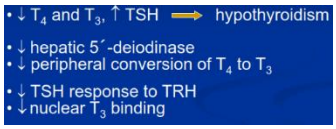
<u>Iodine Deficiency is the most common cause of preventable mental retardation.</u>

How to prevent iodine deficiency

Nearly all cultures include salt in their diet. Iodizing Salt is the most effective, inexpensive, and sustainable way of distributing iodine worldwide. But it doesn't always work well. In some parts of the world, despite iodine repletion, goiter and hypothyroidism persist. Why?

➔ Iron and Vitamin A deficiency.

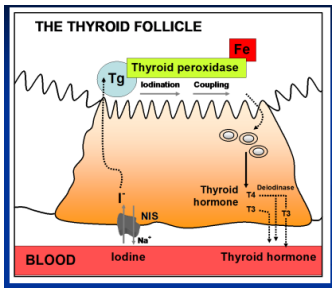
How Vitamin A and Iron deficiency relate to Iodine deficiency.



In both animal and human studies, Fe deficiency impairs thyroid metabolism

→ Iron deficiency anemia in women reduces total T_4 and T_3

Thyroid peroxidase (TPO)



103 kDa enzyme at the apical membrane.

Requires a heme prosthetic group likely to be ferriprotoporphyrin IX.

Peroxidase require Iron as a cofactor → if you have insufficient iron → anemic and reduces ability thyroid synthesis etc.

TPO activity and expression in thyrocyte cell cultures are dependent on:

1. Heme biosynthesis
2. Heme insertion into TPO during ER processing allows targeting to apical pole
3. Further covalent heme binding to TPO at the apical pole (H2O2 dependent)

Iron deficiency anemia reduces thyroid peroxidase activity in rats and causes hypothyroidism

Weanling rats given Fe-deficient diets or pair-fed with Fe diet for 5 weeks.

Hb, TSH, T3 and T4, TPO activity measured.

→Lower TPO activity in anemic mice.

If iron deficiency can lower TPO activity and thereby impair thyroid metabolism, does iron status influence the pathogenesis of ID in regions of coexisting deficiency?

IDA in rats vs. controls: T_3 and T_4

Hb (g/L)	n	T3 (ng/L)	T4 (mcg/L)
>120	12	4.85±1.14	0.39±0.11
<75	12	3.35±0.55	0.27±0.05
<60	12	3.12±0.54	0.24±0.03
<45	12	3.24±0.93	0.21±0.05

Does iron deficiency block a child's ability to use the iodine in iodized salt?

Coexisting deficiencies of iron and iodine are common in Africa

Goiter and IDA in African children (6-12 y)

	Goiter	IDA	Both
Western Côte d'Ivoire (n=1014)	59%	38%	23%
Northern Morocco (n=775)	74%	46%	26%

Study aim: to test the effect of iodine repletion in children with goiter and iron deficiency anemia.

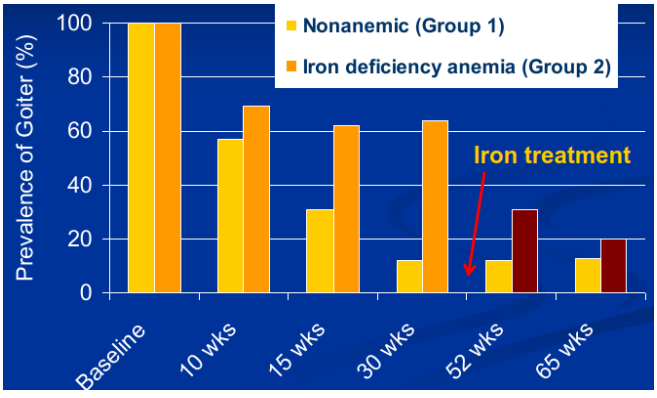
Study design: Two groups of iodine deficient school children (n=110, 6-12 y-olds). One group with Iron deficiency anemia and goiter. One group iron sufficient and goiter. Both given 200 mg oral iodized oil and followed for 30 weeks.

Iron deficiency anemia impairs thyroidal response to iodine

	Goitrous, nonanemic		Goitrous, IDA	
Wks	TSH (mU/L)	T_4 (nmol/L)	TSH (mU/L)	T_4 (nmol/L)
Baseline	2.2 (0.6)	110 (22)	1.6 (0.8)	130 (28)[3]
15	1.0 (0.6)[2]	122 (24)	1.6 (0.6)[3]	96 (17)[1,4]
30	1.2 (0.4)[2]	156 (30)[1]	2.0 (0.4)[4]	123 (30)[4]

No improvement in thyroid function in group with IDA. Goiter reduction is greater in the iron sufficient group after treatment

Anemia impairs response to iodine and iron treatment restores it



Does giving iron tablets to anemic children receiving iodized salt have benefits?

Study design: Ivorian schoolchildren with goiter and anemia. Iodized salt recently introduced to the region. Iron tablets or placebo: RCT, double blind design. 5d/week for 20 weeks.

Thyroid size and goiter rate, Fe vs. placebo

Significant reduciton of goiters in groups with Iron supplements.

Thyroid size	Iron	Placebo
Baseline	5.6	5.8
After 20 weeks %change from baseline	4.3 -22.8	5.1 -12.7

Dual fortification of salt with iodine and iron

Combat anemia and improve iodine efficacy in salt, but adding iron to salt is a challenge because of color changes → a new found Fe compound: micronized ferric pyrophosphate: white color, nonreactive, yet well absorbed!

Study design: Moroccan schooldchildren (n = 377), randomized by HH to two groups. Iodized salt vs. Salt fortified with iodine and FePP.

Salt given to 212 households (2kg/month), for one school year, in Areas of severe endemic goiter epidemic → debilitates generations

Study found: Reduction of Anemia in group with Iron & iodine salt supplement. Only very, very little in group with only iodized salt. Same in Prevalence of goiter, but more of a reduction in group only supplemented with iodized salt (but still less than other). Same in Hypothyroidism.

Thyroid size	Group 1 goiter and nonanemic	Group 2 goiter and anemic
Baseline	8.5	8.1
After iodine %change from baseline	4.6 -45.5	6.3 -21.8

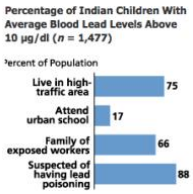
Conclusions: Iron deficiency anemia in children impairs response to iodized salt. Mechanism: impairment of Fe-dependent thyroid peroxidase enzyme. Adding iron to iodized salt not only combats anemia but also increases iodine efficacy.

Interaction between Iron and Lead

Lead poisoning common in children → more hand-to-mouth activity and lead absorbed more efficiently. In developing countered, an increasing hazard due to rapid urbanization, leaded fuels, and industrial pollution. In cities of China, South Asia and Africa, 20-78 % of children have elevated BLL. Both iron deficiency and lead poisoning concentrated in children from lower SES in urban environments. They both may permanently impair neurocognitive development in children.

Iron and lead share a common duodenal transporter, DMT1. Poor dietary iron intake, infections → Iron deficiency anemia → DNMT1 expression in duodenum strongly upregulated → increased lead absorption (also from Lead dust exposure from leaded gas, paint, industrial pollution) → higher severity of lead poisoning.

Both lead poisoning and iron deficiency common in children in developing world



In cities of India, 20-78 % of children have elevated blood lead levels. 50 % of children in developing countries are Fe-deficient. Early in life, both can cause brain damage and may permanently impair cognitive development.

Cross-sectional studies equivocal on the association between ID and BLL:

- Within strata of high, medium, and low environmental lead exposure, children with ID had significantly higher BLL than iron-replete children
- Whether ID increases risk for lead poisoning is unclear; it may simply cluster together with lead exposure in poor urban environments
- Longitudinal study of children, 4- to 5- fold increased risk of subsequent lead poisoning associated with baseline ID.

Does iron fortification reduce BLL in urban, lead-exposed, iron-deficient Indian children?

- Randomized, double-blind controlled, school feeding trial
- Children in Bangalore, India (31 % < 12 y-olds have BLL >= 10 microgram/dl). 5-13 y-olds from urba slum in Bangalore.
- Daily rice meal with 20 mg Fe (as FePP), and rice with no firtification Fe. 6d/wk for 30 wk, supervised
- Baseline and midpoint: dewormed with albendazole (hookworm prevalence almost 50 % in SAC)

Change in iron status:

Zinc protoporphyrin→ measure of iron status not zinc status. High level → a lot of ineffective red blood cells that do not transport iron.

	Time (wk)	Iron group	Control
Serum ferritin (µg/L)	14	16 (2-73)	14 (2-114)
	30	26 (3-95)†‡	16 (2-73)
Transferrin receptor (mg/L)	14	8.1 (4.7-23.4)	8.2 (5.0-22.3)
	30	5.9 (2.4-14.2)†	6.8 (3.2-18.5)†
Zinc protoporphyrin (µmol/mole heme)	14	51 (26-208)	55 (23-279)
	30	34 (12-142)†‡	48 (14-308)
% of children with Fe deficiency	14	70	76
	30	28‡	55

† Significantly different between 14 weeks and 30 weeks (P<0.05)
‡ Significantly different from control group (P<0.05)

	Time (wk)	Iron group	Control
Median (range) BLL (µg/dl)	14	12.1 (3.7-26.8)	12.0 (3.8-25.5)
	30	8.1 (3.1-21.9)†	10.6 (4.4-25.3)
% children with BLL ≥10 µg/dl	14	65	68
	30	29‡	55

† Significantly different between 14 weeks and 30 weeks (P<0.05)
‡ Significantly different from control group (P<0.05)

Median BLL decreased 33 %. %>=10microgram/dl decreased 55 %.

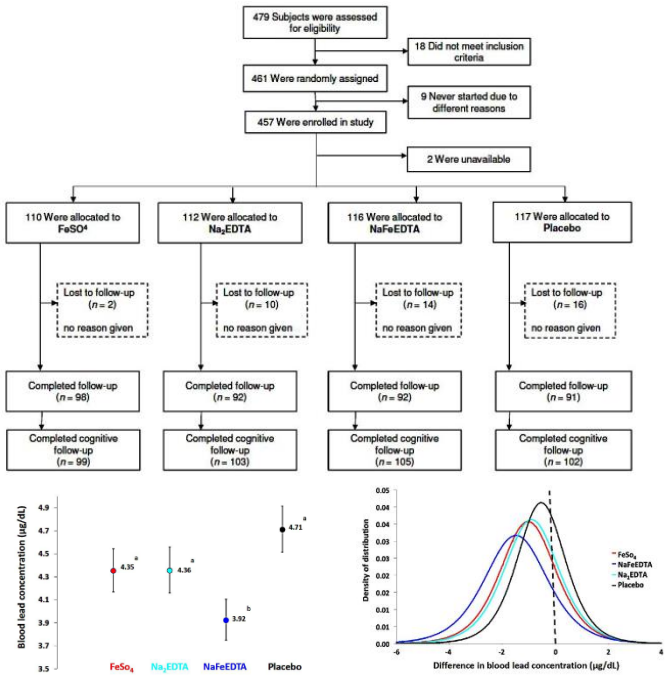
Change in Blood lead levels (about the same?)

Randomized trial of food fortification with iron and ethylene diamine tetra acetic acid (EDTA) to reduce blood lead in children

- Two common food fortificants are ferrous sulphate (FeSO4) and ferric sodium ethylene diamine tetraacetic acid (NaFeEDTA).
- EDTA can chelate iron and lead (all divalent cations)
- Our study aim was to determine the effect of iron and EDTA, alone and in combination, on blood lead concentration (BPb), iron status and cognition

RCT with Iron and EDTA to reduce blood lead in children

- In this 2-by-2 factorial double-blind, placebo-controlled trial, 457 lead exposed Moroccan children were randomized to consume biscuits (6 days/week) containing either: About 8 mg iron as FeSO4. About 8 mg iron as NaFeEDTA containing about 41 mg EDTA. About 41 mg EDTA as Na2EDTA. Placebo for 28 weeks
- Primary outcome was BPb, secondary outcomes were iron status and cognitive outcomes



Conclusions: Lead and Iron

- Food fortification with iron and EDTA additively reduce BPb
- The findings suggest NaFeEDTA is the iron fortification of choice in lead exposed populations
- Iron fortification may be an effective, sustainable strategy to accompany lead abatement

Julia Beckmann, HS2021

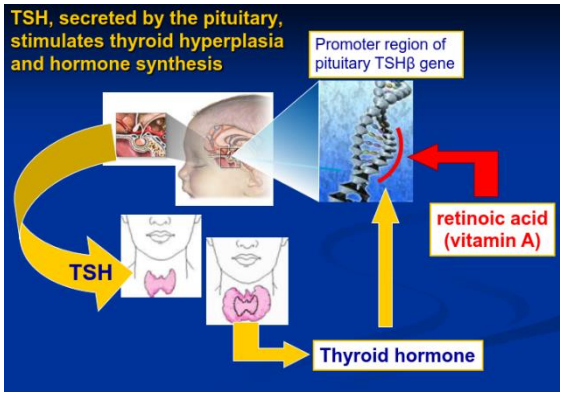
Interaction between Vitamin A and Iodine

Vitamin A deficiency

- Vitamin A is essential for the functioning of the immune system and the eye
    - Vitamin A deficiency (=VAD) affects > 100 million children
    - VAD causes blindness and is responsible for as many as 1 in 4 child deaths in deficient regions
- Vitamin A and iodine deficiencies often coexist in children in developing countries
    - E.g. rural area of West and North Africa, 32-57 % of children suffer from both VAD and goiter
- In areas of endemic goiter, micronutrient status is an important determinant of iodine and thyroid metabolism
    - Se and Fe deficiencies act in concert with iodine deficiency to impair thyroid metabolism and modify response to prophylactic iodine.

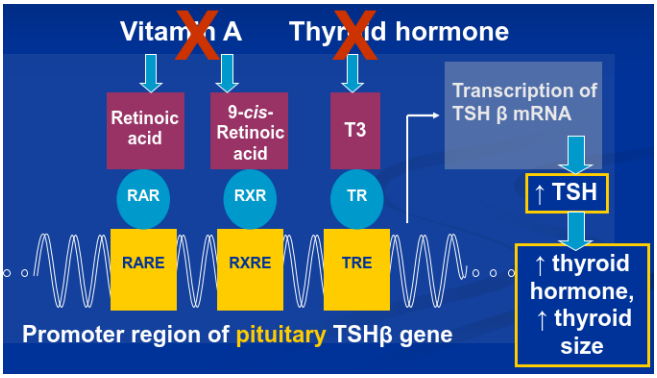
In animals, VA status has a major impact on thyroid metabolism

VAD in rats increased serum TSH and circulating T3, and increased thyroid size → central hyperthyroidism. High dose oral VA decreases TSH and circulating T3 (up to 75% decrease) → central hypothyroidism.



VAD modulates thyroid hormone feedback of TSH secretion

Both the T3-activated thyroid receptor and the VA-activated retinoid X receptor suppress transcription of the TSH-beta gene by occupying half-site on the promoter DNA



Combined VA and iodine deficiencies increase expression of pituitary betaTSH mRNA

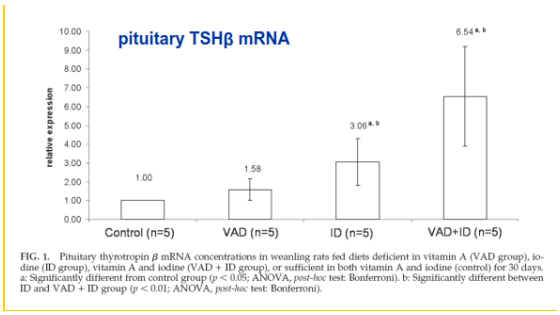
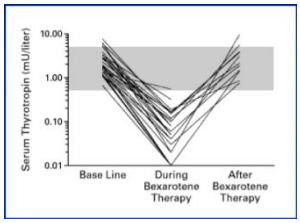


FIG. 1. Pituitary thyrotropin β mRNA concentrations in weanling rats fed diets deficient in vitamin A (VAD group), iodine (ID group), vitamin A and iodine (VAD + ID group), or sufficient in both vitamin A and iodine (control) for 30 days. a: Significantly different from control group ($p < 0.05$; ANOVA, *post-hoc* test: Bonferroni). b: Significantly different between ID and VAD + ID group ($p < 0.01$; ANOVA, *post-hoc* test: Bonferroni).

VA treatment reduces TSHbeta expression and TSH hyperstimulation in combined VA and iodine deficiency

Weanling rats fed diets deficient in VA and iodine for 30 days. Then repleted with iodine and/or vitamin A for 10 days. Group with VAD + ID who were treated showed reduction in TSH expression. Rats who were only deficient in VA and were treated with VA showed a bigger reduction.

Chemotherapy with a synthetic retinoid produced profound clinical hypothyroidism



… through binding to the pituitary RXR and suppression of TSH secretion

The adverse effects of IDD are due to hypothyroidism.
In areas of IDD, could a goitrous child's vitamin A status influence his/her risk for hypothyroidism?

Study aims: Investigate the effects of VAD on thyroid metabolism in children in an are of severe IDD. Compare the efficacy of iodized salt alone to iodized salt given with VA supplementation.

Study design: Moroccan school children (n = 298) with severe IDD and poor VA status enrolled in baseline cross-sectional study. Randomized, double-blind intervention trial.

- IS: iodized salt (25 microgram/gram + placebo)
- IS + VA: iodized salt + oral VA (200'000 IU as retinyl palmitate) at 0 and 5 mo

Intervention study vitamin A status:

IS : iodized salt (25 µg/g) + placebo
IS+VA : iodized salt + oral VA (200,000 IU) at 0 and 5 mo

	Retinol µmol/L		RBP mg/L		VAD %<0.7 µmol/L		Low VA %<1.05 µmol/L	
mo	IS	IS+VA	IS	IS+VA	IS	IS+VA	IS	IS+VA
0	0.80 ± 0.15	0.83 ±0.16	17.4 ± 9.1	18.1 ± 8.3	18	24	81	76
5	0.83 ± 0.14	0.97 ±0.11	19.2 ±10.1	24.5 ±10.0	15	4	72	60
10	0.79 ± 0.11	1.09 ±0.13	20.6 ± 8.8	30.2 ±11.2	20	4	75	42

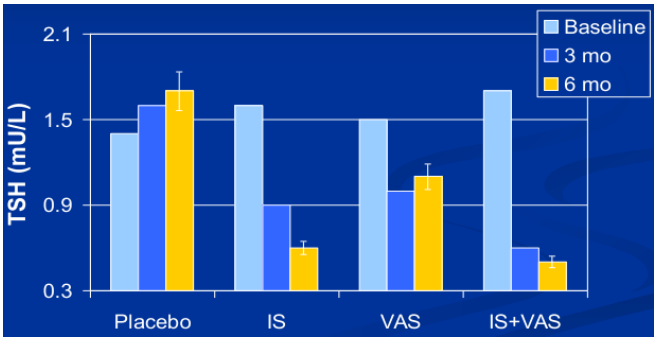
Intervention study thyroid status:

	TSH mU/L		T4 nmol/L		Goiter %		Thyr vol mL	
mo	IS	IS+VA	IS	IS+VA	IS	IS+VA	IS	IS+VA
0	2.1 (0.7-18.0)	2.3 (0.3-20.0)	111 ± 21	109 ± 23	94	92	7.4 (1.9, 8.7)	7.2 (2.3, 16.6)
5	1.7 (0.3-4.4)	1.2 (0.3-4.3)	121 ± 24	118 ± 26	73	67	6.7 (2.1, 13.2)	5.9 (2.0, 12.5)
10	1.6 (0.3-3.0)	0.9 (0.3-2.1)	119 ± 22	116 ± 22	64	52	6.2 (2.1, 11.9)	5.3 (2.2, 12.4)

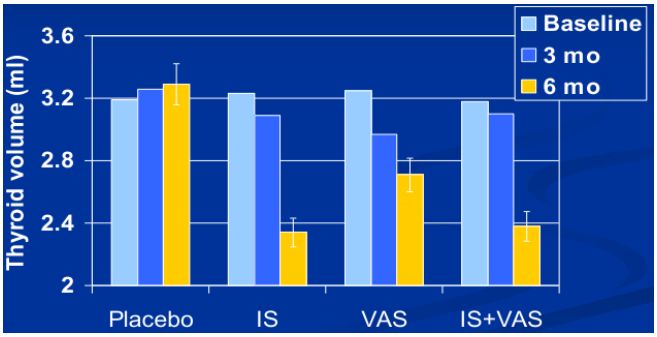
TSH stimulation
— indicated by increased TSH, Tvol, goiter —
reduced by VA treatment

Study design: South African school children (n = 410) with iodine and VA deficiencies. RCT, double-blind 2x2 intervention trial. Four groups: Iodine treatment (200 mg iodine as iodized oil), VA treatment (200'000 IU as retinyl palmitate), Both iodine and VA, Placebo capsule. Followed for 6 months.

Vitamin A repletion reduces TSH in VA- and iodine deficient children:



Vitamin A repletion reduces thyroid size and goiter in VA- and iodine deficient children:



Conclusions

- VA treatment reduces TSH hyperstimulation and enhances the response to iodine reducing risk for goiter and its sequelae
- These findings are likely mediated through the pituitary retinoid receptor and TSH-beta gene expression

The future

- UNICEF/WHO have described the global iodized salt initiative as "probably the most effective public health nutrition program ever"
- However, 1/3rd of children worldwide (over 250 million) remain iodine deficient and goitrous
- Reaching this remaining third will require strategies that also correct other micronutrient deficiencies that affect the response to iodized salt (vitamin A, iron)
- Micronutrient interaction at the molecular level
    - Within the pituitary genome for vitamin A
    - Within the thyrocyte membrane for iron

  Have far-reaching affects on public health of children in developing countries
- Argues strongly for combined approaches to correct these common deficiencies.

B-vitamins, homocysteine, and cardiovascular disease

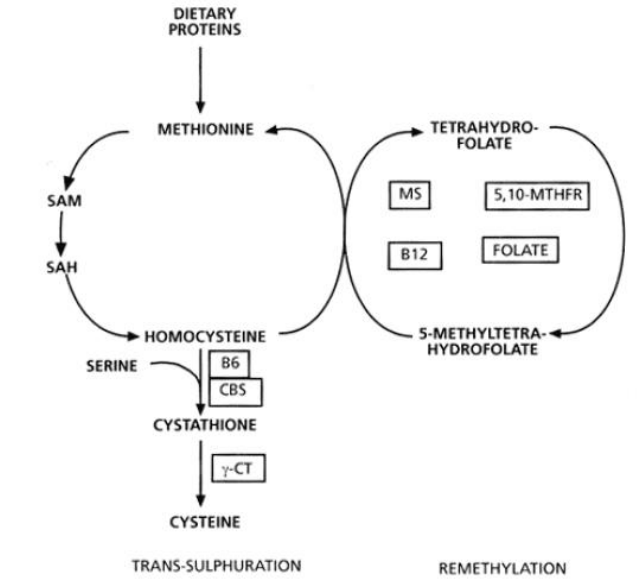
Homocysteine

A non-essential Amino Acid. A metabolite of an essential amino acid (Methionine). Has a thiol group (sulfur, distinguished it from many other amino acids).

→Homocysteine are an emerging risk factor for atherosclerosis and vascular disease. Can B-vitamins (particularly folic acid, vitamin B-12 and maybe riboflavin and B-6) protect against cardiovascular disease?

Background: first proposed interaction (McCully) in 1969. People with a rare genetic defect (cystathione-beta-synthase deficiency, have high homocysteine levels) develop atherosclerosis, and heart attacks already in their teens and twenties. Again linkage showed in 1980s in heterozygotes.

Homocysteine metabolism



Key: CBS = Cystathione-β-synthase; γ-CT = γ-cystathionase; MS = methionine synthase; 5,10-MTHFR = 5,10-methylene-tetrahydrofolate reductase; SAM = S-adenosyl-methionine; SAH = S-adenosyl-homocysteine

You need to know where the main metabolites, homocysteine and the B-vitamins are placed in this diagram → Learn this slide!

5-methyltetra-hydrofolate (methyl-donor, donates to Homocysteine, regenerating methionine!). Here folic acid and B12 are important as cofactors(metabolism of these very closely linked). Homocysteine can also become cysteine and excreted in the kidney. This involved vitamin B6. CBS is the enzyme (genetic defect mentioned before acts here).

What happens to Homocysteine without these?

Potential Atherogenic mechanism of homocysteine

Impact of high levels of homocysteine:

- Triggers disordered connective tissue synthesis (increased sulfation of proteoglycans, sulfur donated by thiol group of homocysteine). Vascular wall is weakened and functions poorly.
- Reduction of thiol group (R-SH + SH-R → RSSR) produces oxidants (e.g. OH radical) which directly damage endothelium (lining of blood vessels) and oxidize LDL, which is a promoter of atherosclerosis
- Increased platelet aggregation
- Activation of coagulation factors V and XII

➔ Increased production of atherosclerotic plaque and increased thrombus formation

➔ Heart disease, Stroke

Some people propose that maybe not the homocysteine's are most dangerous, but some metabolites which are produced only when there are high levels of homocysteine in the blood stream! These metabolites are Homocysteine thiolactone and Homocysteic acid.

High blood homocysteine: A new risk factor for heart disease and stroke

Findings from the Framingham Study: → With increasing Plasma homocysteine level there is more deep venous thrombosis and increased Atherosclerosis of the carotid artery. Lead to large meta-analysis in 1995 of linkage between homocysteine levels and heart disease.

- Homocysteine levels of about 10 micromol or less are consider to be low risk (OR is 1)
- Levels above 10 micromol lead to a massive increase in OR
- Magnitude of risk is similar to that of high cholesterol levels
- An independent risk factor, but may enhance the effect of "conventional" risk factors
- Estimated that a lowering of homocysteine by 3 micromol/l would reduce the risk of
    - Coronary heart disease by 11-16 %
    - Stroke by 19-24 %
- But: only associations!! - too optimistic??

Why is hyperhomocysteinemia so common?

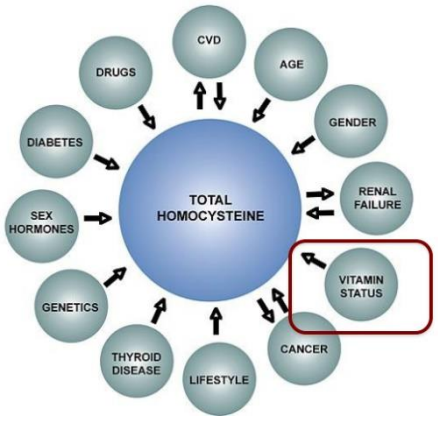
Approximately 40% of the adult male population has plasma homocysteine levels > 10 mcmol/l → elevated level

Are there genetic factors?

- Identical and non-identical twin studies suggest a high heritability of elevated homocysteine levels
- 1 in 200 people are heterozygous for homocystinuria (cystathione-beta-synthase deficiency) causing mild to moderate elevations in homocysteine
- Heterozygotes for several other rare genetic conditions and inherited defects of vitamin B12 metabolism may also contribute

Taken together, possible genetic factors do not explain the population frequency of elevated homocysteine levels, so environmental factors are important.

Risk factor for high blood homocysteine



Environmental factors

Dietary deficiencies of vitamin B12 and vitamins B6 are rare, except among older adults:

- 5-12 % of older adults are vitamin B12 deficient
- 80 % of free-living older adults consume <75 % of the US RDA vitamin B6

Poor dietary folate intake is common throughout the population:

- 50 % of US adults have plasma folate concentrations < 9 nmol/l
- 35-40 % of adults consume < 0.2 mg folate/day
- 60-88 % of adults in the US consume < 0.4 mg folate / day

Folate probably more important to consider than Vitamin B intake!

→ Homocysteine higher in vegetarians, due to low vitamin B12 intake?

3 strategies to achieve optimal folate status

- Natural food sources
- Fortified foods
- Supplements

→ Food folates not as well absorbed as folic acid in fortified foods or supplements

- Food folates are predominantly polyglutamates, must be converted to monoglutamates for absorption
- Compared with folic acid, food folates are
    - Much less stable to cooking (lot of folate loss during boiling, also some from steaming but less)
    - Much less bioavailable

Folates: terminology

- Folic acid:
    - Synthetic form (supplements, fortified foods)
- Folates:
    - Natural forms (plant and animal tissues)

Dietary folate equivalents

- Based on differences in bioavailability between natural folates and added folic acid (FA)
- DFE = microgram natural food folate + 1.6 times microgram FA
- Added FA 60 % higher bioavailability

B-vitamin supplements and homocysteine

In men with moderate hyperhomocysteinemia, daily supplementation with 1 mg folate, 0.4 mg vitamin B12, and 10 mg vitamin B6 produced a sharp decrease ($p<0.001$) in plasma homocysteine levels at 4 (-50%) and 6 weeks (-61%), compared to baseline and placebo.

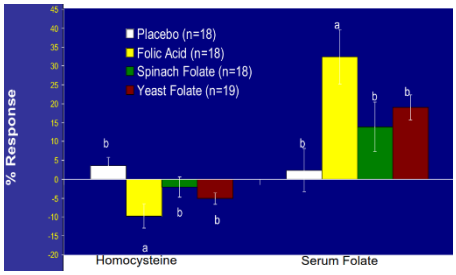
Folate + Vitamin B12 Supplements and Homocysteine

Healthy adult women (n=150) received either folate or folate and vitamin B12 for 8 weeks. The addition of 400 mcg of vitamin B12 resulted in a statistically significant additional lowering of homocysteine (-18%, $p<0.05$) compared to folate alone.

Folate-Fortified Foods lower Plasma Homocysteine

In a double blind, randomized trial, Maliow et al. demonstrated a significant 10-15% reduction of plasma homocysteine by cereal fortified with high doses of folic acid in 75 adults with coronary heart disease.

Response to intervention with food folates or folic acid



Folic acid fortification has been introduced to reduce birth defects, will it also benefit CVD through homocysteine lowering?

- 1998: mandatory folic acid fortification at a level to deliver and extra 100 microgram folate per day
- Reduced neural tube defects in US and Canada
- In US in 1996, FDA mandates flour fortification at 140 microgram/100g; complete by mid-1997
- Jacques et al compared serum folate and homocysteine in Framingham Cohort (middle aged and older adults, n = 1106) before and after fortification

➔ Significant and substantial improvement in folate and homocysteine levels.

Folic acid fortification of flour in 1997 also lead to a Decline in stroke related mortality in the US and Canada

Folic acid is effective at lowering blood homocysteine: a meta-analysis

- Folic acid reduced blood homocysteine by 20-25%
- Vitamin B-12 produced an additional 7 % lowering
- Vitamin B-6 produced no additional effect

Does the homocysteine response to riboflavin depend on genotype?

Polymorphisms in MTHFR common in some populations

- MTHFR converts 5.10-methylene THF to 5-methyl THF
- Methylenetetrahydrofolate reductase (MTHFR): catalyzes reduction of CH2THF to CH3THF
- Cofactor: FAD, Precursor: Riboflavin
- Polymorphic mutations in MTHFR → MTHFR 677C → T Polymorphism. C to T substitution at base pair 677. Alanine/valine change in the amino acid sequence. **Functionally defective enzyme**.

Blood homocysteine in homozygotes for MTHFR C677T (TT genotype) responsive to riboflavin.

Homocysteine (µmol/L)	CC (n = 27)	CT (n = 26)	TT (n = 34)
Baseline	10.7	12.2	17.6
After riboflavin	10.9	11.8	13.0

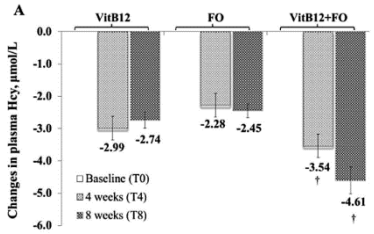
TT genotype responsive to riboflavin supplements → 22 % lowering of homocysteine overall; 40% in those with lower riboflavin status at baseline. No response in CT or CC genotype groups.

Adverse effect of the MTHFR 677C → T variant on homocysteine and stroke risk:

Meta analysis of 140 data sets from 101 genetic studies including 20'885 strokes: the MTHFR 677C → T variant had increased risk for stroke in regions with low folate intake but not in areas with high folate intake due to folate fortification.

The combination of vitamin B-12 and fish oil has a synergistic effect on lowering plasma homocysteine

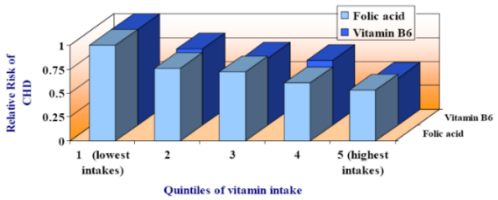
Study objective: to examine the effect of vitamin B-12 and n-3 PUFA on plasma Hcy. Subjects randomly divided into three groups and assigned to receive 1000 microgram of vitamin B-12, 2g fish oil, or 1000 microgram vitamin B-12 and 2g fish oil, respectively for 8 weeks.



➔ Supplemental B-vitamins can reduce homocysteine levels but can they reduce the risk of atherosclerosis?

Folic acid and Vitamin B6 Intake and coronary heart disease

Rimm et al. found a significant reduction in risk of coronary heart disease among 80'000 women at upper quintiles of total energy- and age-adjusted folate and vitamin B6 intake.



Intake of folate and vitamin B6 2-3x higher than the current RDA may be important in the primary prevention of heart disease.

Can B-vitamins reduce the risk of atherosclerosis?

In a preliminary study: treatment with 2.5 mg folate + 25 mg vitamin B6 + 250 mcg vitamin B12 for a mean of 4 years reduced the rate of progression of atherosclerosis in 38 adults with established atherosclerosis and plasma homocysteine levels > 14mcmol/L.

Next a Randomized, placebo-controlled trial: Treatment: 5mg folic acid and 250 mg vitamin B6 for 2 years. Subjects: 150 healthy siblings of patients with premature atherothrombic disease (mean age 46 years).

Treatment effects: Reduction in plasma homocysteine level from 14.7 to 7.4 micromole. Decreased rate of abnormal exercise electrocardiogram (indicates myocardial ischemia).

What about data from randomized controlled trials, with clinical endpoints?

RCTs investigating the effect of B vitamin supplementation on cardiovascular risk

Subjects	Treatment	Baseline HCY	% (actual) ΔHCY	Key findings
VISP 3680 men and women with recent stroke 2004 JAMA	2.5 mg FA 25 mg B6, 0.4 mg B12 (high-dose) *vs.* 0.02 mg FA, 0.2 mg B6, 6 µg B12 (low-dose)	13.4 µmol/L Follow-up for 24 months	At 1 month: ↓15% (2.0 µmol/L); end of study: ↓17% (2.3 µmol/L) with high-dose *vs.* ↓2% (0.3 µmol/L) with low-dose	**No significant effect** on the composite end point (recurrent stroke, CHD event or death) (RR 1.0, 95% CI 0.8–1.1)
NORVIT 3749 men and women with MI in the last seven days 2006 NEJM	Four treatment groups: 0.8 mg FA, 40 mg B6, 0.4 mg B12 (A) 0.8 mg FA, 0.4 mg B12 (B) 40 mg B6 (C) Placebo (D)	13 µmol/L Median follow-up 40 months	At 2 months: A: ↓28% (3.7 µmol/L) B: ↓26% (3.4 µmol/L) C and D: no change At end of study: A: ↓27% (3.6 µmol/L) B: ↓24% (3.1 µmol/L) C and D: no change	**No significant effect** on the composite primary end point (recurrent MI, stroke or sudden CHD death) with A and B *vs.* C and D (RR 1.08, 95% CI 0.93–1.25)

Subjects	Treatment	Baseline HCY	% (actual) ΔHCY	Key findings
HOPE 5522 men and in women with vascular disease or diabetes	2.5 mg FA, 50 mg B6 , 1 mg B12 *vs.* placebo;	12.2 µmol/L each group	At end of study: ↓20% (2.4 µmol/L) *vs.* ↑6% (0.8 µmol/L)	**No significant effect** on the composite primary end point of CV death, MI and stroke (RR 0.95, 95% CI 0.84–1.07)
5442 women with either a history of CVD or 3 or more coronary risk factors 2007 JAMA	2.5 mg FA, 50 mg B6, and 1 mg B12 vs. placebo	Follow up 7.3 years	↓18.5% in the active group over the placebo (n = 150)	**No significant effect** on the composite outcome of myocardial infarction, stroke, coronary revascularization, or CVD mortality. [RR], 1.03; 95% confidence interval [CI], 0.90-1.19

BUT!! → All done in older adults, many with poor kidney function!

VitB12 may be dangerous in those with impaired kidney function

B-vitamins seem to be particularly effective against ischemic stroke (occlusion due to a blood clot)

Reanalysis of the earlier trials showed that subjects with healthy kidney function benefited from B-vitamin therapy, while those with poor kidney function did not. For example, in the VIDP reanalysis, which excluded patients with poor kidney function, there was a significant 34% reduction in the composite outcome of stroke, myocardial infarction or vascular death.

Folic acid supplements reduce the progression of atherosclerosis as measured by carotid intima-media thickness (CIMT): a meta-analysis

- Folic acid supplementation significantly reduced the progression of CIMT
    - Particularly in subjects with chronic kidney disease or cardiovascular disease
- Greater beneficial effect was seen in those with:
    - Baseline CIMT levels >=0.8mm
    - Reduction in the homocysteine concentration >= 30%

Efficacy of folic acid supplementation in stroke prevention: a meta-analysis

- Folic acid supplements significantly reduced risk of stroke by 18%
- Greater benefit in those trials with
    - Treatment duration of more than 36 months
    - Decrease in blood homocysteine of > 20%
    - No fortification of partly fortified grain
    - No history of stroke

B-vitamin supplementation and CVD: the latest meta-analysis shows no effect on heart attack but a 10 % lower risk of stroke

Compared with placebo, supplements of vitamins B6, folate or B12 given alone or in combination:

- No effects on myocardial infarction
- Reduced stroke outcome
- Even bigger effects (-20 to -25% risk) in populations with low folate intake and no food fortification with folate

Conclusions

Epidemiological associations between elevated homocysteine and CVD strong and consistent, but do not prove causality.

In clinical trials, vitamin supplements:

- Reduce homocysteine levels
- No significant effect on heart disease
- Significant but modest reduction in risk of stroke (about 10% lower risk)

Is longer follow-up needed? (till now, RCTS FU 2-7 y), is genotype important (e.g. MTHFR polymorphisms?).

Many neurologist now recommend daily supplementation of about 05.mg FA and 0.5 mg vitamin B12 in those patients with ischemic stroke.

Nutrition and Diabetes

General principles: Diabetes + Obesity

Statistics

- 2019: 463 million people (out of 8.1 billion) have diabetes, China and India about half of those numbers. Predicted number for 2045: 700 millions
- Obesity prevalence in 2019: >770 million People (10%)
- Obesity and Overweight in Switzerland:

	Obesity	Overweight	Both
1992	6.4	21.9	28.3
1997	6.8	28.1	34.9
2002	7.7	29.4	37.1
2007	8.5	30.4	38.9
2012	11.2	30.8	42.0
2017	11.0	31.0	42.0

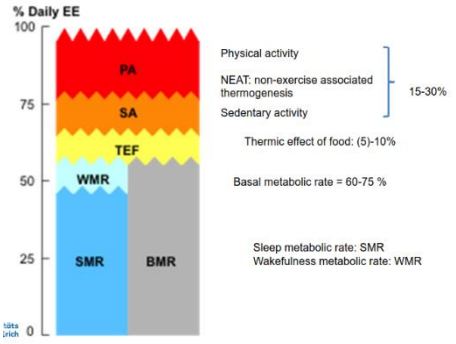
Prevalence of Diabetes in Switzerland - CoLaus Study

- 6188 subjects in area of Lausanne between 35-75 years
- Prevalence of Diabetes mellitus: 6.3 %
  - Type 1 Diabetes mellitus: 2.2 %
  - 0-19 years: 0.2 %

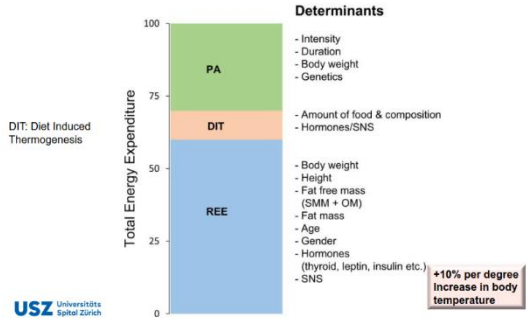
Occurrence of Obesity and Diabetes

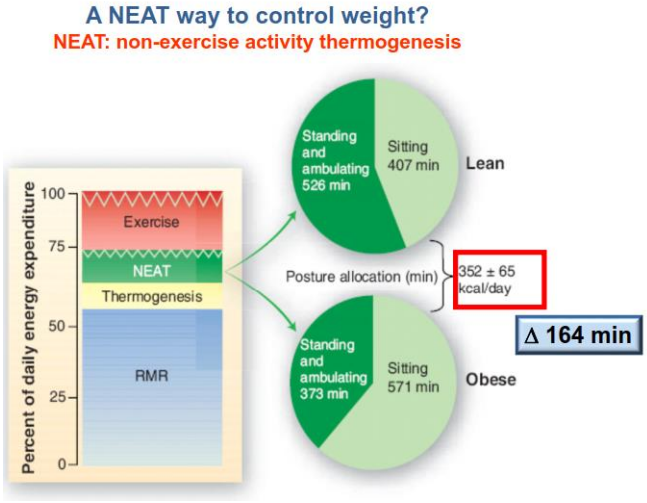
Pre-disposing genes and environment can lead to Obesity (~30-50% persons with obesity or overweight have diabetes), and with more pre-disposing genes can this lead to type 2 diabetes (90 % persons with diabetes have obesity or overweight)

Daily Energy Expenditure: Components



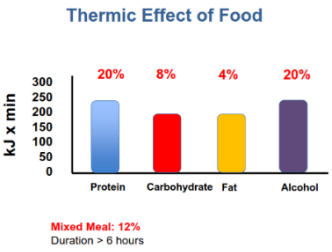
Determinants of energy expenditure:





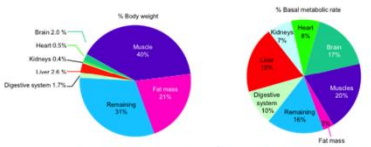
NEAT: non-exercise activity thermogenesis

Just for sitting and standing (Posture allocation) you can burn 352 (+/- 65) kcal/day.



Energy Expenditure of Organs

Even though Organs do not take up the majority of percentage of body weight, they do take up a big part of the Basal metabolic rate.



Organ (65 kg Person)	Energy expenditure (%BMR)
Liver	19
Brain	17
Muscle	20
Kidney	7
Heart	8
Rest (digestive system)	26 (10)

Simple calculation BMR and total EE

- BMR = 24 X Body weight (in kg).
- Acitivty factor: Men - 1.45. Women - 1.25
- Total daily energy expenditure:
  - Men: Body weight (kg) x 35
  - Women: Body weight (kg) x 30

Basics: Diagnosis and Treatment

Hyperglycemia → many organs influence that!!!

Plasma Glucose Criteria for Diagnosis of Diabetes

1. Random plasma glucose >= 11.1 mmol/l (and symptoms of Diabetes mellitus) OR
2. Fasting plasma glucose >= 7 mmol/l (after >= 8 hours fasting) OR
3. Plasma glucose 2 hours after OGTT >= 11.1 mmol/l (75g gkucose)
4. HbA1c > 6.5%

Julia Beckmann, HS2021

Diabetes types

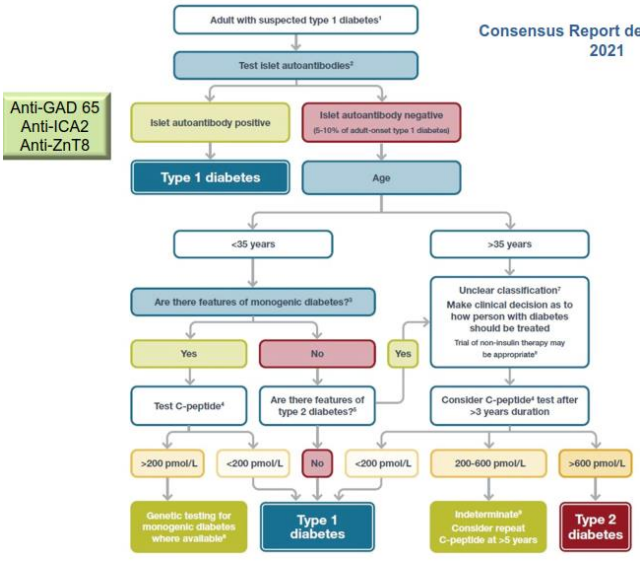
- Type 1 Diabetes mellitus
- Type 2 Diabetes mellitus (Majority)
- Specific forms
    - Genetic defects of Beta-cell function (MODY + mitochondrial Diabetes (3-5 % of all diabetes forms)
    - Genetic defect in insulin action
    - Disease of exocrine Pancreas (chronic pancreatitis, cystic fibrosis, hemochromatosis)
    - Endocrinopathies (Glucagonoma, Cushing, Pheochromocytoma, Acromegaly)
    - Drug induces
    - Infections
    - Rare Forms of Immunogenic Diabetes
    - Other genetic Syndromes associated with Diabetes
- Gestational diabetes

Type 1 Diabetes mellitus

- Type 1 Diabetes is an autoimmune disease
- Destruction of beta-cells by cytotoxic T-Lymphocytes
- Antibodies to beta-cell antigens = marker of disease (not the cause!)
- Absolute deficiency of insulin, which has to be replaced

Found Auto-Antibodies: Anti GAD 65, anti-IA-2, anti ZnT8.

More than 90% of people with diabetes have at least one of those antibodies present at time of diagnosis! The GAD antibody is the least specific, the other two are a lot more (if you have them, you can be practically sure you have T1D)



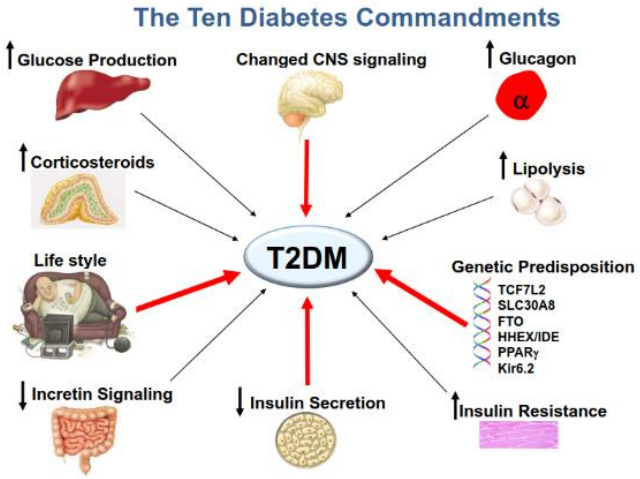
Diabetes screening

- Usually done early, all people over 45 years. Earlier if there are risk factors (positive family history, obesity, etc.)
- Also screening for metabolic syndrome (85-90 % of patients with T2D have metabolic syndrome). Definition: 3 out of 5 criteria fulfilled (Population- and country specific):

Criteria	Men	Women
Waist circumference*	>94-102cm	>80-88cm
Blood Pressure	≥130/85mmHg	
Plasma Triglyceride	≥ 1.7mmol/l	
HDL-Cholesterol	<1.0mmol/l	<1.3mmol/l
Fasting Plasma Glucose	**≥ 5.6 mmol/l**	

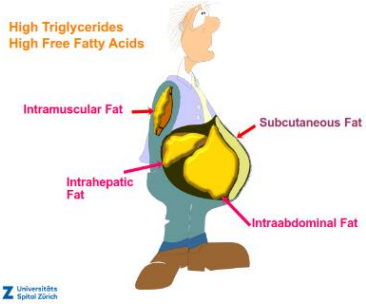
Type 2 diabetes

Pathogenesis: Interplay between increased Blood glucose, Insulin resistance (more Gluconeogenesis in liver, less glucose uptake in fat, less glucose uptake in muscle) leading to Gluco-Lipo-toxicity, leading to Disturbed Insulin secretion by Pancreas (too little and too late insulin secretion). Visceral fat increases risk for T2D.

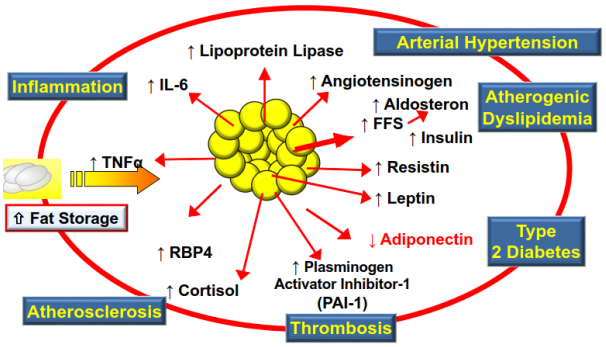


Distinct Fat Distribution in Type 2 Diabetes:

- High Triglycerides
- High free Fatty acids
- Subcutaneous fat is normal
- Intraabdominal and intrahepatic and intramuscular fat → ectopic places! The more of those, the higher the risk for diabetes

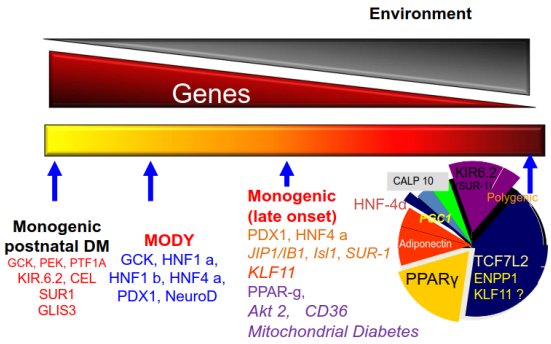


Fat Cell = endocrine Organ



The fat cell is not only a storage of energy, its and endocrine organ. It produces many hormones, many inflammation factors, which all play a role.

Type 2 Diabetes Genes

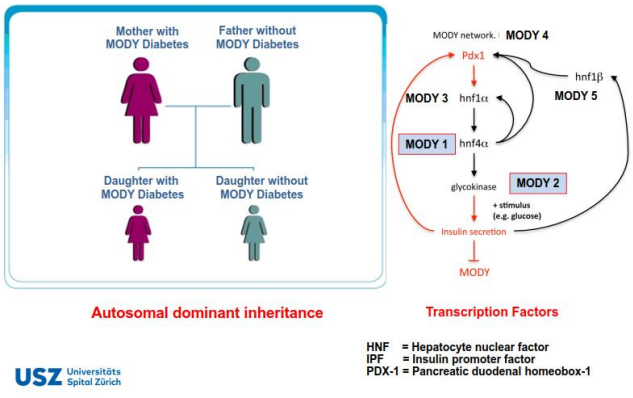


Right → genes typically with T2D → but! Completely polygenic! Genes play a role but for T2D environment is much more important!

MODY

MODY = Maturity onset diabetes of the young

Autosomal dominant inheritance.



Is a form of monogenic diabetes, but there are different mutations that can cause it (MODY1, MODY2, etc.)

Monogenetic Diabetes

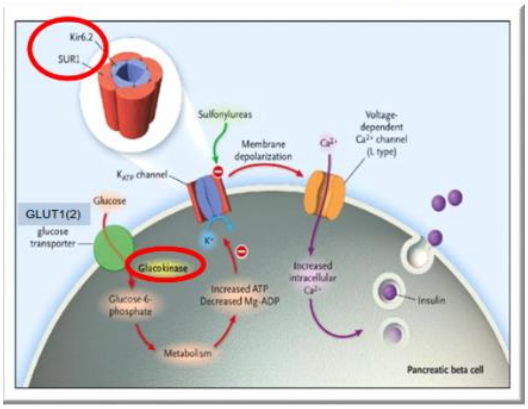
➔ Diabetes caused by a mutation in a single gene

Prevalence

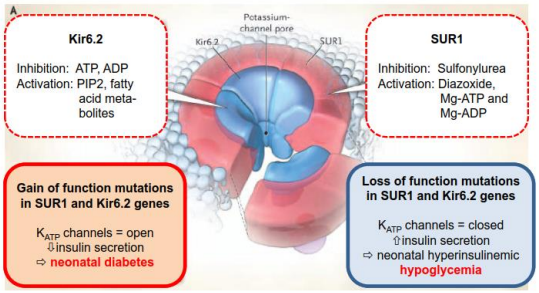
- 3-5 % of all "so called Type 2 Diabetes"
- Type 2 Diabetes: 6.4 % of population (CH)
- 0.25 % population = monogenetic Diabetes
- As common as type 1 diabetes

Mechanisms behind monogenetic Diabetes:

Insulin secretion in the β-cell



Mutated K_{ATP} channels (Kir6.2 and SUR1)



Differential diagnosis from type 2 diabetes:

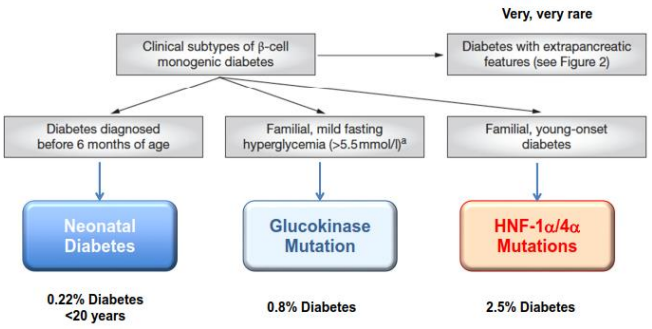
- Young-onset, apparent type 2 diabetes and features of obesity and metabolic syndrome are absent
- Additional features: absence of acanthosis nigricans or polycystic ovary syndrome, elevated or normal HDL-cholesterol and reduced or normal triglycerides

➔ Suspect monogenic diabetes form

Differential diagnosis from type 1 diabetes

- Patients with clinical diagnosis of type 1 with
  - Family history of two of three generation non-insulin independent diabetes
  - Absence of autoantibodies
  - Detection of measurable C-peptide and hyperglycemia outside the honeymoon period (up to 5 years after diagnosis)

➔ Atypical for type 1 diabetes. Test for HNF1alpha mutation (most common transcription factor mutation (58%)



MODY 2	MODY 3
Glukokinase (GCK)-Mutation Defective glucose sensing Defective glycogen synthesis Diagnosis during childhood, or pregnancy (screening GDM) Normal nutrition, no therapy High fasting glucose, normal postprandial glucose, no complications, HbA1c < 7.5 % ➔ Dx often missed, no therapy	HNF-1alpha-Mutation Defective insulin gen transcription → defective insulin secretion Post puberty Sulfonylurea, insulin Diabetes, microvascular complications, Glucosuria ➔ Diabetes, which responds initially really well to sulfonylureas, later requirement of inuslin

Difference MODY - mitochondrial Diabetes?

(about 1.5% of all cases with type 1 and 2 diabetes)

- Inheritance only through mother (mitochondrial DNA), but men are affected as well
- A-to-G transition at Nucleotid Position 3243 of mitochondrial RNA gene
- Classical Diabetes + sensorineural hearing loss (>5 kHz) (60% probability)
- Late onset Diabetes: 35-40 years
- Fasting glucose is often normal
- Insulin secretion defect to glucose (arginine and glucagon maintained, later loss of glucagon secretion)
- No effect of sulfonylurea and metformin is contraindicated due to lactic acidosis
- Different phenotypes: Pigmentation Retina (Macula), muscle weekness, MELAS-Syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

MIDD (maternally inherited Diabetes and Deafness)

Gestational Diabetes (GDM)

Definition:

- Glucose intolerance discovered during pregnancy for the first time
- Definition independent of therapy with insulin or diet, or whether disturbance persists after pregnancy
- Does not exclude possibility of preexisting diabetes or glucose intolerance

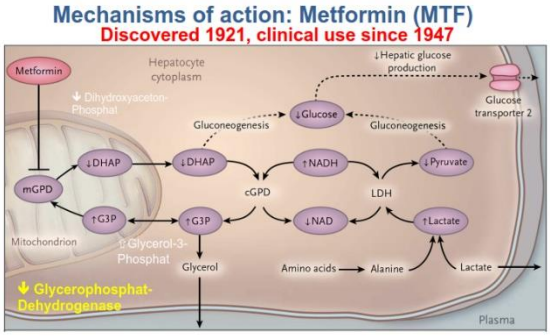
How common is GDM today?

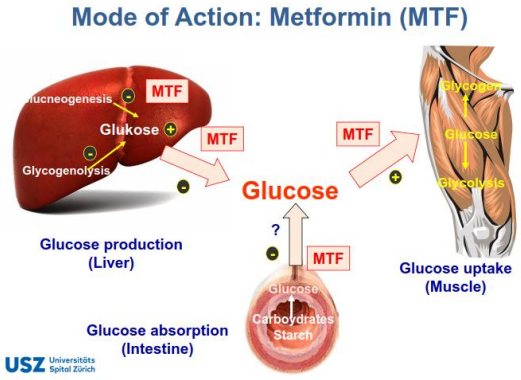
- 23'957 participants in 15 centers around the world (Asia, Australia, Europa, N-America)
- Combined prevalence of GDM: 17.8%
- Center-to-center variability
- In Europe (Ireland, UK) 2/3 have high FPG (=10-11%= and in only 7% 2hr value is elevated

Treatment of Type 2 Diabetes

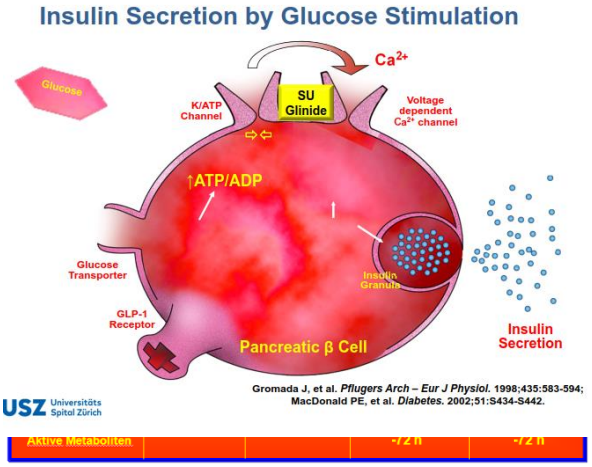
→ In an ideal world, 90% could be treated by lifestyle

There are already a lot of therapies (Glucose self-monitoring, Metformin, Sulfonylureas, GLP-1) and there has been a lot of advances in the last 50 years, which may be a reason for hope.

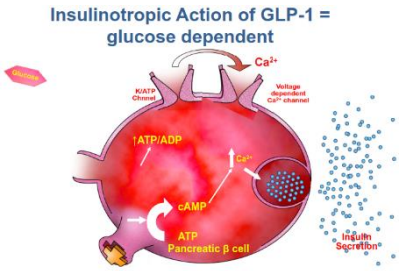


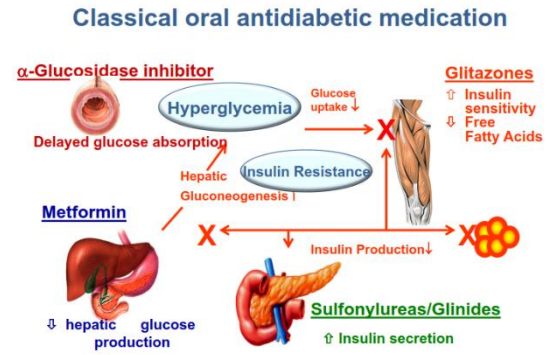


Biggest disadvantage: Size of pill and gastrointestinal side effects.



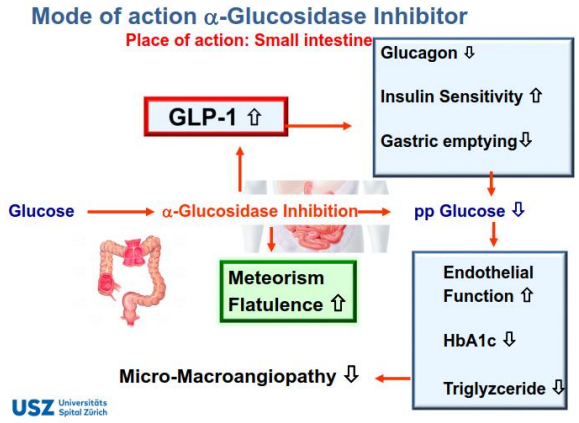
Limited Insulin secretion by GLP-1 Receptor Stimulation without Glucose



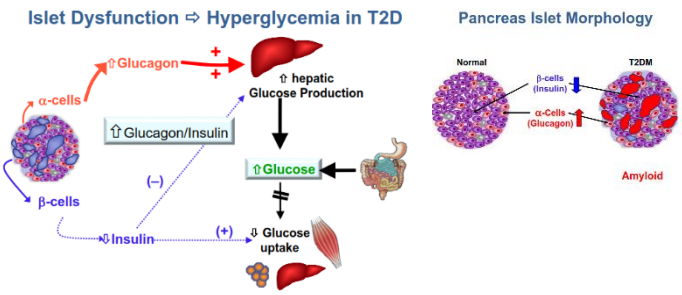


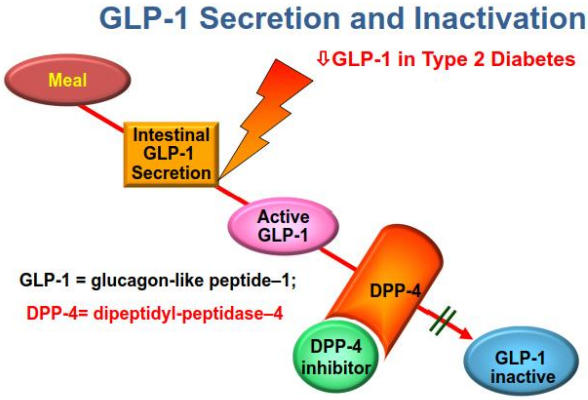
➔ Sulfonylureas/Glinides: more insulin but more hyperglycemia as side effect → gone in Switzerland

➔ Glitazones: take up more glucose, but gain a lot of weight. Also cannot take these if you have heart failure → gone in Switzerland

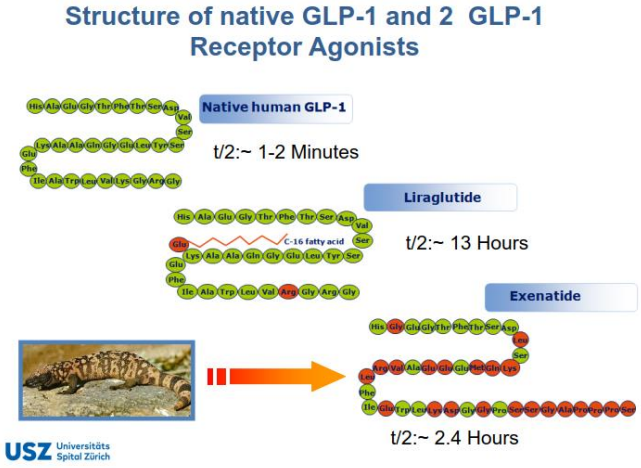


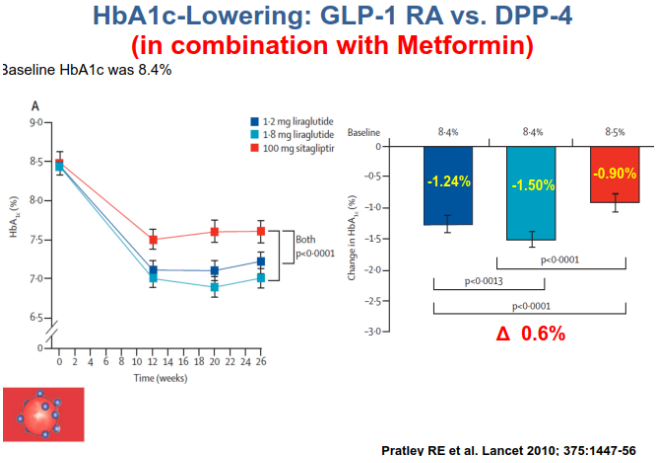
➔ Causes a lot of gas build up → abandoned in Switzerland





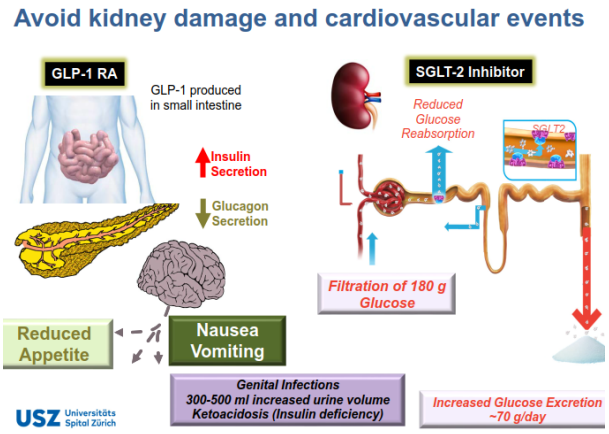
GLP-1 has a very short half-life. It increases insulin secretion and decreases glucagon secretion.



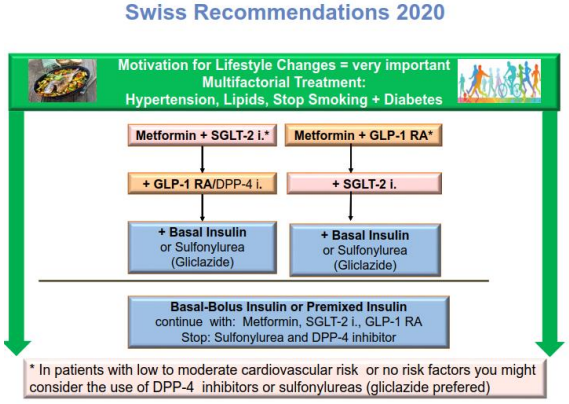


Weight also goes down faster with GLP-1

BUT! Treatment with DPP4 inhibitors basically no side effect. With GLP-1 there are a lot of side effects (will go away after 2-3 months).



SGLT-2 → glucose transporter in the kidney. Side effect of treatment with inhibitors: genital infections because glucose in the urine is a nutrient for fungi. Also increased urine volume. Very rarely ketoacidosis.



Combination treatment in the beginning (Metformin + SGLT-2 or GLP-1). If this is not enough you add the other (SGLT-1 or GLP-1 respectively). DPP-4 is only given when GLP-1 cannot be given or if BMI is below 28. If this is not successful, start adding insulin.

What is the best diet?

1922-1950

- Nutrition changes completely
- Insulin = Miracle and Life saver via anabolic and anticatabolic action (storage of carbohydrates and proteins, inhibition of lipolysis)
- More meals
- 1953 Eliott P. Joslin: "I lay emphasis on carbohydrate values, and teach to a few only the values for protein and fat… If a patient will grasp the carbohydrate values of seven types of food and use his common sense, he will seldom make egregious errors

Overview of diets in 20th century

Year	Carbohydrates (% of Calories)	Proteins (% of Calories)	Fat (% of Calories)
< 1921	Fasting Diet		
1921	20	10	70
1950	40 ⇩	20	40 ⇩
1971	45 ⇧	20	35
1986	bis 60	12-20	<30
1994	*	10-20	* / ** Sugar allowed

Nutrition for type 1 and 2 Diabetes

Type 1, Quantity: Carbohydrates vs. Type 2, Quality : Calories

Without correct weighing or estimating carbohydrates a reasonable control of type 1 diabetes is not possible.

Prevention of diabetes mellitus

You can only increase insulin sensitivity, not insulin secretion!

Finnish Study showed with Early Intervention (weight reduction, Diet, activity), there was a Diabetes Risk Reduction of 58 %.

US Study showed 31 % Reduction with Metformin, 58 % Reduction with Lifestyle.

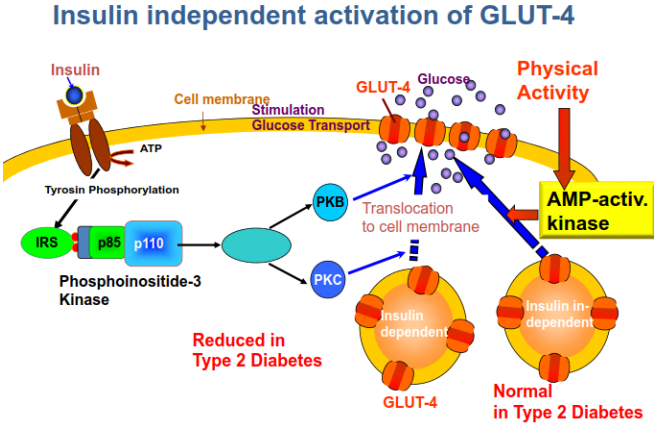
Acarbose (alpha-glucosidase-Inhibitor) → 25 % risk reduction

Xendos Study: Orlistat (Fat resorption inhibitor) → 37 % Risk reduction (with lifestyle)

→ Prevention of diabetes mellitus by lifestyle is possible. But maybe there is a pill that could do it better.

ACT-now trial: 72% Reduction Diabetes risk, but weight gain of 3.9 kg → exactly what you don't want.

➔ Lifestyle intervention trials to prevent diabetes: incidence after primary defined follow-up time: about 14% absolute reduction (4-22%), 50-70% relative reduction)



Lifestyle and weight loss

- Per kilogram weight loss 13% Reduction diabetes Incidence
- 20 kg weight loss → Diabetes disappears in 95%

➔ Diabetes prevention = possible, but hard!!

Activity for weight maintenance in obese people:

- 77-80 min per day (= 3.3-4.1 kcal/kg body weight). 35 min strenuous activity
- 70 kg Person 1 km walking → 70 kcal. 100 kg Person 1 km walking → 100 kcal. 1kg fat → 7000 kcal → 70-100 km

Weight loss in diabetes: How??

Increase in physical activity is good but does not decrease weight. Effect often overestimated. Intake is most important.

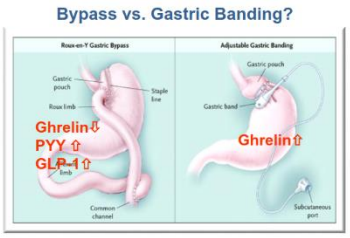
Best diet for weight loss? Can you prevent diabetes by diet alone?

Evidence of nutritional trials: General remarks

- Very limited
- Short follow-up 1-2 years, not life-time
- Best evidence for Mediterranean nutrition
- Unknown factor: gut microbiome (Depends on nutrition)

Diets as treatment often results in a good result at first but regression after a while.

Treatment with surgery



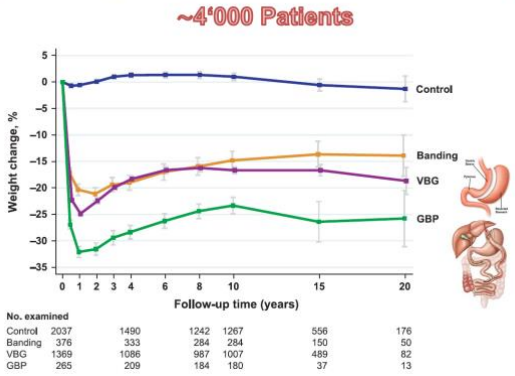
Bypass Chirurgie:

- 8% decrease in uptake of food
- Decreased appetite (hormones)
  - Less Ghrelin
  - More GLP-1
- Decreased weight
- More insulin sensitivity
- More insulin secretion
- No effect, or decreasing effect on diabetes
- Disadvantages: more complications

Indications Gastric Bypass in Switzerland for full reimbursement:

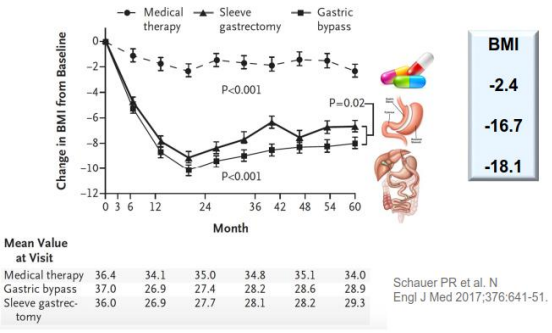
- Dietary counseling and diet over 2 years: without success
  - BMI > 50: 12 months sufficient
- BMI > 35
- Written consent to regular follow-up for 5 years
- Operation in certified obesity center
  - Bariatric surgeon
  - Endocrinologist
  - Nutritionist
  - Psychiatrist

Weight change 20 years after bariatric surgery



Reduction of Mortality by 29% 20 years after bariatric surgery.

Bariatric Surgery vs. Medical Treatment
Randomized Trial, 5 year follow-up



Schauer PR et al. N Engl J Med 2017;376:641-51.

Interventions causing weight loss and impact on cardiovascular risk factors - Review and meta-analysis

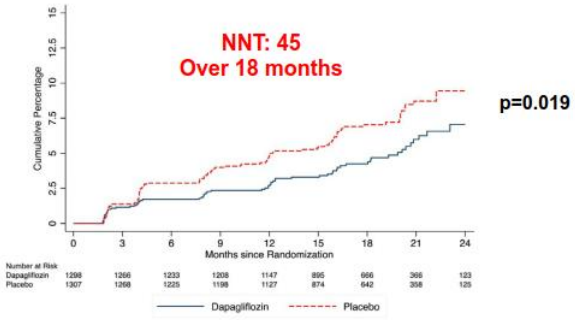
Over 6–12 months interventions that caused **any weight loss** significantly reduced and maintained at two years:

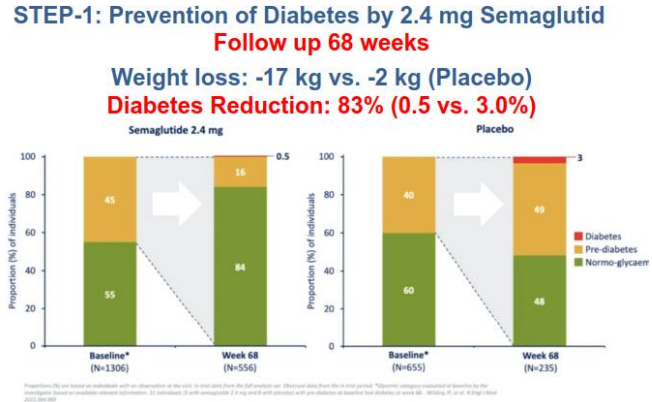
Risk factors	Reduction
Fasting plasma glucose	-0.32 mM, 95% CI 0.43, 0.22
HbA1c	-0.40%, 95% CI 0.52, 0.28)
Systolic Blood Pressure	-2.68 mm Hg, 95% CI 3.37, 2.11)
Diastolic Blood Pressure	1.34 mm Hg, 95% CI 0.29, 0.10
LDL-Cholesterol	-0.20 mM, 95% CI 0.29, 0.10
Triglycerides	-0.13, 95% CI 0.22, 0.03

Multifactorial Treatment

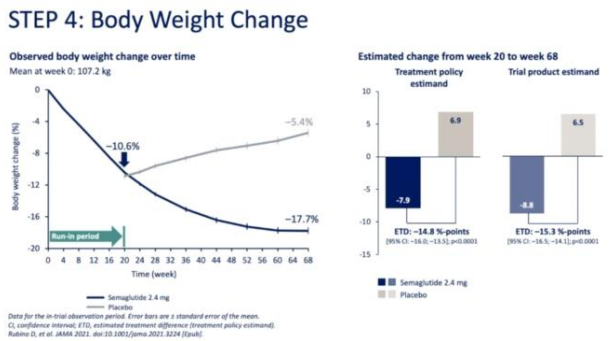
Diabetes prevention with SGLT-2 inhibitors?

- Weight loss is associated with diabetes prevention
- SGLT-2 inhibitors? No dedicated prevention trials, but in DAPA-HF 32% less diabetes in Dapagliflozin group (4.9 % vs. 7.1 %)





Semaglutide: Pre-Diabetes 45%, Wk 68: 16%, Diabetes 0.5%, normal: 84%
Placebo: Pre-Diabetes 40%, Wk 68: 49%, Diabetes 3%, normal 48%



Weight Loss and Diabetes

- After bariatric surgery (bypass-surgery, gastric banding): weight loss: 20 kg:
  - Diabetes disappears in 95%
- DPP: per 1 kg weight >13% reduction Diabetes

Take home message

Diabetes Types?

- Type 1 Diabetes mellitus: 5%
- Type 2 Diabetes mellitus: 90%
- Specific forms: 5%
- Gestational Diabetes: 15% (most will develop Type 2 Diabetes later)

Differential Diagnosis of Type 1 diabetes

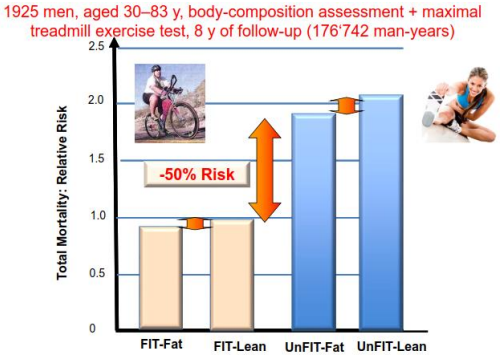
Characteristics	Type 1	Type 2	Glucokinase MODY 2	Other MODY TF	Neonatal Diabetes $Kalium_{ATP\ KCNJ11}$	3243 mito-chondrial Diabetes
Insulin deficiency	yes	no	no	yes	yes	Yes or no
Family history	2-4%	yes	yes	yes	yes	yes (mother)
Age at diagnosis	0.5-100	20-100	birth	<25	< 0.5	25-40
Obesity	no	yes	no	no	no	rare
Islet antiboidies	yes	no	no	no	no	no
C-Peptide (pmol/l)	<330	500-1000	100-700	100-700	<200	100-1700
Glucose	high	variable	NPG ↑	high	high	variable
Acanthosis nigricans	no	yes	no	no	no	no
Frequency (%)	10	80	1, (22 MODY)	1:68 (MODY)	1:400'000	Inner ear: 60

- MODY often misdiagnosed as Type 1 or Type 2 Diabetes
- Diabetes < 6 month: neonatal Diabetes 1:400'000

Lifestyle and Nutrition

- Physical activity and weight loss by changing nutrition habits are independent predictors of diabetes prevention
- Diabetes prevention = feasible, but difficult

Total mortality: Fit-Fat or Unfit-Lean?



Most important take home Message!!!

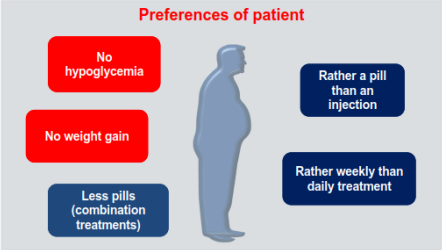
➔ Make physical activity a priority in patient care!!
➔ 30 min per day if healthy, 75 min per day if obese

INTERHEART study

9 classical risk factors explain coronary risk in 90% in men and 94% in women:

- Smoking: 2.87
- ApoB/ApoA1 Ratio: 3.25
- Hypertension: 1.91
- Diabetes: 2.37
- Abdominal Obesity: 1.62
- Psychosocial Factors (Stress, Depression, …): 2.67
- Daily Consumption Vegetables/Fruits: 0.7
- Regular Alcohol: 0.91
- Regular physical activity: 0.86

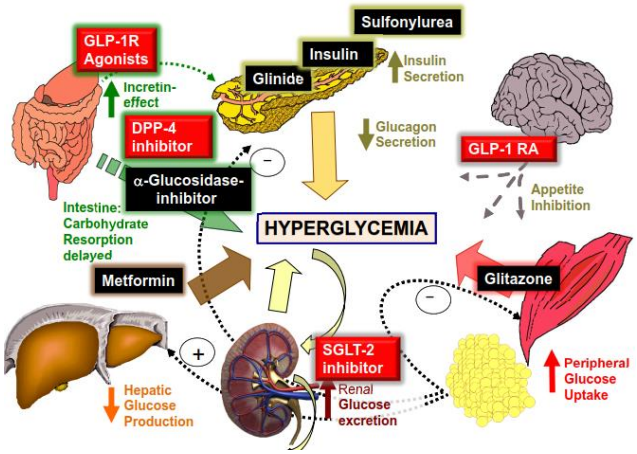
Factors to consider when choosing diabetes medications

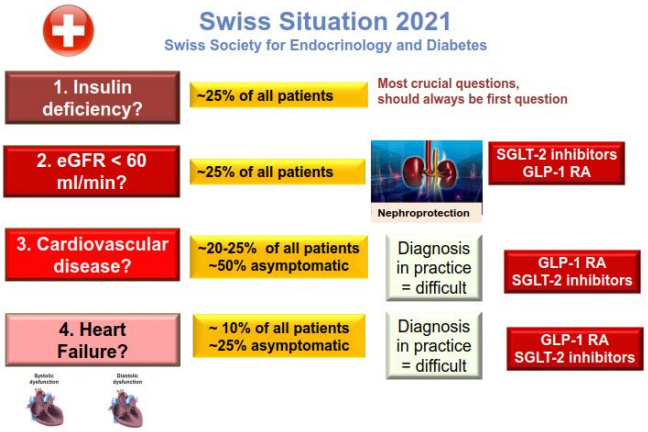


Factors to consider when choosing diabetes medications

Overview of current T2D treatments: Which priorities?

- Rarely used medications not used in treatment recommendations (<5% market share = alpha-glucosidase inhibitors, Pioglitazone, Repaglinide)
- Priority according to treatment strategy



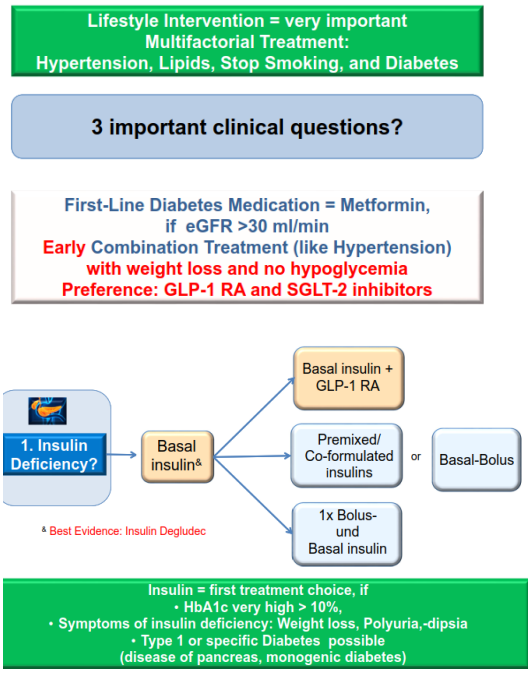


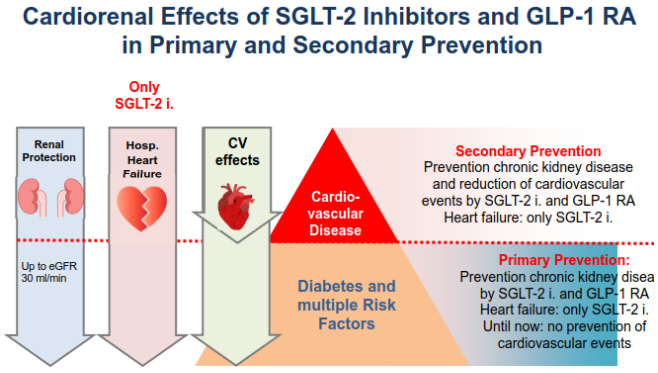
Important characteristics of Type 2 Diabetes

3 Questions:

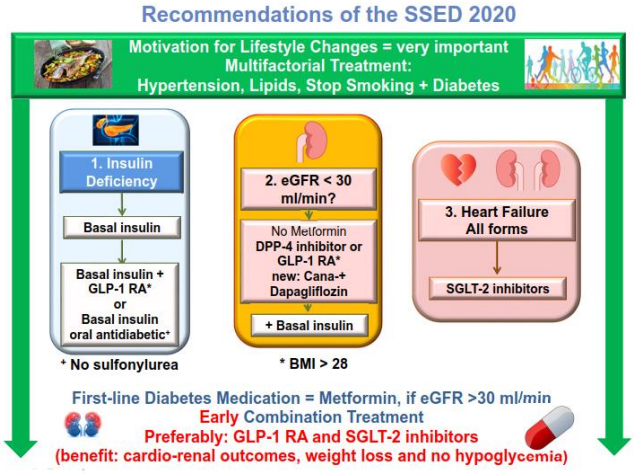
- Insulin Deficiency?
- Kidney function (e-GFR)?
- Treatment or prevention of heart failure?

Multifactorial Treatment

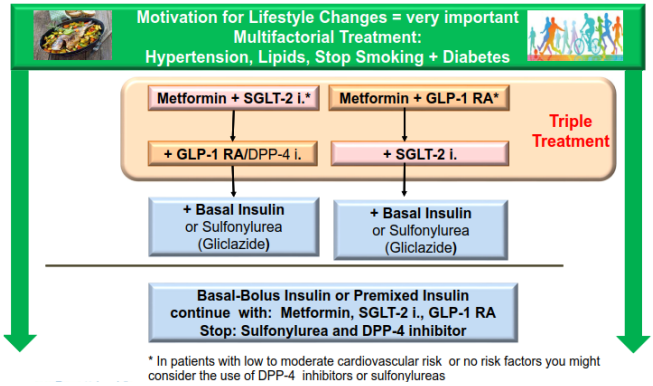




Cardiovascular outcome trials had relatively short follow-up, and were not desiged for primary prevention



Essential Recommendations for general practitioners



Take home message 2021: Individualized treatment targets and strategies

- Patient is in the center. Lifestyle is extremely important
  - Avoid hypoglycemia and weight gain
  - Regular physical activity and healthy nutrition
- Personalised and multifactorial treatmen (no glucocentric treatment):
  - Stop Smoking
  - Blood pressure 130/<80mm Hg (>60 yrs: 130-139)
    - Diastolic blood pressure >70 mm Hg
  - Lipid management (Statin and or Ezetrol, or PCSK9 Treatment)
  - Anti-Platelet Strategy
- HbA1c target and treatment: avoid micro- and macrovascular complications
  - Individualised HbA1c-target 6.0-8.0% (most cases<7.0%)
  - Preferred medications:
    - SGLT-2 Inhibitors, GLP-1 RA, Metformin and DPP-4 inhibitors

Effectiveness of therapies for weight and mortality (controlled studies, meta-analyses, hypothesis)

Therapy	Weight Loss Range (kg)	Mortality Reduction (%)
Lifestyle-Change Programm (Nutrition, activity, behavior)	1.5 - 11 - 20	50% (fit vs. unfit)
Medication (GLP-1 RA, SGLT-2 I.)	3 - 4 - 17	15-32% (CVOT)
Surgery (Gastric Bypass, Gastric Banding)	30 - 76	28-40% (observational)
Lifestyle and Medication (Activity, VLCD+ GLP-1 + SGLT- I.)	28 - 41	65-70% (?)

Progressive weight loss has dose-dependent and tissue-dependent biologic effects

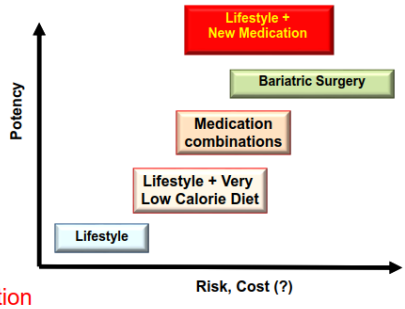
Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity

	5% Weight loss	10% Weight Loss	15% Weight Loss
Intrahepatic triglyceride content	✓	✓✓	✓✓✓
Intra-abdominal adipose tissue volume	✓	✓✓	✓✓✓
Adipose tissue insulin sensitivity	✓	✓	✓
Liver insulin sensitivity	✓	✓	✓
Muscle insulin sensitivity	✓	✓✓	✓✓✓
Beta cell function	✓	✓✓	✓✓✓
Adipose tissue biology*		✓	✓✓
Inflammatory markers		✓	✓✓

*Upregulation of genes involved in cholesterol flux, downregulation of genes involved in lipid synthesis, ECM remodeling and oxidative stress ECM, extracellular matrix

Medical Treatment vs. Surgical Treatment?

- Lifestyle
  - Diet, nutrition
  - Physical Activity
  - Combination
- Medication
  - Single
  - Combination
- Bariatric Surgery
  - Low numbers of T2D (<0.1%)
- Lifestyle and Medication
  - GLP-1 RA and SGLT-2 (almost all patients with T2D)

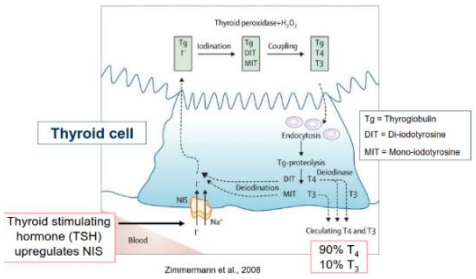


Nutrition and Thyroid Diseases

Iodine: Function

- Only known function of iodine is as constituent of thyroid hormones
- Control embryological development and normal growth
- Control physical and mental development
- Regulate metabolic rate and heat production

Iodine metabolism:



Hypo- and hyperthyroidism

- Hyperthyroidism:
  - Overt: low TSH, high T4
  - Subclinical: low TSH, normal T4
- Hypothyroidism:
  - Overt: high TSH, low T4
  - Subclinical: high TSH, normal T4

Assessing iodine deficiency

Methods to assess iodine nutrition:

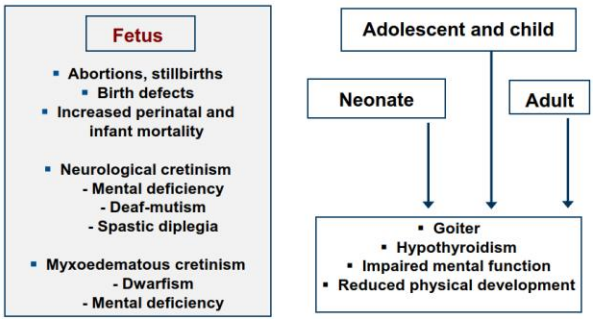
- Thyroid size → goiters. Neck inspection and palpation or thyroid ultrasonography. Usually measured in school age children, less useful in adults.
  Thyroid is goitrous when each lateral lobe has a volume greater than terminal phalanx of thumbs of subject being examined:
  - Grade 0: not palpable or visible
  - Grade 1: palpable but not visible when the neck is in normal position (not visibly enlarged)
  - Grade 2: clearly visible when neck is in a normal position
  - BUT! Palpation of goiter in mild iodine deficiency has poor sensitivity and specificity!
  - A public health problem if goiter prevalence is above 5 % in school children.
- Urinary iodine concentration (UI)
  - A sensitive indicator of iodine intake
  - <20 → severe deficiency, >300 Excess
- Blood thyrotropin (TSH)
- Blood thyroglobulin (Tg)

Iodine deficiency

Large increase in need for iodine during pregnancy and lactation

Since 1990 (113 countries with ID), the number of iodine deficient countries has fallen to just 19.

Consequences of iodine deficiency: iodine deficiency disorders (IDD):

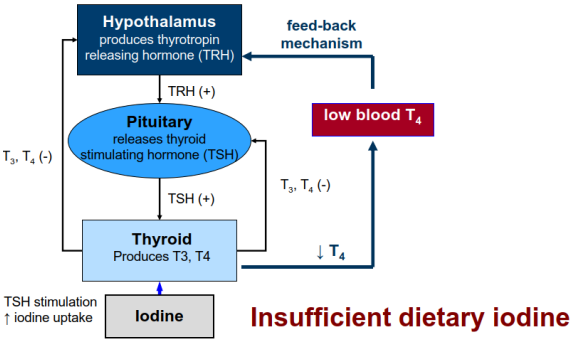


The most visible effect is goiter but the most important effect is retarded cognition and growth.

Severe in utero iodine deficiency → Cretinism (severe mental retardation, deaf-mutism, poor growth (dwarfism), characteristic facial features).

In utero deficiency damages the developing brain → Iodine repletion significantly reduces the prevalence of endemic cretinism. IQ 10-15 points higher in children born to supplemented mothers.

Regulation of thyroid gland



→ with chronic iodine deficiency, Thyroid cells enlarge and multiply → Goiter

→ Thyroid hyperstimulation by TSH causes hypertrophy and hyperplasia of the gland: leads to goiter (simple diffuse goiter: acute or subacute, multinodular goiter: chronic).

Multinodular goiter is disfiguring and often leads to hyperthyroidism: a thyroid nodule becomes "autonomous". It breaks free from control by TSH and begins to produce high amount of thyroid hormone.

Benefits of iodized salt

- ➔ Iodine repletion in newborns sharply decreases infant mortality
- ➔ Correction of mild iodine deficiency in children improves cognition and fine motor skills. Improvement in the overall cognitive score of 0.2 SD vs placebo. IQ increase of 2-3 points.
- ➔ In adults increasing rates of hyperthyroidism with decreasing iodine intake
- ➔ Correction of iodine deficiency in women reduces cholesterol

Intervention strategies for preventing iodine deficiency

Iodized salt: favored method since 1920s; successful programs in 121 countries worldwide. Production, packaging, and distribution should be monitored. Potassium iodide (KI) or potassium iodate (KIO4) can be added by spraying into salt at levels of 10 to 80 ppm. Inexpensive technology. Causes no color or taste changes in salt or when added to foods. → 76% households worldwide have access to well iodized salt. Iodization of salt remains the key strategy to control iodine deficiency in populations. But both household and food industry salt needs to be iodized. In high income countries, iodizing table salt is not enough, processed foods need to contain iodized salt.

Iodized oil injection: Mass injection by local health authority (in New Guinea, China, Nepal), 480 mg iodine/mL, lasts 3-5 years, suitable for isolated villages in developing countries

Iodized oil or iodine tablets (oral): in areas with severe deficiency before salt iodization is fully implemented.

Thyroid cancer

- 4 subtypes make up 95 % of all thyroid cancer
  - Papillary and follicular > anaplastic and medullary
- Marked variability in aggressiveness
  - 10-y survival:
    - 93% for papillary
    - 85% follicular
    - 75% medullary
    - 14% anaplastic

Over the past 3-4 decades, in most countries there has been a large increase in incidence and a small decrease in mortality from thyroid cancer. 10-fold difference in incidence among countries.

Given the lack of increase in mortality, current rise in incidence seems mainly due to improved diagnostic ability to detect small papillary carcinomas with an excellent prognosis.

Iodine status and thyroid cancer

Iodine deficiency is a potent promoter of thyroid tumors initiated by N-nitrosomethylurea (NMU) and also a carcinogen itself.

High BMI predicts higher risk for thyroid cancer, but iodine intake and fish intake do not.

One sequelae of iodine deficiency is increased risk of thyroid cancer in the case of nuclear fallout.

<u>Evidence from animal studies:</u>

Animals on iodine-restricted diets are more likely to develop thyroid cancer.

- Golden hamster, S-D rats on low-iodine diet develop thyroid hyperplasia, nodular goiter…
- … and eventually, in a small percentage of animals, carcinomas
  - All follicular adenocarcinomas
  - 18% incidence in females
  - Rare in males

<u>Human studies on the links between goiter, iodine intake and thyroid cancer:</u>

Current or history of endemic goiter due to iodine deficiency increases risk for thyroid cancer. Pooled analysis of 12 case-control studies: History of goiter predicts increased risk for TC: Odds ratio 5.9 for women, 38.3 for men.

Although it is rare, most TC mortality is due to anaplastic TC, and rates of anaplastic TC are higher in iodine-deficient regions before iodized salt.

Aanaplastic thyroid cancer / total n of thyroid cancer (%)		
Country	*Before iodized salt*	*After iodized salt*
Argentina	15.2	2.6
Austria	28.4	4.9
Germany	11.3	7.3
Switzerland	36.9	13.7

Review: Mean rates **before** iodized salt (16.1%) **after** iodized salt (7.2%)

<u>Papillary thyroid cancer:</u>

- In Austria, increasing rates of PTC since early 80s. Introduction of iodized salt in early 90s.
- In the USA over the past 30 y, there has been an increase in PTC rates, mainly in women, while iodine intakes have fallen in this group.

- In Denmark, increasing rate of PTC before introduction of salt iodization in 2000.
- Incidence rates 1970-98 for PTC in Swiss women increased 25% while population iodine supply remained stable

➔ Papillary thyroid cancer rates are increasing worldwide, in countries with increasing, decreasing and stable iodine intakes

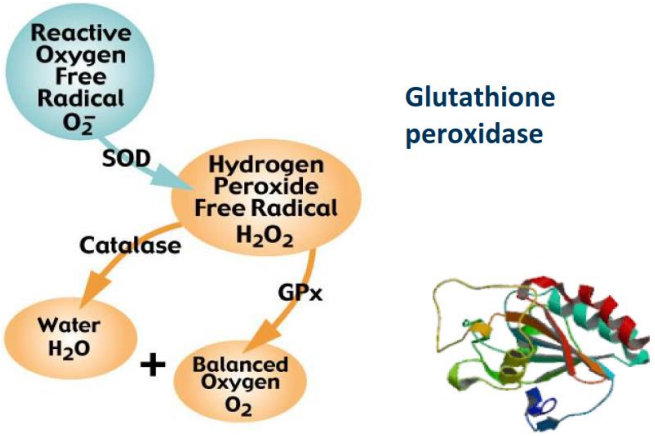
Is the increase due environmental factors and/or greater diagnostic intensity? Increased case findings (improved methods, increased detection and inclusion of occult thyroid cancers)? Increase in pollution (nitrates, PCBs), obesity, radiation from dental/medical imaging.

Case control studies of dietary iodine intake and thyroid cancer

➔ Suggest higher iodine intakes are associated with lower risk of thyroid cancer

Year and country	N	Age	Low vs. high [µg/d]	Outcome	Result
Horn-Ross (2001) US	608F/ 558F	20-74	< 273 vs. > 537	OR = 0.49 (0.29-0.84)	High intake inversely assoc with PTC risk
Truong (2010) (New Caledonia)	293F/ 354F	≥ 18	< 75.0 vs. ≥ 112.6	OR = 1.13 (0.68-1.87)	No assoc
Cléro (2012) (French Polynesia)	229/ 371	>56	≤ 105 vs. 106-175	OR = 0.39 (0.21-0.72) p-trend = 0.03	High intake inversely assoc with TC risk

Selenium and the thyroid gland



Autoimmune diseases of the thyroid

- Hashimoto's disease
- Graves' disease

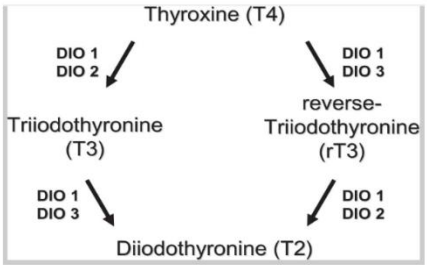
➔ Common, effect up to 10% of women in some countries. Lymphocytic infiltration of the thyroid. Increased antibodies against thyroid proteins. Stimulation/destruction of gland. Leads to hyper- and/or hypothyroidism.

Se-containing antioxidant enzymes in the thyroid

- Se-containing glutathione peroxidases (GSHPx)
- Se-containing flavoenzyme-thioredoxin reductase (TR)

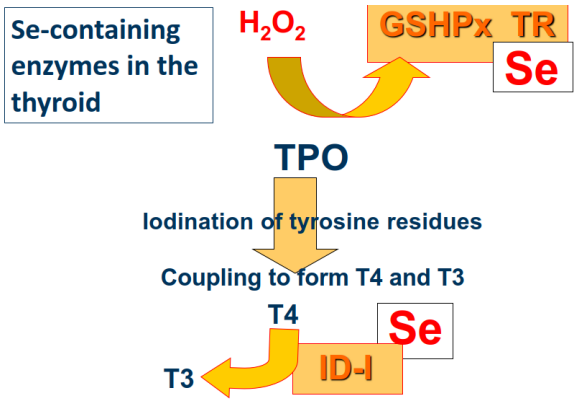
➔ Metabolize H2O2 produced during thyroid hormone synthesis.

Metabolism of thyroid hormones by types 1, 2, and 3 iodothyronine deiodinases



Se-containing enzymes iodothyronine 5' deiodinases

- Type I (ID-I): thyroid and most peripheral tissues
- Type II (ID-II): mainly in CNS, small amounts in thyroid
- Type III (ID-III): not in human thyroid



Hashimoto's thyroiditis

- Hashimoto's thyroiditis often results in hypothyroidism with bouts of hyperthyroidism
- Symptoms include weight gain, depression, sensitivity to heat and cold, chronic fatigue, constipation
- The thyroid gland may become firm, large, and lobulated
- Enlargement of the thyroid is due to lymphocytic infiltration and fibrosis
- Physiologically, antibodies against thyroid peroxidase (TPO) and/or thyroglobulin cause gradual destruction of follicles in the thyroid gland
- Hashimoto's thyroiditis or chronic lymphocytic thyroiditis is an autoimmune disease in which the

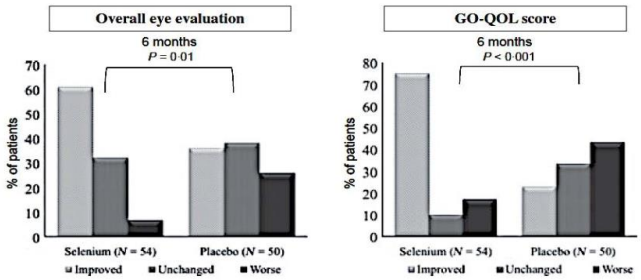
thyroid gland is attacked by a variety of cell- and antibody-mediated immune processes
- It was the first disease to be recognized as an autoimmune disease
- It was first described by the Japanese specialist Hakaru Hasimoto in Germany in 1912.

→ Se supplementation in women postpartum reduces Hasimoto's thyroiditis and hypothyroidism

Graves' disease

- Graves' disease is an autoimmune disorder, in which the body produces antibodies to the receptor for TSH
- These antibodies cause hyperthyroidism because they bind to the TSH receptor and chronically stimulate it. This causes goiter.
- Hyperthyroid symptoms develop such as increased heartbeat, muscle weakness, disturbed sleep, and irritability
- Graves' disease owes its name to the Irish doctor Robert James Graves, who described a case of goiter with exophthalmos in 1835
- It affects up to 2% of the female population, sometimes appears after childbirth, and has a female:male incidence of 5:1 to 10:1
- Bulging eyes

Comparison of the effects of selenium (200 microgram/day for 6 months) vs placebo for patients with mild to moderate Graves' orbitopathy



Vitamin D and the thyroid gland

Viramin D deficiency linked with autoimmune diseases.

Conclusions

- Severe iodine deficiency causes goiter, cretinism and hypothyroidism
- Mild iodine deficiency in children reduces IQ
- Mild iodine deficiency in adults increases risk for multinodular goiter and hyperthyroidism
- Endemic goiter increases risk for thyroid cancer
- Higher rates of aggressive types of thyroid cancer before iodine salt than afterwards
- After nuclear fallout, greater risk of pediatric thyroid cancer in iodine deficient vs. more iodine sufficient areas
- Many longitudinal studies show papillary thyroid cancer increasing in countries that have introduced iodine salt
- But PTC rates increasing in countries with increasing, decreasing and stable iodine intakes
- Much of this increase is likely due to increased case finding of small PTC
- Selenium is an essential component of many enzymes involved in thyroid metabolism and antioxidant defenses in the thyroid
- Selenium supplementation may reduce risk of autoimmune diseases that affect the thyroid

Nutrition, Disease, and the Gut microbiome: a focus on iron and childhood

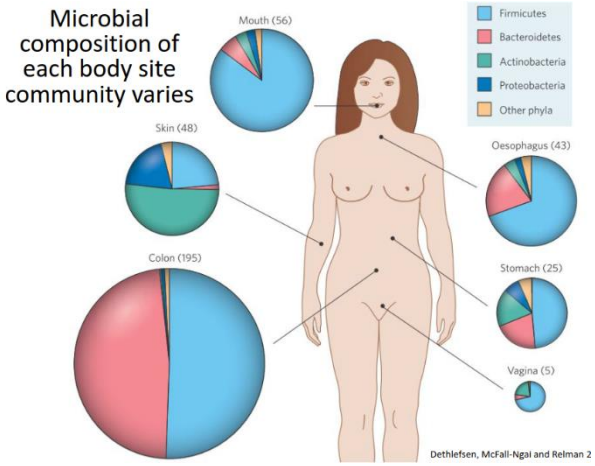
What is the human "microbiome"?

Microbiome: collectively all the microbes at a body site; a community of microbes.

Most of the microbiota are bacteria, but body sites can also harbor yeasts, single-cell eukaryotes, viruses and small parasitic worms.

Biofilm: a community of microbes that live together on a surface.

The microbial community composition in each part of the body is unique. Different people have similar microbial profiles in different body sites but microbial profile varies strongly between sites in the same individual.



Gut microbiome

- Largest reservoir of human microflora
- Estimated to have a hundred times as many genes as there are in the human genome
- >1000 different species of bacteria
- Also fungi, viruses and protozoa

Number, type and function of microbes vary along the gut, but most are found within the colon. Most commonly found genera in adults are Bifidobacterium, Lactobacillus, Bacteroides, Clostridium, Escherichia, Streptococcus and Ruminococcus. ≈60% of the bacteria belong to the Bacteroidetes or Firmicutes phyla. Families share similar gut microbiomes.

A healthy microbial community is essential. Mice raised in a germ-free environment display decreased nutrient absorption, less developed intestines, vitamin deficiency, underdeveloped immune system, heighted sensitivity to pathogens. They can become ill when challenged with as few as 10 Salmonella cells. "Normal" mice can withstand up to a million Salmonella cells before becoming ill.

Gut microbes produce short chain fatty acids (SCFAs): it has enzymes that humans lack for breaking down undigested dietary fiber/carbohydrates + endogenous mucins, producing SCFAs.

SCFA (acetate, propionate and butyrate; usual molar ratios in humans: 60:20:20)(weak acids: pKa ~4.8) lower colonic pH, decrease proliferation of pathogens.

SCFA concentrations are highest in proximal colon, and pH lowest in the proximal colon (pH 5.6) increases towards the distal colon (pH 6.3). More than 95% of the SCFAs rapidly absorbed/metabolized by the host, so fecal SCFAs may not represent those in the proximal colon. The main producers of butyrate are clostridia, eubacteria, and roseburia microbes.

Metabolites of gut microbiota have far-reaching systemic effects → Appetite and body weight. SCFA trigger the release of:

- Gut hormones Glucagon-like peptide-1 (GLP-1) and peptide YY from enteroendocrine L-cells; these regulate food intake by acting on the hypothalamus
- Gastric inhibitory polypeptide (GIP) from enteroendocrine K-cells, a potent promoter of glucose-dependent insulin secretion, acting with GLP-1.

Cardiovascular disease:

- L-carnitine and phosphatidylcholine, both constituents of red meat, are metabolized by intestinal bacteria, releasing trimethylamine (TMA)
- Following absorption to the portal circulation, TMA is converted by hepatic flavin-containing monooxygenase to the atherogenic trimethylamine-N-oxide (TMAO)
- TMAO increases development of atherosclerosis in blood vessels

Fat metabolism: Gut microbiota effects bile acid metabolism by performing deconjugation and dihydroxylation. Cholic acid:

- Lowers hepatic lipogenesis by acting on the farnesoid X receptor
- Increases energy expenditure through fat oxidation by inducing conversion/activation of thyroxine (T4) to T3 in brown adipose tissue (BAT) and skeletal muscle

Benefits for the human host of gut microbiota

- Commensal (non-harmful) mutualistic relationship
- Mineral bioavailability: Bacterial phytases of the large intestine degrade phytic acid present in grains, releasing minerals such as calcium, magnesium and phosphate that are complexed with it, making these available for absorption
- Lipid metabolism: Synthesis of secondary bile acids, important components of lipid transport and turnover in humans, is mediated via bacteria, including Lactobacillus, Bifidiobacterium and Bacteroides.
- Producing vitamins: Bacteria such as Bifidobacterium can generate vitamins

Protection from E.coli by Bifidobacteria

Bifidobacteria can protect from enteropathogenic E.coli infection through production of acetate.

- Genes encoding ATP-binding-cassette-type carbohydrate transporter present in certain bifidobacterial protect mice against death induced by EHEC
- Effect due to increased production of acetate
- Acetate reduces translocation of E.coli Shiga toxin from gut to blood

Diet and the human gut microbiome

- Diet rapidly and reproducibly alters the human gut microbiome
- Two diets consumed ad lib for 5 days by U.S adults
    - Plant-based diet
    - Animal-based diet (meats, eggs and cheeses). Decrease in fiber, increase in protein and fat
- Gut microbiome assessed, including 4 d run-in period on normal diet and 6 days after each diet arm to assess microbial recovery

Results animal-based diet:

- Similarity of each person's microbiota to their baseline decreased on animal-based diet
- Differences 1 day after a tracing dye showed the animal-based diet reached the gut
- Increased numbers of bile-tolerant microorganisms
- Decreased Firmicutes that metabolize dietary plant polysaccharides
- Decreased fecal SCFA

Does microbial community composition impact diseases relate to nutrition?

Example: gut microbial communities may modulate risk for obesity.

Mice that receive a fecal transplant from obese donors not only become obese but do so while eating less food! What might be functionally different about the gut communities in the lean donor and the obese donor?

➔ Energy extraction efficiency from the diet could be a function of the gut community composition

➔ Metagenomic analysis of obese/lean mouse gut microbiotas show: Obese gut microbiome contains more genes predicted to harvest energy from polysaccharides

Do differences in gut microbial ecology among humans affect the efficiency of their energy harvest/storage when consuming a given diet?

Fecal transplants also can heal: a women who suffered from a bacterial infection in her colon was cured after a fecal transplant. Why did this work? What happened in her colon?

Bacteriotherapy

➔ E.g. Fecal transplant

When you have an illness that seems to stem for your gut microbiome → can treat with bacteria, modify your gut bacteria through donors etc.

E.g. when you have an overgrowth of one bacteria in your colon → can lead to diarrhea, weight loss, dehydration etc.

Used to treat CDAD (Clostridium difficile-associated diarrhea) → usually results from prior antibiotic treatment and persistent disruption of gut microbiota. Can be severe, even fatal.

Fecal transplant should have richness (=number of species present), evenness (=relative abundance of each species) and diversity (measures both richness and evenness).

Infant microbiome

- Infant intestine initially a sterile environment
- Various factors determine individuals gut microbiotic composition
    - Gestational age, delivery mode (vaginal vs. C-section), Maternity ward/neonatal unit, feeding mode (breast milk vs. formula), other foods and fluids, antibiotic use, paternal skin, environment
- GI tract of human fetus is sterile
- During birth and shortly thereafter, bacteria from the mother and environment colonize the infant's gut
- Immediately after vaginal delivery, babies may have bacterial strains derived from the mothers gut and vagina
- After C-section, immediate colonization is by skin microbiota
- Vaginally born infants take up to one month for their gut microbiota to be well established; C section babies may take 6 months
- During weaning, the gut environment changes, so dies the microbiome
- Infant microbiota rapidly evolves toward adult profile, established at age 2-3 y
- Microbiota diversity increases during infancy and childhood

Gut microbiota of children in Burkina Faso vs. Europe diverges after weaning!

Burkinabe diet: low in fat and animal protein, rich in starch, fiber, an dplant polysaccharides. Predominantly vegetarian.

European diet: high in fat, animal protein, sugar, starch. Low in fiber.

- Differences in microbiota became evident after the period of predominant breastfeeding
- Higher microbial richness and biodiversity in Burkina Faso samples than in European samples
- Actinobacteria and Bacteroidetes were more represented in Burkina Faso
- Firmicutes and Proteobacteria were more abundant in Europe children
- Infants in Burkina Faso enriched in Bacteroidetes, in particular the Prevotelle enterotype and species associated with fiber utilization
- Greater total short chain fatty acids in fecal samples from Burkinabe children
    - SCFAs are produced when indigestible plant components such as plant polysaccharides are fermented by intestinal microbiota
    - Are precursors for gluconeogenesis, lipogenesis, and protein and cholesterol synthesis
    - SCFA-producing bacteria may prevent establishment of potentially pathogenic intestinal microbes
    - SCFA have protective role against gut inflammation

Microbiome of breastfed vs. formula-fed infants

Results are mixed, e.g.:

- Bifidobacteria dominated the microbiota of breastfed infants, whereas formula-fed infants had higher proportions of Bacteroides and members of the clostridium coccoides and Lactobacillus groups
- Formula fed infants had increased richness of species, with overrepresentation of Clostridium difficile, but no difference in Bifidobacteria compared to breastfed infants.

Home fortification of foods with multiple micronutrient powders (MNPs) for children under two years of age

MNPs developed as an intervention for increasing micronutrient intake, particularly iron, in children < 2 y of age.

Home fortification with multiple micronutrient powders sharply reduces iron-deficiency anemia and iron deficiency. Intervention appeared equally effective in population with different anemia prevalence, at all ages, at all duration of intervention (2 months vs > 6 months) and in settings described as malaria-endemic vs settings where malaria sporadic.

Iron and the gut

Iron from fortification is poorly absorbed and produces large increases in colonic iron. Even highly bioavailable Fe fortificants are absorbed <10%.

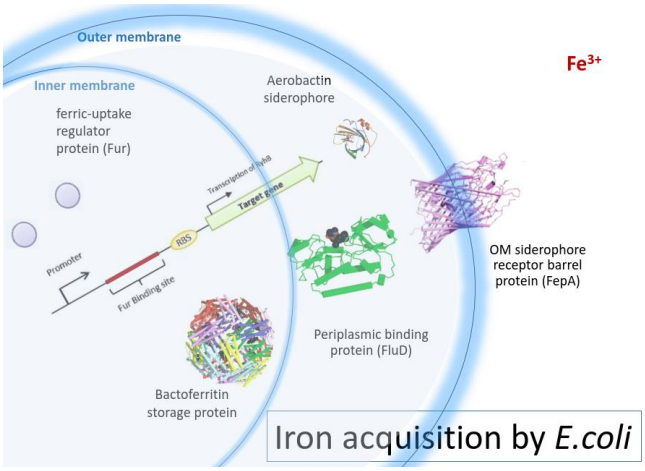
Fe in the body is tightly bound, limiting supply to pathogens, and during infection, iron supply is sharply reduced in the extracellular compartment. But there is no similar system for sequestration of dietary iron in the gut lumen.

Iron supply to the colon is an important determinant of gut microbial community profile. Beneficial "barrier" bacteria, such as Lactobacilli and Bididobacteria, require little or no iron, do not produce siderophores or other active iron carriers. Allows Lactobacilli to grow well in low iron conditions (like in breast milk).

Iron is a growth-limiting nutrient for many gut bacteria, including pathogens. Many strains vigorously compete for unabsorbed iron in the colon, as growth depends on ability to acquire iron.

For most enteric pathogens, iron acquisition plays an essential role in virulence and colonization (500+ bacterial siderophores with high Fe-binding constants).

Beneficial bacteria require little or no iron! Iron acquisition plays an essential role in virulence and colonization. E.g. virulent E.coli strain plasmid has three different Fe uptake systems → heavy genomic investment in iron capture.



Low iron conditions may promote growth of Camplyobacter flagella.

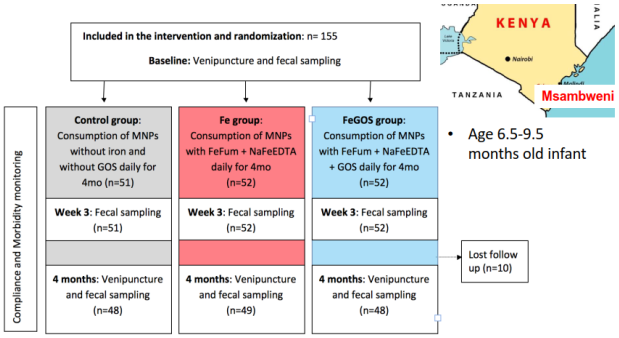
➔ Iron supplements in Africa can be dangerous! Iron supplements given to preschool Tanzanian children increased hospitalizations and mortality.

- Results on a study of effects of iron fortification in African children: → No benefit on anemia or iron status
- Iron fortification increases enterobacteria and decreases Lactobacilli numbers in African children
- Fortification increased gut inflammation (correlated with increase in fecal enterobacteria)
- Study on children in Pakistan supplemented with zinc and iron: increased days with diarrhea, increased incidence of bloody diarrhea and severe diarrhea. In diarrheal stool, increase in Aeromonas spp (common cause of diarrhea in region)
- Other study shows iron fortification adversely affects the gut microbiome, increases pathogen abundance, and induces intestinal inflammation in Kenyan infants

Safer MNP formulations are needed

2 Strategies:

- Reduce the iron dose and maximize absorption to retain efficacy
- Add a component that could mitigate the adverse effects of the iron on the gut microbiome



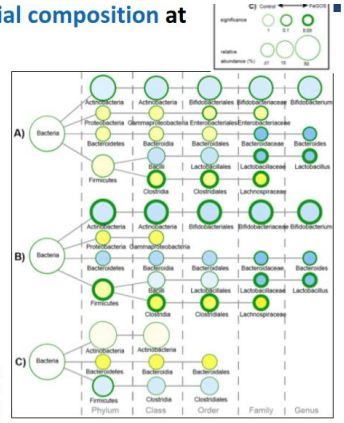
Differences in gut microbial composition at 4 months

A) In Fe, compared to control:
- lower *Lactobacillus* (p=0.048)
- lower *Bifidobacterium* (p=0.058)
- higher *Clostridiales* (p=0.015)
- higher *Enterobacteriaceae* (p=0.086)

B) In Fe, compared to FeGOS:
- lower *Bifidobacterium* (p=0.007)
- lower *Lactobacillus* (p=0.006)
- higher *Clostridiales* (p=0.001)

C) In FeGOS, compared to control
- no significant differences

Nodes represent taxa. Node-size corresponds to the relative abundance (in %). Fold difference calculated as 2log of ratio of relative abundance between groups (0=no difference, 1=twice as abundant). Significance: p value of Mann–Whitney U test.



Paganini et al. *Gut* 2017

Conclusions

- In breastfed, 6 mo old infants in rural Africa, the gut microbiome dominated by Bifidobacteriaceae, but harbours many gram- and gram+ pathogens
- Iron decreases abundances of bifidobacteria and increases enterobacteria, shifting gut balance away from beneficial 'barrier' strains
- Iron in MNPs increases abundances of potential pathogens, particularly Clostridium and EP E. Coli
- These changes in the gut microflora are accompanied by an increase in gut inflammation and, possibly, diarrhea
- Prebiotics given with iron-containing MNPs in the African setting may be beneficial to support gut health, retain natural infant gut microbiome development and to reduce the incidence of RTIs

Nutrition and arthritis

History of the Anti-inflammatory diet

- Attenuation of inflammation with the diet has become a standard in 2000
- 2005 the section Nutrition was founded in the German Society of Rheumatism
- Starting in 2000 all textbooks of nutrition or rheumatism address diet in inflammatory rheumatic disease

At the moment only sufficient evidence for inflammatory rheumatic diseases, but also possible for other diseases.

Issues for diet in rheumatic diseases

More complex than metabolic disorders

- Prevalence of malnutrition in 40 % of the patients
- Attenuation of inflammation (omega-6/omega-3 fatty acids, antioxidants
- Prevention of osteoporosis (calcium, vitamin D)
- Food-intolerance and food sensitivity (common in patients, avoid intolerant or arthritogenic nutrients)

Initiation of inflammation in rheumatic diseases

- Oxygen radicals as well as maybe viruses or bacterial components or genetic disposition stimulate immune cells
- Immune cells produce inflammatory mediators
- Pro-inflammatory mediators cause joint inflammation

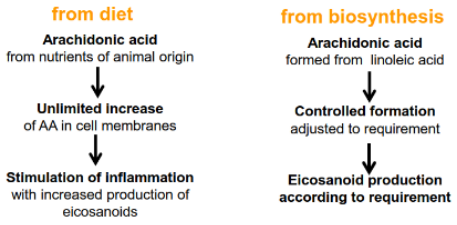
Arachidonic acid (AA): fuels inflammation. Oxygen radicals (formed from stimulated immune cells) activate phospholipase A2 which split AA from the cell membrane and is oxidized by ROS. Free AA is oxidized and transformed to Inflammatory mediators: Eicosanoids, which cause joint inflammation.

More than 80 different components are formed from AA (eicosanoid lipids), most of them pro-inflammatory. Sources of Arachidonate → Phosphatidlycholine and Phosphatidylinositol. Arachidonate can be converted through the enzyme Cyclo-oxygenase (and the isoforms), but some components also from spontaneously. Its still not known what exactly triggers the formation of the different eicosanoids.

Common feature of almost all are a promotion of flammation!

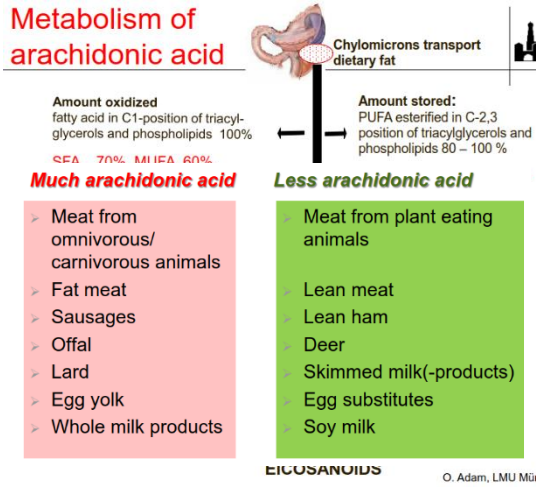
Tromboxanes → blood clotting. Prostacyclins → blood vessel dilate (inflammatory process). Prostaglandins have effects on the gastrointestinal tract and also lungs, kidneys, nerves and genital organs. Leukotrienes (formed by lipo-oxygenase), allergic reaction → vasodilation and secretion increasing effect. Trioxilins → unstable, pro-inflammatory

Sources of arachidonic acid:



In western diet: prevalence of Rheumatoid Arthritis correlates with intake of animal fat and intake of red meat.

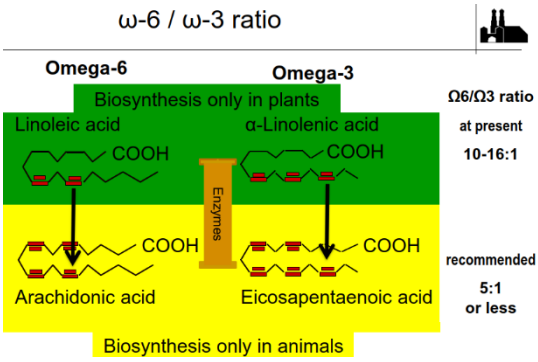
Western diets provide 300-400 mg AA/day. The recommended intake is 50-100 mg AA/day.



Most Plants don't have AA, but some possibly have precursors of it.

AA has a Unique metabolic pathway (different from other FA). AA is preferentially resorbed from the gut and incorporated into chylomicrons. Preferentially it is also transferred to LDL particles, thus more than 90% of AA is incorporated in cell membranes. It is not used for energy production (rate of oxidation is 10%, compared to 50-70% of other FA). This implies that AA remains in the cell membrane. Half-life of AA in cell membrane is several months.

- AA fuels inflammation, but does not cause inflammation (precursors of eicosanoid)
- Limited AA intake is recommendable (normal function)
    - Max. 2 dished with leant meat/week
    - Max. 4 eggs/week
    - Daily ½ L skimmed milk or milk products



Treatment of Rheumatoid Arthritis

EPA ameliorates joint inflammation. EPA replaces arachidonic acid → less Arachidonic acid is oxidized by ROS. EPA inhibits eicosanoid biosynthesis → resulting in amelioration of joint inflammation.

Clinical symptoms improve, if EPA is given to patients on a low AA diet.

Normally EPA is consumed not enough and AA to much in the standard western diet

900mg EPA is recommended for daily intake (in patients?). EPA found in fish but would require a lot of fish consumption. Fish oil as treatment of rheumatoid arthritis often found improvement.

Fasting always improves symptoms in patients with Rheumatoid Arthritis. Improvement is sustained if a vegetarian diet is followed.

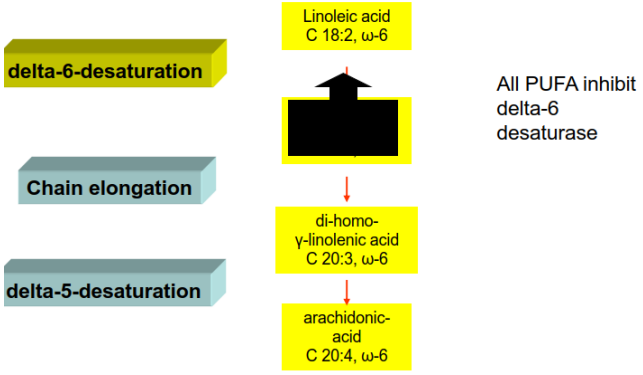
Omega

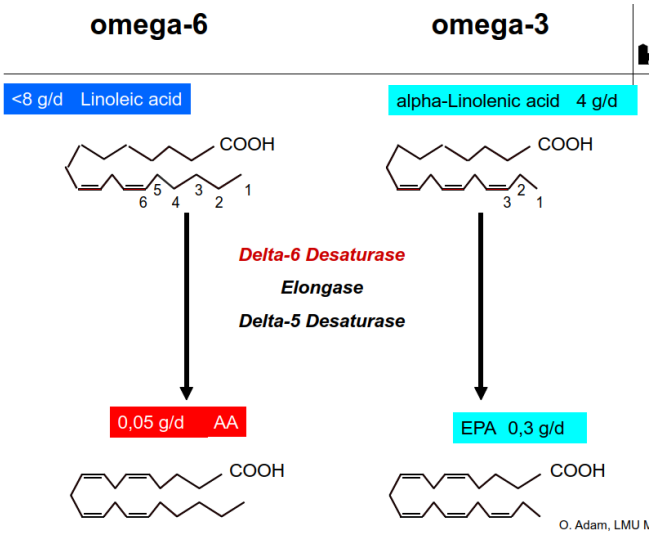
Omega-6 and Omega-3 ratio used to be 1. Now it is 10:1 to 20:1. Recommended is <5:1.

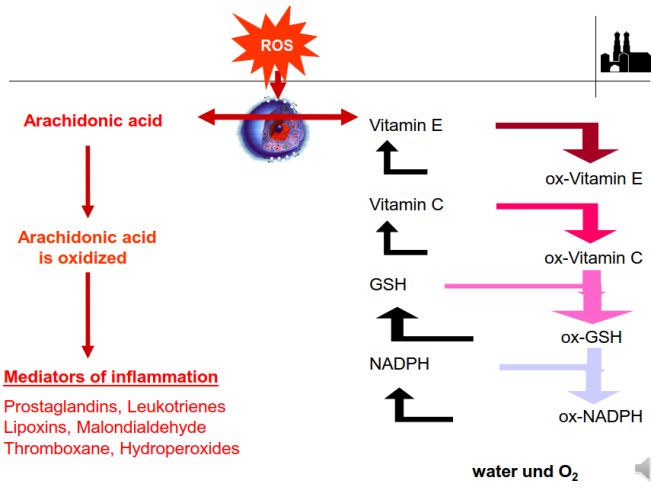
Omega-6 → linoleic acid, can become Arachidonic acid.

Imega-3 → alpha-linolenic acid, can become Eicasapentaenoic acid.

Metabolismus of Linoleic Acid:

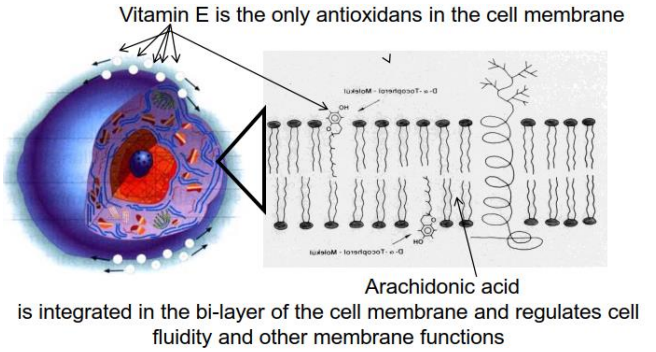






Vitamin E in cell membrane

One molecule vitamin E protects about 100 molecules of PUFA in the cell-membrane from oxidation.



5 studies providing a supply from 200 to 840 mg RRR-alpha-Tocopherol/d yielded inconsistent results. Doses of > 300 Vitamin E increase total mortality → efficacy is doubtful.

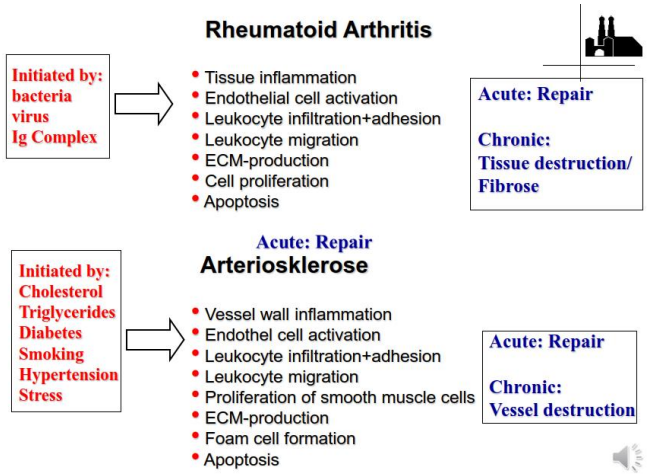
But! → low plasma concentrations correlate with higher prevalence of RA. Concentration of vitamin E in synovial fluid is only 1/3 of plasma concentration.

Selenium

- 6 studies, 4 report improvement of clinical symptoms
- Selenium is low in plasma of RA patients
- Selenium intake is lower than RDA in Europe
- Supplementation advisable, if dietary intake is low

Rheumatoid Arthritis and CV risk

CV- End point	RA	No RA	p
Person years follow-up	6.259	2.381.418	
Myocardial infarction			
Inzidenz/100.000 Person years	272	96	
Number of cases	17	2.279	
Risk adjusted by age (95% CI)*	2.07 (1.28 – 3.34)	1.0	0.002
Multivariate RR (95% CI)#	2.00 (1.23 – 3.29)	1.0	0.005



Lifestyle factors

Recommended

- Regular exercise
- Refrain from smoking
- Alcohol (low%) only in moderation (1/8-1/4)
- Don´t hurry
- work and relax alternately
- satisfactory social contacts: family, friends…

Not recommended

- Lack of exercise
- Smoking
- Regularly and plenty of alcohol
- Stress, hectic
- social withdrawal

Targets/goals of nutritional interventions

- Nutrition counseling and nutritional training
  - Ameliorate inflammation
  - Lower cardiovascular risk
  - Prevent osteoporosis
  - Note illness-related features, e.g. Sicca syndrome, malnutrition, disability, intolerances
- Healthy lifestyles
  - Stop smoking
  - Normal body weight
  - Physical activity
- Consider dietary supplements

Summary: Diet for rheumatoid arthritis

- **Meat:** only twice a week in small portions
- **Fish:** twice a week, one serving of fat fish
- **Soy dishes, and vegetarian dishes:** on the other days
- **Recommended oils:** rape seed, walnut, wheat germ or soybean
- **Prevention of osteoporosis:** daily skimmed milk (½ L) or dairy products, sufficient UV-light or vitamin D supplement
- **Alcohol:** not more than the tolerable dosis (M: 20 g/d, F: 10 g/d)
- **Cooking:** Preserve vitamins and trace elements, use herbs and spices (antioxidants)

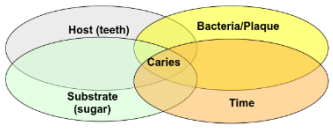
Nutrition and Oral Health

What is caries? → decalcifying process

- "Tooth decay" or "cavity"
- Pathological, decalcifying and dissolving process of enamel and/or dentin(later stages), also root caries
- Starting under bacterial plaque (biofilm) on the tooth surface
- Progressing by undermining deeper into the depth

Cause: organic acids that are formed during the bacterial fermentation of carbohydrates.

Caries formation

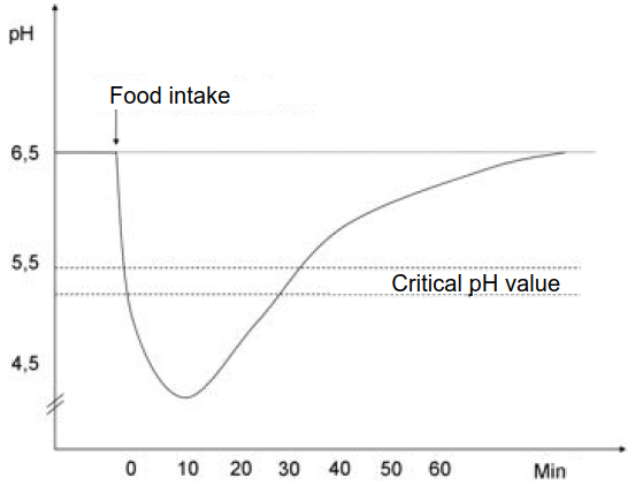


1. Cariogenic microorganisms (plaque)
2. Overexposure to cariogenic substrate (carbohydrates)
3. Production of organic acid
4. Demineralization of enamel and dentin

Influencing factors:

→ Saliva, nutritional influence, behavioral factors, medication, drugs, local factors, genetic components

The Stephan Curve:



→ Diagram of the pH drop after consumption of glucose solution. Within minutes the pH value of the salvia decreased below the critical value of 5.5 (demineralization of tooth substance)

→ Buffer systems ensure a gradual recovery of the pH value (with inter-individual differences taking up to 60 min and longer)

→ The curve is also dependent on the type of sugar ingested

Caries Etiology: Saliva

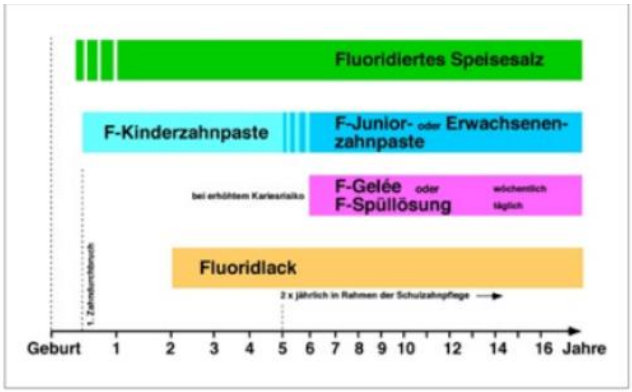
Factors and strength of association with caries risk:

- Flow rate → strong
- Buffering capacity → weak-moderate
- Calcium/phosphate → weak-moderate
- Spez. sIgA → weak-moderate
- pH, other electrolytes & molecules, glucose clearance/concentration, other proteins → no association

Caries Etiology: Nutritional influence

- need of contact between food and teeth → when lab animals were fed through a gastric tube: no caries developed
- special role of carbohydrates: if carbohydrates were fed orally, and other food was administered by a gastric tube: → caries!
- Need for oral microorganisms: germ-free animals fed with highly cariogenic foods: → no caries!

Caries Etiology: Behavioral factors



Optimale Kariesvorbeugung mit Fluorid.

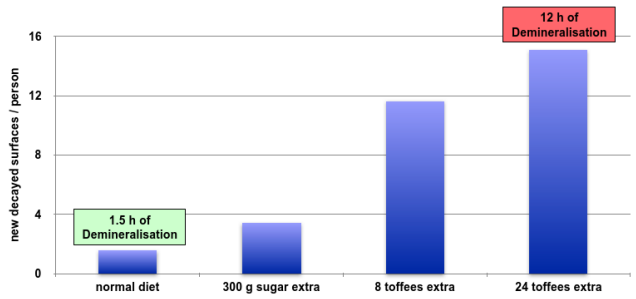
How do fluorides work? They act primarily in the mouth directly on enamel by:

- Increasing the resistance against acids
- Decreasing the rate of decalcification
- Promoting the re-deposition of minerals into already decalcified enamel → initial caries lesions can be stopped or even reversed.

Caries etiology: behavioral influence

Experiment: 3 weeks no oral hygiene and 9 rinses with 10mL 50% sucrose per day → causes initial caries (white spots). Then restoration of oral hygiene and daily NaF rinses → Remineralization of the lesions.

Vipeholm dental caries study:



➔ The caries-causing effect of sugar is large when eaten in sticky form, and the largest when eaten in sticky forms between meals

The Hopewood-House-Study: an extremely tooth-protecting diet leads to very little tooth decy, even with poor oral hygiene and without fluoride.

Conclusions behavioral/nutritional influence:

1. Caries prevalence and incidence must be higher in case of high sugar consumption → yes
2. Caries must occur after high sugar consumption → yes
3. Reduction of sugar consumption decreased tooth decay → yes
4. High consumption of sugar must also cause caries in the animal with the same oral flora → yes
5. The postulated context must be biologically explainable and possible → yes

Caries etiology: medication, drugs

Medical drugs and some psychotropic substances (i.e. heroin) can promote dental caries through various mechanisms by:

- Having a formulation with a high sugar content
- Causing dry mouth (e.g. antidepressants, antihistamines, retinoids, etc…)
- Lowering the buccal pH
- Causing demineralization
- Behavior modification

Caries etiology: genetic components

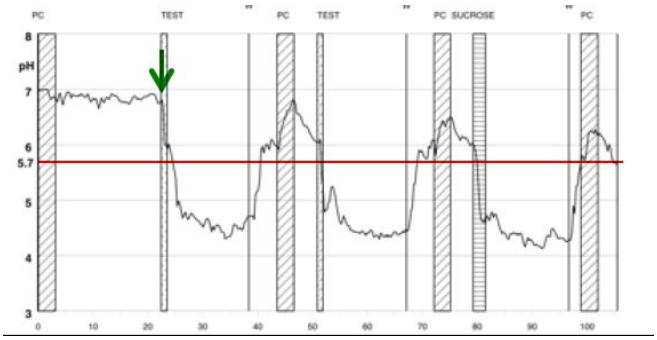
- Role of the tooth hard substances
- Role of inherited salivary parameters
- Role of inherited defects in sugar metabolism
- Role of immune response

Caries etiology: local factors

- Chemical:
  - Bacterial acids → caries
  - Dietary acids → erosion
- Mechanical:
  - Abrasion, Demastication, Attrition
- Multifactorial:
  - Abfraction (wedge-shaped defect)

Healthy food = dental health? → pH-telemetry

- "Automated communications process by which measurements and other data are collected at remote or inaccessible points and transmitted to receiving equipment for monitoring"



Fruit consumption leads to a comparable pH drop as sugar consumption.

Erosion

- Chemically induced tooth hard substance loss
- Without the involvement of microorganisms

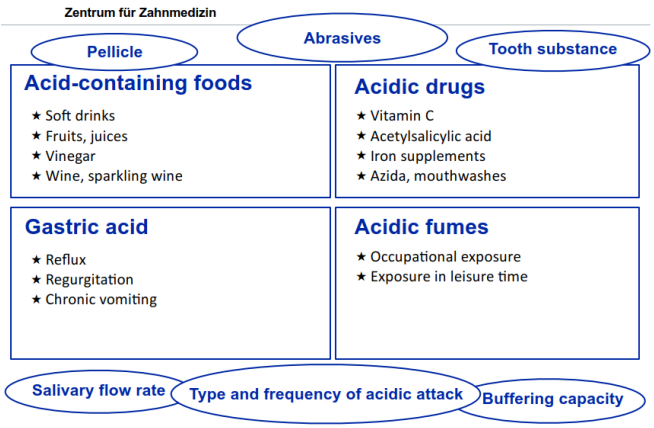
Prevalence in Switzerland: 1/3 of 26-30 y olds, half of 45-50 y olds

Risk groups:

- Patients with gastrointestinal problems
- Wine tasters
- Lactovegetarians
- Competition Swimmers
- Workers in battery and galvanic factories

Caries vs. Erosion:

- Bacterially-induced pH drop to: pH 4-4.5
- pH drop induced by foodstuffs or gastric contents to: pH 1.5-3.0
- frequent vomiting (i.e. bulimia) → 1 min exposure to hydrochloric acid (pH 2.1): 500 nm deep demineralization



Erosions in lacto-vegetarians:

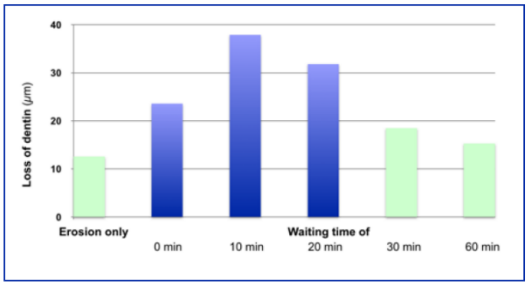
- causes: consumption of vinegar, pickles, citrus fruits, acidic berries

Nutritional risk factors

Erosion risk higher with:

- frequent intake of acidic food and drinks >= 3x/day
- foods with high titration value
- long retention time in mouth
- special drinking habits
- possible additional effects through abrasive foods

Waiting with toothbrushing after erosion?



Periodontitis

- inflammation of the gums and supporting structures of the teeth
- triggered by bacteria (plaque/biofilm)
- with progression of disease the (mostly chronic) inflammation leads to loss of tooth-supporting bone, and ultimately, tooth loss
- about 75% of the population are affected at some point in their life
- around 70% of tooth loss in adults is due to periodontitis
- progression mostly relatively slowly, but “aggressive” forms exist
- if detected early, treatment can stabilize the situation; regular recalls are necessary
- in progressive cases extensive treatment is necessary

Gingivitis

Signs:

- swelling of the gums
- redness of the gums
- bleeding of gums upon touching/brushing/flossing
- tenderness/sensitivity

Treatment:

- Gingivitis is reversible
- Meticulous and regular individual oral hygiene including
- Interdental cleaning (flossing/brushing)
- Optional use of antibacterial mouthwash

Signs: Bad breath, tooth mobility, gum recession, painful chewing, pus.

Risk factors: Smoking, Diabetes type I and II, stress, obesity

Treatment:

- Periodontitis-induced damage is widely irreversible
- Meticulous and regular individual oral hygiene including:
    - Interdental cleaning (flossing/brushing)
    - Systematic periodontal therapy with a dental hygienist
    - Scaling and root planning
    - If necessary further therapy including periodontal surgery
    - Lifelong regular recall

Effects of specific nutrients on periodontitis:

- Nutrition plays an important role in wound healing processes
- Various degree of association between nutritional elements/supplements and periodontal status have been reported
- Nutritional supplementation may benefit periodontal therapeutic outcomes
- A weak but significant relationship between ascorbic acid and dietary calcium intake and increased susceptibility for periodontal disease was found.

The effect of nutrition on periodontal disease: a systematic review:

- Possible relationship between vitamins, minerals & periodontal disease

- Vitamin E, zinc, Lycopene and vitamin B complex may have useful adjunct benefits
- Evidence inadequate to link the nutritional status of the host to periodontal inflammation

Flossing before or after tooth brushing?

- Flossing or any other interdental cleaning method may prevent caries, gingivitis, and periodontitis
- Contradicting recommendations concerning "perfect" timing

Conclusions

➔ The dose makes the poison! Recommendations for prevention of caries:

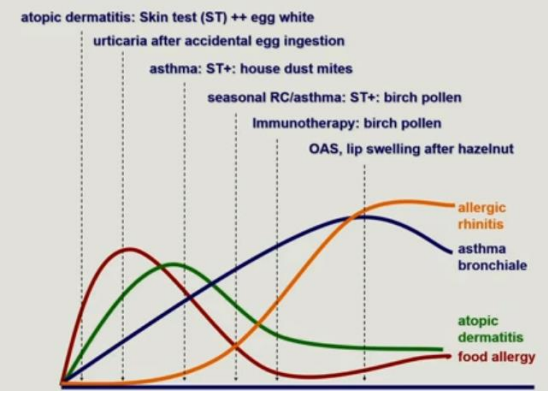
- Daily use of fluoride toothpaste (2x/day)
- Rinsing with little or no water after brushing
- Use of fluoridated table salt (0.025%)
- High risk groups (> 6 years): use of fluoride gel once a week or daily mouthwash with a fluoridated solution
- Wise food choices / reduction of sugar intake
- Reduction of "acidic attacks":
    - Drink in one go or with straw to reduce acid-to-tooth-contact
    - Drink acidic drinks with meals
    - Keep meal times, e.g. avoid snacking of many small portions throughout the day
- Neutralization of the acidity (by rinsing with water, drinking milk or eating cheese)
- Tooth-friendly chewing gums stimulate the salviation
- Individualized, well-instructed and systematic oral hygiene behavior:
    - Harmful techniques/excessive brushing may result in tooth damage
    - Acidic foods soften the tooth surface → increased vulnerability to abrasion
- Watch salivary flow and stimulate low salivation
- Gastrointestinal problems or eating disorders increase the risk for erosion:
    - No tooth brushing immediately after vomiting, but rinsing with fluoride-containing rinse or water
    - Therapy of underlying disease, consultation with specialized dentist
- Regular check-ups at the dentist
- Emphasis on individual oral hygiene including regular cleaning of interdental spaces
- Healthy lifestyle
- No smoking

Food allergy

Important allergenic foods in children

Example of development of allergies in childhood. First Peak of food allergy (Hen's egg, milk, peanuts and nuts make >90 % of food allergies), if person has predisposition → can develop antibodies to a certain allergen.

Binding of IgE to allergen highly specific. IgE antibodies then attach to mast cell and sensitization happens (= presence of IgE antibody to a specific allergen, no allergy yet developed). When neighboring antibodies on a mast cell bind = bridging = mast cell releases mediators → histamine → allergic reaction.



Allergy = presence of IgE and symptoms

In Food allergy of mostly milk and egg in children, up to 80% can get tolerant to it. However, there is also persistence into the adulthood. Mainly if they are allergic to peanut, or fish, shrimp and only few milk and egg allergies.

Adults rarely acquire primary food allergies but get easily sensitized to respiratory allergens (pollen).

Secondary → IgE cross-reactivity → means that antibody is directed one allergen source, and the other allergen source induces the allergic reaction.

Primary food allergy: Primary sensitization via gastrointestinal tract/skin. (can develop tolerance or persist into adulthood, see above).

Secondary food allergy: Secondary sensitization via cross-reactivity (Pollen).

Most frequent food allergy in adults in europe: Nuts

Highest incidence of cross-reactivity is with birch-pollen. People who are allergic also can develop allergies against a lot of different things. In Europe, 20% of adults are sensitized to birch pollen!

New foods, also often bring new allergies!

Allergens

pollen	food
birch	apple, pear, cherry, peach, nectarine, apricot, plum, kiwi, hazelnut, other nuts, almond, celery, carrot
birch & mugwort or mugwort	celery, carrot, spices
plane	maize, chickpea, lettuce, green beans, hazelnut, peach, apple, melon, kiwi, peanuts
ragweed	watermelon and other melons, banana, zucchini, cucumber

How did this happen? Before, People with celeriac allergy also sensitive to spices (90%) and mugwort pollen (87%), carrot (57%)→ carrot-celeriac-mugwort-spice-syndrome. Then later realized they also had birch pollen allergy → birch-carrot-celeriac-mugwort-spice-syndrome.

Now: which allergens are important and look at cross-reactivity in terms of structure and molecules. Like this we can explain this correlations mentioned above.

Nomenclature:

- First 3 character of genus: Betula
- First character of species: verrucose
- Arabic numeral: 1

➔ Bet v 1

➔ Bet v = Birch pollen allergens

You see that when looking at the allergens, some are very similar structure wise, or even the same → cross-reactivity.

Labile proteins → local reaction. Stabile proteins → system. reaction

The Lipid transfer protein (LTP)

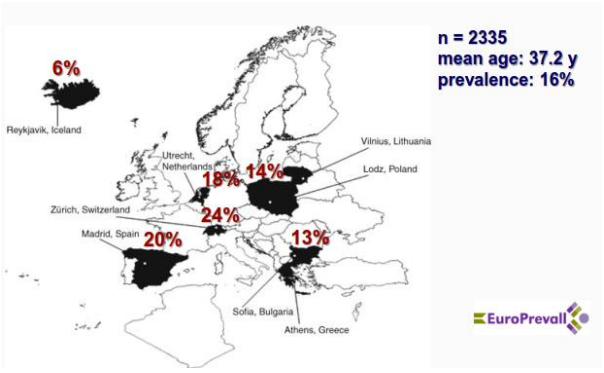
- Not common in Europe but most important allergen in Mediterranean countries
- Stable structure with 4 conserved intramolecular disulfid bonds
- High stability against digestion and heating
    - Increased risk for systematic reaction
    - Allergic reaction against processed foods

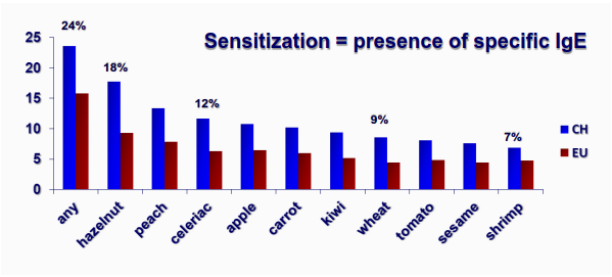
Features of food allergy in adults

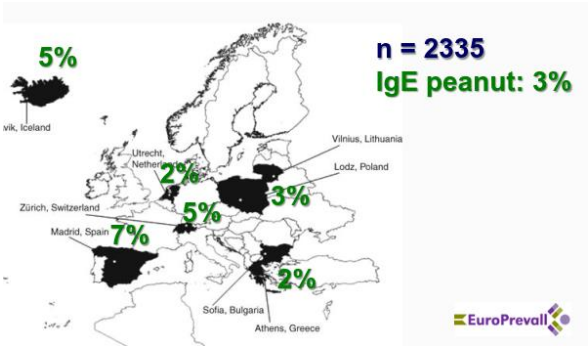
- Fruits, vegetables, nuts
- Bet v 1 mediated in central/eastern/northern Europe
- Primary food allergy, mainly persisting from childhood
- Broader spectrum of involved foods, dietary habits, globalization

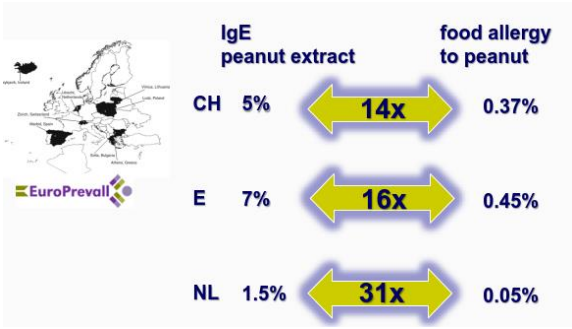
Diagnosis of food allergy

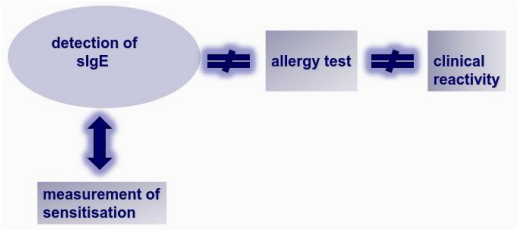
Prevalence and distribution of food sensitization in European adults





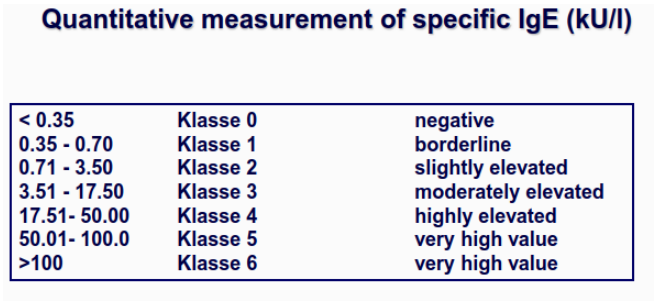


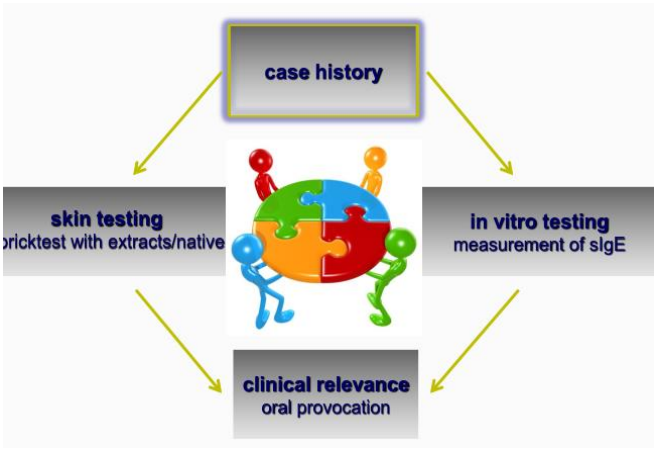




SENSITIZATION IS NOT ALLERGY! Detection of IgE does not predict what symptoms the person hat. It doesn't need to go into reactivity!

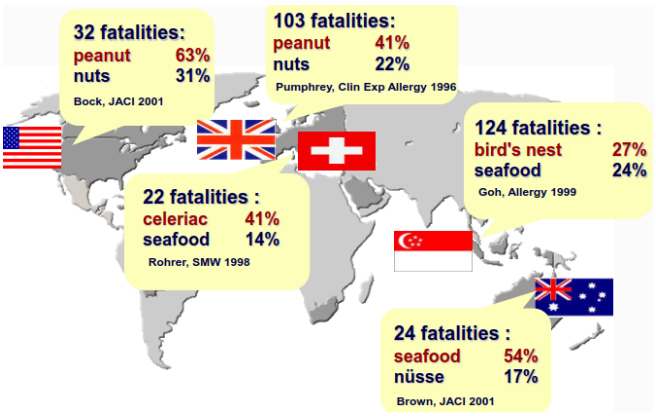
Diagnosis of food allergy: skin-prick-test (SPT)





Clinical manifestation of food allergy

- Local oral symptoms (oral allergy syndrome → OAS: > 80 %), most common symptom
- Skin symptoms: flush, urticaria, angioedema
- Respiratory symptoms: laryngeal edema, rhinitis, bronchospasm
- Gastrointestinal symptoms: Dysphagia, Nausea, emesis, cramps, diarrhea → in adults rarely isolated gastrointestinal symptoms
- Cardiovascular symptoms: hypotension, shock
- Anaphylaxis: severe, life threatening, generalized, hypersensitivity reaction



Treatment of food allergy

➔ Elimination diet
➔ If this fails: emergency drugs

Fatalities due to food allergy

70 % happened outside of the home (Restaurants, Bar, take away, Canteen etc.)

Per Directive, 14 allergenic ingredients must be declared: Cereals, Crustaceans, fish, egg, peanut, soybean, milk, nuts, celery, mustard, sesame seed, Sulphur dioxide, lupin, mollusks

Possible contaminations also must be declared.

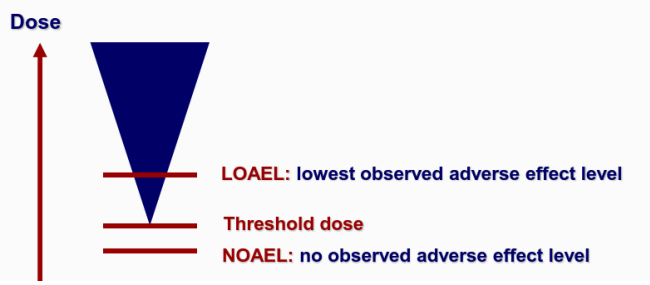
Actual situation: avoid food or any products containing the food. Labelling rules generally cover: only deliberately added ingredients and not contaminations. “May contain” delegated risk to consumer.

Definitions: Threshold

A limit below which a stimulus causes no reaction.

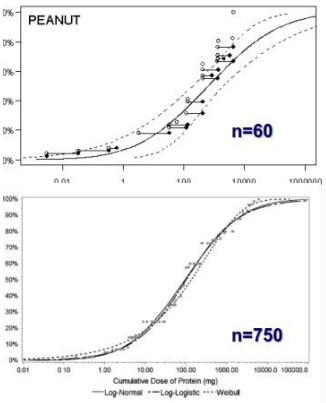
A dose at or below which a response is not seen in an experimental setting.

Different definitions:



Diagnosis:

Threshold dose in peanut allergy



ED 10: 2.8 mg peanut protein
(log-normal model)
= 11.2 mg peanut.

Ballmer-Weber, Mills et al JACI 2015

EuroPrevall

ED 10: 3.8 mg peanut protein
(log-normal model)

Taylor et al. Food Chem Toxicol 2014

Nutrition and kidney disease

Anatomy and Physiology of the kidneys

Renal circulation

- Kidneys (0.5% of body weight) receive 20% of cardiac output
- Highest blood flow of all major organs
- Per 100 g of kidney = about 350 mL blood per min.
    - Comparison: 100 g brain tissue receive 60 mL blood per min.

Glomerular filtration rate (GFR)

GFR = clearance of plasma compound which is not metabolized in the body outside the kidneys and freely passes across the glomerular filter and in the tubular cells is neither reabsorbed, nor actively secreted, nor further metabolized.

Measurement of renal function:

$$C_X = \frac{[U_X] \times V}{[S_X] \times t}$$

- Ideal: INULIN (i.v.)
    - Freely filtered in the glomerulus
    - Not reabsorbed/secreted in the tubules
- For clinical purposes: C_{crea} (Creatinine)
    - Muscle metabolism (end product) +/- stable blood concentration
    - Freely filtered in glomeruli, but 10% active tubular secretion
    - Tubular secretion increases with decreasing kidney function

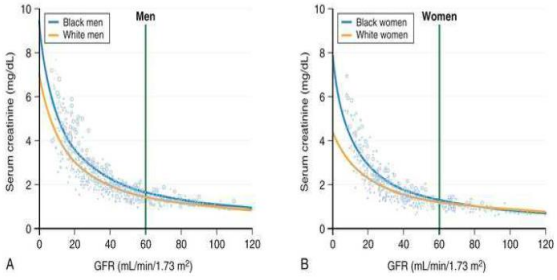
➔ Best index for renal function for clinical purposes

➔ GFR correlates relatively well with structural changes in chronic kidney diseases

➔ GFR varies with organ size and body mass → normalizeation to 1.73 m^2 "standard" body surface

➔ Aging: GFR decreases just by aging after 40 ys. (mean 1ml/min./year)

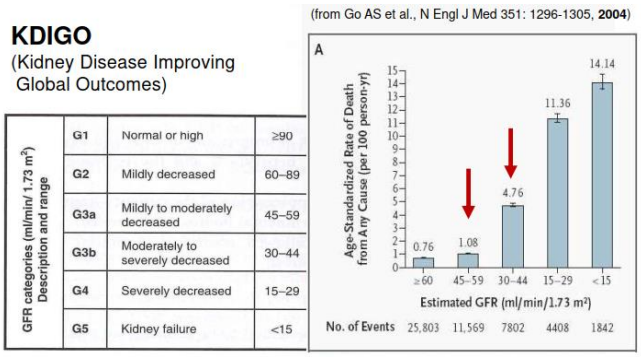
Serum creatinine and GFR:



Relation between serum creatinine levels and measured glomerular filtration rate (GFR) by 125I-iothalamate GFR among black and white men (A) and women (B). (Levey AS, Bosch JP, Lewis JP, et al., Ann Intern Med 1999;130:461-470)

Elevated Serum creatinine occurs under various circumstances: decreased kidney function, dehydration, increasing muscle mass, heavy meat meal.

Chronic kidney disease: atherogenic! → impact of GFR categories on mortality:



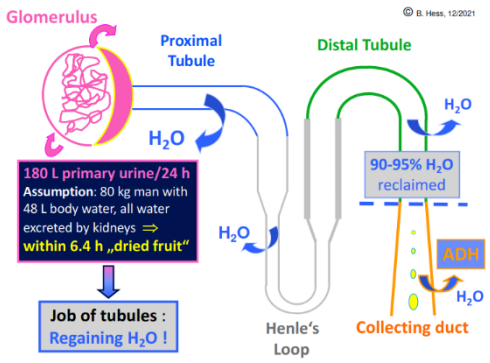
Kidneys - tubular functions

- Absorption: transport tubular lumen → blood
    - Water, sodium & chloride
    - Calcium, magnesium and phosphate
    - Bicarbonate
    - Glucose
    - Proteins, amino acids, urea, uric acid
    - Reabsorption machinery requires 10% of total body oxygen consumption!!!
- Secretion: transport blood → tubular lumen
    - H+ ions, ammonium ions, potassium
    - Organic acids (i.e. drugs), bases (i.e. bicarbonate)

Water balance, fluid intake and kidney function

Regulation of water balance

- Water loss leads to an increase of plasma osmolality (blood is "thicker")
- This is sensed by receptor cells in the hypothalamus
- Reaction of the brain:
    - Thirst, leads to fluid intake, thins blood through external mechanism
    - Increases secretion of anti-diuretic hormones (ADH = Vasopressin), thins blood through internal mechanism → kidneys excrete less water



Julia Beckmann, HS2021

ADH secretion - Regulation

Stimulation of ADH:

➔ H2O is retained, blood is thinned
➔ Less urine volume (darker color)
- Hyperosmolality
- Decreasing blood volume
- Stress (incl. pain)
- Nausea
- Pregnancy
- Hypoglycemia
- Nicotin
- Drugs (e.g. antidepressants)

Suppression of ADH

➔ H2O excreted, blood "thicker"
➔ Increasing urine volume
- Hypoosmolality
- Increasing blood volume
- Alcohol
- Phenytoin (anti-epilectic)

How much fluid intake is "normal"?

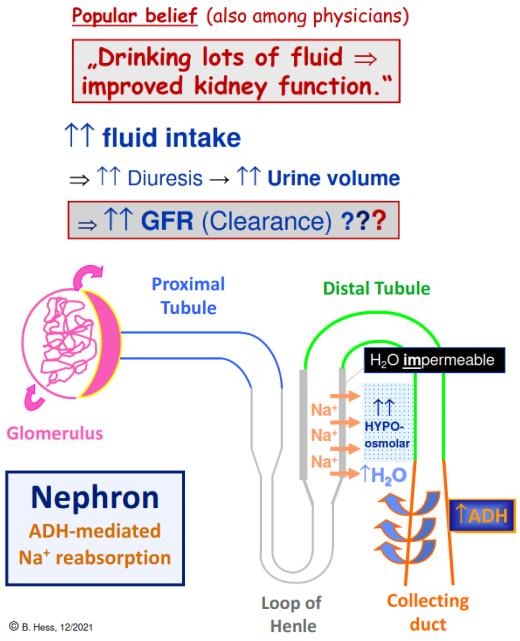
1.7 L/day

How much fluid intake is "healthy"?

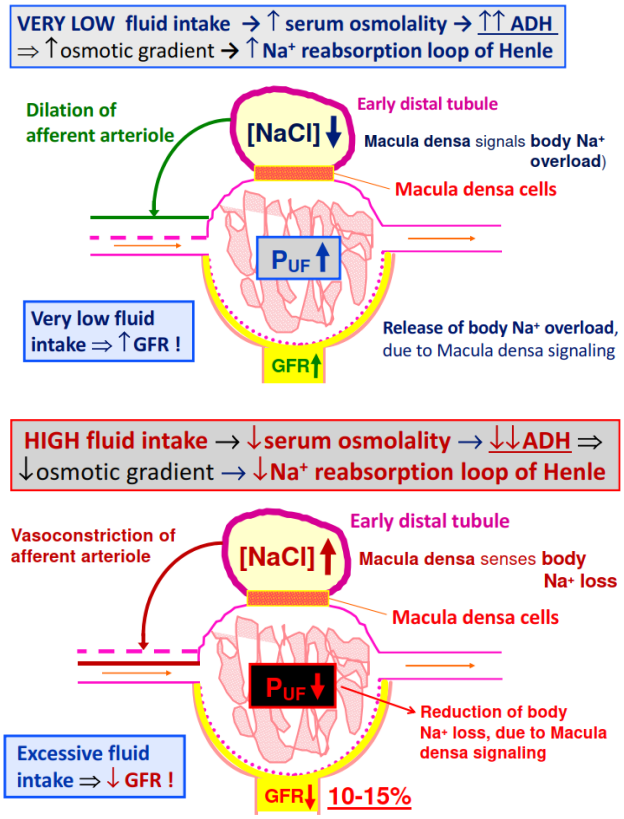
2.5 L/day → from fluids >= 1.5 L, from food: 1L per day

Increased fluid administration is mandatory when:

- Severe perspiration (exercise, stress etc.), very high fever, burns, vomiting, diarrhea, kidney stone disease, recurrent urinary tract infections



Tubuloglomerular feedback (TGF)



"Field evidence" - adults with CKD

CKD WIT (Chronic kidney disease water intake trial)

- **631 patients**, stage 3 CKD, 63% men, mean age 65 years
- Randomization: **Hydration** (316, ↑↑water intake) *vs.* **controls** (315)

	Hydration	Controls	p value
Urine volume (L/d)			
- Prerandomization	1.9	1.9	
- 12 months	2.5	1.9	
- Mean Δ 12 months	0.6	0.0	< 0.001
eGFR (ml/min./1.73 m², CKD-EPI)			
- Prerandomization	43.3	43.6	
- 12 months	41.0	41.7	
- Mean Δ 12 months	-2.3	-1.9	NS

Kidneys and acid-base balance

Urine-pH measurements: indicate, whether or not the body is over acidified. Tests have to be performed at certain times over several days in order to determine the pH value in the body. Mean values below 7 clearly suggest overacidity of the body, values above 7 indicate that everything is alright.

Acid-base metabolism

History: In the pre-agricultural period, nutrition was mainly ALKALI-generating. With Agriculture and live-stock farming → mainly animal protein and grain prod-ucts → ACID-generation!

Physiology:

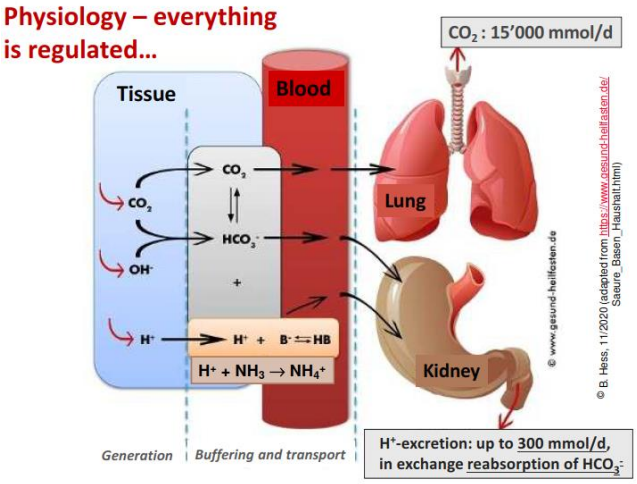
- Nutrition in 21st century: generates net proton loaf of 10-100 mEq/d → chronic "low-grade" metabolic acidosis: normal plasma bicarbonate (main buffer), but most likely intracellular acidosis
- Acid load: from protein metabolism, mainly cati-onic and sulfur-containing amino acids
- Neutralization and elimination of acids:
    - Kidneys (non-carbonic → NH4+) and lungs (carbonic → CO2)
    - Additional neutralization by bone and in-testinal secretion

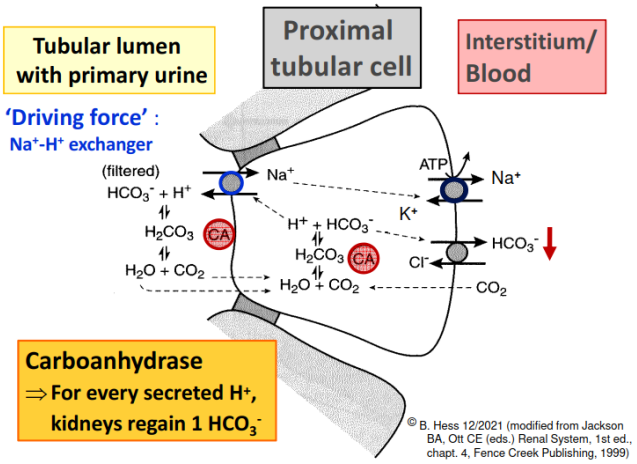
Diet and renal acid-base physiology

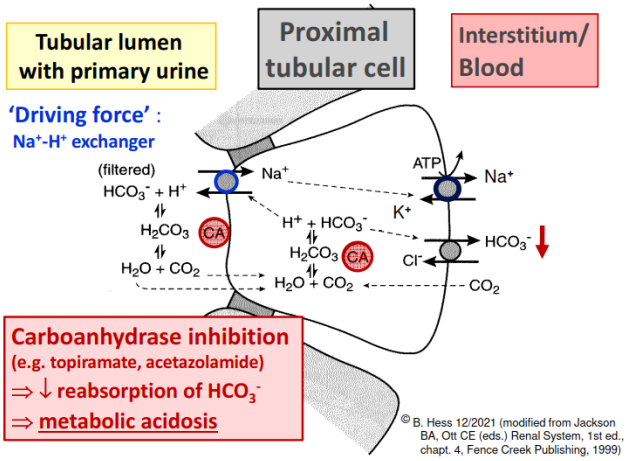
Body metabolism generates from non-carbonic acid metabolism (meat, fish, poultry) excess of up to 100 mmol H+ per day → excreted in urine: urine-pH varies, depending on actual amount of acid to be excreted.

Urine-pH reflects mainly acid-base content of nutrition, but never acid-base balance of whole body metabo-lism!

Food intake → PRAL (potential renal acid load)

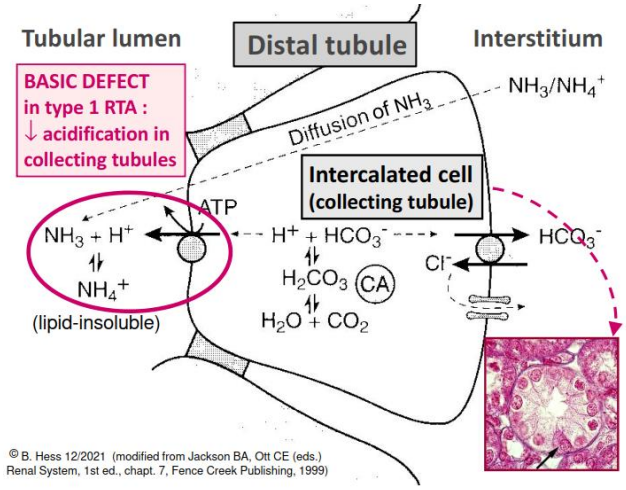




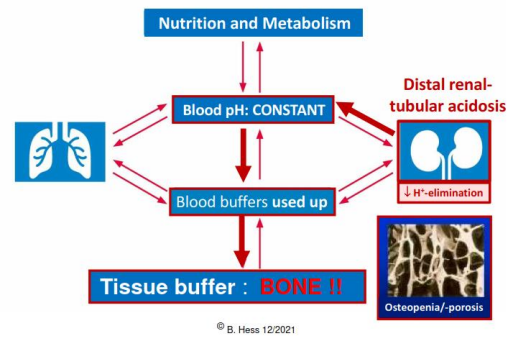


Pathology - Acid overload and urine pH

1. Sinking Bicarbonate-(alkali-)reabsorbiton by renal cells (rare disease)
    a. Proximal renal-tubular acidosis: systemic (blood) acidosis, but urine-pH normal!
2. Excessive Bicarbonate-(alkali-) losses from intesti-nal tract
    a. Massive chronic diarrhea (various dis-eases) → systemic (blood) acidosis, urine-pH low
3. Decreasing acid or H+-excretion by kidneys
    a. Severe chronic kidney disease (renal fail-ure) → accumulation of acid metabolites → systemic acidosis → urine-pH low
    b. Distal renal-tubular acidosis (dRTA) : H+ in-completely excreted by kidneys → urine-pH high
4. Increasing body acid production
    a. Very much increased acid intake: urine-pH low, reflects nutritional habits (excessive amounts of meat, fish, poultry, long-term calorie parenteral nutrition in hospitalized patients)



Target: constant blood pH of about 7.4



Bone effects of excessive acid intake/retention

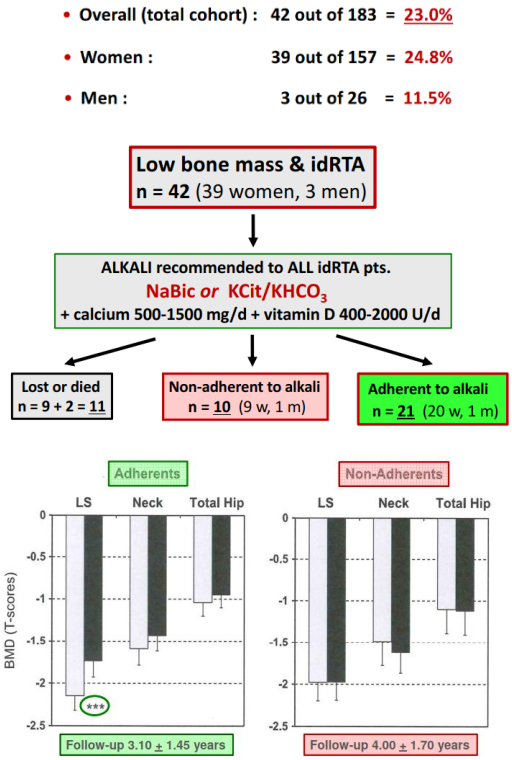
- Protein intake x2 → increase of urinary calcium excretion by 50%. Increased risk for osteopenia/-porosis
- Systemic metabolic acidosis: increasing bone dissolution
  - Direct physio-chemical effect
  - Loss of bone mass: less bone growth, more bone resorption
  - Sinking renal-tubular reabsorption of filtered calcium → negative skeletal calcium balance
- Distal renal-tubular acidosis (dRTA)
  - Chronically decreased renal excretion of H+ ions → retained acid has to be buffered by bone tissue → bone dissolution

Diagnosis of dRTA: NH_4Cl-loading

- Modified NH4Cl-loading → capsules that lead to NH3 + HCl (acid) in the liver
- Normal reaction:
  - Kidneys eliminate extra load of H+ ions
  - Fasting urine pH on day 2: < 5.45
  - Venous bicarbonate: >20.5 mmol/l

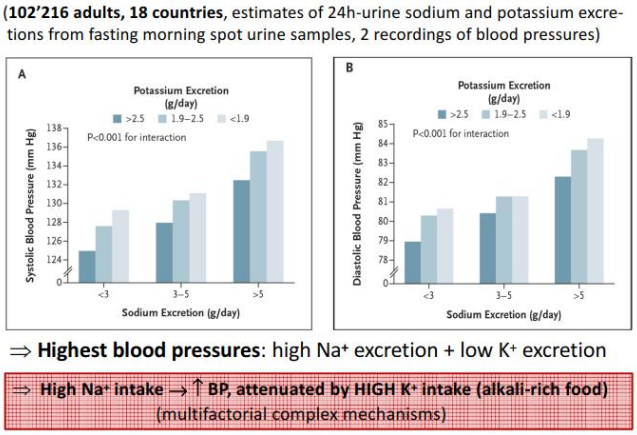
Distal RTA in osteopenia/osteoporosis

Results of a prospective 5 year study: Incomplete dRTA in patients with osteopenia/osteoporosis - prevalences:

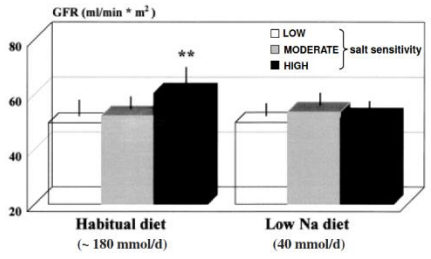


Salt & meat protein intake: impact on kidneys

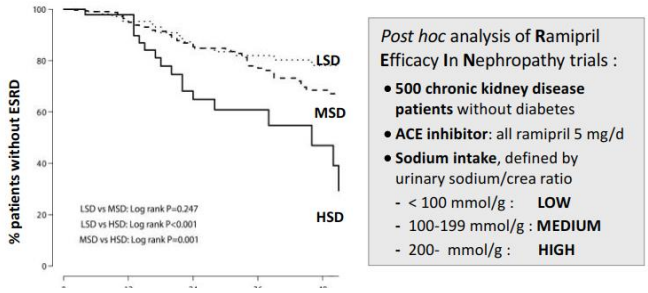
Impact of Na+ and K+ intake on blood pressure



Salt sensitivity & GFR: habitual vs. low Na+ intake in 47 healthy notmotensive men:



Long term impact of salt intake on renal function: The negative effects of sodium on BP values are amplified in CKD patients, as a result of fluid overload and of direct toxicity on the heart, the vascular system, and the kidney.



High dietary salt intake (>14 g/d) increased the risk for ESRD (and blunts the antiproteinuric effect of ACE inhibitors).

Summary: Renal consequences of high salt intake

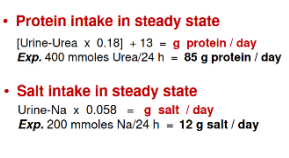
- Rise in blood pressure (more pronounced in salt sensitive individuals/hypertensives)
- Decreased response to antihypertensive therapy (especially salt sensitive hypertensives: elderly, diabetics, blacks)
- Short-term: increased GFR: hypertension → glomerular hyperfiltration
- Long term: decreased GFR: hypertension → chronic glom. Hyperfiltration → progressive fibrosis, faster decreasing GFR
- Increasing albuminuria/proteinuria (glom. Hyperfiltration). Attention: decreasing antiproteinuric effect of RAAS inhibitors

Macula densa: Tubulo-glomerular feedback (TGF) and protein-rich meals

- Protein digestion → higher plasma concentration of amino acids
- More Amino acids filtered in the glomerulus
- Increasing prox. Tubular reabsorption of AAs, co-transport with Na+ → increasing tubular Na+ reabsorption
- Decreasing distal Na+ delivery = sensing of Na+ concentration overload by MD
- More release of prostaglandins and nitric oxide (EDRF)

→ Vasodilation of afferent glomerular arteriole → increasing GFR

Calculations of daily protein and salt intakes from 24-h-urine collections:



Diet in patients with reduced kidney function

Chronic kidney disease (CKD) - definition

1. Kidney damage for >= 3 months, with or without impaired function (decreased GFR), manifested by
   a. Structural changes (histopathology) or,
   b. Markers of kidney damage (proteinuria/albuminuria, hematuria, changes in imaging studies such as scars, small kidneys, polycystic kidneys aso.)

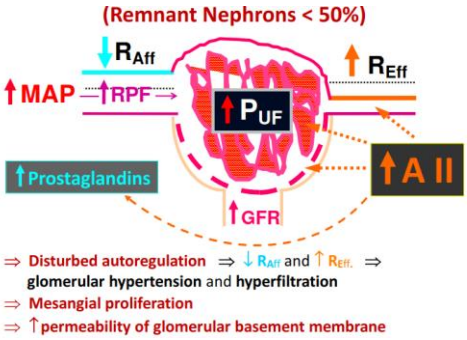
and / or

2. GFR < 60ml/min./1.73 m^2 for >= 3 months, with or without proof of kidney damage

Chronic kidney disease - problems

- Fluid, electrolyte and acid-base metabolism
  - Sodium: impaired handling of strong fluctuations of sodium intake
  - Hyperkalemia (only in severe renal impairment)
  - Hypocalcemia/hyperphosphatemia (early)
  - Hypermagnesemia
  - Metabolic acidosis
- Disturbances in metabolism/organ functions
  - Renal hypertension or renally aggravated essential hypertension
  - Renal bone disease
  - Renal anemia (lack of erythropoietin)
  - Uremic coagulopathy (increased bleeding time)
  - Lipid metabolism(mainly in nephrotic syndrome)
  - Psychologic problems/sleep-apnea

Chronic Nephropathies and A II



TGF & meat protein-rich diet in CKD

See Macula densa: TGF and protein rich meals. Additional vasodilation of afferent glomerular arteriole → increasing GFR leading to increasing chronic hyperfiltration (more workload).

CKD & meat protein overconsumption - consequences

Pre-existing hypertension/hyperfiltration in remnant glomeruli + additional hypertension/hyperfiltration duet to overconsumption of meat protein (amino acids) → more rapid loss of function of remnant glomeruli → faster decline of GFR over time.

Nutrients and progression of CKD

Reduced decline in GFR over time:

- Low sodium diet (< 10g/day)
- Low animal fat, low cholesterol
- Increase in low-fat dairy product consumption
- Coffee: > 6 cups/day vs. < 1 cup/day
- Oral alkali supplements/reduced dietary acid intake

Neutral with respect to GFR decline over time:

- Consumption of whole grains
- Vegetable consumption
- Fruit consumption

CKD - management (diet, drugs)

- **Protein intake : < 1 g/kg BW (normal BW !)**
  - eGFR < 45 ml/min./1.73 m² : 0.6-0.8 g / kg BW
  - Hemodialysis: 1.2-1.4 g/kg BW (malnutrition !)
- **Salt intake (NaCl): < 10 g/d** (24h-U-Na < 172 mmol/d)
  - eGFR < 30 ml/min./1.73 m² : < 7.5 g/d (24h-U-Na < 131 mmol/d)
  - Hemodialysis : < 7.5 g/d (24h-U-Na < 131 mmol/d)
- **Potassium : 4.7 g/d** (24-h-Urine-K 120 mmol/d)
  - eGFR < 30 ml/min./1.73 m² *or* Hemodialysis: < 3 g/d (< 77 mmol/d)

- **Calcium : 800-1000 mg/d** (all stages of CKD)
- **Phosphorus : < 800 mg/d** (all stages of CKD)
  If Ca x P product > 4.4 mmol²/mmol² ⇒ phosphate binder
  - Ca-Carbonate/-acetate 0.5-1 g with meals ⇒ risk of vascular calcifications !
  - Better (probably lower CV morbidity/mortality): Non-calcium-containing products (Sevelamer, Lanthanum carbonate)

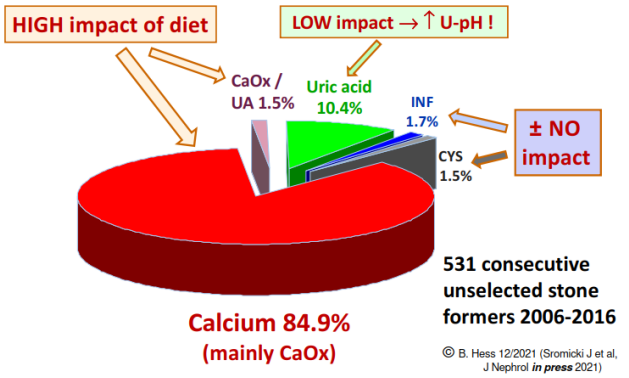
  (Kalantar-Zadeh K & Fouque D, N Engl J Med. 377: 1765-1776, 2017)
- **Metabolic acidosis ⇒ ↑endothelin, ↑A II, ↑TGFβ ⇒ faster decline in GFR ⇒ Alkali treatment :**
  Oral Na-bicarbonate → ↑S-Bic to 24-28 mmol/l ⇒ improves kidney and patient survival (Di Iorio BR et al, J Nephrol 32: 989-1001, 2019)

Diet and kidney stones

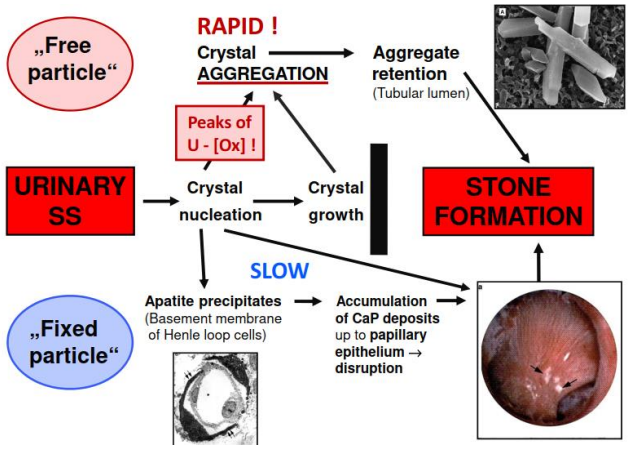
Metabolic evaluation of recurrent stone formers

Careful and individual diet history, as well as urine analysis in diet and on fasting state and stone analysis by IR or X-ray diffraction (mandatory)

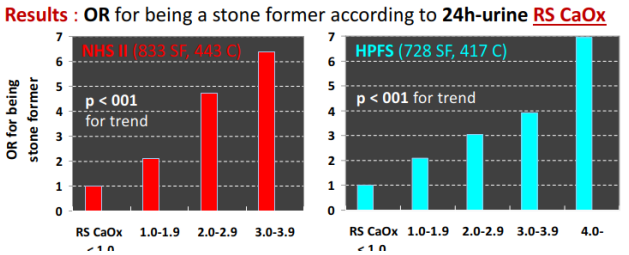
➔ Stone analysis: essential due to impact on dietary management of stone disease!



Focus: Pathophysiology of calcium-oxalate stones



Impact of relative supersaturation (RS) of CaOx in 24h-urines for likelihood of kidney stones:



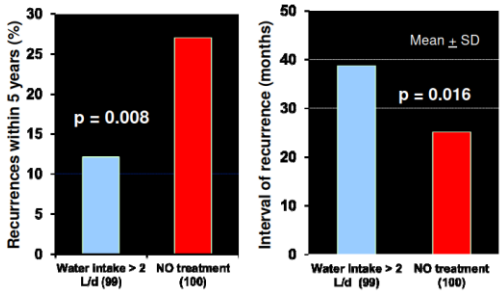
➔ The likelihood of being a stone former increases with higher calcium oxalate relative supersaturation levels in men and women

Diet-induced changes in RS(CaOx) calculated by EQUIL 2 - correlations with urinary parameters

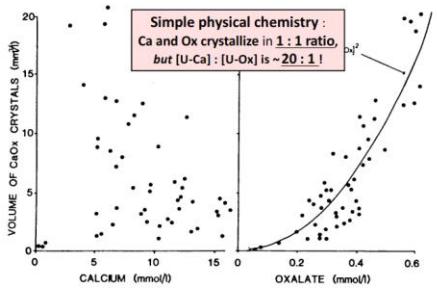
y-axis	x-axis	r	p
ΔRS_{CaOx}	$\Delta U_{Ox} \times V$	0.522	0.0002
	ΔpH	−0.494	0.0004
	ΔVolume	−0.470	0.0009
	ΔGI-Alkali	−0.362	0.013
	$\Delta U_{Ca} \times V$	0.136	NS

⇒ ↓ RS(CaOx) ⇒ ↓ CaOx stone risk
- DILUTION : ↑urine volume
- ↓PROMOTION : ↓urine oxalate (transient peaks: snacks !)
- ↑INHIBITION : ↑alkali intake = ↑urine citrate + ↑U-pH

DILUTION - water intake & CaOx stones

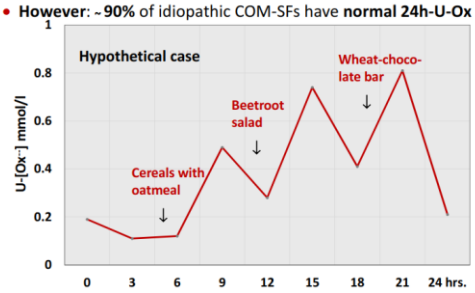


CaOx crystallization in urines – OXALATE (and NOT calcium) is the great PROMOTER !



Transient hyperoxaluria in CaOx stone formers

- Majority of CaOx SFs: **100% COM** ⇒ **hyperoxaluria** expected
- **However**: ~ **90%** of idiopathic COM-SFs have **normal 24h-U-Ox !**



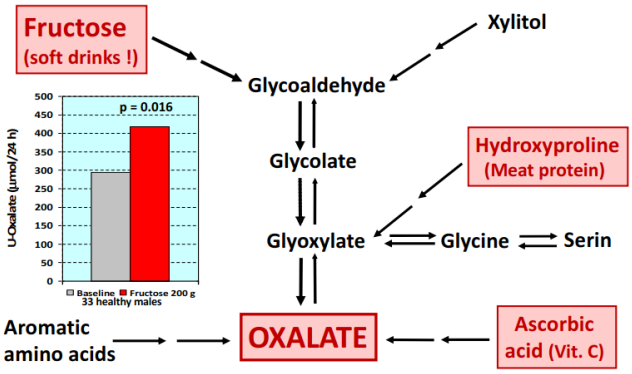
Promotion of particle formation - hypercalciuaria vs. hyperoxaluria

For physico-chemical reasons, even transient increases in OX-- concentration are much more relevant than those in Ca++ conc. For calcium oxalate particle formation in tubular fluid and urine: Oxalate is the great promoter!

Where does urinary Ox come from?

- Diet: 40-50% of urinary Ox from GI absorption
- Endogenous synthesis/metabolism
  - Metabolism of amino acids OH-proline (meat),glycine phenylalanine, tryptophan
  - Breakdown of vitamin C: high intake of vitamin C → increased kidney stone risk
  - High intake of fructose (soft drinks) → glycoaldehyde → glycolate → glyoxylate → oxalate
- Decreased colonization with Oxalobacter formigenes → reduced rate of gut colonization in stone formers

«Metabolic» urinary oxalate - origin



Low oxalate intake - impracticable!

All plant products (vegetables, salad, fruits), cereal-based products (bread, flakes, aso.), chocolate, nuts, berries and black/green tea aso. Contain oxalate → oxalate is unavoidable!

→ Intestinal absorption of oxalate from meals and snacks should be reduced!

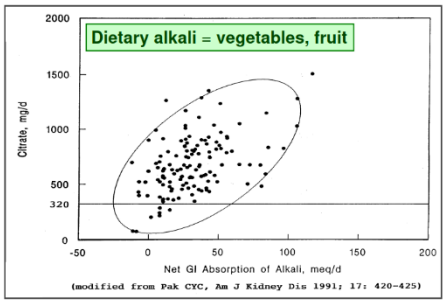
- Increased Ca intake with meals → increased intestinal free Ca
- Increased intestinal CaOx crystallization → decreased Ox absorption → decreased urine-Ox → decreased CaOx-stone risk????

Acid base & stones - urinary citrate

- Citrate: most abundant in human urine
- Citrate: most important (and cheapest) marker of intracellular acid-base-balance: increased acidity of renal cells → decreased citraturia
- Chelator: formation of soluble complexes with calcium → decreased urinary supersaturation of CaOx and Ca-Phosphate
- Crystallization inhibitor: direct inhibition of CaOx- and CaP-growth and aggregation
- Alkalinizer (hepatic transformation of citrate to bicarbonate) → increased urine-pH → increased solubility of uric acid and cystine

→ In every 24h-urine collection "stone", citrate must be measured!

Intake of alkali and urinary citrate



Intracellular acidosis in proximal tubule cells → Hypocitraturia - etiologies

- Any kind of systemic metabolic acidosis
- Incomplete distal renal tubular acidosis
- High dietary acid loads (meat protein!)
- Dietary salt loading → decreasing renin and A II → decreased activity of renal H+-K+-ATPase → decreased H+-elimination → intracellular acidosis
- Malabsoprtion syndromes with chronic diarrhea: chronic loss of alkali
- Carboanhydrase inhibitors: Acetazolamide, Topiramate
- Potassium depletion

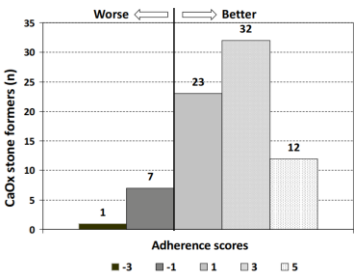
Incomplete distal RTA - diagnosis and features

- Suspicious: fasting U-pH remains > 5.8 → diagnostic: NH4Cl-loading → next day: fasting U-pH >= 5.45
- Rather calcium phosphate (apatite, brushite) stones
- Highly prevalent: women 25%, men 14%
- idRTA patients younger than Non-idRTA stone formers
- more often positive family history
- slightly lower serum potassium (within normal range)
- 1.6 x higher stone disease activity (stones/years of disease)
- 2.5 x more intrarenal calcifications (nephrocalcinosis)
- higher prevalence of hypercalciuria and low U-citrate (< 2 mmol/d)

Simple dietary advice - impact on urine chemistries of 75 idiopathic CaOx-stone formers

Adherence score (24h-urines 3-9 months after advice) :

1.	DILUTION: U-volume	↑ + 1 point	↓ - 1 point
2.	↓ PROMOTION: ↓ U-oxalate		
	- U-calcium	↑ + 1 point	↓ - 1 point
	- U-oxalate	↓ + 1 point	↑ - 1 point
3.	↑ INHIBITION: ↑ U-citrate		
	- U-uric acid (urea)	↓ + 1 point	↑ - 1 point
	- U-citrate	↑ + 1 point	↓ - 1 point
	Adherence Score	Max. 5 points ↔ Min. - 5 points	



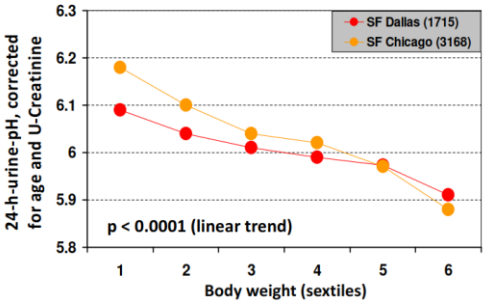
Dietary effects on 24h-urine chemistries

Urine parameter	Before DA	After DA	p value
Volume (ml/d)	2057 ± 79	2573 ± 71	< 0.0001
pH	5.77 ± 0.05	5.78 ± 0.05	0.87
Creatinine (mmol/d)	13.7 ± 0.4	13.3 ± 0.4	0.15
Sodium (mmol/d)	174 ± 7	184 ± 8	0.19
Potassium (mmol/d)	65 ± 2	70 ± 3	0.10
Calcium (mmol/d)	5.49 ± 0.24	7.98 ± 0.38	< 0.0001
Oxalate (mmol/d)	0.34 ± 0.01	0.26 ± 0.01	< 0.0001
Urea (mmol/d)	389 ± 11	383 ± 14	0.91
Phosphate (mmol/d)	29.1 ± 0.9	27.6 ± 1.2	0.25
Uric acid (mmol/d)	3.48 ± 0.12	3.13 ± 0.10	< 0.0001
Citrate (mmol/d)	3.07 ± 0.17	3.36 ± 0.23	0.06
Magnesium (mmol/d)	4.38 ± 0.14	5.41 ± 0.23	< 0.0001

Simple dietary advice to CaOx stone formers - impact on supersaturation (Tiselius' AP(CaPOx) EQ index)

24-h urine parameter (means ± SEM)	BASAL (mean of 2 urines)	FOLLOW-UP	p value
Volume (L)	2.06 ± 0.08	2.58 ± 0.07	< 0.0001
U-Ca (mmol)	5.50 ± 0.24	7.99 ± 0.38	< 0.0001
U-Ox (mmol)	0.34 ± 0.01	0.26 ± 0.01	< 0.0001
U-Mg (mmol)	4.33 ± 0.14	5.41 ± 0.23	< 0.0001
AP (CaOx) index EQ	0.93 ± 0.05	0.73 ± 0.05	< 0.001

Obesity ⇒ «undue» urine acidity (low pH)



Undue urine acidity - ↓ renal NH_4^+ secretion

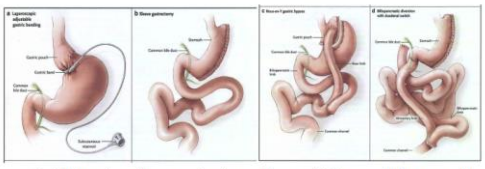
Physiologic insulin effects in proximal tubules

- Stimulation of Na^+/H^+ exchanger 3 (NHE3)
  → ↑ Na^+ absorption, ↑ H^+ secretion
  → ↑ fluid absorption
- ↑ ammonium production from L-glutamine ⇒ ↑ ammonium excretion

Renal-tubular insulin resistance

⇒ ↓ ammoniagenesis ⇒ ↓ ammonium excretion
⇒ ↑ unbound H^+ ions in tubular fluid/urine ⇒ ↓↓ urine pH
⇒ ↑ UA stones (UA solubility 0.54 mmol/l)
⇒ Lifelong treatment with alkali → U-pH permanently ~ 6.5

Bariatric surgery and kidney stones - applied surgical techniques



Gastric band	Sleeve gastrectomy	Roux-en-Y-Bypass	Biliopancreatic Diversion
(purely restrictive)	(restrictive)	(malabsorptive + restrictive)	(strongly malabsorptive)

CaOx stones after malabsorptive bariatric surgery - woman, 43 years, BMI 51 kg/m²

6/2011 Biliopanreatic diversion
- common (absorptive) channel **80 cm**
- **majority** of small intestine **bypassed**

Sequelae
- Body weight : **160 → 85 kg !**
- **Chronic diarrhea**
- **3 kidney stones passed** spontaneously
- **1 x ESWL , 1 x retrograde stone removal**
- Obstructing ureteral stone → **Urosepsis**
- **CT :** potential **nephrocalcinosis**
- **Stone analysis 2012: 80% calcium oxalate-monohydrate (COM)**
  20% calcium oxalate dihydrate (COD)

Case - Woman, 43 years, Marceau Bypass (2)

24-hour urine chemistries (normal values healthy Swiss volunteers)

	---------- Promotors ----------							---- Inhibitors ---	
Date	Vol. (>2000 ml)	$U_{Na} \times V$ (≤ 200)	$U_{Ca} \times V$ (≤ 8.00)	$U_{Ox} \times V$ (≤ 0.440)	$U_{UA} \times V$ (≤ 4.00)	$U_{P} \times V$ (mmol)	$U_{Urea} \times V$ (mmol)	$U_{Cit} \times V$ (≥ 1.90)	$U_{Mg} \times V$ (≥ 2.20)
8/2016	1900	175	1.63	1.691	4.07	48.5	485	0.29	5.21
8/2016	1500	209	3.18	0.945	3.21	47.6	429	0.14	4.77

Chronic watery diarrhea
→ chronic **fluid losses** → high **fluid intake may worsen diarrhea**
→ ↓↓ **fluid intake**

Chronic steatorrhea
→ **Ca soap** formation → ↓ **intest. CaOx binding** + ↑ **transepithelial GI-Ox uptake**
→ ↑GI-Ox absorption

Chronic diarrhea
→ Chronic **bic. losses**
→ **intracellular** and/or **systemic acidosis**
→ ↑ renal citrate reabsorption

Stones after malabsorptive bariatric surgery - prophylaxis and treatment

HIGH fluid intake, regularly **distributed over 24 hrs.**	**Avoid Ox excesses,** ↑↑ **Ca intake 6-8 g/d** WITH meals/snacks	**HIGH amounts** of **alkali** (NaBic, K-Cit) + **bile acid binders**
↓	↓	↓
↑↑ **urine volume (≥ 2 liters/24 h)** → ↓ **urinary CaOx supersaturation**	**Crystallize CaOx in colon** → ↓↓ **Ox absorption** → ↓ **urinary oxalate**	↓ **metab. acidosis** → ↑ **urinary citrate** → ↑ **crystallization inhibition**

SUMMARY - renal stone formation is diet-triggered, but *NOT just* nutritional

- the majority of **individuals on a „wrong diet" never form stones**
- When subjects are **matched** for socio-economic background, **intakes of calcium, oxalate and animal protein** (acid) are **not different** between stone formers and healthy people
- under identical dietary conditions, **recurrent stone formers pass larger urinary crystals / aggregates** than healthy controls ⇒ **genetics !**
- by simply and consequently **increasing intakes of fluid, calcium** (*with meals*) and **alkali** (vegetables, salad, fruit) as well as **lowering protein intake**, urinary **CaOx supersaturation can be significantly lowered**
- Every 4th female and every 7th male calcium stone former exhibit **reduced renal elimination of H^+ ions** *(incomplete dRTA)* ⇒ **lifelong medication (alkali)** needed for prevention of stones/nephrocalcinosis

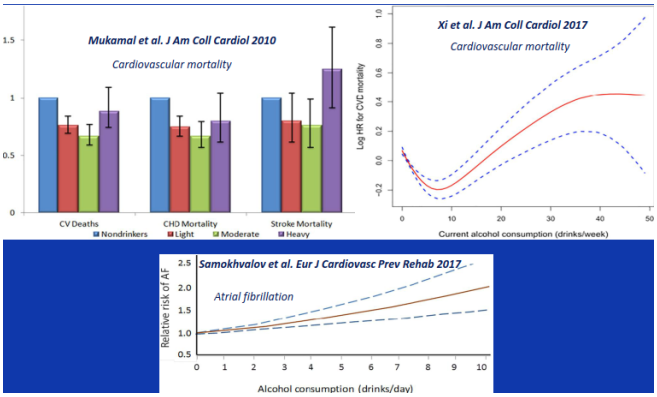
Impact of Alcohol Abuse on gastrointestinal Health and Nutrition

Global Burden of Disease Study 2016: the level of alcohol consumption that minimizes health risks is zero! There might be some benefits when looking at certain aspects, but there are no benefits when looking at the whole organism!

In Europe, alcohol consumption is in a slow decline (not the same in all countries). Risk thresholds for alcohol consumption: 30g/day for men, 20g/day for women (and new: not daily!)

Problem with the young: binge-drinking

Alcohol and cardiovascular risk



Benefit only with small amounts, mortality increases with more consumption. Other cardiovascular problems receive no benefits and correlate with drinking.

Alcohol and T2D

Small amounts may have benefits, but again problems with higher amounts.

Alcohol-associated organ damage in the GI tract

Deleterious dental status, Esophagitis, Gastritis, Liver disease (viral hepatitis, NASH), Chronic/acute pancreatitis, Duodenitis/villous atrophy. Malnutrition.

Ethanol - facts

- Caloric energy 7.1 kcal/g (29 kJ)
- Due to toxicity, metabolic "priority"
- Significant thermogenetic effect
- Increase of resting metabolic rate
- Anti-lipolytic effect (acetate)
- Inhibition of lipid oxidation
- Increase of lipogenesis
- Increase of insulin sensitivity (may be why low levels are beneficial for T2D)

In general one can say there not a lot of valuable nutrient content in alcoholic beverages. The best is beer, which has low alcohol levels and has some nutrients that might be considered beneficial. One important is polyphenols → can have health benefits. Might explain why beer not has such a major harmful impact on health as other alcoholics beverages, if consumed wisely.

Alcohol-associated obesity

- Additional source of calories, substantial amount
- Stimulation of appetite (hyperphagic effect)
- Inhibition of lipid oxidation in liver and fat tissue
- Positive energy balance

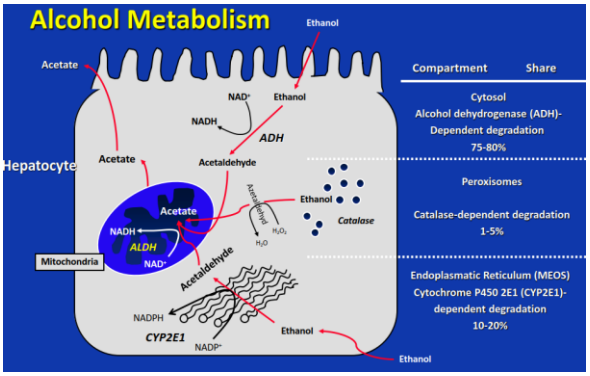
Results of systematic revies of studies 1984-2010: no clear evidence supporting a link between alcohol consumption and weight gain. Subgroup analysis: trend towards weight gain with higher alcohol consumption (>2-4 drinks = 24-48g/day).

If people are heavier they are more likely to develop liver damage/cancer even if they do not drink more than lean people!

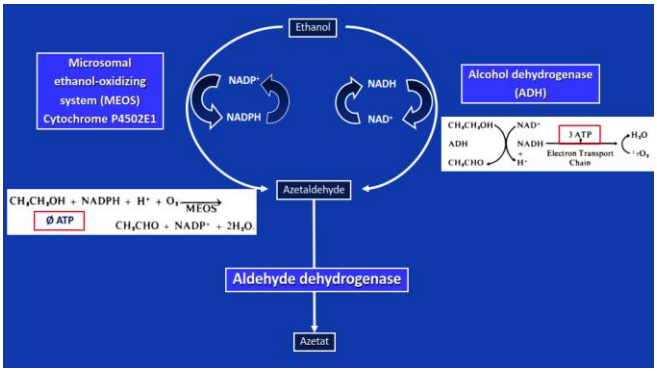
Alcohol metabolism

Hepatocyte → liver cell! Several enzyme system, most important: alcohol dehydrogenase: Ethanol → Acetaldehyde (highly toxic) → into mitochondria → to acetate by aldehyde dehydrogenase → no longer toxic and exhaled.

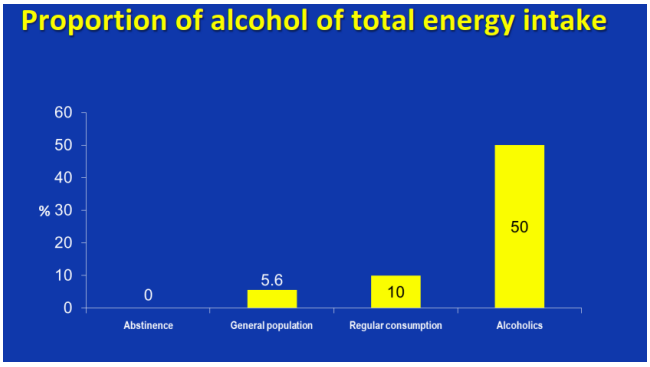
Less important in moderate drinker: MEOS (mitochondrial ethanol oxidizing system in ER). Can also degrade several other toxins. 20% of alcohol degradation. Important, because ADH is not inducible, but MEOS is → the more you drink the more MEOS! ADH does not increase, even with more alcohol consumption! Third: Peroxisomes. Not important in the liver, to some extend in the brain. Also acetaldehyde and acetate. Not a role in alcohol harm, but maybe on its effects on psychiatric disorders.



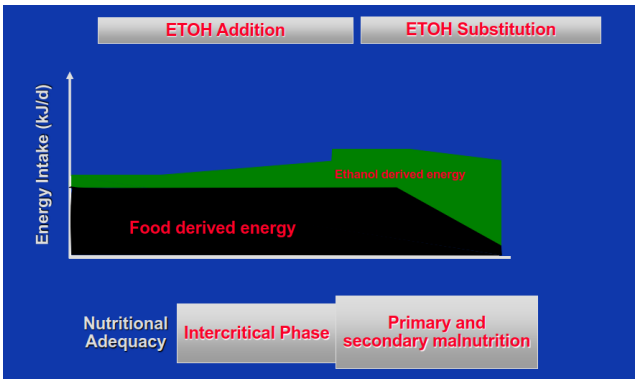
Alcohol - "empty calories"



Alcohol, although its full of calories, uses up ATP to get degraded → only patients who eat properly while they drink gain weight, while people who replace food with alcohol loose weight.

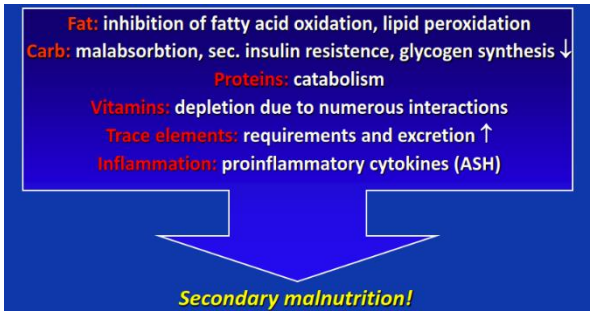


- ➔ How much people replace their food with alcohol
- ➔ This is called ETOH addition and ETOH substitution
- ➔ People who drink start drinking while they still eat properly and the more they drink this food derived energy is replaced by alcohol
- ➔ Causes primary (no nutritional valuable food consumed) and secondary (effects of interaction of alcohol and other nutrients) malnutrition
- ➔ Malnutrition is a major benefactor to mortality!



Alcohol-associated primary malnutrition - causes

- Poor diet (severe alcoholics don't eat right / at all)
- Loss of appetite (dystrophy, esophagitis, gastritis, liver disease)
- Dysgeusia (dental status, micronutrient deficiency)
- Lack of palatability (sodium and protein restriction as part of treatment of liver cirrhosis)
- Nausea, vomiting (esophagitis, gastritis)
- Diarrhea, malabsorption (due to effects of alcohol on GI tract)
- Complications of liver disease (bleeding, encephalopathy, ascites)

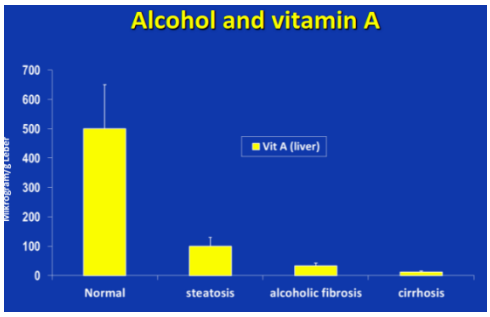


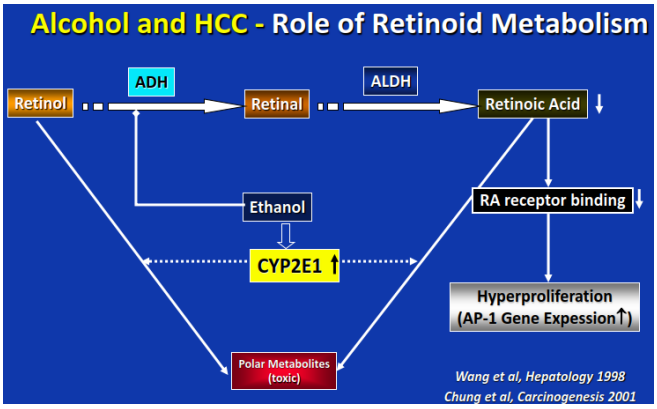
Alcohol and small bowel

- Chronic alcohol consumption causes villous atrophy in the upper small bowel
- Causes of acquired lactose intolerance
- May potentiate celiac disease - gluten intolerance (impact of alcohol on villi)
- Malabsorption of vitamins, iron and trace elements

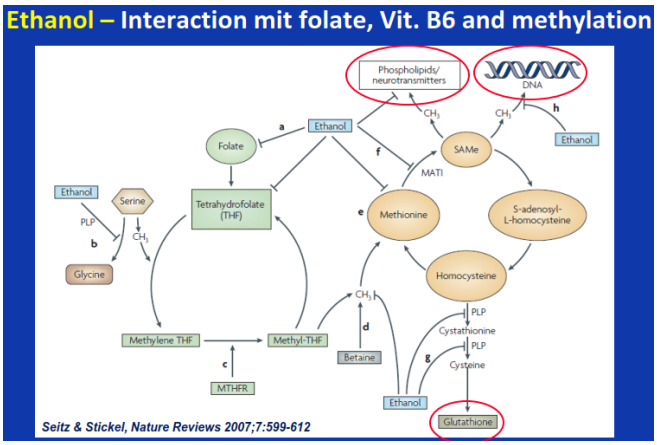
Alcohol and micronutrients

Micronutrient	Clinical syndrome
Vitamin A	Night blindness, infertility
Thiamine	Wernicke-Korsakoff-Encephalopathy, cardiomyopathie (Beri-Beri)
Folate	Anemia, increase of cancer risk
Vitamin D	Osteomalacia, osteopenia
Vitamin E	Reduced antioxidative resistance
Niacine	Pellagra, neuropsychiatric symptoms
Pyridoxalphosphat	Anemia
Zink	Wound healing problems, skin problems, immunodeficiency, diarrhea
Magnesium	Muscle cramps, glucose intolerance
Selenium	Myopathy, cardiomyopathy

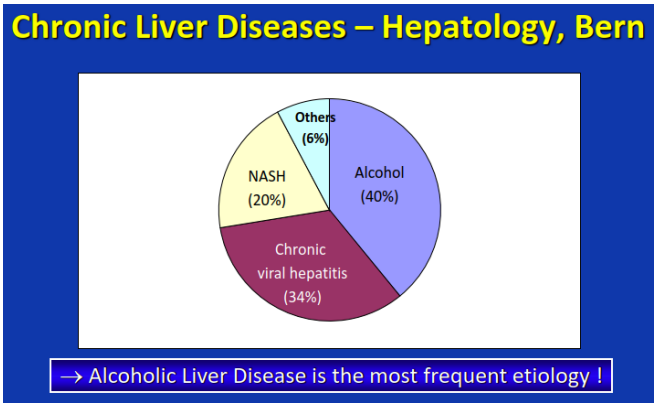




Competition between Retinal and Ethanol → if a lot of alcohol → Retinal doesn't get metabolized anymore → night blindness. Also → retinol gets metabolized to toxic metabolites → cancer.



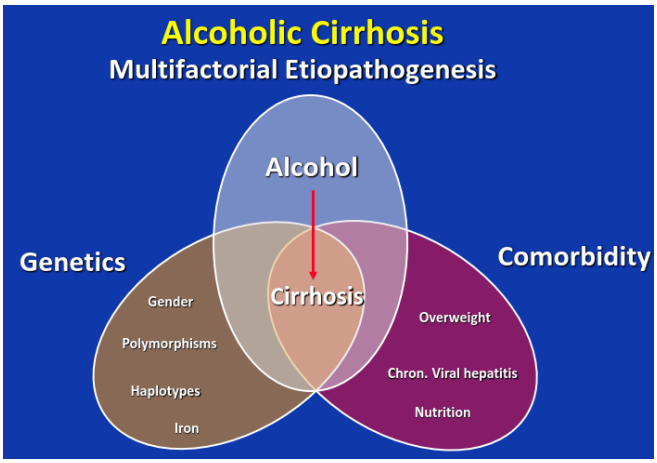
Highly complicated. Through interaction with folate and vit B6 methylation processes are interfered. Methylation is very important for cell integrity and gene expression! This interaction has important impact on cancer conduction and on how we handle xenobiotics in the body! Heavily impacted by alcohol through decrease of folate and vitamin B6.



Now: NASH is biggest slice, chronic viral hepatitis and maybe even alcoholics get smaller. Others are stable. Alcohol is still a strong proportion! Among the most frequent cases seen and still a strong global burden!

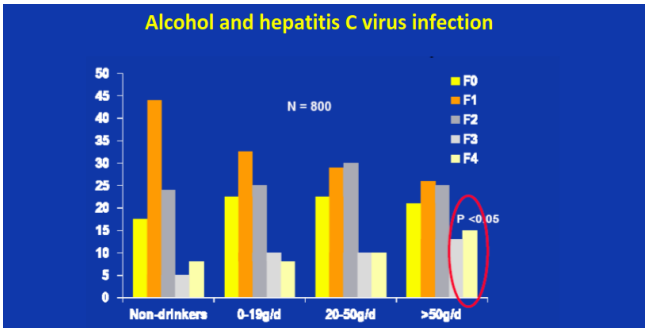
Global Burden of alcoholic liver diseases

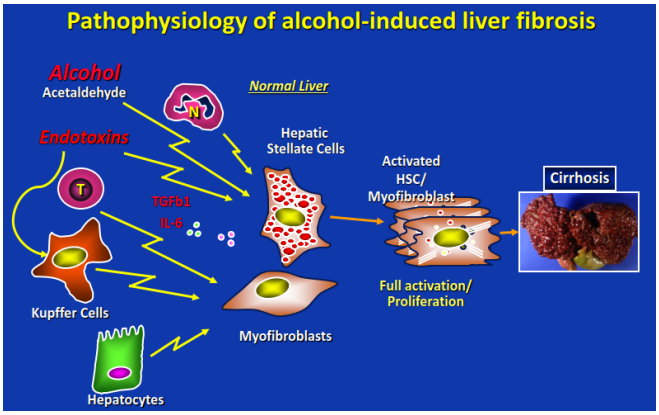
- Worldwide 493'000 deaths and approx.. 15'000'000 disability-adjusted life years (DALYs) due to ALD = approx.. 1% of all death causes
- 48% of all cirrhosis-associated deaths due to alcoholic cirrhosis
- Alcohol-associated HCC responsible for 81'000 deaths
- Assumed by 2030 more than 100'000 deaths



Obesity and risk for alcoholic liver disease

Study	N	Results
Naveau *et al.*	1.604	Cirrhosis and steatosis associated with long standing overweight (>10 Jahre)
Raynard *et al.*	268	Patients with fibrosis (>F2) reveal higher BMI (25 vs. 23 kg/m²)





Important are mesenchymal cells → not hepatocytes but reside in the liver and produce fibrosis → myofibroblasts and hepatic stellate cells. Stimulated by alcohol. Receptor binding sites for TGFb1 and produce activates HSC/myofibroblast → proliferate and lead to cirrhosis.

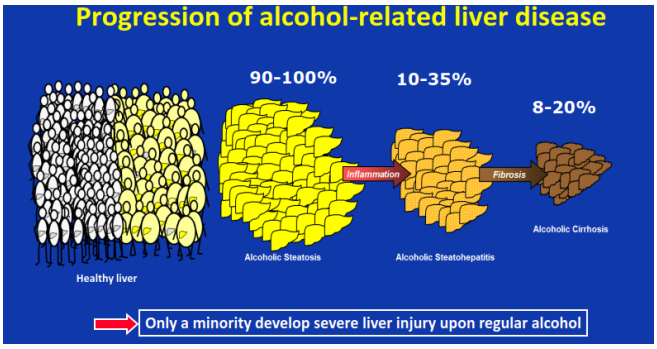
The more advanced cirrhosis, the more likely is mortality! Should be avoided, after progression to a certain level, still chance of death even with alcohol abstinence.

Also: Alcohol-related cirrhosis have much higher mortality when contracting Covid-19!

ALD = alcoholic liver diseases

Liver transplantation for ALD are increasing. Outcome is not bas (very good long term survival rate). Few conditions dampen: higher risk of developing tumors and developing cardiovascular diseases. Low risk of recurrent drinking, very few loose transplant because of drinking.

Phenotypes at risk vary (drunk on Monday afternoon but also snobby wine connoisseur).



Genetic risk for alcoholic liver disease

Evidence from Epidemiology:

- Females are more susceptible towards equal amounts of alcohol
    - Enzyme activity, body compartments, distribution of alcohol (less space in females cause lighter)
- Hispanics are more prone to developing ALD than Blacks and Whites
- Monozygotic twins have a 3-fold higher prevalence of alcoholic cirrhosis than dizygotic twins

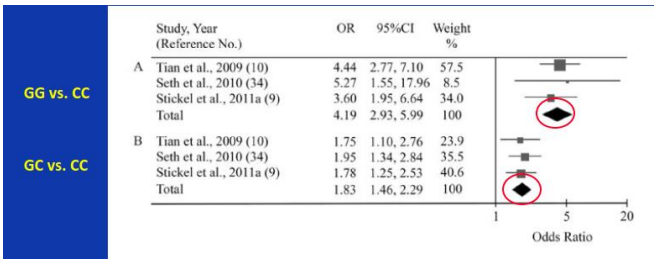
Also thought that drinking behavior might be caused by genetics. But studies didn't find anything. Only found in genotypes who protect people from drinking by having higher amounts of acetaldehyde (more uncomfortable symptoms after drinking → drink less).

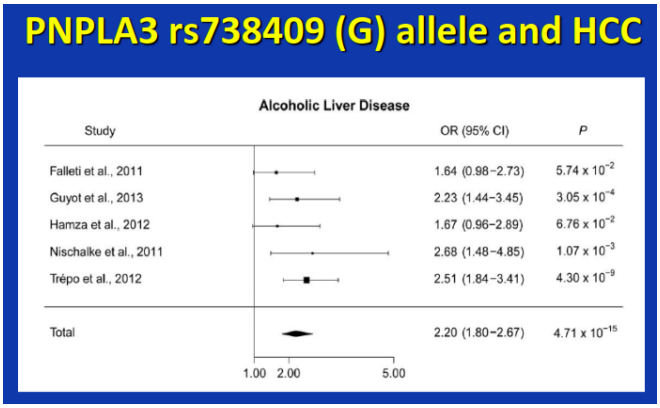
Steatosis in Non-alcoholic fatty liver disease

GWAS in patients with NAFLD: 2-fold higher hepatic fat content in homozygous carriers of PNPLA3 rs738409 (G) allele

PNPLA3 and ALD

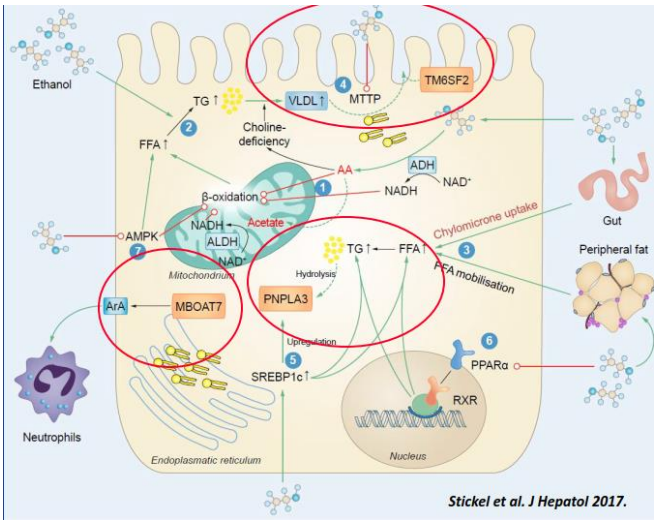
Alcoholic cirrhotic vs. alcoholics without ALD

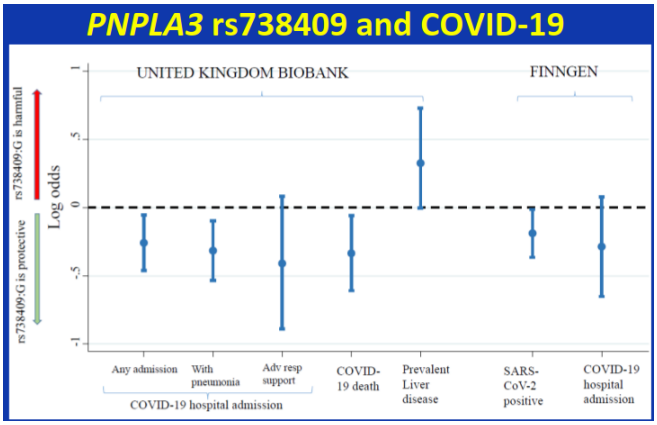




Alcohol produces acute and chronic pancreatitis. It also has a genetic factor (two genetic factors govern the risk for developing, indication but not diagnosis).

GWAS in ALD: PNPLA3, MBOAT7 and TM6SF2



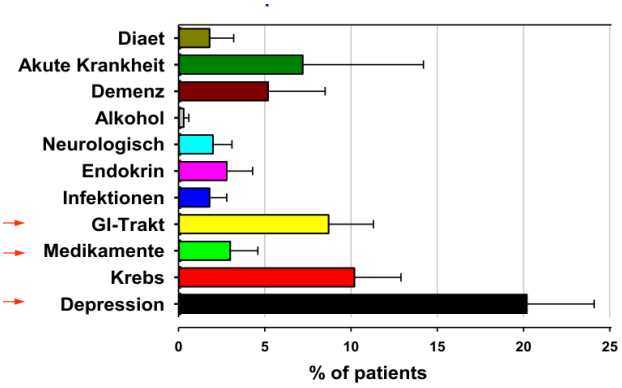


Summary

- Chronic alcohol consumption causes substantial comorbidity in the GI tract
- Prominent examples are direct epithelial damage in the esophagus, stomach and duodenum
- A significant share of morbidity derives from primary and secondary malnutrition
- An individual's risk is partly governed by host genetic factors
- Regarding population-based burden of disease, alcohol's impact in the progression of liver diseases and the pancreas are most important

Interactions between drugs and nutrition

Reasons for unintentional weight loss in geriatric patients



Main reason: Depression, GI-tract

Drug-associated gastrointestinal causes for nutrition problems

- Associated with symptoms (subjective, only the patient feels it, a physician cannot see it): dyspepsia, taste problems, nausea
- Associated with signs (objective): xerostomia, stomatitis (inflammation of the skin of mouth), ulcerations, bone necrosis

Metformin - pharmacology and adverse effects

Drug of choice in T2D

- Decreases hepatic glucose production by inhibiting gluconeogenesis due to stimulation of AMPK
- Is associated with body weight loss → good because other drugs cause weight gain and this is bad in T2D

Adverse reactions

- GIT: Dypepsia, diarrhea, metallic taste, >10%; loss of appeptite
- Reduction of vitamin B12 in serum in ~20% within 6 months (interferes with absorption!)
- Lactacidosis: 0.03 per 1000 patient years (risk factors: age > 60 years, kidney or liver failure, increased formation of lacate)
- Metallic taste

→ Transduction of the receptors in the tongue and Pharynx (facialis nerves) to the brain and thalamus. Many possibilities in this transmission of interference (direct on the nerve, or on receptors etc.)

Taste disturbances

Taste receptors transmit signal when activated by facial nerves to the ZNS. Different tastes (bitter, salty, etc.). Interference with taste is very disturbing for the patient!

Epidemiology: For most drugs no exact data about frequency, depending on drugs. Data mostly from case reports, larger studies are rare → many drugs are affected

Possible causes: Changes in the composition of the saliva, direct effects on taste receptors, inhibition of signal transduction and/or perception.

Taste disturbance associated with terbinafine

- Terbinafin is an antimycotic drug used topically and orally for skin and nail mycoses
- Inhibits squalenepoxidase, an essential enzyme for ergosterol biosynthesis
- Loss of appetite in about 20% and dysgeusia in about 5%
- Clinical course: latency on the average 35 days, Normalization within 4 months after stopping treatment in most patients
- Risk factors:
    - Age > 55 years, BMI <21 kg/m^2
    - Relative risk in the case of both 12.8

Adverse drug reactions affecting the mouth

Objective (taste is subjective)

Don't have to know the drugs, understand the principle

- Xerostomia (glands who produce saliva are disturbed): Anticholinergic drugs, many antidepressants.
- Ulcerations/stomatitis: bisphosphonates, Chemotherapy, Aspirin
- Tissue and bone necrosis: Bisphosphonates
- Hyperplasia of the gingiva: Immunosuppressive drugs

Xerostomia (dry mouth)

Important causes:

- Nasal obstruction → breathing through mouth
- Post radiation due to cancer of the mouth, neck or head
- Destruction/inflammation of salivary glands: Sjoegren's syndrome, sarcoidosis, hemochromatosis

- Anxiety → hyperacitivy of autonomic nerve system
- Drugs: Ipratropium, andidepressants, 1st generation antihistaminids,drugs for stress incontinence

Consequences:

- Dental problems: gingivitis, caries
- Malnourishment

Treatment:

- Try to find out cause and treat that
- Sugar-free chwing gum, artificial saliva, cholinergics (because often causing drugs are anti-cholinergic)

Erosive mucositis associated with alendronate

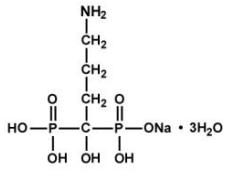
➔ Bisphosphorates

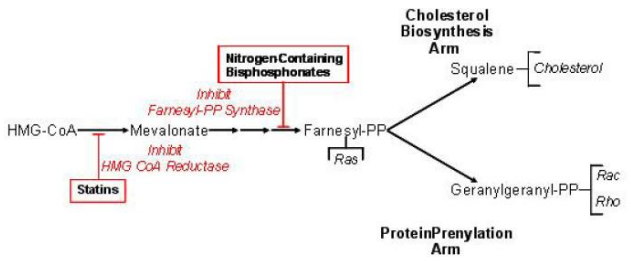
Inhibit enzyme important in cholesterol synthesis and Geranylgeranyl-PP synthesis (important for?????? If inhibited, Protein needing to translocate to plasmamembrane have problems going there) → tendency for apoptosis

Drug Normally don't reach high enough conc. In tissue, only high enough in the bone (where they should go). The bone cells take them up and there they reach high concentration and destroy the bone → chew up matrix of the bone. ?????

When they reach high concentration in other tissues they also destroy.

➔ E.g. women with osteoporosis present with erosive mucositis in the hard palatine with pain and dysphagia
➔ She takes alendronate and always places the tablets behind her tooth prosthesis → caused the erosive mucositis
➔ After she started to swallow tablets immediately → improvement after 2 weeks





Gingival hyperplasia

➔ Overgrowth of gums

Possible Drug causes: Antiepileptics, Immunosuppressive drugs, Calcium antagonists

Risk factors: High serum levels, plaque → TDM, dental hygiene

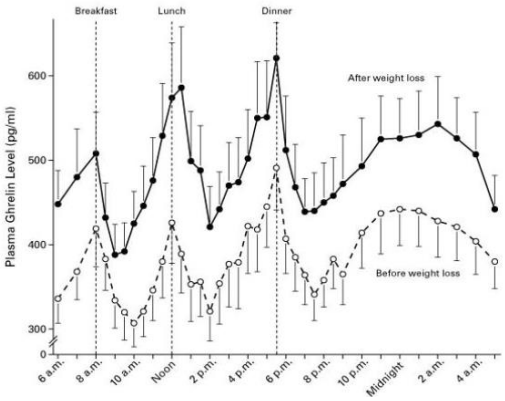
Therapy: Stop medication, surgery in some cases

Regulation of appetite and energy metabolism

- Dorsal vagal complex: important, appetite regulation, also with Hypothalamus and Mesolimbic system(reward for eating → dopamine)! Also Periphery
- Pancreas: Amylin, PP (pancreatic polypeptide) → satiety hormones from the pancreas
- GI: GLP-1, OXM → satiety hromones

➔ Suppress hunger by acting on receptors on Dorsal vagal complex
➔ This also stimulates Hypothalamus. GLP-1 e.g. has also receptors there. Arcuate nucleus: most important nucleus, accumulation of nerves → two regions, one stimulating and the other blocking the appetite. GLP-1 here also stimulates inhibition of appetite (alpha-MSH). Effect on dorsal vagal complex and hyptohalic appetite center and blocks appetite.
➔ Alpha-MSH stimulates secretion of others → inhibition of appetite and stimulation of energy expenditure
➔ Other blockers: from adipose tissue → Leptin → block appetite stimulation and stimulate appetite blocking!
➔ Ghrelin stimulates appetite, produced in stomach, stimulates release of NPY and AgRO. NPY stimulates other hormone secretion → Stimulation of appetite and inhibition of energy expenditure

Plasma concentrations of ghrelin



- 24-h ghrelin plasma profile for 13 adipose patients before and after weight reduction
- Serum concentration of ghrelin increases before eating
- Adipose patients have lower levels

Ghrelin antagonism and weight loss

- Ghrelin needs to be octanoylated in order to bind to the GHSR-1a (growth hormone secretagogue) receptor
- Development of a peptide antagonist inhibiting ghrelin O-acyltransferase (GOAZ, GO-CoA-Tat)
- GO-CoA-Tat inhibits ghrelin acylation by transfected HeLa cells (C) and reduces body weight of mice treated

Appetite regulation - drug targets

- Dopamin stimulates D1 and D2 receptors in N. accumbens → inhibition of appetite
- Dorsal vagal complex contains receptors for GLP1 and other GI hormones → inhibition of appetite
- GLP1 analogous are currently the only centrally acting drugs on the market for weight loss
- 5HT2c receptor agonists (serotonin) stimulate POMC/CART neurons → inhibition of appetite
- Naltrexon inhibitis u-opiod receptors → inhibition of appetite

Problem of GLP-1 : very shot half-life → gets modified to use it as a drug to treat diabetes and obesity.

Drugs affecting appetite and/or energy expenditure

<u>Reduction of appetite</u>

- Liraglutide → GLP-1 analog
- Rimonabant → blocking cannabinoid-1 receptors

<u>Reduce appetite and increase energy expenditure</u>

…

Increase energy expenditure

…

GLP-1 analogues - pharmacology

Two types of drugs allowed to use in Switzerland

- Glucagon-like peptide-1 (GLP-1) is secreted by neuroendocrine cells of the gut after investigation of food
- Acts via activation of GLP-1 receptors in pancreas and hypothalamus
- It stimulates insulin secretion of the beta-cells of the pancreas
- It inhibits glucagon secretion of the alpha-cells of the pancreas and slows down the peristalsis of the stomach
- Reduces appetite
- Liraglutide is a long-acting GLP-1 analogue
- Longer lasting GLP-1 analogues have linger tail → added fatty acid

Liraglutide and weight reduction

- Double-blind, randomized, placebo-controlled study in 3731 obese patients without DM
- Primary endpoint: reduction of body weight
- Secondary endpoints: effect on blood sugar and development of diabetes.
- Adverse reactions: in >=5% of patients: Nausea, Vomiting, Dyspepsia, decreased appetite, Injection-site hematoma

Rimonabant - Pharmacology

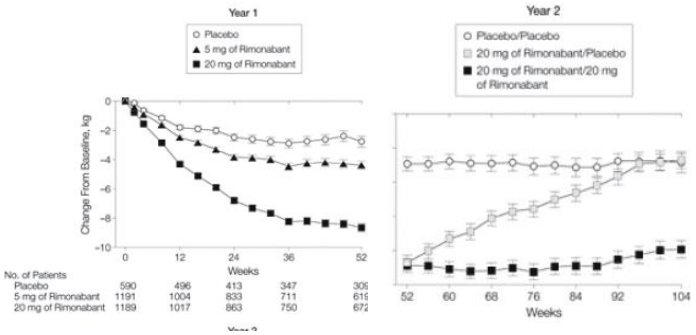
- Inhibitor of CB1-receptors of the endocannabinoid system
- Decreased Food intake

Kidneys and elimination

- Bioavailability 70%
- Half-life 4-6 days
- Protein binding 99%
- Q0 0.99, elimination 5% renally and 95% biliary/feces (50% unchanged)
- Metabolism via CYP3A4 and amidohydrolases

<u>Weight reducing effect:</u>

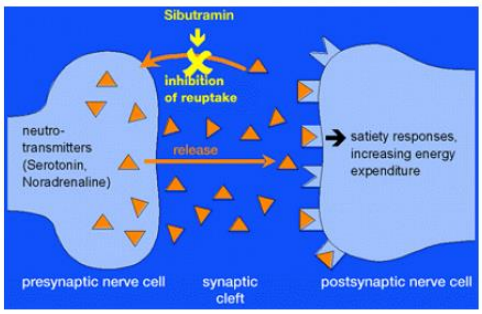
- Study in 3045 adipose patients (BMI >30), Placebo plus diet
- Primary endpoint: change in body weight after 1 year
- Adverse reactions: depressed mood, anxiety



Fluoxetine

- Fluoxetine inhibits reuptake of serotonin specifically
- It was first studied as a weight reduction agent
- Antidepressant activity shown later

Fluoxetine increases body temperature. Not sure why. This is energy consuming, so if one doesn't eat more, one loses weight.



Sibutramin

- Inhibits reuptake of noradrenaline and serotonin
- Decreases appetite and increases feeling of satiety
- Increases thermogenesis and hear rate → increasing energy expenditure
- The effect on body weight has been shown in large controlled studies
- Has been taken from the market in 2010 due to safety concerns (cardiovascular safety)

Effect of sibutramine on body weight

- Randomized, double-blind, placebo-controlled multicenter study
- Primary endpoint: number/fraction of patients keeping >80% of the body weight loss obtained after 6 months

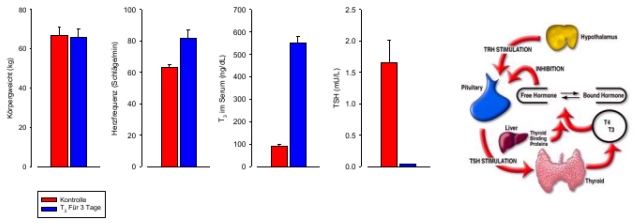
Cardiovascular effects of sibutramine

- Obese patients >55 years-old with pre-existing cardiovascular diseases or with T2D
- Primary endpoint: non-fatal myocardial infarction, stroke, cardiovascular death.

Effects and mode of action of T3 and T4

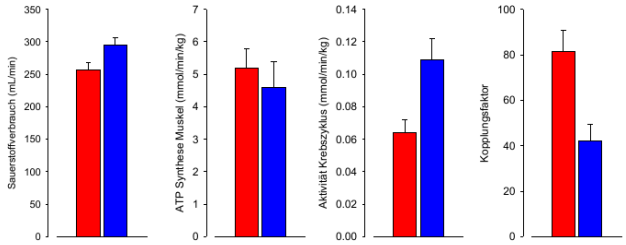
- T4 and T3 are hormones synthesized by the thyroid gland
- They are responsible for normal body growth and for the development of energy metabolism
- At high (supraphysiological) doses, they are associated with a decrease in body weight

Effect of T3 on body composition and function



- 6 healthy volunteers were treated with 100µg T3 every 12h for 3 days

Coupling of oxidative phosphorylation



- 6 healthy volunteers were treated with 100µg T3 every 12h for 3 days

Uncoupling of oxidative phosphorylation

- Under normal conditions, protons flow across F1F0ATPase and produce ATP
- Uncoupling proteins (UCPs) are proton channels bypassing the ATPase
- UCP expression leads to cellular loss of ATP and heat production

Hormones & neurotransmitters affecting body weight

Neurotransmitter or hormone	Effect on body weight	Drugs involved
Dopamin	Reduces appetitie (stimulation of D_1 and D_2 R in n. accumbens)	Bupropion, duloxetin
Serotonin	Reduces appetite by stimulation of $5HT_{2c}$ R and craving for carbohydrates → body weight ↓	SSRI, Lorcaserin
Noradrenaline	Appetite ↓ → body weight ↓ Basal metabolic rate ↑	Amphetamin, ecstasy, SNRI, cocaine
GABA	Overexpression of GAT1 (GABA transport in presynaptic neuron) is associated with obesity in mice	Topiramate (GABA-ergic) decreases body weight in humans
Endocannabinoids	Appetite increased via CB-1R → body weight ↑	Rimonabant inhibits CB-1R → body weight ↓
GLP-1	GLP-1 reduces appetite and increases satiety → body weight ↓	GLP-1 analogues are used to treat diabetes and obesity
Calcium	Calcium signalling reduces appetite → body weight ↓	Cinnarizin, flunarizin and valproate block Ca-channels → body weight ↑
Histamin	H_1-receptor stimulation decreases appetite → body weight ↓	H_1-blockers (pizotifen), cyclic antidepressants, typical neuroleptics → body weight ↑
Thyroxin	Thermogenesis ↑→ basal metabolic rate ↑ → body weight ↓	T3 and T4 (thyroxin)

Orlistat (Xenical®)

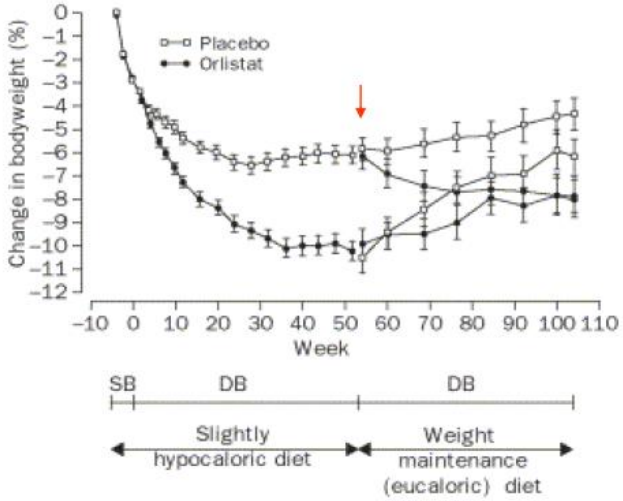
- Lipase inhibitor: covalent binding on serine residue of lipase from stomach and pancreas
- Triglycerides are not cleaves → fecal excretion
- Given when BMI >30, or BMI >28 with cardiac risk factors
- <3% absorbed, 97% fecal elimination

Clinical effects:

- First year (combined with hypocaloric nutrition): 9% body weight reduction (Placebo 5.6%)
- Second year: Body weight reduction 6.7% (Placebo 3.7%), 20% of the patients >10% body weight loss (Placebo 8%)

European Multicenter Orlistat study:

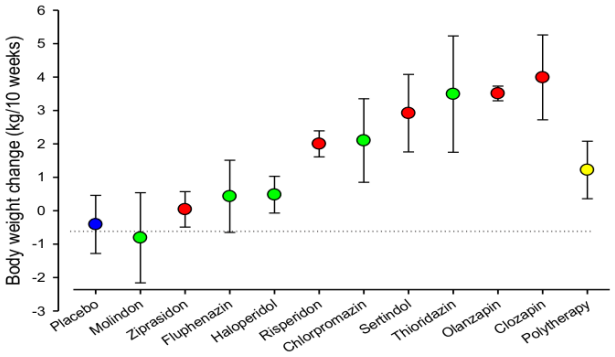
- 743 patients with BMI 28-43 kg/m^2
- Adverse events: Fatty/oily stool, increased defecation, Flatus with discharge, Faecal incontinence, Oily evacuation
- Low Vitamin A, Vitamin D, Vitamin E



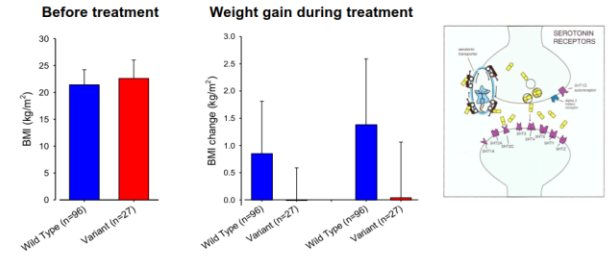
Unintentional body weight gain by psychoactive drugs

- Drugs: antidepressant, Neurileptics, H1-Receptor-blockers
- Mechanisms: H1-receptor-blockage, Serotonin receptor blockage, Block of calcium channels
- Clinical findings: increased intake of Carbohydrates. Body weight gain up to 3-5 kg per 1-2 years of drug therapy
- Prevention and therapy: Discuss problem, no carbohydrate-containing drinks in case of xerostomia. Prefer SSRI or SNRI

Neuroleptics and body weight

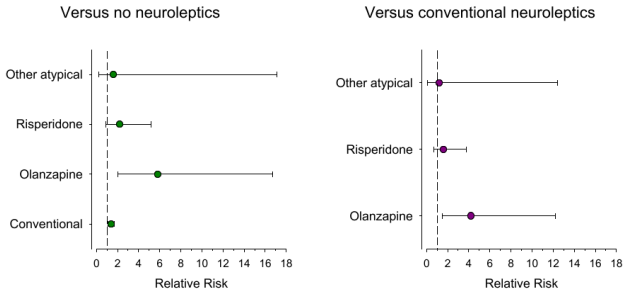


Body weight gain by atypical neuroleptics – risk factor



Wild type: normal $5HT_{2C}$ receptor Variant: -759C/T Polymorphism

Risk for type 2 diabetes



Unintentional weight gain by peripherally acting drugs

- Sulfonylureas, insulin: trophic action of insulin
- PPAR-γ agonists: fat production and water retention
- Testosterone: increase of muscle mass in case of hypogonadism
- Glucocorticoids: local accumulation of fat
- Mineralocorticoids: water retention
- Estrogens: water retention