INFLUENZA DELLA DIETA CHETOGENICA SULLA SALUTE DELL'OSSO

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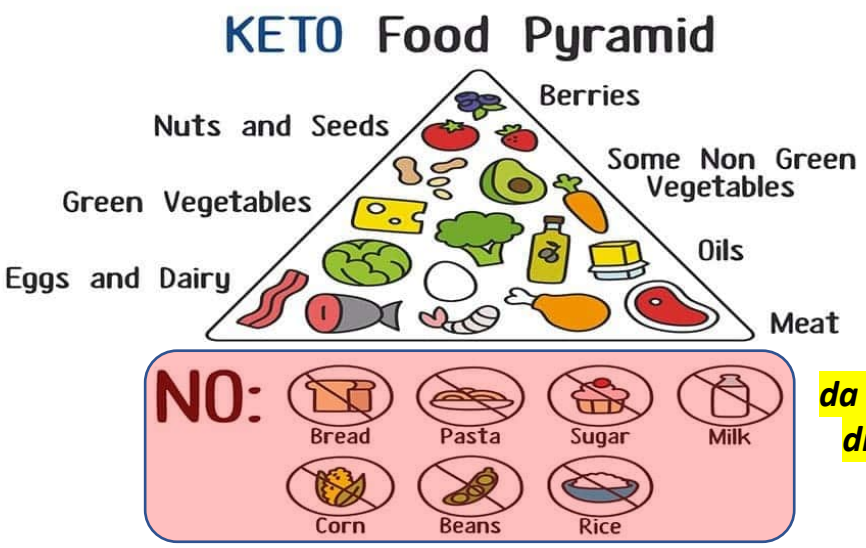
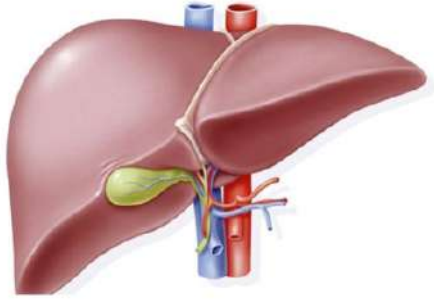
IL TERMINE “CHETOGENICO”, IN GENERALE…

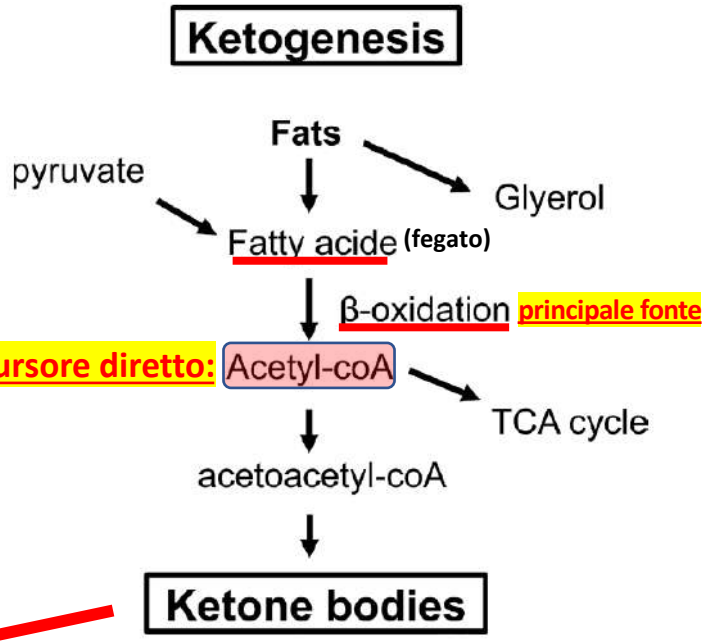
…la capacità di stimolare la produzione di KB da parte di varie cellule del nostro corpo, con un'integrazione < 100 g di glucosio

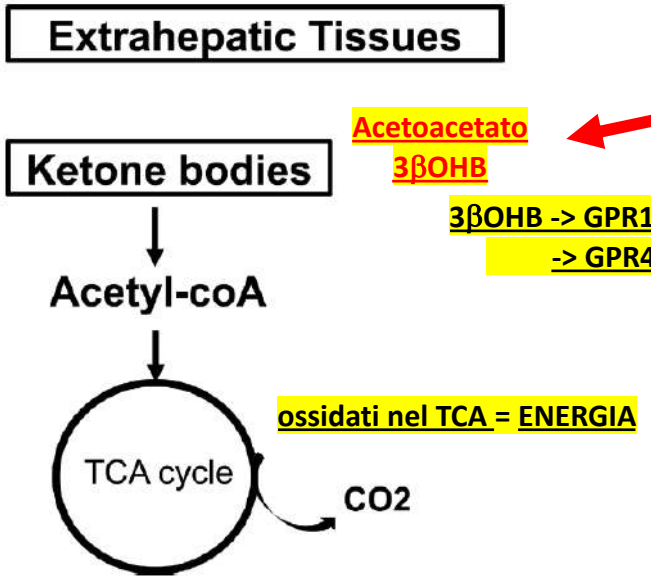


FONTE PRIMARIA DI KB



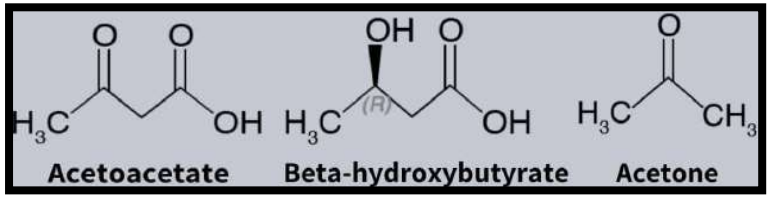
da FFA durante periodi di scarsa assunzione cibo (digiuno), diete restrittive CHO, esercizio fisico intenso prolungato





3βOHB -> GPR109A/HCAR2
-> GPR41/FFAR3

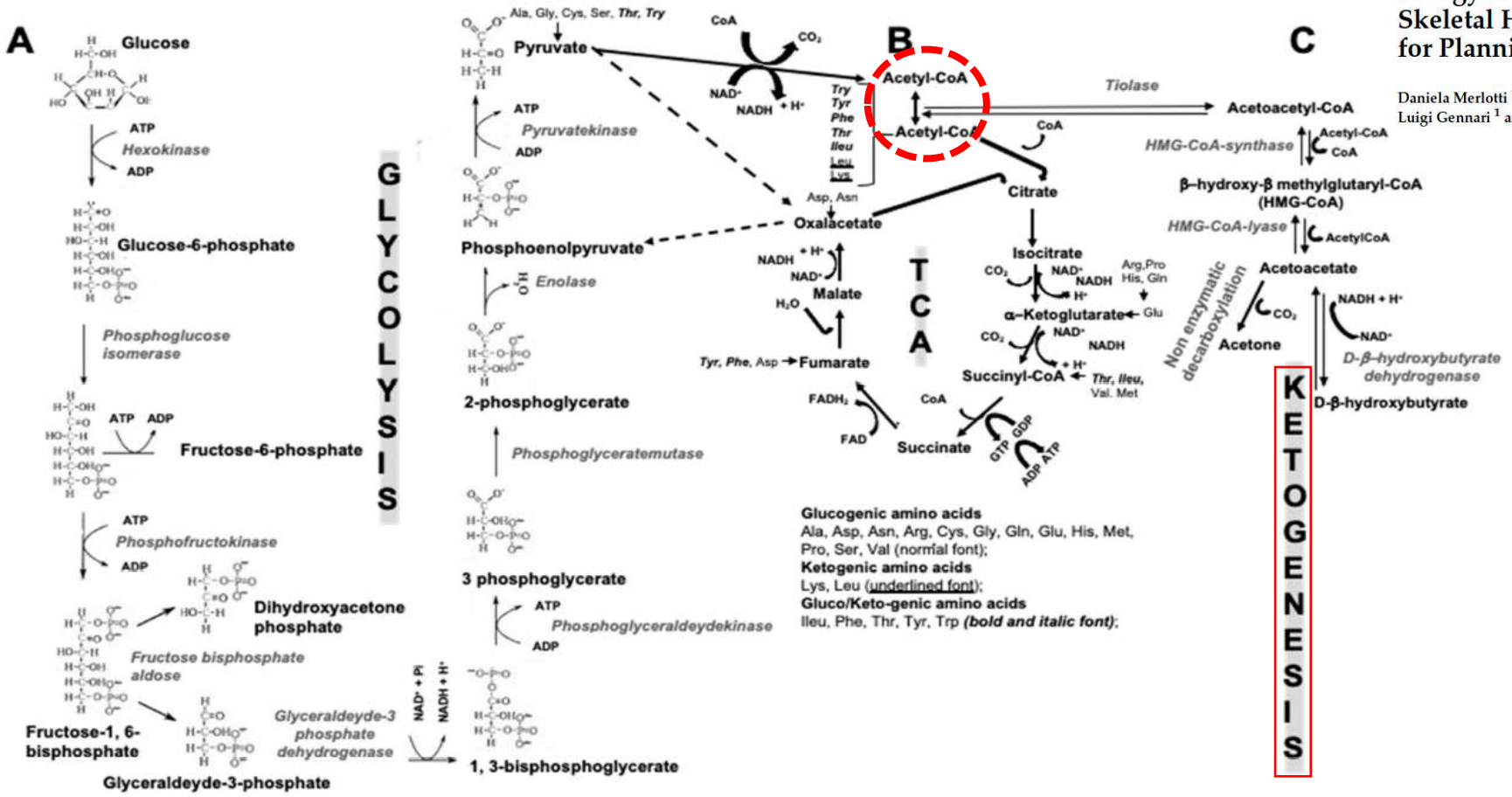
3βOHB: il principale KB nel metabolismo umano



INTERCONNESSIONI TRA GLICOLISI (A), CICLO DEGLI ACIDI TRICARBOSSILICI (TCA) (B), E CHETOGENESI (C)

DIGIUNO PROLUNGATO: gluconeogenesi «sottrae» intermedi al ciclo di Krebs, indirizza Acetil-CoA verso i corpi chetonici

Koeslag JH et al. 1980; Stryer L. 1995



International Journal of Molecular Sciences
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Review

Energy Metabolism and Ketogenic Diets: What about the Skeletal Health? A Narrative Review and a Prospective Vision for Planning Clinical Trials on this Issue

Daniela Merlotti [1], Roberta Cosso [2], Cristina Eller-Vainicher [3], Fabio Vescini [4], Iacopo Chiodini [2,5], Luigi Gennari [1] and Alberto Falchetti [2,*]

FORME di DIETE CHETOGENICHE (KDs)

(1) the “classic” KD;
(2) the modified Atkins diet (MAD);
(3) the medium chain triglyceride diet (MCT);
(4) the low glycemic index diet (LGID).

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Questi regimi si differenziano principalmente nel rapporto lipidi/proteine/CHO

PIU’ RECENTEMENTE: VLCKD = VERY LOW CALORIES KETOGENIC DIET

Mima il digiuno = CHO, < 30 g/die (13% dell'apporto energetico totale), aumento relativo di **grassi (44%) e proteine (43%)**

Assunzione giornaliera totale di energia <800 Kcal.

Importante: VLCKD non è una dieta iperproteica, l’apporto proteico giornaliero è 1,2–1,5 g/kg di p.c. ideale!!!

Daniel S, Soleymani T, Garvey WT. A complications-based clinical staging of obesity to guide treatment modality and intensity. Curr. Opin. Endocrinol. Diabetes Obes. 2013

PER CHI «NASCE» LA DIETA CHETOGENICA?

La dieta chetogenica si è originariamente dimostrata efficace nell'epilessia farmaco-resistente, oltre 100 anni fa.

Effetto anticonvulsivante diretto e ridotta eccitabilità neuronale indotta dai KB

KDT per anni: "confinate" alla terapia di forme epilettiche resistenti ad anticonvulsivanti

1. **Oggi: importante diffusione, con utilizzo "esteso" a obesi gravi, Obesi+DMT2, Obesi ipertesi…**
2. **…quindi la possibilità di incontrare uno di questi nella pratica ambulatoriale quotidiana è in aumento**

Table 2 Indications for the use of VLCKD in metabolic diseases

Strong recommendations	Strength of recommendations and quality of evidence according to GRADE system
Severe obesity	(1 ØØØO)
Management of severe obesity before bariatric surgery	(1 ØØØO)
Sarcopenic obesity	(1 ØØØO)
Obesity associated with type 2 diabetes (preserved beta cell function)	(1 ØØØO)
Obesity associated with hypertriglyceridemia	(1 ØØØO)
Obesity associated with hypertension	(1 ØØØO)
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet	(1 ØØØO)
Weak recommendations	
Obesity associated with dysbiosis of the gut microbiota	(2 ØØØO)
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol	(2 ØØØO)
Obesity associated with non-alcoholic fatty liver disease (NAFLD)	(2 ØØØO)
Obesity associated with heart failure (NYHA I–II)	(2 ØOOO)
Obesity associated with atherosclerosis	(2 ØOOO)
Male obesity secondary hypogonadism	(2 ØØØO)
Obesity associated with polycystic ovary syndrome (PCOS)	(2 ØOOO)
Menopausal transition-related obesity	(2 ØOOO)
Neurodegenerative disorders associated with sarcopenic obesity	(2 ØOOO)

CONSENSUS STATEMENT

Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

M. Caprio[1,2] · M. Infante[3] · E. Moriconi[1,4] · A. Armani[1] · A. Fabbri[3] · G. Mantovani[5] · S. Mariani[4] · C. Lubrano[4] · E. Poggiogalle[4] · S. Migliaccio[6] · L. M. Donini[4] · S. Basciani[4] · A. Cignarelli[7] · E. Conte[7] · G. Ceccarini[8] · F. Bogazzi[9] · L. Cimino[10] · R. A. Condorelli[10] · S. La Vignera[10] · A. E. Calogero[10] · A. Gambineri[11] · L. Vignozzi[12] · F. Prodam[13] · G. Aimaretti[13] · G. Linsalata[14] · S. Buralli[14] · F. Monzani[14] · A. Aversa[15] · R. Vettor[16] · F. Santini[8] · P. Vitti[9] · L. Gnessi[4] · U. Pagotto[11] · F. Giorgino[7] · A. Colao[17] · A. Lenzi[4] on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology

Anche se solitamente esposti a KDT a breve termine, ≈ 3-6 mesi ➡ cicli KDT possono essere ripetuti nel tempo

High Urinary Calcium Excretion and Genetic Susceptibility to Hypertension and Kidney Stone Disease

Andrew Mente,* R. John D'A. Honey,† John M. McLaughlin,* Shelley B. Bull,* and Alexander G. Logan*

*Prosserman Centre for Health Research, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, and Department of Public Health Sciences, and †St. Michael's Hospital, Division of Urology, Department of Surgery, University of Toronto, Toronto, Ontario, Canada

J Am Soc Nephrol, 2006

J Nephrol (2014) 27:477–482
DOI 10.1007/s40620-014-0068-x

REVIEW

Nephrolithiasis and hypertension: possible links and clinical implications

Adamasco Cupisti · Claudia D'Alessandro · Sara Samoni · Mario Meola · Maria Francesca Egidi

International Journal of *Molecular Sciences*

2021

Review

Idiopathic Osteoporosis and Nephrolithiasis: Two Sides of the Same Coin?

Domenico Rendina [1], Gianpaolo De Filippo [2,3], Gabriella Iannuzzo [1], Veronica Abate [1] Pasquale Strazzullo [1] and Alberto Falchetti [4,5,*]

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Online version at http://www.minervamedica.it

Minerva Obstetrics and Gynecology 2021 December;73(6):744-53
DOI: 10.23736/S2724-606X.20.04689-4

REVIEW

BONE HEALTH IN WOMAN'S REPRODUCTIVE LIFE AND POSTMENOPAUSE

Metabolic syndrome and fragility fracture risk

Roberta COSSO [1], Alberto FALCHETTI [1,2] *

Osteoporos Int (2018) 29:31–39
https://doi.org/10.1007/s00198-017-4294-7

ORIGINAL ARTICLE

A meta-analysis of the association between body mass index and risk of vertebral fracture

A. D. Kaze [1] · H. N. Rosen [2] · J. M. Paik [1,3,4]

Osteoporosis International (2021) 32:1079–1091
https://doi.org/10.1007/s00198-020-05764-8

ORIGINAL ARTICLE

The association between overweight/obesity and vertebral fractures in older adults: a meta-analysis of observational studies

Z. Zhang [1,2] · X. Zhou [2] · L. Shu [1,2] · M. Hu [1,2] · R. Gao [2] · X-H. Zhou [2]

Nutrition, Metabolism & Cardiovascular Diseases (2021) 31, 2210–2233

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Management of bone fragility in type 2 diabetes: Perspective from an interdisciplinary expert panel

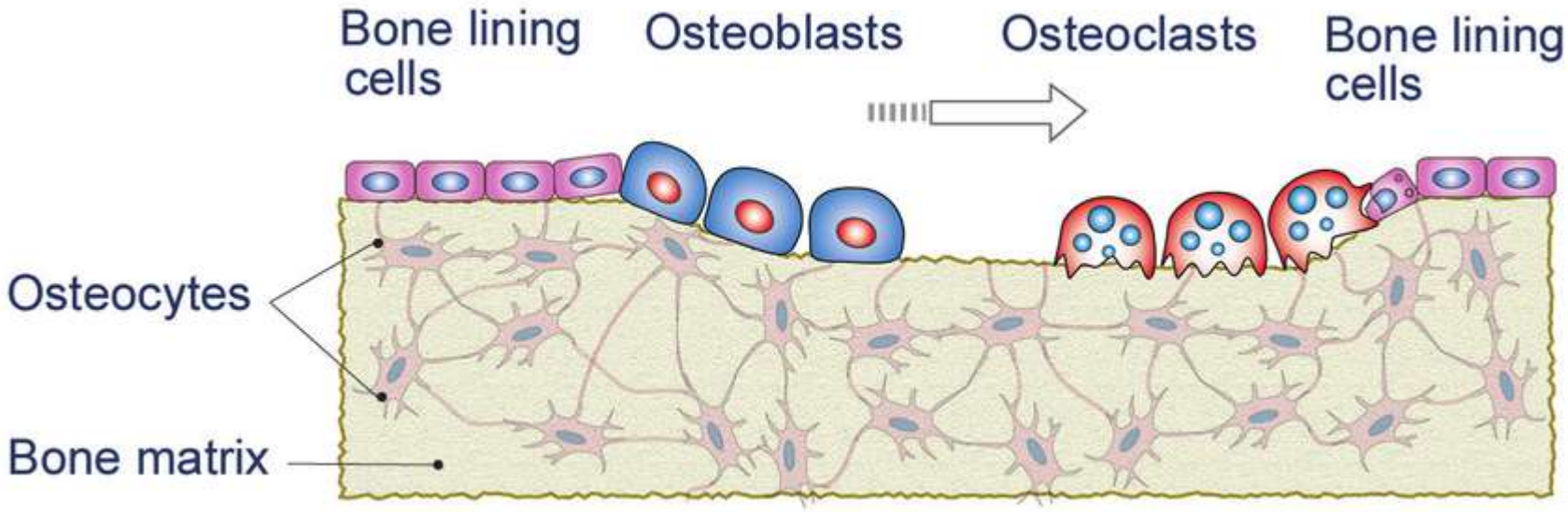
Iacopo Chiodini [a,b,1], Agostino Gaudio [c,1], Andrea Palermo [d], Nicola Napoli [d], Fabio Vescini [e], Alberto Falchetti [a,f], Daniela Merlotti [g,h], Cristina Eller-Vainicher [i], Vincenzo Carnevale [j], Alfredo Scillitani [k], Giuseppe Pugliese [l], Domenico Rendina [m], Antonio Salcuni [n], Francesco Bertoldo [o], Stefano Gonnelli [g], Ranuccio Nuti [g], Vincenzo Toscano [p], Vincenzo Triggiani [q], Simone Cenci [h], Luigi Gennari [g,*]

Falchetti A. Neurology, Practical Update March 2022

PERCHE’ PARLARE DI
DIETOTERAPIA CHETOGENICA E SALUTE OSSEA?

BONE REMODELING: NECESSITÀ DI AUMENTO ENERGETICO

BONE REMODELING UNIT



Ci sono circa 2 milioni di BRU che lavorano in ogni individuo adulto in un dato momento

Il processo di rimodellamento completo richiede circa 100 giorni e l'intero scheletro viene rimodellato ogni 10 anni.

DI CONSEGUENZA: DEVE ESSERE SOSTENUTO UN COSTO ENERGETICO ELEVATO

Lee WC et al. Endocr. Rev. 2017

OSSIDAZIONE ACIDI GRASSI: SENSIBILE AL «cAMP/PKA SIGNALING» ATTIVATO DAL PTH

OBL IMMATURI > uso glucosio
OBL MATURI > uso acidi grassi

DOPO INDUZIONE OSTEOGENICA

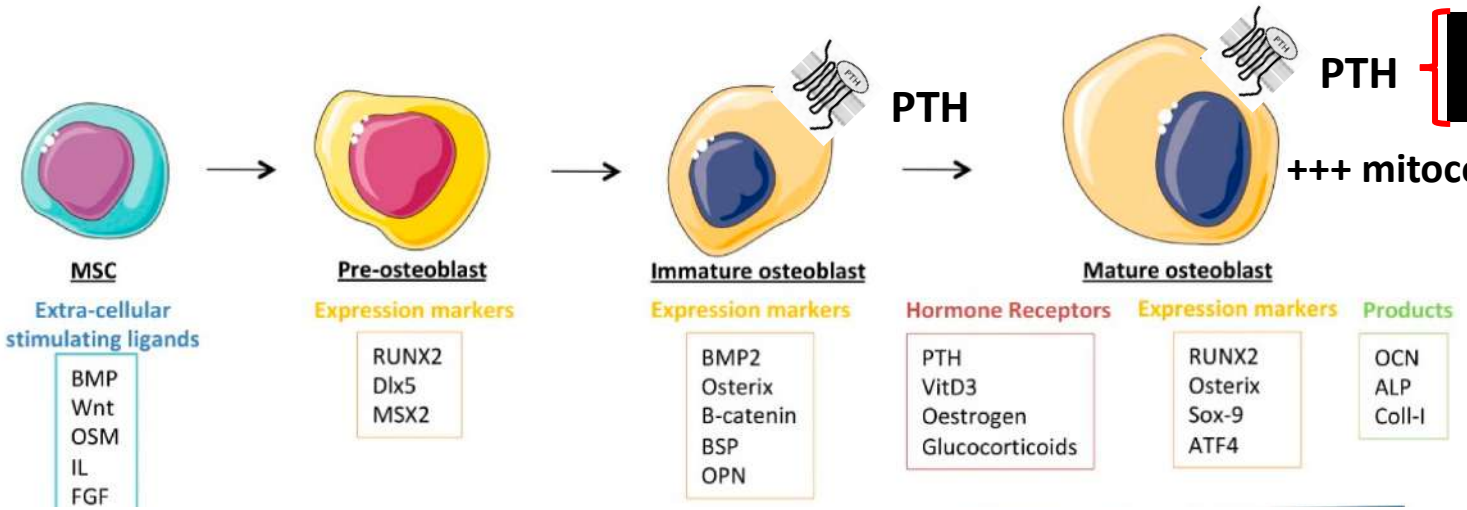
OBL IN VIA DI «MATURAZIONE» = > ESPRESSIONE DI GENI COINVOLTI NELL'OSSIDAZIONE DI ACIDI GRASSI A CATENA LUNGA

El Refaey M et al. 2015; Chen LQ et al. 2015; Glatz JFC et al. 2010; Kushwaha P et al. 2018; Schweikhard ES et al. 2012; Zoch ML et al. 2016

Fase differenziativa cellulare associata a β-ossidazione di acidi grassi
(produzione di >100 ATP per molecola di palmitato), in risposta a stimolazione anabolica di Wnt.

β-ossidazione degli acidi grassi è in grado di produrre KB a partire dai lipidi alimentari o da quelli di deposito

Pegorier JP et al 1989; Gerhart-Hines Z et al , 2011



PTH → Stimola glicolisi aerobica via IGF1, entrata GLU e consumo O_2
Sopprime ingresso di glucosio nel TCA

+++ mitocondri per forti richieste energetiche di sintesi proteica

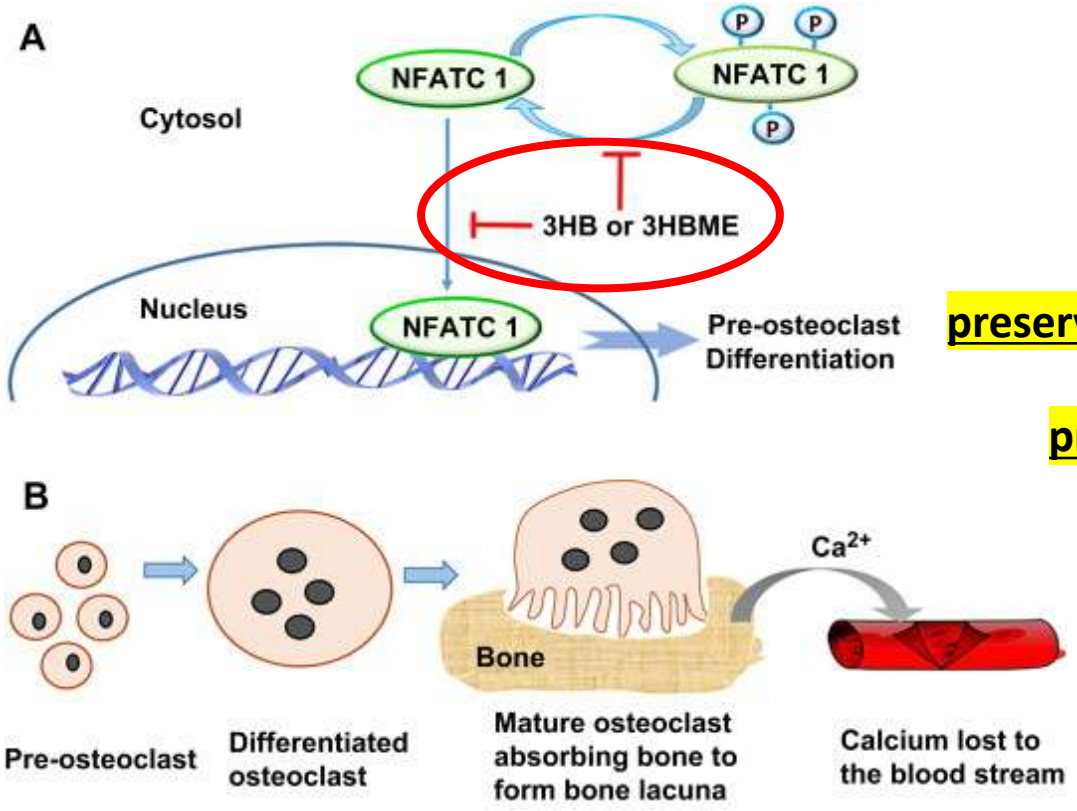
Inibizione farmacologica β-ossidazione altera differenziazione dell'OBL *in vitro*

Frey JL et al 2015

CORPI CHETONICI: NON SOLO EFFETTI SU OBL

3βOHB E SUO DERIVATO METIL-ESTERE

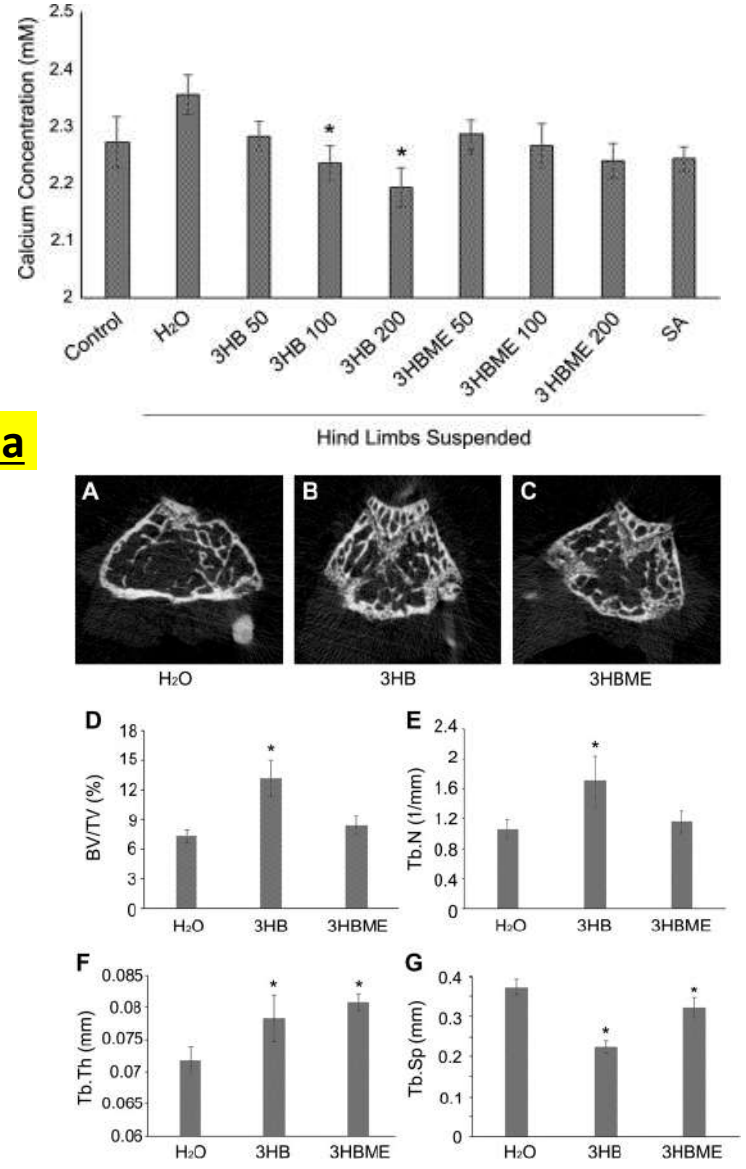
inibiscono sviluppo osteoporosi nei topi, sotto microgravità simulata



preservate microstruttura ossea

e

proprietà meccaniche



HB e 3HBME: ↓espressione di NFATc1 indotta da microgravità e ↓l'attività OCL

Cao Q et al, 2014

Perché la salute delle ossa potrebbe risentirne?

PROBLEMI «OSSEI» EMERGENTI DA VARI STUDI, PREVALENTEMENTE OSSERVAZIONALI E "CASE REPORT"

PREVALENTEMENTE SU POPOLAZIONI PEDIATRICHE

Studi di follow-up a lungo termine:

~20% bambini con AED cronica e KDT (≥ 6 anni) -> incremento incidenza di fx. e ridotta BMD;

Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. Dev. Med. Child Neurol. 2007, 48, 978–981

Falchetti A. Practical Update, Neurology 2022

Ritardo di crescita e sviluppo scheletrico in bambini con epilessia farmacoresistente sottoposti a KDT

1) **Bassa BMD significativamente associata a durata KDT e può anche associarsi a ritardo di crescita.**

2) **KDT che inducono un alto grado di chetosi: scarsa crescita con correlazione negativa tra crescita e livelli KB;**

Table 3. IGF-1 levels and their correlation to 3βOHB blood levels in famine, and IGF-1 levels KDs relationship.

IGF-1, 3βOHB, and Famine	IGF-1 and KDs
IGF-1 levels reduce into famine [87].	IGF-1 levels may be reduced up to 46% after 7 days of KD [88].
3βOHB blood levels and IGF-1 related growth speed inversely correlated [89].	KD-induced famine-like metabolic state may reduce either the IGF-1 levels or its bioavailability [89,90].

↓uptake GLU ↓consumo O_2

↓maturazione/attivazione OBL?

3) **IGF-1 anabolico sull'osso: ++ in acquisizione massa ossea (adolescenti) e mantenimento architettura scheletrica (adulti), parametri che possono influenzare il rischio di successiva frattura.**

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KDT-BMD E METABOLISMO DEL CALCIO

- **ELEVATA INCIDENZA CALCOLI RENALI CON IPERCALCIURIA:** effetto maggiore della KDT sul metabolismo del calcio ?
- **L'USO DI AED ASSOCIA A:** ridotta BMD sia in adulti che bambini
- **ADULTI EPILETTICI IN AED FIN DALL'INFANZIA:** BMD inferiore *vs*. adulti epilettici che iniziano AED nella vita adulta
- **CHETOSI CRONICA:** bilancio minerale osseo negativo (capacità tampone?) e/o ridotta 25OHD -> $1,25(OH)_2D_3$ (?)

Yasar E et al, Eur. J. Paediatr. Neurol. 2018; Ko A et al, Ann. Pediatr. Endocrinol. Metab. 2020; Hahn TJ et al, Calcif. Tissue Int. 1979; Sheth RD et al, J. Pediatr. 1995; Petty S et al, Neurology 2005; Babayigit A et al, Pediatr. Neurol. 2006; Sheth RD et al, Int. Rev. Neurobiol. 2008; Sampath A et al, J. Child Neurol. 2007

Calcio come tampone prodotto dallo scheletro attraverso riassorbimento attivo dell'osso?

calciuria direttamente correlata all'escrezione acida netta, non compensata d'aumentato assorbimento intestinale di calcio.

Barzel US, Massey LK. Excess Dietary Protein Can Adversely Affect Bone. J. Nutr. 1998; Fenton TR et al. J. Bone Miner. Res. 2009

STUDI CLINICI SUL KDT E SALUTE OSSEA

BMC/BMD/FRATTURE

- **Ritardato aumento L2-L4-BMD/BMC (270 Caucasici)** in giovani maschi *vs*. femmine, non correlato alle fasi puberali.
- **Ridotta BMD femorale nel 77% in bambini-adolescenti USA (173 pz)** con paralisi cerebrale.
- **Fratture nel 26% dei bambini di età > 10 anni**.
- **Studio Australiano (63 pz):** 68% dei soggetti in KDT (almeno 6 mesi) con BMD Z-score più basso alla fine del trattamento.

CALCOLI/FRATTURE

- **Studio di coorte Statunitense (195 pz):** 13% dei bambini ha sviluppato **calcoli renali**.
- **Dopo somministrazione di potassio-citrato:** i calcoli renali **continuano a verificarsi in 1 bambino su 20 in KDT**.
- **Studio Olandese su 68 bambini in KDT: 8,8% ha subito una frattura** durante la KDT e **8,8% ha avuto calcoli renali**.

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COSA FARE PER «ATTENUARE» PERDITA DI BMC-BMD E ALTRO DURANTE KDT?

CONOSCERE IL TIPO DI KDT

- **ADEGUATO APPORTO: calcio, citrati e vitamina D (la VLCKD li prevede).**

Fenton TR et al. J. Bone Miner. Res. 2009

- **CITRATO DI K (VLCKD): protettivo per nefrolitiasi da aciduria ed ipocitraturia indotte da KDT.**

Fuleihan GE-H et al, Bone 2008; Palermo A et al, Rev. Endocr. Metab. Disord. 2019

Obesità grave

Screening-Esami
Personalizzazione

"Recommend a maximum 12-week weight-loss program with VLCKD as part of a multidisciplinary weight management strategy to adult severely (class 2 or higher) obese patients not responsive to standardized diet as a second line option"

FASE DI CHETOSI
(poche settimane)
600-800 kcal/die
(VLCD) + K

Reintroduzione alimenti a basso indice glicemico
800→1500 kcal/die

Reintroduzione alimenti a più alto indice glicemico
800→1500 kcal/die

Mantenimento
1500-2000 Kcal/die

«ASSENZA DI LATTE/LATTICINI»

Attività fisica

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ALTRI SOGGETTI «INATTESI»

Ten healthy, physically active UK men, age 24 ± 3 yrs., nonsmokers, not suffered a bone fracture or injury of any type in the previous 12 mo., free from musculoskeletal injury, not taking any medication, and not suffering from any condition known to affect bone metabolism. Two randomized, repeated-measures, counterbalanced 7-day experimental trials, involving either placebo (PBO) or CHO ingestion during 120 min of treadmill running [149]	Clinical trial	Immediate and short-term bone metabolic responses to CHO feeding during treadmill running; β-CTX, P1NP, OPG, OC, PTH, leptin, GLP-2, and IL-6, cortisol, insulin, serum calcium, albumin, and phosphate.	*CHO feeding during exercise attenuated the β-CTX and P1NP responses in the hours following exercise, indicating an acute effect of CHO feeding on bone turnover.*
Ten physically active UK men with at least one bout of endurance running per week, free from fracture in the previous 12 months and any condition known to affect bone metabolism. Free from musculoskeletal injury [149]	Clinical trial	Effect of an overnight fast vs. feeding of a single mixed meal, on the bone metabolic response to an acute bout of treadmill running; three-day food diary, β-CTX, P1NP, OC, OPG, cortisol, bone ALP, PTH, albumin-adjusted calcium, phosphate, leptin, and ghrelin	*Bone markers not significantly differ from baseline on follow up 1–4. Fasting had a minor effect on the bone metabolic response to subsequent acute, endurance exercise, reducing the duration of the increase in β-CTX during early recovery, but no effect on changes in bone formation markers. Reduction of duration of the β-CTX response with fasting not fully explained by changes in PTH, OPG, leptin or ghrelin*
Nine UK male runners, age 21 ± 1.9 years, completing a morning and afternoon high-intensity interval running protocol (interspersed by 3.5 h) under dietary conditions: high CHO availability, reduced CHO but high fat availability, or reduced CHO and reduced energy availability [150]	Clinical trial	Effects of post-exercise CHO and caloric restriction on the modulation of skeletal muscle cell signaling pathways as well as indicators of bone metabolism.	*Post-exercise circulating βCTX was significantly lower in high CHO compared to low CHO-high fat and low CHO and reduced energy availability*
Twenty-five males, and 5 females Australian World-class race walkers completing 3.5-weeks of energy-matched high CHO or ketogenic low-carbohydrate, high-fat diet followed by acute CHO restoration [152]	Clinical trial	Diet-exercise interactions related to bone markers in elite endurance athletes after a 3.5-week ketogenic low-CHO, high-fat diet and subsequent restoration of CHO feeding; serum CTX, P1NP, OC assessed at rest (fasting and 2 h post meal) and after exercise (0 and 3 h) at baseline, after the 3.5-week intervention (Adaptation) and after acute CHO feeding (Restoration)	*Markers of bone modeling/remodeling were impaired after short-term LCHF diet, and only a marker of resorption recovered after acute CHO restoration.*

«Alterazione» dei BTMs

ALTRI PROBLEMI, PIU' «RECENTI»

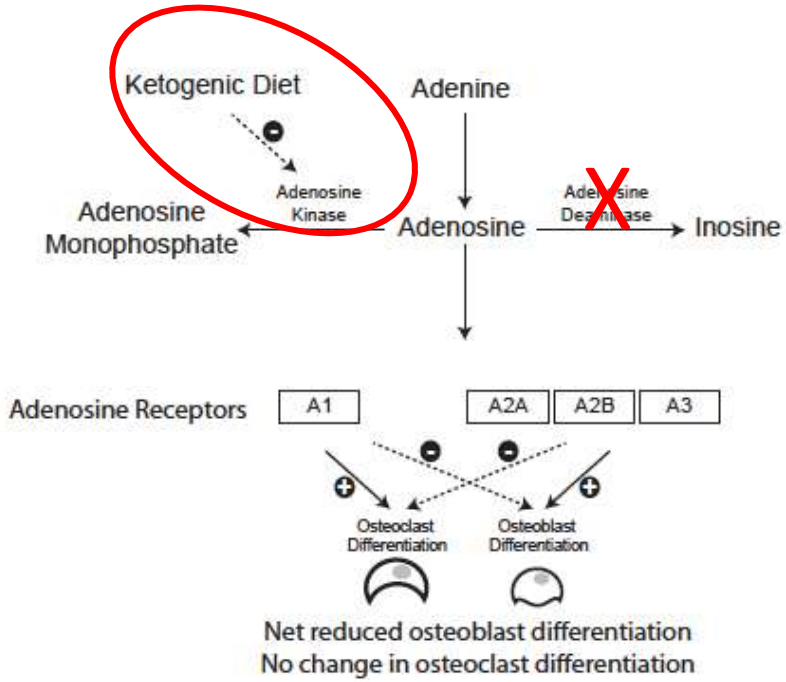
<u>IPERCALCEMIA CHETOSICA</u>: può verificarsi dopo anni di KDT in bambini in AED (soprattutto se con < f.ne renale).

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 2, e485–e495
doi:10.1210/clinem/dgaa759
Clinical Research Article

Clinical Research Article

Hypercalcemia in Children Using the Ketogenic Diet: A Multicenter Study

Colin P. Hawkes,[1,2] Sani M. Roy,[3] Bassem Dekelbab,[4] Britney Frazier,[5] Monica Grover,[6] Jaime Haidet,[7] James Listman,[8] Sarianne Madsen,[9] Marian Roan,[10] Celia Rodd,[11] Aviva Sopher,[12] Peter Tebben,[13] and Michael A. Levine[1,2]



- **<u>MECCANISMO SCONOSCIUTO</u>: ridotta attività di OBL e di formazione ossea?**
- **<u>BAMBINI IN TERAPIA AED E KDT PER LUNGHI PERIODI</u>: screening anche per sviluppo d'ipercalcemia chetosica.**

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Somministrazione I.V. di 3βOHB aumenta la concentrazione di PTH e del CTX

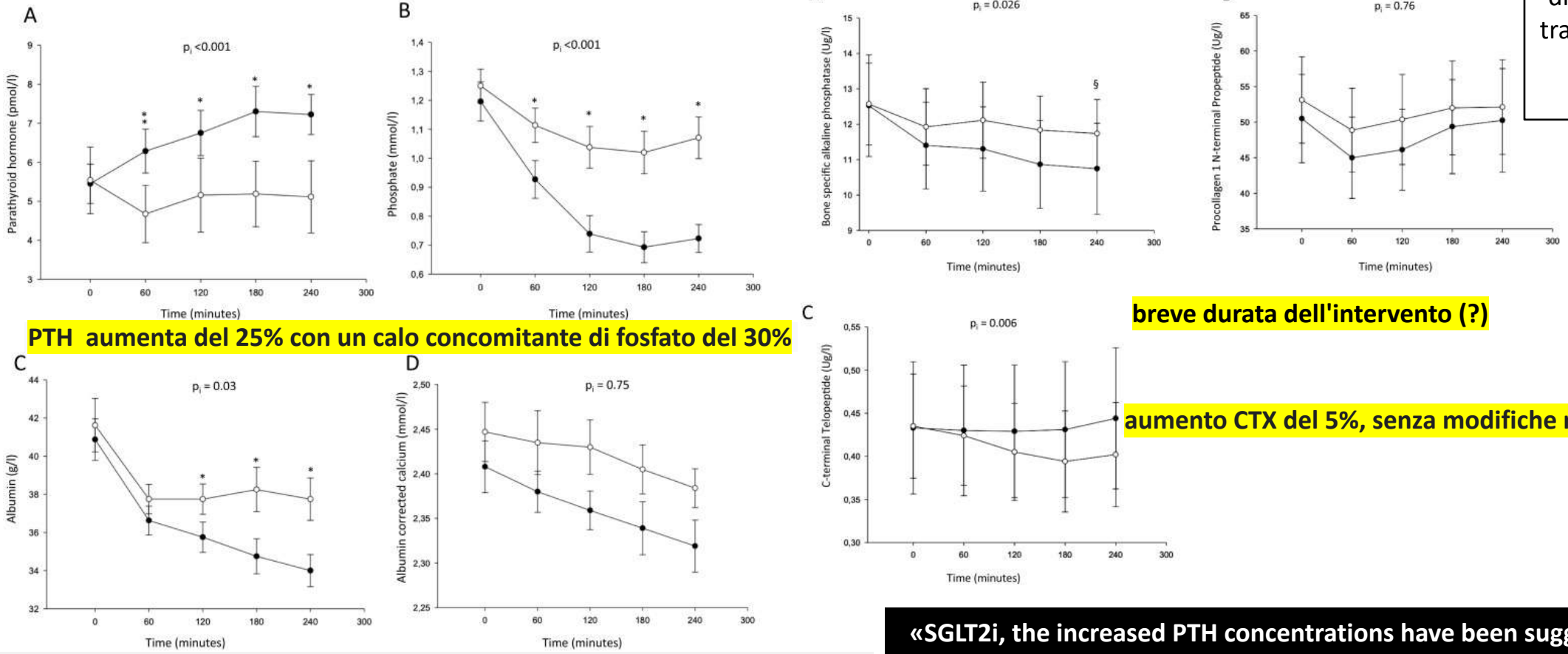
8 soggetti sani, età 50-70 anni

disponibile come DL-Na3OHB and a D-3OHB monoestere chetone

effetti distinti su pH: monoestere è «acido» mentre il sale è «alcalino»

DL-Na3OHB infuso per 4 h ad una concentrazione di 75 g/l e velocità di infusione di 0,18 mg/kg/h

Digiuno overnight prima di ciascuno dei 2 bracci di trattamento (cross-over) di durata 4h, separati da almeno 2 settimane



PTH aumenta del 25% con un calo concomitante di fosfato del 30%

breve durata dell'intervento (?)

aumento CTX del 5%, senza modifiche nel PINP

Aumento PTH: probabilmente da alcalosi metabolica e riduzione secondaria Calcio-ione per somministrazione di Na-3OHB

«SGLT2i, the increased PTH concentrations have been suggested to occur because of increased concentrations of PO, which, most likely, is due to an increased tubular reabsorption of PO»

Svart M et al. 3-Hydroxybutyrate administration elevates plasma parathyroid hormone in a pilot human randomized, controlled, cross over trial. Bone 153 (2021)

DOI: 10.1111/epi.17169

Epilepsia

FULL-LENGTH ORIGINAL RESEARCH 2022

Substantial early changes in bone and calcium metabolism among adult pharmacoresistant epilepsy patients on a modified Atkins diet

Ellen Molteberg[1,2] | Erik Taubøll[2,3] | Magnhild Kverneland[1] | Per Ole Iversen[2,4,5] | Kaja Kristine Selmer[1,6] | Karl Otto Nakken[1] | Dag Hofoss[1] | Per Medbøe Thorsby[7]

PRINCIPALI «CARENZE»

DIVERSE TIPOLOGIE DI STUDI

Osservazionali/Retrospettivi/Case reports…

Durata globale dello studio

Outcomes diversi e non sempre chiari

Parametri valutati e metodologie

Scarsa considerazione LSC (BTMs – DXA)

POPOLAZIONI DIVERSE PER

Numerosità del campione

Etnia

Età

Attività fisica

KDT (tipo, durata)

PROBLEMA MOLTO COMPLESSO

Abstract

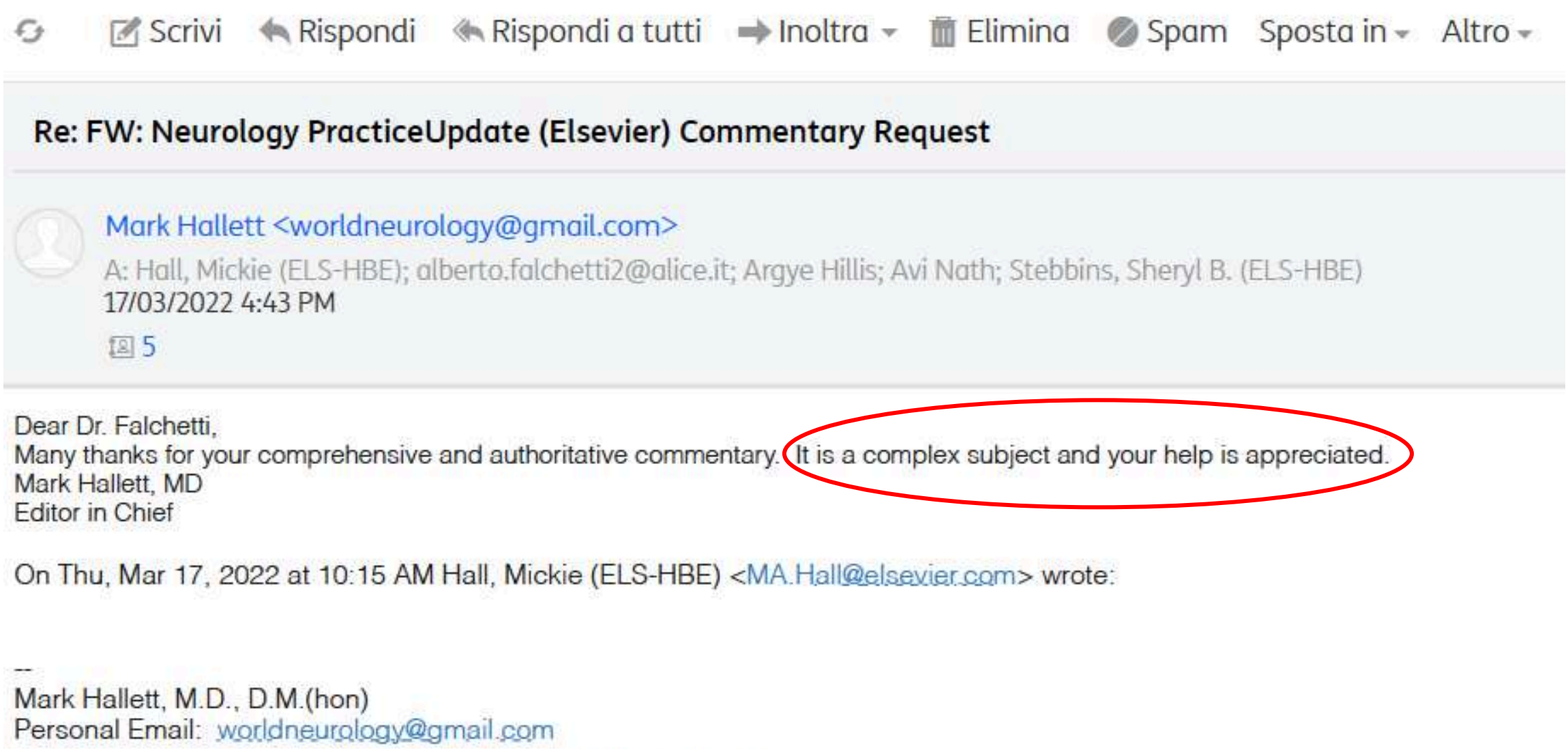
Objective: The aim of this study was to investigate whether the modified Atkins diet (MAD), a variant of the ketogenic diet, has an impact on bone- and calcium (Ca) metabolism.

Methods: Two groups of adult patients with pharmacoresistant epilepsy were investigated. One, the diet group ($n = 53$), was treated with MAD for 12 weeks, whereas the other, the reference group ($n = 28$), stayed on their habitual diet in the same period. All measurements were performed before and after the 12 weeks in both groups. We assessed bone health by measuring parathyroid hormone (PTH), Ca, 25-OH vitamin D (25-OH vit D), 1,25-OH vitamin D (1,25-OH vit D), phosphate, alkaline phosphatase (ALP), and the bone turnover markers procollagen type 1 N-terminal propeptide (P1NP) and C-terminal telopeptide collagen type 1 (CTX-1). In addition, we examined the changes of sex hormones (estradiol, testosterone, luteinizing hormone, follicle-stimulating hormone), sex hormone-binding globulin, and leptin.

Results: After 12 weeks of MAD, we found a significant reduction in PTH, Ca, CTX-1, P1NP, 1,25-OH vit D, and leptin. There was a significant increase in 25-OH vit D. These changes were most pronounced among patients <37 years old, and in those patients with the highest body mass index (≥25.8 kg/m^2), whereas sex and type of antiseizure medication had no impact on the results. For the reference group, the changes were nonsignificant for all the analyses. In addition, the changes in sex hormones were nonsignificant.

Significance: Twelve weeks of MAD treatment leads to significant changes in bone and Ca metabolism, with a possible negative effect on bone health as a result. A reduced level of leptin may be a triggering mechanism. The changes could be important for patients on MAD, and especially relevant for those patients who receive treatment with MAD at an early age before peak bone mass is reached.

COSI' COMPLESSO CHE ANCHE AUTOREVOLI NEUROLOGI….



Scrivi Rispondi Rispondi a tutti Inoltra Elimina Spam Sposta in Altro

Re: FW: Neurology PracticeUpdate (Elsevier) Commentary Request

Mark Hallett <worldneurology@gmail.com>
A: Hall, Mickie (ELS-HBE); alberto.falchetti2@alice.it; Argye Hillis; Avi Nath; Stebbins, Sheryl B. (ELS-HBE)
17/03/2022 4:43 PM
5

Dear Dr. Falchetti,
Many thanks for your comprehensive and authoritative commentary. It is a complex subject and your help is appreciated.
Mark Hallett, MD
Editor in Chief

On Thu, Mar 17, 2022 at 10:15 AM Hall, Mickie (ELS-HBE) <MA.Hall@elsevier.com> wrote:

--
Mark Hallett, M.D., D.M.(hon)
Personal Email: worldneurology@gmail.com

Chief of the Medical Neurology Branch and Chief Human Motor Control Section; NIH, Bethesda, MD.
Past-President of the International Federation of Clinical Neurophysiology.

TAKE HOME MESSAGES

DAL PUNTO DI VISTA PRATICO:

I pz. che vediamo seguono regimi di KDT?

Perché?

Quale tipo di KDT?

Da/per quanto tempo?…

Familiarità per Fx/malattie metaboliche ossee e Ca/P?

CONSIDERARE SEMPRE:

Rischio clinico per Fx (DMT2 lunga durata, dismobili…)

Ipercalciuria/calcolosi pre-durante-post KDT…

Integrazioni citrato, minerali, vitamine…

European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis

Giovanna Muscogiuri[a, b] Marwan El Ghoch[c] Annamaria Colao[a, b]
Maria Hassapidou[d] Volkan Yumuk[e] Luca Busetto[f] Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO)

Table 2. Parameters monitored during a VLCKD

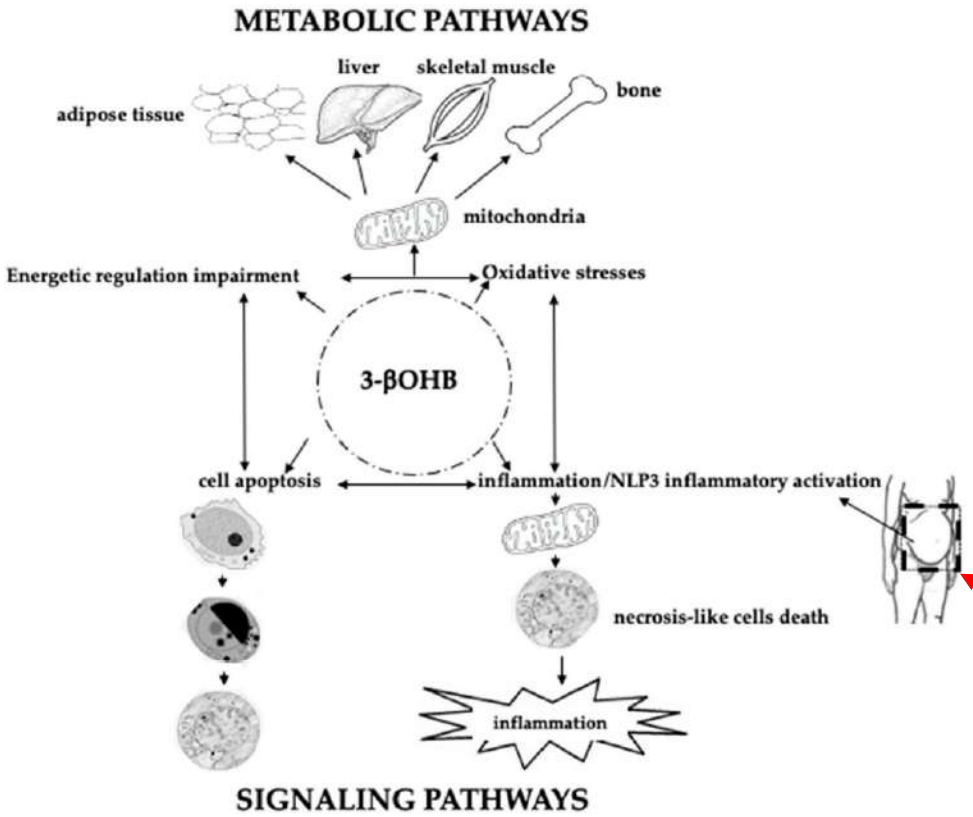
Parameters	Baseline	During the active stage	At the end of the active stage	At the end of the reintroduction stage
Antropometric assessment				
Weight, height, and BMI	X	X	X	X
Body composition and hydration status (by bioelectrical impedance analysis)	X	X	X	X
Laboratory assessment				
Complete blood count with platelets	X	X	X	X
Sodium, potassium, magnesium, and inorganic phosphate	X	X	X	X
Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine, γ-GT, and total and direct bilirubin)	X	X	X	X
Fasting lipid profile	X			X
25(OH)D, calcium	X			X
Glucose and insulin	X			X
β-hydroxybutyrate (capillary blood or urine)		X		
TSH and FT4	X			
Complete urinalysis and microalbuminuria (urine)	X	X	X	X

Obes Facts 2021;14:222–245

NECESSARIO PER STUDI FUTURI UN APPROCCIO MULTISPECIALISTICO COMPRENDENTE ANCHE UN ESPERTO DEL MTB. OSSEO

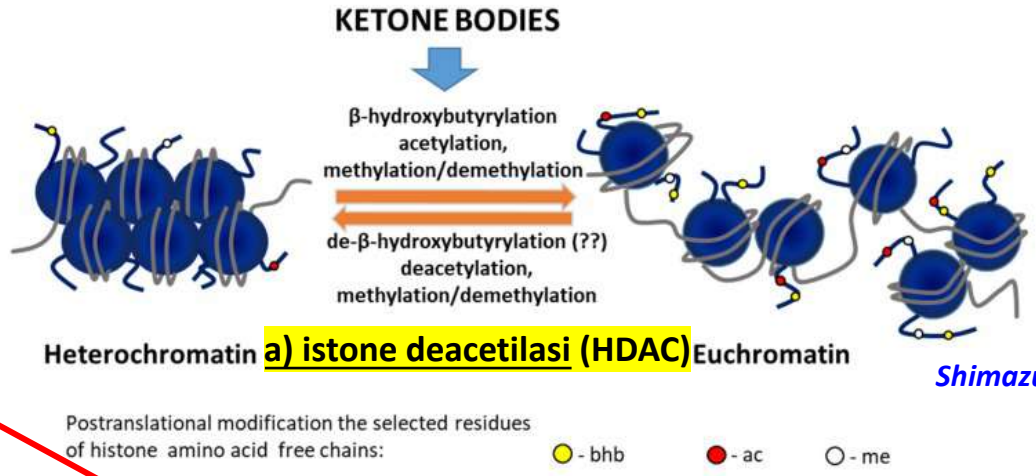
GRAZIE PER L’ATTENZIONE

3βOHB: preserverebbe il muscolo dall'infiammazione sistemica e difenderebbe da ipoglicemia insulino-indotta



3βOHB lega HCAR ed inbisce…

Møller N. JCEM 2020



Shimazu T et al. Science 2013

b) **Modula** interazione FFA/recettori degli acidi grassi liberi [FFAR (GPCRs)]
c) **Riduce** attività NOD-, LRR-, NLRP3 inflammasoma

Promuove trascrizione genica per fattori di resistenza allo stress ossidativo

International Journal of *Molecular Sciences*
MDPI

Review

Energy Metabolism and Ketogenic Diets: What about the Skeletal Health? A Narrative Review and a Prospective Vision for Planning Clinical Trials on this Issue

Daniela Merlotti [1], Roberta Cosso [2], Cristina Eller-Vainicher [3], Fabio Vescini [4], Iacopo Chiodini [2,5], Luigi Gennari [1] and Alberto Falchetti [2,*]

3βOHB: molecola di segnalazione?

EPIGENETICS (summarization of main processes)

Gene expression control by: DNA methylation
Histone deacetylation

International Journal of
Molecular Sciences

MDPI

Review

Energy Metabolism and Ketogenic Diets: What about the Skeletal Health? A Narrative Review and a Prospective Vision for Planning Clinical Trials on this Issue

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Acid-Ash Proteins Diet

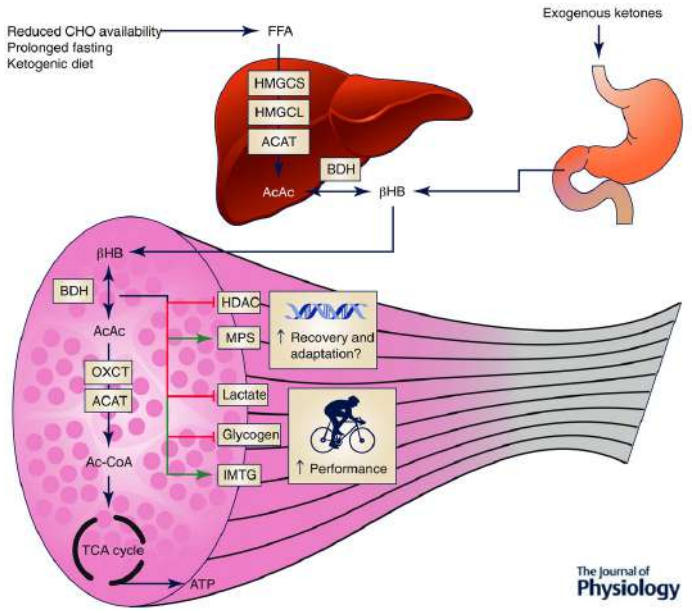
DIETA RICCA DI PROTEINE «ACID-ASH» (ipotesi che identifica proteine e cereali come causa di rilascio di calcio dallo scheletro per tamponare il carico acido della dieta e aumentare l'escrezione urinaria di calcio):

associato ad un'eccessiva perdita di calcio dovuta al suo contenuto acidogenico = **IPERCALCIURIA**

Fenton TR et al. J. Bone Miner. Res. 2009

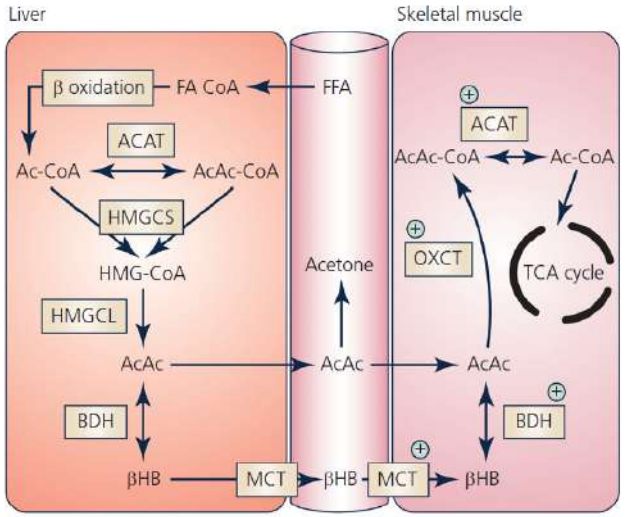
SOGGETTI «INATTESI» CHE USANO KDT…

Ten healthy, physically active UK men, age 24 ± 3 yrs., nonsmokers, not suffered a bone fracture or injury of any type in the previous 12 mo., free from musculoskeletal injury, not taking any medication, and not suffering from any condition known to affect bone metabolism. Two randomized, repeated-measures, counterbalanced 7-day experimental trials, involving either placebo (PBO) or CHO ingestion during 120 min of treadmill running [149]	Clinical trial	Immediate and short-term bone metabolic responses to CHO feeding during treadmill running; β-CTX, P1NP, OPG, OC, PTH, leptin, GLP-2, and IL-6, cortisol, insulin, serum calcium, albumin, and phosphate.	*CHO feeding during exercise attenuated the β-CTX and P1NP responses in the hours following exercise, indicating an acute effect of CHO feeding on bone turnover.*
Ten physically active UK men with at least one bout of endurance running per week, free from fracture in the previous 12 months and any condition known to affect bone metabolism. Free from musculoskeletal injury [149]	Clinical trial	Effect of an overnight fast vs. feeding of a single mixed meal, on the bone metabolic response to an acute bout of treadmill running; three-day food diary, β-CTX, P1NP, OC, OPG, cortisol, bone ALP, PTH, albumin-adjusted calcium, phosphate, leptin, and ghrelin	*Bone markers not significantly differ from baseline on follow up 1–4. Fasting had a minor effect on the bone metabolic response to subsequent acute, endurance exercise, reducing the duration of the increase in β-CTX during early recovery, but no effect on changes in bone formation markers. Reduction of duration of the β-CTX response with fasting not fully explained by changes in PTH, OPG, leptin or ghrelin*
Nine UK male runners, age 21 ± 1.9 years, completing a morning and afternoon high-intensity interval running protocol (interspersed by 3.5 h) under dietary conditions: high CHO availability, reduced CHO but high fat availability, or reduced CHO and reduced energy availability [150]	Clinical trial	Effects of post-exercise CHO and caloric restriction on the modulation of skeletal muscle cell signaling pathways as well as indicators of bone metabolism.	*Post-exercise circulating βCTX was significantly lower in high CHO compared to low CHO-high fat and low CHO and reduced energy availability*
Twenty-five males, and 5 females Australian World-class race walkers completing 3.5-weeks of energy-matched high CHO or ketogenic low-carbohydrate, high-fat diet followed by acute CHO restoration [152]	Clinical trial	Diet-exercise interactions related to bone markers in elite endurance athletes after a 3.5-week ketogenic low-CHO, high-fat diet and subsequent restoration of CHO feeding; serum CTX, P1NP, OC assessed at rest (fasting and 2 h post meal) and after exercise (0 and 3 h) at baseline, after the 3.5-week intervention (Adaptation) and after acute CHO feeding (Restoration)	*Markers of bone modeling/remodeling were impaired after short-term LCHF diet, and only a marker of resorption recovered after acute CHO restoration.*



2016

«Alterazione» dei BTMs



European Guidelines for Obesity Management in Adults with a Very Low-Calorie Ketogenic Diet: A Systematic Review and Meta-Analysis

Giovanna Muscogiuri[a, b] Marwan El Ghoch[c] Annamaria Colao[a, b]
Maria Hassapidou[d] Volkan Yumuk[e] Luca Busetto[f] Obesity Management
Task Force (OMTF) of the European Association for the Study of Obesity (EASO)

Obes Facts 2021;14:222–245

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Fasting lipid profile	X			X
25(OH)D, calcium	X			X
Glucose and insulin	X			X
β-hydroxybutyrate (capillary blood or urine)		X		
TSH and FT4	X			
Complete urinalysis and microalbuminuria (urine)	X	X	X	X

NON ADEGUATO DISEGNO SPERIMENTALE PER DATI RILEVANTI SULL'OSSO

DIVERSE TIPOLOGIE DI STUDI

- Osservazionali/Retrospettivi/Case reports…
- Durata globale dello studio
- Outcomes diversi e non sempre chiari
- Parametri valutati e metodologie
- Scarsa considerazione LSC (BTMs – DXA)

POPOLAZIONI DIVERSE PER

- Numerosità del campione
- Etnia
- Età
- Attività fisica
- KDT (tipo, durata)

ALTRI FATTORI LIMITANTI

Poco considerate valutazioni basali d'intake di calcio…
Storia familiare per fratture da fragilità non considerata
Scarsa attenzione per fattori di rischio clinico per fratture/ipercalciuria/calcolosi renale
Pochi studi: correlazione KBs (sangue, urine) e salute ossea

PROBLEMA MOLTO COMPLESSO

Falchetti A. Practical Update, Neurology 2022

POSSIBILI CAUSE D'INCIDENZA DI FX E RIDUZIONE BMD/BMC IN AED + KDT DI LUNGA DURATA

SCHEMATICAMENTE IPOTIZZATE E RIASSUNTE COME SEGUE

1) **ambiente ad alto "*carico acido*" attraverso KB generati;**
2) **alterazioni osservate nei livelli circolanti di vitamina D;**
3) **diminuzione livelli circolanti di fattori di crescita per uso concomitante di antiepilettici e ridotta/assente mobilità**

Falchetti A. Neurology, Practical Update March 2022