OBESITA' E ORMONI

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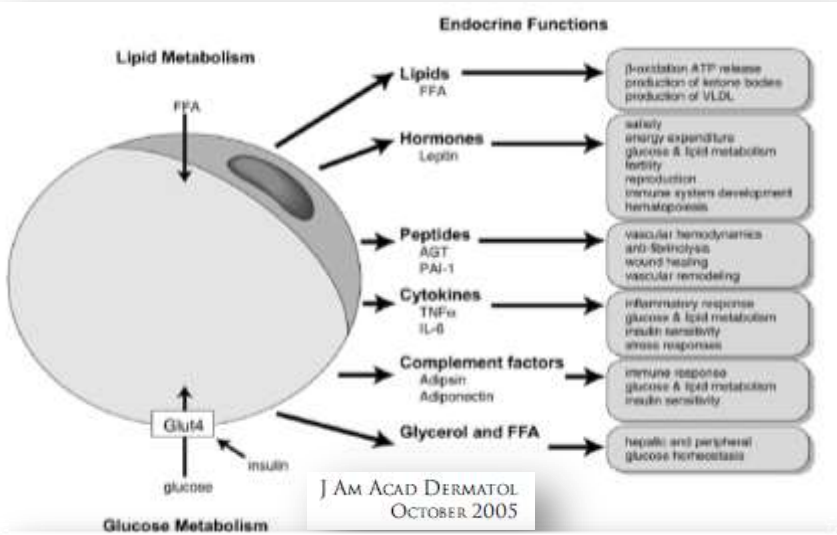
QUALI ORMONI?

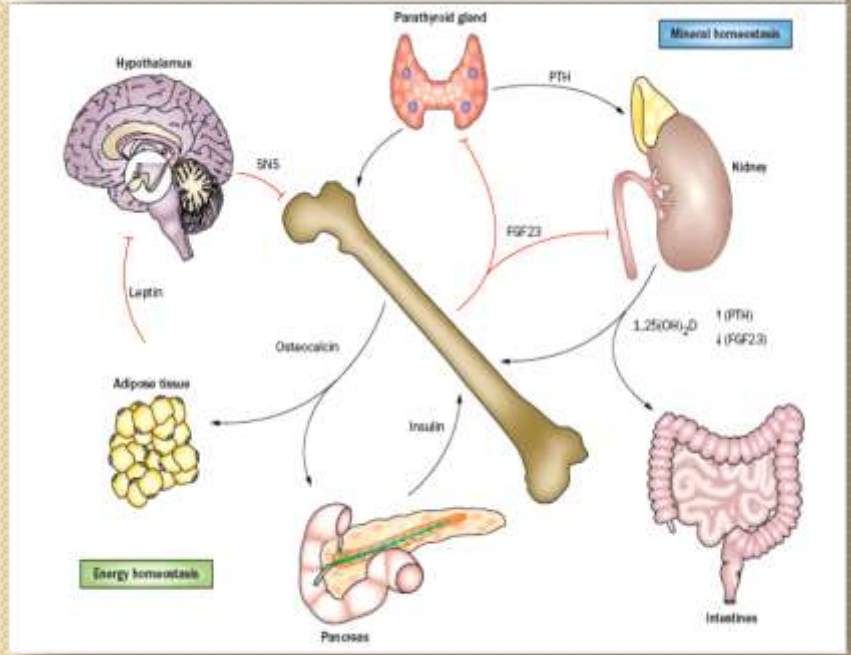
ENDOCRINE FUNCTIONS OF ADIPOCYTE



J Am Acad Dermatol
October 2005

The skeleton as an endocrine organ

Douglas J. DiGirolamo, Thomas L. Clemens and Stavroula Kousteni



THE METABOLIC HORMONE FGF21

Stimulus (transcriptional inducer)	Tissue source of FGF	Target tissue	Effect
Starvation (PPARα, CREB-H)	Liver	CNS	↑ Hepatic fatty acid oxidation, ketogenesis and gluconeogenesis ↑ Growth hormone resistance ↓ Ovulation ↓ Wheel-running activity
Fasting/refeeding, overfeeding (PPARα, PPARγ)	Liver WAT	BAT WAT	↑ Glucose uptake and fatty acid storage
Cold (ATF2)	BAT WAT	BAT WAT	↑ Thermogenesis ↑ Browning of WAT
Ketogenic, low amino acid/protein diets (PPARα, ATF4)	Liver	CNS BAT	↑ Hepatic fatty acid oxidation and ketogenesis ↑ Thermogenesis and weight loss
Mitochondrial dysfunction, pancreatitis (ATF4)	Skeletal muscle Pancreas	N/K[a]	N/K
Pharmacology		CNS BAT WAT	*Beneficial* ↑ Thermogenesis and weight loss ↑ Browning of WAT ↑ Glucose uptake ↑ Insulin sensitivity ↓ Blood triglyceride levels ↓ Blood cholesterol levels ↑ Lifespan
			Adverse ↑ Bone loss ↑ Glucocorticoids

Cell Metabolism 17, May 7, 2013 ©2013

Trends in Endocrinology and Metabolism January 2015, Vol. 26, No. 1

Pleiotropic Roles of Bile Acids in Metabolism

Bile Acids Affect the Microbiome and Vice Versa

Farnesoid X Receptor, the First Bile Acid-Responsive Receptor

FXR Activation Modulates Several Distinct Metabolic Pathways

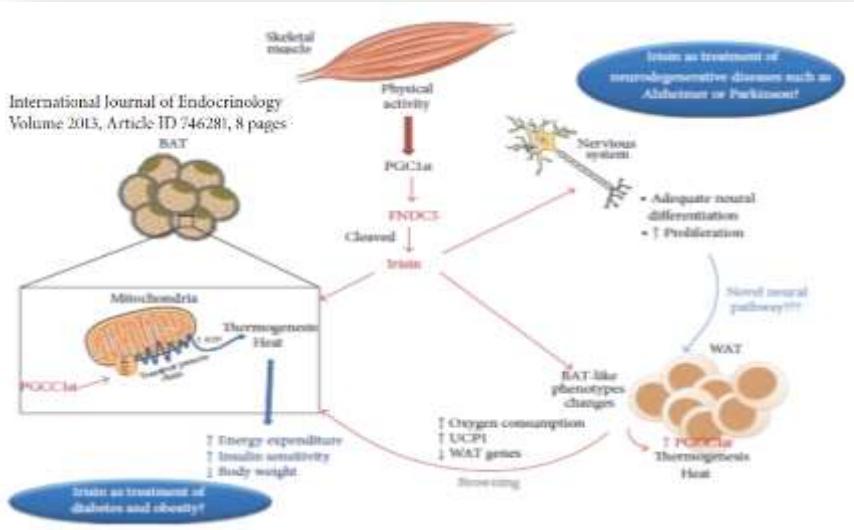
- *(1) Lipoprotein Metabolism*
- *(2) Glucose Metabolism*
- *(3) Cholestasis, Inflammation, and Hepatoprotection*

Bile Acids Activate the Pregnane X Receptor (PXR) and the Vitamin D Receptor (VDR)

Bile Acid-Responsive G Protein-Coupled Receptor, TGR5

- *(1) TGR5 and the Immune System*
- *(2) TGR5 and Energy Metabolism*
- *(3) TGR5 and Glucose Metabolism*

Skeletal muscle



The gut–brain axis in obesity

Origin, effects, receptors and altered levels of gastrointestinal hormones after Roux-en-Y gastric bypass (RYGB) and in obese subjects.

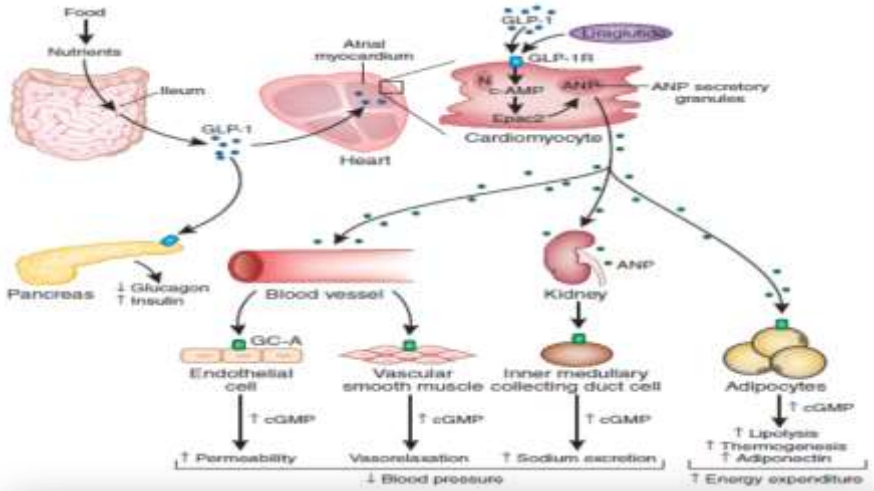
Gastrointestinal hormones	Major secretion site	Effects on food intake	Receptor	Other effects	Serum levels	
					After RYGB	In obese subjects
Ghrelin	Stomach	↑	GHS-R	Growth hormone secretion ↑ Gastric motility ↑ Vasodilatation ↑ Cardiac contractility ↑	Unclear	↓
Glucagon-like peptide 1	Ileum (L cell)	↓	GLP-1R	Insulin secretion ↑ β-cell proliferation ↑ β-cell gene expression ↑ Gastric acid secretion ↓ Gastric emptying ↓ Apoptosis ↓	↑	↓
Peptide YY 3–36	Ileum (L cell)	↓	Y2-R	Gastric acid secretion ↓ Pancreatic and intestinal secretion ↓ Gastrointestinal motility ↓	↑	↓
Gastric inhibitory polypeptide	Duodenum and jejunum (K-cell)	Unknown	GIP-R	Fat deposition ↑ Triglyceride accumulation ↑ Insulin secretion ↑ β-cell proliferation ↑ Apoptosis ↓ Bone formation ↑	↓ (Diabetics)	↑
Cholecystokinin	Duodenum and jejunum (I-cell)	↓	CCK 1, 2	Gastric emptying ↓ Pancreatic secretion ↑ Gallbladder contraction ↑	No change	Unclear
Pancreatic polypeptide	Pancreas (PP-cell)	↓	Y4, Y5	Gastric emptying ↓ Leptin levels (white adipose tissue) ↓	No change	↓
Oxyntomodulin	Ileum (L cell)	↓	GLP-1R	Gastric acid secretion ↓ Gastric emptying ↓	↑	Unknown
Glucagon	Pancreas (α-cell)	↓	GCGR	Blood glucose ↑ Energy expenditure ↑	↑	Unclear
Amylin	Pancreas (β-cell)	↓	AMY1–3	Gastric emptying ↓ Gastric acid secretion ↓	↓	↑

Best Practice & Research Clinical Gastroenterology 28 (2014) 559–571

A gut-heart connection in cardiometabolic regulation

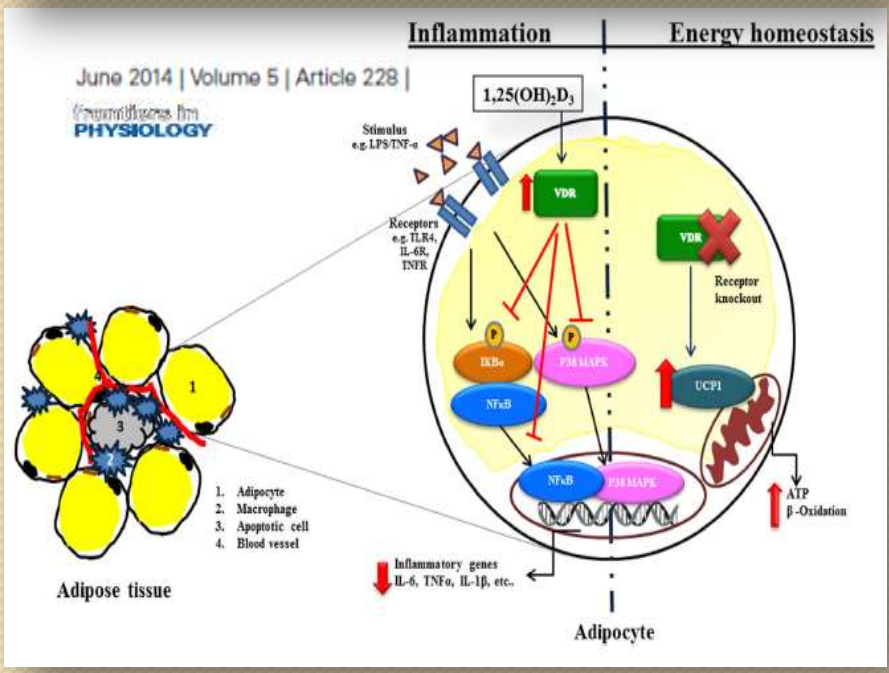
VOLUME 19 | NUMBER 5 | MAY 2013 NATURE MEDICINE

Alessia Buglioni & John C Burnett Jr



Vitamin D and adipose tissue—more than storage

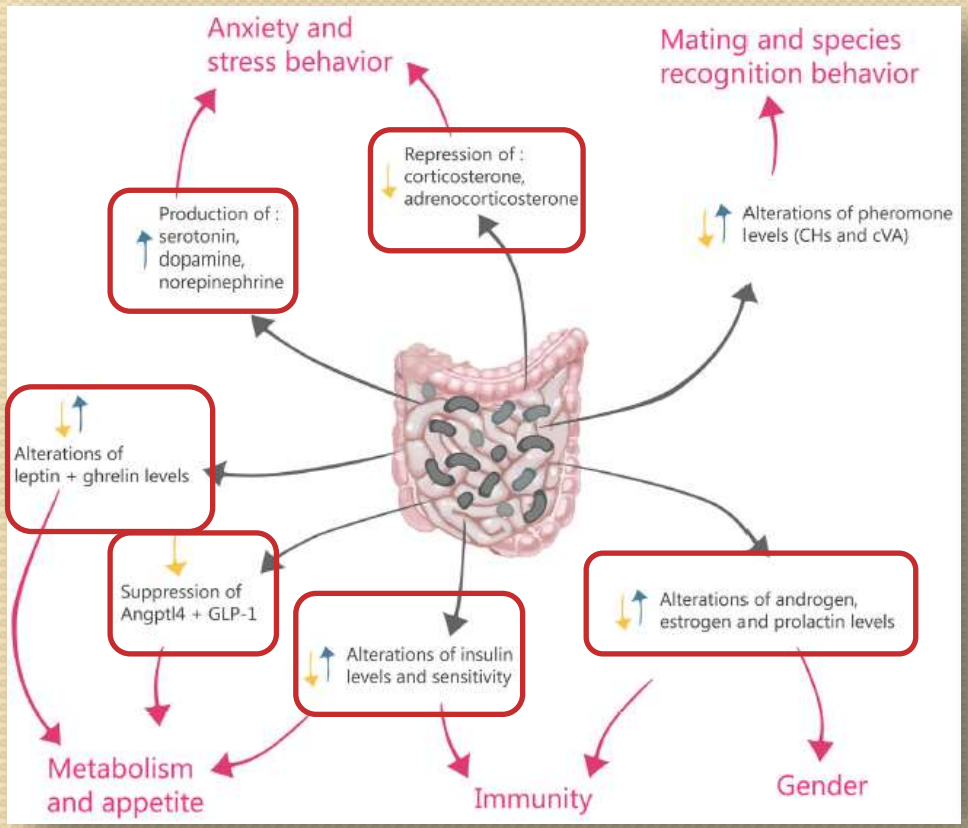
Shivaprakash J. Mutt[1,2], Elina Hyppönen[3,4,5], Juha Saarnio[6], Marjo-Riitta Järvelin[2,7,8,9] and Karl-Heinz Herzig[1,2,10]**



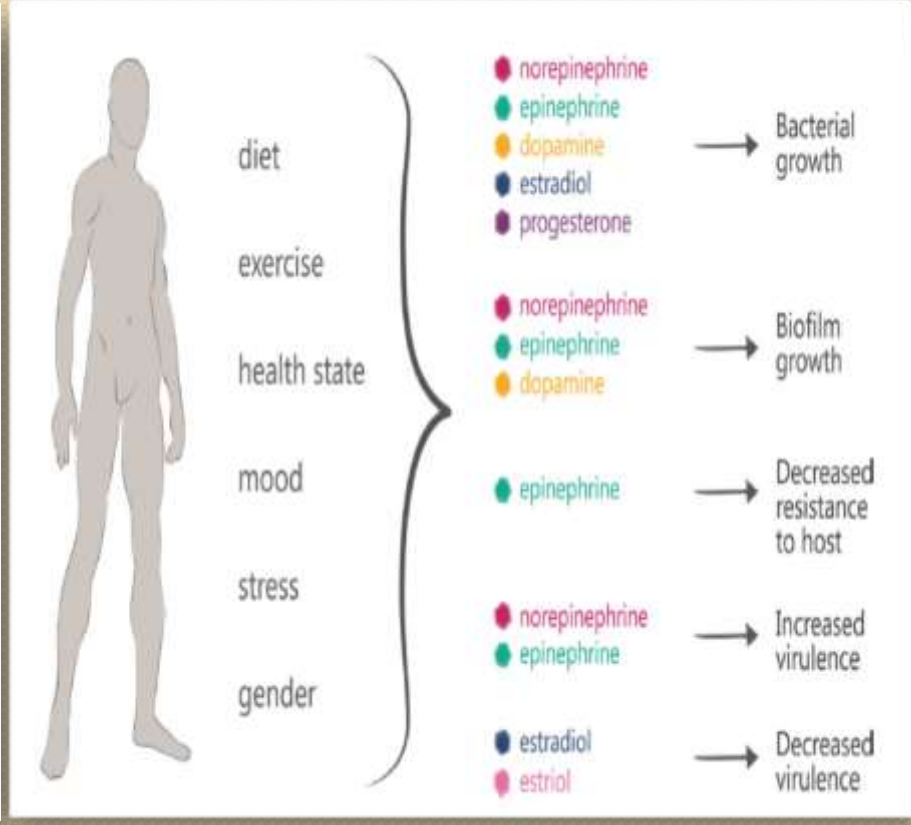
Microbial endocrinology: the interplay between the microbiota and the endocrine system

Hadar Neuman[1], Justine W. Debelius[2], Rob Knight[2,$] and Omry Koren[1,*]

FEMS Microbiology Reviews Advance Access published February 19, 2015



The effects of the gut microbiota on the host via hormones. Gray arrows and text refer to the effects of the gut microbiota on various hormone levels. Pink arrows and text refer to the effects of these hormonal alterations on host outcomes (e.g. behavior).

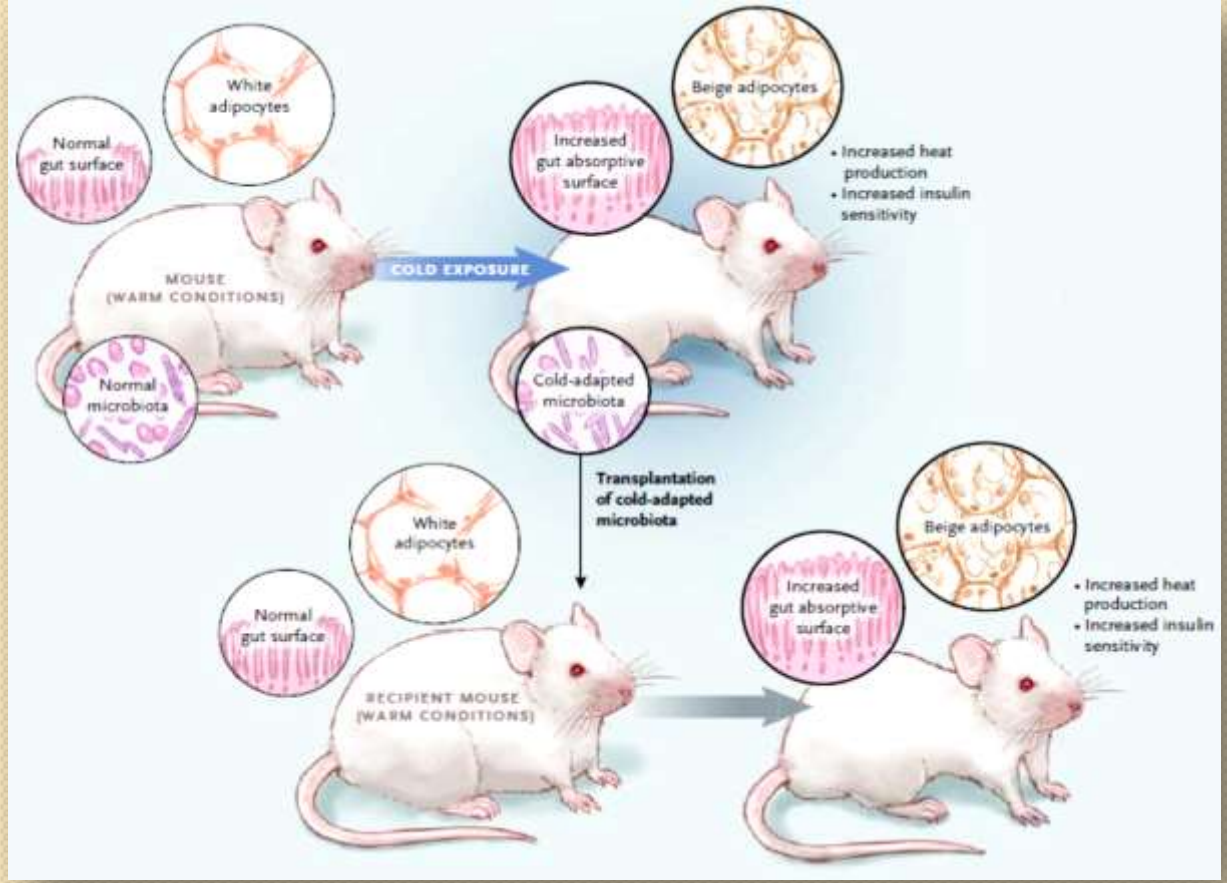


Host effects on the microbiota. A variety of host factors (such as diet, exercise, mood, general health state, stress and gender) lead to alterations in hormonal levels, which in turn lead to a variety of effects on the microbiota (including growth, virulence and resistance).

Burning Fat by Bugging the System

N ENGL J MED 374;9 NEJM.ORG MARCH 3, 2016

Evan D. Rosen, M.D., Ph.D.



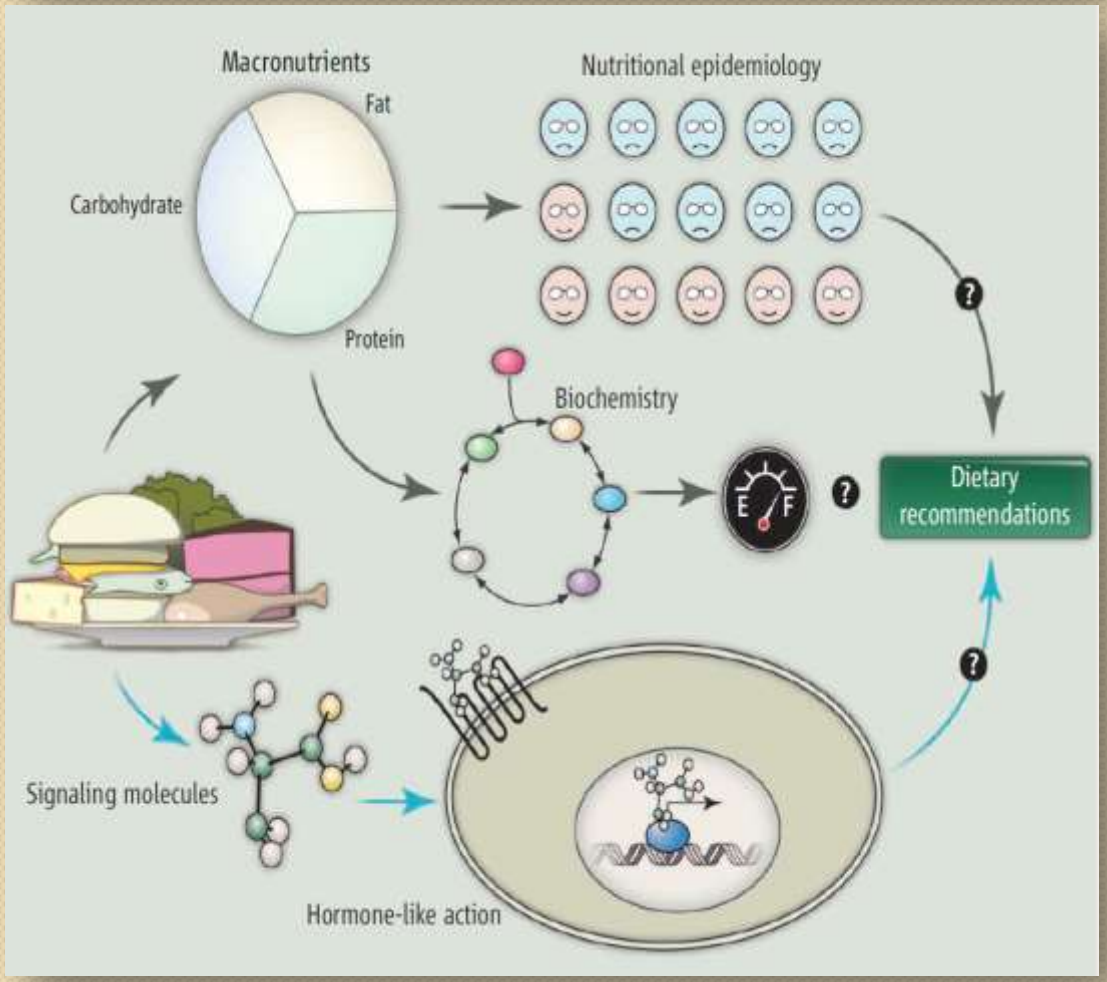
Cold exposure causes browning of white fat in mice, with increased insulin sensitivity and heat production in addition to weight loss. Chevalier and colleagues reported that cold exposure also changes the composition of the gut microbiota and causes a large increase in the absorptive surface of the gut. Transplantation of the cold-adapted microbiota from cold-exposed mice is sufficient to promotebrowning, enhanced insulin sensitivity, and increased intestinal surface area in warm recipient mice. A companion article from the same group suggests that antibiotic therapy, which depletes the gut microbiota, also induces browning and weight loss.

Chevalier C, Stojanović O, Colin DJ, et al. Gut microbiota orchestrates energy homeostasis during cold. Cell 2015; 163: 1360-74. Suárez-Zamorano N, Fabbiano S, Chevalier C, et al. Microbiota depletion promotes browning of white adipose tissue and reduces obesity. Nat Med 2015; 21: 1497-501.

Food as a Hormone

SCIENCE VOL 339 22 FEBRUARY 2013

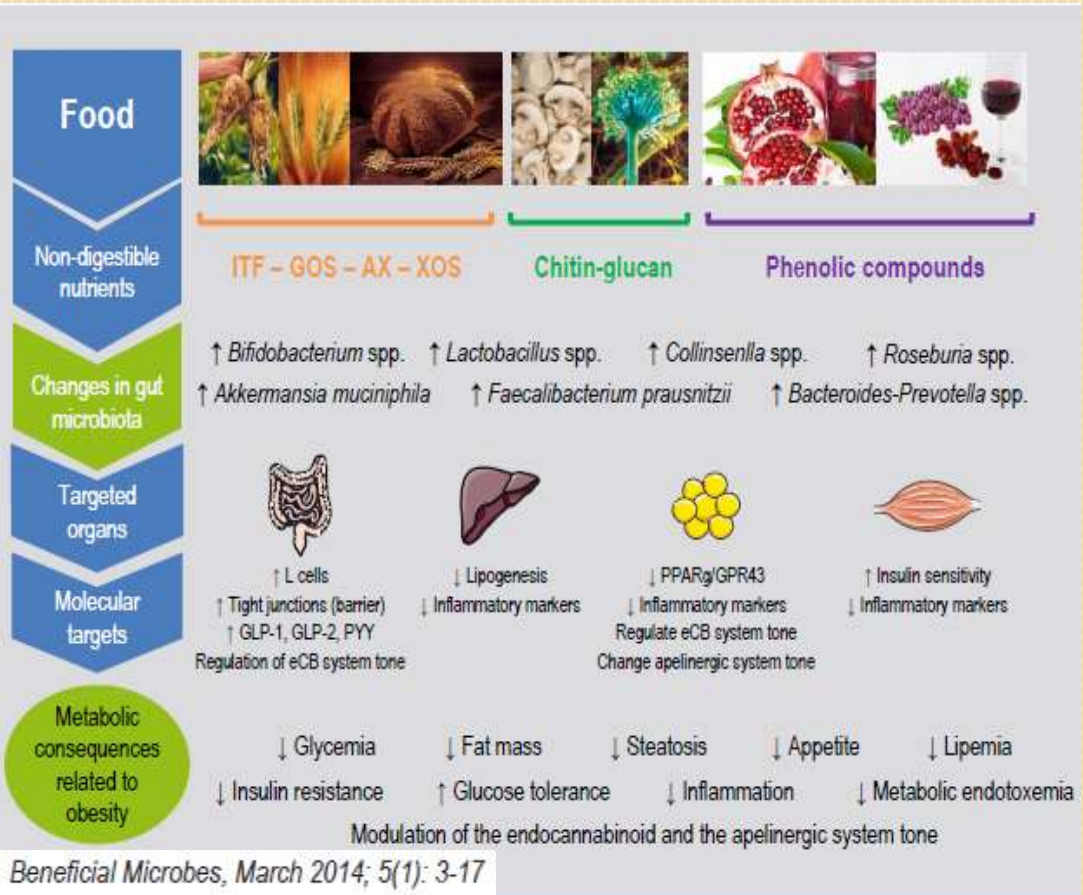
Karen K. Ryan and Randy J. Seeley



Nutritional epidemiology and biochemical approaches, focusing primarily on the relationship between macronutrient consumption and metabolic outcomes, **have not provided a translatable scientific basis to recommend diets that improve metabolic health for a broad range of people.**

Alternatively, understanding our diets as a collection of signaling molecules, having hormone-like actions via cell surface and nuclear receptor signaling, may provide new insights into the relationship between what we eat and metabolic disease. Moreover, this framework may eventually allow us to make dietary recommendations from the bottom up—based on the ability of specific foods to alter relevant signaling pathways.

EFFECT OF NON-DIGESTIBLE NUTRIENTS WITH PREBIOTIC PROPERTIES ON HOST PATHOPHYSIOLOGY RELATED TO OBESITY.



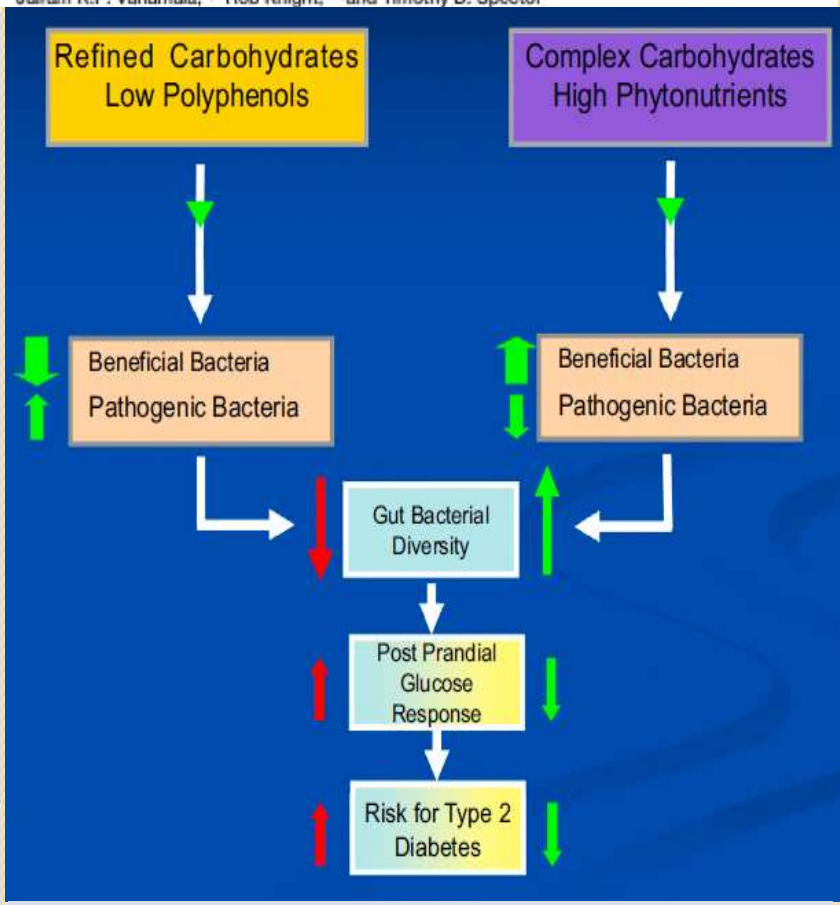
Beneficial Microbes, March 2014; 5(1): 3-17

In intervention studies in animals and humans, non-digestible nutrients with prebiotic properties, such as inulin-type fructans, galacto-oligosaccharides, arabinoxylan and arabinoxylan oligosaccharides derived from wheat, fungal chitin-glucan and several phenolic compounds present in pomegranate or grapes, have been shown to change the gut microbiota composition by favouring bacteria that confer health benefits to the host. **Prebiotics reinforce the gut barrier and promote gut hormones that control appetite, glucose homeostasis and systemic inflammation**. The prebiotic approach also counteracts hepatic steatosis (lipogenesis), hepatic insulin resistance, and adiposity by modifying gene expression at the tissue level. LPS = lipopolysaccharide, APJ = apelin receptor, eCB = endocannabinoid.

Can Your Microbiome Tell You What to Eat?

Cell Metabolism 22, December 1, 2015

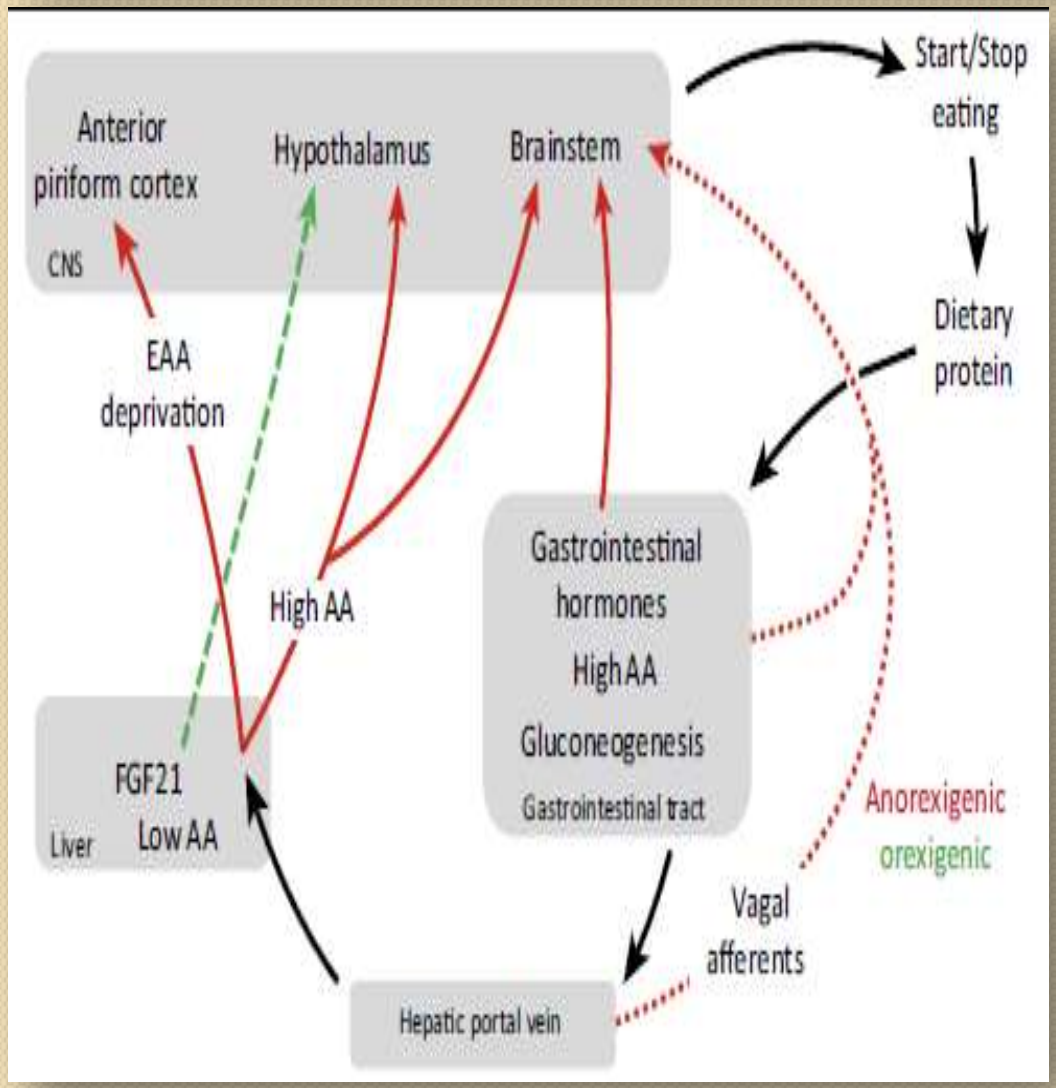
Jairam K.P. Vanamala,[1,2] Rob Knight,[3,*] and Timothy D. Spector[4]



Modulation of Gut Bacterial Diversity with Food Approach to Prevent Type 2 Diabetes .
Food patterns that provide both complex carbohydrates and greater levels of phytonutrients such as polyphenols can increase gut bacterial diversity and reduce postprandial glucose response. Such communities may protect against type 2 diabetes. The personalized nutrition approach. may help us understand which of these types of features will apply to everyone and which will need to be applied to specific individuals

Protein-dependent regulation of feeding and metabolism

Christopher D. Morrison and Thomas Laeger



The mechanisms driving macronutrient-specific food intake are poorly defined.

A large number of behavioral studies indicate that both the **quantity and quality of dietary protein can markedly influence food intake and metabolism**, and that **dietary protein intake may be prioritized over energy intake.**

Dietary protein within the gastrointestinal tract activates both endocrine and vagal signals, which act in a **primarily anorexigenic** fashion in the hypothalamus and brainstem.

Absorbed amino acids are delivered to the liver via the hepatic portal vein. **Reduced amino acid supply to the liver increases hepatic FGF21 secretion**, which acts in the brain to **increase both food intake and energy expenditure**, likely via effects in the hypothalamus.

Amino acids are transported out of the liver and into the general circulation, and **circulating amino acids can act in both the hypothalamus and brainstem to suppress food intake**.

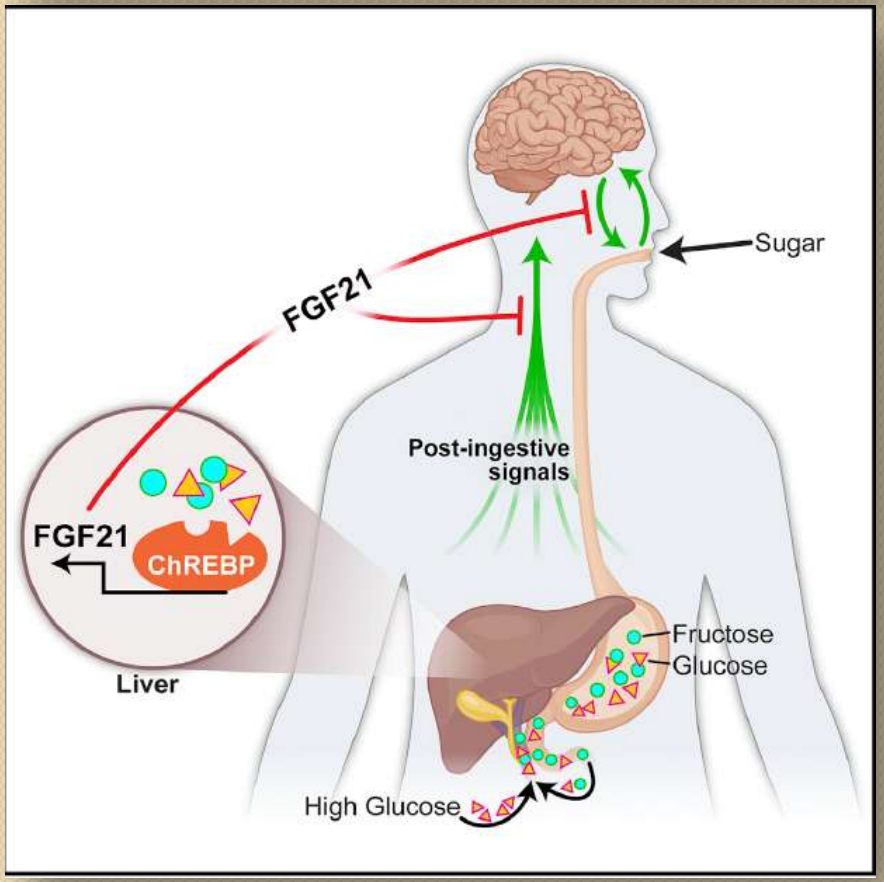
Finally, imbalances in dietary or circulating amino acid concentrations are **detected in the anterior piriform cortex (APC),** with activation of the APC reducing food intake.

These various mechanisms allow animals to detect and adaptively respond to diets that are high, low, or imbalanced in amino acid content.

Trends in Endocrinology and Metabolism May 2015, Vol. 26, No. 5

FGF21 Mediates Endocrine Control of Simple Sugar Intake and Sweet Taste Preference by the Liver

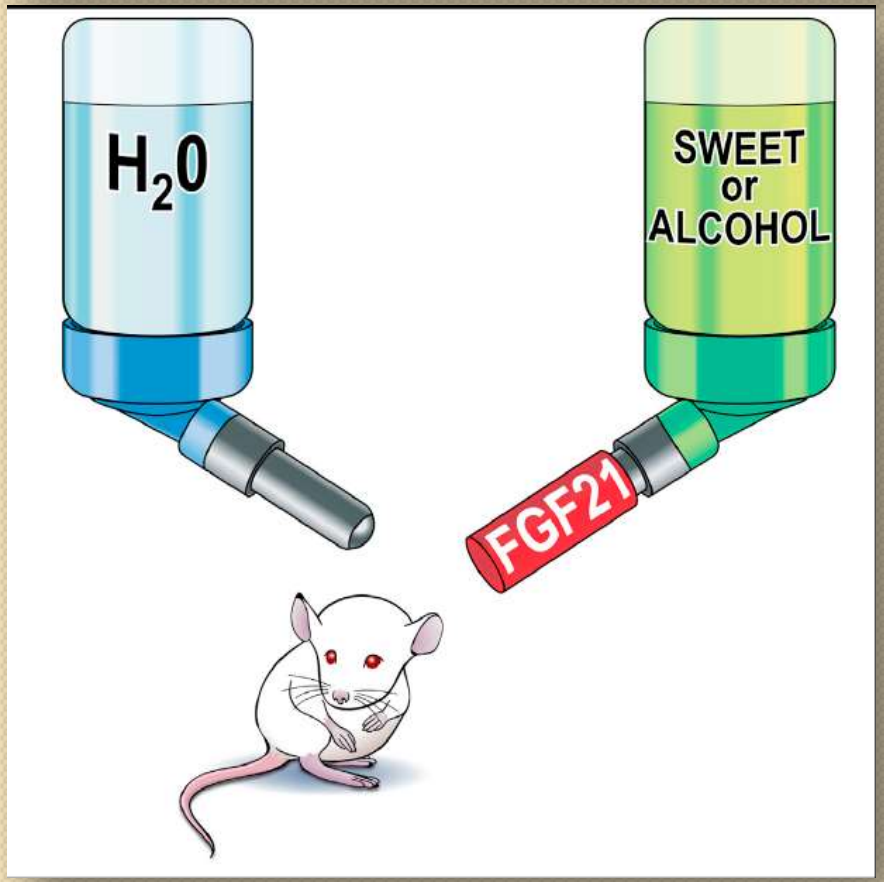
von Holstein-Rathlou et al., 2016, Cell Metabolism *23*, 335–343



Cravings for sweet foods are common, yet the mechanisms that influence the ''sweet tooth'' are not well-defined. In response to carbohydrate intake, the liver produces FGF21 to selectively suppress sugar appetite by acting on the PVN. **The liver functions as a post-ingestive regulator of macronutrient preference**: Carbohydrate activates hepatic ChREBP increasing production of FGF21 from the liver and FGF21 acts on the PVN to suppress sugar intake.

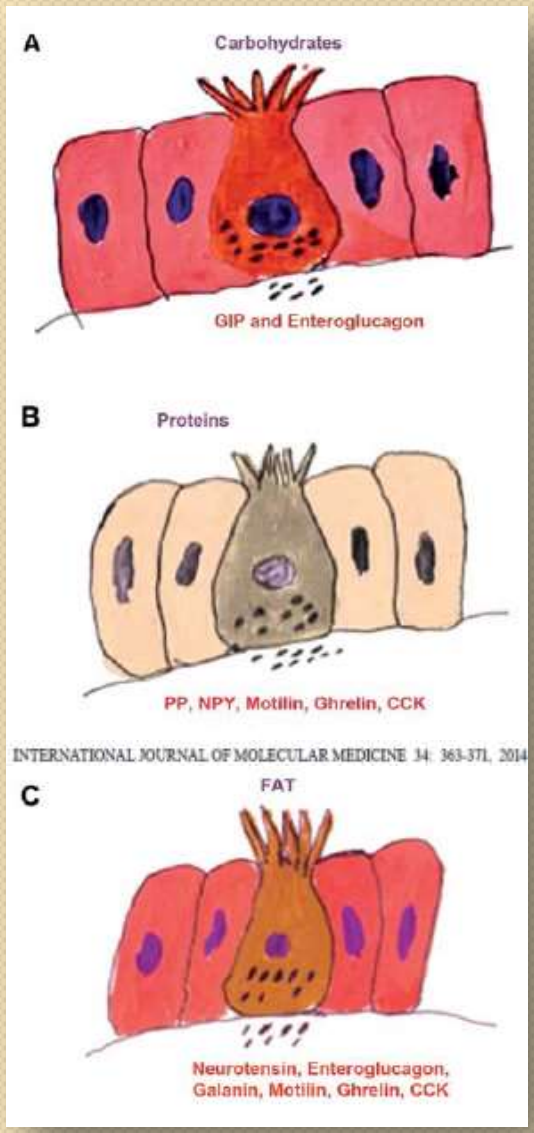
FGF21 Regulates Sweet and Alcohol Preference

Talukdar et al., 2016, Cell Metabolism *23*, 344–349



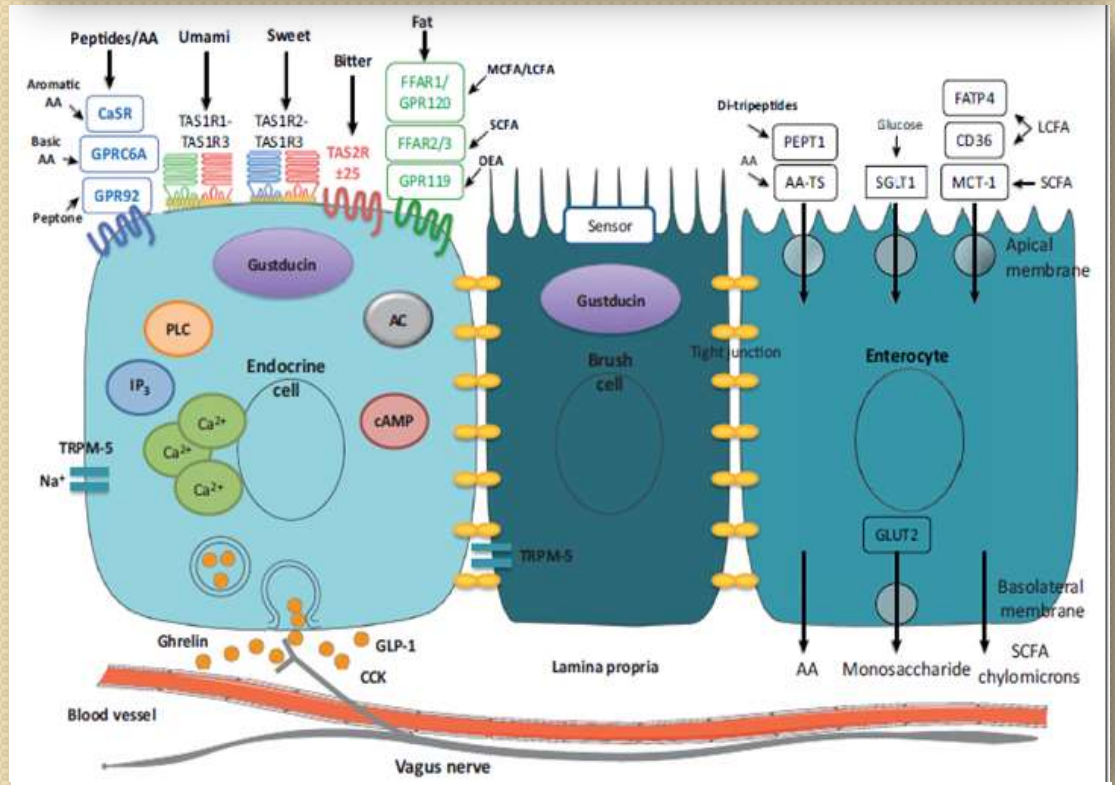
FGF21 has well-established beneficial metabolic effects. FGF21 seems also to be able to suppresses sweet and alcohol preference in mice, and sweet preference in monkeys, by acting on the CNS. These effects are associated with decreased dopamine, a key neurotransmitter used in reward pathways.

INTERACTION BETWEEN INGESTED NUTRIENTS AND GUT ENDOCRINE CELLS



Nutrient sensing in the gut: new roads to therapeutics?

Trends in Endocrinology and Metabolism February 2013, Vol. 24, No. 2

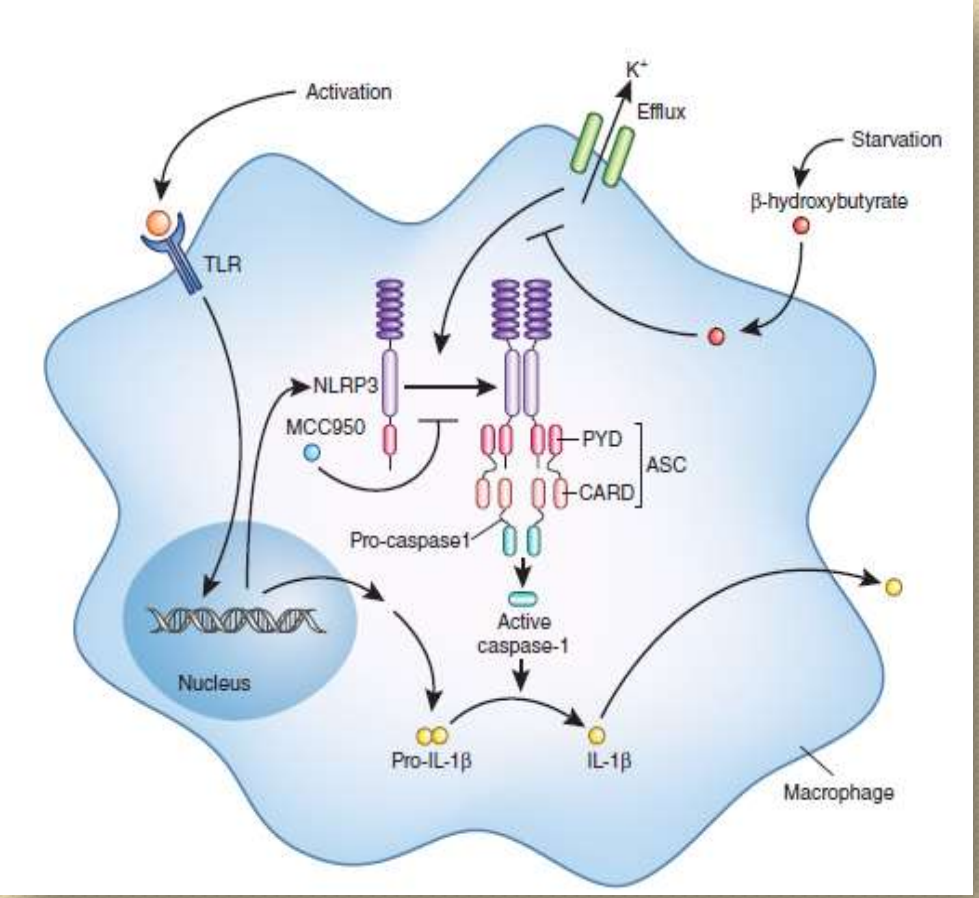


Simplified model of the pathways involved in chemosensory signaling in the gastrointestinal mucosa.

Nutrients (sweet, bitter, fat, amino acids) are sensed by different G protein-coupled receptors (GPCRs) as well as transporters in several cell types (endocrine cell, brush cell, enterocyte) of the epithelial lining that cross-regulate each others expression. **The GPCRs induce, via distinct G proteins (gustducin), the release of second messengers that lead to the release of gut peptides which can communicate directly, via the bloodstream, or indirectly, via the vagal nerve, with the hypothalamus to control food intake**. AA, amino acid; AA-TS, amino acid transport systems

The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease

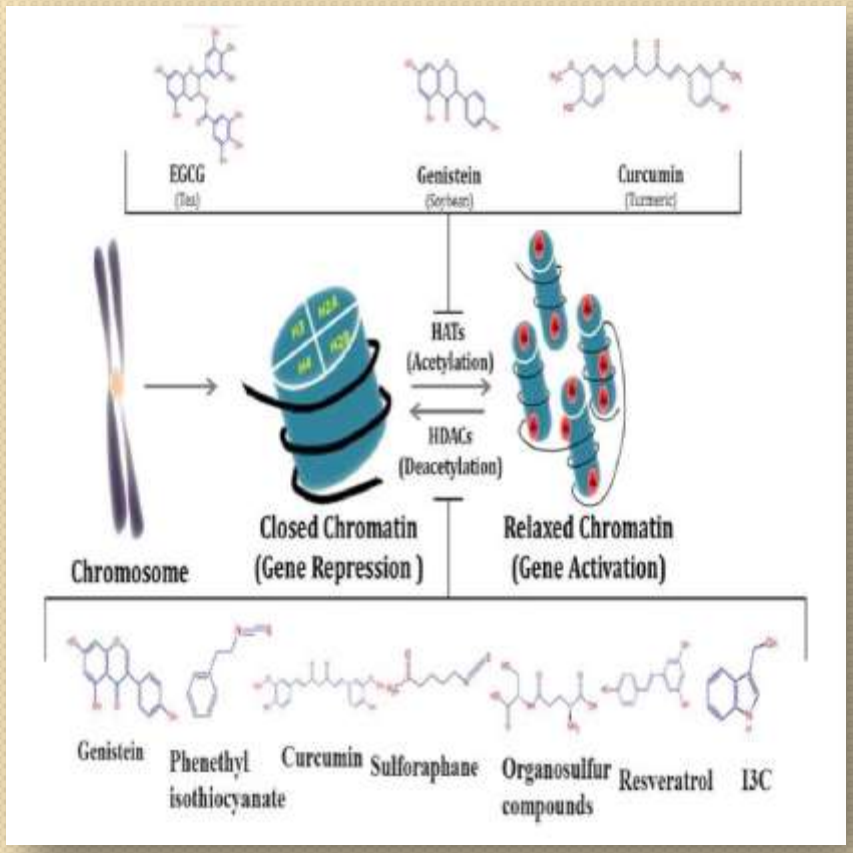
The ketone bodies β-hydroxybutyrate (BHB) and acetoacetate (AcAc) support mammalian survival during states of energy deficit by serving as alternative sources of ATP[1]. BHB levels are elevated by starvation, caloric restriction, high-intensity exercise, or the low-carbohydrate ketogenic diet[2]. Prolonged fasting reduces inflammation; however, the impact that ketones and other alternative metabolic fuels produced during energy deficits have on the innate immune response is unknown[2–6]. We report that BHB, but neither AcAc nor the structurally related short-chain fatty acids butyrate and acetate, suppresses activation of the NLRP3 inflammasome in response to urate crystals, ATP and lipotoxic fatty acids. BHB did not inhibit caspase-1 activation



In response to activation of innate immune receptors by stimuli such as microbial ligands, transcription of pro-inflammatory genes including those encoding NLRP3 and pro-IL1β is induced. Transcription of proinflammatory genes primes components of the NLRP3 inflammasome complex. Upon stimulation with a variety of endogenous and exogenous signals, a common characteristic of which is the induction of K+ efflux from the activated cell, the NLRP3 inflammasome assembles as a complex with ASC and pro-caspase-1. As a consequence, caspase-1 cleaves pro-IL-1β into its active form for secretion. **β-hydroxybutyrate inhibits K+ efflux and prevents NLRP3 activation**.

The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: A review

Gene 562 (2015) 8–15



Inhibition of histone acetylation is done mostly by **phytochemicals** such as EGCG, genistein and curcumin through **inactivation of hystone acetyl transferase**. Inhibition of deacetylation of relaxed chromatine is also accomplished by some other phytochemicals, named as sulforaphane, curcumin, genistein, organosulfur compounds, resveratrol by means of **inactivation of histone deacetylase enzymes.**

OBESI: GOLOSI O INQUINATI?

Sale l'enfasi e l'interesse per la teoria secondo la quale, alla base dell'obesità, ci siano fenomeni di disregolazione metabolica legati all'inquinamento.

Figura 1. Fotografia di topi di 4 mesi che mostra la differenza nel peso corporeo tra un topo di controllo (destra) e un topo trattato in epoca neonatale con dietilstilbestrolo (destra). Newbold R.R., Reprod Toxicol 2007; 23(3): 290-296.

L'obesità, definibile anche come eccesso di tessuto adiposo (>25% negli uomini e >30% nelle donne), rappresenta una emergenza sanitaria a livello internazionale. Secondo un'indagine dell'ISTAT, gli adulti obesi in Italia sono circa 4,7 milioni, il 9% in più rispetto al 1999-2000. Dei 120 mila individui intervistati, il 34,2% ha dichiarato di essere in sovrappeso e il 9,8% di essere obeso, sulla base del calcolo dell'indice di massa corporea (BMI). Il Progetto Cuore parla di stime più alte: risultano in sovrappeso il 50% degli uomini (obesi il 18%) e il 34% delle donne (obese il 22%), contro, rispettivamente il 42% degli uomini (9% obesi) e il 34% (22% obese) delle donne dell'indagine ISTAT (Tabella 1). L'obesità, peraltro, quando è prevalentemente viscerale caratterizza la cosiddetta sindrome metabolica, si associa ad insulino-resistenza, dislipidemia, ipertensione, infiammazione ed è un fattore di rischio per molte malattie quali cardiopatie, ipertensione, ictus, malattie respiratorie, artrite e alcuni tipi di tumore. La cronica alterazione dell'equilibrio energetico, introito calorico vs dispendio, è il meccanismo patogenetico essenziale che conduce all'obesità e di conseguenza si pensa allo stile di vita modificato, tipico delle società industrializzate, come causa principale dell'epidemia: l'aumentato e modificato introito calorico, a base di cibi ricchi di grassi, zuccheri ed amidi raffinati, associato ad una progressiva riduzione dell'attività fisica, interagendo con il cosiddetto "genotipo risparmiatore", promuoverebbero l'obesità. In letteratura, però, non esistono dati inequivocabili a suffragio dell'assunto che le persone obese mangino di più e diversamente dalle magre. Nello studio NHANES I 1971-1975, ad esempio, è emerso che "l'introito calorico globale e l'introito calorico aggiustato per attività fisica ed età non è maggiore nei soggetti obesi rispetto ai magri e che fattori diversi dall'iperalimentazione dovrebbero essere considerati nell'eziologia dell'obesità". In realtà, oltre allo stile di vita, molte altre cose sono cambiate nelle società moderne: dopo la seconda guerra mondiale sono stati prodotti in sempre maggiore quantità composti chimici industriali che alterano l'ambiente in cui viviamo e rendono l'esposizione umana inevitabile. Oggi si ritiene che, oltre all'iperalimentazione, potrebbero essere ritenuti in grado di indurre obesità alcune sostanze, definite come "INTERFERENTI ENDOCRINI" (IE), presenti nell'ambiente ed in grado di modificare l'equilibrio funzionale ormonale, inducendo eventi avversi sia a carico di un singolo organismo che della sua progenie. Tali agenti esogeni sono in grado di modificare i meccanismi di espressione genica e di conseguenza di indurre lo sviluppo di numerose e gravi patologie, anche tumorali e nello specifico caso di comportarsi come "OBESIOGENI AMBIENTALI", in grado cioè di alterare i meccanismi di controllo e di sviluppo del tessuto adiposo e del bilancio energetico. Gli IE sono composti lipofili di basso peso molecolare e sono in grado da un lato di accumularsi nel tessuto adiposo e dall'altro di legarsi ad una serie di recettori nucleari quali quelli per gli ormoni sessuali, i recettori per i proliferatori perossisomiali (PPARs), i recettori X epatici (LXR), i recettori X per i retinoidi (RXR), i recettori per gli ormoni tiroidei (TR) ed i recettori per i glucocorticoidi (GR). Tutti questi siti recettoriali sono stati studiati come possibili bersagli intracellulari degli IE in grado di indurre le alterazioni metaboliche caratteristiche dell'obesità complicata.

Il tessuto adiposo fino all'inizio degli anni '90 era considerato come un semplice deposito di calorie sotto forma di trigliceridi. Successivamente, la scoperta dell'ormone leptina e via via di numerose altre sostanze ad azione endocrina prodotte dalle cellule adipose, la presenza in esse di diversi tipi di recettori nucleari e di membrana, hanno motivato una riqualificazione degli "adipociti" come cellule endocrine. Gli interferenti endocrini si annidano tra le decine di migliaia di sostanze chimiche correntemente in uso, sono diffusi nelle matrici ambientali, in genere a concentrazioni molto basse per ogni singola molecola e raggiungono l'organismo attraverso il sangue od il latte materno prima e attraverso gli alimenti, l'aria o per contatto diretto dopo; essi non vengono facilmente metabolizzati e si concentrano prevalentemente nel tessuto adiposo. La lista degli IE accertati è già lunga e si arricchisce progressivamente. Va sottolineato che elemento comune a tutti gli IE noti è che essi agiscono come miscele molto eterogenee, a volte potenziandosi a vicenda e che per essi non può essere stabilita una soglia di rischio come avviene per le sostanze tossiche in genere: quantità anche infinitesimali di ciascuno di essi sono, infatti, per definizione in grado di disturbare il sistema endocrino. L'azione di interferenza endocrina si esplica a livello nucleare, con attività agonista o antagonista, a livello della sintesi ormonale, a livello del trasporto plasmatico degli ormoni ed a livello della loro degradazione. Gli inquinanti organici persistenti (Persistent Organic Pollutants – POPs) sono in grado di alterare la funzione mitocondriale, riducendo l'efficienza energetica del mitocondrio stesso e la produzione di ATP ed è decisamente noto come nell'obesità e nel diabete mellito di tipo 2 sia presente un danno mitocondriale.

Sono classificabili come POPs i pesticidi organoclorurati (DDT, PCBs), il policlorodibenile (PCBs), gli organostannici (TBT), alcuni plastificanti (ftalati) oltre che alcuni prodotti farmaceutici (atrazina) e ormoni naturali o sintetici.

I pesticidi organoclorurati, per bioaccumulo, si depositano nei grassi animali e gli uomini sono esposti attraverso il consumo di latte, pesce e carne. Ebbene, negli uomini il BMI e la massa grassa sembrano essere correlati ai livelli circolanti di tali composti così come la riduzione del dispendio energetico che si verifica durante il dimagrimento. Gli organostannici sono composti chimici utilizzati in svariati settori, ad esempio in campo industriale come catalizzatori e stabilizzatori o in agricoltura come pesticidi. L'interesse nei confronti dei dialchil- e trialchil-derivati (tra cui il DBTC ed il TBTC) è dovuto alla loro dimostrata azione immunotossica nei roditori e alla potenzialità di interferenza endocrina e di alterazione del metabolismo adipocitario. Tali sostanze sono in grado di modulare il sistema immunitario, alterando la funzione linfocitaria e macrofagica, predisponendo allo sviluppo di allergie o malattie autoimmuni. In tal caso appare suggestivo il collegamento con l'infiammazione "sine materia" caratteristica dell'obeso con sindrome metabolica. È recente la pubblicazione di un editoriale su JNCI in cui alcuni importanti ricercatori facenti parte della AAAS (Accademia Americana per l'Avanzamento della Scienza) hanno presentato i risultati di uno studio condotto dal Centro Americano per il Controllo e la Prevenzione delle Malattie, in cui sono illustrati i risultati di test su animali in cui si dimostra l'esistenza di un chiaro collegamento tra l'obesità e determinate sostanze inquinanti ad azione interferente endocrina. Tali autori affermano che "environmental chemicals, not just overeating, may cause obesity". Infatti, l'esposizione prenatale degli animali da esperimento a xenobiotici ambientali a dosi inferiori di quelle trovate nei tessuti umani, come bisfenolo A, tributilstagno (componenti di plastiche di uso comune) o estrogeni sintetici come il dietilstilbestrolo (DES), è in grado di riprogrammare il metabolismo energetico, adipocitario e intermedio ed in tal modo indurre obesità e patologia neoplastica nell'animale adulto, pur in presenza di normale apporto calorico e regolare esercizio fisico (Figura 1). Il tessuto adiposo bianco sembrerebbe essere sia il sito d'accumulo che di azione dei POPs che sono in grado di modificare la differenziazione, il metabolismo e la funzione degli adipociti, in tal modo influenzando lo sviluppo delle malattie associate ad obesità. L'alterata regolazione del peso corporeo e del bilancio energetico di alcuni pazienti obesi potrebbe, quindi, essere motivata dall'alterazione di diversi meccanismi omeostatici, coinvolgenti ad esempio grelina, leptina ed altre citochine.

Oltre ad indurre direttamente aumento della massa adiposa, i POPs sembrano quindi partecipare alla genesi dell'obesità complicata e della sindrome metabolica: i risultati del National Health Examination Survey 1999-2002 hanno dimostrato come le concentrazioni sieriche di policlorobifenili diossino- e non diossino-simili ed i pesticidi organo clorurati correlino significativamente con la prevalenza di sindrome metabolica tra soggetti adulti non diabetici. Con la prevalenza dei singoli componenti, tra le varie sottodiassi, i pesticidi organoclorurati sono quelli più strettamente associati ad insulino-resistenza ed, insieme ai policlorobifenili non-diossino simili, potrebbero essere associati ad aumentata prevalenza di diabete mellito. Alla luce di queste recenti acquisizioni, il paradigma dell'obesità come risultato esclusivo di scelte personali riguardanti la quantità e la qualità del cibo ingerito e l'attività fisica svolta, dovrebbe essere rivisto per un nuovo approccio che tenga conto anche di un ambiente qualitativamente modificato da xenobiotici chimici, al fine di rivedere le strategie di gestione e di prevenzione per un controllo più efficace dell'epidemia obesità.

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Cattedra di Medicina Interna
Dip. di Psicopatologia Medica,
Università La Sapienza di Roma

INDICE DI MASSA CORPOREA	18-24	25-34	35-44	45-54	55-64	65-69	70-74	75-79	80 e più	TOTALE
MASCHI										
Sottopeso	3,3	0,9	0,4	0,4	0,3	0,4	0,7	1,2	2,2	0,9
Normopeso	76,2	62,3	47,1	36,0	31,2	31,4	31,7	38,2	45,7	46,2
Sovrapeso	17,9	31,7	42,7	49,9	53,3	51,9	52,6	48,2	43,5	42,5
Obeso	2,6	5,2	9,9	13,6	15,2	16,3	15,0	12,4	8,6	10,5
FEMMINE										
Sottopeso	16,3	10,8	5,4	2,6	2,0	1,8	2,5	3,4	5,4	5,8
Normopeso	73,8	72,3	69,5	57,7	47,0	41,9	41,2	42,4	48,8	58,6
Sovrapeso	8,3	13,4	19,6	29,4	36,5	41,1	40,6	40,3	34,5	26,6
Obeso	1,7	3,5	5,5	10,3	14,5	15,2	15,7	14,0	11,3	9,1
MASCHI E FEMMINE										
Sottopeso	9,7	5,8	2,9	1,5	1,2	1,1	1,7	2,5	4,3	3,4
Normopeso	75,0	67,3	58,2	47,0	39,3	37,0	36,9	40,7	47,7	52,6
Sovrapeso	13,1	22,6	31,2	39,5	44,7	46,7	46,0	43,5	37,5	34,2
Obeso	2,1	4,3	7,7	11,9	14,8	15,7	15,4	13,3	10,4	9,8

Tabella 1. Persone di 18 anni e più secondo l'indice di massa corporea per classe di età e sesso - Anno 2005 (per 100 persone dello stesso sesso e classe di età). Dati ISTAT.

Obesity and endocrine disease

Obesità

- Primitiva
- Secondaria

Genetic
Monogenic disorders:
Melanocortin-4 receptor mutation
Leptin deficiency
Proopiomelanocortin deficiency
Syndromes
Prader-Willi
Bardet-Biedl
Cohen
Alstrom
Fröhlich
Neurologic
Brain injury
Brain tumor
Consequences of cranial irradiation
Hypothalamic obesity
Endocrine
Hypothyroidism
Cushing syndrome
Growth hormone deficiency
Pseudohypoparathyroidism
Psychological
Depression
Eating disorders
Drug-induced
Tricyclic antidepressants
Oral contraceptives
Antipsychotics
Anticonvulsants
Glucocorticoids

Arq Bras Endocrinol Metab. 2009;53/2

Obesity and endocrine disease

Endocrine changes in obesity and after weight loss

Hormone	Obesity	Fasting/weight loss
T3	↑	↓
T4	N	N
r T3	↓	↑
TSH	N	N
TSH after TRH	N/↑/↓	
Basal prolactin	N	N
Prolactin response to hypoglycemia	N/↓	N/↓
Prolactin response to TRH	N/↓	N
Basal cortisol		N
Basal ACTH		N
Urinary free cortisol		N/↑
Cortisol production rate		↑
Cortisol metabolic rate		↑
17-OH-corticosteroids		↑
GH	↓	↑
GH production rate	↓	↑
GH metabolism rate	↑	
GH response to GHRH	↓	N/↓
GH response to hypoglycemia	↓	N/↓
IGF-I	N	
Free IGF-I	↑	
IGFBP-3	N/↑	

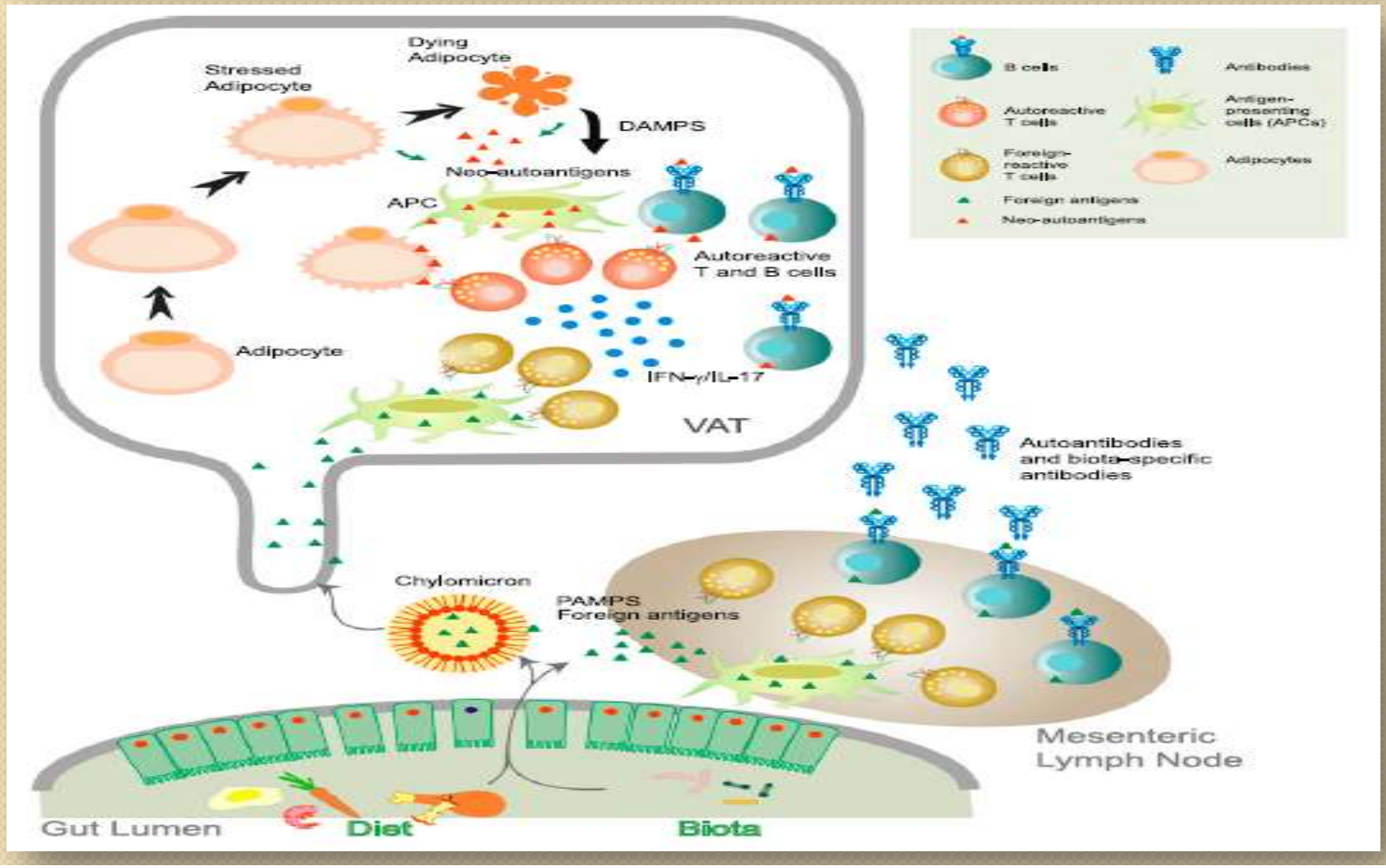
Endocrinol Metab Clin N Am
32 (2003) 895–914

Endocrine Gland	Hormonal Alteration
Endocrine Pancreas	Hyperinsulinemia
Adipose tissue	Hyperleptinemia. Decreased Adiponectin
Pituitary	Decreased basal and stimulated GH Decreased response to stimuli of Prolactin
Gonads	Woman: Decreased SHBG. Increased Estrogens and Androgens. Man: Decreased SHBG. Decreased Total and Free Testosterone
Adrenals	Free urinary cortisol increased and normal plasmatic cortisol
Gastrointestinal Hormones	Decreased Ghrelin
Thyroid	Increased TSH and free T3

Mini-Reviews in Medicinal Chemistry, 2013, *Vol. 13, No. 3*

Are Obesity-Related Insulin Resistance and Type 2 Diabetes Autoimmune Diseases?

Diabetes 2015;64:1886–1897 | DOI: 10.2337/db14-1488



Proposed pathways, centered in the VAT, to autoimmune responses during obesity. Intrinsic inflammatory changes cooperate with **obesity-associated dysbiosis in the gut to initiate self- or microbe-specific adaptive immune responses in the VAT,** generating a feedforward inflammatory loop that worsens insulin signaling. Long-term caloric excess causes hypertrophy and ER stress in white adipocytes, leading to the release of adipokines and chemo-attractants that help activate and/or recruit innate cells, such as macrophages, and adaptive immune cells, such as B and T cells, to the VAT. **Obesity-associated dysbiosis contributes to increased gut permeability, facilitating leakage of microbial products and oral antigens across the gut epithelium. Together with lipid excess and dying adipocytes**, these serve **as potential sources of antigens** and costimulatory signals for the activation of VAT B and T cells, a process that can potentially take place **in the draining lymph nodes or locally in the VAT**. Activated B and T cells, in turn, contribute to VAT inflammation through the secretion of inflammatory cytokines and antibodies or through cross talk with other immune cells. DAMPs, danger-associated molecular patterns. PAMPs, pathogen-associated molecular patterns.

IPOTIROIDISMO E SINDROME METABOLICA

Insulino-resistenza

Ipertensione arteriosa

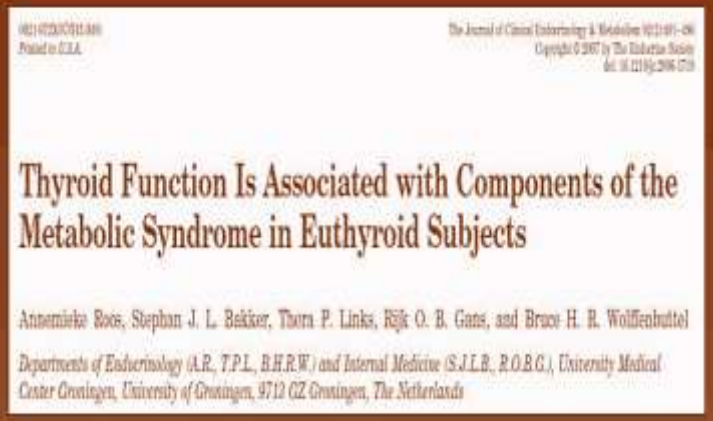
Alterata tolleranza ai carboidrati

Obesità centrale

Dislipidemia

↑ Fibrinogeno

↑ PAI-1



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Thyroid Function Is Associated with Components of the Metabolic Syndrome in Euthyroid Subjects

Annemieke Roos, Stephan J. L. Bakker, Thera P. Links, Rijk O. B. Gans, and Bruce H. R. Wolffenbuttel

Departments of Endocrinology (A.R., T.P.L., B.H.R.W.) and Internal Medicine (S.J.L.B., R.O.B.G.), University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands

low normal FT4 levels were significantly associated with increased insulin resistance and with four of five metabolic syndrome traits. These findings are consistent with an increased cardiovascular risk in subjects with low normal thyroid function.

FT4 levels are significatly associated with insulin resistance

Introducing the Thyroid Gland as Another Victim of the Insulin Resistance Syndrome

J. Rezzonico, M. Rezzonico, E. Pusiol, F. Pitoia, H. Niepomniszcze

Thyroid 2008; 18: 461-464

Insulin is a thyroid growth factor that stimulates proliferation of thyroid cells in culture.

117 women (age 32.2 ± 7 yrs) were evaluated by a thyroid US and basal and postprandial serum insulin and divided into 4 groups: G1, subjects with IR and obesity; G2, obesity without IR; G3, IR and normal weight; and G4, control group without IR and normal weight.

Thyroid volume showed the following values: G1, 17 ± 3 mL; G2, 13.8 ± 2.8 mL; G3, 16.2 ± 2.1 mL; and G4,12.1 ± 2.4 mL. No significant differences between G1 and G3, but differences between G1 and G2, and G3 and G4 were significant at $p < 0.05$.

The percentage of nodular thyroid glands was : G1, 50%; G2, 23.8%; G3, 61%; G4, 16.1%. Differences between G1 and G2 and G3 and G4 were statistically significant ($p < 0.005$ and $p < 0.001$, respectively).

The higher levels of insulin cause increased thyroid proliferation. Clinical manifestations are larger thyroid volume and formation of nodules.

SINDROME DI CUSHING E SINDROME METABOLICA

La sindrome di Cushing è una obesità secondaria

Insulino-resistenza

Ipertensione arteriosa

Alterata tolleranza ai carboidrati

Obesità centrale

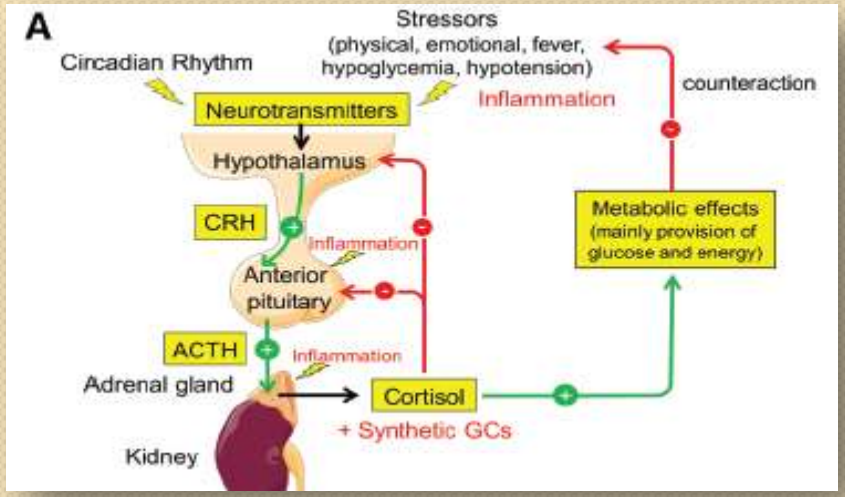
Dislipidemia

↑ Fibrinogeno

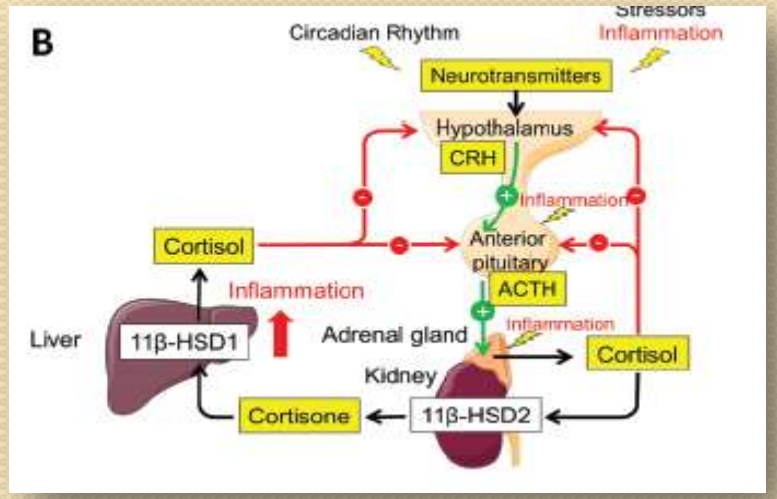
↑ PAI-1

Rev Endocr Metab Disord (2010) 11:141–145

FUNCTION AND DYSFUNCTION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN INFLAMMATION.



A) The central circadian oscillator and different stressors (physical, emotional, fever, hypoglycemia, or hypotension) during physiological stress reactions trigger the hypothalamus to release CRH. CRH acts on the anterior pituitary and induces release of ACTH, which in turn stimulates the adrenal gland to produce and release cortisol. **Cortisol exhibits its known metabolic effects (mainly provision of glucose and energy), which serve to counteract the stressor**. Inflammation can also trigger the HPA axis. In the physiological regulation of the HPA axis, cortisol release is terminated by negative feedback regulation of cortisol on the hypothalamus and anterior pituitary.



B) A new concept for the feedback loop: the **hepato-hypothalamic–pituitary–adrenal–renal axis**. The HPA axis is extended by GC metabolism: **cortisol is converted to cortisone mainly by the kidney, via 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2,** in order to protect the nonspecific mineralocorticoid receptor from activation by cortisol. **The major organ for converting cortisone to cortisol is the liver, via 11β-HSD1**. In chronic inflammation, conversion from cortisone to cortisol by 11β-HSD1 is increased. This may amplify negative feedback and explain HPA dysfunction in inflammation.

Spies *et al. Arthritis Research & Therapy* 2014, **16(Suppl 2)**:S3

PCOS E SINDROME METABOLICA

Insulino-resistenza

Ipertensione arteriosa

Alterata tolleranza ai carboidrati

Obesità centrale

Dislipidemia

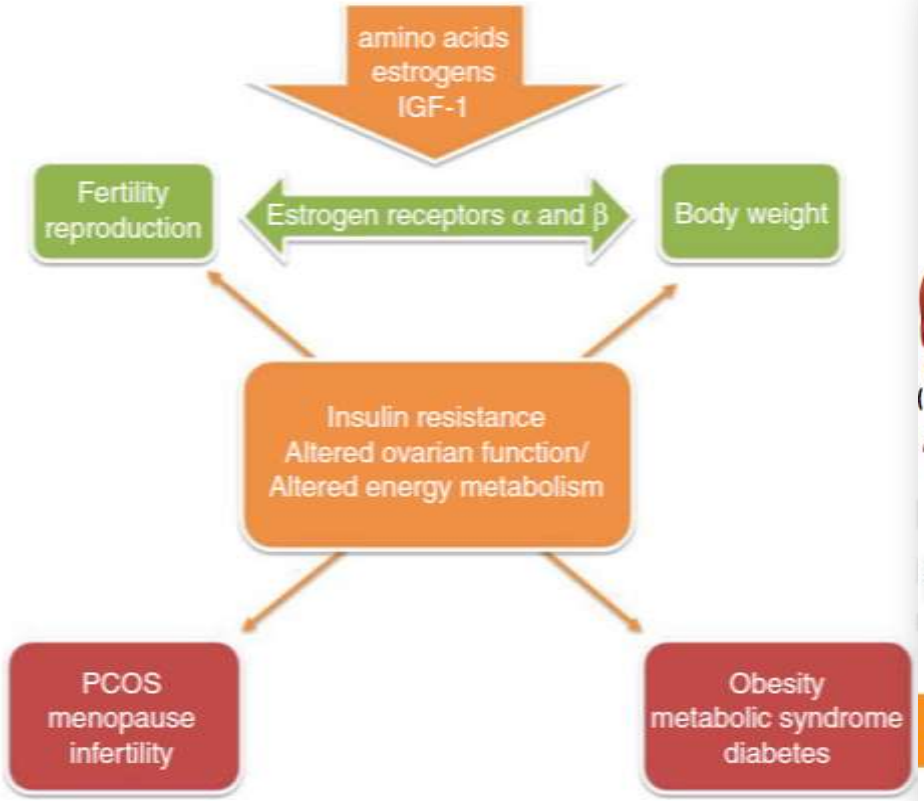
↑ Fibrinogeno

↑ PAI-1

Norman RJ, Dewailly D, Legro RS, Hickey TE Lancet. 2007 25;370(9588):685-97

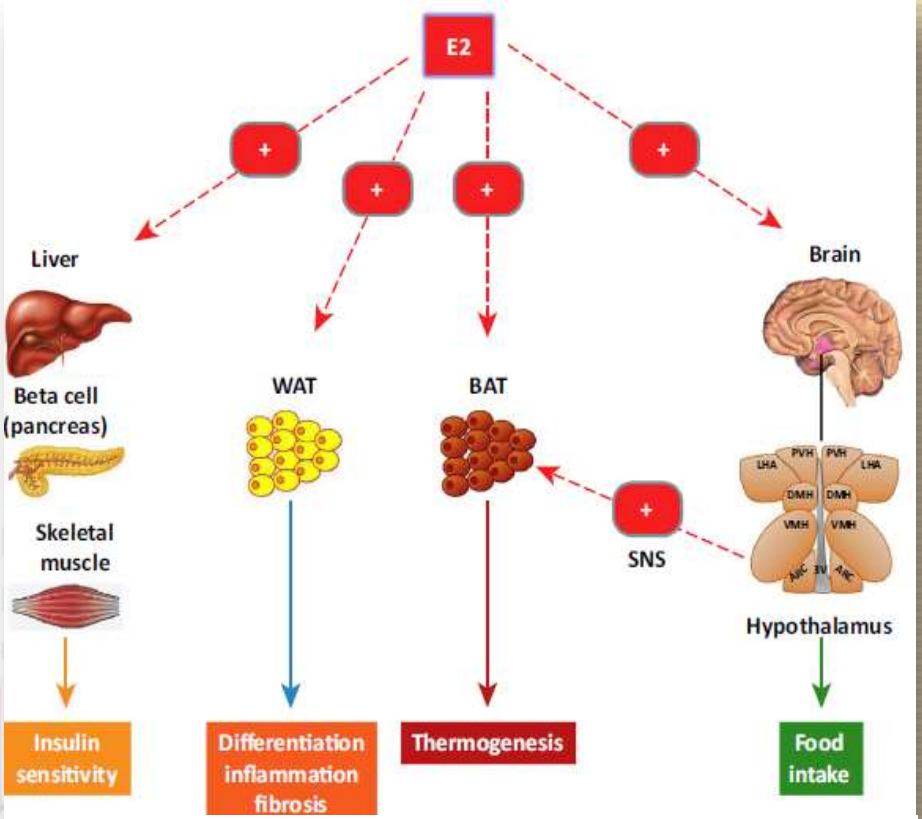
Ovarian Function and Obesity

Estrogens and the control of energy homeostasis: a brain perspective



Reciprocal regulation of energy metabolism and ovarian function in order to guarantee a metabolic status tuned to reproductive needs. The alteration of one or both of these compartments may lead to metabolic and/or reproductive diseases

C.Lubrano, Multidisciplinary Approach To Obesity 2015, Pp 73-82



Peripheral and central actions of E2 on the regulation of energy homeostasis. E2 acts at a peripheral level to regulate multiple aspects of energy homeostasis and metabolism. It modulates insulin sensitivity by acting on pancreas, liver, and skeletal muscle. E2 **also acts on WAT to control fat distribution, differentiation, and fibrosis** and **on BAT to induce thermogenesis.** In addition to these effects, E2 also impacts the hypothalamus to regulate BAT function through the sympathetic nervous system (SNS) and food intake.

IPOGONADISMO MASCHILE E SINDROME METABOLICA

Insulino-resistenza

Ipertensione arteriosa

Alterata tolleranza ai carboidrati

Obesità centrale

Dislipidemia

↑ Fibrinogeno

↑ PAI-1

Kupelian V et al, J Clin Endocrinol Metab. 2006 Mar;91(3):843-50

IPERPARATIROIDISMO E SINDROME METABOLICA

Insulino-resistenza

Ipertensione arteriosa

Alterata tolleranza ai carboidrati

Obesità centrale

Dislipidemia

Aritmie cardiache

Ipertrofia venticolare

Calcificazioni miocardiache

Delfini E et al, Metabolism. 2007 Jan;56(1):30-6

IPERALDOSTERONISMO E SINDROME METABOLICA

Insulino-resistenza

Ipertensione arteriosa

Alterata tolleranza ai carboidrati

Obesità centrale

Dislipidemia

Stress ossidativo

Disfunzione Endoteliale

Fallo F et al, Curr Hypertens Rep. 2007 Apr;9(2):106-11

GHD DELL'ADULTO E SINDROME METABOLICA

Insulino-resistenza

Ipertensione arteriosa

Alterata tolleranza ai carboidrati

Obesità centrale

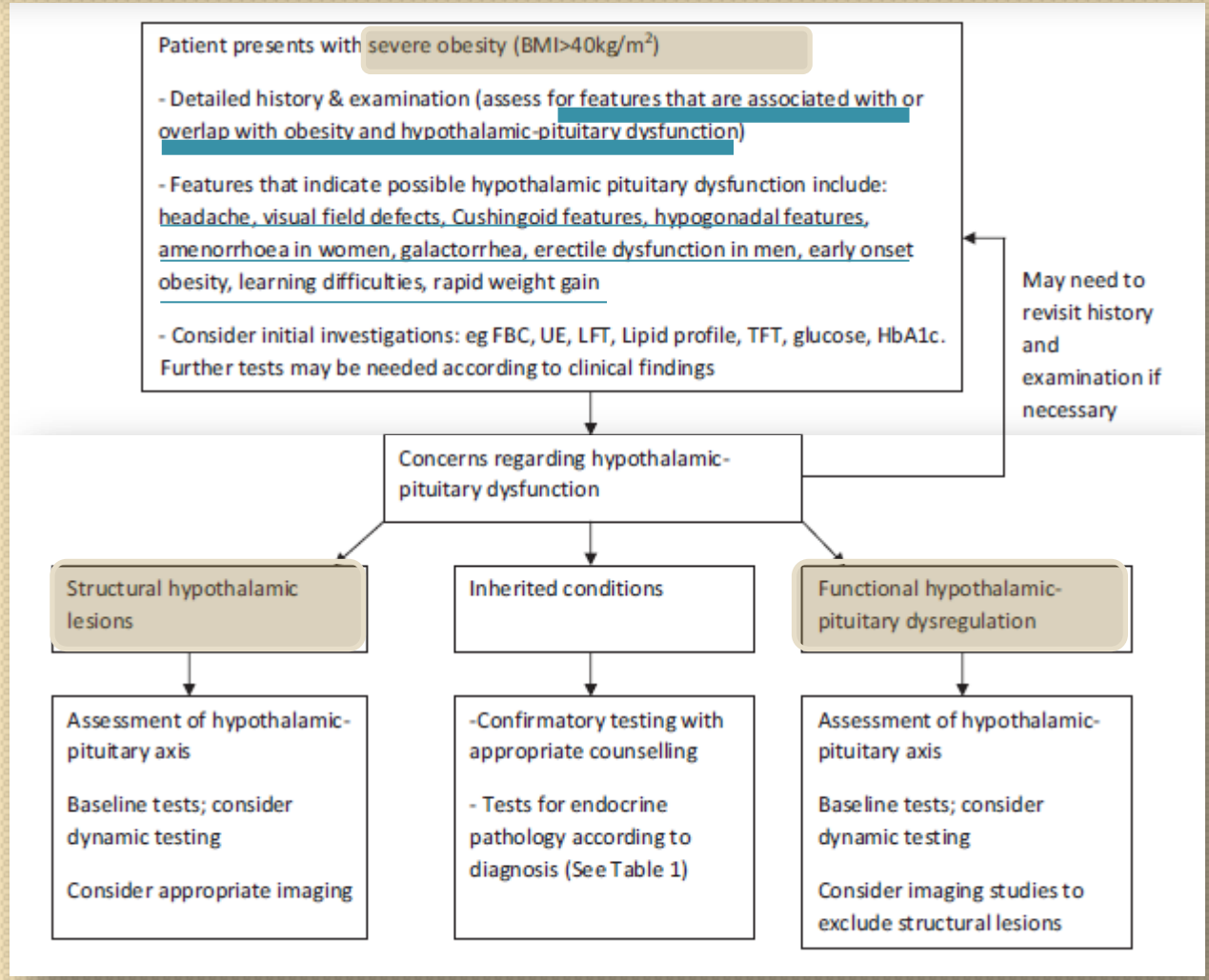
Dislipidemia

Fibrinogeno

↑ PAI-1

How to approach endocrine assessment in severe obesity?

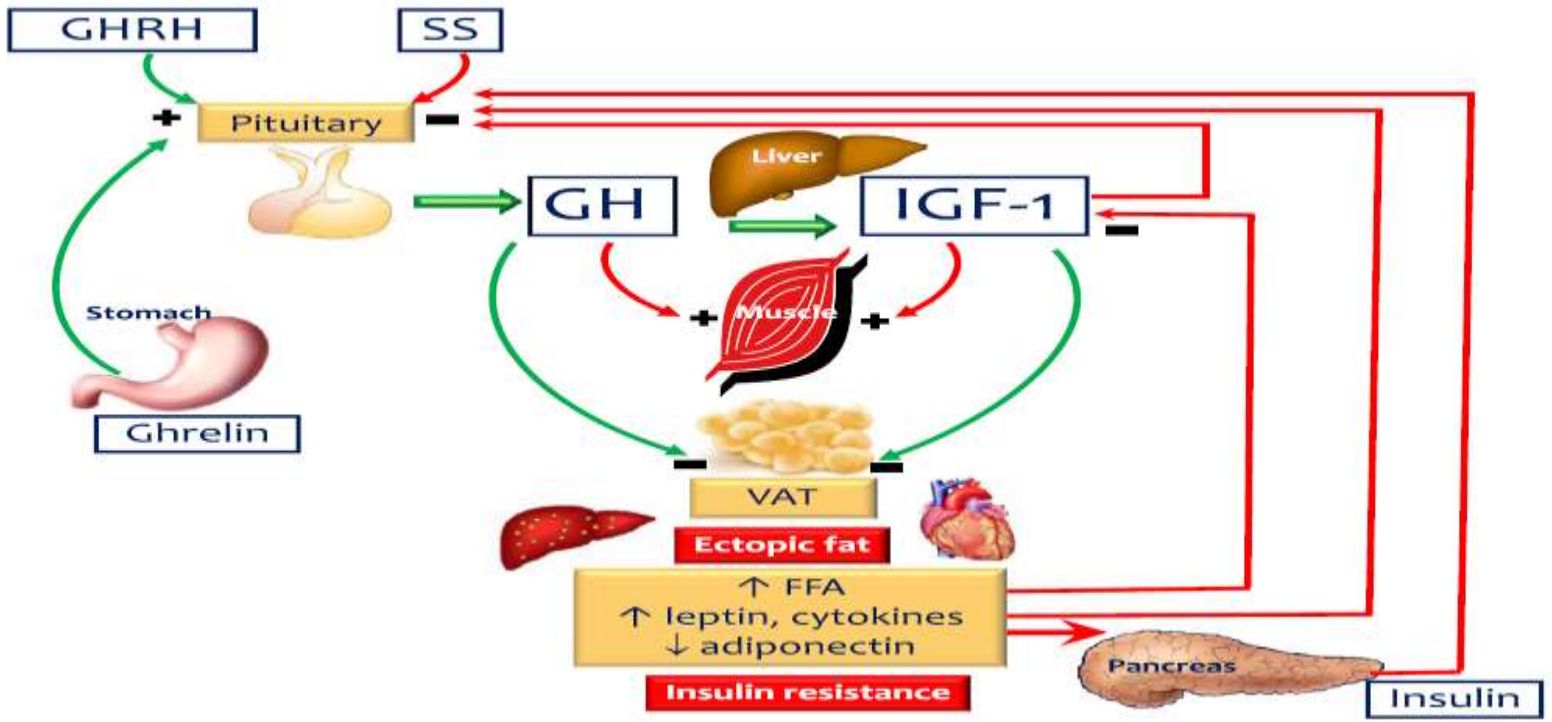
Ian W. Seetho and John P. H. Wilding



Clinical Endocrinology (2013) 79, 163–167

The complex relationship between obesity and the somatropic axis: The long and winding road

Growth Hormone & IGF Research 24 (2014) 221–226



Increased central SRIH tone	drugs capable of decreasing hypothalamic SRIH secretion improve GH response to GHRH	drugs capable of decreasing hypothalamic SRIH secretion are unable to fully normalize the GH response to GHRH
GHRH deficiency	decreased number of GHRH peaks	normal serum and cerebrospinal fluid concentrations of GHRH
	decreased GHRH gene expression in the genetically obese rat	normal GHRH release in response to L-dopa
GHRP ligand deficiency	brilliant GH response to GHRPs	
Somatotrope cell insufficiency	lack of GH response to repeated GHRH administration	brilliant GH response to GHRPs
Increased NEFA levels	normalization of GH secretion after drug-induced reduction of plasma NEFA concentrations	
Increased free IGF-I levels	elevated concentrations of plasma free IGF-I	

International Journal of Obesity (1999) 23, 260–271

Adult Growth Hormone Deficiency

Signs and symptoms of adult GH deficiency
▪ Increased adipose tissue mass (especially visceral adipose tissue)
▪ Decreased lean body mass ▪ Decreased skeletal muscle strength ▪ Decreased exercise performance ▪ Decreased cardiac capacity
▪ Decreased BMD and increased risk of fracture ▪ Atherogenic lipid profile ▪ Thin, dry skin
▪ Psychosocial problems and decreased quality of life; problems can include fatigue, depression, anxiety, impaired sleep and social isolation

Idiopathic Acquired Adult GHD: Enhancing Diagnostic Precision

Exhaustive History	Age Childhood health Brain tumor Motor vehicle accident or other trauma Contact sports Cerebrovascular thrombosis or hemorrhage Mood disorder Hyperparathyroidism
Physical examination	Body weight Abdominal obesity BMI
Pituitary MRI	Subtle changes Partially empty sella Stalk integrity New lesion development

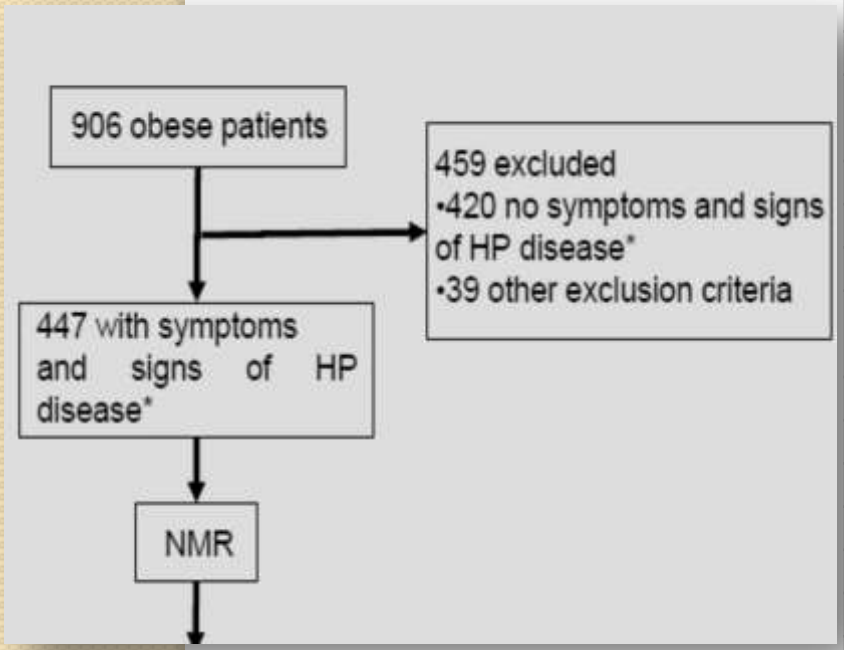
Kargi, A. Y. & Merriam, G. R. *Nat. Rev. Endocrinol.* **9**, 335–345 (2013)

Obesità e GHD
La nostra esperienza

Severe growth hormone deficiency and empty sella in obesity: a cross-sectional study

Endocrine (2015) 49:503–511

Carla Lubrano · Marta Tenuta · Daniela Costantini · Palma Specchia · Giuseppe Barbaro · Sabrina Basciani · Stefania Mariani · Alfredo Pontecorvi · Andrea Lenzi · Lucio Gnessi

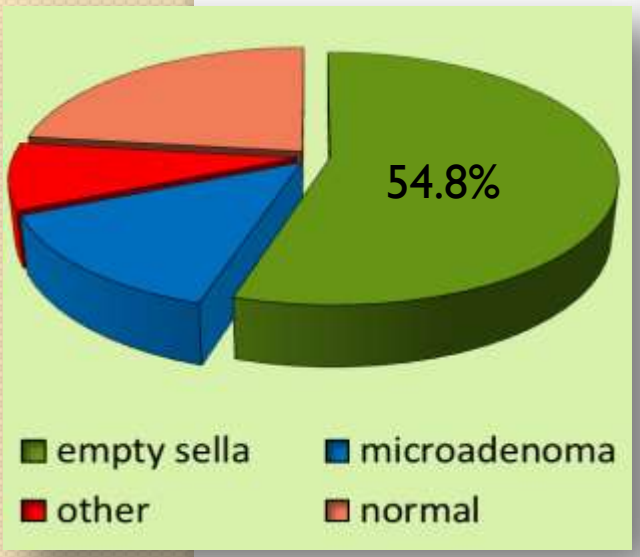


906 obese patients years 2007-2013

Symptoms
Headaches
Visual impairment, visual field defects
Depression, changes in mood, "bipolar" diagnosis, cognitive slowing, impairment of attention and memory
Loss of drive, fatigue, general muscle weakness, tiredness
Sleep disorders
Decreased quality of life (QoL)
Sexual difficulties (painful intercourse, low libido, erectile dysfunction, dyspareunia)
Menstrual difficulties (iiregular/discontinued/painful periods), early menopause
Polyuria, polidipsia
Objective signs
Ginecosmastia, beast's tenderness
Galactorrea
Unusual hair loss or growth
Coarsened facial feature, enlarged hands and feet
Visceral obesity
Decreased muscle mass and strength
Osteoporosis, osteopenia
Arthritis, aching joints
Anamnestic reports
Head injury with hospitalization*
Infertility???

Centro di Alta Specializzazione per la Cura dell'Obesità (CASCO)

Sezione di Fisiopatologia Medica, Endocrinologia e Scienza dell'Alimentazione,



906 obese patients

459 excluded
•420 no symptoms and signs of HP disease*
•39 other exclusion criteria

447 with symptoms and signs of HP disease*

49,34%

NMR

Empty sella:
- **27% di pazienti non selezionati**
- **54.8% pazienti sintomatici**

184 with signs and symptoms of GHD' submitted to GHRH + arginine test

70

GHD:
- **7.7% di pazienti non selezionati**
- **15.6% di pazienti sintomatici**

to

Confronto tra pazienti obesi GHD (70) e pazienti obesi di controllo (114)

	Normal	GHD*	P value
n.	114	70	
ES	62	69	
NP	37	1	
MA	10	0	
OPA	5	0	
Gender (F/M)	99/15	48/22	
Age (yrs)	45.33±13.16	47.94±9.96	ns
Height (m)	1.63±0.08	1.65±0.11	ns
Weight (Kg)	100.92±21.64	116.80±31.65	<0.001
BMI (Kg/m2)	38.02±7.11	42.70±10.16	<0.001
WC (cm)	118.43±16.43	128.90±18.81	<0.001
WHR	0.98±0.09	0.95±0.07	<0.01
HR (beats/min)	69.31±9.86	72.11±9.64	ns
SBP (mmHg)	127.62±16.41	133.05±15.21	<0.05
DBP (mmHg)	80.21±9.98	82.37±9.69	ns
Total-C (mmol/l)	5.15±0.92	5.3±1.07	ns
TG (mmol/l)	1.52±0.95	1.96±1.31	<0.05
Glucose (mmol/l)	5.31±0.89	5.85±0.98	<0.001
Insulin (pmol/L)	157.17±116.05	207.52±147.10	<0.05
HOMA-IR	5.43±4.20	8.18±6.33	<0.001
HbA1c (%)	5.75±1.05	6.27±1.04	<0.01
HbA1c (mmol/mol)	39±3.15	45±3.12	<0.01
SLVD (mm)	30.48±3.37	32.45±3.93	<0.001
DLVD (mm)	49.53±3.92	51.68±4.23	<0.001
EFT (mm)	8.08±1.12	8.49±0.99	<0.05
Hip BMD (g/cm2)			
MetS**	56 (49%)	46 (66%)	<0.05

- Atherogenic lipid profile
- Decreased cardiac capacity
- Decreased BMD and increased risk of fracture
- Increased adipose tissue mass (especially visceral adipose tissue)
- Decreased lean body mass

Prevalence of metabolic syndrome in patients according to GHRH+arginine test

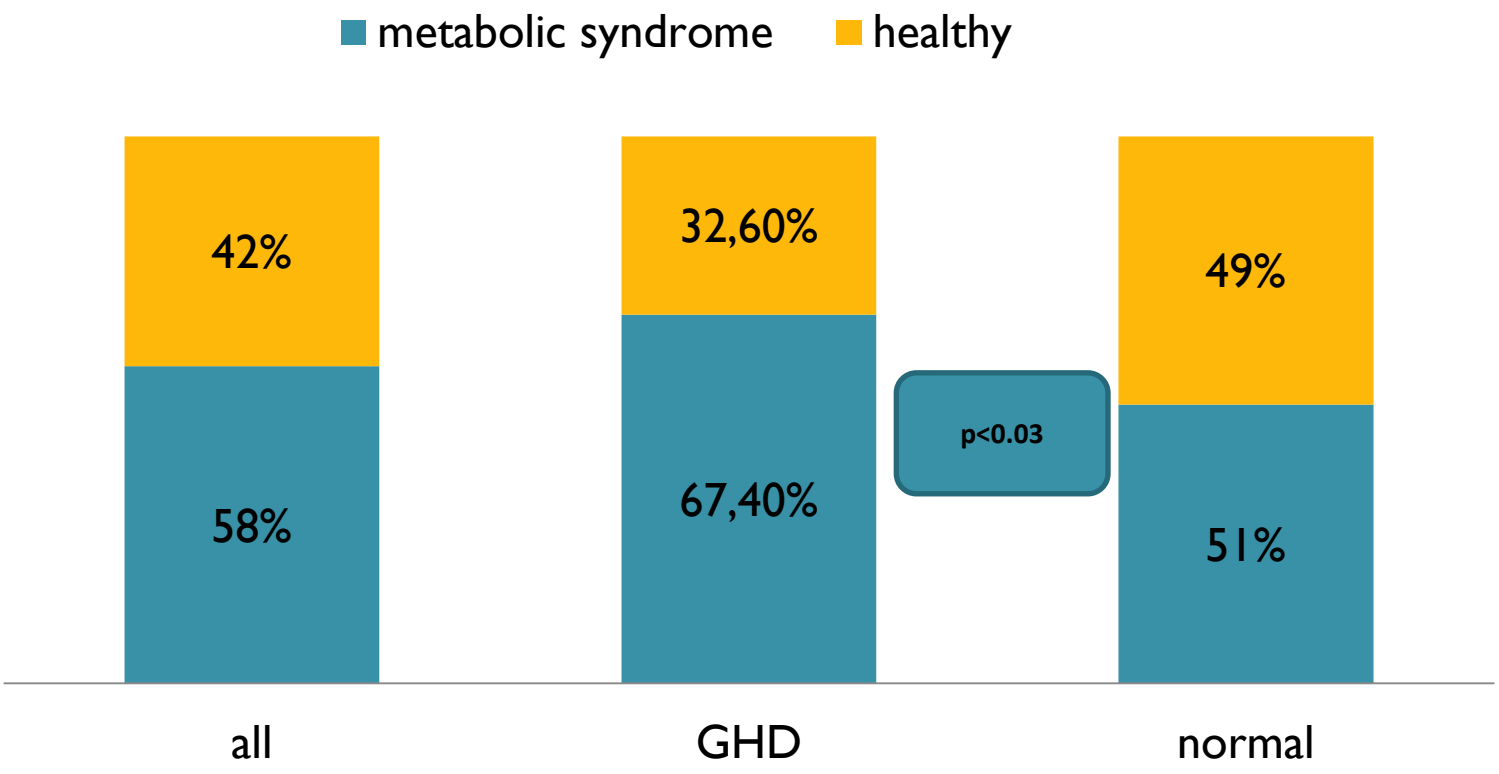


Table 2 Linear correlation analyses comparing AUC of GH response to GHRH plus arginine test and diagnostic parameters of MetS

	Mean ± SD	Pearson *R*	*p*
AUC (μg/L/h)	301.34 ± 312.61		
WC (cm)	122.42 ± 18.05	−0.39	0.000
SBP (mmHg)	129.62 ± 16.15	−0.19	0.012
DBP (mmHg)	81.00 ± 9.90	−0.18	0.020
HDL-C (mmol/L)	1.13 ± 0.19	0.19	0.020
Triglycerides (mmol/L)	1.66 ± 1.00	−0.24	0.001
Glucose (mmol/L)	5.51 ± 0.96	−0.32	0.000
Insulin (pmol/L)	176.13 ± 130.50	−0.22	0.005
HOMA-IR	6.46 ± 5.25	−0.27	0.000

AUC area under the curve, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-C* high density lipoprotein cholesterol, *HOMA-IR* homeostasis model assessment of insulin resistance

Table 3 Multiple linear regression analysis for the association between GH peak (A) and HOMA-IR (B) and selected covariates adjusted for sex and age

Covariates	*β*	SE	*T* (138)	*B*	SE	*p* value
(A) Dependent variable, GH peak						
Intercept			36.81915	10.30003	3.57467	0.000517
BMI (kg/m^2)	−0.083590	0.133891	−0.15673	0.25105	−0.62431	0.533682
WC (cm)	−0.111171	0.133418	−0.08991	0.10790	−0.83326	0.406456
UFDI	−0.194511	0.085731	−3.70997	1.63517	−2.26886	0.025175
ES	0.437956	0.082668	11.97970	2.26126	5.29780	0.000001
(B) Dependent variable, HOMA-IR						
Intercept			0.78472	3.042892	3.877664	0.434033
BMI (kg/m^2)	0.230181	0.144283	1.59534	0.148831	0.093291	0.113046
WC (cm)	0.062239	0.147945	0.42069	0.018510	0.043999	0.674670
GH peak (μg/L)	−0.219659	0.083342	−2.63563	−0.101282	0.038428	0.009412

(A) $R = 0.58162782$, $R^2 = 0.33829092$ adjusted $R^2 = 0.30376697$

(B) $R = 0.45273682$, $R^2 = 0.20497063$ adjusted $R^2 = 0.18069492$

QUALE OBESITÀ?




Is Obesity a Disease?

Definition of "disease"

1. Impairment of normal functioning of some aspect of the body
2. Characteristic signs or symptoms
3. Resultant harm or morbidity to the entity affected

AMA

AMERICAN MEDICAL ASSOCIATION

Features

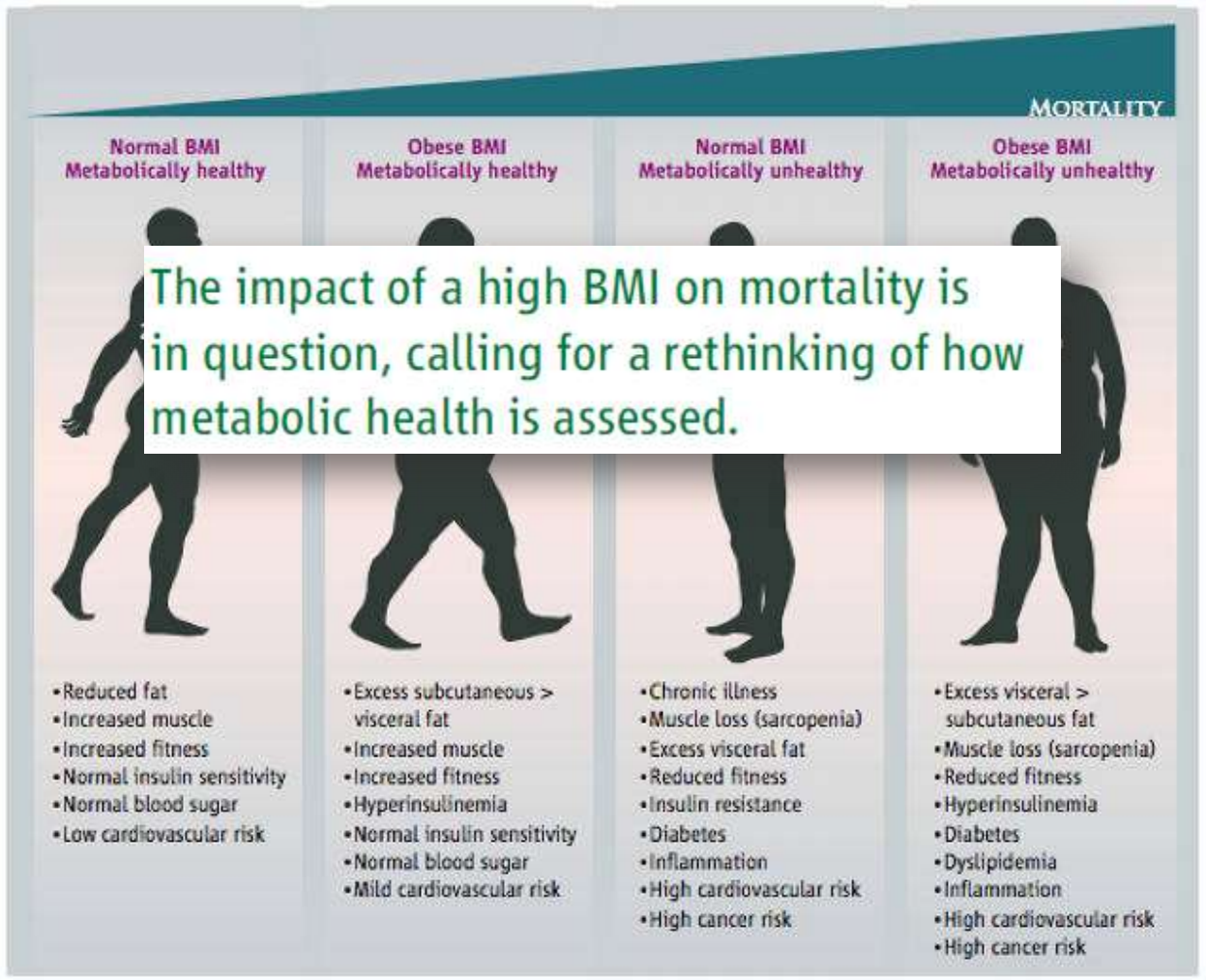
Obesity is a chronic disease
Obesity has many causes
[illegible]

25th Jun2013: AMA says obesity is a disease

Weight regain may be slow but is often rapid
Medications do not work if not taken
Treatment is often more frustrating than the underlying disease

The Health Risk of Obesity—Better Metrics Imperative

Rexford S. Ahima and Mitchell A. Lazar SCIENCE VOL 341 23 AUGUST 2013



Harmonizing the Metabolic Syndrome

A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity

Table 1. Criteria for Clinical Diagnosis of the Metabolic Syndrome

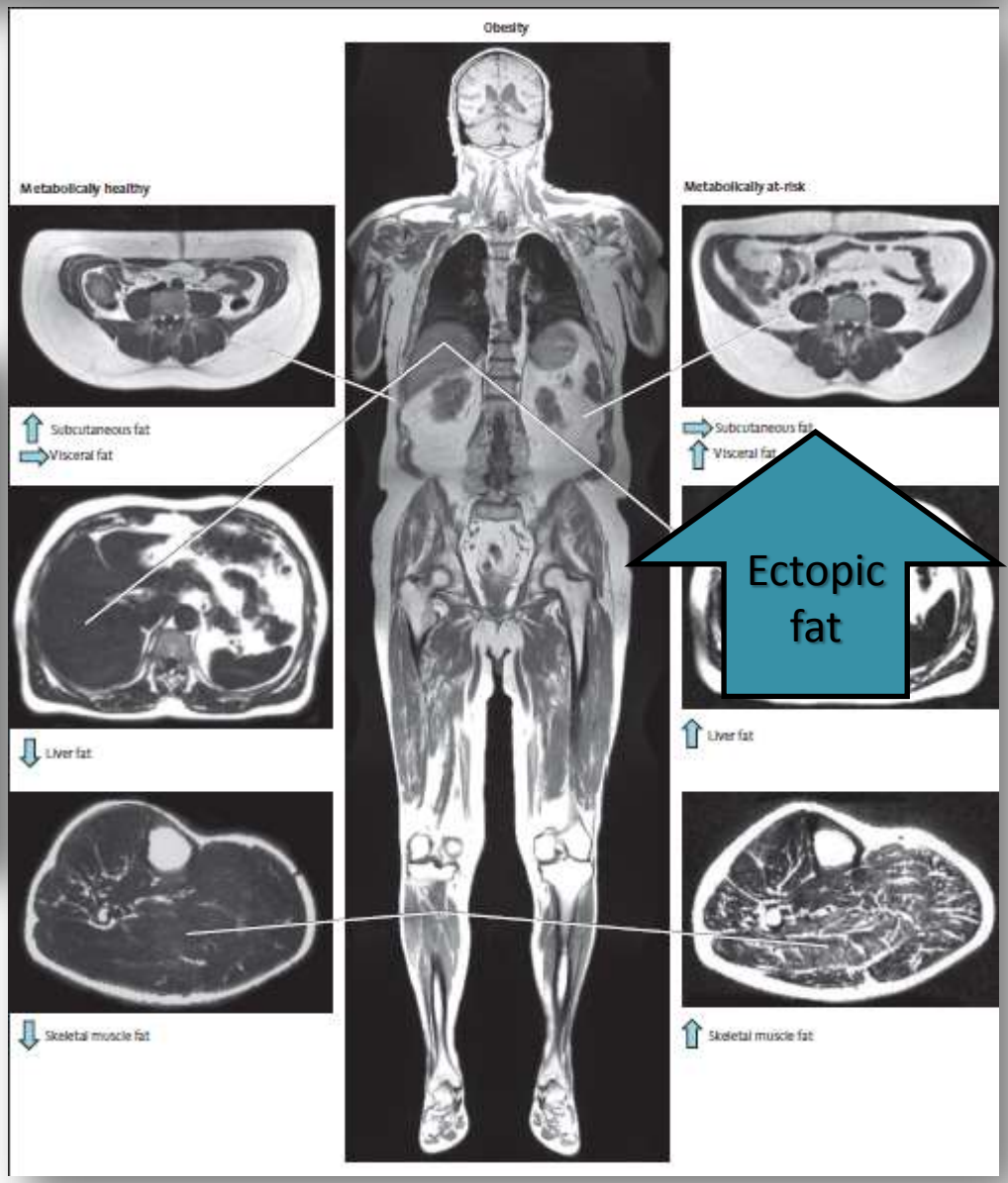
Measure	Categorical Cut Points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

(*Circulation*. 2009;120:1640-1645.)

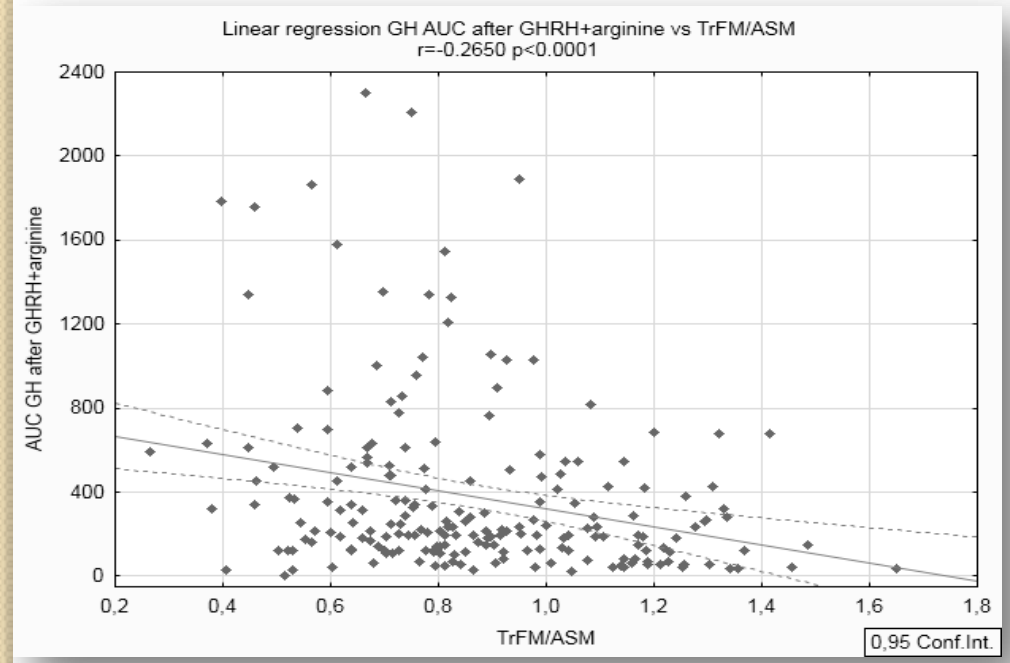
Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications

Norbert Stefan, Hans-Ulrich Häring, Frank B Hu, Matthias B Schulze

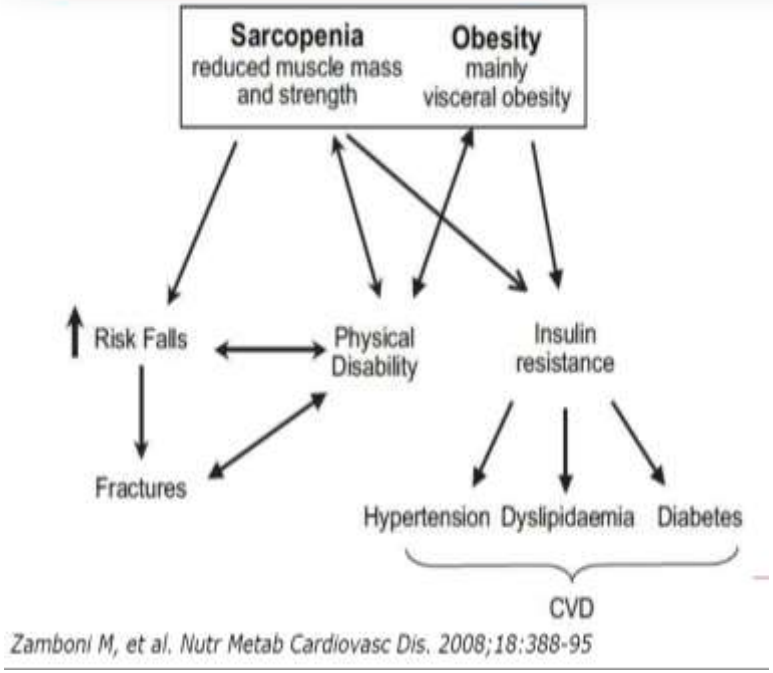
Metabolically abnormal	BMI: Normal weight	Overweight	Obese
Metabolically healthy	Metabolically healthy normal weight	Metabolically healthy overweight	Metabolically healthy obese (MHO)
Metabolically unhealthy	Metabolically unhealthy normal weight	Metabolically unhealthy overweight	Metabolically unhealthy obese (MUHO)



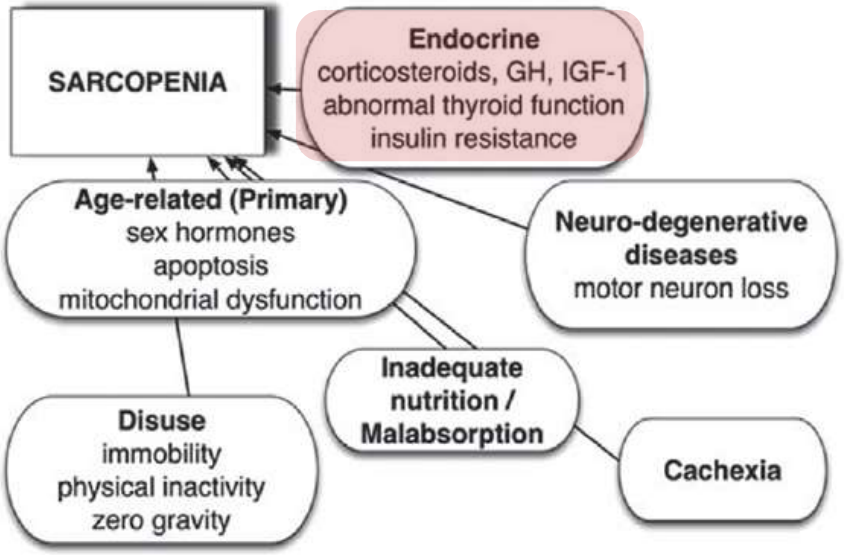
www.thelancet.com/diabetes-endocrinology Published online August 30, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70062-7



Sarcopenic obesity

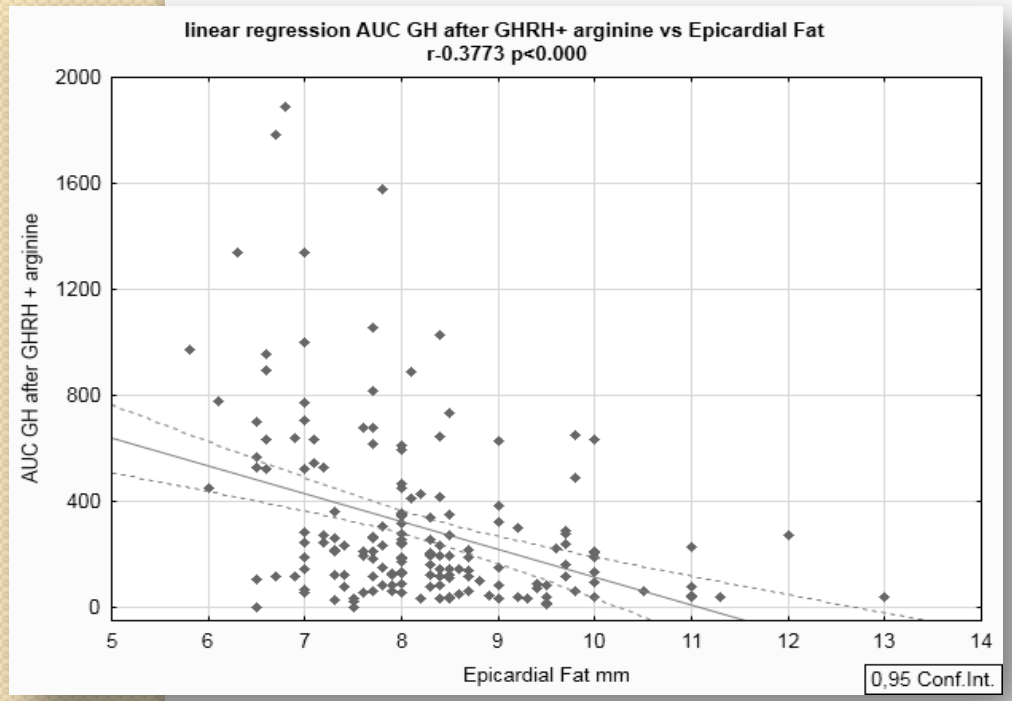


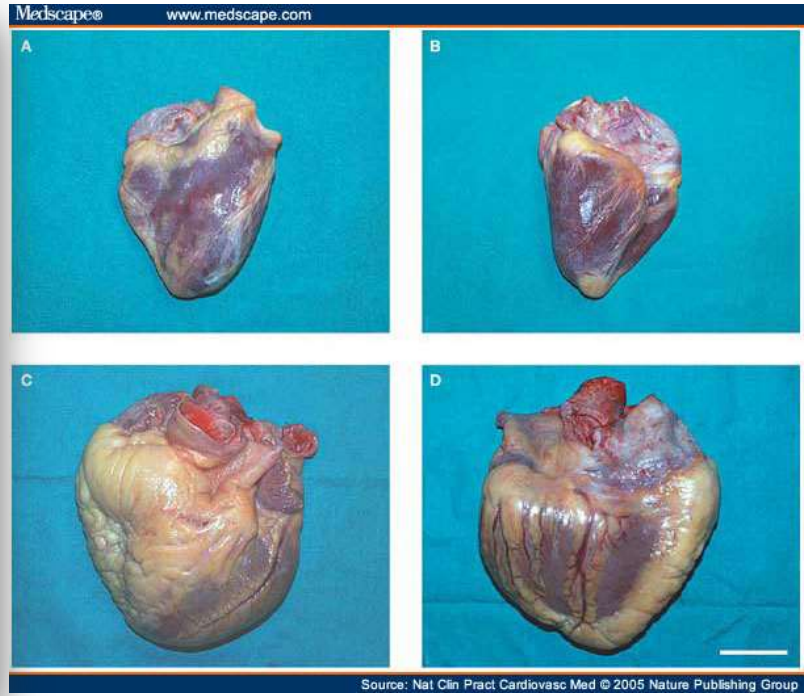
Zamboni M, et al. Nutr Metab Cardiovasc Dis. 2008;18:388-95



Epicardial fat: From the biomolecular aspects to the clinical practice

Gianluca Iacobellis[a,*], Alexis E. Malavazos[b], Massimiliano M. Corsi[c,d]





Epicardial fat is the visceral fat depot of heart. It is a metabolically active organ with anatomical and functional contiguity to the myocardium. A dichotomous role has been attributed to the epicardial fat. Under physiological conditions, epicardial fat displays biochemical and thermogenic cardio-protective properties. Under pathological circumstances epicardial fat can locally affect the heart and coronary arteries through vasocrine or paracrine secretion of pro-inflammatory cytokines. Epicardial fat can be measured with imaging techniques. Epicardial fat thickness reflects intra-abdominal and myocardial fat and correlates with metabolic syndrome and coronary artery disease. Epicardial fat measurement may play a role in the stratification of the cardio-metabolic risk and serve as therapeutic target. Weight loss and anti-inflammatory drugs targeting the fat may modulate epicardial fat. Because epicardial and myocardial tissues share the same coronary arterial supply it is reasonable to hypothesize that improved local vascularisation may resume epicardial fat to its physiological role.

The International Journal of Biochemistry & Cell Biology 43 (2011) 1651–1654

Decreased Muscle Mass in Nonalcoholic Fatty Liver Disease: New Evidence of a Link Between Growth Hormone and Fatty Liver Disease?

Table 3. Unadjusted and Adjusted Odds Ratios (ORs) With 95% Confidence Intervals (CIs) of Having Nonalcoholic Fatty Liver Disease (NAFLD) by Quartiles of SMI After Adjusting for Potential Compounding Factors

HEPATOLOGY, Vol. 59, No. 5, 2014

	Quartiles of SMI (%)				
	Q4	Q3	Q2	Q1	P for trend
Unadjusted	1	3.42 (1.30, 8.96)	4.03 (1.56, 10.40)	5.88 (2.33, 14.84)	0.002
Model 1	1	3.99 (1.49, 10.64)	5.22 (1.96, 13.88)	8.25 (3.12, 21.82)	<0.001
Model 2	1	3.93 (1.45, 10.66)	5.27 (1.96, 14.22)	7.38 (2.71, 20.12)	0.001
Model 3	1	3.39 (1.10, 10.39)	4.13 (1.38, 12.32)	5.16 (1.63, 16.33)	0.041

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, smoking status, and physical activity.
Model 3: adjusted for age, sex, smoking status, physical activity, homeostasis model of insulin resistance (HOMA-IR), high sensitivity C-reactive protein (hsCRP), and 25(OH)D levels.

Fatty Liver Index Associates with Relative Sarcopenia and GH/ IGF- 1 Status in Obese Subjects

Eleonora Poggiogalle*, Carla Lubrano, Lucio Gnessi, Stefania Mariani, Andrea Lenzi, Lorenzo Maria Donini

Table 3. Stepwise linear regression analysis using FLI as dependent variable.

Model	Unstandardized Coefficients§		Standardized coefficients	t	p
	B	SE	Beta		
GH (ug/mL)	-1.267	0.505	-0.133	-2.508	0.013
TrFM/ ASM ratio	25.095	5.953	0.271	4.215	<0.001
(Costant)	-31.850	9.823	n. a.	-3.242	0.002
R^2 = 0.734; R^2 adj. = 0.720; SEE = 11.13					

§ After adjustment for age, BMI, total FM, FFM, truncal FM, and ISI- Matsuda

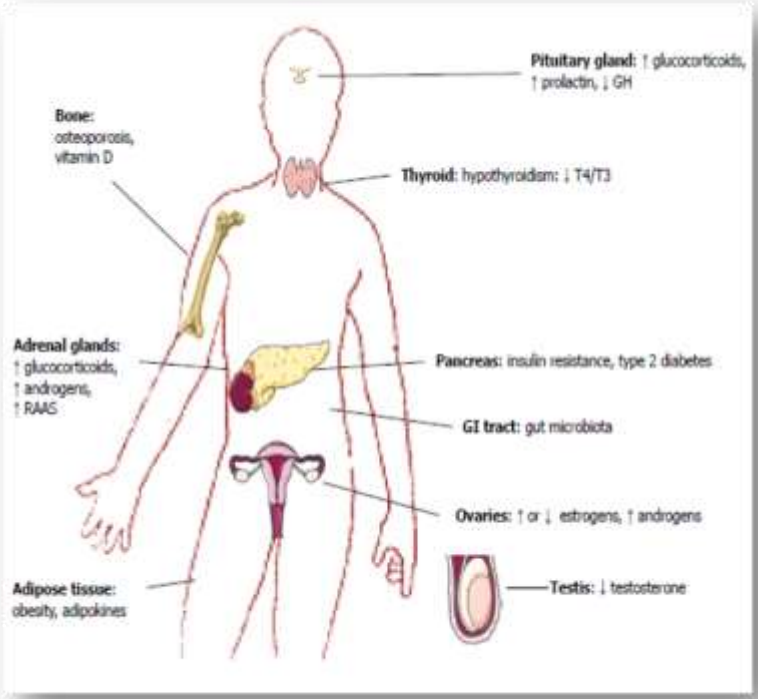
Legend: FLI = fatty liver index; GH = growth hormone; TrFM/ ASM = truncal fat mass/ appendicular skeletal muscle; SE = standard error; SEE = standard error of the estimate; BMI = body mass index; FM = fat mass; FFM; = fat- free mass, ISI = insulin sensitivity index; n.a. = not available.

Stepwise linear regression analysis showed that GH levels were significantly negatively correlated with FLI, while the TrFM/ ASM ratio was positively associated with FLI, after adjustment for age, BMI, total fat mass, truncal fat mass, fat- free mass, and ISI- Matsuda.

PLOS ONE | DOI:10.1371/journal.pone.0145811 January 7, 2016

Endocrine causes of nonalcoholic fatty liver disease

World J Gastroenterol 2015 October 21; 21(39): 11053-11076

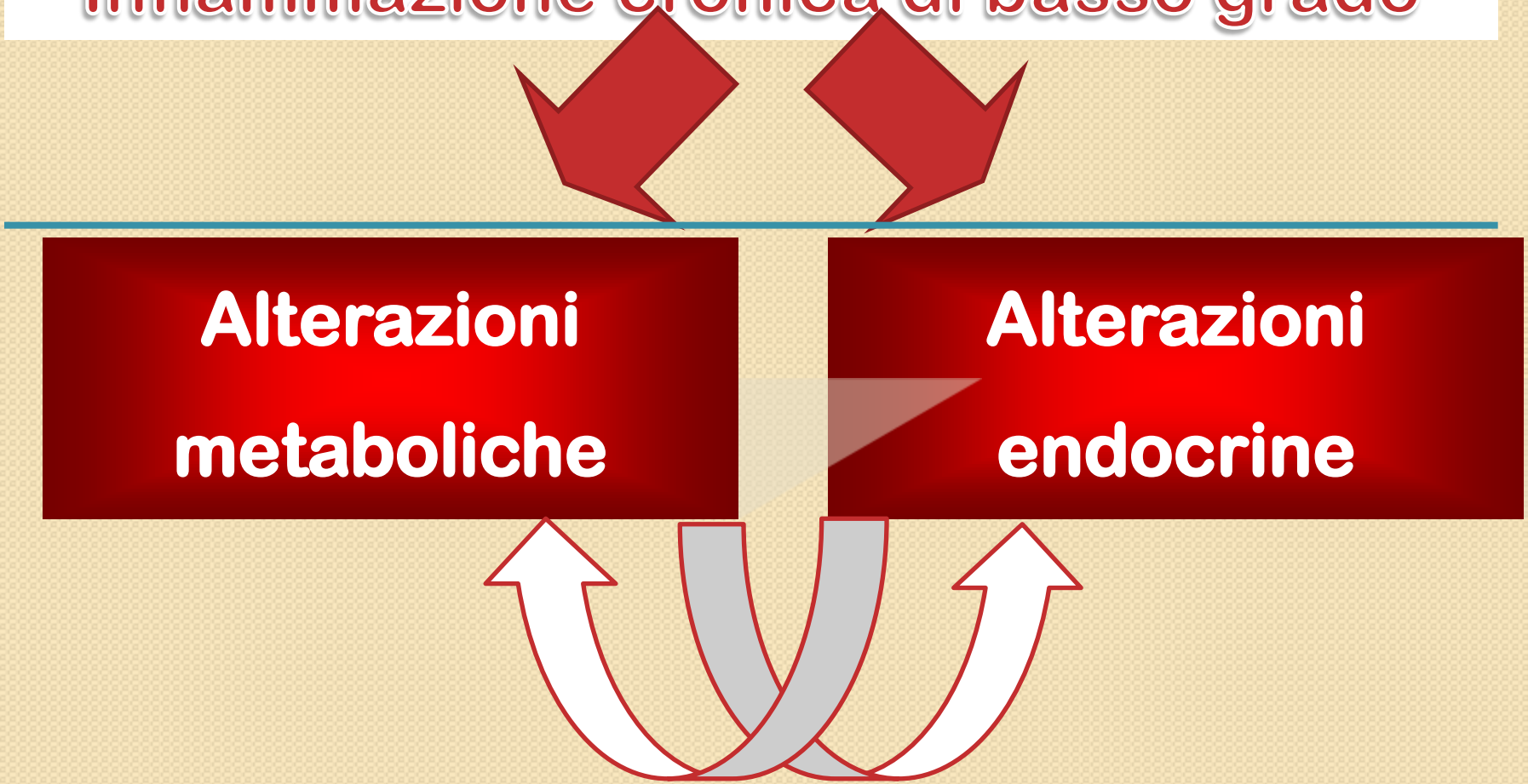


NAFLD with metabolic alterations such as type 2 diabetes is well described and related to insulin resistance, with NAFLD being recognized as the hepatic manifestation of metabolic syndrome. However, NAFLD may also coincide with endocrine diseases such as polycystic ovary syndrome, hypothyroidism, growth hormone deficiency or hypercortisolism. It is therefore essential to remember, when discovering altered liver enzymes or hepatic steatosis, that endocrine diseases can cause NAFLD. Indeed, the overall prognosis of NAFLD may be modified by treatment of the underlying endocrine pathology.

Sindrome Metabolica

obesità viscerale

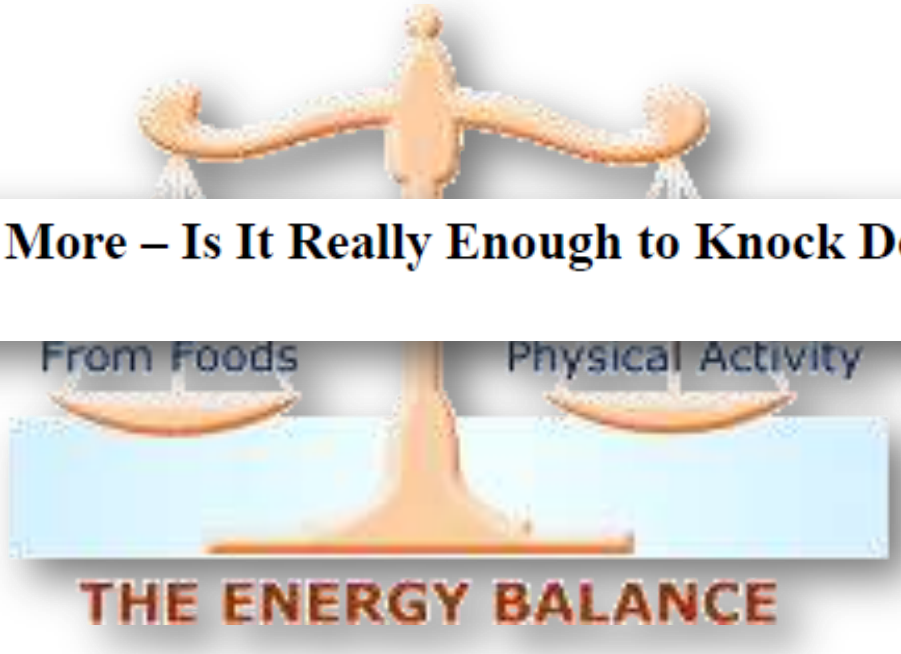
Infiammazione cronica di basso grado



QUALE TERAPIA?

The body weight depends only on our will?

Eat Less and Exercise More – Is It Really Enough to Knock Down the Obesity Pandemia?



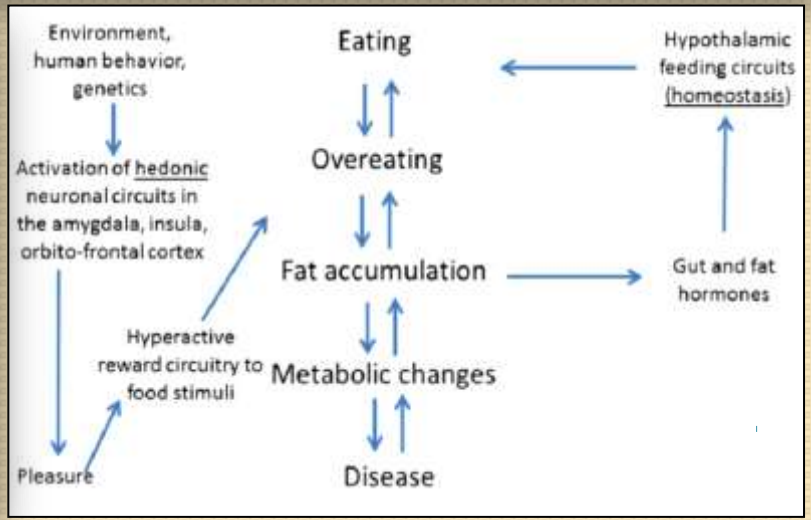
Obesity Bias, Medical Technology, and the Hormonal Hypothesis: Should We Stop Demonizing Fat People?

The American Journal of Medicine (2015) 128, 456-460

There is adequate evidence to demonstrate that bias toward obese individuals by health professionals is common. Bias predisposes to errors in medical judgment and care. There is also evidence to show that the pathophysiology of obesity is more complex than eating too much and moving too little. Widespread obesity is a new phenomenon in the United States and reflects changes in culture, including food, at many levels. The modern abundance of low-cost, available, palatable, energy-dense processed foods and the ability of these foods to activate central nervous system centers that drive food preference and overeating appear to play an important role in the obesity epidemic. The usual hormonal systems that promote body weight homeostasis appear to have been counterbalanced by pleasurable (hedonic) influences these foods generate in higher neurologic networks, including the limbic system. The use of medical technology, such as functional magnetic resonance imaging, to quantitate hedonic responses to food, enhance taste, and effectively develop and market commercial food products has produced new areas of ethical concern and opportunities to better understand eating and satiety. These developments further demonstrate the urgency to address the bias that exists toward obese patients.

THE HORMONAL HYPOTHESIS OF OBESITY

Because insulin is the primary hormone controlling fat deposition, the most likely evidence-based successor to the set-point theory of weight control appears to be a "hormonal hypothesis" of weight control.[13] The natural extrapolation of this hypothesis is that not only the calories in foods but also the composition and kind of foods consumed play a central role in the physiology of obesity. Certain food components, such as high fructose corn syrup, ratios of salt, sugar, and fat, and flavor enhancers, seem central to the process.[27,28] This is not a new idea, but one for which consensus has grown as data have accumulated.



Probability of an Obese Person Attaining Normal Body Weight: Cohort Study Using Electronic Health Records

Objectives. We examined the probability of an obese person attaining normal body weight.

Methods. We drew a sample of individuals aged 20 years and older from the United Kingdom's Clinical Practice Research Datalink from 2004 to 2014. We analyzed data for 76 704 obese men and 99 791 obese women. We excluded participants who received bariatric surgery. We estimated the probability of attaining normal weight or 5% reduction in body weight.

Results. During a maximum of 9 years' follow-up, 1283 men and 2245 women attained normal body weight. In simple obesity (body mass index = 30.0–34.9 kg/m^2), the annual probability of attaining normal weight was 1 in 210 for men and 1 in 124 for women, increasing to 1 in 1290 for men and 1 in 677 for women with morbid obesity (body mass index = 40.0–44.9 kg/m^2). The annual probability of achieving a 5% weight reduction was 1 in 8 for men and 1 in 7 for women with morbid obesity.

Conclusions. The probability of attaining normal weight or maintaining weight loss is low. Obesity treatment frameworks grounded in community-based weight management programs may be ineffective. (*Am J Public Health.* Published online ahead of print July 16, 2015: e1–e6. doi:10.2105/AJPH.2015.302773)

TABLE 2—Annual Probability of Achieving Normal Weight by Initial BMI Category and Gender: United Kingdom, 2004–2014

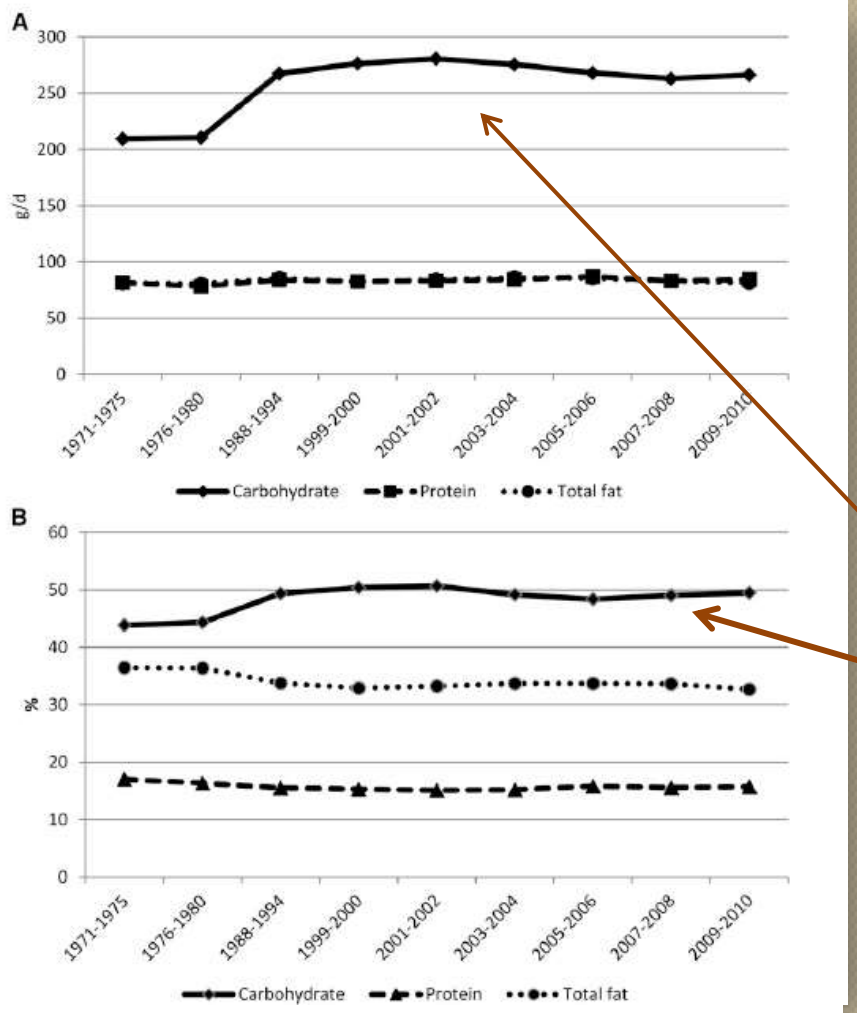
Initial BMI Category	No. Participants	No. Person-Years During Follow-Up	No. Attaining Normal BMI	Annual Probability of Attaining Normal BMI, Estimate (95% CI)
Men, kg/m^2				
30.0–34.9				1 in 210 (197, 225)
35.0–39.9				1 in 701 (619, 797)
40.0–44.9				in 1290 (1023, 1651)
≥ 45.0				1 in 362 (300, 442)
Women, kg/m^2				
30.0–34.9				1 in 124 (118, 131)
35.0–39.9				1 in 430 (390, 475)
40.0–44.9				1 in 677 (599, 769)
≥ 45.0				1 in 608 (527, 704)

Note. BMI = body mass index; CI = conf

TABLE 3—Annual Probability …**m, 2004–2014**

Initial BMI Category				Annual Probability of Attaining 5% Reduction in Body Weight
Men, kg/m^2				
30.0–34.9	27 966	135 394	11 869	1 in 12
35.0–39.9	27 490	118 266	13 805	1 in 9
40.0–44.9	14 767	57 099	8 100	1 in 8
≥ 45.0	6 481	20 900	4 177	1 in 5
Women, kg/m^2				
30.0–34.9	27 251	123 567	12 792	1 in 10
35.0–39.9	27 373	116 042	13 972	1 in 9
40.0–44.9	26 716	103 849	15 208	1 in 7
≥ 45.0	18 451	63 397	11 340	1 in 6

Trends in energy intake among adults in the United States: findings from NHANES[1–3]



Mean adjusted intakes of macronutrients among adults aged 20–74 y by NHANES study period. A: Results shown as absolute intake in grams per day. B: Results shown as percentage of energy intake. Results were adjusted for age, sex, race or ethnicity, educational status, and BMI

Background: Energy intake is a key determinant of weight.

Objective: Our objective was to examine trends in energy intake in adults in the United States from 1971–1975 to 2009–2010.

Design: The study was a trend analysis of 9 national surveys in the United States that included data from 63,761 adults aged 20–74 y.

Results: Adjusted mean energy intake increased from 1955 kcal/d during 1971–1975 to 2269 kcal/d during 2003–2004 and then declined to 2195 kcal/d during 2009–2010 (*P*-linear trend < 0.001, *P*-nonlinear trend < 0.001). During the period from 1999–2000 to 2009–2010, no significant linear trend in energy intake was observed ($P = 0.058$), but a significant nonlinear trend was noted ($P = 0.042$), indicating a downward trend in energy intake. Significant decreases in energy intake from 1999–2000 to 2009–2010 were noted for participants aged 20–39 y, men, women, and participants with a BMI (in kg/m^2) of 18.5 to <25 and ≥ 30.

Conclusions: After decades of increases, mean energy intake has decreased significantly since 2003–2004. *Am J Clin Nutr* 2013;97:848–53.

Obesity, Abdominal Obesity, Physical Activity, and Caloric Intake in US Adults: 1988 to 2010

Uri Ladabaum, MD, MS,[a,b] Ajitha Mannalithara, PhD,[a,b] Parvathi A. Myer, MD, MHS,[a,b] Gurkirpal Singh, MD[a,b]

BACKGROUND: Obesity and abdominal obesity are associated independently with morbidity and mortality. Physical activity attenuates these risks. We examined trends in obesity, abdominal obesity, physical activity, and caloric intake in US adults from 1988 to 2010.

METHODS: Univariate and multivariate analyses were performed using National Health and Nutrition Examination Survey data.

RESULTS: Average body mass index (BMI) increased by 0.37% (95% confidence interval [CI], 0.30-0.44) per year in both women and men. Average waist circumference increased by 0.37% (95% CI, 0.30-0.43) and 0.27% (95% CI, 0.22-0.32) per year in women and men, respectively. The prevalence of obesity and abdominal obesity increased substantially, as did the prevalence of abdominal obesity among overweight adults. Younger women experienced the greatest increases. The proportion of adults who reported no leisure-time physical activity increased from 19.1% (95% CI, 17.3-21.0) to 51.7% (95% CI, 48.9-54.5) in women, and from 11.4% (95% CI, 10.0-12.8) to 43.5% (95% CI, 40.7-46.3) in men. Average daily caloric intake did not change significantly. BMI and waist circumference trends were associated with physical activity level but not caloric intake. The associated changes in adjusted BMIs were 8.3% (95% CI, 6.9-9.6) higher among women and 1.7% (95% CI, 0.68-2.8) higher among men with no leisure-time physical activity compared with those with an ideal level of leisure-time physical activity.

CONCLUSIONS: Our analyses highlight important dimensions of the public health problem of obesity, including trends in younger women and in abdominal obesity, and lend support to the emphasis placed on physical activity by the Institute of Medicine.

 • The American Journal of Medicine (2014) 127, 717-727

Secular differences in the association between caloric intake, macronutrient intake, and physical activity with obesity

Background: To determine whether the relationship between caloric intake, macronutrient intake, and physical activity with obesity has changed over time.

Methods: Dietary data from 36,377 U.S. adults from the National Health and Nutrition Survey (NHANES) between 1971 and 2008 was used. Physical activity frequency data was only available in 14,419 adults between 1988 and 2006. Generalised linear models were used to examine if the association between total caloric intake, percent dietary macronutrient intake and physical activity with body mass index (BMI) was different over time.

Results: Between 1971 and 2008, BMI, total caloric intake and carbohydrate intake increased 10–14%, and fat and protein intake decreased 5–9%. Between 1988 and 2006, frequency of leisure time physical activity increased 47–120%. However, for a given amount of caloric intake, macronutrient intake or leisure time physical activity, the predicted BMI was up to 2.3 kg/m^2 higher in 2006 that in 1988 in the mutually adjusted model ($P < 0.05$) Obesity Research & Clinical Practice (2015)

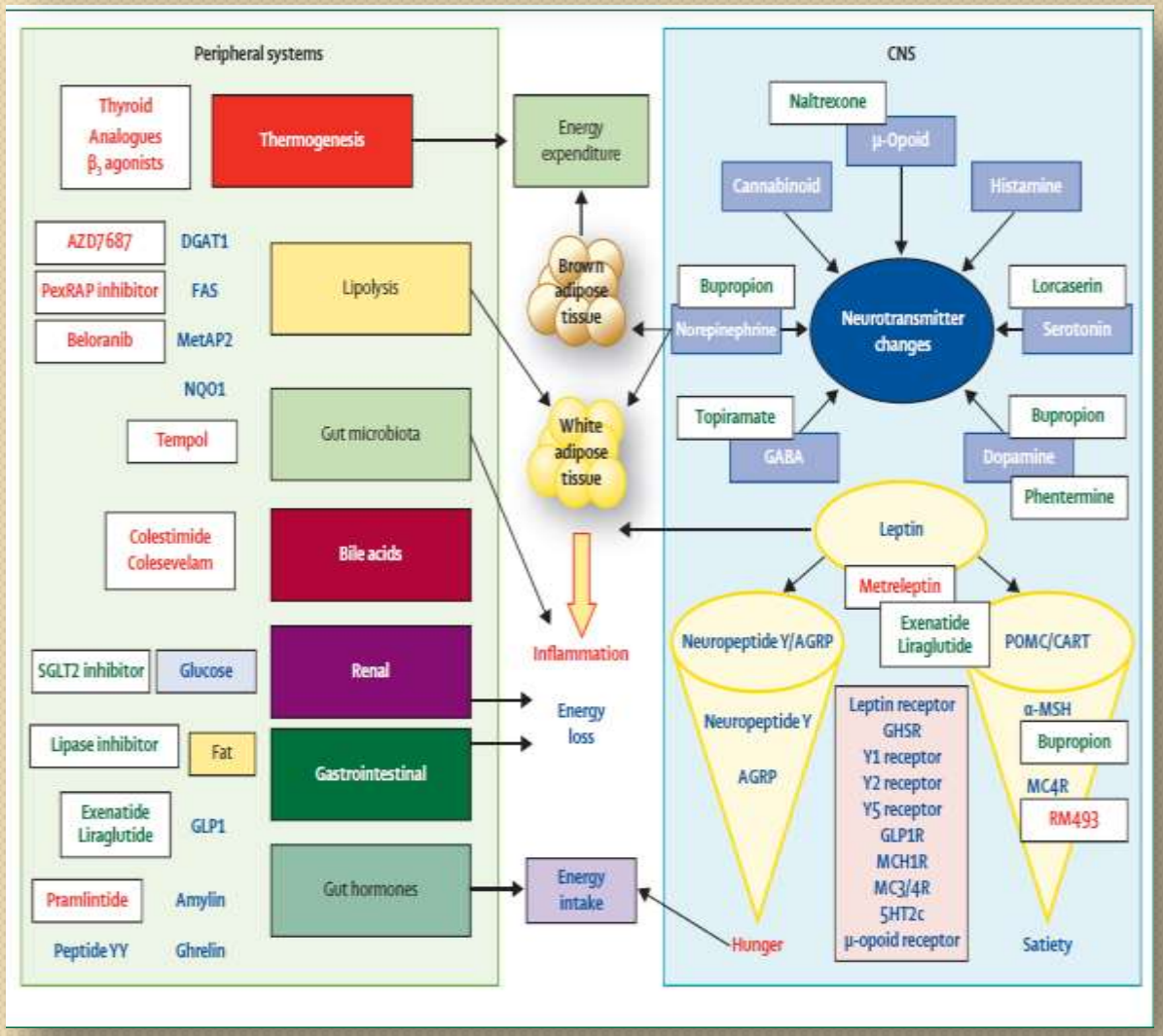
There are different types of obesity that need to be treated in different ways.

Table 1. A Guide to Selecting Treatment

Treatment	BMI Category (kg/m^2)				
	25–26.9	27–29.9	30–34.9	35–39.9	≥40
Diet, physical activity, and behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy		With comorbidities	+	+	+
Surgery				With comorbidities	

Management of obesity

George A Bray, Gema Frühbeck, Donna H Ryan, John P H Wilding



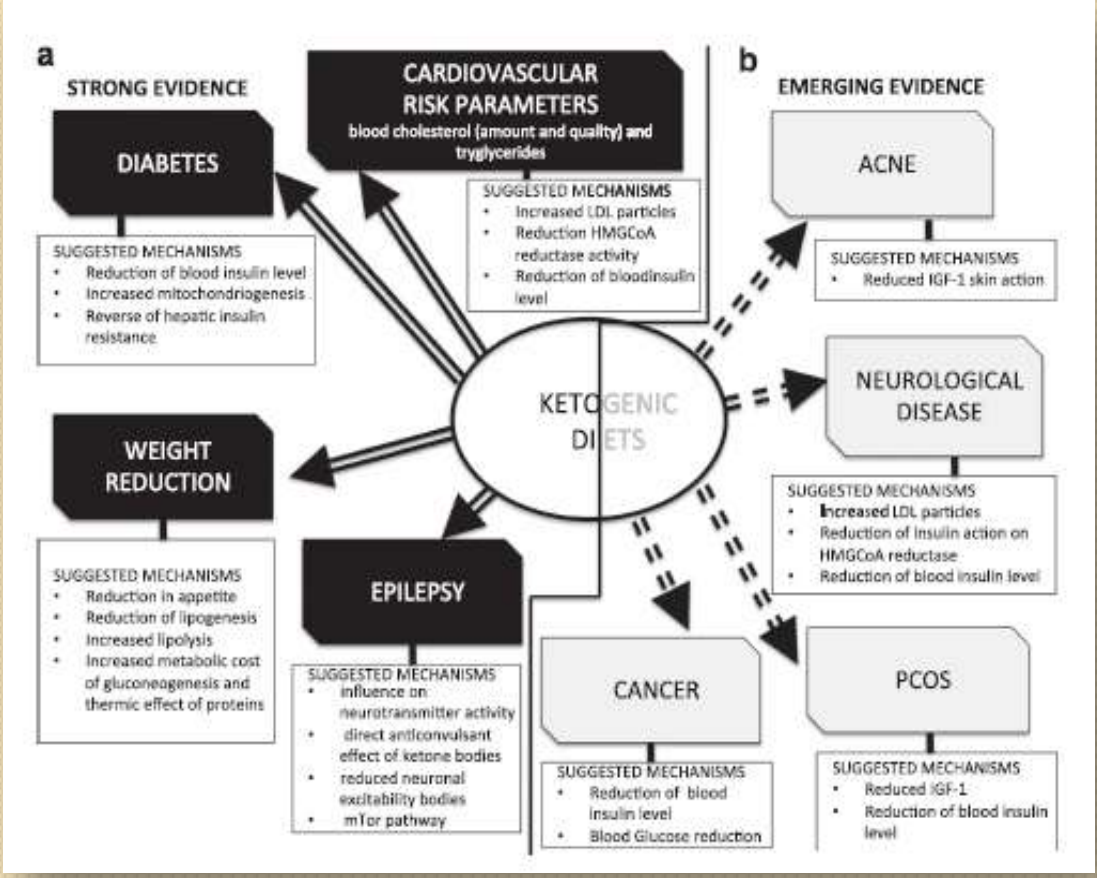
Targets for anti-obesity drugs

Inside the white boxes green names stand for already approved drugs, whereas red names represent drugs in phase 1–3 development. The intermediate area represents where the effects of both central and peripheral actions converge—namely, on the two main components of the energy balance equation: energy intake and expenditure.. Most of the drugs tested in clinical trials are aimed at peripheral systems. Thus, thyroid analogues and β3 adrenergic agonists induce thermogenesis by activation of brown adipose tissue, thereby increasing energy expenditure. Enzymes involved in lipid metabolism, such as DGAT, FAS, MetAP2, and NQO1 are also being targeted. The gut microbiome and the regulation of bile acids represent further targets to combat obesity. The lipase and SGLT2 inhibitors favour energy loss by the gastrointestinal and renal elimination of fat and glucose, respectively. Agonism of pancreatic and intestinal hormones like amylin and GLP-1 has also been shown to be useful for weight loss.

DGAT1=diacylglycerol O-acyltransferase aminotransferase 1. PexRAP=peroxisomal reductase activating PPARγ. FAS=fatty acid synthase. MetAP2=methionyl aminopeptidase 2. NQO1=NAD(P)H dehydrogenase: quinone oxidoreductase 1.

www.thelancet.com Published online February 8, 2016

Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets



Very-low-carbohydrate diets or ketogenic diets have been in use since the 1920s as a therapy for epilepsy and can, in some cases, completely remove the need for medication. From the 1960s onwards they have become widely known as one of the most common methods for obesity treatment. Recent work over the last decade or so has provided evidence of the therapeutic potential of ketogenic diets in many pathological conditions, such as diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer
and the amelioration of respiratory and cardiovascular disease risk factors. The possibility that modifying food intake can be useful for reducing or eliminating pharmaceutical methods of treatment, which are often lifelong with significant side effects, calls for serious investigation.

European Journal of Clinical Nutrition (2013) **67**, 789–796

Metabolic Syndrome Among Marijuana Users in the United States: An Analysis of National Health and Nutrition Examination Survey Data

Metabolic Syndrome Component	Marijuana Use Category: Never Used* (Reference) n = 3847 Mean (SE)	Past Use† n = 3623 Mean (SE)	P-Value	Current Use‡ n = 1008 Mean (SE)	P-Value
Waist circumference, cm§					
Males	100.7 (0.55)	100.5 (0.48)	.75	**93.8 (0.75)**	**<.0001**
Females	93.4 (0.48)	92.7 (0.57)	.26	91.9 (1.10)	.17
Systolic blood pressure, mm Hg	117.7 (0.40)	118.1 (0.29)	.36	**119.4 (0.48)**	**.01**
Diastolic blood pressure, mm Hg	71.0 (0.41)	**72.0 (0.33)**	**.03**	70.3 (0.40)	.18
HDL cholesterol, mg/dL§					
Males	45.4 (0.37)	**47.0 (0.40)**	**.01**	**51.1 (0.84)**	**<.0001**
Females	57.2 (0.47)	**59.4 (0.68)**	**.02**	57.7 (0.90)	.60
Triglycerides, mg/dL	127.7 (2.95)	132.8 (2.76)	.25	126.4 (4.1)	.81
Fasting glucose, mg/dL	99.6 (0.51)	**98.4 (0.38)**	**.03**	**97.3 (0.78)**	.02

Bold values were significant, $P < .05$.
*Defined as participants with no report of lifetime marijuana use, even once.
†Defined as participants who used marijuana before in lifetime but not in the last 30 days.
‡Defined as participants who used marijuana at least once in the last 30 days.
§Sex-specific standardized cut-off values.

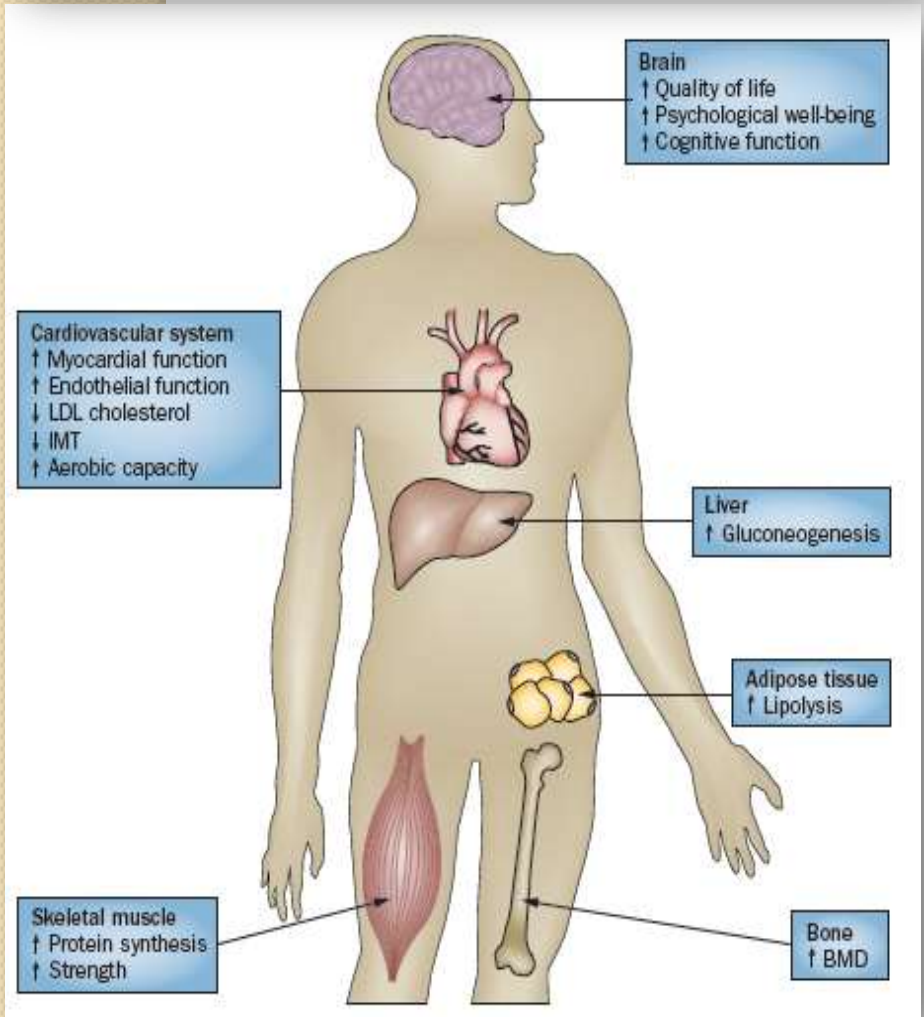
- Current and past marijuana users have lower odds of presenting with metabolic syndrome than those with no history of marijuana use, depending on the age group.
- There was a lower prevalence of metabolic syndrome among current and past marijuana users when compared with never users.
- Individual metabolic syndrome component mean estimates varied across use categories but were generally lower among marijuana users compared with never users, with the exception of blood pressure.

Table 3 Adjusted* Odds of Metabolic Syndrome by Marijuana Use Category by Age Group, National Health and Nutrition Examination Surveys, 2005-2010

	Reference Group = Never Used Marijuana: Metabolic Syndrome AOR (95% CI)
Overall sample	
Past use	0.76 (0.57-1.02)
Current use	0.69 (0.47-1.00)
Emerging adults	
Past use	0.62 (0.30-1.27)
Current use	**0.46 (0.24-0.89)**
Adults	
Past use	1.14 (0.81-1.61)
Current use	1.05 (0.70-1.56)
Middle-aged adults	
Past use	**0.61 (0.40-0.91)**
Current use	**0.49 (0.25-0.97)**

The American Journal of Medicine (2016) 129, 173-179

Adult Growth Hormone Deficiency



Clinical Consequence	Effect of GH Replacement
Body composition	
General and central adiposity	Decrease
Reduce lean mass	Increase
Reduced bone mass	Increase
Function	
Reduced exercise capacity	Improve
Muscle weakness	Improve
Impaired cardiac function	Improve
Hypohydrosis	Improve
Quality of life	
Low mood	Improve
Fatigue	Improve
Low motivation	Improve
Reduced satisfaction	Improve
Cardiovascular risk profile	
Abnormal lipid profile	Improve
Insulin resistance	Improves in long term
Inflammatory markers	Decrease
Intimal media thickening	Decrease
Cardiovascular and cerebrovascular events	Unknown
Laboratory	
Blunted peak GH to stimulation	
Low IGF-I	Increase
Hyperinsulinemia	Increase
High LDL- and low HDL-cholesterol	Improve
Longevity	Unknown

J Clin Endocrinol Metab, June 2013, 98(6):2187–2197

The end-organ effects of liothyronine for levothyroxine substitution therapy in primary hypothyroidism, a randomized, double-blind, cross-over study

F. S. Celi [1,*], J. D. Linderman [1], M. Zemskova [2], S. Smith [1], M. C. Skarulis [1], P. W. Butler [2], G. Csako [3], R. Costello [3], F. Pucino [1]

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2010

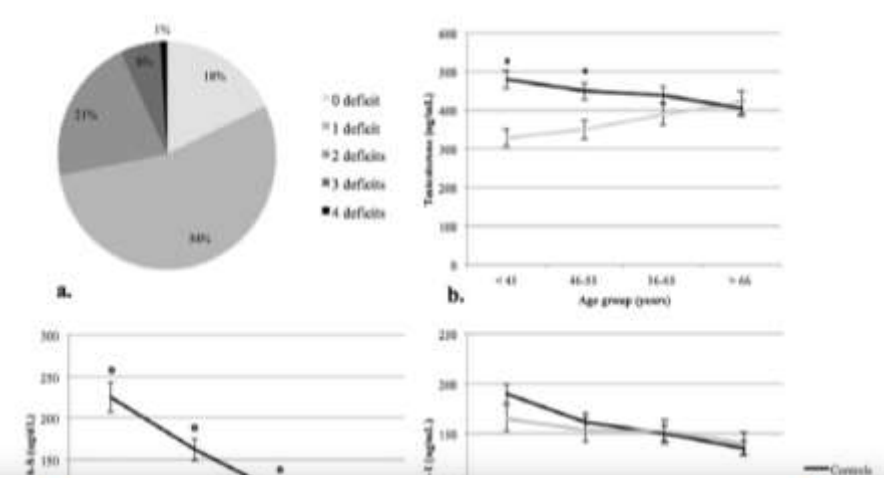
- Equivalent doses of LT-4 and L-T3 replacement therapy result in a differential hormonal response at end organ targets of thyroid hormone action.

- These effects were evident in the liver, as indicated by changes in serum cholesterol and SHBG levels, while no differences were observed in cardiovascular parameters or in insulin sensitivity.

- **L-T3 treatment resulted in a significant weight loss. In humans replacement with L-T4 alone may not achieve a euthyroid state at all targets of TH action.**

Multiple hormone deficiencies in chronic heart failure

International Journal of Cardiology 184 (2015) 421–423



Hormone replacement therapy in heart failure

Curr Opin Cardiol 2015 May;30(3):277-84

- CHF is associated to a wide array of anabolic derangements, including GH and testosterone deficiency, L-T_3 syndrome, and insulin resistance, which carry prognostic significance.
- Testosterone therapy demonstrated to increase the exercise tolerance and well being in both male and female CHF patients.
- GH replacement therapy appears to be associated with left ventricular reverse remodeling and increased exercise capacity.
- L-T_3 syndrome is observed particularly in advanced CHF, but despite short-term benefits, no long-term data

IGF-1 predicts survival in chronic heart failure. Insights from the T.O.S.CA. (Trattamento Ormonale Nello Scompenso CArdiaco) registry

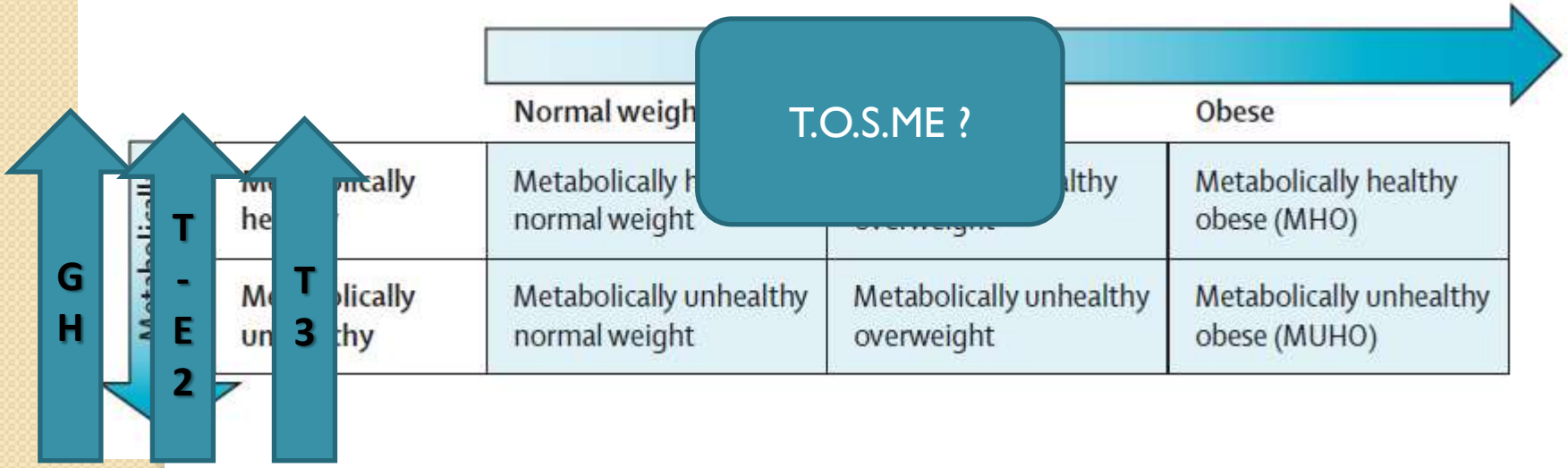
In the last decade, a growing body of evidence has led to the **hypothesis that chronic heart failure (CHF) is indeed a multiple hormone deficiency syndrome (MHDS),** characterized by a **reduced anabolic drive that bears relevant functional and prognostic implications.** Of note, GH or testosterone replacement therapy provides beneficial effects, particularly on exercise tolerance and well-being .

Table 1. Summary of prevalence and clinical correlates of hormonal deficiencies and of effects of hormonal therapies

	Observational studies			Interventional studies: Functional outcomes	
	Prevalence	Prognostic information	Type of study	Acute administration	Chronic administration
GH deficiency	30–40%	Low IGF-1 is associated with lower muscle strength and higher neurohormonal activation	PR, CS	Reversal of endothelial dysfunction	Improved exercise tolerance
		Low IGF-1 predicts all-cause mortality	OB, PR	Enhanced LV contractility	Reverse LV remodeling
		GH deficiency is associated with poor functional status	PR, CS		
Testosterone deficiency	≈25%	Associated with reduced exercise tolerance	PR, CS	Increased cardiac output	Improved exercise tolerance
					Improved insulin sensitivity
					Improved muscle strength
Low-T_3 state	13–30%	Associated with increased all-cause mortality	OB, PR	Neurohormonal deactivation	Increased cardiac output
Insulin resistance	≈33% (in nondiabetics)	Associated with more severe HF symptoms, worse functional capacity, and poor survival	PR, CS		Improved exercise tolerance (metformin)
					Improved exercise tolerance and LV ejection fraction (GLP-1 agonist)

Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications

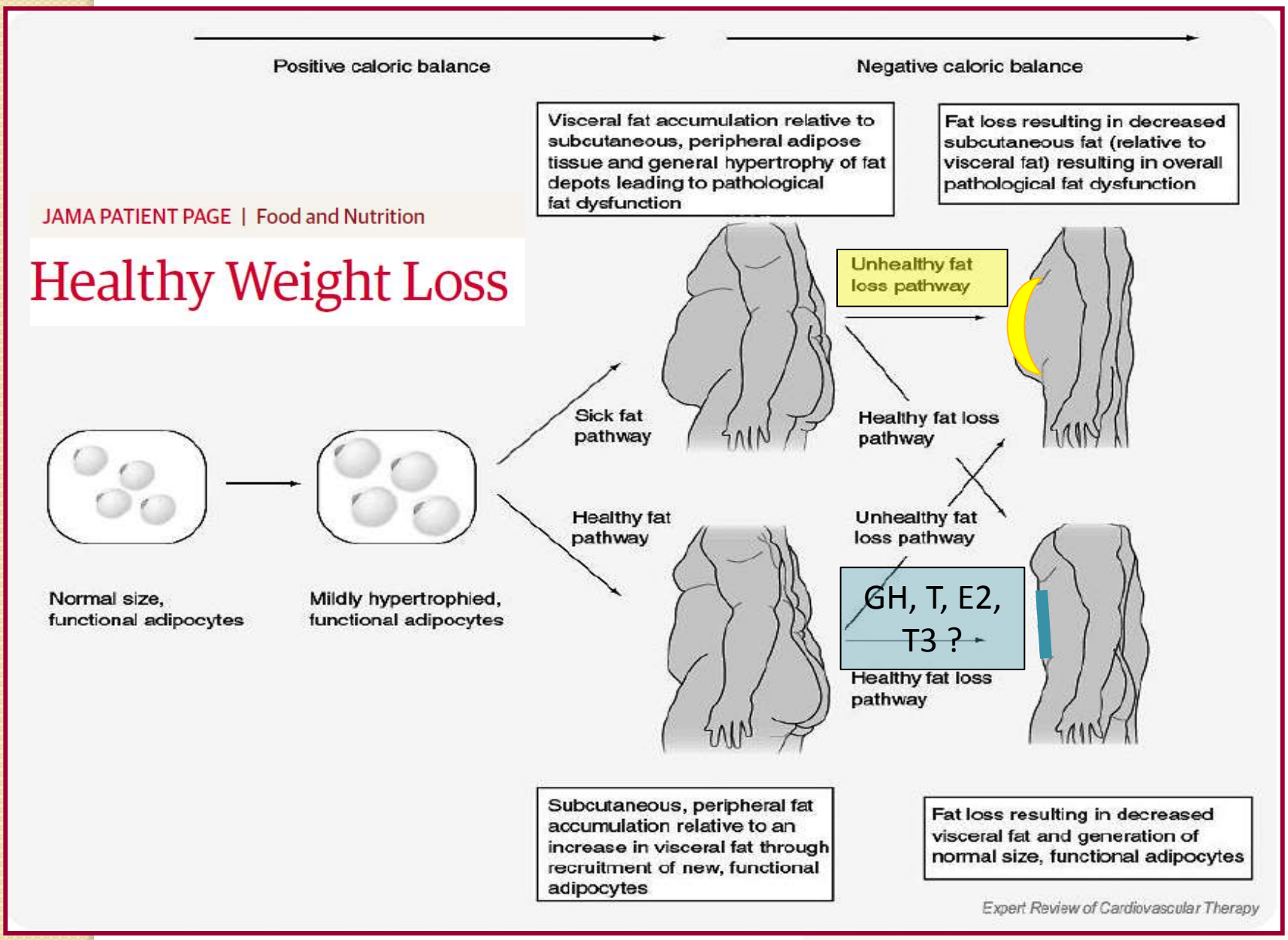
Norbert Stefan, Hans-Ulrich Häring, Frank B Hu, Matthias B Schulze



- Absence of abdominal obesity on the basis of waist circumference (men ≤102 cm, women ≤88 cm)
- Absence of metabolic syndrome components—eg, normal blood pressure, normal lipid values, normal fasting glucose concentrations (at times also including normal C-reactive protein concentrations)
- Insulin sensitive on the basis of the homoeostatic model assessment of insulin resistance (HOMA-IR)
- High level of cardiorespiratory fitness

- Increased adipogenesis in subcutaneous adipose tissue
- Increased de-novo lipogenesis in adipocytes from subcutaneous adipose tissue
- Decreased mitochondrial iron transport into the mitochondrial matrix
- Increased adiponectin and decreased inflammatory pathway signalling

www.thelancet.com/diabetes-endocrinology Published online August 30, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70062-7



Int J Clin Pract, October 2008, 62, 10, 1474–1483

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