

CLINICAL EFFICACY OF LITHOLEXAL® FOR THE TREATMENT OF OSTEOPOROSIS

LITHOLEXAL® BONE HEALTH



MEDICAL INFORMATION FOR PROFESSIONAL USE

RESEARCH SYNOPSIS

All clinical guidelines are in consensus that adjunctive therapy with calcium and vitamin D is an imperative part of the medical management of osteoporosis and osteopenia. Supplementation is necessary due to a high prevalence of nutritional deficiency in high-risk individuals; this denotes a failure in obtaining the recommended intakes from dietary sources. Furthermore, most interventional evidence for the efficacy of anti-resorptive therapy is based on coadministration with a form of calcium supplement.

Osteoporosis adjunctive therapy is well documented to alleviate secondary hyperparathyroidism and reduces the risk of falling and femur fracture. However, conventional options are as of yet restricted to poorly-absorbed rock-based salts of calcium. Promisingly, the discovery of a marine-based multimolecular complex, LithoLexal[®], as a novel form of Disease-Modifying Adjunctive Therapy (DMAT), has recently closed this gap. With its unique microstructure, LithoLexal[®] not only takes the benefits of conventional therapies to the next level in terms of providing bioavailable and bioaccessible minerals but also provides a spectrum of Disease-Modifying Effects verified by several in-vivo and clinical research studies.

The superiority of LithoLexal[®] to calcium carbonate has been confirmed by head-to-head comparisons.

As shown by in-vivo studies, starting LithoLexal® therapy early after ovariectomy can potently protect the normal mineral content, trabecular structure and biomechanical properties of bones, while calcium carbonate largely fails to produce significant effects. Clinical evidence also suggests that LithoLexal® yields more potent and sustained parathyroid hormone (PTH)-suppressing effects relative to calcium carbonate and tricalcium phosphate. Suppressing PTH is one of the mechanisms through which LithoLexal® modifies both serum and urinary levels of osteoclastic activity biomarkers in postmenopausal women. Higher calcium and magnesium bioavailability and target-tissue exposure or up to 10-fold increase in strontium content of bones also have crucial roles in the superior efficacy of LithoLexal® over inorganically-sourced supplements in the prevention and treatment of osteoporosis.

Furthermore, **LithoLexal**[®] has been described as potent enough to neutralise the detrimental effects of acidogenic high-fat diets on bones. Supplementation of high-fat diets with LithoLexal[®] leads to maintaining equivalent or enhanced bone structure, stiffness and resistance to fracture compared to subjects on a normal diet.



A Natural, Calcium-Rich Marine Multi-Mineral Complex Preserves Bone Structure, Composition and Strength in an Ovariectomised Rat Model of Osteoporosis Effect of Lithothamnium Sp and Calcium Supplements in 3 Strain- And Infection-Induced Bone Resorption A Mineral-Rich Extract from The Red Marine Algae 5 Lithothamnion Calcareum Preserves Bone Structure and Function in Female Mice on a Western-Style Diet Preservation of Bone Structure and Function by Lithothamnion Sp. Derived Minerals The Effects of a Mineral Supplement (Aquamin F[®]) and its Q Combination with Multi-Species Lactic Acid Bacteria (LAB) on Bone Accretion in an Ovariectomized Rat Model Magnesium Supplementation Through Seaweed Calcium Extract Rather than Synthetic Magnesium Oxide Improves Femur Bone Mineral Density and Strength in Ovariectomized Rats Calcium Supplementation and Parathyroid Hormone 13 Response to Vigorous Walking in Postmenopausal Women Effect of Calcium Derived from Lithothamnion Sp. on Markers 15 of Calcium Metabolism in Premenopausal Women Supplementation with Calcium and Short-Chain Fructo-Oligosaccharides Affects Markers of Bone Turnover but Not Bone Mineral Density in Postmenopausal Women Comparison of the Effects of LithoLexal® and Generic Mineral 10 Supplements on Key Biomarkers of Bone Turnover - A Double-Blind, Active-Controlled, Pilot Trial in Postmenopausal Women

Notes

LithoLexal®

of $p \le 0.05$ was considered significant. and mechanical results. A difference ectermine afferences between the

Results

Trabecular Bone Structure

Aquamin Prevents a Significant Loss of Trabecular Bone

Three-dimensional and two-dimensional representative micrographs from each of the groups are shown in Fig. 1. These slices and reconstructions show an intact and wellconnected trabecular microstructure in the control samples. A significant loss of trabecular bone structure following 20 weeks of ovariectomy is evident in the centre of the OVX + calcium carbonate samples. In contrast, the trabecular structure is preserved when Aquamin administration began at week 0 (OVX + Aquamin). The Aquamin delay group has a structure which appears intermediate between the OVX + calcium carbonate and OVX + A-Quantitative analysis shows that as early as week 2, the

OVX + calcium carbonate group displayed large changesin structural parameters relative to the healthy controls, indicating the development of osteopenia (Fig. 2). Significant losses in bone volume fraction (BV/TV) were observed in this group by week 8 (33, 95% CI (21, 45), P = 0.038). Trabecular separation (Tb.Sp) was

Calcium-Rich Marine Mu

significantly increased in the OVX + calciumgroup by week 12 (57, 95% CI (55, 58), p = 0.04trabecular number (Tb.N) was significantly reduce group by week 20 (47, 95% CI (30, 65), p = 0.0significant changes were measured in trabecular th (Tr.Th) between groups over the study period. Treatment with Aquamin resulted in a sign preservation of bone volume fraction by week 20 re to the OVX + calcium carbonate group (13, 95) (1,21), p = 0.049). No significant differences were sured in individual parameters, e.g. Tr. N or Tr. Sp betv OVX + calcium carbonate and the Aquamin-treated

Trabecular and Cortical Bone Composition Aquamin Prevents a Significant Loss of Hydroxyapatite Content and Mineral in Trabecular Bone

Hydroxyapatite content measured using microCT indicated a significant reduction in the HA content of trabecular bone by week 20 as seen in the OVX + calcium carbonategroup in comparison to the non-OVX controls (37.5 mg HA/cm^3 , 95% CI (10, 65), p = 0.022) (Fig. 3). Beginning oral administration of Aquamin at week 0 prevented this HA loss in trabecular bone. Following OVX, trabecular HA content was significantly greater in the Aquamin group than in the calcium carbonate group (29.5 mg HA/cm^3 , 95% CI (18, 41), p = 0.044). Beginning administration of Aquamin 8 weeks following ovariectomy (Aquamin delay) was also sufficient to see a significant preservation of HA



A NATURAL, CALCIUM-RICH MARINE MULTI-MINERAL COMPLEX PRESERVES BONE STRUCTURE, COMPOSITION AND STRENGTH IN AN **OVARIECTOMISED** RAT MODEL OF **OSTEOPOROSIS**

Brennan O, Sweeney J, O'Meara B, Widaa A, Bonnier F, Byrne HJ, O'Gorman DM, O'Brien FJ Publication: Calcif Tissue Int. 2017;101(4):445-55.

Abstract:

Calcium supplements are used as an aid in the prevention of osteopenia and osteoporosis and also for the treatment of patients when used along with medication. Many of these supplements are calcium carbonate based. This study compared a calcium-rich, marine multi-mineral complex (Aquamin) to calcium carbonate in an ovariectomised rat model of osteoporosis in order to assess Aquamin's efficacy in preventing the onset of bone loss. Animals were randomly assigned to either non-ovariectomy control (Control), ovariectomy (OVX) plus calcium carbonate, ovariectomy plus Aquamin or ovariectomy plus Aquamin delay where Aquamin treatment started 8 weeks post OVX. At the end of the 20-week study, the trabecular architecture was measured using micro computed tomography, bone composition was assessed using Fourier transform infrared spectroscopy and the mechanical properties were assessed using nanoindentation and three-point bend testing. The study demonstrates that oral ingestion of Aquamin results in less deterioration of trabecular bone structure, mineral composition and tissue

level biomechanical properties in the tibia of rats following ovariectomy than calcium carbonate. This study has shown that in an animal model of osteoporosis, Aquamin is superior to calcium carbonate at slowing down the onset of bone loss.

Conclusion:

This active-control study on a model of postmenopausal osteoporosis has verified the superior efficacy of LithoLexal® compared with calcium carbonate. Infrared spectroscopy indicated that ovariectomised animals on LithoLexal[®] preserved the same level of bone mineralisation as normal controls, which was significantly higher than that of the calcium carbonate group. The loss of hydroxyapatite has particularly been prevented in trabecular bones. This effect has led to higher bone volume fraction and almost normalised bone delayed administration of LithoLexal® after ovariectomy has also been proved relatively effective in restoring the normal bone structure and mineral content. In contrast, supplementation with calcium carbonate has largely failed to hinder the postmenopausal decay in bones microstructure and





SUPPLEMENTS IN STRAIN- AND INFECTION-INDUCED BONE RESORPTION de Albuquerque Taddei SR, Madeira MF, de Abreu Lima IL, Queiroz-Junior CM,

LITHOTHAMNIUM

SP AND CALCIUM

EFFECT OF

de Albuquerque Tadder SR, Madeira MF, de Abreu Lima IL, Queiroz-Junior CM, Moura AP, Oliveira DD, Andrade I Jr, da Glória Souza D, Teixeira MM, da Silva TA Publication: Angle Orthod. 2014;84(6):980-8.

Abstract:

Objective: To investigate the effect of Lithothamnium sp (LTT) supplement, a calcium-rich alga widely used for mineral reposition, on strain-induced (orthodontic tooth movement [OTM]) and infection-induced bone resorption (periodontal disease [PD]) in mice.

Materials and Methods: Mice were divided into two bone resorption models: one with an orthodontic appliance and the other with PD induced by the oral inoculation of Aggregatibacter actinomycetencomitans (Aa). Both groups were fed a regular diet (vehicle), LTT-rich diet (LTT), or calcium-rich diet (CaCO3). Alveolar bone resorption (ABR), the number of osteoclasts, and the levels of tumor necrosis factor α (TNF- α), calcium, and vitamin D3 were evaluated.

Results: The number of osteoclasts was reduced in LTT and CaCO3 mice, which led to diminished OTM and infection-induced alveolar bone loss. In addition, LTT- and calcium-treated groups also presented decreased levels of TNF- α in periodontal tissues and increased levels of calcium in serum. Conclusions: These results indicate that the LTT supplement influences ABR, probably due to its calcium content, by affecting osteoclast function and local inflammatory response, thus modulating OTM and PD.

Conclusion:

Inflammatory cells and cytokines are cardinal pro-resorptive elements that play integral roles in the development of osteoporosis. In this study, the in-vivo effects of a marine-derived mineral complex (as in LithoLexal®) on infection-induced bone resorption and inflammatory markers are evaluated. Administration of the marine-based multimineral complex abolished the infection-induced bone resorption and expression of TNF- α as well as the activity and presence of neutrophils in bone tissues. This research supports the anti-inflammatory properties of LithoLexal® that underlie its anti-resorptive activity which is proven to be superior to that of the rock-based calcium carbonate.

Original Article

Effect of Lithothamnium sp and calcium supplements in strain- and infection-induced bone resorption

Silvana Rodrigues de Albuquerque Taddei+³⁴; Mila Fernandes Moreira Madeira-⁴⁴; Izabella Lucas de Abreu Luma-⁴⁴; Çelso Martino Queiroz-Junior-4; Adriana Pedrosa Moura-4; Dauro Douglas Oliveira; Ildeu Andrade Jr⁴; Danielle da Glória Souza^{3,5}; Mayro Martino Teiveiraki: Tarrilla Americha da Silva J

ABSTRACT Objective: To investigate the effect of Lithothamnium sp (LTT) supplement, a calcium-rich widely used for mineral reposition, on strain-induced (orthodontic tooth movement [OTM])

Intellation-Induced bone relocation (periodicatal disease) (PD) in mice. monostimic applications of the other with PD induced by the call including of Aggregatibation actionomic applications of the other with PD induced by the call including of Aggregatibation actionomycetecomitans (Aa). Both groups were led a regular del vehicle), LTH-dn diel (LTL, actionomic del CaCo). Alveolar bone receiption (ABR), the number of obscichalis, and the levels of theorem concess factor cr (NT=-), calcium, and vitamin D3 were evaluated. PM and theorem concess factor cr (NT=-), calcium, and vitamin D3 were evaluated. OTM and interform-induced alveolar but Tard colocal, mice, which led to diminished Bealtism: The number of callocations ware added in LTT and calcium-treated groups also Conclusions: There are table in the LTT supplement Induces ABR, proceeding due to its calcium context, by affecting obscicular turction and local inflammatory response, thus modulating OTM and DP (Aggrege D-orthor. 2014-845-96-96.)

TRODUCTION

¹These authors contributed equally to the work presented in this article. ² Immunopharmacology, Department of Biochemistry and Immunology, Institute of Biological Sciences, Universidade Foderal de Minas Geraris, Biol HoritorentMG, Brazil. ³ Assistant Professor, Department of Morphology, Institute of Health Sciences, Universidade Foderal da Bahia, Saivador/BA,

 Assistant Professor: Department of Microbiology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Biol Netizante/MG, Bazil.
 *PhD student, Department of Cellular Biology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Beio Hotzente/MG, Brazil.
 *Assistant Professor, Department of Biochemistry and Immu-

Minai Gerais, Bob HorizontMA, Brazil. 'Chaiman, Department of Chrodontics, School of Denistry, Postficu Universidade Católica de Minas Geneia (PUC Minas), Associate Professor, Department of Chrodontics, School of Denistry, Portificia Universidade Católica de Minas Geneia (PUC Minas), Bol HorizontAMR, Brazil * Associate Professor, Department of Biochemistry and immunology, Institute of Biological Sciences, Universidade resorption (ABR). During OTM, the applied forces generate a transmit inflammatory process that allows teeth to be moved through the alveolar bone.¹ On the ther hand, PD is a chronic inflatence that allows tory disorder caused by oral biofilm bacteria, including Aggregatibacter actionnycetemcomitans (Aa), which List Polareza: Denatment of Rochemistry and Immunoform

Institute of Biological Sciences, Universidade Federal de Minas Gerais, Belo Houtontel/MG, Brazil ¹ Associate Professor, Department of Oral Pathology, Faculty of Dentistry, Universidade Federal de Minas Gerais, Belo Horizontel/MG, Brazil. Corresponding author: Ildeu Andrade Jr, Department of Orthodontics, School of Dentistry, Pontificia Universidade

Antibolinitas, School of Demany, Polinitad Orientaade Sabilaa de Minas Gerais (PUC-Minas), Av Doom José Gaspar 500, CEP 31.270-901, Belo Horizonte/MG, Brazil e-mail: lideuandrade@pucminas.br) Accepted: January 2014. Submitted: August 2013. "Valished Online: April 15, 2014

DOI: 10.2319/080313-579

Differences in cortical thickness and in trabecular number, thickness, and space are evident

A

C 4

3

Nmm v

Fig. 2 Bone strength measurements from female mice in the three diet groups. Femora were tested to failure in four-point bending. Values for each parameter are means and standard deviations for females. Statistical significance of each parameter was assessed by ANOVA followed by paired group comparisons. Asterisks are placed on the HFWD + supplement group: * statistically significant

mprovement relative to the MN76A group, ** statistically ignificant improvement relative both AIN76A and HFWD < 0.05). Data are based on ht mice in the AIN76A diet up, four mice in the HFWD p, and 10 mice in the VD + supplement group

s of both tibiae and femora (Tables 3, 4, Fig. 1). s most surprising was that female animals on the with the mineral-rich extract had better bone al properties than females on the low-fat (AIN76A) en though the AIN76A animals had comparable els. The most dramatic effects were seen in the r region, where there was a large increase in traumber and thickness and a concomitant reduction lar space in the mineral-supplemented HFWD



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overcome in the presence of the mineral-rich A MINERAL-RICH supplement. In fact, female mice receiving the mineral-rich supplement in the HFWD had better EXTRACT FROM THE bone structure/function than did female mice on the low-fat chow diet. Female mice on the **RED MARINE ALGAE** mineral-supplemented HFWD had higher plasma levels of TRAP than mice of the other groups. LITHOTHAMNION There were no differences in the other two markers. Male mice showed little diet-specific CALCAREUM differences by micro-CT. PRESERVES BONE STRUCTURE AND Conclusion: In addition to causing obesity and FUNCTION IN FEMALE cardiometabolic disorders, a high-fat diet is a known risk factor for osteoporosis. Findings MICE ON A WESTERNof the present study suggest that long-term administration of LithoLexal[®] can nullify STYLE DIET the detrimental effects of a high-fat diet on

Aslam MN, Kreider JM, Paruchuri T, Bhagavathula N, DaSilva M, Zernicke RF, Goldstein SA, Varani J Publication: Calcif Tissue Int. 2010;86(4):313-24.

Abstract:

The purpose of this study was to determine whether a mineral-rich extract derived from the red marine algae Lithothamnion calcareum could be used as a dietary supplement for prevention of bone mineral loss. Sixty C57BL/6 mice were divided into three groups based on diet: the first group received a high-fat Western-style diet (HFWD), the second group was fed the same HFWD along with the mineral-rich extract included as a dietary supplement, and the third group was used as a control and was fed a low-fat rodent chow diet (AIN76A). Mice were maintained on the respective diets for 15 months. Then, long bones (femora and tibiae) from both males and females were analyzed by three-dimensional micro-computed tomography (micro-CT) and (bones from female mice) concomitantly assessed in bone strength studies. Tartrate-resistant acid phosphatase (TRAP), osteocalcin, and N-terminal peptide of type I procollagen (PINP) were assessed in plasma samples obtained from female mice at the time of sacrifice. To summarize, female mice on the HFWD had reduced bone mineralization and reduced bone strength relative to female mice on the low-fat chow diet. The bone defects in female mice on the HFWD were

density of both cortical and trabecular bones in female subjects. It is noteworthy that high-fat-fed female animals which received LithoLexal[®] had comparable or better bone structural properties compared to animals on a low-fat diet. This structural augmentation has also led to stiffer bones with a higher fracture resistance level.

A Mineral-Rich Extract from the Red Marine Algae Lithothamnion calcareum Preserves Bone Structure and Function in Female Mice on a Western-Style Diet

· Ronald F. Zernich

Accepted: 31 January 2010/Pr Media LLC 2010

I. N. Aslam · T. Paruchuri · N. Bhagavathula · M. DaSilv Department of Pathology, University of Michigan Medical School, 1301 Catherine Street, SPC 5602, Ann Arbor, MI 48109, USA

In fact, femate mice sectoring the structure/function than in the HFWD had better bow-fat chow diet. Female mice o female mice on the low-fat chow diet. Female mice o TRAP than mice of the other groups. Ther

Springe

Values are means and standard monus in each diet group. deviations. Statistical significance of each parameter was assessed by ANOVA followed by paired group comparisons. Statistical significance at the p < 0.05 level is indicated by asterisks. Single asterisk by the HFWD + minerals indicates statistically significant improvement relative to HFWD alone; double asterisk by the HFWD+minerals indicates statistically significant improvement relative to control; triple asterisk by the control+ minerals indicates statistically significant improvement relative to control. c µ-CT images: a representative 3D µ-CT image of he trabecular region from the mur of a female mouse in each iet group is shown. Histological images: matoxylin and eosin-stained tions of decalcified bone tal femoral condyles) from a se (at 18 months) in two fat diet groups are shown



ted in Fig. 3a. Mice on the HFWD demone in ductility compared to mice on the control e seen by the decrease in stiffness and the ecement ratio. The displacement ratio was re to diet. Consistent with the decrease in

bone stiffness, mice on the HFWD demonstrated an increase in maximum load value as compared to mice on the control diet [8]. In mice treated with the minerals, biomechanical properties were improved. Specifically, bone stiffness was enhanced (36 % at 5 months, 3 % at 12 months, and 32 % at

PRESERVATION OF BONE STRUCTURE AND FUNCTION BY LITHOTHAMNION SP. DERIVED MINERALS

Aslam MN, Bergin I, Jepsen K, Kreider JM, Graf KH, Naik M, Goldstein SA, Varani J Publication:

Biol Trace Elem Res. 2013;156(1-3):210-20.

Abstract:

Progressive bone mineral loss and increasing bone fragility are hallmarks of osteoporosis. A combination of minerals isolated from the red marine algae, Lithothamnion sp. was examined for ability to inhibit bone mineral loss in female mice maintained on either a standard rodent chow (control) diet or a high-fat western diet (HFWD) for 5, 12, and 18 months. At each time point, femora were subjected to µ-CT analysis and biomechanical testing. A subset of caudal vertebrae was also analyzed. Following this. individual elements were assessed in bones. Serum levels of the 5b isoform of tartrate-resistant acid phosphatase (TRAP) and procollagen type I propeptide (P1NP) were also measured. Trabecular bone loss occurred in both diets (evident as early as 5 months). Cortical bone increased through month 5 and then declined. Cortical bone loss was primarily in mice on the HFWD. Inclusion of the minerals in the diet reduced bone mineral loss in both diets and improved bone strength. Bone mineral density was also enhanced by these minerals. Of several cationic minerals known to be important to bone health, only strontium was significantly increased in bone tissue from animals fed the mineral diets, but the increase was large (5-10 fold). Serum levels of TRAP were consistently higher in mice receiving the minerals, but levels of P1NP were not. These data suggest that trace minerals derived from marine red algae may be used to prevent progressive bone mineral loss in conjunction with calcium. Mineral supplementation could find use as part of an osteoporosisprevention strategy.

Conclusion:

Replicating the findings of the previous study, this in-vivo research confirmed that LithoLexal[®] protects bones against the pro-resorptive influence of a high-fat Western-pattern diet. Micro-CT scanning has revealed that long-term LithoLexal® therapy enhances the density of trabecular bones by up to 82% and bone volume by up to 50%. Overall, the impact of LithoLexal® supplementation was more prominent femoral and vertebral bones. Structural and mineralisation improvement has led to boosted bone biomechanical properties, i.e. stiffness in long bones and resistance to compression fracture in vertebrae. Of clinical importance is the ability of LithoLexal® to dramatically increase the level of strontium in bones (up to 10 fold) in both normal and high-fat diet groups. Strontium is known to reduce the risk of fracture and increase bone density in osteoporotic individuals.

Biol Trace Elem Res DOI 10.1007/s12011-013-9820-

Preservation of Bone Structure and Function by Lithothamnion sp. Derived Minerals

Muhammad Nadeem Aslam - Ingrid Bergin -Karl Jepsen - Jaclynn M. Kreider - Kristin H. Graf Madhav Naik - Steven A. Goldstein - James Varani

Received: 21 August 2013 / Accepted: 10 September 2013 © Springer Science+Business Media New York 2013

Abstract Progressive brow moteral loss and increasing bone fingility are lalments of osteopororist. A combinition on minerais isolated from the red marine algae, Lithothammion gav, was examined for ability to inhibit bone mineral loss in ferate mine maintained on effer a standard rodent chow (control) det or a high-faw stenth def (HWD) for 5, 12, and 18 months. At each time point, femora were subjected to u-tc? ranalysias and bioneclivinal testing. A subset of earlied was absonable to bones, Semu beyool fuely to bone of lattrate-resistant acid phosphatuse (TRAP) and procollages type 1 propedide (1PA) were also measured. Tinkechan bone loss occurred in both dest (exident a early as 3 months). Cartical hose increased through months and have HFWD Cartical hose increased through months of marker through the phosphetic (1PA) were also measured. Tinkechan bone loss occurred in both dest (exident a early as 3 months) Cartical hose increased through months of marker through the hose loss occurred to both models (or stentard through and the hose through the semineral loss in hose distant and improved hose strength. Bone mineral domainy was also enhanced by these minerals. Or sevent carinaris minerals, hosen to be inceptive. Not sevent strontium was significantly increased in hose tasse from annuals fod the mineral discs, path the increase was large

Electronic supplementary material The online version of this article (doi:10.1007/s12011-013-9820-7) contains supplementary material, which is available to authorized users.

Department of Pathology, The University of Michigan, 1301 Catherine Road, Box 5602, Ann Arbor, MI 48109, USA

L Bergin The Unit for Laboratory Animal Medicine, The University of

K. Jepsen - J. M. Kreider - K. H. Graf - S. A. Goldstein Department of Orthopaedic Surgery, The University of Michigan, July 1991 (2019) 101 (2019) 101 (2019) 2019

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(5-10 fold). Serum levels of TRAP were consistently higher in mice receiving the minerals, but levels of P1NP were not. These data suggest that trace minerals derived from marine red algae may be used to prevent progressive bone mineral loss in conjunction with calcium. Mineral supplementation could find use as part of an osconorosis prevention strategy.

Keywords Bone · Bone mineral density · Bone mineral content · Calcium · Minerals · Osteoporosis · Red marine algae · Strontjum · Trace elements

Abbreviation

AIN76A	American Institute of Nutrition 76A
ANOVA	Analysis of variance
BMD	Bone mineral density
GRAS	Generally regarded as safe
HFWD	High-fat western-style diet
μ-CT	Microcomputed tomography
PINP	N-terminal propeptide of type I procollage
TRAP	Tartrate-resistant acid phosphatase (5b)
2D	Two-dimensional
3D	Three-dimensional

Introduction

Oncoperons is a condition characterized by low hone must, how home mixed content, and microarchicktural detrimtion leading to enhanced hone fragility and consequent interases risk of hone fracture [1]. Although in the white populiaton, men accound for up to 30 % of the ostopownic high fractures [2], ostoporosis is widely regarded as a condition primarily affecting apointnopousal work on [2, 3]. Genetic, factors underlie susceptibility, but environmental variables (including diffe) [4] assoggased to play a role. In particular

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Serum biochemical analysis

In the serum biochemical analysis, the OVX group showed a two fold higher level of ALP than the sham group (sham group: 593 ± 19.9 IU/L and OVX group: 1159 \pm 103.6 IU/L), and such high level of ALP was significant in the LAB group (927 \pm 63.4 IU/L) and the AQF group $(880\pm89.3 \text{ IU/L})$. Particularly, the LAB + AQF group (683 \pm 46.7 IU/L) showed the greatest decrease in ALP. In the neasurement of CA and IP, there was no significant fference between the sham group and the OVX group, d between the OVX group and the LAB + AQF group. croarchitecture of the trabecular bone bone mineralization, the BMC and BMD in the tibia were measured using XCT Research SA+. As shown in Fig. 4,

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emoval of an ovary is known to accelerate bone loss. As oned, the level of ALP increased in the ovariectomized which indicates the mal-metabolism of the bone. To he if AQF and/or LAB can affect the microarchiof the bone tissue, the morphological changes in the ar bone (TbB) in the distal femoral metaphysis mined. Fig. 2 shows that TbB stained with H&E I more poorly in the OVX group [Fig. 2 (C)] than n group, whereas its area increased after treatment and the LAB + AQF mixture [Fig. 2 (E) and (F)]. ate that LAB + AQF are effective in recovering decrease in the BMD of the OVX group (288.03 ± 29.66) ration of the bone microarchitecture with AQF mg/mm²) than in that of the sham group (709.53 ± 6.47) mg/mm²) (Fig. 4B). The effect of treatment with LAB

and AQF mixture was further confirmed by B in the distal femoral metaphysis with

astal portion of femur. removed after 14 weeks ment with Aquamin F and 1 months after ovariector operation, (B) sham operat diet, (C) ovariectomized at control, (D) ovariectomized with lactic acid bacteria (1) kg B.W., respectively), (E) mized and treated with Aqua mg/kg BW, (F) ovariecton treated with lactic acid bact 10⁷ CFU/kg B.W., respectiv Aquamin F 50 mg/kg BW treat micro-CT. More severe resorption of the TbB was ob. in the OVX group [Fig. 3 (C)] than in the sham group

treatment with LAB alone did not significantly affect

bone tissue of the rats [Fig. 3 (D)]. In contrast, the T

were better developed in both the AQF and LAB + A

BMC and BMD are commonly used to assess bone

mineralization. To assess the effect of AQF or/and LAB on

the BMC of the OVX group (5.22 \pm 0.53 mg/mm) decreased

more significantly than that of the sham group (11.79 \pm

0.47 mg/mm). Although the LAB group (5.00 ± 0.36 mg/

mm) did not show a significant difference, the BMCs of

the AQF (7.87 \pm 0.43 mg/mm) and LAB + AQF (9.43 \pm

0.81 mg/mm) groups increased more significantly than did

that of the OVX group (*P*<0.0001, respectively). When the

BMCs of the AQF and the LAB + AQF groups were

compared, the LAB + AQF group showed an approximately

30% higher BMC than the AQF group (Fig. 4A; P<0.0001).

On the other hand, ovariectomy led to a more significant

groups than in the sham group [Fig. 3 (E) and (F)].

Effect on bone mineralization

OF A MINERAL SUPPLEMENT (AQUAMIN F[®]) AND ITS COMBINATION WITH MULTI-SPECIES LACTIC ACID BACTERIA (LAB) ON BONE ACCRETION IN AN OVARIECTO-

THE EFFECTS

Lee HG, Lee TH, Kim JH, Seok JW, Lee SH, Kim YH, Kim JE, Chung MJ, Yeo MH Publication: Biomed Sci Lett. 2010;16(4):213-20.

MIZED RAT MODEL

Abstract:

Although an adequate intake of calcium (Ca) is recommended for the treatment and prevention of osteoporosis, the intake of Ca should be restricted because of its low rate of intestinal absorption. The purpose of this experiment was to identify the effect of the combined administration of Aquamin F (AQF) (a calcium agent) and lactic acid bacteria (LAB) on osteoporosis. Thirty ovariectomized (OVX) rats and six control rats were assigned to the following six groups, with six animals per group: sham Ca-deficient diet (Ca-D), OVX, LAB, AQF, and LAB-AQF. During the experiment, the body weight was measured; and after the experiment was completed, the serum biochemical analysis, the alkaline phosphatase, calcium, and inorganic phosphorus leves were measured. The tissue of the femur was stained and then scanned via CT. The body weight of the OVX group increased more significantly than that of the control group. The results of the bone mineral content (BMC). Bone mineral density (BMD), serum biochemical analysis and histological test on the femur epiphysis showed no difference between the OVX group and the LAB group, whereas the results of the AQF group were more significant than those of the OVX group. In particular, the LAB+AQF group showed more significant increases in the aforementioned results than the AQF group. This experiment showed that the combined administration of AQF and LAB in ovariectomized rats more significantly increased bone density than did a single administration of either AQF or LAB.

Conclusion:

The main aim of this study was to investigate whether or not lactic acid probiotics can enhance the efficacy of LithoLexal® in treating postmenopausal osteoporosis. Results were conclusive in that long-term LithoLexal[®] therapy with or without probiotics can improve trabecular bone structure and prevent the postmenopausal However, adding lactic acid probiotics further improves these therapeutic effects especially in curbing the rate of bone turnover and preventing the loss of bone minerals after ovariectomy.

I Exp Biomed Sci 2010 16(4): 213-220

The Effects of a Mineral Supplement (Aquamin F[®]) and Its Combination with Multi-Species Lactic Acid Bacteria (LAB) on Bone Accretion in an Ovariectomized Rat Model

Hyun-Gi Lee¹, Tac-Hee Lee¹, Jung-Ha Kim², Ju-Won Scol², Seung-Hoon Lee¹, Yong-Hwan Kim¹, Jin-Eung Kim¹, Myung-Jun Chung¹ and Moon-Hwan Yeo¹²

emter, Cellbiotech Ca., Lui, 134, Gaegolovi, Wolgot-myun, Gimpost, Gyunggi-do 415-871, Korea neut of Family Medicine, Chung-Ang, University Medical Center, "Department of Nuclear Medicine Chung-ang University Hospital. 22-41 Heustexol-doing, Dangial-gu, Scoul, Korea. 221 Heukscol-doing, Dongial-gu Scoul 156-756, Korea

hough an adequete intake of calcium (Ca) is recommended for the treatment at Among an analyze mass or occurs (1, a) to economicate of an analysis of the processors to consequences, are take of Ca shade be restricted because of this own are of intesting absorption. The purpose of this experiment was to learling the effect of the combined administration of Aquania F (AOF) (a calcium agent) and hacks acid bateria ABA) on onesporose. This you encommong (ONX) rata and a second rate was easily and the following six groups this second rate of the combined of the experiment of the combined of the following the experiment, the ody weight was assumed, and after the experiment was completed, the second bornerial analysis, the alkaline to ody weight was assumed, and after the experiment was completed, the second bornerial analysis, the alkaline rooty weight was measured, and and the experiment was completed, the setuin notementaria analysis, the ankant sophatase, eachering, and inorganic phosphorus leves were measured. The tissue of the femar was stained and the anned via CT. The body weight of the OVX group increased more significantly than that of the control group. Th sults of the bone mineral content (BMC). Bone mineral density (BMD), serum biochemical analysis and histologica st on the ferrar epiphysis showed no difference between the OVX group and the LAB group, whereas the results or a AQF group were use significant that those of the OVX group. In particular, the LAB+AQF group showed mor ignificant increases in the aforementioned results than the AQF group. This experiment showed that the combine significant increases in the aroteneous of the significant increases in the AQF got administration of AQF and LAB in ovariectomized rats more signifi-administration of either AQF or LAB. Key Words: Osteoporosis, Ovariectomy, Lactic acid bacteria, Aquam antly increased bone density than did a single

INTRODUCTION
Interported is a systemic hone disease that increases in the elderly population. There are about three finds proper with osteporosis, including mild cases in boots. Its may symptoms are a decrease in the BMD (tab), edd, and the increases in the elderly population. There are about three finds proper with osteporosis, is a host to be symptom edd. Symptoms are a decrease in the BMD (tab), edd, and the symptom series adverses in the BMD (tab), edd, and the symptom series adverses in the decrease in the elderly population. There are about three million property with osteporosis, is an elder of the increase in the elderly population. There are about the first symptom symptoms are adverses in the BMD (tab).
Norme, and is a major case of bone factures in the decleta's population. There are about the symptom symptom symptom symptom symptom symptom symptom symptom. The symptom symptom

estrogen for six to eight years accelerates bone mass loss (Whitney et al., 2002). Decrease in estrogen is related to

*p < 0.05, **p < 0.01, *** p < 0.001 compared to Sham group; **** p < 0.01 compared to OVX group; ****p < 0.01 compared to OVX group; *****p < 0.01 compared to OVX group; supplementation [17]. In this study, the OVX group did not show any significant Supportion and the first in this study, the OVA group and not show any significant changes in bone strength when Mg (0.1% of diet) was supplied only from MgO. However, when the same amount (0.1%) of Mg was provided in the form of seaweed Ca extract, the OVX rats showed improved femur strength indicating that supplying Mg as a food extract has pronounced effects on bone mineralization compared to supplying Mg In 1994, Strause and colleagues examined the effects of Ca supplementation alone, microminerals only (copper, manganese, and zinc), or both Ca and micromineral supplementation on bone status in postmenopausal women. They observed that lumbar bone loss was prevented only when Ca was combined with micromineral supplementation [23]. In addition to high amounts of Ca as a major ingredient and considerable amounts of Ca as a major ingredient amounts of Ca as a ma Mg, seaweed Ca extract also contained other microminerals such as manganese (0.007%) and boron (0.0025%). Manganese (Mn) is an essential mineral in activating glycosyltransferase, the enzyme synthesizing glycosaminoglycan chain of proteoglycan, and Mn deficiency induces a delay in long bone development [24]. In our previous study, Mn Supplementation in the OVX rats increased serum osteocalcin, a sensitive bone formation narker [25]. Boron is also known to enhance bone mineral balance, although the bechanism of action is uncertain. A study in the OVX rats showed that a combination of Son and estrogen improved the intestinal absorption of calcium, phosphorus, and Agnesium, and supplementation of boron increased bone mass in spongy bones [26, 27]. estestant, and supprementation of our more able to the times in sponse to the second s r a boron-deficient diet produced positive results in bone metabolism and in maintaining ium homeostasis. Therefore, additional investigation is warranted if a certain bination of other microminerals residing in seaweed Ca extract contributes to improved this study, we could observe significantly improved bone mineralization and th in femoral bone by use of the seaweed Ca extract diet. Also the mentation of Mg in the form of seaweed Ca extract showed more pronounced on bone metabolism compared to the supplementation of inorganic Mg (MgO) 1 not affect calcium balance. However, a caution is necessary before we a direct relationship between Mg in seaweed Ca extract and bone strength is seaweed Ca extract contains other microminerals which may play an l role in bone metabolism. Further investigation is required to understand amounts of Mg, provided in different forms (a food extract or inorganic I amounts of this, provided in anterent forms (a root contact of more sums) and affect bone metabolism differently and how these in vivo findings might

MAGNESIUM SUPPLEMENTATION THROUGH SEAWEED CALCIUM EXTRACT RATHER THAN **SYNTHETIC** MAGNESIUM OXIDE **IMPROVES FEMUR BONE MINERAL** DENSITY AND STRENGTH IN **OVARIECTOMIZED** RATS

Bae YJ, Bu SY, Kim JY, Yeon JY, Sohn EW, Jang KH, Lee JC, Kim MH Publication: Biol Trace Elem Res. 2011;144(1-3):992-1002.

Abstract:

Commercially available seaweed calcium extract can supply high amounts of calcium as well as significant amounts of magnesium and other microminerals. The purpose of this study was to investigate the degree to which the high levels of magnesium in seaweed calcium extract affects the calcium balance and the bone status in ovariectomized rats in comparison to rats supplemented with calcium carbonate and magnesium oxide. A total of 40 Sprague-Dawley female rats (7 weeks) were divided into four groups and bred for 12 weeks: sham-operated group (Sham), ovariectomized group (OVX), ovariectomized with inorganic calcium and magnesium supplementation group (OVX-Mg), and ovariectomized with seaweed calcium and magnesium supplementation group (OVX-SCa). All experimental diets contained 0.5% calcium. The magnesium content in the experimental diet was 0.05% of the diet in the Sham and OVX groups and 0.1% of the diet in the OVX-Mg and OVX-SCa groups. In the calcium balance study, the OVX-Mg and OVX-SCa groups were not significantly different in calcium absorption compared to the OVX group. However, the femoral bone mineral density and strength of the OVX-SCa group were higher than those of the OVX-Mg and OVX groups. Seaweed calcium with magnesium

supplementation or magnesium supplementation alone did not affect the serum ALP and CTx levels in ovariectomized rats. In summary, consumption of seaweed calcium extract or inorganic calcium carbonate with magnesium oxide demonstrated the same degree of intestinal calcium absorption, but only the consumption of seaweed calcium extract resulted in increased femoral bone mineral density and strength in ovariectomized rats. Our results suggest that seaweed calcium extract is an effective calcium and magnesium source for improving bone health compared to synthetic calcium and magnesium supplementation.

Conclusion:

In this study, scientists have sought to compare the bioactivity of marine-derived versus rock-based calcium/magnesium supplements in a model of postmenopausal osteoporosis. At a same dosage level, the marine-derived multimolecular LithoLexal® provided superior bone-protection efficacy that led to higher femoral bone area, mineral content and strength compared with inorganic supplements. Producing superior denotes that LithoLexal® has a higher target-tissue availability which underlies its LithoLexal[®] had higher urine magnesium excretion reflecting the higher bioavailability of organic magnesium in LithoLexal[®] relative to inorganic forms in generic supplements.

Biol Trace Elem Res (2011) 144:992-1002 DOI 10.1007/s12011-011-9073-2

Magnesium Supplementation through Seaweed Calcium Extract Rather than Synthetic Magnesium Oxide Improves Femur Bone Mineral Density and Strength in Ovariectomized Rats

Yun Jung Bae - So Young Bu - Jae Young Kim -Jee-Young Yeon - Eun-Wha Sohn - Ki-Hyo Jang Jae-Cheol Lee - Mi-Hyun Kim

Received: 9 March 2011 / Accepted: 4 May 2011 / Published online: 17 May 2011 © Springer Science+Business Media, LLC 2011

Abstract Commercially available seaweed calcium extract can supply high amounts of calcium as well as significant amounts of magnesium and other microminerals. The purpose of this study was to investigate the degree to which the high levels of magnesium in seaweed calcium extrat affects the calcium balance and the bone stutis in ovariectomized rats in comparison to rats supplemented with calcium carbonate and magnesium oxide. A total of 40 Sprague-Dawley femde rats (f) weeks) were divided into four groups and bred for 12 weeks: sham-operated group (Sham), ovariectomized group (OVX-SQ), and ovariectomized with seaweed calcium and magnesium supplementation group (OVX-SQ). All experimental dist scontained 0.5% calcium. The magnesiam content in the experimental dist was 0.05% of the diet in the Sham and OVX groups and 0.1% of the diet in the OVX-Mg and OVX-SCa groups. In the calcium absorption compared to the OVX group Awover, the formolatione mineral density and strength of the OVX-Mg and OVX-SCa groups were not significantly different in calcium absorption compared to the OVX group shower, the formolation and menine and strength of the OVX-Mg and OVX-SCa groups were not significantly different in aclium absorption compared to the OVX group. Source, the formolation and strength of the OVX-SCa groups were not significantly different in the OVX-SCa groups and the strength of the OVX-Mg and OVX-SCa groups.

Y. J. Bae Department of Food and Nutritional Sciences, Hanbuk University, Dongducheon 483-120, South Korea

S. Y. Bu Division of Food Science, Kyungil University, Gyeongsan 712-701, South Korea

J. Y. Kim Research Center for Biophamaceutical Lead Molecule, Bucheon 420-743, South Korea

J.-Y. Yeon Department of Food and Nutrition, Sookmyung Women's University, Seoul 140-742, South Korea

E.-W. Sohn Department of Herbal Medicine Resource, Kangwon National University, Samcheok 245-711, South Kores

K.-H. Jang · J.-C. Lee · M.-H. Kim (25) Department of Food and Nutrition, Kangwon National University, Samcheok 245-711, South Korea

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as previously described (1,3). For PTH and CTX, serum samto assess sums in plasma volume in response to exercise, is of variation (CV) are as previously described (1,5). For First and (1,7), south same ples were stored at -80° C for subsequent batch analysis. CTX (Nordic Bioscience Diagnostics, Herlev, Denmark) was measured by ELISA. Intra- and interassay CV were 2.7%-10.3% and 2.5%-9.2%, respectively, for CTX. Intact PTH was measured by a two-site chemiluminescent enzyme-labeled immunometric assay on an Immulite 1000 analyzer (Siemens, Tarrytown, NY); intra- and inter-assay CV were 2.9%-3.5% and 4.8%-6.8%, respectively.

Statistical methods. The primary outcome was the change in PTH from immediately before to immediately after exercise; changes in iCa and CTX were secondary outcomes. Because these experiments were considered pilot studies to inform future research on whether Ca supplementation before exercise influences skeletal adaptations to exercise training,

Α



Ca

-0.4

Time, min Serum ionized Ca (iCa) before, during, and after exercise Plac ontrol and Ca supplementation conditions and the change ately before to immediately after exercise (right). Arrows imption of placebo or Ca-enriched beverage. The top Apperiment 1 and the bottom panel for Experiment 2. Aperiment 1 and the bottom panel for Experiment 2. shange, $*P \le 0.05$, $**P \le 0.001$; between-group differ-

LEMENTATION, PTH, AND EXERCISE



FIGURE 2—Serum PTH before, during, and after exercise (left) under Control and Ca supplementation conditions and the change from imcontrol and Ca supplementation conditions and the change from im-mediately before to immediately after exercise (right). Arrows indicate mediately before to immediately after exercise (right). Arrows indicate consumption of placebo or Ca-enriched beverage. The top Panel is for Experiment 1 and the bottom neural is for Experiment 2. Within group consumption of placebo or Ca-enriched beverage. The top panel is for Experiment 1 and the bottom panel is for Experiment 2. Within-group change *D < 0.05, **D < 0.001. Reference difference *D < 0.05. Experiment 1 and the bottom panel is for Experiment 2. Within-group change, *P < 0.05, **P < 0.001; Between-group difference, $\ddagger P < 0.05$.

NPPLIED

SCIENCES

the primary tests of interest were the within-condition changes in the outcomes. However, we also evaluated whether the changes in outcomes from before to after exercise were different under control versus Ca conditions. Both types of comparisons were based on a paired *t*-test. Because changes in CTX in response to acute exercise have been found to peak 30 min after exercise (6), the change in CTX was evaluated from before to 30 min after exercise. To avoid the probability of type I and type II errors for the comparisons of secondary outcomes, we relied on the consistency across measures rather than adjusting for multiple comparisons. Unless otherwise stated, data are reported as mean \pm SD or mean with 95% confidence interval (CI). All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary NC).

RESULTS

EXP 1. Participants were age 61 ± 4 yr (body mass index = **EAF** 1. Failucipains were age of ± 4 yr (body mass muck) 27.2 ± 4.4 kg·m⁻², $\dot{VO}_{2peak} = 24.5 \pm 3.6$ mL·min⁻¹·kg⁻¹, $\lim_{t \to \infty} \frac{1}{2} + \frac{1}$ 1.07, and 250H vitamin D level = 36.6 ± 14.7 ng·mL⁻¹). The effects of preexercise Ca dosing on serum iCa, PTH, and CTX from -60 min to immediately before exercise were included in Figures 1a, 2a, and 3a for descriptive pur-

poses only. Statistical analyses focused on changes from ight © 2014 by the American College of Sports Medicine. Unauthorized reproduction of this article is prohibited. Medicine & Science in Sports & Exercise 2009

CALCIUM SUPPLEMENTATION AND PARATHYROID HORMONE RESPONSE **TO VIGOROUS** WALKING IN POSTMENOPAUSAL WOMEN

Shea KL1, Barry DW, Sherk VD, Hansen KC, Wolfe P, Kohrt WM Publication: Med Sci Sports Exerc. 2014;46(10):2007-13.

Abstract:

Introduction: Disruptions in calcium (Ca) homeostasis during exercise may influence skeletal adaptations to exercise training. In young men, vigorous cycling causes increases in parathyroid hormone (PTH) and bone resorption (C-terminal telopeptides of type I collagen [CTX]); responses are attenuated by Ca supplementation. The study aimed to determine whether vigorous walking causes similar increases in PTH and CTX in older women and how the timing of Ca supplementation before and during exercise influences these responses.

Methods: In experiment 1, 10 women ($61 \pm 4 \text{ yr}$) consumed 125 mL of either a Ca-fortified (1 g·L) or control beverage every 15 min during exercise starting 60 min before and continuing during 60 min of exercise. In experiment 2, 23 women (61 ± 4 yr) consumed 200 mL of a Ca-fortified (1 g·L) or control beverage every 15 min starting 15 min before and continuing during 60 min of exercise. The exercise was treadmill walking at 75%-80% V[·]O2peak.

Results: In experiment 1, serum ionized Ca decreased in the control condition (P < 0.001), but not with Ca supplementation. PTH increased after exercise on both days (Ca, P = 0.05; control, P = 0.009) but was attenuated by Ca supplementation (8.3 vs 26.1 pg·mL; P = 0.03). CTX increased only

on the control day (P = 0.02). In experiment 2, serum ionized Ca decreased on Ca and control days (Ca and control, P < 0.001), but less so on the Ca day (P = 0.04). PTH (Ca and control, P <0.001) and CTX (Ca, P = 0.02; control P = 0.007) increased on the Ca and control day, and there were no differences in the changes.

Conclusion: The timing of Ca supplementation may be a key mediator of Ca homeostasis during acute exercise. Further research is necessary to determine how this influences skeletal adaptations to training.

Conclusion:

The superior anti-resorptive effect of LithoLexal[®] is partly mediated by its PTH-suppressive activity. This has been substantiated by this acute clinical experiment where administration of LithoLexal[®] to postmenopausal women potently suppressed the increased secretion of PTH and prevented its subsequent rise in bone resorptive activity. A notable point is that LithoLexal[®] has been the most effective when administered 60 minutes before exercise

Calcium Supplementation and Parathyroid Hormone Response to Vigorous Walking in Postmenopausal Women

2007

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o maiched-pair and	38.0 34.0 39.0 42.0	37.0 33.0	·	45.0 32	35.0 22.0	7.
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rinary calcium excretion

In contrast to the relatively unchanged serum calcium ues, treatment with Aquamin F resulted in a significantly ater urinary calcium concentration and total amount of ium excreted than placebo (P = .004, and P = .006, retively) (Table 1). In contrast, the urinary calcium conation and total calcium excretion amounts during the Im carbonate treatment were not significantly different blacebo (P = .36 and P = .95, respectively) (Table 1).

ain effect of treatment across all timepoints from 60 nin was significant (P = .04) and treatment by time on approached statistical significance (P = .055). matched-pair comparisons at each timepoint re-

PERCENT CHANGE IN SERUM PTH

vealed significant group differences at 90, 120, and 2 between Aquamin treatment and placebo and at between calcium treatment and placebo. Table 2 sho effect of treatment on serum PTH concentration and ure 1 shows the percent change in PTH level relati baseline (time 0) to observe the relative changes in centration. Relative to time 0, the serum PTH concentration for all treatments decreased during the first 60 min a dosing. At 90 min, immediately before consumption of meal, the serum PTH concentration for the placebo treatm increased back to baseline levels and then decreased w further sampling before returning to baseline levels again 360 min. In contrast to the changes in serum PTH seen wi placebo, the serum PTH concentration after the Aquamin treatment continued to decrease after 60 min and remained significantly lower than the PTH concentration for placebo at 90, 120, and 240 min (P = .003, .017, and .030, respectively). The serum PTH concentration after the calcium carbonate treatment was intermediate between the Aquamin F and the placebo treatment responses, being significantly decreased at

PLACEBO

FIG. 1. Percent change in serum PTH levels over time. *Compared with placebo, the decrease in PTH concentration following Aquamin FTM treatment was significant at 90, 120, and 240 min (P = .003, P = .017, and P = .030, respectively) while calcium carbonate treatment was significantly different from placebo treatment only at 90 min (P=.026). Arrows indicate the timing of meals. PTH, parathyroid hormone. Color images available online at www.liebertpub.com/jmf

EFFECT OF CALCIUM DERIVED FROM LITHOTHAMNION SP. ON MARKERS OF CALCIUM METABOLISM IN PREMENOPAUSAL WOMEN

Zenk JL, Frestedt JL, Kuskowski MA Publication: J Med Food. 2018;21(2):154-8.

Abstract:

A double-blind crossover pilot trial tested the hypothesis that botanically derived calcium could demonstrate greater influence over calcium metabolism markers compared with a nonplant-derived calcium carbonate supplement or placebo. Twelve fasting female subjects received a single oral dose of Aquamin F™ (derived from the marine algal Lithothamnion sp.), or calcium carbonate, or placebo. Blood and urine samples were collected at baseline and over 12h to evaluate ionized and total calcium and parathyroid hormone (PTH). Subjects treated with Aquamin F demonstrated significantly greater urinary clearance of calcium after 12h compared with placebo (P=.004). Following a meal at 90 min, subjects treated with Aquamin F demonstrated a more prolonged suppression of serum PTH concentration (significantly lower than placebo at 90, 120, and 240 min). Calcium carbonate provided an intermediate response; urinary clearance was not significantly different from placebo treatment and PTH was only significantly lower than placebo at 90 min. Aquamin F may demonstrate greater influence over these markers of calcium metabolism than calcium carbonate or placebo, as suggested by a greater calciuric response and a more prolonged suppression of serum PTH concentrations following a meal in premenopausal women.

Conclusion:

This was a head-to-head double-blind trial that directly compared the pharmacokinetics and clinical effects of LithoLexal® with calcium carbonate. Controlled observations confirmed that LithoLexal® exhibits a more potent and sustained PTH-suppressing efficacy which indirectly means having superior osteoclast-inhibitory bioactivity compared to the generic form of calcium. This stemmed from the higher bioavailability and systemic exposure of calcium from LithoLexal® than calcium carbonate presented by its more prominent urinary excretion rate. This study supports LithoLexal[®] as a superior osteoporosis mineral supplement from both efficacy and bioavailability aspects.

FULL COMMUNICATION

Effect of Calcium Derived from Lithothamnion sp. on Markers

John L. Zenk^{1,*} Joy L. Frestedt² and Michael A. Kuskowski³

v and menopauso		129 -	61	· · ·	IVI	U(n = 100)	
Years since menonau		48.2 4	1.5 01	.3 ± 6.4		100)	P
Height, m		10.2 ± 5	5.0 ¹³ .	1 ± 1.5	60	1.4 ± 6.3	
Weight, kg		12 1	49.4	± 4.8	13.	1 ± 1.5	0.53
Waist circumferor		10.1 ± 8.	1	15	47.8	3 ± 5.6	0.45
BMI, kg/m ²		^{1.6} ± 0.1	12.0	± 7.2		19	0.06
Family Osteon-		09.6 ± 11.8	3 ^{1.61}	± 0.1	12.6	±75	0.20
Previous horm		86.7 ± 11.3	72.3 ±	13.5	1.61	+ 0 1	0.67
Alcohol use of replacement the		26.8 ± 4.3	89.5 <u>+</u>	13.6	70.2 +	- 0.1 + 12.0	0.84
Smoking w	se, %	24	28.0 <u>+</u>	52	87.7 +	- 12.9 - 12.0	0.31
Never a		39	17		27.3 +	12.3	0.28
Past on d		65	39		26	4.8	0.25
Curront			55		20		0.20
Escore		67			20 70		0.20 0.17
		28	63		/3		0.17
Europar vertebrae 1–4		5	29		0.		0.03
			20		67		0.78
Doil	-	0.8 + 12	3		30		
Daily total calcium intaka s	-(- 1.2).8 + n n	-01-		9		
Dally vitamin D intake from FFQ, g	0	1 + 10	-07		o -		
Daily fiber intake from FFQ, μg	0.	9 ± 0.0	0.7 ± 1.0		0.7 ± 1.1		
Estimated osteopenia	4 0	0 - U.4	0.2 ± 1.2	-0	1.7 ± 0.9	0.1	1
Physical activity Mrt	17.2	' — Z.6	0.9 ± 0.4	0.	1 ± 1.1	0.58	9
Urine DPD, nmol/m	2	- 5.7	4.6 ± 2.8	0.9	9 ± 0.4	0.51	
Urine CTX, ma/ma	10	13	18.8 ± 6.4	5.1	± 2.8	0.68	
Serum CTX, ug/	1.9 -	± 0.3	54	18.2	± 5.9	0.24	
Serum osteocol	0.2 ±	2.5	1.8 ± 0.3	5	7	0.17	
Serum vitamin p	0.3 ±	0.1	8.2 ± 2.4	1.9 -	- N 3	0.42	
Insufficient (< 50	U.6 ±	0.2	0.3 ± 0.1	7.9 +	2.0	0.04	
Serum total of the mol/L) vitamin D	20.6 ± 7	7.8	0.6 ± 0.2	0.3 +	2.U N 2	0.56	
asma PTL	56.2 ± 1	9.6	18.9 ± 6.7	0.6 +	0.Z] ว	0.16	
ml ml	40.2 ± 6.0	ŋ 5	5.8 ± 17.7	19.6 + 0	J.Z	0.32	
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cemon and ANOVA PTH, parathurs of ty	pe L colle	m; CaFOS	- 10.0	631		0.04 N 97	
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maltodextrin group. After controlling for baseline interactions

between BMD and treatment group, this effect was apparent only in those with a higher total-body BMD at baseline (P =.03) (Table 2). The change in spinal BMD was significantly naller in the CaFOS group compared with Ca (P = 0.02) and altodextrin (P = 0.03) after 24-mo intervention. After attrolling for baseline interactions between BMD and treatnt group, this effect was apparent only for those with mean line spinal BMD but not at the lower or higher values. hermore, there was a greater decline in urine CTX in the roup compared with the maltodextrin group after 12- and o supplementation (P = 0.04 and P = 0.04, respectively).

andomized, controlled study of postmenopausal women, entation with Ca or CaFOS did not significantly alter of bone loss at any site based on intention-to-treat compared with the maltodextrin-supplemented group no intervention. Nevertheless, those supplemented with //academic.oup.com/jn/article-abstract/144/3/297/4637676

CaFOS had significantly less decline in total-body BMD at 24 mo compared with the Ca group, which is the appropriate control for testing an scFOS intervention. Secondary analysis of BTMs revealed a greater reduction in markers of bone resorption and formation in the Ca group compared with the maltodextrin group at 12 mo; effects that suggest enhanced Ca absorption and a resultant reduction in bone turnover in the first year. Furthermore, a greater reduction in the marker of bone resorption CTX in the CaFOS group compared with the maltodextrin group at 12 mo, together with a greater reduction in the bone formation marker osteocalcin at 24 mo compared with the maltodextrin group, would suggest that less bone turnover is occurring and a more positive Ca balance is evident in the CaFOS treatment group and that it is maintained longer than with Ca supplementation alone. Osteocalcin is the only BTM to be significantly lower in the CaFOS group compared with the maltodextrin group at 24 mo. It may be the case that formation is reduced as the resorption markers are reaching a state of homeostasis in the presence of Ca balance; however, this interpretation is speculative and requires additional investigation. Calcium, fructo-oligosaccharides, and bone health 301

(P = 0.03) BMD compared with the maltodextrin SUPPLEMENTATION group, although this effect was restricted to those with higher total-body and mean spinal BMD WITH CALCIUM at baseline, respectively. Although the change in BMD observed did not differ between the AND SHORT-CHAIN groups, the greater decline in BTMs in the Ca and CaFOS groups compared with the maltodextrin FRUCTOgroup suggests a more favorable bone health **OLIGOSACCHARIDES** profile after supplementation with Ca and CaFOS. Supplementation with CaFOS slowed the rate of total-body and spinal bone loss in postmenopausal AFFECTS MARKERS women with osteopenia-an effect that warrants additional investigation. OF BONE TURNOVER BUT NOT BONE Conclusion: This randomised controlled trial has MINERAL DENSITY IN provided evidence that the therapeutic POSTMENOPAUSAL profile of LithoLexal[®] can be enhanced by coadministration of a type of prebiotic, short-chain fructo-oligosaccharide (scFOS), WOMEN in postmenopausal women. Data shows that

Slevin MM, Allsopp PJ, Magee PJ, Bonham MP, Naughton VR, Strain JJ, Duffy ME, Wallace JM, Mc Sorley EM Publication: J Nutr. 2014;144(3):297-304.

Abstract:

This 24-mo randomized, double-blind, controlled trial aimed to examine whether supplementation with a natural marine-derived multi-mineral supplement rich in calcium (Ca) taken alone and in conjunction with short-chain fructo-oligosaccharide (scFOSs) has a beneficial effect on bone mineral density (BMD) and bone turnover markers (BTMs) in postmenopausal women. A total of 300 non-osteoporotic postmenopausal women were randomly assigned to daily supplements of 800 mg of Ca, 800 mg of Ca with 3.6 g of scFOS (CaFOS), or 9 g of maltodextrin. BMD was measured before and after intervention along with BTMs, which were also measured at 12 mo. Intention-to-treat ANCOVA identified that the change in BMD in the Ca and CaFOS groups did not differ from that in the maltodextrin group. Secondary analysis of changes to BTMs over time identified a greater decline in osteocalcin and C-telopeptide of type I collagen (CTX) in the Ca group compared with the maltodextrin group at 12 mo. A greater decline in CTX was observed at 12 mo and a greater decline in osteocalcin was observed at 24 mo in the CaFOS group compared with the maltodextrin group. In exploratory subanalyses of each treatment group against the maltodextrin group, women classified with osteopenia and taking CaFOS had a smaller decline in total-body (P = 0.03) and spinal

scFOS intensifies the preventive effect of LithoLexal® on the declining trend of bone mineral density after menopause. In addition, LithoLexal[®] with and without prebiotics significantly decreased serum and urinary women unveiled that individuals with higher baseline bone density had better final outcomes showing that early commencement of treatment improves efficacy.

entation with Calcium and Short-Chain Fructo-Oligosaccharides Affects Markers of one Turnover but Not Bone Mineral Density in

Mary M. Slevin, Philip J. Allsopp, Pamela J. Magee, Maxine P. B. Marsa F. Duffy, Julie M. Wallace, and Emeir M. Mc Sorley*

The Journal of Nutrition Nutrition and Disease

COMPARISON OF THE EFFECTS OF LITHOLEXAL® AND **GENERIC MINERAL** SUPPLEMENTS ON **KEY BIOMARKERS** OF BONE TURNOVER - A DOUBLE-BLIND, ACTIVE-CONTROLLED PILOT TRIAL IN POSTMENOPAUSAL WOMEN

Shandon OP Under submission

Abstract:

Osteoporosis is a clinically-silent disease that affects more than 30% of postmenopausal women worldwide. Add-on treatment with a bioavailable mineral supplement is often necessary for prevention and treatment of osteopenic/ osteoporotic patients since high-risk individuals commonly fail to supply their needs from dietary sources. However, the bioavailability and bioactivity of different forms of minerals are not equal and depend on their composition, microscopic structure and pharmaceutical formulation. In this double-blind, controlled, clinical trial, we compared the effects of LithoLexal®, a multi-mineral complex with a lattice structure derived from Lithothamnion corallioides, on key biomarkers of bone turnover. Sixty consented post-menopausal women were randomised to receive either placebo or 600 mg (200 mg TID)

of LithoLexal®, calcium carbonate (CaCO_z) or tricalcium phosphate (TCP) for three months. Before and after the intervention, plasma levels of parathyroid hormone (PTH), osteocalcin, and bone alkaline phosphatase (BAP) plus urinary levels of deoxypyridinoline (DPD adjusted for creatinine) were measured. Plasma PTH was significantly suppressed by LithoLexal® therapy compared with the placebo. The mean PTH-reducing effect of LithoLexal® was more potent than both CaCO, and TCP. Urinary DPD excretion rate, a specific marker of bone resorption and osteoclastic activity, was reduced by LithoLexal® by more than 21%, while it did not change or increased in other groups. Plasma osteocalcin, a marker of bone formation, was declined in both CaCO, and TCP groups while slightly increased by LithoLexal® therapy. None of the interventions induced a significant alteration in plasma concentration of BAP. Our findings indicate that LithoLexal[®], provides higher bone protective and turnover suppressive efficacy compared to ${\rm CaCO}_{\scriptscriptstyle \rm z}$ and TCP in post-menopausal women as evaluated by key biomarkers.

Conclusion:

In this clinical study with both placebo and active control, the impact of treatment with LithoLexal[®] on bone turnover was postmenopausal women. One of the most notable observations in this study is the significant effect of LithoLexal® on the circulating level of PTH, which was more than 3 times stronger than the effect of TCP and 2 times more potent than CaCO₂. Knowing that PTH accelerates bone remodelling and reduces bone density, this effect means that LithoLexal[®] can provide more effective bone protection than the commonly-used TCP and CaCO, The significantly lower levels of the bone resorption biomarker, DPD, is another indication confirming that LithoLexal®

Notes



Notes





Nordic Medical is founded on a philosophy dedicated to scientific research and clinical documentation.

Addressing **'Healthy Ageing'** by utilising a clinical approach is the basis of the last 15 years of research and development of our unique brands.

This has resulted in the discovery of **breakthrough** natural ingredients, formulations and technologies - utilised worldwide.

Our products are researched, developed and produced under pharmaceutical protocol and marketed in the form of:

- OTC/OTX pharmaceuticals
 OTC/OTX/Rx cosmeceuticals
 OTC/OTX/Rx medical devices
 OTC/OTX/Rx nutraceuticals