Approaching Geriatric Care with Novel Nutritional Therapeutics and Case Studies

Presented by Michael Jurgelewicz, DC, DACBN, DCBCN, CNS

.

Disclosures

- Director of Product Development, Research & Clinical Support – Designs for Health, Inc.

Learning Objectives:

1. Discuss traditional and functional laboratory assessments for the geriatric patient
2. Define risk factors and prevention strategies for the aging population
3. Determine nutritional therapeutics for the geriatric patient

Statistics

- On average, a 65-year-old can expect to live another 17 years.
- Nearly 95% have at least one chronic condition, and nearly 80% of have two or more.
- The leading causes of death among older adults in the U.S. are heart disease, cancer, stroke, chronic lower respiratory diseases, Alzheimer's disease, and diabetes.
- Chronic diseases can limit a person's ability to perform daily activities, cause them to lose their independence, and result in the need for institutional care, in-home caregivers, or other long-term services.
- Multiple chronic diseases account for 2/3 of all health care costs and 93% of Medicare spending.
- Less than 3% of U.S. health care dollars is spent on prevention to improve overall health.

https://www.ncoa.org/article/get-the-facts-on-healthy-aging

Challenges in the Aging Population

- Chronic disease
  - Affects activities of daily living (ADLs)
  - Reduced quality of life
  - Increased mortality risk
- Seniors' life expectancy is increasing as well as the risk of developing chronic disease increases with age.
- Certain diseases occur more often in the senior population
- The prevalence of co-morbid conditions makes treating elderly patients different from other populations.
- Over one-third of seniors have two or more chronic diseases.
- Many of these patients are on numerous medications which can have interactions or serious side effects.

https://www.canada.ca/en/public-health/services/publications/diseases-conditions/aging-chronic-diseases-profile-canadian-seniors-report.html

Falls

- More than 1 out of 4 older adults falls each year
- Falls are the leading cause of fatal and nonfatal injuries among older adults, causing hip fractures, head trauma, and death.
- Older adults are hospitalized for fall-related injuries five times more often than for injuries from other causes
- Fear of falling can lead older adults to limit their activities, which can result in more falls, further physical decline, depression, and social isolation

https://www.ncoa.org/article/get-the-facts-on-healthy-aging

Prevalence of Chronic Disease in Seniors

- Hypertension (65.5%)
- Osteoarthritis (54.0%)
- Ischemic Heart Disease (42%)
- Osteoporosis (36.9%)
- Two or more chronic diseases (37%)

https://www.canada.ca/en/public-health/services/publications/diseases-conditions/aging-chronic-diseases-profile-canadian-seniors-report.html

Risk Factors of Chronic Disease in Seniors

- Smoking
- Alcohol
- Diet
- Sedentary Lifestyle
- Obesity
- Underweight
- Sleep Disturbance
- Social Isolation

https://www.canada.ca/en/public-health/services/publications/diseases-conditions/aging-chronic-diseases-profile-canadian-seniors-report.html

Lab Evaluations

- Hs-CRP
- OxLDL
- Lp(a)
- LipoFraction NMR with Lipids
- Apo B
- Insulin
- HA1c
- Homocysteine
- Vitamin D 25-OH
- OmegaCheck
- Iron panel with ferritin
- CBC w/diff
- CMP-14

Additional Assessments Considerations

- Calcium Score
- Carotid intima-media thickness (CIMT) test
- Grip strength
- Bone Health/Resorption Assays
  - Collagen Type I C-Telopeptide (CTx), blood
  - Amino-terminal propeptide of type I collagen (P1NP), blood
  - Collagen Cross-Linked N-Telopeptide (NTx), Urine
  - Pyrlinks-D, urine

Dietary and Lifestyles Recommendations

- Incorporate an anti-inflammatory, antioxidant-rich diet
- Consume a diet that includes 1 g/kg to 1.5 g/ kg of protein per day to support muscle protein synthesis
- Get adequate sleep (~7-9 hours)
- Incorporate an exercise routine that includes resistance training
    - Osteoporosis
        - High intensity strength training and low impact weight-bearing exercise
        - Light walking at least 4 hrs. a week
    - Elderly (balance disability)
        - Muscle strengthening and balance training
        - Whole-body vibration
    - Prevention
        - Weight-bearing endurance and plyometric exercise 3-5 times a week
        - Resistance exercise of moderate to high loading 2-3 times a week for 30-60 min.

Foundational Support

- Vitamin D
  - 50-80 ng/ml (125-200 nmol/l)
  - Provide with supplemental and dietary vitamin K
- Magnesium
  - <50% meet AI (AI: 250mg female and 345mg male)
  - Glycinate, malate, glycerophosphate, and orotate forms have high bioavailability.
  - Oxide, carbonate, and hydroxide forms are poorly absorbed and are commonly used as laxatives
  - 300 to 500 mg QD
- EPA/DHA
  - 1:1 ratio
  - ~3 grams QD

Calcium β-Hydroxy-β-MethylButyrate Monohydrate (HMB)

***Vicia faba* Protein Bioactive Peptides**

Annatto Delta & Gamma Tocotrienol Isomers

Specific Bioactive Collagen Peptides

Vitamin K2 (MK-4)

Creatine Monohydrate

Calcium β-Hydroxy-β-MethylButyrate Monohydrate (HMB)

Increases Muscle Strength & Quality

Increase Lean/Fat-Free Body Mass in Ageing Adults

Improves Functions of Daily Living

Improves Mobility

Reduces Fatigue

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Review

Efficacy of β-hydroxy-β-methylbutyrate supplementation in elderly and clinical populations

Peter J. Fitschen M.S. [a], Gabriel J. Wilson Ph.D. [b], Jacob M. Wilson Ph.D. [c], Kenneth R. Wilund Ph.D. [a,d,*]

[a] Division of Nutritional Sciences, University
[b] Department of Nutritional Sciences, Rutgers
[c] Department of Health Sciences and Human
[d] Department of Kinesiology and Community

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Muscle
Wasting

Introduction

Muscle loss is common throug
may begin as young as 30 y of ag
muscle mass is lost between the fi
and rates of muscle loss can reach u
age [2,3]. Moreover, low levels of m
been correlated with decreased ph
quality of life [5], and increased m
exists in many clinical populations
or acquired immune deficiency syn
wasting is common. Indeed, low l
populations have been correlate
function, decreased quality of life, p
and increased mortality [7–10].
maintain or potentially increase lea
populations are needed. Recently,
(HMB) has been researched for its
these populations. The present revi
for use of HMB in human elderly a

* Corresponding author. Tel.: +217-265-6
E-mail address: kwilund@illinois.edu (K. R. Wilund).

dehydrogenase and ultimately enters the citric acid cycle.

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Table 1
Summary of β-hydroxy-β-methylbutyrate supplementation studies in elderly humans

Study	Dosage (daily)	Length of study	Exercise	Results and comments
Vukovich et al., 2001 [27]	HMB 3 g	8 wk	2 d strength training and 3 d aerobic exercise	HMB ($n = 14$) ↑ LBM by 0.8 kg measured by calipers ($P = 0.08$); no difference in LBM measured by DXA or strength between HMB and placebo groups ($n = 17$)
Flakoll et al., 2004 [28]	HMB 2 g, arginine 5 g, lysine 1.5 g	12 wk	none	HMB ($n = 27$) ↑ LBM by 0.7 kg measured by BIA ($P = 0.08$); HMB ↑ leg extensor strength by 3 kg, ↑ grip strength, and ↓ "timed up-and-go" test time by 2.3 s; no changes in LBM, leg strength, grip strength, or "timed up and go" test time in placebo ($n = 23$) group
Baier et al., 2009 [23]	HMB 2–3, arginine 5–7.5 g, lysine 1.5–2.25	1 y	none	HMB ($n = 40$) ↑ LBM by 0.55 kg measured by DXA; no change in LBM in control group ($n = 37$); no change in bone mineral density, strength, physical function, or quality of life in either group
Hsieh et al., 2010 [26]	HMB 2 g	4 wk	none	subjects receiving tube feeding; HMB ($n = 39$) ↑ bodyweight, BMI, hip, and calf circumference; HMB ↓ nitrogen excretion; no changes in BMI, hip, or calf circumference in control group ($n = 40$)
Fuller et al., 2011[29]	HMB 2–3 g, arginine 5–7.5 g, lysine 1.5–2.25 g	1 y	none	additional analysis of Baier et al. [23]; vitamin D status affected strength gains; HMB + adequate vitamin D status ↑ total body strength by 21%; no change in strength in HMB-supplemented subjects with vitamin D deficiency or in placebo group

↑, increased; ↓, decreased; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual x-ray absorptiometry; HMB, β-hydroxy-β-methylbutyrate; LBM, lean body mass

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Original Research

Effects of Beta-Hydroxy-Beta-Methylbutyrate Supplementation on Older Adults with Sarcopenia: A Randomized, Double-Blind, Placebo-Controlled Study

C. Yang[1,], Y. Song[1,*], T. Li[1], X. Chen[1], J. Zhou[1], Q. Pan[3], W. Jiang[4], M. Wang[5], H. Jia[1,2]*

1. School of Public Health, Southwest Medical University, Luzhou City, Sichuan Province, China; 2. Center for Evidence-Based Medicine, Southwest Medical University, Luzhou City, Sichuan Province, China; 3. West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China; 4. Department of Rehabilitation, The Affiliated Hospital of Southwest Medical University, Luzhou City, Sichuan Province, China; 5. Department of Nutrition, The Affiliated Hospital of Southwest Medical University, Luzhou City, Sichuan Province, China; * Chan Yang and Yu Song contributed equally to this work and share first authorship.

Corresponding Author: Hong Jia, School of Public Health, Southwest Medical University, Luzhou City, Sichuan Province, China, jhong_lzs@163.com

Abstract

OBJECTIVES: Sarcopenia is recognized as a major public health concern because of its association with several adverse health events. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation reportedly delays the loss of muscle mass and function; however, the effect of HMB on sarcopenia remains inconclusive. We aimed to evaluate the impact of HMB intervention on muscle strength, physical performance, body compositions, and inflammatory factors in older adults with sarcopenia.

DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING AND PARTICIPANTS: This study included subjects aged ≥60 years with sarcopenia which were assigned to the HMB group (HMBG, n=18) and the placebo group (PG, n=16).

INTERVENTION: The HMBG and PG were supplied with HMB and placebo products twice daily for 12 weeks, and both received resistance exercise training twice a week in 12 weeks.

MEASUREMENTS: Hand grip strength was selected as the primary outcome; gait speed, five-time chair stand test, body composition and inflammatory indicators were selected as the secondary outcomes. The differences in changes from baseline between the two groups were analyzed using the analysis of covariance(ANCOVA).

RESULTS: After the 12-week intervention, the HMBG demonstrated significantly greater improvements in handgrip strength (4.61(95%CI:2.93,6.28) kg, P<0.001), gait speed (0.11(95%CI:0.02,0.20)m/s, P=0.014), five-time chair stand test (-3.65 (95%CI:-5.72, -1.58)s, P=0.001), muscle quality (2.47(95%CI:1.15,3.80),kg·kg^{-1} P=0.001) and tumor necrosis factor-like weak inducer of apoptosis (-15.23(95%CI:-29.80,-0.66)pmol/mL, P=0.041) compared with the PG; no significant differences in skeletal muscle mass, skeletal muscle index, and other body composition parameters were found between the two groups.

CONCLUSION: In older adults with sarcopenia, HMB significantly enhance the effect of resistance exercise training on muscle strength, physical performance, muscle quality, and reduced inflammatory factors. Therefore, HMB supplementation could be an effective treatment for sarcorpenia. The trial protocol was registered at http://www.chictr.org.cn/showproj.aspx?proj=47571 as ChiCTR2000028778.

Key words: β-hydroxy-β-methylbutyrate, sarcopenia, aging, randomized controlled trial.

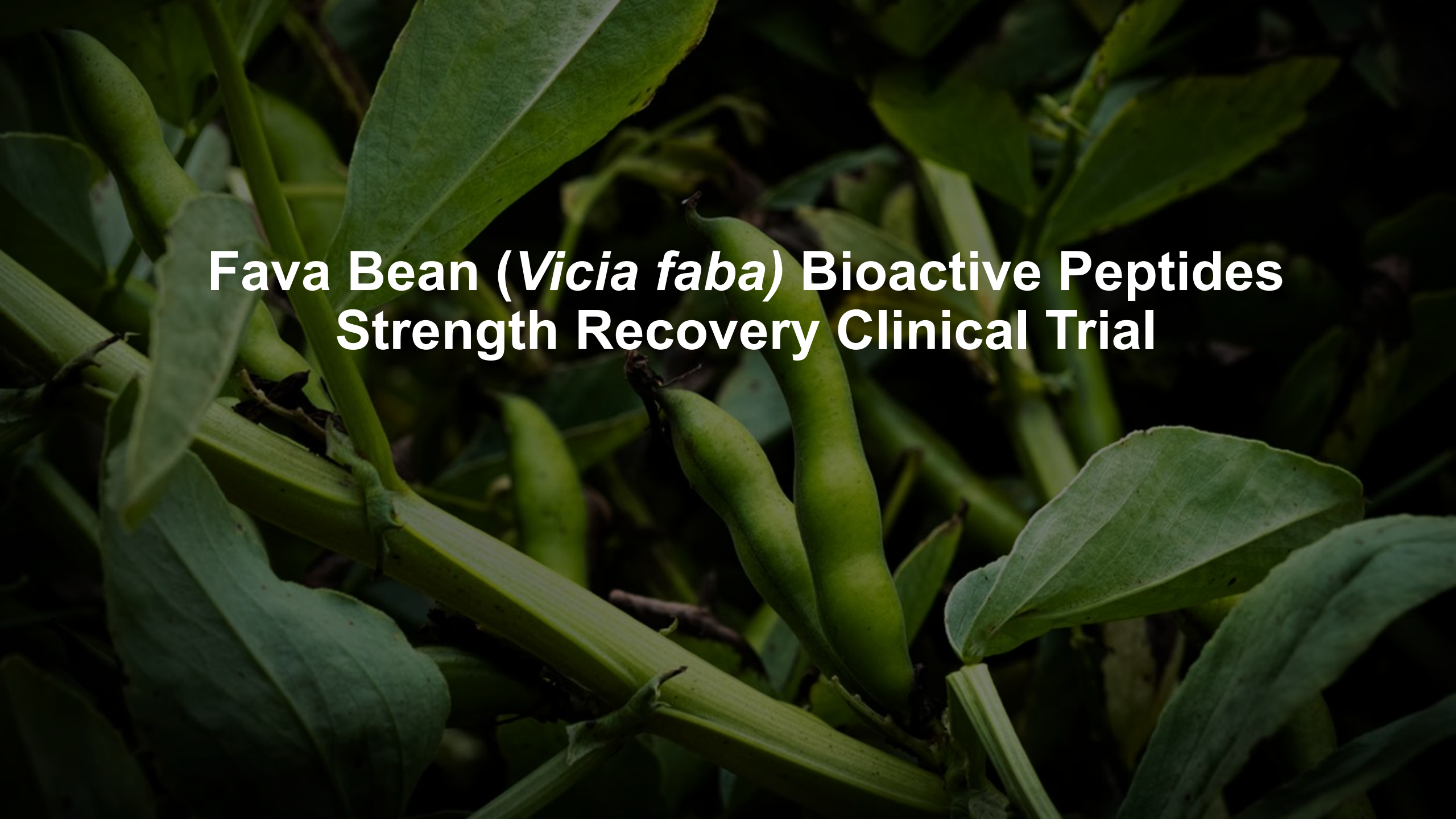
Introduction

Sarcopenia is a geriatric syndrome characterized by a generalized and progressive loss of muscle mass, muscle strength, and function with a risk of adverse health outcomes including falls, fractures, disability, and mortality (1). The current prevalence of sarcopenia in the older Asian population ranges from 6.8–25.7%, which presents a major public health problem that places a heavy burden on healthcare systems in an aging society (2). Thus, effective interventions are needed to prevent or delay sarcopenia.

Nutritional supplementation, especially beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of leucine, which is an essential branched-chain amino acid with an anabolic role in the muscles (3), has been demonstrated to be an efficient intervention to improve muscle mass and function (4-6). The main mechanisms of the positive effect of HMB on muscles are as follows: increasing protein synthesis by stimulating the target of rapamycin (mTOR) signaling pathway leading to myogenic cell proliferation, and increasing serum concentrations of IGF-1; decreasing protein breakdown by downregulating the catabolic signaling pathways including ubiquitin-proteasome and autophagy-lysosome systems; enhancing muscle repair by increasing proliferation of satellite cells and decreasing inflammatory factors; and improving aerobic capacity by increasing mitochondrial biogenesis and fat oxidation (7, 8). Previous studies have indicated that the concentration of plasma HMB is positively associated with muscle mass and strength regardless of an older person's health status (9-11). However, in skeletal muscle, only 5–10% of α-ketoisocaproic acid (KIC) synthesized from leucine is transmitted to the liver and converted to HMB by the cytosolic enzyme KIC dioxygenase (5). Moreover, HMB and KIC dioxygenase levels in the plasma are inversely correlated with age (11, 12). These findings strongly support the rationale for HMB supplementation in older adults. Additionally, resistance exercise training (RET) is well defined as an effective regimen for building up strength as well as preventing muscle atrophy and weakness (13). However, RET probably induces fatigue, muscular injury, inflammatory reaction, and exercise-induced proteolysis (3), all of which are relieved by HMB (7, 14).

RESULTS: After the 12-week intervention, the HMBG demonstrated significantly greater improvements in handgrip strength (4.61(95%CI:2.93,6.28) kg, P<0.001), gait speed (0.11(95%CI:0.02,0.20)m/s, P=0.014), five-time chair stand test (-3.65 (95%CI:-5.72, -1.58)s, P=0.001), muscle quality (2.47(95%CI:1.15,3.80),kg·kg^{-1} P=0.001) and tumor necrosis factor-like weak inducer of apoptosis (-15.23(95%CI:-29.80,-0.66)pmol/mL, P=0.041) compared with the PG; no significant differences in skeletal muscle mass, skeletal muscle index, and other body composition parameters were found between the two groups.
CONCLUSION: In older adults with sarcopenia, HMB significantly enhance the effect of resistance exercise training on muscle strength, physical performance, muscle quality, and reduced inflammatory factors. Therefore, HMB supplementation could be an effective treatment for sarcorpenia. The trial protocol was registered at http://www.chictr.org.cn/showproj.aspx?proj=47571 as ChiCTR2000028778.

Yang C, et al. (2023) Effects of Beta-Hydroxy-Beta-Methylbutyrate Supplementation on Older Adults with Sarcopenia: A Randomized, Double-Blind, Placebo-Controlled Study. *J Nutr Health Aging* *27*(5):329-339. doi: 10.1007/s12603-023-1911-1.



Fava Bean (*Vicia faba)* Bioactive Peptides Strength Recovery Clinical Trial

nutrients

MDPI

Article

Improved Strength Recovery and Reduced Fatigue with Suppressed Plasma Myostatin Following Supplementation of a *Vicia faba* Hydrolysate, in a Healthy Male Population

Alish Kerr [1,†], Luke Hart [2,†], Heidi Davis [1], Audrey Wall [1,*], Seán Lacey [3], Andrew Franklyn-Miller [2], Nora Khaldi [1] and Brian Keogh [1]

1 Nuritas Ltd., Joshua Dawson House, D02 RY95 Dublin, Ireland
2 SSC Sports Medicine, Unit C10, Gulliver's Retail Park, Northwood Avenue, Santry, D09 C523 Dublin, Ireland
3 Research Integrity & Compliance Officer, Munster Technological University, T12 P928 Cork, Ireland
* Correspondence: wall.audrey@nuritas.com; Tel.: +353-1430-1290
† These authors contributed equally to this work.

Kerr A, et al. (2023). Improved Strength Recovery and Reduced Fatigue with Suppressed Plasma Myostatin Following Supplementation of a *Vicia faba* Hydrolysate, in a Healthy Male Population. *Nutrients, 15*(4):986.doi: 10.3390/nu15040986.

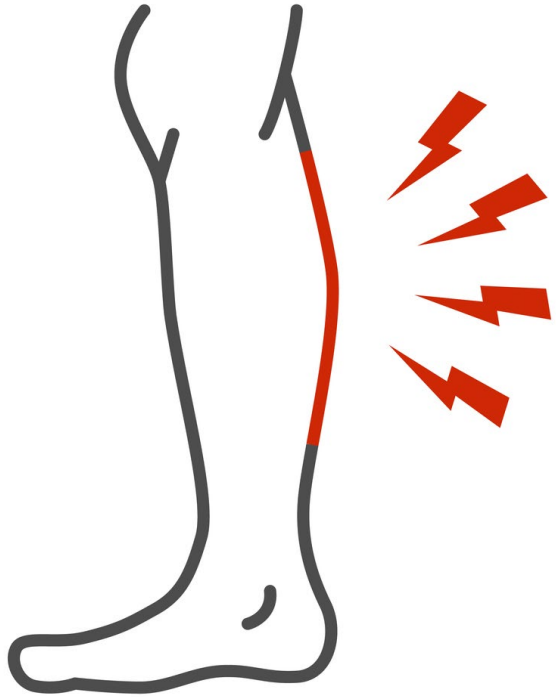
Background

- Muscle mass and sarcopenia are important factors through ageing.
- Delayed onset muscle soreness (DOMS) following exercise can impact muscle function.
- Identifying bioactive peptides in a nutrient-dense food source is a time consuming.
- Artificial intelligence (AI) and machine learning (ML) can decipher dense molecular networks within food identify distinct bioactive peptides that can target a specific health need at a fraction of the time and cost.

- AI & ML techniques have identified active peptide networks/hydrolysates that could increase muscle protein synthesis, decrease muscle breakdown, & reduce inflammation.
- Preclinical studies have demonstrated that two peptides [NPN_1 (PeptiStrong™)] had a significant increase in protein synthesis and reduction in proinflammatory cytokines
- Previous research has demonstrated several nutritional therapeutics in reducing DOMS and supporting muscle health (i.e. whey protein, omega-3 fatty acids, creatine, pomegranate juice, etc.).

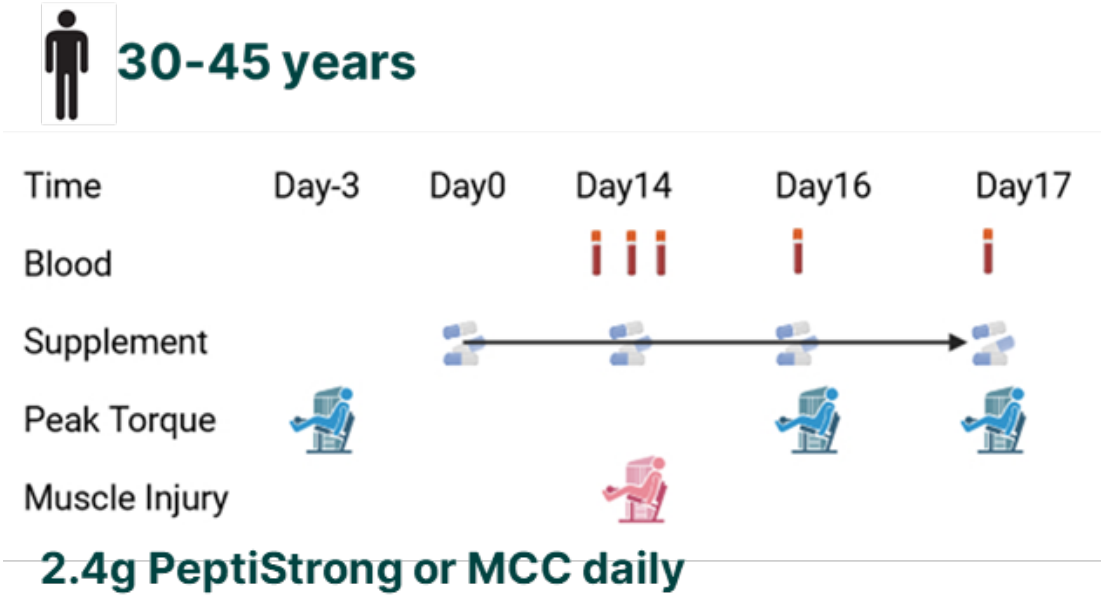
Objective

- The purpose of this study was to investigate the effect of NPN_1 supplementation on strength recovery in healthy men



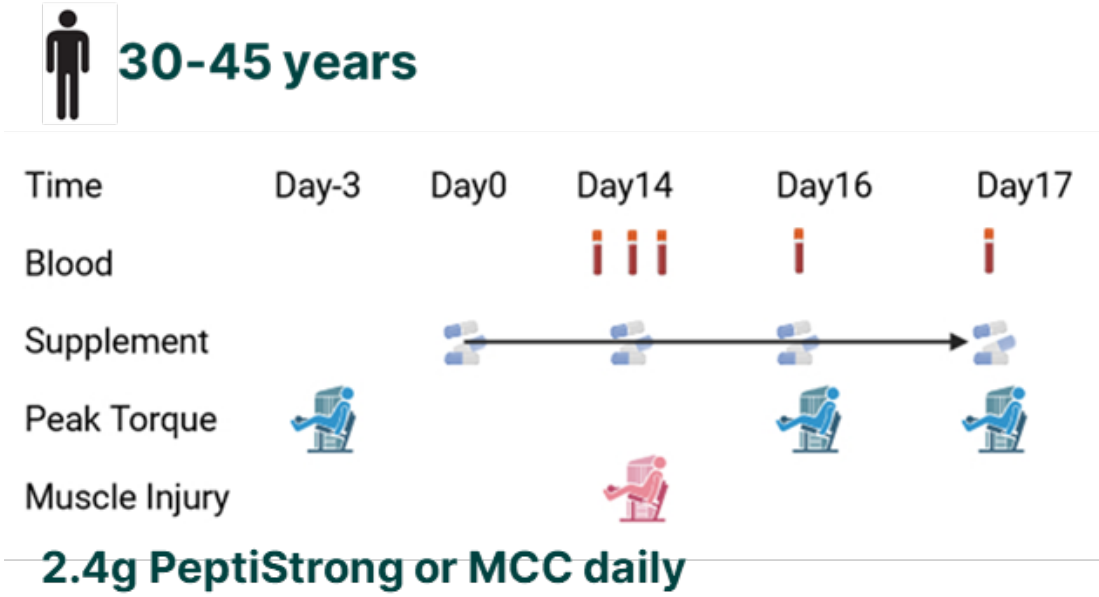
Methods

- A randomized, double-blind, placebo-controlled pilot study
- Subjects were allocated to placebo [microcrystalline cellulose (MCC)] or NPN_1 (PeptiStrong™) supplementation with their first meal of the day
- Subjects were recruited from internal databases at the study site, advertisements on social media, and notice boards in public buildings
- 30 healthy, non-smoking, moderately active (exercise 1–3 times per week) males between 30 and 45 years of age

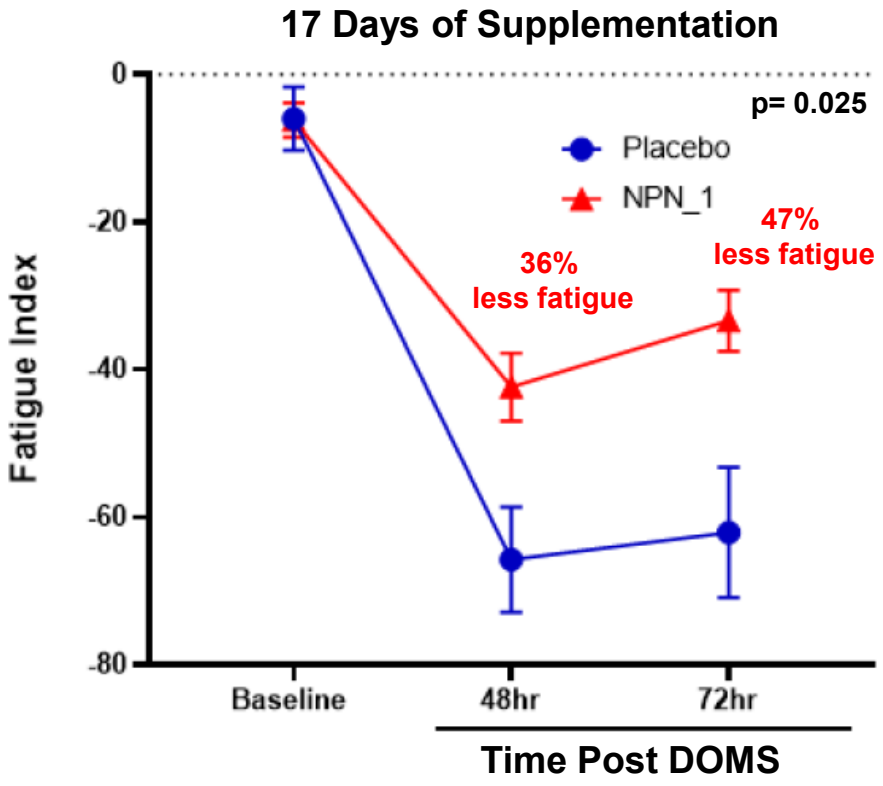


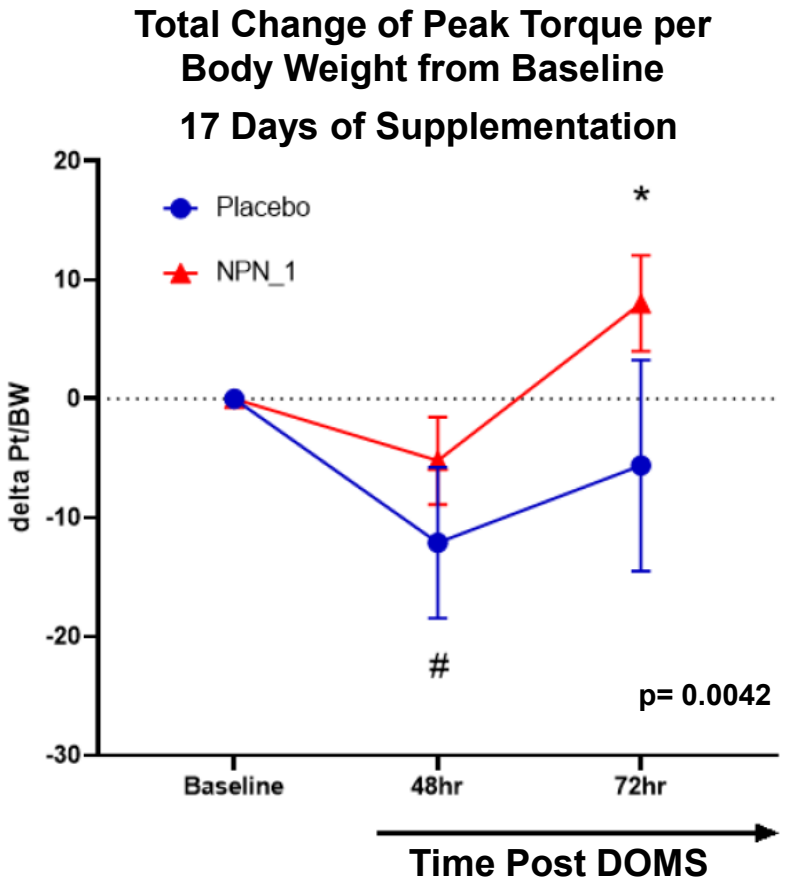
Methods (Cont'd)

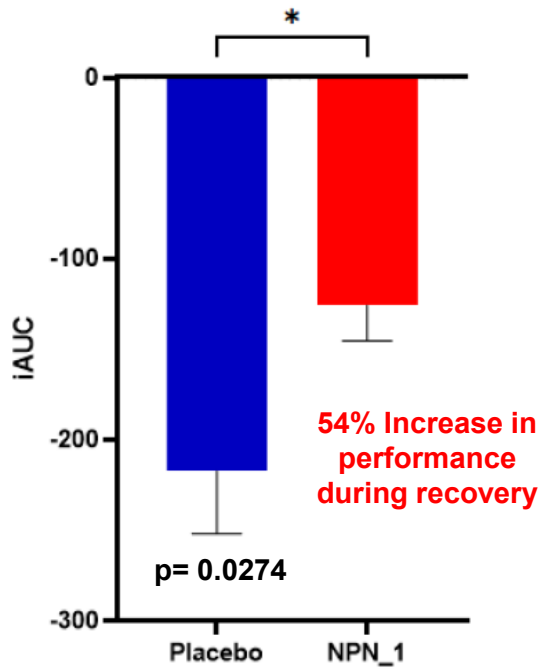
- Baseline strength measurements were taken prior to supplementation.
- 14 days post-supplementation, exercise-induced muscle damage (EIMD) was performed to induce DOMS
- Strength measurements were repeated at 48 h and 72 h post-EIMD exhaustive exercise routine
- Blood samples were collected prior to the onset of DOMS-inducing exercise and 0, 2, 48 and 72 h following completion of the routine.
- This trial was approved by the IRB "Sports Surgery Clinic Research Ethics Committee" (PN20.004.01)



Results

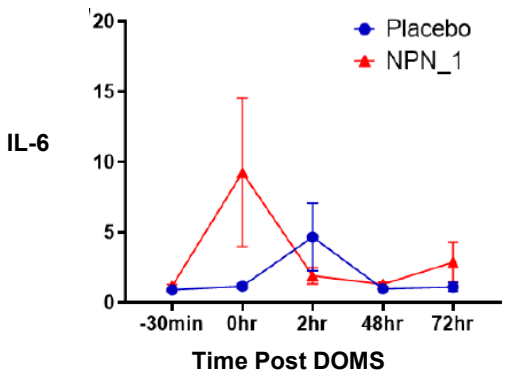

17 Days of Supplementation
p= 0.025
Placebo
NPN_1
36%
less fatigue
47%
less fatigue
Fatigue Index
0
-20
-40
-60
-80
Baseline
48hr
72hr
Time Post DOMS

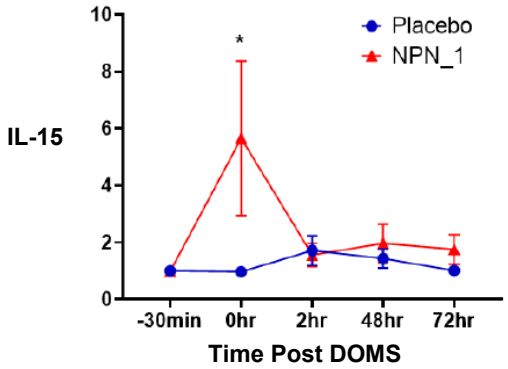

Total Change of Peak Torque per
Body Weight from Baseline
17 Days of Supplementation
Placebo
NPN_1
*
#
p= 0.0042
delta Pt/BW
20
10
0
-10
-20
-30
Baseline
48hr
72hr
Time Post DOMS

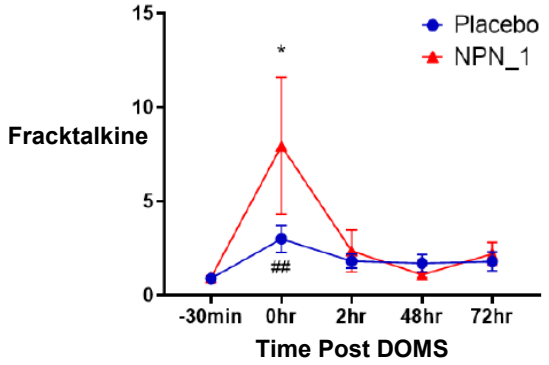

*
iAUC
0
-100
-200
-300
54% Increase in
performance
during recovery
p= 0.0274
Placebo
NPN_1

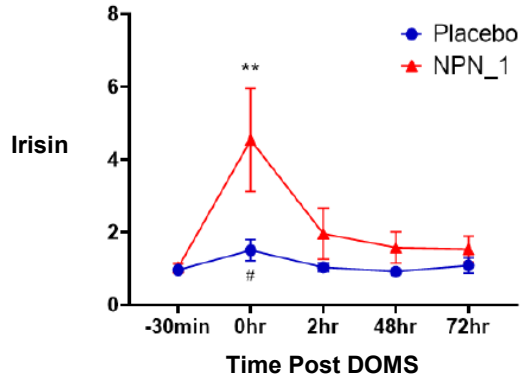
Results (Blood Biomarkers)

Transient increases can benefit muscle health









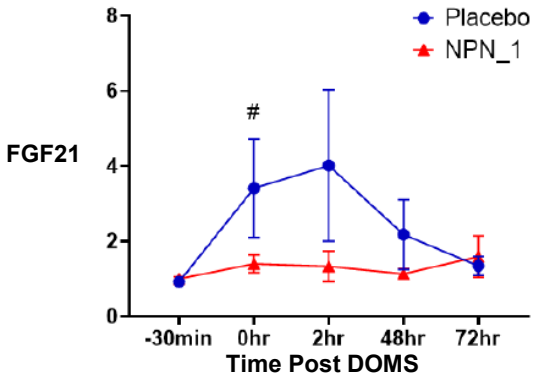
IL-6
Increases protein synthesis
Promotes satellite cell proliferation

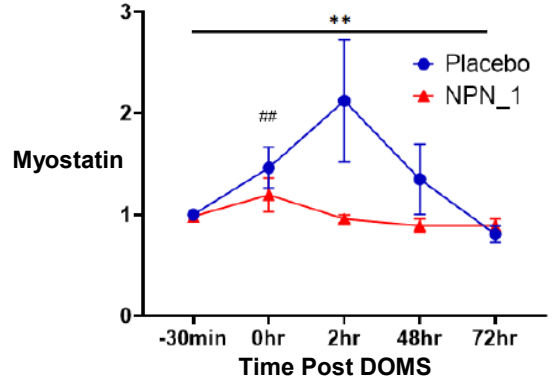
IL-15
Increases protein synthesis
Promotes myoblast differentiation

Fracktalkine
Attracts cells that promote regeneration

Irisin
Increases protein synthesis
Promotes GLUT4 expression

Transient suppression can benefit muscle health





FGF21
Decreases protein synthesis

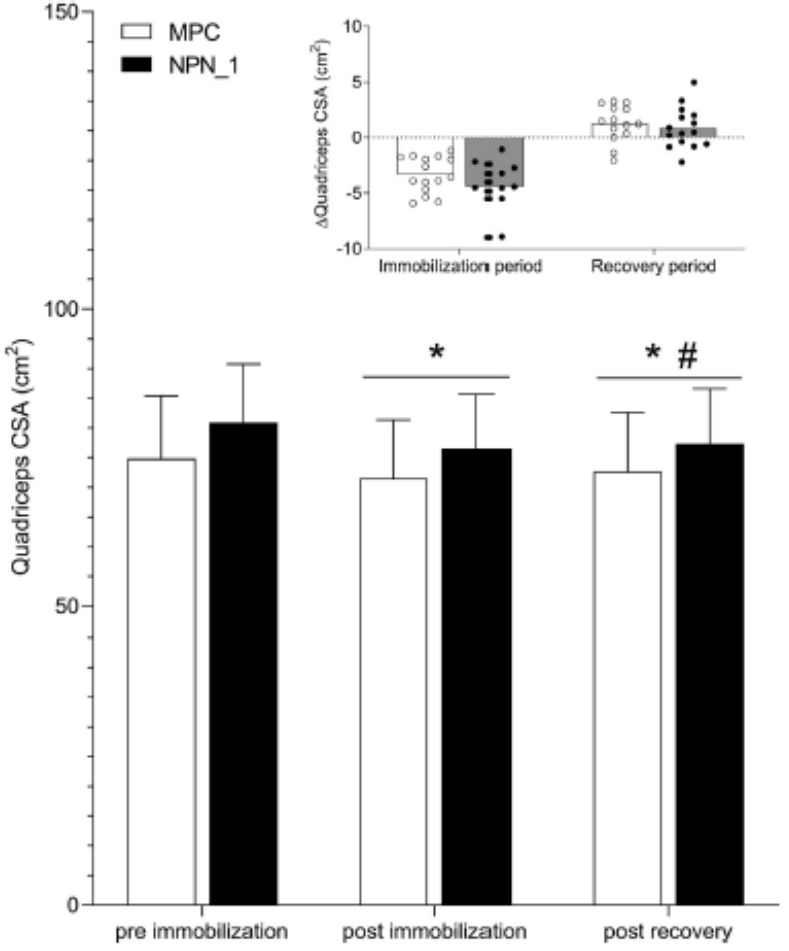
Myostatin
Inhibits protein synthesis

*** or # p < 0.05**
**** or ## p < 0.005**
***** or ### p < 0.0005**

Subjects are supplemented for 14 days prior to first blood draw

Discussion

- In preclinical studies, NPN_1 supplementation was shown to induce expression of genes involved in myogenesis (mTOR and MYF5) in a murine model of atrophy as well as p-S6 expression.
- A recent study with NPN_1 supplementation on short-term immobilization and subsequent recovery
  - Similar effect to milk protein concentrate (MPC) for recovery of muscle mass & strength
  - NPN_1 group regained muscle strength to the level measured at baseline; MPC group did not
  - Highly significant for a plant protein source to outperform an animal source.
  - This effect was not observed with a raw unhydrolyzed material indicating the effect is mediated by the AI-predicted bioactive peptides.



Weijzen, M.E., Holwerda, A.M., Jetten, G.H., Houben, L.H., Kerr, A., Davis, H., Keogh, B., Khaldi, N., Verdijk, L.B. and van Loon, L.J., 2023. Vicia Faba peptide network supplementation does not differ from milk protein in modulating changes in muscle size during short-term immobilization and subsequent remobilization, but increases muscle protein synthesis rates during remobilization in healthy young men. *The Journal of Nutrition 152*, 1718-1729.

Takeaway Points

- Delayed onset muscle soreness (DOMS) following exercise can impact muscle function.

- NPN_1 supplementation improved strength recovery, reduced fatigue, and suppressed myostatin expression following exercise induced muscle damage.

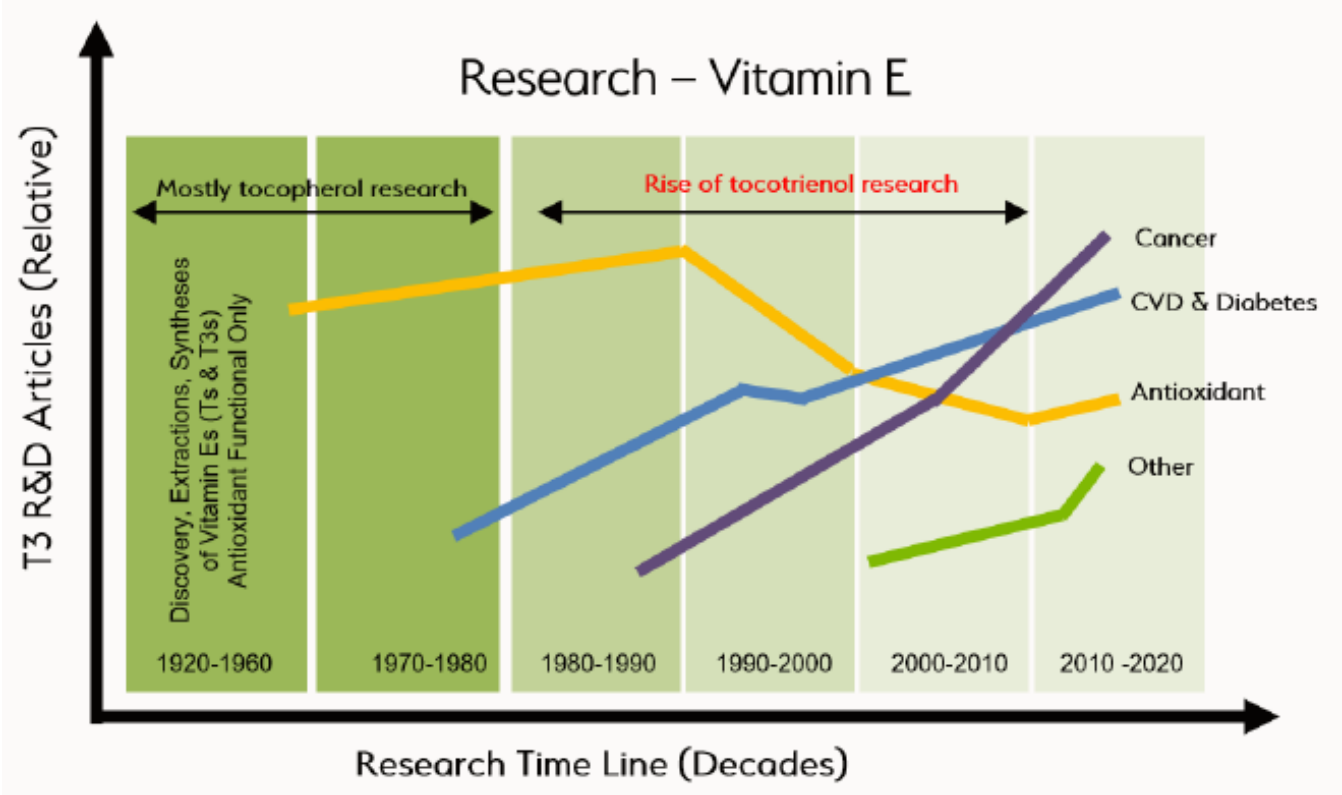
- The release of myostatin post-DOMS was positively modulated from NPN_1 supplementation.

- The supplementation group recovered at 48 h and exceeded baseline values; the placebo group did not fully recover at 72 h.

- NPN_1 supplementation may reduce DOMS severity and improve recovery resulting in a faster return to training.

Annatto Tocotrienol Human Clinical Trials

- Cardiovascular (Inflammation, Dyslipidemia)
- Osteoporosis
- Non-alcoholic Fatty Liver Disease (NAFLD)
- Metabolic Syndrome, Prediabetes, & Diabetes
- Cancer



Clinical & Experimental Cardiology

Qureshi et al., J Clin Exp Cardiolog 2015, 6:4
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Research Article Open Access

Impact of δ-Tocotrienol on Inflammatory Biomarkers and Oxidative Stress in Hypercholesterolemic Subjects

Asaf A Qureshi[1*], Dilshad A Khan[2], Wajiha Mahjabeen[2], Anne M Trias[3], Neerupama S

[1]Department of Basic Medical Sciences, University of Missouri-Kansas City, MO, USA

[2]Department of Chemical Pathology & Endocrinology, Armed Forces Institute of Pathology,

[3]American River Nutrition, Inc. Hadley, MA, USA

[4]Division of Pharmacology and Toxicology, School of Pharmacy, University of Missouri-Kar

*Corresponding author: Asaf A Qureshi, Department of Basic Medical Sciences, 2411
64108, USA, Tel: 816-235-5789; E-mail: qureshia@umkc.edu

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Abstract

Background: Tocotrienols have hypocholesterolemic, anti
studies using tocotrienol-rich fraction (TRF) from palm oil yielde
to presence of tocopherols in TRF mixture.

Objectives: The impact of tocopherol-free δ-tocotrienol on in
cytokines/proteins, their gene expression, and microRNAs was

Design: Hypercholesterolemic (n=31; serum cholesterol >5
hypercholesterolemic subjects were given increasing doses of
Step-1 diet for 4 weeks each during a 30 week study period.
malondialdehyde (MDA), δ-glutamyl-transferase (δ-GT), total
and microRNAs were determined.

Results: All concentrations of δ-tocotrienol reduced serum
dose (250 mg/d) decreased serum NO (40%), CRP (40%), MD
TAS levels increased 22% (P<0.001). The 500 mg/d and 750 m
stress compared to the 250 mg/d dose. Inflammatory plasma cy
15-17% (P<0.05-0.01), while cardiac angiogenic fibroblast gr
factor (PDGF) were decreased by 11% and 14% (P<0.05-0.01)
Similar results were obtained for cytokine gene expression. S
miRNA-133, miRNA-155, miRNA-223, miRNA-372, miRNA
cardiovascular disease and cancer were modulated by δ-tocotri

Conclusions: In a dose-dependent study of 125-750 mg/d
oxidative stress parameters with a 250 mg/d dose in hyper
therapeutic alternative natural product for the maintenance of he

Keywords: Tocotrienols; Inflammatory biomarkers; Serum NO; hsCRP, Malondialdehyde; γ-GT; Total antioxidant status; Plasma cytokines; Circulatory miRNAs

Abbreviations:

AHA Step-1 diet: American Heart Association Step-1 diet; CRP: C-reactive Protein; FGF-b: Fibroblast Growth Factor-b; IFN-γ: Interferon-γ; FGF-b: Fibroblast Growth Factor-b; mRNA: Messenger Ribonucleic Acid; miRNA: MicroRNA; NO: Nitric Oxide; PDGF: Platelet-derived Growth Factor; ROS: Reactive Oxygen Species; TAS: Total Antioxidant Status; TNF-α: Tumor Necrosis Factor-alpha

Abstract

Background: Tocotrienols have hypocholesterolemic, anti-inflammatory, and anti-cancer properties. Clinical studies using tocotrienol-rich fraction (TRF) from palm oil yielded inconsistent results with regards to its efficacy due to presence of tocopherols in TRF mixture.

Objectives: The impact of tocopherol-free δ-tocotrienol on inflammatory and oxidative stress biomarkers, plasma cytokines/proteins, their gene expression, and microRNAs was studied in hypercholesterolemic subjects.

Design: Hypercholesterolemic (n=31; serum cholesterol >5.2 mmol/L) subjects were enrolled in the study. All hypercholesterolemic subjects were given increasing doses of δ-tocotrienol (125, 250, 500, 750 mg/d) plus AHA Step-1 diet for 4 weeks each during a 30 week study period. Serum nitric oxide (NO), C-reactive protein (CRP), malondialdehyde (MDA), δ-glutamyl-transferase (δ-GT), total antioxidant status (TAS), cytokines/proteins, cDNA, and microRNAs were determined.

Results: All concentrations of δ-tocotrienol reduced serum levels of NO, CRP, MDA, δ-GT. The most effective dose (250 mg/d) decreased serum NO (40%), CRP (40%), MDA (34%), δ-GT (22%) significantly (P<0.001), while TAS levels increased 22% (P<0.001). The 500 mg/d and 750 mg/d doses were less effective in improving oxidative stress compared to the 250 mg/d dose. Inflammatory plasma cytokines (resistin, IL-1 δ, IL-12, IFN- δ) were reduced 15-17% (P<0.05-0.01), while cardiac angiogenic fibroblast growth factor-b (FGF-b) and platelet-derived growth factor (PDGF) were decreased by 11% and 14% (P<0.05-0.01), respectively, with 250 mg/d δ-tocotrienol treatment. Similar results were obtained for cytokine gene expression. Several plasma miRNAs (miRNA-16-1, miRNA-125a, miRNA-133, miRNA-155, miRNA-223, miRNA-372, miRNA-10b, miRNA-18a, miRNA-214) associated with cardiovascular disease and cancer were modulated by δ-tocotrienol treatment.

Conclusions: In a dose-dependent study of 125-750 mg/d, δ-tocotrienol maximally reduced inflammation and oxidative stress parameters with a 250 mg/d dose in hypercholesterolemic subjects, and may be a potential therapeutic alternative natural product for the maintenance of health during aging process.

April 27, 2015

Osteoporosis International
https://doi.org/10.1007/s00198-017-4356-x

ORIGINAL ARTICLE

Tocotrienol supplementation suppressed bone resorption and oxidative stress in postmenopausal osteopenic women: a 12-week randomized double-blinded placebo-controlled trial

C.-L. Shen[1] · S. Yan

Received: 25 May 2017 /A

Abstract

Summary Tocotrienc
tation decreased conc
postmenopausal oste
Introduction Tocotrie
women. The purpose
specific alkaline pho
kappaB ligand (sRA
deoxyguanosine (8-C
Methods Eighty-nine
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blood and urine samp
12-week study.
Results Relative to th
the 12-week study pe
concentrations and a
not affect serum OPG
NTX level, BALP/N
Conclusions Twelve-
suppressing bone remodeling regulators in postmenopausal women with osteopenia. Such osteoprotective TT's effects may be, in part, mediated by an inhibition of oxidative stress.
Trial registration ClinicalTrials.gov identifier: NCT02058420. Title: Tocotrienols and bone health of postmenopausal women.

Keywords Antioxidant · Bone metabolism · Osteoporosis · Tocotrienols · Women · 8-OHdG

Introduction Tocotrienols (TT) have been shown to benefit bone health in ovariectomized animals, a model of postmenopausal women. The purpose of this study was to evaluate the effect of 12-week TT supplementation on bone markers (serum bone-specific alkaline phosphatase (BALP), urine N-terminal telopeptide (NTX), serum soluble receptor activator of nuclear factor-kappaB ligand (sRANKL), and serum osteoprotegerin (OPG)), urine calcium, and an oxidative stress biomarker (8-hydroxy-2′-deoxyguanosine (8-OHdG)) in postmenopausal women with osteopenia.

Methods Eighty-nine postmenopausal osteopenic women (59.7 ± 6.8 year, BMI 28.7 ± 5.7 kg/m^2) were randomly assigned to three groups: (1) placebo (430 mg olive oil/day), (2) low TT (430 mg TT/day, 70% purity), and (3) high TT (860 mg TT/day, 70% purity). TT, an extract from annatto seed with 70% purity, consisted of 90% delta-TT and 10% gamma-TT. Overnight fasting blood and urine samples were collected at baseline, 6, and 12 weeks for biomarker analyses. Eighty-seven subjects completed the 12-week study.

Results Relative to the placebo group, there were marginal decreases in serum BALP level in the TT-supplemented groups over the 12-week study period. Significant decreases in urine NTX levels, serum sRANKL, sRANKL/OPG ratio, and urine 8-OHdG concentrations and a significant increase in BALP/NTX ratio due to TT supplementation were observed. TT supplementation did not affect serum OPG concentrations or urine calcium levels throughout the study period. There were no significant differences in NTX level, BALP/NTX ratio, sRANKL level, and sRANKL/OPG ratio between low TT and high TT groups.

Conclusions Twelve-week annatto-extracted TT supplementation decreased bone resorption and improved bone turnover rate via suppressing bone remodeling regulators in postmenopausal women with osteopenia. Such osteoprotective TT's effects may be, in part, mediated by an inhibition of oxidative stress.

ORIGINAL ARTICLE LIVER

Effects of delta-tocotrienol supplementation on liver enzymes, inflammation, oxidative stress and hepatic steatosis in patients with nonalcoholic fatty liver disease

Muhammad Amjad Pervez[1], Dilshad Ahmet Khan[1], Aamir Ijaz[1], Shamrez Khan[2]
[1]Armed Forces Institute of Pathology, National University of Medical Sciences, Islamabad, Pakistan
[2]Armed Forces Institute of Radiology, National University of Medical Sciences, Islamabad, Pakistan

Cite this article as: Pervez MA, Khan DA, Ijaz A, Khan S. Effects of Delta-tocotrienol Supplementation on Liver Enzymes, Inflammation, Oxidative stress and Hepatic Steatosis in Patients with Nonalcoholic Fatty Liver Disease. Turk J Gastroenterol 2018; 29: 170-6.

ABSTRACT

Background/Aims: *Non-alcoholic fatty liver disease (NAFLD) is a growing public health problem worldwide and is associated with increased morbidity and mortality. Currently, there is no definitive treatment for this disease. δ-Tocotrienol has potent anti-inflammatory and antioxidant properties and may reduce liver injury in NAFLD. The present study aims to evaluate the efficacy and safety of δ-tocotrienol in the treatment of NAFLD.*

Materials and Methods: *The present study was a randomized, double-blind, placebo-controlled pilot study conducted in patients aged >20 years, belonging to both sexes, having ultrasound-proven fatty liver disease, having a fatty liver index (FLI) of ≥60, and persistent elevation of alanine transaminase. A total of 71 patients were assigned to receive either oral δ-tocotrienol (n=35, 300 mg twice daily) or placebo (n=36) for 12 weeks. At the baseline and at the end of the study, clinical and biochemical parameters, including lipid profile, liver function tests, high-sensitivity C-reactive protein (hs-CRP), and malondialdehyde (MDA) were measured. Body mass index and FLI were calculated, and ultrasound grading of hepatic steatosis was performed.*

Results: *Out of 71 enrolled patients, 64 patients, 31 in the δ-tocotrienol group and 33 in the placebo group, completed the study. After 12 weeks of supplementation, δ-tocotrienol showed greater efficacy than placebo by decreasing serum aminotransferases, hs-CRP, MDA, and FLI score (p<0.001). However, it did not improve hepatic steatosis on ultrasound examination. No adverse effects were reported.*

Conclusion: *δ-Tocotrienol was safe, and it effectively improved aminotransferase levels and inflammatory and oxidative stress markers in patients with NAFLD. Large-scale randomized clinical trials are warranted to further support these findings.*

Keywords: *δ-Tocotrienol, non-alcoholic fatty liver disease, aminotransferase, C-reactive protein, malondialdehyde, fatty liver index*

morbidity and mortality worldwide. Its prevalence is likely to increase over time owing to the epidemics of obesity and diabetes. In addition to the development of fatty liver, NAFLD may progress to hepatocellular injury, inflammation, and necrosis, which are known as non-alcoholic steatohepatitis (NASH). NASH may progress to fibrosis, cirrhosis, and hepatocellular carcinoma. It is expected to surpass hepatitis C virus infection as the leading cause of cirrhosis and hepatocellular carcinoma in a decade or so (2).

nosis. However, it is an invasive and costly procedure and is impractical owing to high disease prevalence. It is highly operator-dependent, is associated with sampling error, and major complications occur in 0.1%–2.3% of cases. Thus, this method is unsuitable for screening and follow-up of patients with NAFLD (3). Alternately, non-invasive diagnostic methods, e.g., liver ultrasonography (USG) and fatty liver index (FLI), have been developed to determine liver fat content (4). Several studies have shown that USG has

ORCID IDs of the authors: M.A.P. 0000-0001-8562-4733; D.A.K. 0000-0002-5993-6239; A.I. 0000-0002-0190-0081; S.K. 0000-0002-7026-4613.

Address for Correspondence: **Dilshad Ahmed Khan** E-mail: **directoracademics@numspak.edu.pk**
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DOI: **10.5152/tjg.2018.17297**

Study Parameters	Results
Weight Loss	9.7lbs
BMI	30.7 → 29.2
Waist Circumference	100.2 → 97.98
Triglycerides	9.9%↓
ALT & AST	15.6%↓ & 14.6%↓
hsCRP	18.0%↓
FLI (steatosis)	11.1%↓
HOMA-IR	

March 2018

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DOI: 10.1002/ptr.7113

RESEARCH ARTICLE

WILEY

Effects of delta-tocotrienol supplementation on *Glycemic Control*, oxidative stress, inflammatory biomarkers and miRNA expression in type 2 diabetes mellitus: A randomized control trial

Wajiha Mahjabeen[1] | Dilshad Ahmed Khan[1] | Shakeel Ahmed Mirza[2] | Muhammad Amjad Pervez[1]

[1]Department of Chemical Pathology, Armed Forces Institute of Pathology, National University of Medical Sciences, Rawalpindi, Pakistan
[2]Mega Medical Complex Hospital, The Mall, Rawalpindi, Pakistan

Correspondence
Dilshad Ahmed Khan, Pathology Department, Armed Forces Institute of Pathology, National University of Medical Sciences, Rawalpindi, Pakistan.
Email: dakhan@cpsp.edu.pk

Funding information
National Research Program for Universities (NRPU), Higher Education Commission, Grant/Award Number: 5954

The study aimed to ascertain the effects of delta-tocotrienol (δT3) supplementation on glycemic control, oxidative stress, inflammation and related micro-ribonucleic acid (miRNA) expression in patients with type 2 diabetes mellitus (T2DM). Total 110 patients of T2DM on oral hypoglycemic agents, were randomly divided into tocotrienol and placebo groups and given 250 mg δT3 or cellulose soft gel capsule once daily respectively for 24 weeks. Glycemic control, oxidative stress, inflammatory biomarkers, and miRNAs expression were measured in serum at baseline and end of the intervention by using standard laboratory methods. Compared to the placebo, δT3 supplementation resulted in a significant ($p \leq .05$) reduction [mean difference (95% confidence interval)] in plasma glucose [−0.48 (−0.65, −0.30)], insulin [−1.19 (−1.51, −0.87)], homeostatic model assessment of insulin resistance [−0.67 (−0.86, −0.49)], glycosylated hemoglobin [−0.53 (−0.79, −0.28)], malondialdehyde [−0.34 (−0.45, −0.22)], high sensitive-C-reactive protein[−0.35 (−0.54, −0.16)], tumor necrosis factor-alpha [−1.22 (−1.62, −0.83)], and interleukin-6[−2.30 (−2.91, −1.68)]. More than twofold downregulation in miRNA-375, miRNA-34a, miRNA-21, and upregulation in miRNA-126, miRNA-132 expression was observed in the δT3 group compared to the placebo. The study demonstrated that δT3 supplementation in addition to oral hypoglycemic agents, improved glycemic control, inflammation, oxidative stress, and miRNA expression in T2DM without any adverse effect. Thus, δT3 might be considered as an effective dietary supplement to prevent long-term diabetic complications.

KEYWORDS
delta-tocotrienol, glycemic control, inflammation, microRNAs, oxidative stress, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a hyperglycemic state, due to inadequate insulin secretion or ineffective insulin action on the liver and peripheral tissues (Saeedi et al., 2019). Persistent hyperglycemia in T2DM patients induces oxidative stress and chronic inflammation. Chronic inflammation is one of the major elements for the commencement of insulin resistance and the increase of fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) in these patients. High sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are the main biochemical markers used for evaluating the inflammatory status of the disease.

The study aimed to ascertain the effects of delta-tocotrienol (δT3) supplementation on glycemic control, oxidative stress, inflammation and related micro-ribonucleic acid (miRNA) expression in patients with type 2 diabetes mellitus (T2DM). Total 110 patients of T2DM on oral hypoglycemic agents, were randomly divided into tocotrienol and placebo groups and given 250 mg δT3 or cellulose soft gel capsule once daily respectively for 24 weeks. Glycemic control, oxidative stress, inflammatory biomarkers, and miRNAs expression were measured in serum at baseline and end of the intervention by using standard laboratory methods. Compared to the placebo, δT3 supplementation resulted in a significant ($p \leq .05$) reduction [mean difference (95% confidence interval)] in plasma glucose [−0.48 (−0.65, −0.30)], insulin [−1.19 (−1.51, −0.87)], homeostatic model assessment of insulin resistance [−0.67 (−0.86, −0.49)], glycosylated hemoglobin [−0.53 (−0.79, −0.28)], malondialdehyde [−0.34 (−0.45, −0.22)], high sensitive-C-reactive protein[−0.35 (−0.54, −0.16)], tumor necrosis factor-alpha [−1.22 (−1.62, −0.83)], and interleukin-6[−2.30 (−2.91, −1.68)]. More than twofold downregulation in miRNA-375, miRNA-34a, miRNA-21, and upregulation in miRNA-126, miRNA-132 expression was observed in the δT3 group compared to the placebo. The study demonstrated that δT3 supplementation in addition to oral hypoglycemic agents, improved glycemic control, inflammation, oxidative stress, and miRNA expression in T2DM without any adverse effect. Thus, δT3 might be considered as an effective dietary supplement to prevent long-term diabetic complications.

ORIGINAL ARTICLE

Effects of delta-tocotrienol supplementation on glycaemic control in individuals with prediabetes: A randomized controlled study

Farhana Suleman[1], Dilshad Ahmed Khan[2], Muhammad Amjad Pervez[3], Mohammad Aamir[4]

Abstract

Objective: To study the effects of delta-tocotrienol on glycaemic control parameters in individuals with pre-diabetes.

Method: The randomised control trial was conducted at the Armed Forces Institute of Pathology, Rawalpindi, Pakistan, from July 15 to November 15, 2019, and comprised individuals aged 18-60 years having fasting plasma glucose of 5.6 to 6.9 mmol/L or glycosylated haemoglobin of 5.7 to 6.4%. They were randomised into group A receiving 300mg delta-tocotrienol and group B receiving a placebo once daily for 12 weeks. Weight, height, waist circumference, fasting plasma glucose, insulin and glycosylated haemoglobin were measured at the beginning and end of the trial to assess any change. Body mass index and homeostatic model assessment-insulin resistance were also calculated. Data was analysed using SPSS 21.

Results: Of the 77participants, 40(52%) were in group A and 37(48%) in group B. Group A showed significantly greater reduction in terms of fasting plasma glucose, glycosylated haemoglobin, insulin and homeostatic model assessment-insulin resistance index ($p \leq 0.001$) post-intervention.

Conclusion: Delta-tocotrienol supplementation was found to have a significant effect in improving glycaemic control parameters in persons with pre-diabetes. Futures larger scale clinical trials are needed to confirm these findings.

Clinical Trial Number: SLCTR/2019/024.

Keywords: Delta-tocotrienol, Pre-diabetes, Supplementation, HbA1c, HOMA index. (JPMA 72: 4; 2022)

DOI: https://doi.org/10.47391/JPMA.966

Introduction

Pre-diabetes mellitus (PDM) is defin hyperglycaemia characterised by glyc above normal but below the diagnosti diabetes mellitus (T2DM). It comprise glucose (IFG) and impaired glucose tole asymptomatic condition that leads to conversion rate of 5-10%. The worldwid is estimated at 316 million; a figure pr to 471 million by 2035.[2] The perso develop T2DM in due course of time World Health Organisation (WHO) 201 adults had diabetes in 2014. The increa in African and Asian countries.[3] Diabete Pakistan shows a prevalence of 10% an females respectively.[4]

The pathogenesis of PDM involves insulin resistance (IR) primarily affecting the skeletal muscle, liver and adipose tissue. IR promotes hypersecretion of insulin from the β-cells of pancreas. Over time, insulin hypersecretion causes beta cell exhaustion that leads to hyperglycemia.[5]

[1,3,4]Department of Chemical Pathology, Armed Forces Institute of Pathology, National University of Medical Sciences, Rawalpindi, Pakistan; [2]Department of Pathology, Armed Forces Institute of Pathology, National University of Medical Sciences, Rawalpindi, Pakistan.

Correspondence: Dilshad Ahmed Khan. e-mail: dakhan@cpsp.edu.pk

γ- and δ-tocotrienol, possess potent anti-diabetic properties. Thus γ- and δ-tocotrienol are shown to significantly improve fasting plasma glucose (FPG) and HbA1c by improving insulin sensitivity in animal models. In addition, they prevent systemic complications of obesity and diabetes by suppressing inflammation and oxidative stress (OS).[7] However, no human study has assessed the anti-diabetic effects of δ-tocotrienol in PDM population. The current study was planned to ascertain the effects of supplementation of 300mg δ-tocotrienol on glycaemic control parameters in PDMs.

Conclusion

Delta-tocotrienol supplementation at a dose of 300mg daily for 12 weeks resulted in favourable changes in glycaemic homeostasis in human volunteers with PDM.

Collagen

- The body is not only composed of complete proteins, but 25-30% collagen.
- Collagen protein is renewed at comparable rates as other proteins in the body, such as muscle.
- Collagen is also a significant component in many tissues as follows: 75% of skin, 50% of cartilage, 65-80% of tendons, 70% of ligaments, 10-11% of muscle, and 23% of cortical bone, 10% of lung, 12-24% of aorta, and 30% of tooth dentin.

Specific Bioactive Collagen Peptides

- Great source of supplementation glycine
- Cardiovascular
  - Supports healthy blood pressure
- Bone Health
  - Bone mineral density
  - Reduced fracture risk
  - Accelerated fracture healing
- Joint Health
  - Reduces osteoarthritis symptoms
  - Improves cartilages structures
  - Improves joint function
  - Reduces pose exercise joint pain
- Sarcopenia

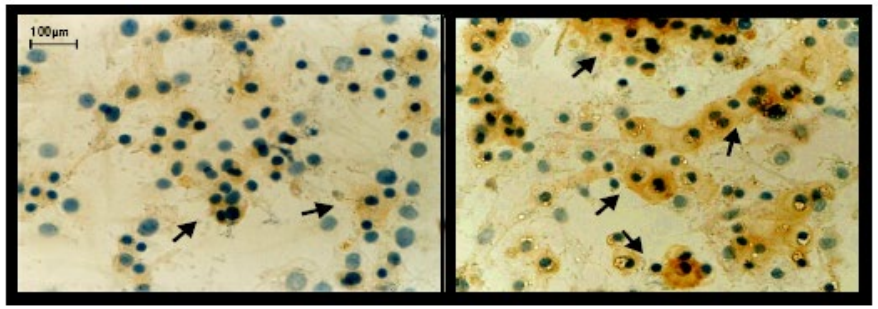
Evolution in Joint Care Therapy

- First generation
  - Pain killers and anti-inflammatory medicine
  - Address symptoms; and offer some short-term relief and improved mobility
- Second generation
  - Chondroitin, glucosamine, methylsulfonylmethane (MSM)
  - Anti-inflammatory effect and pain relief
  - Suggested to stimulate proteoglycan synthesis

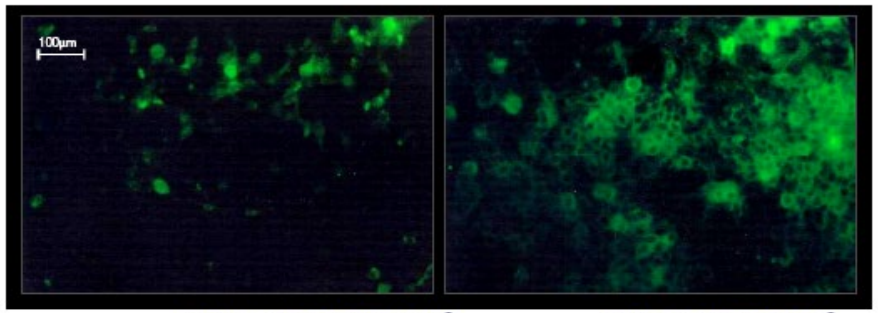
Collagen Hydrolysate

FORTIGEL® - Efficacy -

Collagen
new synthesis of
Type II collagen
(brown color)



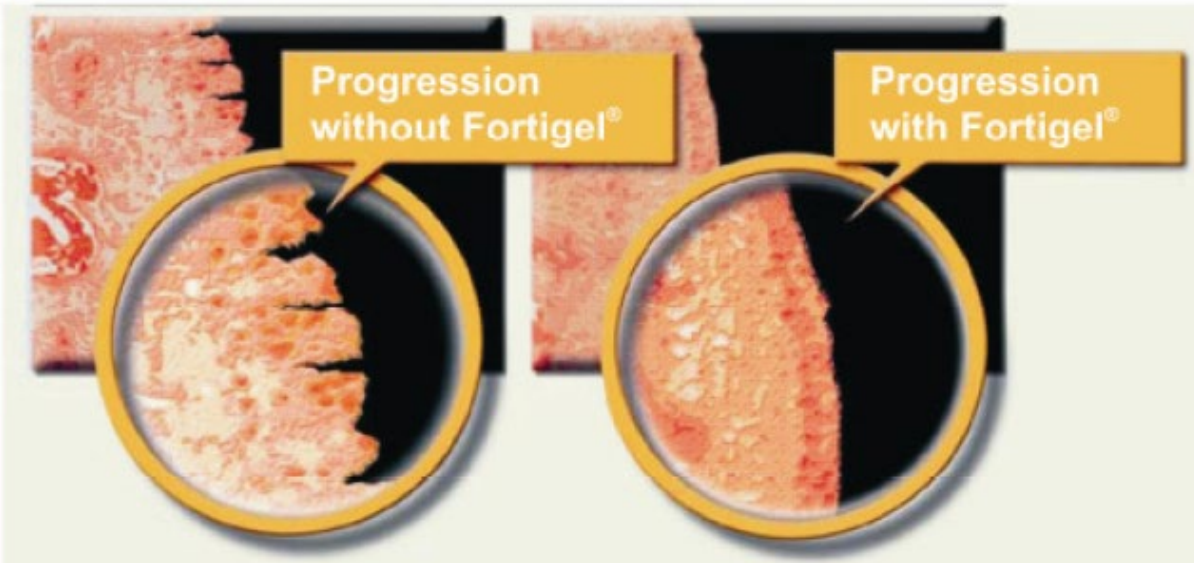
Proteoglycans
new synthesis of
Aggrecan
(green color)



Without FORTIGEL® With FORTIGEL®

Oesser et al. (2006) Annals of the Rheumatic Diseases

Change in joint cartilage after 3 months (tissue sections)[1]



1) Oesser S. et al. (2007) Osteoarthritis Cartilage 15: C61-C62, 94

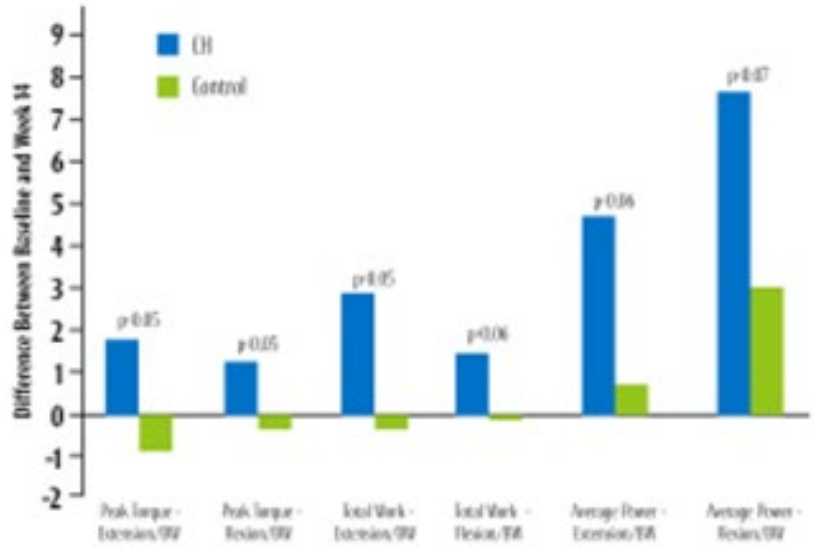
Rippe Study (2005) Confirms Significant Improvements in Joint Function in Patients with Mild Osteoarthritis

Design:

- Randomized, double blind, placebo controlled
- 250 patients with symptoms of mild osteoarthritis
- Therapy: 10 g CP* or placebo
- 14 weeks trial
- pain, stiffness, mobility, flexibility and isometric / isokinetic leg strength assessments

Results

- Consumption of CP* showed significant improvements in joint function by means of isometric and isokinetic leg strength assessments in patients with mild osteoarthritis of the knee



* FORTIGEL®

Rippe et al. Medcine & Science in Sports & Exercise (2005)

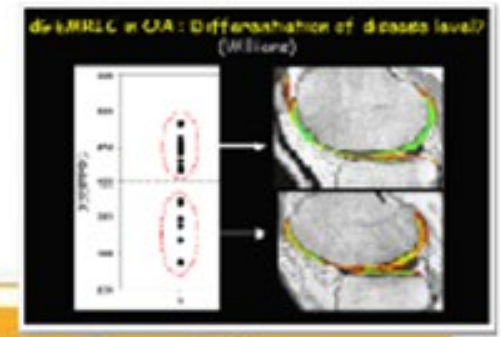
Harvard University / Tufts Medical Center Study (2009) Visualized the Joint Health Effect of Collagen Peptides*

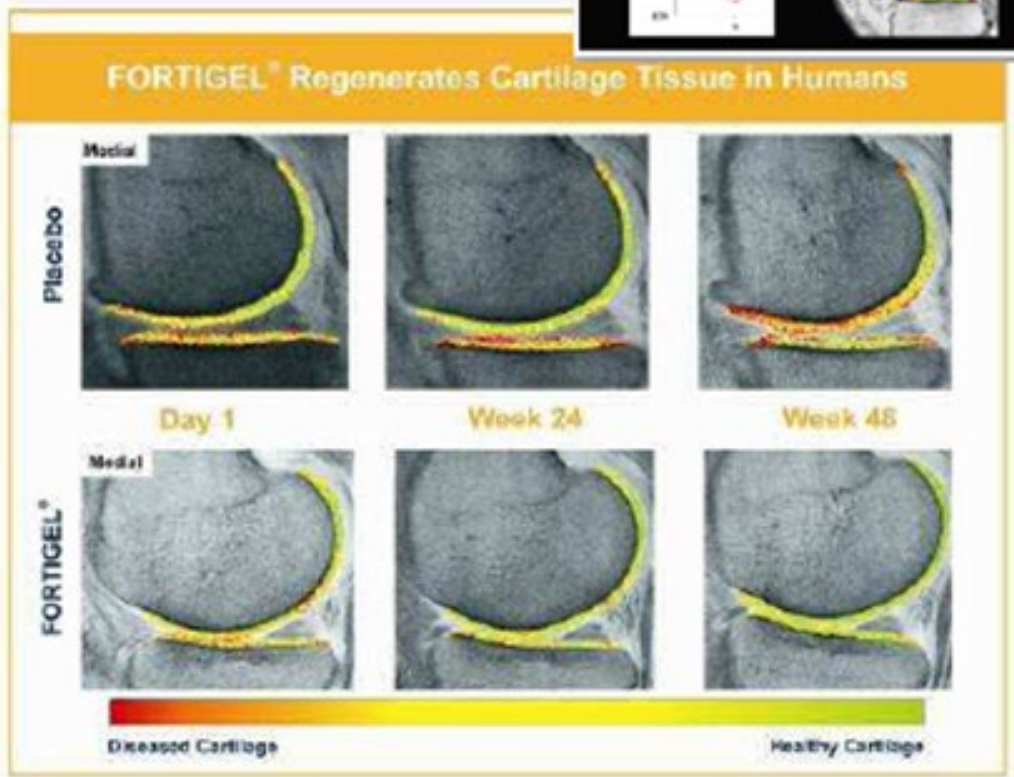
Design:

- Prospective, randomized, double blind, placebo controlled
- 30 individuals with mild grade of Osteoarthritis (Kellgrean grade 1 – 2)
- Therapy: 10 g CP* or placebo
- 11 months trial
- dGEMRIC data

Results

- Proteoglycan density in the knee joint cartilage was significantly increased after CP* treatment





* FORTIGEL®

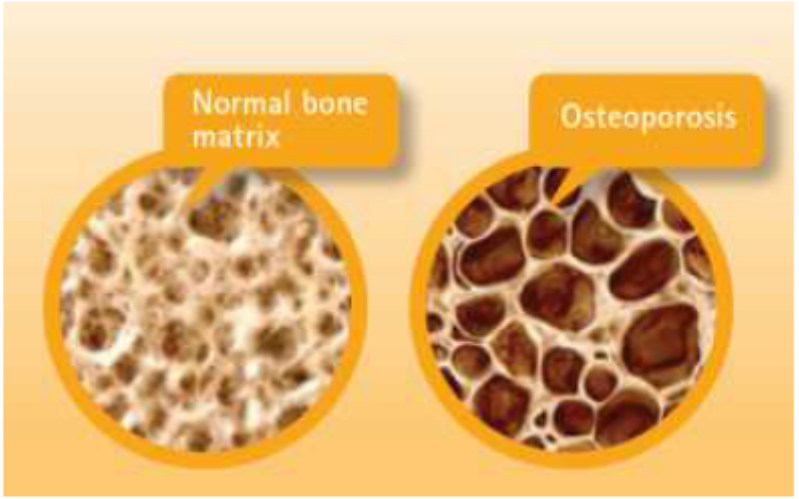
Collagen Peptides

- Several studies on collagen suggest that oral supplementation may provide beneficial effects on bone metabolism, especially in the calcium-deficient condition such as osteopenia and osteoporosis without side effects.
- ~ 5 grams/d

- *Nomura, Y., Oohashi, K., Watanabe, M. and Kasugai, S. 2005. Increase in bone mineral density through oral administration of shark gelatine to ovariectomized rats. Nutrition, 21:1120-1126.*
- Wu, J., Fujioka, M., Sugimoto, K., Mu, G. and Ishimi, Y. 2004. Assessment of effectiveness of oral administration of collagen peptide on bone metabolism in growing and mature rats. Journal of bone and mineral metabolism, 22: 547-553.

Bone Structure and Role of Collagen in Bones

- 70 % inorganic minerals (mainly calcium-phosphate)
- 20 % organic material from which collagen type I is 95%
- 10% water
- Bone cells
  - osteoblasts for bone formation
  - osteoclasts for bone resorption



Collagen is essential for bone flexibility and elasticity

Bone collagen provides the framework for calcium mineralization

A weak collagen matrix provides insufficient calcium binding sites

Bone Structure and Role of Collagen in Bones

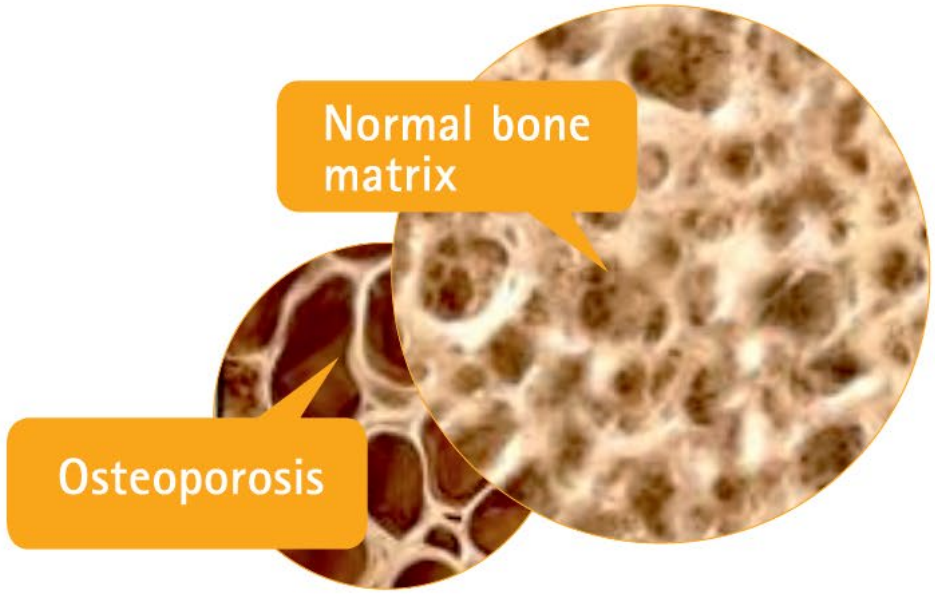


Fig. 1 Healthy versus osteporotic bone:
Bone quality is determined not only by mineral density but also by organic mass (representing 20% of total bone mass), composed of protein and cells, of which collagen represents 80-90%.

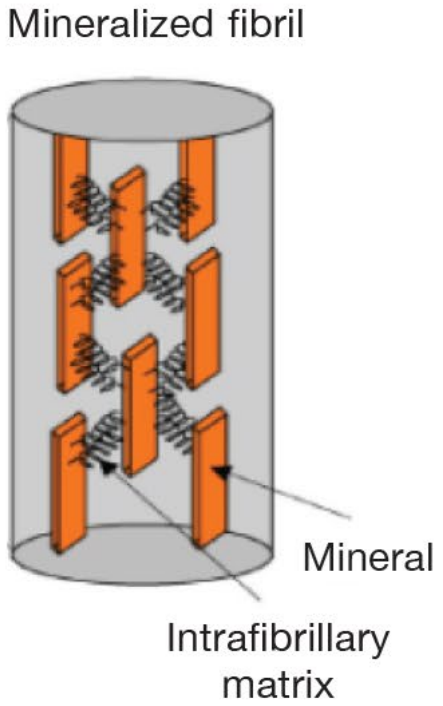


Fig. 2 Bone intrafibrillary matrix components: collagen fibrils & proteoglycans which bind calcium-phosphate crystals[46]

nutrients

MDPI

Article

Specific Collagen Peptides Improve Bone Mineral Density and Bone Markers in Postmenopausal Women—A Randomized Controlled Study

Daniel König [1,*], Steffen Oesser [2], Stephan Scharla [3], Denise Zdzieblik [1] and Albert Gollhofer [1]

1 Department for Nutrition, Institute for Sports and Spor
Schwarzwaldstr. 175, 79117 Freiburg, Germany; Denise
AG@sport.uni-freiburg.de (A.G.)
2 CRI, Collagen Research Institute GmbH, Schauenburge
steffen.oesser@cri-mail.org
3 Independent Reasercher, Salinenstr. 8, 83435 Bad Reich
* Correspondence: Daniel.Koenig@sport.uni-freiburg.de;

Received: 4 December 2017; Accepted: 9 January 2018; Publ

Abstract: Introduction: Investigations in rodents as w
anabolic influence of specific collagen peptides (SCP
(BMD). The goal of the study was to investigate the eff
SCP vs. placebo (CG: control group) on BMD in postr
reduction in BMD. **Methods:** 131 women were enr
double-blinded investigation. The primary endpoint w
the spine after 12 months. In addition, plasma levels
of type I collagen (P1NP) and C-telopeptide of type I
total of 102 women completed the study, but all subje
analysis (age 64.3 ± 7.2 years; Body Mass Index, BM
T-score femoral neck −1.4 ± 0.5). In the SCP group
neck increased significantly compared to the control
CG −0.03 ± 0.18; ANCOVA $p = 0.030$; T-score femo
ANCOVA $p = 0.003$). P1NP increased significantly
increased significantly in the control group ($p = 0.01$
the intake of SCP increased BMD in postmenopausa
of BMD. In addition, SCP supplementation was asso
indicating increased bone formation and reduced bon

Keywords: osteoporosis; collagen hydrolysate; SCP;

1. Introduction

The etiology of osteoporosis includes a lack of phys
drug ingestion and non-modifiable factors, such as
Adequate prevention or therapy of osteoporosis is a very important goal for individual and public health, because osteoporotic bone fractures are responsible for chronic pain, inactivity and invalidity in the elderly. It is estimated that, worldwide, every third women, and one in five men over the age of 50, will sustain an osteoporotic-induced bone fracture [1]. At present, there are a number of therapeutic approaches for the prevention and treatment of osteoporosis. Non-pharmacological approaches, such as daily physical activity, smoking cessation and reduction of alcohol consumption,

Abstract: Introduction: Investigations in rodents as well as in vitro experiments have suggested an anabolic influence of specific collagen peptides (SCP) on bone formation and bone mineral density (BMD). The goal of the study was to investigate the effect of 12-month daily oral administration of 5 g SCP vs. placebo (CG: control group) on BMD in postmenopausal women with primary, age-related reduction in BMD. **Methods:** 131 women were enrolled in this randomized, placebo-controlled double-blinded investigation. The primary endpoint was the change in BMD of the femoral neck and the spine after 12 months. In addition, plasma levels of bone markers—amino-terminal propeptide of type I collagen (P1NP) and C-telopeptide of type I collagen (CTX 1)—were analysed. **Results:** A total of 102 women completed the study, but all subjects were included in the intention-to-treat (ITT) analysis (age 64.3 ± 7.2 years; Body Mass Index, BMI 23.6 ± 3.6 kg/m^2; T-score spine −2.4 ± 0.6; T-score femoral neck −1.4 ± 0.5). In the SCP group ($n = 66$), BMD of the spine and of the femoral neck increased significantly compared to the control group ($n = 65$) (T-score spine: SCP +0.1 ± 0.26; CG −0.03 ± 0.18; ANCOVA $p = 0.030$; T-score femoral neck: SCP +0.09 ± 0.24; CG −0.01 ± 0.19; ANCOVA $p = 0.003$). P1NP increased significantly in the SCP group ($p = 0.007$), whereas CTX 1 increased significantly in the control group ($p = 0.011$). **Conclusions:** These data demonstrate that the intake of SCP increased BMD in postmenopausal women with primary, age-related reduction of BMD. In addition, SCP supplementation was associated with a favorable shift in bone markers, indicating increased bone formation and reduced bone degradation.

Jan. 16, 2018

J Musculoskelet Neuronal Interact 2020; 20(1):12-17

Journal of Musculoskeletal and Neuronal Interactions JMNI

Original Article

Effect of calcium and vitamin D supplementation with and without collagen peptides on bone turnover in postmenopausal women with osteopenia

Chrysoula Argyrou[1]*, Efthy
Konstantinos Makris[2], Geo

[1]Laboratory for Research of the Musc
Athens, KAT General Hospital of Athe
* equal contribution

Abstract

Objectives: Collagen peptides
the present randomized prospect
the tolerability of 3-month suppl
with osteopenia. **Methods**: Fifty-
received a sachet containing 5 g
D3 and group B received a
and 400 IU vitamin D3
decreased by 11.4% (p=0.058)
presented bett compliance in c
may reflect the reduction of the
CPs supplements. The addition o
bone metabolism. Clinical Trial ID

Keywords: Collagen Peptides, B

Introduction

Osteoporosis is undoubtedly c
diseases affecting older indiv
consequences[1]. Osteopenia, defi

Abstract

Objectives: Collagen peptides (CPs) seem to exert beneficial effects on bone and may have a role as a treatment option. In the present randomized prospective study, we aimed to examine the efficacy, as expressed by changes in P1NP and CTX, and the tolerability of 3-month supplementation of calcium, vitamin D with or without bioactive CPs in postmenopausal women with osteopenia. **Methods**: Fifty-one female, postmenopausal women with osteopenia were allocated to two groups: Group A received a sachet containing 5 g CPs, 3.6 g calcium lactate (equivalent to 500 mg of elemental calcium) and 400 IU vitamin D3 and group B received a chewable tablet containing 1.25 g calcium carbonate (equivalent to 500 mg of elemental calcium) and 400 IU vitamin D3 daily. **Results**: In group A, the P1NP levels significantly decreased by 13.1% (p<0.001) and CTX levels decreased by 11.4% (p=0.058) within 3 months of supplementation. In group B, P1NP and CTX did not change. Group A presented better compliance in comparison to group B and no adverse events contrary to group B. **Conclusions**: These findings may reflect the reduction of the increased bone turnover in postmenopausal women with the use of calcium, vitamin D and CPs supplements. The addition of CPs in a calcium and vitamin D supplement may enhance its already known positive effect on bone metabolism. Clinical Trial ID: NCT03999775.

Keywords: Collagen Peptides, Bone Turnover Markers, Calcium Supplement, Osteopenia, Postmenopausal Women

The study was supported by Vivapharm SA. The necessary amount of Colabone® sachets, containing 5 g bioactive collagen peptides (Fortibone®), 3.6 g calcium lactate (equivalent to 500 mg of elemental calcium) and 400 IU vitamin D3 for the conduction of the study was also provided by Vivapharm SA. The authors have nothing to declare.

Corresponding author: Kalliopi Lampropoulou-Adamidou, MD, MSc, PhD, Orthopaedic Surgeon, Laboratory for Research of the Musculoskeletal System "Th. Garofalidis", Medical School, National & Kapodistrian University of Athens, KAT General Hospital of Athens, Greece, 10 Athinas Str., Kifissia, PC: 14561, Athens, Greece
E-mail: klampropoulou@gmail.com
Edited by: P. Makras
Accepted 30 July 2019

antiresorptive or anabolic agents[2]. Collagen peptides (CPs), also called collagen hydrolysates produced by hydrolysis of collagen, have also been shown to have high oral bioavailability and could have a place as a treatment option[3-9].

Type I collagen comprises approximately 95% of the entire collagen content of bone. Bone matrix, unlike other connective tissues, possesses the unique ability to become calcified. Spindle or plate-shaped crystals of hydroxyapatite are found between and around collagen fibers, oriented in the same direction as collagen fibers are[10-12]. Nowadays, it is well-documented that type I collagen molecules are involved in the mechanical properties of bone[12,13]. Collagen

March 3, 2020

British Journal of Nutrition (2016), 116, 569–570

British Journal of Nutrition

Letter to the Editor

Exceptional body composition changes attributed to collagen peptide supplementation and resistance training in older sarcopenic men

(First published online 6 June 2016)

The results reported by Zdzieblik *et al.*[1], on gains in fat-free mass (FFM: mean 4·2 (SD 3·3) kg) and loss of body fat (mean −5·5 (SD 3·2) kg) in older sarcopenic men receiving 15 g/d of collagen peptides while resistance training for 12 weeks, are extraordinary. The algebraic difference between the collagen peptide-supplemented and placebo groups in terms of FFM reported by Zdzieblik *et al.*[1] was approximately 1·3 kg, which is 2·7 and 5·6 times greater than the standardised mean differences reported in meta-analyses from Cermak *et al.*[2] and Finger *et al.*[3], which examined the impact of protein supplementation on resistance exercise-induced gains in FFM. Neither meta-analysis reported an impact of protein supplementation on loss of fat mass.

We note that the 4·2 kg gain in FFM in the collagen peptide-supplemented group is unrivalled by any study of protein supplementation in older resistance training sarcopenic men[2,3]. One study, in which men with COPD received 100 mg of testosterone enanthate (injected weekly), comes close to the findings of Zdzieblik *et al.*[1], but in this study men receiving testosterone and performing resistance training gained only 3·3 kg of FFM and lost 1·1 kg of fat mass[4]. Were the observed changes[1] in whole-body FFM representative of skeletal muscle tissue or are changes in other tissues responsible for the greater gains in whole-body FFM?

The constituent amino acid content and protein dose (15 g/d) of collagen peptides ingested contained only 0·4 g of leucine and 1·7 g of arginine, which stimulate muscle protein synthesis and blood flow, respectively[1]; however, this dose of leucine would have been insufficient to induce any effect on muscle protein synthesis[5,6]. In addition, 1·7 g of arginine would not have affected blood flow[6,7]. In their study, Zdzieblik *et al.*[1] proposed that the provision of collagen peptides could enhance creatine synthesis. We find this proposition unlikely given the daily provision of only 1·7 g of arginine and 3·3 g of glycine, as there is no evidence that muscle creatine production is substrate-limited. If this thesis were true, then supplemental protein from almost any source (containing similar quantities of arginine and glycine) would promote the same gains in muscle mass and this has not been seen[2,3].

Collagen peptide-supplemented subjects lost a reported 5·5 kg of fat mass. This loss of fat mass, in 12 weeks, is approximately 80 % of that seen in older men following a hypoenergetic diet (−3138 kJ/d) (−750 kcal/d) or −3·1 MJ/d) while exercising for 6 months[8]. There is no obvious mechanism for the magnitude of loss of fat mass. It is n
protein supplementation i
training reported an effect
In sum, the changes in bo
older men, who exercised t
consumed 15 g of collagen
little in the way of plausibl
that either leucine and argin
the synthesis of muscle cre
changes. The simultaneous
subjects, of a magnitude on
weight loss trials, is simila
explanation than is given

Acknowledgements

All authors contributed to
and all agreed on the final
S. M. P. reports having re
and expenses for travel fro
a grant from Pepsico. D. P.-
from The Beef Checkoff
compensation for advisory
National Dairy Council and
reports having received co
All other authors report
otherwise.

Stuart M. Phillips[1], Kevi
Lex B. Ver

[1]Department
[2]Health and
Fa
Universi
[3]Department of Huma
School of Nutriti
Metabolism (NUTRIM), Maastricht University
6200 MD Maastricht, The Netherlands

The results reported by Zdzieblik *et al.*[1], on gains in fat-free mass (FFM: mean 4·2 (SD 3·3) kg) and loss of body fat (mean −5·5 (SD 3·2) kg) in older sarcopenic men receiving 15 g/d of collagen peptides while resistance training for 12 weeks, are extraordinary. The algebraic difference between

We note that the 4·2 kg gain in FFM in the collagen peptide-supplemented group is unrivalled by any study of protein supplementation in older resistance training sarcopenic men[2,3]. One study, in which men with COPD received 100 mg

In sum, the changes in body composition in these sarcopenic older men, who exercised three times weekly for 12 weeks and consumed 15 g of collagen peptides, are remarkable[1]. We find little in the way of plausible mechanistic evidence to suggest that either leucine and arginine or arginine and glycine, to allow the synthesis of muscle creatine, could be responsible for such changes. The simultaneous substantial loss of fat mass in these subjects, of a magnitude on par with that seen in much longer weight loss trials, is similarly noteworthy and deserves more explanation than is given by the authors in their article.

Phillips, S, et al. (2016) Exceptional body composition changes attributed to collagen peptide supplementation and resistance training in older sarcopenic men, Br J Nutr 116(3):569-70. doi: 10.1017/S000711451600221X.

Vitamin K2 (MK-4)

Vitamin K2 (MK-4)

- High dose (45 mg) of MK-4 maximizes tissue stores and may compensate for inadequate conversion of Vitamin K1 to K2.
- Supplementation with 45 mg MK-4 per day resulted in increased bone density and reduced fracture rate.- *Ushiroyama T, Ikeda A, Ueki M. Effect of continuous combined therapy with vitamin K(2) and vitamin D(3) on bone mineral density and coagulofibrinolysis function in postmenopausal women. Maturitas. 2002;41(3):211-221. doi:10.1016/s0378-5122(01)00275-4.*
- *Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials [published correction appears in JAMA Intern Med. 2018;178(6):875-876]. Arch Intern Med. 2006;166(12):1256-1261. doi:10.1001/archinte.166.12.1256*
- The same dose was shown to reduce arterial stiffness by 16% and achieve a slower than average progression in arterial calcification- *Ikari Y, Torii S, Shioi A, Okano T. Impact of menaquinone-4 supplementation on coronary artery calcification and arterial stiffness: an open label single arm study. Nutr J. 2016;15(1):53. doi:10.1186/s12937-016-0175-8*

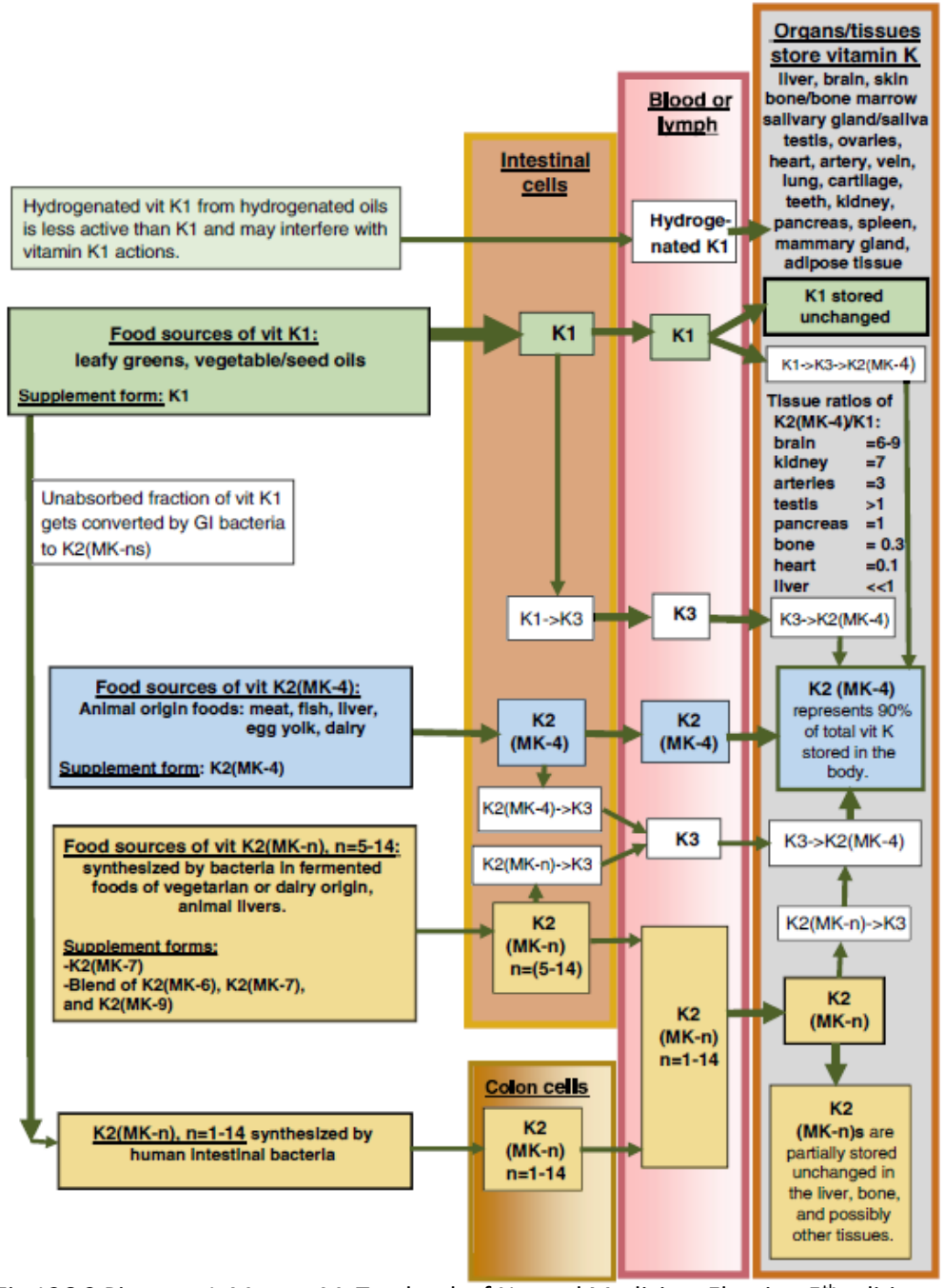


Fig 126.2 Pizzorno J, Murray M. Textbook of Natural Medicine. Elsevier, 5th edition. Chapter 126 Vitamin K. P. 1-34

Creatine Monohydrate

Open Access Journal of Sports Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis

Philip D Chilibeck[1]
Mojtaba Kaviani[2]
Darren G Candow[3]
Gordon A Zello[4]

[1]College of Kinesiology, University of Saskatchewan, Saskatoon, SK, [2]School of Nutrition and Dietetics, Acadia University, Wolfville, NS, [3]Faculty of Kinesiology and Health Studies, University of Regina, Regina, [4]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada

Journal of
Clinical Medicine

MDPI

Review

Effectiveness of Creatine Supplementation on Aging Muscle and Bone: Focus on Falls Prevention and Inflammation

Darren G. Candow [1,*], Scott C. Forbes [2], Philip D. Chilibeck [3], Stephen M. Cornish [4], Jose Antonio [5] and Richard B. Kreider [6]

1 Faculty of Kinesiology and Health Studies, University of Regina, Regina, SK S4S 0A2, Canada
2 Department of Physical Education, Brandon University, Brandon, MB R7A 6A9, Canada; ForbesS@BrandonU.CA
3 College of Kinesiology, University of Saskatchewan, Saskatoon, SK S7N 5B2, Canada; phil.chilibeck@usask.ca
4 Faculty of Kinesiology and Recreation Management, University of Manitoba, Winnipeg, MB R3T 2N2, Canada; Stephen.Cornish@umanitoba.ca
5 Department of Health and Human Performance, Nova Southeastern University, Davie, FL 33314, USA; Exphys@aol.com
6 Department of Health and Kinesiology, Texas A&M University, College Station, TX 77843-4253, USA; rbkreider@tamu.edu
* Correspondence: Darren.Candow@uregina.ca

Case Studies

Case Study

- History
  - 72-Year-Old Female
  - Osteoporosis

- Medications
  - Low-dose Aspirin (81 mg)

Study Result

Narrative & Impression

DEXA BONE DENSITY SPINE AND HIP (YBC YH LM WH)

Clinical: osteoporosis. Patient is postmenopausal.

A DEXA scan of the lumbar spine (L1-L4) and left total hip and femoral neck was perfo

8/25/2020 8:25 AM
Lumbar spine__BMD 0.645 g/cm2 : T-Score -3.7
Total hip_____BMD 0.622 g/cm2 : T-Score -2.6
Femoral neck __BMD 0.517 g/cm2 : T-Score -3.0

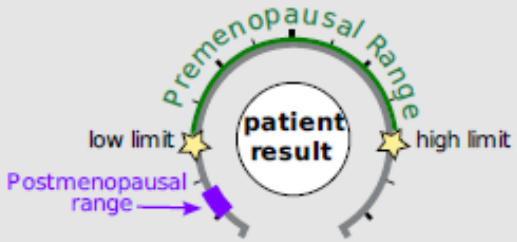
August 8, 2018 from North Haven office Yale New Haven Hospital
Lumbar spine_____ BMD 0.704 g/cm2: T-Score -3.1
Total hip_____ BMD 0.400 g/cm2: T-Score -2.9
Femoral neck _____BMD 0.561 g/cm2: T-Score -2.6

July 2, 2007 from Yale New Haven Hospital long Warf
Lumbar spine_____ BMD 0.839 g/cm2: T-Score -1.9
Total hip_____ BMD 0.790 g/cm2: T-Score -1.2
Femoral neck _____BMD 0.656 g/cm2: T-Score -1.7

Prior examinations were performed on a different unit. Statistical significance of change

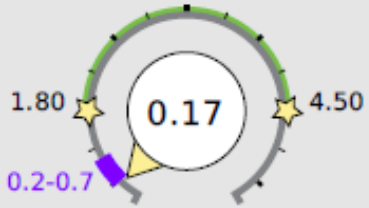
Hormone Testing Summary

Key (how to read the results):

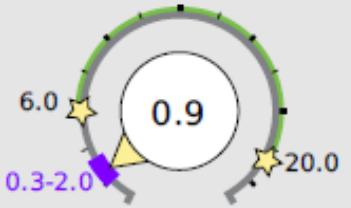


Sex Hormones

See Pages 2 and 3 for a thorough breakdown of sex hormone metabolites



Estradiol(E2)



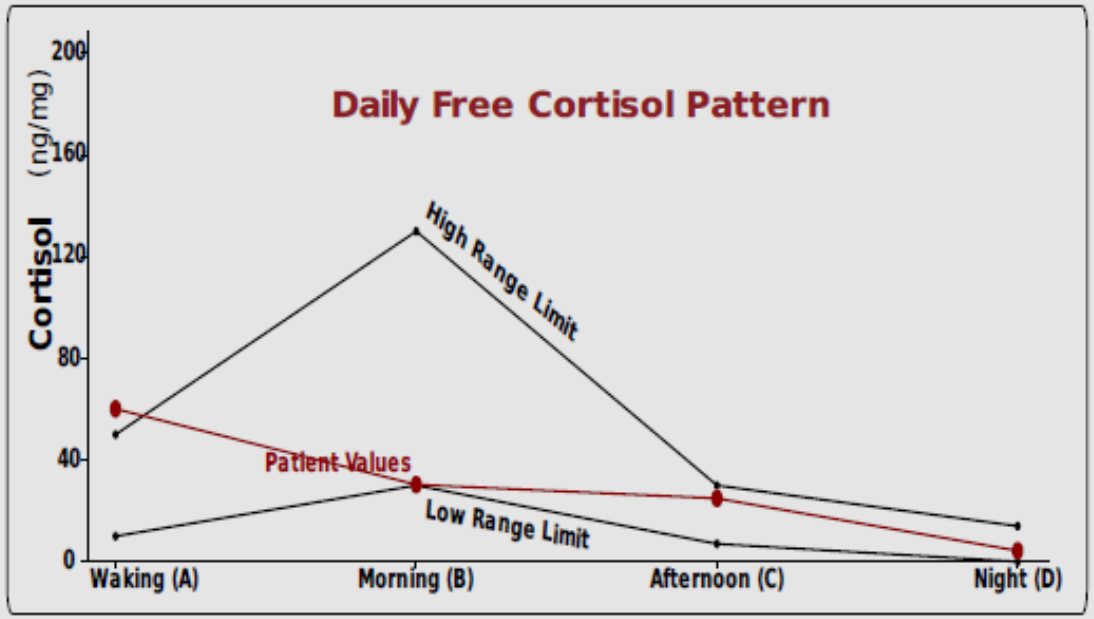
Progesterone
(Serum Equivalent, ng/mL)

Progesterone Serum Equivalent is a calculated value based on urine pregnanediol.

Testosterone

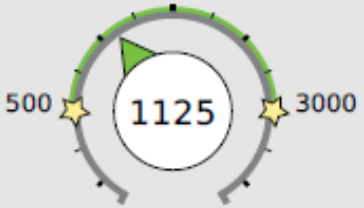
Adrenal Hormones

See pages 4 and 5 for a more complete breakdown of adrenal hormones

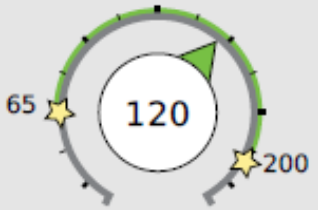


Total DHEA Production

Age	Range
20-39	1300-3000
40-60	750-2000
>60	500-1200

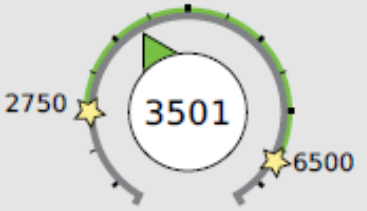


Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)



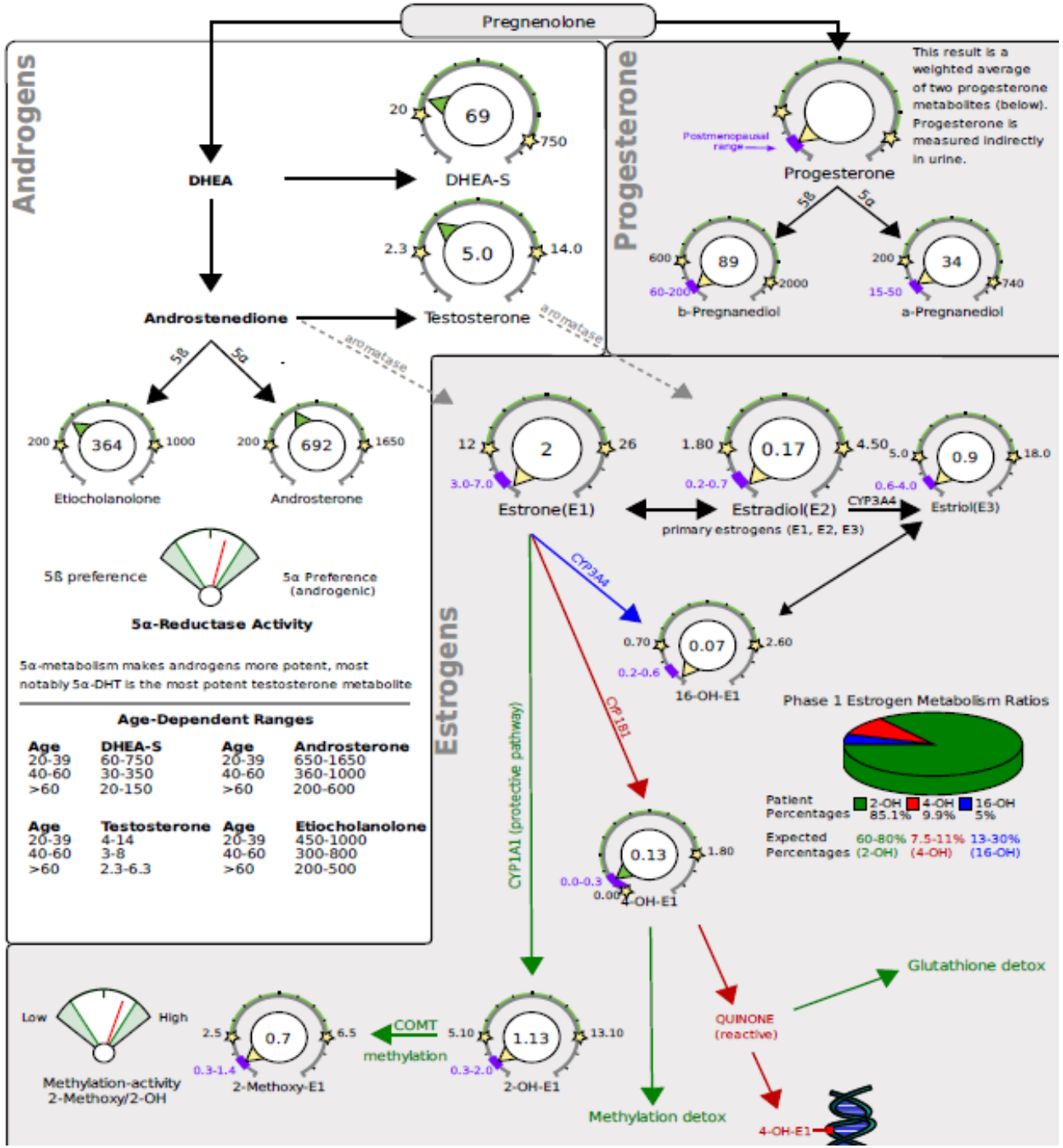
24hr Free Cortisol
(A+B+C+D)

cortisol metabolism



Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

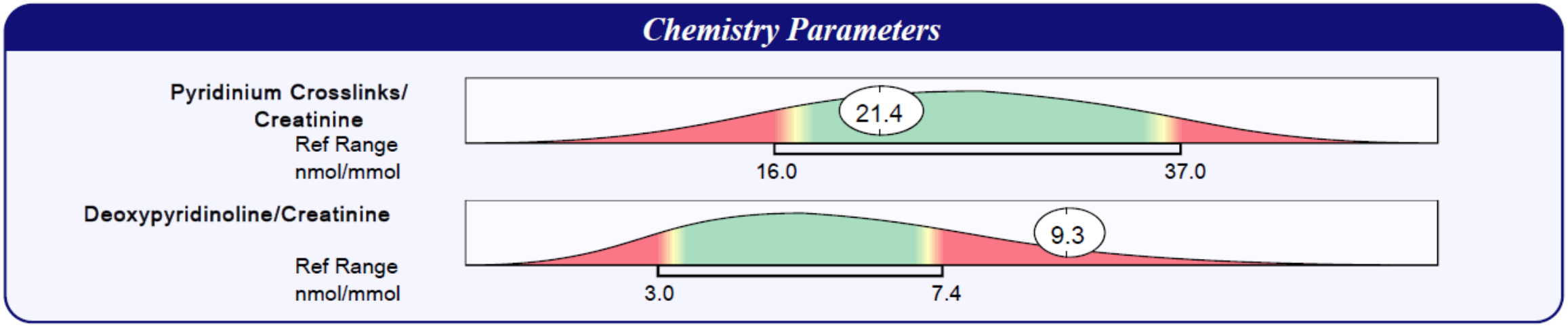

Pregnenolone
Androgens
DHEA
20
69
750
DHEA-S
2.3
5.0
14.0
Androstenedione
Testosterone
aromatase
aromatase
5ß
5α
200
364
1000
Etiocholanolone
200
692
1650
Androsterone
5ß preference
5α Preference (androgenic)
5α-Reductase Activity
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
Age-Dependent Ranges
Age DHEA-S
20-39 60-750
40-60 30-350
>60 20-150
Age Androsterone
20-39 650-1650
40-60 360-1000
>60 200-600
Age Testosterone
20-39 4-14
40-60 3-8
>60 2.3-6.3
Age Etiocholanolone
20-39 450-1000
40-60 300-800
>60 200-500
Progesterone
This result is a weighted average of two progesterone metabolites (below). Progesterone is measured indirectly in urine.
Postmenopausal range
Progesterone
5ß
5α
600
89
2000
60-200
b-Pregnanediol
200
34
740
15-50
a-Pregnanediol
Estrogens
12
2
26
3.0-7.0
Estrone(E1)
1.80
0.17
4.50
0.2-0.7
Estradiol(E2)
primary estrogens (E1, E2, E3)
CYP3A4
5.0
0.9
18.0
0.6-4.0
Estriol(E3)
CYP3A4
CYP1B1
CYP1A1 (protective pathway)
0.70
0.07
2.60
0.2-0.6
16-OH-E1
Phase 1 Estrogen Metabolism Ratios
Patient Percentages
2-OH 85.1%
4-OH 9.9%
16-OH 5%
Expected Percentages
60-80% (2-OH)
7.5-11% (4-OH)
13-30% (16-OH)
0.13
1.80
0.0-0.3
0.00
4-OH-E1
Glutathione detox
QUINONE (reactive)
Low
High
Methylation-activity 2-Methoxy/2-OH
2.5
0.7
6.5
0.3-1.4
2-Methoxy-E1
COMT
methylation
5.10
1.13
13.10
0.3-2.0
2-OH-E1
Methylation detox
4-OH-E1

Initial Laboratory Results
Laboratory tests ordered and rationale

- **Bone Resorption Assessment (Urine)**

Bone Resorption Assessment (Urine)

4/21/2021



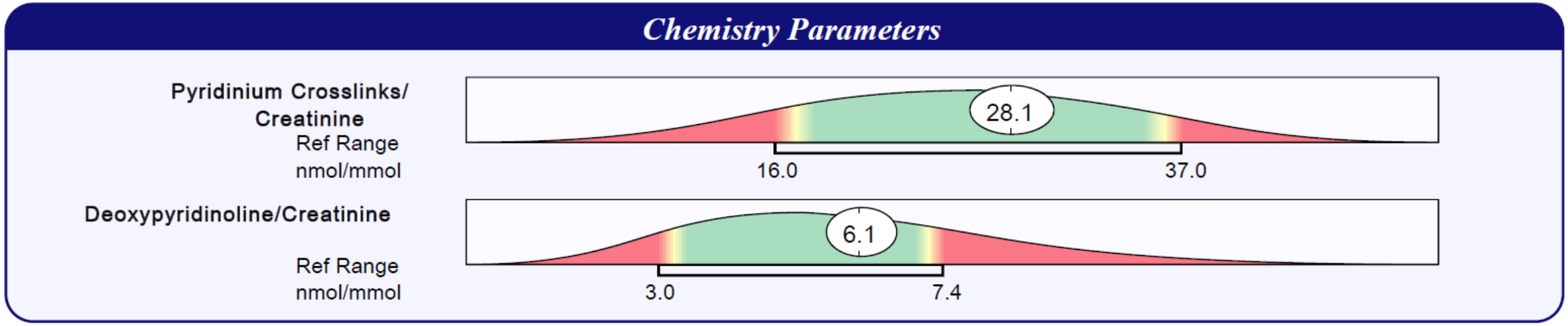
Treatment

Nutrient Support

- Vitamin D 10,000 IU with K, 1 softgel QOD with a meal
- Specific Bioactive Collagen Peptides (12.5 grams), 1 scoop QD
- Comprehensive Bone Support Formula (Vitamin D/K, Calcium, Magnesium, Zinc, Genistein), 2 capsules BID with meals
- Delta & Gamma Tocotrienol Isomers 300 mg, 1 softgel QD with a meal
- DHEA 10 mg, 2 capsules QD with a meal
- Vitamin K (MK-4) 15 mg BID with meals

Bone Resorption Assessment (Urine)

9/30/2021



Comments From the Doctor's Office

noted in both the spine and the hip using the dietary regimen and exercise that you have outlined. No intervention recommended at this time. Repeat bone density in 2 years

Written by Scott E. Cooper, MD on 11/5/2021 12:38 PM EDT
Seen by patient Patricia M Donnelly on 11/13/2021 9:57 AM

Study Result

Narrative & Impression

DEXA BONE DENSITY SPINE AND HIP

INDICATION: osteoporosis. Vitamin D. Calcium supplementation. Family history of osteoporosis. Ovaries removed or nonfunctioning.

SITE:

AP SPINE:
BMD (g/cm2): 0.72
T-SCORE (SD vs young adult): -3
Z-SCORE (SD vs age matched): -0.7

FEMORAL NECK:
BMD (g/cm2): 0.573
T-SCORE (SD vs young adult): -2.5
Z-SCORE (SD vs age matched): -0.5

TOTAL HIP:
BMD (g/cm2): 0.646
T-SCORE (SD vs young adult): -2.4
Z-SCORE (SD vs age matched): -0.8

IMPRESSION:
The bone mineral density of the lumbar spine and femoral neck reveal osteoporosis. The bone mineral density of the total hip reveals osteopenia. The patient is at moderate increased risk for fracture. Repeat DEXA bone densitometry in approximately 2 years on the same unit is advised for reassessment. When compared to the study of 8/25/2020, there has been a 10.9% increase in the bone mineral density of the left femoral neck and an 11.7% increase in the bone mineral density of the lumbar spine.

World Health Organization criteria for BMD interpretation classify patients as:
Normal (T-score at or above -1.0),
Osteopenic (T-score between -1.0 and -2.5),or
Osteoporotic (T-score at or below -2.5).
The presence of vertebral abnormalities such as scoliosis or osteophytes, or aortic/ligamentous calcifications can alter readings of the lumbar spine. In such cases, readings of the hips are

Case Study

- History
  - 57-Year-Old Female
  - Osteoporosis
  - Back pain
  - Hot flashes
  - Dyslipidemia

- Medications
  - Edarbi 40 mg
  - Levothyroxine 50 mg
  - Forteo 20 mg-started last month

Exam Date: 10/19/2021

[redacted]

EXAM: DXA DUAL ENERGY BONE MINERAL DENSITOMETRY AXIAL

CLINICAL INDICATION: Post menopausal. Screening for osteoporosis. History of breast cancer. Anastrozole.

FINDINGS:
Lumbar spine: T-score is -3.0
Left Hip: Lowest T-score is -3.3

INTERVAL CHANGE: When compared to the prior study dated 10/8/2019, there has been a statistically significant 16.1% decrease in the bone mineral density of the lumbar spine and a statistically significant 12.4% decrease in the bone mineral density of the left hip.

IMPRESSION: WHO classification is osteoporosis, lowest T-score is -3.3 in the left femoral neck.

Labs

Previous Blood Chemistries:

- 5/17/22- Thyroid Peroxidase Ab (64 H), Thyroglobulin Ab (149 H), Ferritin (172 H)
- 4/20/22- Steatosis Score (0.75H), GGT (148 H), ALT (62 H), Total Cholesterol (327 H), Glucose (102 H), Serum Calcium (10.5 H), Albumin (5.1 H), Alkaline Phosphatase (175 H), LDL Cholesterol (219 H)
- 2/8/22- Hs-CRP (1.6 FH), Total Cholesterol (294 H), LDL Cholesterol (182 H), Homocysteine (10.5 H), TPO Ab (56 H), Thyroglobulin Ab (116 H)
- 1/26/22- Lymphocytes (3.4 H), Glucose (101 H), Calcium (10.5 H), Albumin (5.0 H), Alkaline Phosphatase (181 H), AST (46 H), ALT (80 H), Total Cholesterol (310 H), LDL Cholesterol (197 H),
- 12/21/21- Glucose (107 H), Calcium (10.3 H), Total Cholesterol (239 H), LDL Cholesterol (135 H)
- 9/17/21- Glucose (100 H), Lymphocytes (3.4 H), Total Cholesterol (248 H), LDL Cholesterol (141 H), Triglycerides (158 H)

Treatment (1/29/22)

Dietary Intervention

- Follow a strict gluten-free diet

Nutrient Support

- Specific Bioactive Collagen Peptides (12.5 grams), 1 scoop QD
- Comprehensive Bone Support Formula (Vitamin D/K, Calcium, Magnesium, Zinc, Genistein), 2 capsules BID with meals
- Delta & Gamma Tocotrienol Isomers 300 mg, 1 softgel QD with a meal
- Vitamin K (MK-4) 15 mg TID with meals

Initial Laboratory Results
Laboratory tests ordered and rationale

- **Bone Resorption Assessment (Urine)**
- **Hs-CRP, Homocysteine, OmegaCheck, Thyroid antibodies, TSH, free T3, free T4, free and total Testosterone, Estradiol, SHBG, DHEA sulfate, Lipid Fractionation Panel, Iron panel w/ferritin**

2/8/22

Cardiometabolic Report

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
INFLAMMATION						
hs-CRP		1.6	<1.0	1.0-3.0	>3.0	mg/L

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
METABOLIC						
Insulin	11.9		≤19.6	N/A	>19.6	uIU/mL
Homocysteine		10.5	<10.4	N/A	≥10.4	umol/L
FATTY ACIDS						
OmegaCheck® (Whole Blood: EPA+DPA+DHA)[4]	7.6		≥5.5	3.8-5.4	≤3.7	% by wt
Arachidonic Acid/EPA Ratio	6.0			3.7-40.7		
Omega-6/Omega-3 Ratio	5.2			3.7-14.4		
Omega-3 total	7.6					% by wt
EPA	2.1			0.2-2.3		% by wt
DPA	1.4			0.8-1.8		% by wt
DHA	4.1			1.4-5.1		% by wt
Omega-6 total	39.7					% by wt
Arachidonic Acid	12.6			8.6-15.6		% by wt
Linoleic Acid	24.2			18.6-29.5		% by wt

Bone Resorption Assessment (Urine)

2/25/22

Code	Test Name	Result/Notes	Reference Values/Key
Dpd	Pyrilinks-D - CREAT. Normalized (urine)	14.2 Elevated	*Elevated (Adults): > 7.2 Std. Units*

Treatment

Dietary Intervention

- Follow a strict gluten-free diet

Nutrient Support

- Vitamin D 6000 IU, 3 capsules with a meal
- Methylation Support, 1 capsule BID with meals
- Specific Bioactive Collagen Peptides (12.5 grams), 1 scoop QD
- Comprehensive Bone Support Formula (Vitamin D/K, Calcium, Magnesium, Zinc, Genistein), 2 capsules BID with meals
- Delta & Gamma Tocotrienol Isomers 300 mg, 1 softgel QD with a meal
- Vitamin K (MK-4) 15 mg TID with meals

5/17/22

Cardiometabolic Report

Test Name	Current Result & Relative Risk		Reference Range/Relative Risk Categories				Historical Result & Relative Risk
	Optimal	Non-Optimal	Optimal	Moderate	High	Units	02/08/2022 / /
INFLAMMATION							
hs-CRP	0.8		<1.0	1.0-3.0	>3.0	mg/L	1.6
METABOLIC							
Homocysteine	8.1		<10.4	N/A	≥10.4	umol/L	10.5
FATTY ACIDS							
OmegaCheck® (Whole Blood: EPA+DPA+DHA)(2)	9.0		≥5.5	3.8-5.4	≤3.7	% by wt	7.6
Arachidonic Acid/EPA Ratio		3.3 L		3.7-40.7			6.0
Omega-6/Omega-3 Ratio	4.5			3.7-14.4			5.2
Omega-3 total	9.0					% by wt	7.6
EPA		3.3 H		0.2-2.3		% by wt	2.1
DPA	1.2			0.8-1.8		% by wt	1.4
DHA	4.5			1.4-5.1		% by wt	4.1
Omega-6 total	40.8					% by wt	39.7
Arachidonic Acid	10.9			8.6-15.6		% by wt	12.6
Linoleic Acid	27.7			18.6-29.5		% by wt	24.2

10/20/22

Cardiometabolic Report

Test Name	Current Result & Relative Risk		Reference Range/Relative Risk Categories				Historical Result & Relative Risk	
	Optimal	Non-Optimal	Optimal	Moderate	High	Units	06/08/2022	05/17/2022
INFLAMMATION								
hs-CRP	0.6		<1.0	1.0-3.0	>3.0	mg/L		0.8
Homocysteine	8.0		<10.4	N/A	≥10.4	umol/L		8.1
VITAMINS/SUPPLEMENTS								
Vitamin D, 25-Hydroxy by LC-MS/MS[2]	67.0		≥30.0	20.0-29.9	<20.0 OR >150.0	ng/mL		

Bone Resorption Assessment (Urine)

11/10/22

Code	Test Name	Result/Notes	Reference Values/Key
Dpd	Pyrilinks-D - CREAT. Normalized (urine)	7.5 Elevated	*Elevated (Adults): > 7.2 Std. Units*

Exam Date: 01/18/2023

[redacted]

[redacted]

EXAM: DXA DUAL ENERGY BONE MINERAL DENSITOMETRY AXIAL

CLINICAL INDICATION: Screening for osteoporosis. Post-menopausal. Malignant neoplasm of nipple and areola, unspecified female breast.

FINDINGS:
Lumbar spine: T-score is -1.9
Left Hip: Lowest T-score is -2.7

INTERVAL CHANGE: There is a 15.9% improvement in lumbar spine bone mineral density compared to 10/19/2021, which is statistically significant. There is a 5.7% improvement in left hip bone mineral density compared to 10/19/2021, which is statistically significant.

IMPRESSION: WHO classification is osteoporosis; lowest T-score is -2.7 in the left femoral neck.

Labs

2023-2024 Blood Chemistries:

- 2/7/24- OxLDL (67 H), Apo B (120 H), Lp(a) (137 H)
- 10/11/23- Glucose (100 H), Calcium (10.3 H), Total Cholesterol (272 H), LDL Cholesterol (153 H)
- 9/8/23- OxLDL (69 H), Total Cholesterol (278 H), LDL Cholesterol (166 H)
- 5/31/23- Calcium Score (249.9)
- 5/25/23- OxLDL (83 H), Total Cholesterol (347 H), LDL Cholesterol (226 H), Ferritin (183 H)

Treatment (2/25/24)

Dietary Intervention

- Continue a strict gluten-free diet

Nutrient Support

- Vitamin D 6000 IU, 3 capsules with a meal
- Methylation Support, 1 capsule BID with meals
- Specific Bioactive Collagen Peptides (12.5 grams), 1 scoop QD
- Comprehensive Bone Support Formula (Vitamin D/K, Calcium, Magnesium, Zinc, Genistein), 2 capsules BID with meals
- Delta & Gamma Tocotrienol Isomers 300 mg, 1 softgel QD with a meal
- Vitamin K (MK-4) 15 mg TID with meals
- Add Niacin CRT 1000 mg, 2 tablets with dinner

4/24/24

Cardiometabolic Report

Test Name	Current Result & Relative Risk		Reference Range/Relative Risk Categories				Historical Result & Relative Risk	
	Optimal	Non-Optimal	Optimal	Moderate	High	Units	02/07/2024	09/08/2023
INFLAMMATION								
OxLDL	37		<60	60-69	≥70	U/L	67	69
LIPIDS								
Lipid Panel								
Cholesterol, Total		225	<200	N/A	≥200	mg/dL		278
HDL Cholesterol	113		≥50	N/A	<50	mg/dL		84
Triglycerides	68		<150	150-199	≥200	mg/dL		140
LDL Cholesterol	97		<100	100-129	≥130	mg/dL (calc)		166
Chol/HDL-C	2.0		≤3.5	3.6-5.0	>5.0	calc		3.3
Non-HDL Cholesterol	112		<130	130-189	≥190	mg/dL (calc)		194
TG/HDL-C	0.6		<2.0	2.0-3.0	>3.0	calc		1.7
Lipoprotein Fractionation, NMR								
LDL-P(1)	876		<935	935-1816	>1816	nmol/L		
Small LDL-P	<154		<467	467-820	>820	nmol/L		
LDL Size	21.7		>20.5	N/A	≤20.5	nm		
HDL-P	43.2		>32.8	29.2-32.8	<29.2	umol/L		
Large HDL-P	>20.1		>7.2	5.3-7.2	<5.3	umol/L		
HDL Size	11.7		>9.0	8.7-9.0	<8.7	nm		
Large VLDL-P	1.7		<3.7	3.7-6.1	>6.1	nmol/L		
VLDL Size		49.8	<47.1	47.1-49.0	>49.0	nm		

4/24/24

Test Name	Current Result & Relative Risk		Reference Range/Relative Risk Categories				Historical Result & Relative Risk	
	Optimal	Non-Optimal	Optimal	Moderate	High	Units	02/07/2024	09/08/2023
Apolipoproteins								
Apolipoprotein B	70		<90	90-119	≥120	mg/dL	120	
Lipoprotein (a)	41		<75	75-125	>125	nmol/L	137	

4/24/24

Test Name	Current	02/07/2024	09/08/2023	05/25/2023	10/20/2022	Units
INFLAMMATION						
OxLDL	37	67	69	83		U/L
LIPIDS						
Lipid Panel						
Cholesterol, Total	225		278	347	299	mg/dL
HDL Cholesterol	113		84	100	90	mg/dL
Triglycerides	68		140	91	134	mg/dL
LDL Cholesterol	97		166	226	182	mg/dL (calc)
Chol/HDL-C	2.0		3.3	3.5	3.3	calc
Non-HDL Cholesterol	112		194	247	209	mg/dL (calc)
TG/HDL-C	0.6		1.7	0.9	1.5	calc
Lipoprotein Fractionation, NMR						
LDL-P[(1)]	876					nmol/L
Small LDL-P	<154					nmol/L
LDL Size	21.7					nm
HDL-P	43.2					umol/L
Large HDL-P	>20.1					umol/L
HDL Size	11.7					nm
Large VLDL-P	1.7					nmol/L
VLDL Size	49.8					nm

Case Study

- History
  - 66-Year-Old Female
  - Osteoporosis (Dx: May 2023)
  - Osteoarthritis (Dx: 2010)

- Medications
  - Prescribed Fosamax for 1 month; did not tolerate side effects

Labs

Previous Blood Chemistries:

- 5/23/2023- DEXA L-Spine T-score (-3.4); Femur T-score (-2.0)
- 5/22/2023- Glucose (109 H), A/G Ratio (2.5 H), Total Cholesterol (227 H), LDL Cholesterol (158 H)

Initial Laboratory Results
Laboratory tests ordered and rationale

- **Hs-CRP, OxLDL, LipoFraction NMR with Lipids, Lp(a), HA1c, Insulin, Homocysteine, OmegaCheck, Iron Panel with Ferritin, DHEA-S, ANA panel, RA Factor, CCP Ab**
- **Bone Resorption Assessment (Urine)**

4/2/2024

Cardiometabolic Report

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
INFLAMMATION						
hs-CRP		2.2	<1.0	1.0-3.0	>3.0	mg/L
OxLDL	52		<60	60-69	≥70	U/L
LIPIDS						
Lipid Panel						
Cholesterol, Total		216	<200	N/A	≥200	mg/dL
HDL Cholesterol	74		≥50	N/A	<50	mg/dL
Triglycerides	65		<150	150-199	≥200	mg/dL
LDL Cholesterol		126	<100	100-129	≥130	mg/dL (calc)
Chol/HDL-C	2.9		≤3.5	3.6-5.0	>5.0	calc
Non-HDL Cholesterol		142	<130	130-189	≥190	mg/dL (calc)
TG/HDL-C	0.9		<2.0	2.0-3.0	>3.0	calc
Lipoprotein Fractionation, NMR						
LDL-P[1]		1440	<935	935-1816	>1816	nmol/L
Small LDL-P	339		<467	467-820	>820	nmol/L
LDL Size	21.3		>20.5	N/A	≤20.5	nm
HDL-P	33.9		>32.8	29.2-32.8	<29.2	umol/L
Large HDL-P	14.5		>7.2	5.3-7.2	<5.3	umol/L
HDL Size	10.1		>9.0	8.7-9.0	<8.7	nm
Large VLDL-P	<1.5		<3.7	3.7-6.1	>6.1	nmol/L

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
VLDL Size		46.6	<47.1	47.1-49.0	>49.0	nm
Apolipoproteins						
Lipoprotein (a)		30	<75	75-125	>125	nmol/L
METABOLIC						
Insulin		7.1	≤18.4	N/A	>18.4	uIU/mL
HbA1c		5.6	<5.7	5.7-6.4	>6.4	%
Estimated Average Glucose		113	<117	117-137	>137	mg/dL
Homocysteine		9.6	<10.4	N/A	≥10.4	umol/L
FATTY ACIDS						
OmegaCheck® (Whole Blood: EPA+DPA+DHA)[2]		6.9	≥5.5	3.8-5.4	≤3.7	% by wt
Arachidonic Acid/EPA Ratio		6.4		3.7-40.7		
Omega-6/Omega-3 Ratio		6.0		3.7-14.4		
Omega-3 total		6.9				% by wt
EPA		1.8		0.2-2.3		% by wt
DPA		1.8		0.8-1.8		% by wt
DHA		3.2		1.4-5.1		% by wt
Omega-6 total		41.0				% by wt
Arachidonic Acid		11.6		8.6-15.6		% by wt
Linoleic Acid		26.7		18.6-29.5		% by wt

4/2/2024

Results (Non-Cardiometabolic)

Test Name	Current Result In Range	Current Result Out of Range	Reference Range	Units	Lab
HORMONES					
DHEA-S	126.7		9.4-246.0	ug/dL	Z4M
For additional information, please refer to https://www.clevelandheartlab.com/biotinFAQ/ (this link is being provided for infor purposes only).					
ANEMIA/IRON METABOLISM					
Ferritin	31		18-300	ng/mL	Z4M
For additional information, please refer to https://www.clevelandheartlab.com/biotinFAQ/ (this link is being provided for infor purposes only).					
Iron, Total	97		45-160	mcg/dL	Z4M
Iron Binding Capacity	360		250-450	mcg/dL (calc)	Z4M
% Saturation	27		16-45	% (calc)	Z4M
IMMUNE					
ANA Screen,IFA, with Reflex to Titer and Pattern					
ANA SCREEN, IFA(AMD)	Negative		Negative		AMD
ANA IFA is a first line screen for detecting the presence of up to approximately 150 autoantibodies in various autoimmune d IFA result suggests ANA-associated autoimmune disease is not present at this time, but is not definitive. If there is high clini Syndrome, testing for anti-SS-A/Ro antibody should be considered. Anti-Jo-1 antibody should be considered for clinically su myopathies. AC-0: Negative International Consensus on ANA Patterns https://doi.org/10.1515/cclm-2018-0052 For additiona to http://education.QuestDiagnostics.com/faq/FAQ177 (This link is being provided for informational/ educational purposes or					
Cyclic Citrullinated Peptide Ab					
Cyclic Citrullinated Peptide (CCP) IgG(QPT)	<16			UNITS	QPT
Reference Range Negative: <20 Weak Positive: 20-39 Moderate Positive: 40-59 Strong Positive: >59					
Rheumatoid Factor					
RHEUMATOID FACTOR(AMD)	<14		<14	IU/mL	AMD

Bone Resorption Assessment (Urine)

4/8/2024

Code	Test Name	Result/Notes	Reference Values/Key
Dpd	Pyrilinks-D - CREAT. Normalized (urine)	8.1 Elevated	*Elevated (Adults): > 7.2 Std. Units*

Treatment

Nutrient Support

- Specific Bioactive Collagen Peptides (12.5 grams), 1 scoop QD
- Comprehensive Bone Support Formula (Vitamin D/K, Calcium, Magnesium, Zinc, Genistein), 2 capsules BID with meals
- Delta & Gamma Tocotrienol Isomers 300 mg, 1 softgel QD with a meal
- DHEA 10 mg, 2 capsules with breakfast
- Replace Vitamin K (MK-7) 100 mcg with Vitamin K (MK-4) 45 mg in with meals (divided dosing)

12/9/2024

Cardiometabolic Report

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units	Historical Result & Relative Risk: 04/02/2024	/ /
INFLAMMATION								
hs-CRP		1.4	<1.0	1.0-3.0	>3.0	mg/L	2.2	
LIPIDS								
Lipid Panel								
Cholesterol, Total	178		<200	N/A	≥200	mg/dL	216	
HDL Cholesterol	66		≥50	N/A	<50	mg/dL	74	
Triglycerides	48		<150	150-199	≥200	mg/dL	65	
LDL Cholesterol	98		<100	100-129	≥130	mg/dL (calc)	126	
Chol/HDL-C	2.7		≤3.5	3.6-5.0	>5.0	calc	2.9	
Non-HDL Cholesterol	112		<130	130-189	≥190	mg/dL (calc)	142	
TG/HDL-C	0.7		<2.0	2.0-3.0	>3.0	calc	0.9	

UND = UNDETECTABLE INC = INCOMPUTABLE

Medical Information For Healthcare Providers: If you have any questions about any of the tests in our Cardiometabolic Report, please call Cleveland HeartLab Client Services at 866.358.9828, option 1 to arrange a consult with our clinical education team.

Results (Non-Cardiometabolic)

Test Name	Current Result: In Range	Current Result: Out of Range	Reference Range	Units	Lab	Historical Results: 04/02/2024	/ /
HORMONES							
DHEA-S	170.4		9.4-246.0	ug/dL	Z4M	126.7	
For additional information, please refer to https://www.clevelandheartlab.com/biotinFAQ/ (this link is being provided for informational/educational purposes only).							
Estradiol[1]		<5		pg/mL	Z4M		
Reference range for female (adults): Follicular phase: 27 - 156 pg/mL; Ovulatory phase: 48 - 314 pg/mL; Luteal phase: 33 - 298 pg/mL; Postmenopausal: <5 - 50 pg/mL; Pregnancy, 1st Trimester: 154 - 3065 pg/mL; Pregnancy, 2nd Trimester 1561 - 18,950 pg/mL; Pregnancy, 3rd							

Results (Non-Cardiometabolic)

Test Name	Current Result: In Range	Current Result: Out of Range	Reference Range	Units
Trimester 10,030 - >30,000 pg/mL. For additional information, please refer to https://www.clevelandheartlab.c for informational/educational purposes only).				
Testosterone, Free, Bioavailable and Total, MS				
TESTOSTERONE, TOTAL, MS[2] (AMD)		47 H	2-45	ng/dL
For additional information, please refer to http://education.questdiagnostics.com/faq/TotalTestosteroneLCMSMSFAQ165 (This link is being provided for informational/educational purposes only.)				
TESTOSTERONE, FREE[(AMD)]	3.6		0.2-5.0	pg/mL
TESTOSTERONE, BIOAVAILABLE[(AMD)]	6.6		0.5-8.5	ng/dL
SEX HORMONE BINDING GLOB[(AMD)]	57		14-73	nmol/L
ALBUMIN[(AMD)]	4.0		3.6-5.1	g/dL

Bone Resorption Assessment (Urine)

12/9/2024

Code	Test Name	Result/Notes	Reference Values/Key
Dpd	Pyrilinks-D - CREAT. Normalized (urine)	4.8 Normal	*Elevated (Adults): > 7.2 Std. Units*

Case Study

- History
  - 62- Year-Old Female
  - Breast Cancer survivor
  - Dyslipidemia
  - Inflammation
  - Dysglycemia
  - Stage 3 CKD (2020)
  - Cognitive symptoms (Mother had AD)
- Medications
  - N/A

Labs

Previous Blood Chemistries:

- 12/7/20- Vitamin B12 (1485 H), Creatinine (1.35 H), eGFR (42 L), Homocysteine (14.5 H)
- 7/30/20- LDL Cholesterol (108 H), HA1c (5.9 H), Vitamin D 25-OH (42.7 FL), Homocysteine (13.2 H), Creatinine (1.45 H), eGFR (39 L), Chloride (109 H), Vitamin B12 (1315 H)
- 6/26/20- Vitamin B12 (1315 H), Folate (>20.0)

Arch Neurol. 1998 Nov;55(11):1449-55.

Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease.

Clarke R[1], Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM.

Author information

Abstract

BACKGROUND: Recent studies suggest that vascular disease may contribute to the cause of Alzheimer disease (AD). Since elevated plasma total homocysteine (tHcy) level is a risk factor for vascular disease, it may also be relevant to AD.

OBJECTIVE: To examine the association of AD with blood levels of tHcy, and its biological determinants folate and vitamin B12.

DESIGN: Case-control study of 164 patients, aged 55 years or older, with a clinical diagnosis of dementia of Alzheimer type (DAT), including 76 patients with histologically confirmed AD and 108 control subjects.

SETTING: Referral population to a hospital clinic between July 1988 and April 1996.

MAIN OUTCOME MEASURES: Serum tHcy, folate, and vitamin B12 levels in patients and controls at entry; the odds ratio of DAT or confirmed AD with elevated tHcy or low vitamin levels; and the rate of disease progression in relation to tHcy levels at entry.

RESULTS: Serum tHcy levels were significantly higher and serum folate and vitamin B12 levels were lower in patients with DAT and patients with histologically confirmed AD than in controls. The odds ratio of confirmed AD associated with a tHcy level in the top third (> or = 14 micromol/L) compared with the bottom third (< or = 11 micromol/L) of the control distribution was 4.5 (95% confidence interval, 2.2-9.2), after adjustment for age, sex, social class, cigarette smoking, and apolipoprotein E epsilon4. The corresponding odds ratio for the lower third compared with the upper third of serum folate distribution was 3.3 (95% confidence interval, 1.8-6.3) and of vitamin B12 distribution was 4.3 (95% confidence interval, 2.1-8.8). The mean tHcy levels were unaltered by duration of symptoms before enrollment and were stable for several years afterward. In a 3-year follow-up of patients with DAT, radiological evidence of disease progression was greater among those with higher tHcy levels at entry.

CONCLUSIONS: Low blood levels of folate and vitamin B12, and elevated tHcy levels were associated with AD. The stability of tHcy levels over time and lack of relationship with duration of symptoms argue against these findings being a consequence of disease and warrant further studies to assess the clinical relevance of these associations for AD.

Initial Laboratory Results
Laboratory tests ordered and rationale

1. OmegaCheck, Hs-CRP, Iron panel with ferritin, HA1c, lipid panel, CMP-14, CBC w/diff, TMAO

Treatment Program

Dietary Intervention

- Complete 7-day food diary

Nutrient Support

- Increase Vitamin D from 4000 IU to 6000 IU
- N-acetyl-cysteine 1800 mg, 2 capsules QD
- Delta and gamma tocotrienol isomers 300 mg, 1 softgel QD with a meal

Oral *N*-acetylcysteine reduces plasma homocysteine concentrations regardless of lipid or smoking status[1,2]

Wulf Hildebrandt,[5,8,10] Roland Sauer,[5,7,10] Gabriel Bonaterra,[3,8] Klaus A Dugi,[4,9] Lutz Edler,[6] and Ralf Kinscherf[3,8]*

Departments of [3]Anatomy and Cell Biology III and [4]Internal Medicine I, University of Heidelberg, Heidelberg, Germany; Departments of [5]Immunochemistry and [6]Biostatistics, Deutsches Krebsforschungszentrum, Heidelberg, Germany; and [7]Department of Neurology, University Hospital Erlangen, Erlangen, Germany

ABSTRACT

Background: Elevated total plasma homocysteine (tHcy) is considered to be an independent cardiovascular disease risk factor, although tHcy lowering by B-vitamins improves only certain clinical endpoints. *N*-acetylcysteine (NAC), a thiol-containing antioxidant, acutely lowers tHcy and possibly also blood pressure. However, to our knowledge, at present no conclusive long-term evaluation exists that controls for factors such as hyperlipidemia, smoking, medication, and disease stage, all of which affect the thiol redox state, including tHcy.

Objective: We reanalyzed 2 double-blind, placebo-controlled trials in unmedicated middle-aged men, one in a hyperlipidemic group (HYL group; $n = 40$) and one in a normolipidemic group (NOL group; $n = 42$), each stratified for smokers and nonsmokers.

Design: We evaluated the effect of 4 wk of oral NAC (1.8 g/d) on tHcy (primary endpoint), plasma thiol (cysteine), and intracellular glutathione concentrations as well as on blood pressure. The HYL group had total cholesterol >220 mg/dL or triglycerides >150 mg/dL.

Results: NAC treatment significantly ($P = 0.001$, multivariate analysis of variance for repeated measures) lowered postabsorptive plasma concentrations of tHcy by −11.7% ± 3.0% (placebo: 4.1% ± 3.6%) while increasing those of cysteine by 28.1% ± 5.7% (placebo: 4.0% ± 3.4%) with no significant impact of hyperlipidemia or smoking. Moreover, NAC significantly decreased systolic ($P = 0.003$) and diastolic ($P = 0.017$) blood pressure within all subjects with a significant reduction in diastolic pressure in the HYL group ($P = 0.008$) but not in the NOL group. An explorative stepwise multiple regression analysis identified *1*) post-treatment cysteine as well as *2*) pretreatment tHcy and *3*) albumin plasma concentrations as being significant contributors to tHcy reduction.

Conclusions: Four weeks of oral NAC treatment significantly decreased plasma tHcy concentrations, irrespective of lipid or smoking status, and lowered systolic blood pressure in both normolipidemic and hyperlipidemic men, with significant diastolic blood pressure reductions in the HYL group only. Increased oral intake of cysteine may therefore be considered for primary or secondary prevention of vascular events with regard to the 2 independent risk factors of hyperhomocysteinemia and arterial hypertension. *Am J Clin Nutr* doi: 10.3945/ajcn.114.101964.

Keywords: homocysteine, *N*-acetylcysteine, atherosclerosis, oxidative stress, blood pressure

INTRODUCTION

Elevated total plasma homocysteine (tHcy)[11] has long been considered to be an independent risk factor for cardiovascular diseases (1–7) and other age-related degenerative diseases (1, 8–10). Homocysteine is pro-oxidative, proinflammatory, and procoagulative and induces endothelial lesions along with proatherogenic gene expression, which can be reversed by folate/B-vitamin intervention in mammals (9). In humans, experimental hyperhomocysteinemia causes endothelial dysfunction, which is ameliorated by antioxidants and/or tHcy lowering (11, 12). In well-defined cohorts with coronary artery disease or extracranial carotid-artery stenosis, tHcy concentrations of up to 20 μmol/L strongly predict myocardial infarction (MI) or mortality (6, 13, 14). However, unexpectedly, large-scale interventional trials and consecutive meta-analyses failed to show a clear benefit of tHcy lowering by ~25% through folate/B-vitamins for MI, stroke, or death by any cause (4, 15–18), thus refuting the concept of tHcy as a causal cardiovascular disease risk factor (2, 3, 19–21). Because recent analyses that controlled for confounders such as statins or folate fortification detected a benefit of folate/B-vitamins for stroke (22–24), tHcy may conditionally be a therapeutic target. Therefore, an alternative agent for (more) effective tHcy lowering may be desirable, especially for conditions

[1] Supported by the German Cancer Research Center (DKFZ), Heidelberg, Germany.

[2] Supplemental Table 1 is available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

[8] Present address: Institute of Anatomy and Cell Biology, University of Marburg, Marburg, Germany.

[9] Present address: Boehringer Ingelheim Pharma GmbH , Biberach, Germany.

[10] These authors contributed equally to this work.

*To whom correspondence should be addressed. E-mail: roland.sauer@uk-erlangen.de.

[11] Abbreviations used: GSH, glutathione; GSSG, oxidized glutathione; HYL group, hyperlipidemic group; MANOVA, multivariate ANOVA; MI, myocardial infarction; NAC, *N*-acetylcysteine; NOL group, normolipidemic group; oxLDL, oxidized LDL; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; tHcy, total plasma homocysteine.

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group; $n = 42$), each stratified for smokers and nonsmokers.
Design: We evaluated the effect of 4 wk of oral NAC (1.8 g/d) on tHcy (primary endpoint), plasma thiol (cysteine), and intracellular glutathione concentrations as well as on blood pressure. The HYL group had total cholesterol >220 mg/dL or triglycerides >150 mg/dL.
Results: NAC treatment significantly ($P = 0.001$, multivariate analysis of variance for repeated measures) lowered postabsorptive plasma concentrations of tHcy by −11.7% ± 3.0% (placebo: 4.1% ± 3.6%) while increasing those of cysteine by 28.1% ± 5.7% (placebo: 4.0% ± 3.4%) with no significant impact of hyperlipidemia or smoking. Moreover, NAC significantly decreased systolic ($P = 0.003$) and diastolic ($P = 0.017$) blood pressure within all subjects with a significant reduction in diastolic pressure in the HYL group ($P = 0.008$) but not in the NOL group. An explorative stepwise multiple regression analysis identified *1*) post-treatment cysteine as well as *2*) pretreatment tHcy and *3*) albumin plasma concentrations as being significant contributors to tHcy reduction.
Conclusions: Four weeks of oral NAC treatment significantly decreased plasma tHcy concentrations, irrespective of lipid or smoking

Labs (3/17/21)

Cardiometabolic Report

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
METABOLIC						
TMAO (Trimethylamine N-oxide)(1)	<0.3		<6.2	6.2-9.9	≥10.0	uM
Homocysteine		13.6	<10.4	N/A	≥10.4	umol/L

Labs (11/16/21)

Cardiometabolic Report

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
INFLAMMATION						
hs-CRP		2.2	<1.0	1.0-3.0	>3.0	mg/L
LIPIDS						
Lipid Panel						
Cholesterol, Total		209	<200	N/A	≥200	mg/dL
HDL Cholesterol	73		≥50	N/A	<50	mg/dL
Triglycerides	93		<150	150-199	≥200	mg/dL
LDL Cholesterol, Calculated		117	<100	100-129	>129	mg/dL (calc)
Chol/HDL-C	2.9		≤3.5	3.6-5.0	>5.0	calc
Non-HDL Cholesterol		136	<130	130-189	≥190	mg/dL (calc)
TG/HDL-C	1.3		<2.0	2.0-3.0	>3.0	calc
Lipoprotein Fractionation, NMR						
LDL-P[5]		1270	<935	935-1816	>1816	nmol/L
Small LDL-P	244		<467	467-820	>820	nmol/L
LDL Size	21.6		>20.5	N/A	≤20.5	nm
HDL-P	46.6		>32.8	29.2-32.8	<29.2	umol/L
Large HDL-P	9.4		>7.2	5.3-7.2	<5.3	umol/L
HDL Size	9.2		>9.0	8.7-9.0	<8.7	nm
Large VLDL-P	2.7		<3.7	3.7-6.1	>6.1	nmol/L
VLDL Size		48.8	<47.1	47.1-49.0	>49.0	nm

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units
METABOLIC						
Glucose	75		65-99	100-125	<65 OR ≥126	mg/dL
HbA1c		5.7	<5.7	5.7-6.4	>6.4	%
Estimated Average Glucose		117	<117	117-137	>137	mg/dL
TMAO (Trimethylamine N-oxide)[2]	<0.3		<6.2	6.2-9.9	≥10.0	uM
METHYLMALONIC ACID[4] (AMD)	150			87-318		nmol/L
Homocysteine		13.8	<10.4	N/A	≥10.4	umol/L
VITAMINS/SUPPLEMENTS						
Vitamin D, 25-Hydroxy by LC-MS/MS[3]	75.7		≥30.0	20.0-29.9	<20.0 OR >150.0	ng/mL
FATTY ACIDS						
OmegaCheck® (Whole Blood: EPA+DPA+DHA)[1]	7.4		≥5.5	3.8-5.4	≤3.7	% by wt
Arachidonic Acid/EPA Ratio	4.2			3.7-40.7		
Omega-6/Omega-3 Ratio	5.2			3.7-14.4		
Omega-3 total	7.4					% by wt
EPA	2.2			0.2-2.3		% by wt
DPA	1.5			0.8-1.8		% by wt
DHA	3.7			1.4-5.1		% by wt
Omega-6 total	38.6					% by wt
Arachidonic Acid	9.3			8.6-15.6		% by wt
Linoleic Acid	27.3			18.6-29.5		% by wt

Labs (11/16/21)

Results (Non-Cardiometabolic)

Test Name	Current Result In Range	Current Result Out of Range	Reference Range	Units
ROUTINE PANELS				
Comprehensive Metabolic Panel				
Glucose	75		65-99	mg/dL
Calcium, Total	9.4		8.5-10.5	mg/dL
Sodium	137		136-145	mmol/L
Potassium	4.2		3.5-5.1	mmol/L
Chloride	102		95-108	mmol/L
CO_2 (Carbon Dioxide, Bicarbonate)	22		21-33	mmol/L
BUN (Blood Urea Nitrogen)	20		8-23	mg/dL
Creatinine		1.26 H	0.50-0.99	mg/dL
BUN/Creatinine Ratio	16		6-22	calc
Albumin	4.6		3.5-5.5	g/dL
Total Protein	7.2		6.1-8.0	g/dL
Globulin	2.6		1.8-3.8	g/dL
ALP (Alkaline Phosphatase)	71		<150	U/L
ALT (Alanine Amino Transferase)	12		6-29	U/L
AST (Aspartate Amino Transferase)	15		10-35	U/L
Bilirubin, Total	0.6		<1.3	mg/dL
eGFR, Non-African descent		45 L	≥60	mL/min/1.73 m²
eGFR, African descent		52 L	≥60	mL/min/1.73 m²
ANEMIA/IRON METABOLISM				
Ferritin	55		18-300	ng/mL
For additional information, please refer to https://www.clevelandheartlab.com/biotinFAQ/ (this link is being pro purposes only).				
Iron	54		30-140	ug/dL
TIBC	326		228-438	ug/dL

Results (Non-Cardiometabolic)

Test Name	Current Result In Range	Current Result Out of Range	Reference Range	Units
% Transferrin Saturation	17		15-50	%
HEMATOLOGY				
CBC with Automated Differential				
WBC	5.0		3.8-10.8	K/uL
RBC	4.46		3.80-5.10	M/uL
Hemoglobin	13.2		11.7-15.5	g/dL
Hematocrit	40.6		35.0-45.0	%
MCV	91.0		80.0-100.0	fL
MCH	29.6		27.0-33.0	pg
MCHC	32.5		32.0-36.0	g/dL
Red Cell Distribution Width	14.4		11.0-15.0	%
Platelet Count	245		140-400	K/uL
Mean Platelet Volume	10.8		7.5-12.5	fL
Neutrophil %	48.9		38.0-80.0	%
Neutrophil Absolute	2.45		1.50-7.80	K/uL
Lymphocyte %	35.3		15.0-49.0	%
Lymphocyte Absolute	1.77		0.85-3.90	K/uL
Monocyte %	10.6		0.0-13.0	%
Monocyte Absolute	0.53		0.20-0.95	K/uL
Eosinophil %	4.0		0.0-8.0	%
Eosinophil Absolute	0.20		0.00-0.50	K/uL
Basophil %	1.2		0.0-2.0	%
Basophil Absolute	0.06		0.00-0.20	K/uL

Treatment Program 11/30/21

Dietary Intervention

- Complete 7-day food diary

Nutrient Support

- Vitamin D 6000 IU, 3 drops QD
- N-acetyl-cysteine 1800 mg, 2 capsules QD
- Delta and gamma tocotrienol isomers 300 mg, 1 softgel QD with a meal
- Methylation Support, 1 capsule QD with a meal

Labs (6/3/22)

Cardiometabolic Report

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units	Historical Result & Relative Risk: 11/16/2021	03/17/2021
INFLAMMATION								
hs-CRP		1.2	<1.0	1.0-3.0	>3.0	mg/L	2.2	
LIPIDS								
Lipid Panel								
Cholesterol, Total		221	<200	N/A	≥200	mg/dL	209	
HDL Cholesterol	85		≥50	N/A	<50	mg/dL	73	
Triglycerides	65		<150	150-199	≥200	mg/dL	93	
LDL Cholesterol, Calculated		120	<100	100-129	>129	mg/dL (calc)	117	
Chol/HDL-C	2.6		≤3.5	3.6-5.0	>5.0	calc	2.9	
Non-HDL Cholesterol		136	<130	130-189	≥190	mg/dL (calc)	136	
TG/HDL-C	0.8		<2.0	2.0-3.0	>3.0	calc	1.3	
Lipoprotein Fractionation, NMR								
LDL-P[(2)]		1186	<935	935-1816	>1816	nmol/L	1270	
Small LDL-P	<154		<467	467-820	>820	nmol/L	244	
LDL Size	21.7		>20.5	N/A	≤20.5	nm	21.6	
HDL-P	47.4		>32.8	29.2-32.8	<29.2	umol/L	46.6	
Large HDL-P	14.5		>7.2	5.3-7.2	<5.3	umol/L	9.4	
HDL Size	9.8		>9.0	8.7-9.0	<8.7	nm	9.2	
Large VLDL-P	<1.5		<3.7	3.7-6.1	>6.1	nmol/L	2.7	
VLDL Size	45.7		<47.1	47.1-49.0	>49.0	nm	48.8	

Labs (6/3/22)

Test Name	Current Result & Relative Risk: Optimal	Current Result & Relative Risk: Non-Optimal	Reference Range/Relative Risk Categories: Optimal	Moderate	High	Units	Historical Result & Relative Risk: 11/16/2021	03/17/2021
METABOLIC								
Glucose	71		65-99	100-125	<65 OR ≥126	mg/dL	75	
HbA1c	5.5		<5.7	5.7-6.4	>6.4	%	5.7	
Estimated Average Glucose	111		<117	117-137	>137	mg/dL	117	
TMAO (Trimethylamine N-oxide)(1)	0.3		<6.2	6.2-9.9	≥10.0	uM	<0.3	<0.3
Homocysteine		10.7	<10.4	N/A	≥10.4	umol/L	13.8	13.6
VITAMINS/SUPPLEMENTS								
Vitamin D, 25-Hydroxy by LC-MS/MS(3)	75.0		≥30.0	20.0-29.9	<20.0 OR >150.0	ng/mL	75.7	

Results (Non-Cardiometabolic)

Test Name	Current Result: In Range	Current Result: Out of Range	Reference Range	Units	Lab	Historical Results: 11/16/2021	03/17/2021
ROUTINE PANELS							
Comprehensive Metabolic Panel							
Glucose	71		65-99	mg/dL	Z4M	75	
Calcium, Total	9.4		8.5-10.5	mg/dL	Z4M	9.4	
Sodium	139		136-145	mmol/L	Z4M	137	
Potassium	4.1		3.5-5.1	mmol/L	Z4M	4.2	
Chloride	102		95-108	mmol/L	Z4M	102	
CO_2 (Carbon Dioxide, Bicarbonate)	21		21-33	mmol/L	Z4M	22	
BUN (Blood Urea Nitrogen)	20		8-23	mg/dL	Z4M	20	

Labs (6/3/22)

Results (Non-Cardiometabolic)

Test Name	Current Result		Reference Range	Units	Lab	Historical Results	
	In Range	Out of Range				11/16/2021	03/17/2021
Creatinine		1.15 H	0.50-0.99	mg/dL	Z4M	1.26 H	
BUN/Creatinine Ratio	17		6-22	calc	Z4M	16	
Protein, Total	7.2		6.1-8.0	g/dL	Z4M	7.2	
Albumin	4.5		3.5-5.5	g/dL	Z4M	4.6	
Globulin	2.7		1.8-3.8	g/dL (calc)	Z4M	2.6	
Albumin/Globulin Ratio	1.7		1.0-2.5	calc	Z4M		
ALP (Alkaline Phosphatase)	67		<150	U/L	Z4M	71	
ALT (Alanine Amino Transferase)	14		6-29	U/L	Z4M	12	
AST (Aspartate Amino Transferase)	19		10-35	U/L	Z4M	15	
Bilirubin, Total	0.4		<1.3	mg/dL	Z4M	0.6	
eGFR, Non-African descent		50 L	≥60	mL/min/1.73 m²	Z4M	45 L	
eGFR, African descent		58 L	≥60	mL/min/1.73 m²	Z4M	52 L	
HORMONES							
Parathyroid Hormone, Intact		92 H	14-64	pg/mL	Z4M		

Treatment Program 6/15/22

Nutrient Support

- Vitamin D 6000 IU, 3 drops QD
- Delta and gamma tocotrienol isomers 300 mg, 1 softgel QD with a meal
- N-acetyl-cysteine 1800 mg, 2 capsules QD
- Methylation Support, 1 capsule QD with a meal

Labs (3/16/23)

Cardiometabolic Report

Test Name	Current Result & Relative Risk		Reference Range/Relative Risk Categories			Units	Historical Result & Relative Risk	
	Optimal	Non-Optimal	Optimal	Moderate	High		06/03/2022	11/16/2021
INFLAMMATION								
hs-CRP	0.8		<1.0	1.0-3.0	>3.0	mg/L	1.2	2.2
LIPIDS								
Lipid Panel								
Cholesterol, Total		220	<200	N/A	≥200	mg/dL	221	209
HDL Cholesterol	98		≥50	N/A	<50	mg/dL	85	73
Triglycerides	67		<150	150-199	≥200	mg/dL	65	93
LDL Cholesterol, Calculated		107	<100	100-129	>129	mg/dL (calc)	120	117
Chol/HDL-C	2.2		≤3.5	3.6-5.0	>5.0	calc	2.6	2.9
Non-HDL Cholesterol	122		<130	130-189	≥190	mg/dL (calc)	136	136
TG/HDL-C	0.7		<2.0	2.0-3.0	>3.0	calc	0.8	1.3
Lipoprotein Fractionation, NMR								
LDL-P[(2)]		989	<935	935-1816	>1816	nmol/L	1186	1270
Small LDL-P	<154		<467	467-820	>820	nmol/L	<154	244
LDL Size	21.8		>20.5	N/A	≤20.5	nm	21.7	21.6
HDL-P	47.4		>32.8	29.2-32.8	<29.2	umol/L	47.4	46.6
Large HDL-P	18.2		>7.2	5.3-7.2	<5.3	umol/L	14.5	9.4
HDL Size	10.4		>9.0	8.7-9.0	<8.7	nm	9.8	9.2
Large VLDL-P	1.9		<3.7	3.7-6.1	>6.1	nmol/L	<1.5	2.7
VLDL Size		49.6	<47.1	47.1-49.0	>49.0	nm	45.7	48.8

Labs (3/16/23)

Test Name	Current Result & Relative Risk		Reference Range/Relative Risk Categories				Historical Result & Relative Risk	
	Optimal	Non-Optimal	Optimal	Moderate	High	Units	06/03/2022	11/16/2021
METABOLIC								
Glucose	86		65-99	100-125	<65 OR ≥126	mg/dL	71	75
HbA1c	5.4		<5.7	5.7-6.4	>6.4	%	5.5	5.7
Estimated Average Glucose	108		<117	117-137	>137	mg/dL	111	117
TMAO (Trimethylamine N-oxide)(1)	0.3		<6.2	6.2-9.9	≥10.0	uM	0.3	<0.3
Homocysteine		10.4	<10.4	N/A	≥10.4	umol/L	10.7	13.8
VITAMINS/SUPPLEMENTS								
Vitamin D, 25-Hydroxy by LC-MS/MS(3)	74.0		≥30.0	20.0-29.9	<20.0 OR >150.0	ng/mL	75.0	75.7

Results (Non-Cardiometabolic)

Test Name	Current Result In Range	Current Result Out of Range	Reference Range	Units	Lab	Historical Results 06/03/2022	Historical Results 11/16/2021
ROUTINE PANELS							
Comprehensive Metabolic Panel							
Glucose	86		65-99	mg/dL	Z4M	71	75
Calcium, Total	9.9		8.5-10.5	mg/dL	Z4M	9.4	9.4
Sodium	137		136-145	mmol/L	Z4M	139	137
Potassium	4.6		3.5-5.1	mmol/L	Z4M	4.1	4.2
Chloride	100		95-108	mmol/L	Z4M	102	102
CO_2 (Carbon Dioxide, Bicarbonate)	22		21-33	mmol/L	Z4M	21	22
BUN (Blood Urea Nitrogen)	17		8-23	mg/dL	Z4M	20	20

Labs (3/16/23)

Results (Non-Cardiometabolic)

Test Name	Current Result In Range	Current Result Out of Range	Reference Range	Units	Lab	Historical Results 06/03/2022	Historical Results 11/16/2021
Creatinine		1.19 H	0.50-1.05	mg/dL	Z4M	1.15 H	1.26 H
BUN/Creatinine Ratio	14		6-22	calc	Z4M	17	16
Protein, Total	7.1		6.1-8.0	g/dL	Z4M	7.2	7.2
Albumin	4.4		3.5-5.5	g/dL	Z4M	4.5	4.6
Globulin	2.7		1.8-3.8	g/dL (calc)	Z4M	2.7	2.6
Albumin/Globulin Ratio	1.6		1.0-2.5	calc	Z4M	1.7	
ALP (Alkaline Phosphatase)	72		<150	U/L	Z4M	67	71
ALT (Alanine Amino Transferase)	13		6-29	U/L	Z4M	14	12
AST (Aspartate Amino Transferase)	19		10-35	U/L	Z4M	19	15
Bilirubin, Total	0.5		<1.3	mg/dL	Z4M	0.4	0.6
eGFR		51 L	≥60	mL/min/1.73 m²	Z4M		

The eGFR is based on the CKD-EPI 2021 equation. To calculate the new eGFR from a previous Creatinine or Cystatin C result, go to https://www.kidney.org/professionals/kdoqi/gfr%5Fcalculator.

Historical eGFR							
eGFR, Non-African descent				mL/min/1.73 m²	Z4M	50 L	45 L
eGFR, African descent				mL/min/1.73 m²	Z4M	58 L	52 L

GENERAL CHEMISTRY

Inorganic Phosphate (Phosphorus)	4.0		2.5-4.5	mg/dL	Z4M		

HORMONES

Parathyroid Hormone, Intact		80 H	14-64	pg/mL	Z4M	92 H	

ANEMIA/IRON METABOLISM

Ferritin	40		18-300	ng/mL	Z4M		55

For additional information, please refer to https://www.clevelandheartlab.com/biotinFAQ/ (this link is being provided for informational/educational purposes only).

Iron	53		30-140	ug/dL	Z4M		54

nutrients

MDPI

Article

Correlation between Serum 25-Hydroxyvitamin D Level and Peripheral Arterial Stiffness in Chronic Kidney Disease Stage 3–5 Patients

Chung-Jen Lee [1], Yi-Jen Hsieh [2], Yu-Li Lin [2,3], Chih-Hsien Wang [2,3], Bang-Gee Hsu [2,3,*] and Jen-Pi Tsai [3,4,*]

[1] Department of Nursing, Tzu Chi University of Science and Technology, Hualien 97010, Taiwan; gugilee@msn.com

[2] Division of Nephrology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien 97010, Taiwan; hij@mail.tcu.edu.tw (Y.-J.H.); nomo8931126@gmail.com (Y.-L.L.);

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as well as highly sensitive CRP in subclinical atherosclerosis patients [21]. Akdam et al. found that 94.1% of patients with advanced CKD had 25-hydroxyvitamin D levels less than 30 ng/mL and there was a tendency to decrease as the CKD stage increased [22]. Moreover, there was an inverse association between 25-hydroxyvitamin D levels and augmentation indexes as well as non-significantly higher iPTH level [22]. Garcia-Canton et al. found that 18.5% of stage 4–5 CKD patients had adequate 25-hydroxyvitamin D levels (>30 ng/mL) and that lower 25-hydroxyvitamin D was associated with higher vascular calcification scores, determined from plain X-ray images [23]. Our results showed there was negative relationship between 25-dihydroxyvitamin D and iPTH and evidence had shown that down-regulation of vitamin D could up-regulate the production of iPTH, which might lead to arterial hypertension and adverse vascular remodeling and resulting in vascular wall calcification [14,22,37]. Moreover, in this study, patients in the PAS group were found to have higher iPTH than control group, and we considered that level of iPTH could play

in CKD patients [1]. Evidence has shown that the stiffening of vascular walls, which may result from dysregulation of elastin and collagen production, oxidative stress, disordered mineral metabolism, and low-grade inflammation, can increase the risk of myocardial strain, ischemia, and future CVD in CKD patients [2,3]. To assess arterial stiffness requires specific techniques while a few non-invasive methods have been developed. Among them, brachial-ankle pulse wave velocity (baPWV) is a simple, non-invasive means of determining the stiffness of large to medium-sized arteries and is a predictor of the risk of cardiovascular (CV) events and mortality in the general population and DM, HTN, and CKD patients independent of other CV risk factors [4–7]. In addition, baPWV had been found to be associated with decline of estimated glomerular filtration rate of CKD stage

Labs (3/16/23)

Results (Non-Cardiometabolic)

Test Name	Current Result		Reference Range	Units	Lab	Historical Results	
	In Range	Out of Range				06/03/2022	11/16/2021
HEAVY METALS							
ZINC(AMD)	61		60-130	mcg/dL	AMD		

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute Chantilly, VA. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

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Communication

Clinical Significance of Trace Element Zinc in Patients with Chronic Kidney Disease

Hirotaka Fukasawa [1,*], Ryuichi Furuya [1], Mai Kaneko [1], Daisuke Nakagami [1], Yuri Ishino [1], Shuhei Kitamoto [1], Kyosuke Omata [1] and Hideo Yasuda [2]

[1] Renal Division, Department of Internal Medicine, Iwata City Hospital, Iwata 438-8550, Shizuoka, Japan
[2] First Department of Medicine, Hamamatsu University School of Medicine, Hamamatsu 431-3192, Shizuoka, Japan
* Correspondence: hfukasawaucsd@gmail.com

Abstract: The trace element zinc is essential for diverse physiological processes in humans. Zinc deficiency can impair growth, skin reproduction, immune function, maintenance of taste, glucose metabolism, and neurological function. Patients with chronic kidney disease (CKD) are susceptible to zinc deficiency, which is associated with erythropoiesis-stimulating agent (ESA) hypo-responsive anemia, nutritional problems, and cardiovascular diseases as well as non-specific symptoms such as dermatitis, prolonged wound healing, taste disturbance, appetite loss, or cognitive decline. Thus, zinc supplementation may be useful for the treatment of its deficiency, although it often causes copper deficiency, which is characterized by several severe disorders including cytopenia and myelopathy. In this review article, we mainly discuss the significant roles of zinc and the association between zinc def

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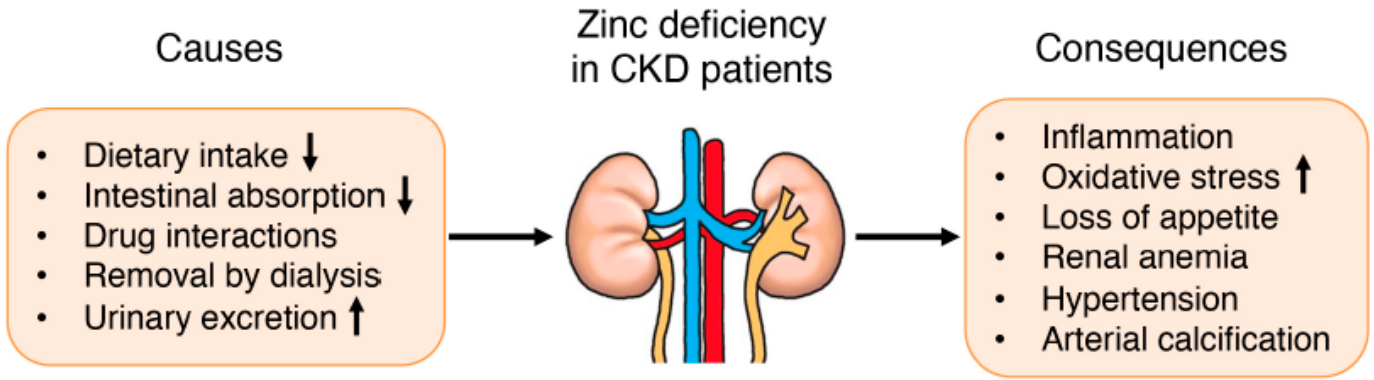
catalyzes the dismutation of superoxide (O^-) [9,10]. Thus, zinc acts as an antioxidant agent and zinc deficiency is associated with an increased risk of cardiovascular disease [11,12].

On the other hand, zinc deficiency is characterized by non-specific symptoms including weight loss, growth retardation, alopecia, dermatitis, prolonged wound healing, taste disturbance, appetite loss, and cognitive decline [13,14]. Therefore, zinc deficiency is often overlooked.

According to the recommended dietary zinc intakes from practical guidelines, the ideal daily dose for adults is 8 mg/day for women and 11 mg/day for men [15]. The dietary zinc content and its bioavailability can influence the efficiency of zinc absorption as well as an individual's zinc status. Dietary zinc is actively absorbed throughout the small intestine; the main dietary sources of zinc include seafood (especially oysters), crustaceans,



7. Conclusions and Future Perspectives

CKD patients are susceptible to zinc deficiency, which may often cause ESA hypo-responsive anemia, nutritional problems, or cardiovascular diseases as well as non-specific symptoms including dermatitis, prolonged wound healing, taste disturbance, and appetite loss. Although zinc supplementation is a useful treatment for CKD patients with its deficiency, risk of ZICD should be noted. Further studies are needed to determine how to manage zinc deficiency in CKD patients.

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Research

Metabolic profiling distinguishes three subtypes of Alzheimer's disease

Dale E. Bredesen[1, 2]

[1] Mary S. Easton Center for Alzheimer's Disease Research, Department of Neurology, University of Califor
Angeles, CA 90095, USA;
[2] Buck Institute for Research on Aging, Novato, CA 94945, USA

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Correspondence to: Dale E. Bredesen, MD; E-mail: dbredesen@mednet.ucla.edu or dbredesen@buckinstitute.org

Abstract: The cause of Alzheimer's disease is incompletely defined, and no truly effective therapy exists. However, multiple studies have implicated metabolic abnormalities such as insulin resistance, hormonal deficiencies, and hyperhomocysteinemia. Optimizing metabolic parameters in a comprehensive way has yielded cognitive improvement, both in symptomatic and asymptomatic individuals. Therefore, expanding the standard laboratory evaluation in patients with dementia may be revealing. Here I report that metabolic profiling reveals three Alzheimer's disease subtypes. The first is inflammatory, in which markers such as hs-CRP and globulin:albumin ratio are increased. The second type is non-inflammatory, in which these markers are not increased, but other metabolic abnormalities are present. The third type is a very distinctive clinical entity that affects relatively young individuals, extends beyond the typical Alzheimer's disease initial distribution to affect the cortex widely, is characterized by early non-amnestic features such as dyscalculia and aphasia, is often misdiagnosed or labeled atypical Alzheimer's disease, typically affects ApoE4-negative individuals, and is associated with striking zinc deficiency. Given the involvement of zinc in multiple Alzheimer's-related metabolic processes, such as insulin resistance, chronic inflammation, ADAM10 proteolytic activity, and hormonal signaling, this syndrome of Alzheimer's-plus with low zinc (APLZ) warrants further metabolic, genetic, and epigenetic characterization.

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INTRODUCTION

Alzheimer's disease represents a major healthcare problem, with over five million Americans estimated to suffer from this disease, and a recent study showing that AD has now become the third leading cause of death, trailing only cardiovascular disease and neoplasia [1]. The cause(s) of AD remain incompletely determined, and there is currently no truly effective treatment. However, accumulating data suggest important contributions from metabolic abnormalities such as insulin resistance, metabolic syndrome, chronic inflammation, hypovitaminosis D, hormonal deficiencies, and hyperhomocysteinemia, among others [2]. Despite this, most clinical evaluations of patients with cognitive decline do not include extensive metabolic or genomic evaluations. Furthermore, given the perceived poor prognosis for AD, in patients with evidence of amyloid-β accumulation by amyloid PET imaging or, indirectly, by cerebrospinal fluid profile, there has been little incentive to perform extensive evaluations of hormonal status, nutritional status, toxicity status, metal status, gastrointestinal permeability, or other laboratory evaluations perceived by healthcare systems as "non-standard." However, studies such as the recent FINGER study [3] suggest that metabolic factors may play important roles in the neurodegenerative process, at least early in the pathogenetic process. Recent results from the evaluation of neural exosomes and nanosomes support the notion that metabolic abnormalities are present in patients with cognitive decline, often years prior to diagnosis of AD [4]. Therefore, it may be productive, both from the standpoint of identifying novel

Table 1. Patients with the third subtype of Alzheimer's disease described in the text, Alzheimer's-plus with low zinc.

Patient	Age at onset	Initial Symptoms	ApoE4?	Zinc	Other
1M	65	Visual agnosia	- (3/3)	56	MRI:general atrophy, mild FLAIR
2M	59	Dyscalculia, aphasia	- (2/3)	59	MRI:general atrophy, mild FLAIR; FDG PET: frontal, temporal, parietal abnl.
3F	50	Dyscalculia	- (3/3)	56	MRI:general atrophy, mild FLAIR; CSF +
4F	64	Dyscalculia, prosopagnosia, word finding	Declined	59	Cu:Zn=3:1
5M	55	Dyscalculia	- (3/3)	ND	MRI:general atrophy, CSF +
6F	57	Dyscalculia	+ (3/4)	70	MRI:general atrophy, mild FLAIR; amyloid PET +

Treatment Program 4/4/23

Nutrient Support

- Vitamin D 6000 IU, 3 drops QD
- N-acetyl-cysteine 1800 mg, 2 capsules QD
- Delta and gamma tocotrienol isomers 300 mg, 1 softgel QD with a meal
- Methylation Support, 2 capsules QD with a meal
- Zinc 30 mg, 1 capsule QD with a meal

Labs (11/3/23)

						Historical Result & Relative Risk	
						08/03/2023	03/16/2023
METABOLIC							
Homocysteine	9.9	<10.4	N/A	≥10.4	umol/L	10.6	10.4
HORMONES							
Parathyroid Hormone, Intact	63	14-64		pg/mL	Z4M	69 H	80 H

@DRMICHAELJURGELEWICZ

Thank You

http://www.linkedin.com/in/michaeljurgelewicz
https://www.researchgate.net/profile/Michael-Jurgelewicz
email: drj@designsforhealth.com