DIFFERENCES IN NUTRITIONAL INTAKE AND BONE HEALTH AMONG ADULTS WITH AND WITHOUT CELIAC DISEASE: DATA FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2009-2014

by

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of
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A Thesis submitted in partial fulfillment of the requirements for the degree of Nutrition and Food Studies, Master of Science at George Mason University

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DEDICATION

I dedicate this thesis to my parents for their support as I decided to pursue my master's degree, and to my fiancé, Troy. Thank you for your love and encouragement.

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I would like to thank my committee members for their guidance and support as I developed and executed this project, as well as their unique perspectives throughout: Dr. Slavin for challenging me to think deeper and more critically about my analysis and results; Dr. Gallo for her contributions and expertise on bone health; and Dr. Frankenfeld for providing invaluable instruction on statistical analysis and Stata software. I would also like to thank NHANES and WWEIA staff and participants for making this study possible.

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LIST OF ABBREVIATIONS

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D
25(OH)D, 25-hydroxyvitamin D
25(OH)D2, 25-hydroxyvitamin D2
25(OH)D3, 25-hydroxyvitamin D3
AGA, American Gastrointestinal Association
AMPM, Automated Multiple-Pass Method
BMC, Bone Mineral Content
BMD, Bone Mineral Density
BMI, Body Mass Index
CAPI, Computer-Assisted Personal Interview Software
CD, Celiac Disease
CDC, Centers for Disease Control and Prevention
CI, Confidence Interval
DGA, Dietary Guidelines for Americans
DXA, Dual-Energy X-ray Absorptiometry
DRI, Dietary Reference Intake
EAR, Estimated Average Requirement
EMA, Endomysial Antibody Assay
FGF-23, Fibroblast Growth Factor-23
GFD, Gluten-Free Diet
IgA, Immunoglobulin A
IgA anti-tTG, Immunoglobulin A Anti- Tissue Transglutaminase Antibody
IQR, Interquartile Range
IOM, Institute of Medicine
ISE, Ion Selective Electrode
MEC, Mobile Examination Center
NHANES, National Health and Nutrition Examination Survey
NIH, National Institute of Health
QA/QC, Quality Assurance and Quality Control Protocols
RDA, Recommended Dietary Allowance
SD, Standard Deviation
TRP, Transient Receptor Potential
tTG, Tissue Transglutaminase
UHPLC-MS/MS, Ultra-High Performance Liquid Chromatography-Tandem Mass Spectrometry
USDA, United States Department of Agriculture

ABSTRACT

DIFFERENCES IN NUTRITIONAL INTAKE AND BONE HEALTH AMONG ADULTS WITH AND WITHOUT CELIAC DISEASE: DATA FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2009-2014

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Background: Celiac disease is a gastrointestinal malabsorptive disorder characterized by intestinal villous atrophy and triggered by an autoimmune response to gluten, leading to malnutrition and secondary conditions including osteoporosis. There is still a scarcity of information on the nutritional intake of adults with celiac disease as it relates to their bone health.

Objective: To evaluate differences in nutritional intake of calcium, vitamin D, and phosphorus; serologic concentrations of these nutrients; and bone health among adults with and without celiac disease.

Design: Cross-sectional data was retrieved from the National Health and Nutrition Examination Survey (NHANES) cycles 2009-10, 2011-12, and 2013-14. Data including self-reported dietary and supplement intake from 24-hour recalls, serologic nutrient status, and dual x-ray absorptiometry (DXA) scans were collected from 50 serologically

positive (EMA+) adults with celiac disease. The serologically positive (EMA+) participants were an average age of 42 years old (range 18-80 years). Results were compared with those of 15,176 control subjects using multiple linear regression modelling controlled for age, sex, and race/ethnicity.

Results: Adults with celiac disease consumed significantly more total calcium (Ca) (1608 vs. 1152 mg Ca/day, $p = 0.031$) than the control group. They had significantly higher serum phosphorus concentrations (4.0 vs. 3.8 mg/dL, $p = 0.002$) than the controls. In the multiple-adjusted model, positive serologic (EMA+) status predicted a 344.2 kcal (95% CI: 6.6, 681.8) increase in daily caloric intake, -0.1 g/cm^2 (95% CI: -0.2, 0.0) decrease in femur BMD, -0.4 g (95% CI: -0.6, -0.1) decrease in femoral neck BMC, and -0.1 g/cm^2 (95% CI: -0.1, 0.0) decrease in femoral neck BMD.

Conclusion: Despite greater overall calcium intake, adults who tested positive for celiac disease (EMA+) had lower serum calcium concentrations and lower overall bone mass than adults without celiac disease.

CHAPTER 1. LITERATURE REVIEW

Introduction

An estimated 1 in 141 Americans have celiac disease,[1] which causes nutrient malabsorption and a host of symptoms such as abdominal bloating and pain, fatigue, weight loss, failure to thrive, peripheral neuropathy, irritability, depression, and behavioral issues.[2] Celiac disease is also associated with poor bone health, osteopenia, and osteoporosis.[3] The only current treatment option for celiac disease is strict, lifelong adherence to a gluten-free diet, but there is a scarcity of data examining the relationship between dietary intake and bone health in adults with celiac disease. A number of nutrients have been identified for their critical roles in bone health. This review will explore existing literature on the nutrients integral to bone health (calcium, vitamin D, and phosphorus), and the effects of celiac disease on dietary intake, nutrient absorption, and bone health.

Celiac Disease

Celiac disease is a gastrointestinal malabsorptive autoimmune disorder that affects an estimated 1 in 141 people in the United States, most of whom are undiagnosed.[1] As defined by an international, multidisciplinary task force in 2011, "Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy

precipitated by exposure to dietary gluten in genetically predisposed people."[4] Celiac disease is triggered by exposure to gluten, a protein peptide sequence found in wheat (gliadin), barley (hordein), and rye (secalin).[5] When individuals with celiac disease ingest gluten, they experience damage to the mucosal lining of the small intestine, presented by villous atrophying and resulting in nutrient malabsorption and a host of secondary symptoms.[6]

The effects of celiac disease are produced by a T-cell-mediated response to gluten, and several serologic tests screen for celiac disease antibodies.[7] Serologic testing identifies Immunoglobulin A (IgA) antibodies against gliadin, endomysium, and tissue transglutaminase. A systematic review found that the most accurate antibody assays measure anti-tissue-transglutaminase (anti-tTG) antibodies and anti-endomysial antibodies (anti-EMAs).[8] The Tissue Transglutaminase Antibodies (tTG-IgA) test is the most sensitive serological test and is the most commonly used. In order to check for false positives or false negatives, an IgA Endomysial antibody (EMA) may also be assessed. The tTG-IgA has a specificity of 90-95% and a sensitivity of 90-96%. With a 100% specificity, the EMA test is considered the gold standard.[9] An endoscopic biopsy of the duodenum is required to confirm diagnosis.[8] This biopsy looks for atrophy of the small intestinal villi. To add to the diagnostic challenges, individuals must still be consuming gluten in order to test positive. Strict adherence to a gluten-free diet aids in mucosal lining recovery, masking the characteristic inflammation and immune-antibody response, and villi damage key to diagnosing celiac disease.

The only current treatment option for celiac disease is complete avoidance of gluten through a gluten-free diet. Total elimination of gluten is difficult since it is an ingredient in many staples of the American diet and cross contamination from shared food preparation surfaces is a concern.[10] Some individuals never reach full mucosal recovery and continue to experience symptoms on a gluten-free diet.[11] A histologic follow-up of people diagnosed with celiac disease on gluten-free diets found a remission rate of 65% within two years, 85.3% within 5 years, and 89.9% over the long term.[12] 7% of the patients had persisting villous atrophy and resulting malabsorption.

Nutrient deficiencies are highly prevalent among individuals with celiac disease due to the damage to the intestinal mucosal lining present with the disease.[13] In a cohort study of 30 adults with celiac disease, over half had poor vitamin status despite several years of following a gluten-free diet.[14] There are long-term risks for poor vitamin status due to malabsorption among individuals with celiac disease. Individuals with celiac disease are at increased risk for developing comorbidities due to nutrient deficiencies. Although the classical manifestation of celiac disease is gastrointestinal in nature, celiac disease may present with non-gastrointestinal manifestations as well. Non-gastrointestinal symptoms of celiac disease include anemia, gluten-related ataxia, dermatitis herpetiformis, and connective tissue diseases.

The risk of developing nutrient deficiencies and other health conditions increases the longer the disease goes untreated.[12, 14, 15, 13] Celiac disease can go untreated due to lack of diagnosis or due to partial or complete noncompliance to the gluten-free diet. Compliance to the gluten-free diet has been reported to be 36-80% among individuals

diagnosed with celiac disease and the earlier the diagnosis, the more likely the individual is to adhere to the diet.[16] Up to 60% of individuals diagnosed with celiac disease following a gluten-free diet are only partially compliant, whether deliberately or unknowingly.[17] Failure to completely adhere to a gluten-free diet has been linked to increased anxiety and depression[18] and overall lower quality of life.[19, 20]

Impact of Celiac Disease on Bone Health

Individuals with celiac disease may present a range of bone defects and disorders due to inadequate vitamin D, calcium, and phosphorus intake and/or absorption. Conditions like osteopenia and osteoporosis, which affect bone mass, will also negatively affect bone strength, leading to increased susceptibility to fracture. Studies have found that 22-40% of celiac disease patients have osteopenia, and as many as 36% of celiac disease patients in the United States have osteoporosis at the lumbar spine, femoral neck, and/or radius.[21] There is an added risk of osteoporosis among newly diagnosed celiac disease patients and those with refractory celiac disease.[3] Early diagnosis of celiac disease, along with strict adherence to the gluten-free diet and long-term observation, are likely critical for full bone mineral recovery and complete remission from celiac disease. Maximum bone mass is developed by the time an individual reaches 25 years of age.[22] individuals diagnosed later in life may ultimately reach a lower peak bone mass due to failure to deposit sufficient bone mass within this critical window.

Patients with symptomatic celiac disease, marked by classic intestinal malabsorption, may have low BMD due to malabsorption of calcium and vitamin D.[23] Poor bone health in celiac disease patients may also be present even in the absence of

gastrointestinal manifestations.[24, 25] In patients with asymptomatic celiac disease, the cause of bone structure deterioration is less understood. One study found that the bone derangement is the first symptom to be identified in otherwise asymptomatic patients, and symptomatic patients had significantly more deterioration of the bone structure than asymptomatic patients.[26] However, other studies found no association between BMD and presence or severity of symptoms in celiac disease patients.[27, 28]

Current guidelines by the American Gastrointestinal Association (AGA) and the National Institute of Health (NIH) recommend assessing bone mineral density (BMD) in celiac disease patients at diagnosis and as routine follow-up.[29, 30] The AGA recommends testing newly diagnosed celiac disease patients for micronutrient deficiencies, and has identified vitamin D as a necessary consideration due to its role in bone health.[31] There are no current guidelines for assessing serum calcium and phosphorus concentrations in celiac disease. Both guidelines are vague regarding frequency of follow-up assessment, highlighting the need for studies which provide support for this.

Bone Metabolism

Bones are dynamic organs continuously undergoing growth, modeling, and lifelong remodeling in order to repair damage, adapt to new loads, and regulate extracellular calcium concentrations. Bone mass formation is rapid in the fetus and infant and slows down until adolescence, when individuals experience a growth spurt.[32] Most of an individual's bone mass is formed by the age of 18, though this continues to develop until the mid-20's.[33] Bones grow at growth plates in long bones and proliferate the epiphyseal and metaphyseal, followed by mineralization and new bone formation.

Physiologic influences and mechanical forces cause the bone to undergo modeling, or reshaping. During this process, bone is removed or added with the support of osteoblasts and osteoclasts. This ensures appropriate bone mass and shape is attained during growth.[34] According to Wolff's law, long bones change shape and become stronger to adapt to increased physiological demand.[35]

Bone microdamage is repaired through remodeling, a lifelong process that is critical for maintaining strength and mineral homeostasis. There are four stages of remodeling: activation, resorption, reversal, and formation.[36] During activation, the bone endosteum is removed and multinucleated preosteoclasts form and bind to the bone matrix. Osteoclasts lower the pH of each bone matrix compartment in order to mobilize bone mineral. Old bone is removed over the following 2-4 weeks through osteoclastic resorption.[37] Osteoclasts dissolve the mineral matrix and decompose the osteoid matrix, and irregular cavities called Howship's lacunae appear on the trabecular bone surface. The reversal phase follows bone resorption and marks the transition to bone formation. During bone formation, osteoblasts release calcium and phosphate-containing cells to synthesize osteoid matrix and cells while osteoclasts resorb bone cavity and detach from the bone surface. Osteoblasts synthesize osteoid matrix and bone.

Bone health can be assessed by using technology like dual-energy x-ray absorptiometry (DXA) to measure bone mass. This method takes low-dose x-ray scans of the whole body or regional sites like the spine, femur, hip, or forearm. Bone mineral content (BMC) and density (BMD) refer to the amount of bone mineral in bone tissue. Bone mass is responsible for 50-70% of bone strength, along with geometry, material

properties, and microstructure.[38] Development of bone mass is closely linked to dietary intake and serum nutrient levels of a number of nutrients. When serum concentrations of calcium and phosphorus are low, bone modeling increases and calcium and phosphorus stores are sustained through osteoclastic resorption. Over time, this results in decreased BMD, which will also negatively affect bone strength, and increased susceptibility to fracture, osteopenia, and eventually osteoporosis.[39]

Osteopenia and osteoporosis are diseases characterized by poor BMD. They are assessed using the T-score measurement of BMD, or the number of standard deviations below the mean bone mineral density of a thirty-year-old man or woman. The World Health Organization defines a T-score of -1.0 and -2.5 as the criteria for osteopenia, and a T-score of -2.5 or lower as the criteria for osteoporosis.[40] Osteopenia and osteoporosis are of critical concern among the adult celiac disease population due to intestinal malabsorption of calcium and vitamin D.[41]

Nutrients Integral to Bone Health

Calcium, vitamin D, and phosphorus are all essential nutrients for bone mineral deposition and skeletal integrity. There is synergy among these nutrients, such that inadequate serum concentrations of calcium, vitamin D, or phosphorus, due to either restricted dietary intake or malabsorption, can cause decreased absorption and reduced serum concentrations of one another.[42] Calcium, vitamin D, and phosphorus concentrations are inter-dependent as their concentrations are regulated by the parathyroid hormone (PTH) and Fibroblast Growth Factor-23 (FGF-23) (See **Figure 1**). When serum calcium levels drop, PTH secretion by the parathyroid glands increases.

This decreases urinary calcium excretion, increases urinary excretion of phosphorus, and stimulates bone resorption. Calcium and phosphate are released from skeletal tissue to restore serum calcium concentrations. PTH stimulates the conversion of vitamin D to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in the kidneys, which results in increased calcium and phosphorus absorption by the intestines.

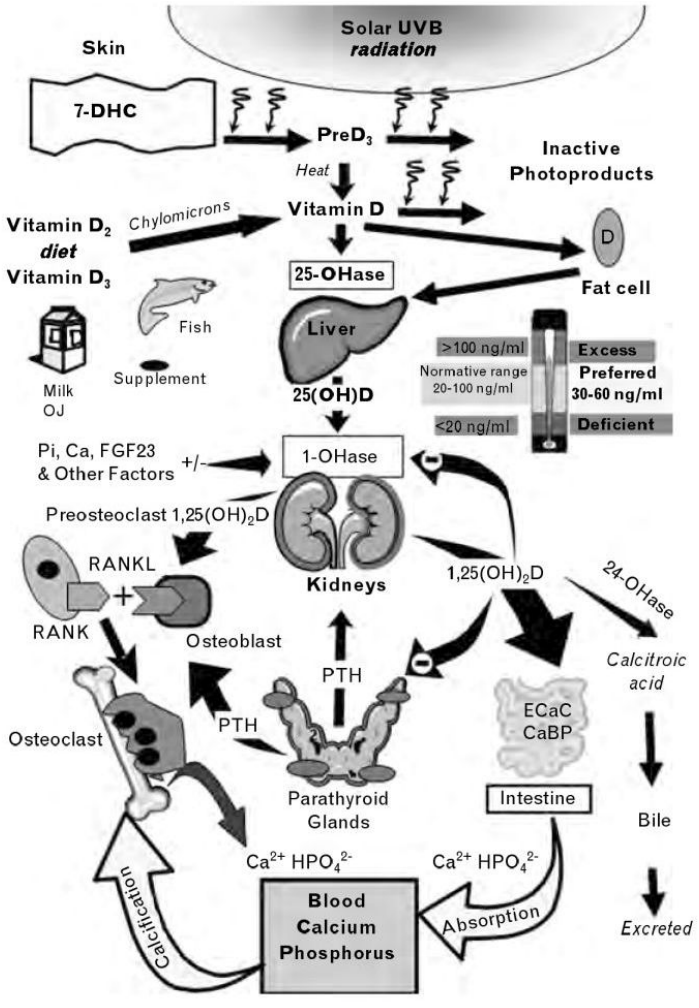

Figure 1. Vitamin D synthesis and metabolism for calcium, phosphorus, and bone metabolism regulation[43]

FGH-23 is critical for phosphorus homeostasis. When phosphorus intake increases, FGF-23 is secreted from osteoblasts and osteocytes, inhibiting 1,25(OH)D production and promoting increased urinary phosphorus excretion. High serum phosphorus levels suppress the conversion of vitamin D to the active form in the kidneys. Increased urinary excretion of phosphorus causes serum calcium levels to rise and stabilize. When vitamin D concentrations fall, calcium absorption is decreased, triggering increased PTH secretion. Serum PTH, which promotes bone resorption and urinary phosphorus excretion, remains elevated and bone mineralization cannot occur.

Due to the critical roles of calcium, vitamin D, and phosphorus in bone mineralization, the consequences of deficiencies in any of these nutrients are dire. Deficiencies are of particular concern for celiac disease patients, who are at increased risk of nutrient malabsorption due to intestinal villous atrophy, leading to bone loss and secondary conditions as a result.

Calcium

Calcium is the primary constituent for bone mineral deposition with approximately 99% of the total body calcium stored in the skeleton.[44] Calcium is present in the skeleton as hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) and is critical for bone and tooth formation by providing their structure and hardness. The remaining 1% of the total body calcium is found in the extracellular fluid, blood, and cellular fluid. It also carries other functions in the body, to include neurotransmitter release and muscle contraction.

The Recommended Daily Allowance (RDA) of calcium is 1,000 mg/d for males ages 19-70 and women ages 19-50.[45] This increases to 1,200 mg/d for males over the age

of 70 and females over the age of 51 due to decreased intestinal absorption of calcium with age.[46] Dairy products are the primary source of calcium in the American diet, with 300 mg calcium in an 8-ounce glass of milk and 400 mg of calcium in an 8-ounce serving of yogurt. Non-meat sources like soybeans, nuts and seeds, broccoli, spinach, chard, rhubarb, and eggshell, contain calcium as well. However, the calcium is not as readily absorbed if the source also contains oxalic or phytic acid, which bind to the calcium in the gastrointestinal tract and inhibit absorption.[47] Additionally, a number of foods are fortified with calcium, to include orange juice and breakfast cereals.

Digestion & Absorption of Calcium

Calcium is absorbed through active and passive transport processes dependent on dietary intake. Active transcellular calcium transport process occurs in the duodenum when calcium intake is low. During active transport, calcium is transported across the enterocyte and into the extracellular fluid and blood. Transient Receptor Potential (TRP) cation channels then allow calcium to enter the intestinal epithelial cells. Passive absorption takes place in the jejunum and ileum. Ionized calcium moves through the tight and intermediate junctions, through the basolateral membrane, to enter the blood. Because there is more time available for passive absorption in the jejunum and ileum, this pathway is preferred when calcium intake is high.

A healthy intestine absorbs approximately 25-35% of the total ingested calcium.[48] Vitamin D mediates active calcium transport across the intestinal mucosa and facilitates absorption through the intestine. It is involved in the synthesis of calbindin, a transport protein that carries calcium across the mucosal cell from the brush border membrane to

the basolateral side. PTH promotes calcium absorption by increasing calcium resorption by the kidneys and by stimulating vitamin D activation. When serum calcium concentrations decrease, PTH production is stimulated to restore the calcium levels.

Dietary calcium is present in several forms of elemental calcium with varying degrees of solubility. Calcium carbonate is a concentrated form of calcium, and has greater bioavailability than calcium citrate. Calcium citrate yields between 22-27% as much elemental calcium as calcium carbonate.[49, 50] In other words, individuals must take a larger dose of a calcium carbonate supplement than a calcium citrate supplement in order to receive a similar amount of elemental calcium.

Calcium Deficiency

The range for serum calcium levels is narrow, 8.5 to 10.5 mg/dL in adults. Because serum calcium only accounts for 1% of the total body calcium, serum calcium concentration is not an ideal diagnostic measure for total body calcium.[51] Despite this, it is useful for the monitoring and surveillance of bone, kidney, parathyroid gland, and gastrointestinal tract disorders.

Calcium homeostasis is vital for the proper functioning of processes dependent on calcium. It is maintained through the intestine, the kidney, and bone by an endocrine network of calcium-regulating hormones including PTH, calcitonin, and 1,25-dihydroxyvitamin D (See **Figure 2**). When serum calcium concentrations decrease, PTH secretion is increased, leading to increased bone resorption, calcium reabsorption, and the conversion of 25-hydroxyvitamin D (25(OH)D) to $1,25(OH)_2D$. This ultimately results in

increased calcium absorption in the gastrointestinal tract. The kidney retains and balances systemic calcium by regulating its excretion into urine.

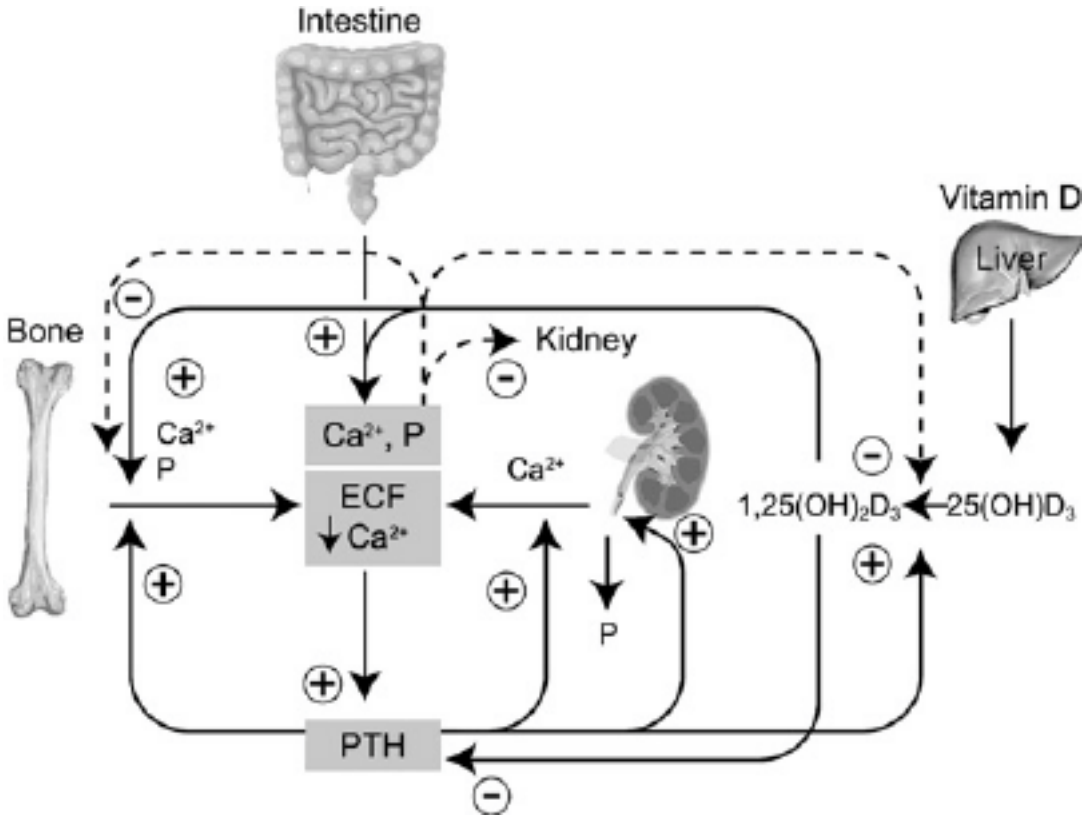

Figure 2. Coordinated regulation of calcium homeostasis[52]

Vitamin D

Vitamin D is a fat-soluble vitamin that plays a critical role in skeletal growth and bone strength by promoting calcium and phosphorus absorption. It is also essential for non-endocrine roles including cell differentiation and immune functions. There are two major forms of vitamin D: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3).

Ergocalciferol is created when plant-derived materials are exposed to ultraviolet light. Cholecalciferol is produced by humans and animals in response to sunlight and is available through some dietary sources like fish. Both are thought to have the same biological activity[53] and travel to the kidneys and liver to form $1,25(OH)_2D$.

The RDA for vitamin D for adult ages 19-70 years is 15 μg/d.[45] Vitamin D needs increase to 20 μg/d in adults over the age of 70 due to decreased absorption and decreased ability of the skin to produce vitamin D3 with age.[54] The best sources of dietary vitamin D are of animal origin, like liver, beef, veal, egg yolk, dairy products, herring, salmon, and tuna. Americans also consume additional dietary vitamin D from vitamin D-fortified foods, which include cereal, milk, grain products, and juices.[55] Americans do not typically consume enough foods that are naturally high in vitamin D alone, so fortification is necessary in order for Americans to achieve the RDA.[56]

Digestion & Absorption of Vitamin D

Dietary vitamin D does not require digestion and is absorbed from micelle with the help of fat and bile salts by passive diffusion. Most vitamin D is absorbed in the jejunum and ileum of the small intestine. Once absorbed, it is packaged into chylomicron to be transported into the lymphatic system and blood. Endogenously produced vitamin D is metabolized to $25(OH)D_3$ (calcidiol) in the liver and secreted into the blood. It is converted to $1,25(OH)_2D_3$ (Calcitriol) by the kidneys and then transported in the blood.

25(OH)D has a half-life of 2-3 weeks and includes both vitamin D intake and vitamin D produced endogenously from exposure sunlight. $1,25(OH)_2D_3$ is the biologically active form of vitamin D, and there are less circulating levels of $1,25(OH)_2D$

than 25(OH)D. The half-life of $1,25(OH)_2D$ is shorter than that of 25(OH)D at 4-6 hours and consequently, 25(OH)D best reflects vitamin D status.[57] Additionally, calcitriol signals increased calcium absorption in the intestine. An individual deficient in vitamin D will present decreased intestinal calcium absorption, causing an increased production of PTH in order to regulate calcium homeostasis. As PTH concentrations rise, so do levels of $1,25(OH)_2D$, further rendering $1,25(OH)_2D$ insufficient for assessing vitamin D status.[58]

Vitamin D Deficiency

Vitamin D status is assessed by measuring the total of $25(OH)D_2$ and $25(OH)D_3$ concentrations. Sufficiency and optimal levels of vitamin D are areas of controversy. The Institute of Medicine advises that normal serum 25(OH)D concentrations range two standard deviations (SD) from the average of healthy individuals.[59] These values can vary in individuals depending on where they are geographically situated, but a concentration below 27.5 nmol/L is considered a reference value for vitamin D deficiency. The Endocrine Society clinical practice guidelines recommend that adults over the age of 18 maintain serum 25(OH)D concentrations of at least 30 ng/mL.[57] The normal range for 25(OH)D also varies throughout the year due to variation in sunlight exposure. As sunlight exposure falls during the winter, serum 25(OH)D decreases, serum PTH increases, and bone density decreases.[60] This seasonal variation can be prevented by increasing vitamin D intake through diet and supplementation during the winter.[61]

Deficiency in vitamin D can result in muscle weakness and skeletal mineralization defects like rickets and osteomalacia. Vitamin D deficiency can result

from inadequate intake, inadequate sun exposure, or impaired vitamin D activation. Since vitamin D is a fat soluble vitamin, disorders causing fat malabsorption, like celiac disease, can result in vitamin D deficiency.[58] Even a moderate deficiency in vitamin D can pose increased risk of bone loss, muscle weakness, and fracture.[61] Adults deficient in vitamin D may develop osteomalacia, which is characterized by soft bone and impaired bone mineralization.[62] Healthy individuals with sufficient exposure to sunlight are able to maintain adequate vitamin D concentrations.[63]

Phosphorus

Phosphorus plays a vital role in bone mineralization, skeletal development, energy transfer, cell membrane phospholipid content, and cell signaling. Phosphorus is found throughout the body in the form of phosphate and 85% of body phosphorus can be found in the skeletal tissue.[20] The remaining 15% of the body phosphorus performs non-osseous functions in the body. Phosphate and sugar groups alternate to make up the backbones of DNA and RNA. Phosphorus also plays a role in energy metabolism by forming phosphate bonds like the nucleoside triphosphates adenosine triphosphate (ATP), creatine phosphate, and uridine triphosphate (UTP). Cell membranes contain phospholipids as part of their essential structure. Phosphate also acts as the main intracellular buffer in acid-base balance. Finally, phosphate has an indirect role in oxygen delivery by aiding in 2,3-diphosphoglycerate synthesis.

The RDA for phosphorus for adults is 700 mg/day.[59] Phosphorus is found in a variety of foods including meat, poultry, fish, dairy, eggs, nuts, legumes, cereals, and even soft drinks in the form of phosphoric acid. Dietary phosphorus can be organic or

inorganic. Organic phosphorus is hydrolyzed and absorbed through the intestinal tract as inorganic phosphate. Inorganic phosphorus is more readily absorbable than organic phosphorus and exists as salts that are not protein-bound.

Digestion & Absorption of Phosphorus

Phosphorus is readily absorbed in the small intestine as inorganic phosphate and transported into the epithelial cells. Serum phosphorus concentrations are regulated by endocrine hormones PTH, vitamin D, calcitonin, and FGF-23. When phosphorus concentrations rise, the kidneys excrete excess phosphorus. Calcitonin decreases serum phosphorus levels by promoting its use in bone mineralization. When serum phosphorus concentrations are low, PTH and $1,25(OH)_2D$ stimulate phosphate resorption from the bone, causing concentrations to rise. In the kidneys, the 1-alpha hydroxylase enzyme is stimulated to increase the conversion of 25(OH)D to $1,25(OH)_2D$ to allow for increased phosphorus absorption in the intestine.

Phosphorus Deficiency

Normal serum phosphate concentrations range between 2.5 and 4.5 mg/dL.[65] Because 85% of the body's phosphorus is found in skeletal tissue, serum measurements do not provide a complete picture of the total body phosphorus stores.[66] Phosphorus deficiency is rare in humans, seen in individuals with renal and gastrointestinal disorders.[67] Individuals taking antacids, phosphate binders, and calcium are also at increased risk of developing the deficiency since these medications bind to the phosphorus in the gastrointestinal tract and decrease the amount of phosphate available

for absorption. Serum phosphate concentrations measured by biochemical labs are generally accepted as deficient at less than 1.2 mg/dL.[68, 69]

Dietary Intake Among Individuals With Celiac Disease

Celiac disease patients following a gluten-free diet may have different dietary intake and body composition from healthy individuals. A case-control study of 71 celiac disease patients found lower total energy intake in the celiac disease patients compared to the control group (9686 ± 1569 and 11297 ± 1318 kJ/d in males and 6736 ± 1318 and 7740 ± 1715 kJ/d in females). Energy sources among the celiac disease patients were proportionally higher in fat and lower in carbohydrates.[70] Both male and female celiac disease patients had significantly lower weight and BMI than the control subjects.

Another study examining dietary intake among adolescents with celiac disease found that the gluten-free diet posed additional nutritional risks for the group.[71] The study analyzed dietary intakes and measured compliance to the gluten-free diet through IgA and anti-EMA antibodies. Of the 47 celiac disease patients, 25 reported adhering to the gluten-free diet and 22 did not. Although all subjects had normal energy intake, the adolescents with celiac disease who adhered to the gluten-free diet had low carbohydrate, calcium, fiber, and iron intakes. The resulting nutritional imbalances highlight the importance of proper nutrition instruction for individuals adapting to the gluten-free diet during the nutritional rehabilitation for celiac disease.

Only one study has been published insofar examining dietary intake as it relates to the bone health of adult celiac disease patients. Pazianas et al[72] assessed the body mass index (BMI), dietary intake, serologic indices of bone health, and BMD of 24 female

adults with celiac disease who were being treated with a gluten-free diet and 20 normal subjects. The celiac disease patients had significantly higher dietary calcium and protein intake ($p < 0.05$), and significantly lower whole body, spine, and trochanter BMD ($p < 0.05$) than the control group. The study found an inverse relationship between PTH and amount of time adhering to the gluten-free diet, which is promising for the long-term effects of the gluten-free diet on bone metabolism in individuals with celiac disease. In addition, the celiac disease patients had higher calcium intake than the control group. While increased calcium intake seemed to mitigate decreased calcium absorption in this group, it did not result in normalized BMD. Since all of the subjects were being treated for celiac disease at the start of the study, the direct effects of adopting a gluten-free diet on BMD are unknown.

Nutrient Status of Individuals with Celiac Disease

Calcium

Intestinal malabsorption of calcium is a key pathophysiological aspect of bone disorders in celiac disease.[73] A cross-sectional study of 32 newly diagnosed adults with celiac disease and 27 healthy controls found an association between low urinary calcium excretion and presence of celiac disease.[74] The low urinary calcium excretion is an indicator of low intestinal absorption of calcium. Intestinal absorption and urinary calcium excretion improved by 52% ($p < 0.0001$) in celiac patients after six months of a gluten-free diet. Although this study primarily examined calcium absorption with respect to hypocalciuria, the low calcium absorption among these individuals poses risk of developing related bone diseases osteopenia and osteoporosis.

A cohort study of 18 adult women diagnosed with celiac disease examined the effect of a gluten-free diet on mineral and bone metabolism within this group through a strontium calcium absorption test.[75] At the time of diagnosis, 11 (61%) of the 18 patients had low plasma and urinary calcium, 25(OH)D, and phosphorus. The study found frequent intestinal calcium malabsorption and elevated PTH at the time of diagnosis. Calcium absorption normalized after 12 months of following a gluten-free diet. However, the study remained inconclusive whether a gluten-free diet had a positive effect on bone mineral density once celiac-induced damage had been done.

The relationship between calcium malabsorption and bone mineralization remains uncertain. Walters et al[24] compared the BMD as measured by dual energy x ray absorptiometry (DXA) of 34 asymptomatic celiac disease patients following a gluten-free diet for at least two years and 10 newly diagnosed, untreated patients. The newly diagnosed, untreated patients had significantly lower mean age adjusted Z-scores ($p < 0.001$) for total body, lumbar spine, and femur. While the newly diagnosed, untreated patients had reduced bone mineralization at the time of diagnosis, this was not completely restored after one year of following a gluten-free diet. It is thus unclear whether calcium malabsorption present with celiac disease results in impaired bone mineralization.

Vitamin D [25(OH)D]

A number of studies have found that celiac disease patients have lower serum 25(OH)D concentrations compared to normal subjects.[3, 73, 76, 77] Since serum 25(OH)D concentration is one index of bone metabolism and remodeling, it is can be used in identifying individuals at-risk for low BMD, osteopenia, and ultimately osteoporosis.[73]

The low serum 25(OH)D concentrations in celiac disease patients has been linked to osteoporosis in this population, and the risk increases as the disease progresses in severity.[22]

A cross-sectional study found that lower bone mineral density in women with untreated, active celiac disease could be attributed to significantly lower 25(OH)D and significantly higher $1,25(OH)_2D$ in these women (14 ng/mL and 57 ng/mL, respectively $p < 0.05$) compared to women with treated celiac disease [24 ng/mL and 42 ng/mL, respectively $p < 0.05$) and healthy subjects (27 ng/mL and 25 ng/mL, respectively $p < 0.05$).[73] This is supported by an international cross-sectional study of 272 individuals that found significantly lower serum 25(OH)D levels among individuals with celiac disease compared to healthy subjects (20.2 ± 10.5 ng/ml and 30.3 ± 12.3, respectively $p = 0.003$).[77] The authors of this study suggested routinely checking vitamin D levels of celiac disease patients.

Another study found low 25(OH)D concentrations (<7 nmol/L) in celiac disease patients even in those with otherwise normal BMD, putting them at risk for osteoporosis in the long term.[3] Seventy-seven celiac disease patients were examined and of those, 28 were newly diagnosed and 49 were previously diagnosed. Twenty-six percent of the celiac disease patients had osteoporosis (Z-score $\leq$ -2.5 SD), compared to 5% of the control subjects. Further, 35% of the celiac disease patients and 17% of the control subjects had low BMD at the lumbar spine; and 31% of the celiac disease patients and 16% of the control subjects had low BMD at the femoral neck. With regards to vitamin D, 64% of men and 71% of women presented low 25(OH)D concentrations. This

suggests that a low serum vitamin D level, which is associated with low BMD, is a typical biochemical abnormality among celiac disease patients and puts them at increased risk of osteoporosis.

Corazza et al[73] suggested that abnormal 25(OH)D levels are due to an increase in PTH. The 17 untreated celiac disease patients had significantly lower 25(OH)D concentrations and BMD, and significantly higher PTH and $1,25(OH)_2D$ compared to 14 treated celiac disease patients and the control group ($p < 0.05$ for all parameters). In order to prevent increased bone turnover and reduce their risk of bone abnormalities, celiac disease patients should be treated through a gluten-free diet. This supports the current practice of adherence to a gluten-free diet as treatment for celiac disease: Furthermore, Corazza and colleagues concluded that there is a need for studies on individuals with subclinical forms of celiac disease. This group is likely at just as great a risk, if not more, of developing osteoporosis as those presenting more observable or severe symptoms.

Phosphorus

Relatively little has been studied on the phosphorus status of individuals with celiac disease. Because there is a known relation between phosphorus, calcium, and vitamin D status[78, 30, 80], and individuals with celiac disease are at increased risk for having abnormal plasma 25(OH)D and calcium levels,[74, 73, 75, 77] their serum phosphorus concentrations should be assessed as well. Individuals with celiac disease may present low or elevated concentrations of serum phosphorus and this can be caused by a number of factors, to include intestinal malabsorption and abnormal levels of other key nutrients like calcium and 25(OH)D.

As with the normal population, phosphorus deficiency in individuals with celiac disease is rare. One study found low plasma phosphate (<0.71 nmol/l) in 9% of their study participants, which consisted of 35 patients with newly diagnosed celiac disease.[81] Although this did not reach statistical significance in the overall sample, likely due to the small sample size, it does suggest a possibility of phosphorus malabsorption in some celiac disease patients. Other studies found no statistically significant difference in serum phosphorus status between celiac disease patients and normal subjects.[82, 83]

Although not significantly different, one study found a trend ($p = 0.07$) for slightly elevated serum alkaline phosphatase levels in newly diagnosed and untreated celiac disease patients as compared to treated patients.[3] The authors of the study hypothesized that this was caused by hypocalciuria found in the celiac disease patients, which could result in a rise in serum alkaline phosphatase.

These findings were supported by a cross-sectional study on 20 untreated and 12 treated women with celiac disease.[84] The untreated patients had elevated serum alkaline phosphatase levels, as well as significantly lower BMD as compared to treated patients and controls ($p < 0.01$). However, the cause of the elevated serum alkaline phosphorus levels was not explained in this study. This study also found that individuals with untreated celiac disease had reduced fat mass and BMD ($p < 0.001$) when compared to those with treated celiac disease and those without celiac disease.

Low Bone Mineral Density Among Individuals With Celiac Disease

A cross-sectional study of 77 celiac disease patients found an increased risk of osteopenia and osteoporosis among individuals with untreated celiac disease.[3] Celiac

patients had significantly lower BMD of the lumbar spine and femoral neck than the control subjects. However, there was not a significant difference in BMD between treated and untreated celiac disease patients. Of the celiac disease patients, 49 were following a gluten-free diet at the time of the study and 28 were not. The study additionally found that low serum 25(OH)D was one of the associated variables of low BMD and suggests that celiac disease is a risk factor for osteoporosis.

A seminal 1990 study on BMD among adult celiac disease patients demonstrated the importance of early diagnosis and treatment through a gluten-free diet.[25] Molteni et al measured forearm BMD using peripheral single photon absorptiometry of 29 patients with celiac disease who were not treated and 22 adhering to a gluten-free diet since childhood. The untreated group presented significantly lower BMD compared to those who were treated and control subjects (619.4 +/- 68.5 mg/cm^2 vs. 669.1 +/- 39.3 mg/cm^2, $p < 0.01$ and 673.2 +/- 42.7 mg/cm^2, $p < 0.001$, respectively). They additionally found no correlation between BMD and presence of malabsorptive symptoms. This signals the importance of understanding other dietary or pathophysiological causes of low bone mass in adults with celiac disease.

Research on children with celiac disease has found significantly lower BMC evaluated by DXA in those with celiac disease compared to healthy subjects ($p < 0.001$).[85] Early diagnosis and treatment through a gluten-free diet has been found to promote recovery of bone mineralization. After one year on a gluten-free diet, child celiac disease patients no longer had significantly different lumbar and whole skeleton BMD values than control subjects, with a mean growth increment of 0.07 g/cm compared

to 0.05 g/cm in normal children ($p < 0.05$). In this case, the children were diagnosed early enough to promote full mucosal recovery through complete adherence to the gluten-free diet.

However, a separate study found that while following a gluten-free diet aids in improving nutrient absorption and bone health among individuals with celiac disease, it may not undo all of the damage caused by long-term deficiencies. A case-control study of 19 celiac children following a gluten-free diet for at least 2 years and 19 control subjects examined the effects of calcium and vitamin D supplementation on bone mineral density.[87] While the celiac patients showed an increase in bone mineral density after 24 months of supplementation compared to the controls, they still had lower overall bone mineral density than the controls ($p < 0.05$) .

Adults with celiac disease experience similar improvements in bone health by following a gluten-free diet, though complete recovery is even less common. One study on adult celiac disease patients found low BMD values in many patients following a gluten-free diet, supporting the argument that the gluten-free diet fails normalize bone mass in adults and long-term follow-up of celiac disease patients is critical for preventing further bone loss.[88]

Adults with celiac disease have significantly lower BMC when diagnosed in adulthood than if diagnosed during childhood.[70] This is despite strict compliance to the gluten-free diet and complete absence of the serologic antibodies, likely because they have passed the window for peak bone mass development. On top of this, persistent villous atrophy present with celiac disease may be associated with low bone mineral

density.[89] Villous atrophy is persistent among celiac disease patients who do not follow the gluten-free diet; complete adherence is crucial in order to minimize risk of bone disease among this population.

Summary

Since celiac disease is a gastrointestinal malabsorptive disorder and individuals with celiac disease are at increased risk of bone conditions like osteopenia and osteoporosis,[90, 3, 82] it is important to better understand the intersection between nutrient status and bone health in individuals with celiac disease. As many as 36% of celiac disease patients have osteoporosis and up to half have osteopenia.[21] Three key nutrients have been identified for their roles in bone health: calcium, vitamin D, and phosphorus. Studies have found that some individuals with celiac disease have lower serum calcium and 25(OH)D concentrations than those without celiac disease. [24, 73, 75] Less has been studied on the relationship between phosphorus and celiac disease, though research suggests that individuals with celiac disease may be at increased risk of phosphorus malabsorption.[81] Dietary intake of individuals with celiac disease has been less-explored, yielding questions of whether there are dietary differences leading to poor bone health on top of the malabsorption present with the disease.

Table 1.1. A comparison of dietary intake, serologic indices of bone health, and bone mineral density between treated and untreated individuals with celiac disease and adults without celiac diseases: a review of literature

Study	Study design	Country	No. of participants	Age (yrs.)	Measurements	Results
Corazza et al[73]	Cross-sectional	Italy	31 CD patients (17 untreated, 14 treated), 24 controls	20-66 (range)	BMD, serum calcium, serum 25(OH)D, serum 1,25-vitamin D, PTH	Significantly lower BMD and 25(OH)D, significantly higher 1,25-vitamin D and PTH in untreated celiacs
Molteni et al[75]	Cohort	Italy	18 CD patients	36.8	Serum calcium, urinary calcium, serum 25(OH)D, serum phosphorus	Abnormal plasma and urinary calcium and phosphorus at diagnosis; significantly reduced 25(OH)D and elevated alkaline phosphatase in some participants
Kemppainen et al[3]	Case-control	Finland	77 CD patients (28 newly diagnosed, 49 previously diagnosed)	46	Serum 25(OH)D, Serum alkaline phosphatase, BMD	Significantly lower BMD at lumbar spine and femoral neck in celiac patients; 26% of celiac patients had osteoporosis at lumbar spine vs. 5% of normal subjects
Vilppula et al[81]	Cohort	Finland	35 CD patients	52-76 (range)	Disease history, dietary compliance, BMD, serum 25(OH)D	Good dietary compliance; serum 25(OH)D levels increased significantly after following GFD
Caraceni et al[82]	Case-control	Italy	20 untreated CD patients	--	Serum phosphorus, serum PTH	Higher than normal alkaline phosphatase and PTH in untreated patients; decreased bone turnover after one year on GFD
Albulova et al[83]	Cohort	Russia	47 CD patients	--	Serum 25(OH)D3, serum 1,25-vitaminD, serum alkaline phosphatase, serum calcium, serum phosphorus, serum PTH, BMD	Significantly reduced BMD in CD patients; Impaired calcitriol synthesis in patients with osteoporosis; Decreased BMD accompanied by elevated PTH
Gonzalez et al[84]	Cross-sectional	Argentina	32 CD patients (20 untreated; 12 treated)	38	Serum 25(OH)D, alkaline phosphatase; BMD	Normal serum 25(OH)D and elevated serum alkaline phosphatase levels; significantly lower body weight and BMD at lumbar spine and total skeleton in untreated celiac disease patients
Muzzo et al[87]	Case-control	Chile	19 children with CD; 19 control	6-15 (range)	Dietary intake, BMD	Significant increase in BMD at femoral neck and femoral neck in children with Celiac disease upon following GFD
Walters et al[24]	Cohort	United Kingdom	34 asymptomatic CD patients	54	BMD	Significantly lower BMD in untreated celiacs compared to treated celiacs and normal subjects

Molteni et al[25]	Case-control	Italy	29 untreated, 22 treated CD patients	13-56 (range)	BMD	Significantly lower BMD in untreated patients than controls; bone derangements common in celiacs diagnosed in adulthood
Mora et al[85]	Case-control		33 CD patients; 255 controls	9	BMC	BMC increased significantly after 1.28 years on GFD
Bardella et al[70]	Case-control	Italy	72 CD patients; 142 controls	27	Dietary intake, BMC, BMD	Significantly lower energy intake in CD patients than controls; significantly lower BMC in female adults diagnosed in adulthood than male CD patients, females diagnosed at childhood, and controls
Selby et al[76]	Cohort	United Kingdom	35 CD patients on GFD	51	Serum 1,25-vitamin D, serum PTH, BMD	BMD lower than expected for age and gender; negative relationship between BMD and PTH concentration

CHAPTER 2. NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY DATA (CYCLES 2009-10, 2011-12, AND 2013-14) IN RELATION TO CELIAC DISEASE AND BONE HEALTH

Introduction

With increasing public awareness and medical diagnosis of celiac disease, there is a growing body of research on the long-term health consequences due to nutrient malabsorption present with the disease.[25, 72] Nutrient malabsorption is a common manifestation of celiac disease,[90] caused by intestinal villous atrophy, making dietary intake and nutrient absorption of utmost consideration when assessing celiac disease patients. Studies on the bone health of celiac disease patients have found an association between low BMD and increased risk of osteoporosis within this group.[3, 82] Between a quarter and half of celiac disease patients have osteopenia, and as many as 36% of celiac disease patients have osteoporosis.[21] Although the classical presentation of celiac disease is nutrient malabsorption due to intestinal villous atrophy, studies have found low BMD even in patients without this gastrointestinal manifestation.[23] There is some dissent as to whether the risk for bone deterioration and osteoporosis increases with the severity of the disease. A number of studies have found that the longer someone goes untreated for celiac disease, the greater their risk of osteoporosis and other bone abnormalities.[3, 25, 89]

Other studies found no association between degree of bone deterioration and severity or treatment of the disease.[91]

Serum calcium, 25(OH)D, and phosphorus are key serologic indices of bone health. Studies have found low serum calcium and 25(OH)D concentrations in celiac disease patients.[24, 73, 75] Another study found low serum 25(OH)D concentrations even in celiac disease patients with normal BMD, suggesting long-term risk of bone deterioration among this group triggered by low 25(OH)D concentrations.[27] Less has been explored on the relationship between serum phosphorus status and celiac disease, likely due to the low overall prevalence of phosphorus deficiency within the United States population. One study did identify the risk of phosphorus malabsorption in celiac disease patients, though this did not reach statistical significance.[81] Other studies found no association between serum phosphorus concentrations and celiac disease.[82, 83]

There is still a scarcity of studies examining the dietary intake of celiac disease patients, particularly with regards to nutrients that are essential for bone health. One study did assess dietary calcium intake of celiac disease patients and found that although the previously diagnosed celiac disease patients consumed greater amounts of dietary calcium, they still had lower BMD compared to normal subjects.[72] Vitamin D intake and synthesis, in the forms of $25(OH)D_2$ and $25(OH)D_3$, as well as phosphorus intake, should also be included in the assessment for a more robust evaluation of the relationship between dietary intake and bone health in celiac disease patients. More analysis is needed to correlate dietary intake and serologic indices of bone health in adults with celiac disease. This is critical in order to better understand the effects of celiac disease on

nutrient status and bone health. Identifying correlations between dietary intake and supplement use, serum nutrient status, and celiac disease status will provide a more complete picture for proposing treatment plans and future studies.

Improved knowledge of dietary intake of pertinent nutrients could be useful in understanding the unique nutritional considerations of individuals with celiac disease. Currently the only treatment option for celiac disease is lifelong, strict adherence to a gluten-free diet. Since some celiac disease patients adhering to a gluten-free diet continue to experience poor nutrition status and/or deficiencies, [13] it is important to develop additional guidelines for long-term disease management. Observing adults with undiagnosed celiac disease would be particularly beneficial here since they are untreated and will have active manifestations of the disease.

Therefore, in order to address these gaps in the literature, we aimed to comprehensively examine exogenous intake of calcium, vitamin D, and phosphorus on serologic concentrations of those nutrients and bone health in individuals with and without celiac disease. Key to this study is the distinction of adults with serologically positive celiac disease through the immunoglobulin-A tissue transglutaminase (IgA-tTG) and tissue transglutaminase endomysial antibody assay (tTG-EMA) serologic tests. Relying on self-reported data for this carries validity bias of its own,[92] particularly due to increased prevalence of adults without celiac disease following the gluten-free diet as a health trend.[93] Instead, we have identified individuals based on a series of more accurate celiac disease assessments.[94]

Using secondary data, this study aimed to achieve its goal of better understanding the intersection of diet and bone health in adults with celiac disease through the comparative analysis of dietary and supplemental calcium, vitamin D, and phosphorus intake; serologic concentrations of calcium, 25(OH)D, and phosphorus; and bone mineral density in adults with and without serologically positive (EMA+) celiac disease.

Methods

The study used data for adults from the National Health and Nutrition Examination Surveys (NHANES). NHANES is a national, population-based, cross-sectional, multi-year study conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) and it provides nationally representative health and nutrition statistics on noninstitutionalized civilians of the United States. In order to select study samples, NHANES uses a stratified multistage probability design with random sampling of the civilian noninstitutionalized population and over-sampling of certain subgroups.[95]

Subjects

Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) 2009-10, 2011-12, and 2013-14 cycles were used.[96, 97, 98] Demographic data, laboratory data, and dietary interview data were analyzed in adults aged 18-80. Adolescents have higher energy and nutrient needs than adults due to critical bone development that takes place for this age group.[99] As such, this study examines individuals who have completed puberty. In order to be included in this study, subjects were required to have completed the dietary intake component and participated in the

IgA-tTG serologic tests for celiac disease and the tTG-EMA serologic test, if applicable, as well as at least one of the additional laboratory components needed for this study: standard biochemistry profile for serum calcium and phosphorus concentrations, and serum 25(OH)D to assess vitamin D status. Subjects were excluded if they were pregnant at the time of the assessment.

This study employed secondary data analysis on publically available, de-identified statistical data from NHANES without any identifying participant personal information. Consent forms were collected for all NHANES participants at the time of the study and no further ethics approval was required for conducting this study.

Demographics

Demographics data, including age, sex, race/ethnicity, education level, poverty income ratio, and pregnancy status, were administered at an in-person interview and collected using the computer-assisted personal interview (CAPI) software. Race/ethnicity were split into two categories: "Caucasian" consisting of Non-Hispanic whites and "non-Caucasian" consisting of Mexican Americans, other Hispanics, non-Hispanic Blacks, and other race including multi-racial. Participants were additionally divided into two categories by education level: those completing high school or less, and those completing college or more. Poverty income ratio was a continuous variable calculated as the ratio of family income to the survey year's poverty guidelines. For the demographics table, poverty income ratios were categorized as below poverty level (< 1.0), at poverty level (1.0), and above poverty level (> 1.0).[100]

Anthropometrics

Anthropometric assessments were collected at the Mobile Examination Center (MEC). Weight was collected using a digital floor scale and measured to 0.1 kg. Standing height was measured to the nearest millimeter using a wall-mounted stadiometer. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared. Weight status was determined according to the following BMI categories for adults: underweight, normal or healthy weight (< 24.9 kg/m^2); and overweight or obese (≥ 25.0 kg/m^2).[101]

Celiac Disease Diagnosis Status & Medical History Assessment

NHANES employs two steps of serologic tests for selected participants to screen for celiac disease antibodies that develop as a T-cell-mediated response to gluten.[7, 102] The Tissue Transglutaminase-Immunoglobulin A (tTG-IgA) test is the most sensitive serological test for celiac disease and is the first test used. The tTG-IgA test identifies IgA antibodies against gliadin, endomysium, and tissue transglutaminase. In order to check for false positives, an IgA Endomysial antibody (EMA) is assessed for those testing positive for celiac disease through the tTG-IgA serologic test. With 100% specificity, the EMA test is considered the gold standard serologic test for diagnosing celiac disease.[9] Someone testing negative for the EMA serologic test will therefore be given no celiac disease diagnosis.

NHANES administers a medical history questionnaire in which participants report a previous medical diagnosis of celiac disease. The questionnaire also asks participants

whether they are on a gluten-free diet. This information was used to determine whether the participants were being treated for celiac disease by following a gluten-free diet.

The subjects are divided into two groups: 1) serologically positive (EMA+) participants consisting of those testing serologically positive (EMA+) for celiac disease though the Immunoglobulin-A-Endomysial Antibody (IgA-EMA) serologic test; and 2) a control group consisting of individuals testing serologically negative for celiac disease and reporting no history of celiac disease diagnosis when asked in the medical history questionnaire.

Dietary Assessment

Each participant completed a 24-hour dietary recall administered by an in-person interviewer in the NHANES mobile examination center (MEC). The 24-hour recall was conducted using the United States Department of Agriculture (USDA) Automated Multiple-Pass Method (AMPM). Information was collected on all foods, beverages, vitamins, minerals, and supplements consumed during the 24-hour time period. While one day of dietary recall is not necessarily sufficient due to day-to-day variability in dietary intake among individuals, it yielded a greater proportion of responses than the telephone interview.[103]

Data on total nutrient intake through food and beverage consumption comes from the USDA Food and Nutrient Database for Dietary Studies respective versions for each cycle.[104, 105, 106] Data on total nutrient intake through vitamins, minerals, and supplements comes from the NHANES Dietary Supplement Database 1999-2014.[107] This study distinguished between “dietary” and “total” intake, with dietary intake consisting of food

and beverages consumption, and total intake consisting of food, beverage, vitamin, mineral, and supplement intake.

Biochemical Nutrient Assessment

Serum specimens are processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis according to NHANES quality assurance and quality control protocols (QA/QC).[108] Calcium concentration is measured in select participants using indirect ion selective electrode (ISE) methodology.[109] Vitamin D status is assessed by ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS).[110] This test principally detected total $25(OH)D_3$ and $25(OH)D_2$ in serum. Serum phosphorus and serum alkaline phosphatase concentrations are determined by using a timed-rate method.[111]

Bone Mineral Composition & Density

Bone mineral content (BMC) and bone mineral density (BMD) of the femur, femoral neck, and total spine were measured using dual-energy x-ray absorptiometry (DXA) in the MEC.[112] Whole body DXA scans were performed using QDR 4500A (Hologic, Inc. Bedford, Massachusetts) beam bone densitometers, using software version Discovery v12.4. Bone composition data was unavailable from the 2011-12 cycle.

Statistical Analysis

The statistical analysis of the data was performed using STATA data analysis and statistical software, version 14.0 (College Station, TX).[113] NHANES is conducted using nationally representative samples, but the two-year cycle sample size is relatively small

and it is not geographically representative. This study used data the three cycles when data on celiac disease was collected (2009-10, 2011-12, and 2013-14) in order to increase sample size and geographic representation. We took sample weights into consideration during the statistical analysis in order to account for sample size variability between cycles, non-response, and the complex survey design of NHANES. Statistical significance for all tests used in the analysis was set at $p < 0.05$.

Descriptive data including sex, race/ethnicity, education level, poverty income ratio, and BMI categories, are reported as frequencies and sample percent distributions. Continuous variables including BMI, age, dietary intake, supplement intake, serum nutrient concentrations, and BMD are reported as means and standard errors, with 95% confidence intervals among these groups. Survey-weighted linear regression was used to assess variance in descriptive and continuous data among and between groups.

Linear regression models were used to assess positive serologic (EMA+) status as a predictor of dietary and supplement intake, serologic nutrient status, and bone health, adjusted for the identified confounding factors. Age, sex, race/ethnicity, energy intake, and poverty income ratio were identified as confounding variables that correlate with the variables in this study (celiac disease status, dietary and supplement intake, serologic nutrient concentrations, BMC, and BMD). Mean of beta-coefficient and 95% confidence intervals (CI) were reported in multivariate regression models.

Objectives

The overall aim of this study was to examine the effects of dietary intake of calcium, vitamin D, and phosphorus on serologic concentrations of those nutrients and bone health in individuals with celiac disease. Three objectives were established.

Objective 1: To assess and compare dietary and total intake of calcium, vitamin D, and phosphorus in adults with and without serologically positive (EMA+) celiac disease.

Hypothesis 1: The null hypothesis states that there is no difference ($p > 0.05$) in dietary and total intake of calcium, vitamin D, and phosphorus between adults with and without serologically positive (EMA+) celiac disease. The alternative hypothesis states that there is a significant difference ($p < 0.05$) in dietary and total intake of calcium, vitamin D, and phosphorus between adults with and without serologically positive (EMA+) celiac disease.

Objective 2: To assess and compare serologic concentrations of calcium, 25(OH)D, and phosphorus in adults with and without serologically positive (EMA+) celiac disease.

Hypothesis 2: The null hypothesis states that there is no difference ($p > 0.05$) in serologic concentrations of calcium, 25(OH)D, and phosphorus between adults with and without serologically positive (EMA+) celiac disease. The alternative hypothesis states that adults with serologically positive (EMA+) celiac disease have significantly lower ($p < 0.05$) serologic concentrations of calcium, 25(OH)D, and phosphorus compared to those without celiac disease.

Objective 3: To assess and compare bone health in adults with and without serologically positive (EMA+) celiac disease.

Hypothesis 3: The null hypothesis states that there is no difference ($p > 0.05$) in BMD of the femur, femoral neck, and lumbar spine between adults with and without serologically positive (EMA+) celiac disease. The alternative hypothesis states that adults with serologically positive (EMA+) celiac disease have significantly lower ($p > 0.05$) BMD of the femur, femoral neck, and lumbar spine compared to those without celiac disease.

Results

There was no difference in sex or poverty income ratio between groups (**Table 2.2**). The mean age of the serologically positive (EMA+) participants was 42, while the mean age of the control group was 46 ($p = 0.048$). Although no difference in mean BMI, a greater proportion of the serologically positive (EMA+) group were underweight or normal weight (BMI < 25.0 kg/m^2) than the control group (50% vs. 30%, respectively, $p = 0.047$). Race/ethnicity differed significantly between groups ($p = 0.000$). Serologically positive (EMA+) participants were mostly non-Hispanic white (72%), while the control group had a lower proportion non-Hispanic white (44%). Education levels differed between the groups as well, with 74% of the serologically positive (EMA+) participants holding an associate's degree or higher, compared to 54% of the control group.

The serologically positive (EMA+) participants consumed significantly more total calcium (Ca) than the control group (1608 mg Ca/day vs. 1152 mg Ca/day, $p = 0.001$), than the control group (**Table 2.3**). In addition, their diets were significantly denser in calcium and as compared to the diets of the control group (663 mg / 1,000 kcal Ca vs. 565 mg / 1,000 kcal Ca, $p = 0.031$). No statistically significant differences in phosphorus and vitamin D intake or macronutrient density were observed.

The serologically positive (EMA+) participants had significantly higher serum phosphorus concentrations than the control group (4.0 vs. 3.8 mg/dL, $p = 0.028$). No statistically significant differences in serum concentrations of total calcium, 25(OH)D, $25(OH)D_2$, or $25(OH)D_3$ were observed.

Differences were further examined by using linear regression models (**Table 2.4**), adjusted for age, sex, race/ethnicity, energy intake, and poverty income ratio. Positive serologic (EMA+) status predicted a 344.2 kcal (95% CI: 6.6, 681.8) increase in daily caloric intake. Positive serologic (EMA+) status also predicted greater phosphorus (P) density in this group's diets (β: 49.0 mg /1,000 kcal P, 95% CI: 5.3, 92.6).

Positive serologic (EMA+) status predicted a -0.1 g/cm^2 (95% CI: -0.2, 0.0) decrease in femur BMD, -0.4 g (95% CI: -0.6, -0.1) decrease in femoral neck BMC, and -0.1 g/cm^2 (95% CI: -0.1, 0.0) decrease in femoral neck BMD. No differences in BMC of the femur or BMC or BMD of the total spine were observed between the serologically positive (EMA+) participants and the control group.

Discussion

This was the first study to explore the relationship between calcium, vitamin D, and phosphorus intake, serologic concentrations of these nutrients, and bone mineral density in adults with undiagnosed celiac disease. This study found that adults with serologically positive (EMA+) celiac disease had lower bone mineral density than adults without celiac disease, despite consuming greater amounts of calcium. They additionally had higher serum phosphorus and alkaline phosphatase concentrations than adults without celiac disease

Demographics

A majority of the serologically positive (EMA+) participants were non-Hispanic white, approximately 72%. This supports other research, which has found that celiac disease affects predominately the non-Hispanic white population in the United States.[114] Approximately 54% of the serologically positive (EMA+) participants were female. This supports other studies that have reported over half of the celiac disease population as female.[114, 115]

The prevalence of undiagnosed celiac disease in this study is 1 in 305. The true prevalence of celiac disease is difficult to ascertain and there is not a largely accepted prevalence of undiagnosed celiac disease in the United States. A well-accepted study estimated that 1 in 141 people in the United States have celiac disease, though this includes both diagnosed and undiagnosed celiac disease.[1] Studies have found that the prevalence of celiac disease in western European countries, where the populations are predominantly white or Caucasian, ranges from 1 in 130 to 1 in 300.[116, 114]

Dietary Intake

Positive serologic (EMA+) status predicted higher daily caloric intake in this study. They consumed significantly more dietary calcium than the control group, with and without supplementation factored in. This finding supports the 2004 study by Pazianas et al[72] which also found that individuals with celiac disease consumed greater amounts of dietary calcium than those without celiac disease. Like Pazianas et al., we also found that lower BMD in adults with celiac disease than those without celiac disease, despite higher calcium intake among this group.

Nutrient density of the participants' diets was also examined to confirm whether the differences in nutrient intake were specifically due to differences in caloric intake. The serologically positive (EMA+) participants had consumed diets significantly denser in calcium than the control group. Positive serologic (EMA+) status also predicted greater phosphorus density of this group's diets. In other words, the higher caloric intake of the serologically positive (EMA+) participants not only contributed to higher nutrient intake as mere consequence, but the quality of their diets was richer and denser in key nutrients as well.

Each group met the estimated average requirement (EAR) of calcium of 800 mg/day, but only the serologically positive (EMA+) participants met the RDA of calcium of 1,000 mg/day.[45] Neither of the groups met the EAR for vitamin D of 10 μg/day through dietary intake alone, but both met the RDA for vitamin D of 15 μg/day with supplement use included.[45] Both groups met the EAR and RDA for phosphorus for adults of 700 mg/day through diet alone.[59]

Serologic Nutrient Status

Although serologically positive (EMA+) participants had significantly higher serum phosphorus concentrations than the control group and positive serologic (EMA+) status predicted elevated serum alkaline phosphatase concentrations, these outcomes were not clinically significant.[66] The latter outcome does, however, support other studies that have found higher serum alkaline phosphatase concentrations in adults with untreated celiac disease.[75, 82, 84] Alkaline phosphatase is critical for bone mineralization as it hydrolyzes pyrophosphate, which inhibits mineral formation, and provides inorganic

phosphate, which promotes mineralization.[117] Elevated concentrations can therefore indicate skeletal disorders and bone abnormalities.

Bone Health

Positive serologic (EMA+) status predicted lower BMC and BMD of the femoral neck than the control group, as well as lower BMD of the femur. Similar results have been documented by other studies on adults with untreated celiac disease.[3, 21] No differences were found in BMD of the lumbar spine from this study. This differs from other studies that have found lower BMD of the lumbar spine in individuals with untreated celiac disease than those without celiac disease.[24, 26, 118]

The lower overall BMD in adults with celiac disease participating in this study supports existing research that have found an association between poor bone health and celiac disease, and presence of osteoporosis in as many as one-third of adults with celiac disease.[3, 25, 91] This is greater than the normal adult population in the United States, and in 2008 the Centers for Disease Control (CDC) and NHANES assessed that 9% of the normal adult population in the United States has osteoporosis.[119]

The key finding of this study is that although adults with serologically positive (EMA+) celiac disease consumed significantly greater amounts of dietary calcium and phosphorus than adults without celiac disease, they had lower overall bone mass. This study proposes that poor bone health and osteoporosis in adults with celiac disease are not due to poor dietary intake. It is plausible that there is an impaired mechanism, likely related to absorption, preventing the uptake and utilization of these nutrients for their

bone health functions. However, the underlying cause of the poor bone health of the participants with serologically positive (EMA+) celiac disease is unknown.

Dietary treatment through a gluten-free diet may help to reverse some of the damages related to celiac disease in the serologically positive (EMA+) participants, though there is some dissent as to whether they would see improvements in BMD. Kemppainen et al[3] found significantly lower BMD of the femoral neck in adults with celiac disease regardless of treatment status than adults without celiac disease. Another study by Meyer et al[21] examining BMD of the femoral neck among individuals with treated and untreated celiac disease similarly found no difference between the two groups. However, Ciacci et al[120] measured femoral and lumbar spine BMD in adults with Celiac disease in a longitudinal study found improvements to BMD after one year of adhering to a calcium-rich, gluten-free diet.

Strengths and Limitations

This is the first study to examine dietary intake of adults with untreated, undiagnosed celiac disease with regards to bone health. This filled a gap in Celiac disease literature on individuals with subclinical forms of celiac disease, identified by Corazza and colleagues.[73] This group is likely at just as great a risk, if not more, of developing osteoporosis as those presenting more observable or severe symptoms resulting in diagnosis. This study was also the first to examine dietary intake and bone health of adults with celiac disease using a nationally representative sample.

Strengths of this study lie in the quality of the NHANES data used in this secondary analysis. The serologic tests used to diagnose celiac disease and measure

serum nutrient concentrations are considered the gold standard for their respective functions. There is no gold standard for dietary assessment, but the AMPM approach used to collect dietary intake is widely regarded as accurate due to the quality assurance that takes place during data processing.[121, 122] DXA is widely accepted as an effective clinical tool for evaluating BMD and identifying osteopenia and osteoporosis.[123]

Limitations to this study include the study design, sample size, types of data available, and the recall bias that is present with dietary recall. As a cross-sectional study, we were not able to determine causality. The sample size of the dietary analysis was comparable to or larger than other studies examining bone health of celiac disease patients.[91, 75, 73] However, BMD was not assessed for all of the participants, which limited the scope of our analysis. Third, this study would have benefited from including serologic PTH and magnesium status in the regression for a more robust understanding of the nutrient status of celiac disease patients; however, neither was assessed during the NHANES cycles included in this secondary analysis. Finally, there may be validity or recall biases that are inherent to self-reported data.[124]

Conclusion

This study filled a gap in celiac disease literature by examining the role of dietary intake of calcium, vitamin D, and phosphorus in serologic indices of those nutrients and bone mineral density. Previous literature had found a relationship between nutrient deficiencies and severity of the disease, and separately correlated low bone mineral density with presence of celiac disease. While nutrient malabsorption is a known classical manifestation of celiac disease, the dietary behaviors of celiac disease patients prior to

diagnosis is less understood. This is a critical piece in an overall picture of bone health among individuals with celiac disease. A future longitudinal study on dietary intake in adults with celiac disease as they are treated with a gluten-free diet would enhance our understanding of the intersection of diet and bone health among this group.

Table 2.2. Demographic characteristics of study participants

	Serologically Positive (EMA+) (n=49)		Control (n=15,176)		
Variable	**n**	**%**	**n**	**%**	***P***
Sex					0.825
Male	23	46	7503	49	
Female	27	54	7673	51	
Race/Ethnicity					0.000
Caucasian	36	72	6654	44	
Non-Caucasian	14	28	8522	56	
Education Level					0.009
High School or less	12	26	6647	46	
Associates Degree or above	34	74	7729	54	
Poverty Income Ratio					0.961
Below Poverty Level (<1.0)	11	22	3266	22	
Poverty Level (1.0)	0	0	37	0	
Above Poverty Level (>1.0)	39	78	11873	78	
BMI (kg/m^2)					0.047
< 25.0	25	50	4602	30	
$\geq$ 25.0	25	50	10574	70	
Following a gluten-free diet?					0.626
Yes	2	4	180	1	
No	48	96	14992	99	
Variable	**Mean**	**SE**	**Mean**	**SE**	***p***
Age (years)	42	[36.7-46.6]	46	[45.7-47.2]	0.048
BMI (kg/m^2)	26.9	[24.0-29.8]	28.8	[28.6-29.0]	0.178

* P-values are based on survey-weighted frequencies; statistical significance was set at $p < 0.05$.

Table 2.3. Comparison of dietary intake, serologic nutrient concentrations, and bone mineral composition between study groups

	Serologically Positive (EMA+) (n=50)			Control (n=15,176)			
Variable	**Mean**	**95% CI**		**Mean**	**95% CI**		***P***
Energy (kcal)	2577	2158	2995	2182	2158	2206	0.067
Macronutrients							
Protein (g)	99	81	117	84	83	85	0.092
Protein (g/1,000 kcal)	39	36	42	39	39	40	0.762
Carbohydrates (g)	308	269	347	262	259	265	0.021
Carbohydrates (g/1,000 kcal)	124	115	133	122	121	123	0.653
Fat (g)	92	74	110	83	81	84	0.326
Fat (g/1,000 kcal)	35	33	37	37	37	38	0.067
Micronutrients, Diet							
Calcium (mg)	1386	1125	1647	998	983	1014	0.004
Vitamin D (mcg)	7	5	9	5	5	5	0.056
Phosphorus (mg)	1796	1464	2127	1421	1406	1437	0.028
Micronut., Diet & Supplement							
Calcium (mg)	1608	1341	1874	1152	1132	1173	0.001
Calcium (mg/1,000 kcal)	663	574	753	565	555	574	0.031
Vitamin D (mcg)	18	11	25	15	14	16	0.319
Vitamin D (mcg/1,000 kcal)	9	4	14	8	8	9	0.767
Phosphorus (mg)	1799	1469	2130	1428	1413	1444	0.029
Phosphorus (mg/1,000 kcal)	709	668	749	669	664	675	0.055
Serum nutrient concentrations							
Total calcium (mg/dL)	9.3	9.2	9.5	9.4	9.4	9.5	0.084
25(OH)D (nmol/L)	75.8	62.3	89.2	67.6	64.9	70.4	0.204
$25(OH)D_2$ (nmol/L)	3.0	0.6	5.4	3.3	2.7	3.8	0.802
$25(OH)D_3$ (nmol/L)	72.8	58.3	87.3	64.4	61.9	66.9	0.212
Phosphorus (mg/dL)	4.0	3.9	4.1	3.8	3.8	3.8	0.002
Alkaline phosphatase (U/L)	71.7	64.2	79.1	66.1	65.6	66.7	0.136
Bone Mineral Content							
Femur (g)	35.553	32.201	38.904	36.524	36.200	36.849	0.534
Femoral neck (g)	4.209	3.886	4.533	4.319	4.286	4.351	0.464
Total spine (g)	65.398	56.336	74.460	63.912	63.384	64.439	0.714
Bone Mineral Density							
Femur (g/cm^2)	0.902	0.831	0.974	0.965	0.959	0.971	0.064
Femoral neck (g/cm^2)	0.768	0.712	0.824	0.817	0.811	0.822	0.061
Total spine (g/cm^2)	1.012	0.942	1.082	1.032	1.026	1.037	0.539

***** P-values are based on survey-weighted regressions; statistical significance was set at $p < 0.05$.

Table 2.4. Multiple linear regression models of interest for nutrient intake, status, and bone mineral density in serologically positive (EMA+) participants vs. control group.*

Variable	β-Coefficient	P-value	95% CI	
Energy Intake				
Kilocalories (kcal) (n=14,009)	Intercept = 2945			
Celiac disease status (ref=control)	344.2	0.046	6.6	681.8
Age, years	-10.3	0.000	-11.2	-9.3
Sex (ref=Male)	-695.2	0.000	-730.0	-660.5
Race (ref=Caucasian)	78.8	0.000	41.2	116.4
Poverty Income Ratio	5.8	0.334	-6.2	17.8
$R^2 = 0.1618$				
Calcium				
Dietary intake (mg) (n=14,009)	Intercept = 106.3			
Celiac disease status (ref=control)	213.3	0.007	62.3	364.3
Age, years	-0.9	0.002	-1.5	-0.4
Sex (ref=Male)	34.6	0.002	13.7	55.4
Race (ref=Caucasian)	107.9	0.000	84.5	131.3
Poverty Income Ratio	6.4	0.093	-1.1	13.9
Energy intake (kcal)	0.4	0.000	0.4	0.4
$R^2 = 0.3690$				
Total intake (mg) (n=14,009)	Intercept = -124.2			
Celiac disease status (ref=control)	281.7	0.008	75.9	487.6
Age, years	3.9	0.000	3.4	4.4
Sex (ref=Male)	155.6	0.000	129.2	182.0
Race (ref=Caucasian)	157.1	0.000	130.3	183.8
Poverty Income Ratio	20.9	0.000	12.3	29.6
Energy intake (kcal)	0.4	0.000	0.4	0.4
$R^2 = 0.2815$				
Nutrient Density (mcg/1,000 kcal) (n=14,008)	Intercept = 430.6			
Celiac disease status (ref=control)	112.1	0.011	27.4	196.7
Age, years	2.6	0.000	2.3	2.9
Sex (ref=Male)	100.5	0.000	87.4	113.6
Race (ref=Caucasian)	77.6	0.000	64.7	90.5
Poverty Income Ratio	9.5	0.000	4.9	14.1
Energy intake (kcal)	-0.1	0.000	0.1	0.0
$R^2 = 0.1137$				

Phosphorus				
Nutrient Density (mg/1,000 kcal) (n=14,008)	Intercept = 691.3			
Celiac disease status (ref=control)	49.0	0.029	5.3	92.6
Age, years	0.4	0.001	0.2	0.7
Sex (ref=Male)	-11.9	0.000	-18.3	-5.5
Race (ref=Caucasian)	18.9	0.000	9.4	28.4
Poverty Income Ratio	7.7	0.000	4.9	10.5
Energy intake (kcal)	0.0	0.000	0.0	0.0
$R^2 = 0.0410$				
Serum alkaline phosphatase (U/L) (n=14,008)	Intercept = 66.0			
Celiac disease status (ref=control)	7.6	0.041	0.3	14.8
Age, years	0.2	0.000	0.1	0.2
Sex (ref=Male)	-1.0	0.041	-1.9	0.0
Race (ref=Caucasian)	-3.5	0.000	-4.7	-2.3
Poverty Income Ratio	-1.6	0.000	-2.0	-1.3
Energy intake (kcal)	0.0	0.771	0.0	0.0
$R^2 = 0.0410$				
Serum phosphorus (mg/dL) (n=14,005)	Intercept = 3.7			
Celiac disease status (ref=control)	0.2	0.009	0.0	0.3
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	0.2	0.000	0.2	0.2
Race (ref=Caucasian)	0.0	0.027	0.0	0.1
Poverty Income Ratio	0.0	0.168	0.0	0.0
Energy intake (kcal)	0.0	0.015	0.0	0.0
$R^2 = 0.0271$				
Femur				
BMD, g/cm^2 (n=7,035)	Intercept = 1.1			
Celiac disease status (ref=control)	-0.1	0.014	-0.2	0.0
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-0.1	0.000	-0.1	-0.1
Race (ref=Caucasian)	0.0	0.000	0.0	0.0
Poverty Income Ratio	0.0	0.000	0.0	0.0
Energy intake (kcal)	0.0	0.015	0.0	0.0
$R^2 = 0.2467$				
Femoral Neck				
BMC, g (n=7,035)	Intercept = 5.5			

Celiac disease status (ref=control)	-0.4	0.012	-0.6	-0.1
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-1.0	0.000	-1.0	-0.9
Race (ref=Caucasian)	0.0	0.216	-0.1	0.0
Poverty Income Ratio	0.0	0.004	0.0	0.0
Energy intake (kcal)	0.0	0.004	0.0	0.0
$R^2 = 0.3926$				
BMD, g/cm^2 (n=7,035)	Intercept = 1.1			
Celiac disease status (ref=control)	-0.1	0.005	-0.1	0.0
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-0.1	0.000	-0.1	-0.1
Race (ref=Caucasian)	0.0	0.000	0.0	0.0
Poverty Income Ratio	0.0	0.024	0.0	0.0
Energy intake (kcal)	0.0	0.013	0.0	0.0
$R^2 = 0.2713$				

***** Full multiple linear regression models for this study can be found in Appendix A (See **Appendix A**).

CHAPTER 3. SUMMARY

The results of this study suggest that individuals with celiac disease are unable to fully absorb and utilize the nutrients they consume for optimal bone health. While this is not in itself surprising, it is the first to document the dietary calcium, vitamin D, and phosphorus intake of adults with celiac disease. Participants from this study with celiac disease consume greater amounts of calcium than those without celiac disease, but have lower serum calcium concentrations and lower overall bone mass. Since this group is at risk for bone deformities and osteoporosis, these results provide insight into the rehabilitative needs for newly diagnosed celiac disease patients as well as the requirements for long-term disease management.

More thorough guidelines should be established for preventing, identifying, and treating bone loss in celiac disease patients. The American Gastrointestinal Association (AGA) and the National Institute of Health (NIH) recommend assessing BMD in celiac disease patients at diagnosis and as routine follow-up.[29, 30] While AGA recommends testing newly diagnosed celiac disease patients for micronutrient deficiencies,[31] there are no recommendations for frequency of follow-up care. Since the serologically positive (EMA+) participants presented low bone mass in this study, long-term follow-up will be critical in treating celiac disease patients. This follow-up should include consultations

with a dietitian regarding dietary intake, assessment of serologic calcium and vitamin D status, and BMD examination.

Poor bone health is a known complication of celiac disease, often resulting in osteopenia and osteoporosis as the disease progresses. This study has contributed to the knowledge of the bone health of individuals with celiac disease by documenting their dietary calcium, vitamin D, and phosphorus intake. Adults with celiac disease had lower BMD than normal adults despite higher dietary calcium, vitamin D, and phosphorus intake and normal serum nutrient concentrations, suggesting impaired utilization of these nutrients with regards to their bone health functions. This presents a vital need for additional research on the pathology of bone loss in adults with celiac disease, as well as more thorough guidelines for treating bone loss and preventing further degradation during the rehabilitation of adults with celiac disease.

The results from this study provide insight for future studies on dietary intake, nutritional status, and bone health of individuals with celiac disease. In particular, additional research on dietary intake will improve current literature on the bone health of individuals with celiac disease. Few studies have specifically examined dietary intake within this population. Although this study examined dietary intake of individuals with serologically positive (EMA+) celiac disease, most of these participants were not following a gluten-free diet. It would be beneficial to continue observing these participants as they adopt a prescribed gluten-free diet in order to better understand the rehabilitative needs of this group when it comes to bone health. A future longitudinal study could also examine dietary intake over time as it correlates with bone mass.

Additionally, an absorption study on serum nutrient concentrations following oral consumption may provide insight to the effects of celiac disease on the absorption of these nutrients.

Improved understanding of what individuals with celiac disease are eating would also add to the greater picture of their bone health. A future study could conduct a food group analysis in order to explain differences in nutrient intakes between groups. From the perspective of bone health, the forms of calcium and vitamin D could impact absorption. It would be beneficial to measure how many servings dairy and non-dairy alternatives this group consumes. Also, are individuals with undiagnosed celiac disease avoiding certain food groups that they associate with the symptoms they experience? This could result in dietary imbalances and nutrient deficiencies.

Once the dietary intake of this group is better understood, these results support nutritional interventions for individuals with celiac disease in order to improve bone health. It would be worth exploring the effects dietary calcium, vitamin D, and phosphorus supplementation on bone health in order to ascertain whether supplementation improves nutritional status and bone health of individuals with celiac disease. While this group meets or exceeds their RDA for each of these nutrients, supplementation may be necessary in order to meet their needs for bone health if malabsorption is present. Another consideration for this could be whether the age of diagnosis or severity of the disease affects the individual's response to dietary supplement treatment.

Exploring the bioavailability and absorption of nutrients in celiac disease patients would also advance current literature. This study remains uncertain why the serologically positive (EMA+) participants presented significantly lower BMD than the control group, despite significantly higher dietary calcium, vitamin D, and phosphorus intake. Although nutrient malabsorption is a known clinical presentation of celiac disease, it would be beneficial to understand any additional mechanisms hindering the bone health of these individuals despite adequate dietary calcium, vitamin D, and phosphorus intake.

One theory to be explored proposes that impaired calbindin synthesis in individuals with celiac disease results in the mechanical failure of the body to properly absorb and utilize dietary calcium. Calbindin refers the calcium-binding proteins that carry calcium across the brush border membrane of the intestine. Calbindin is dependent on vitamin D for synthesis. Literature suggests that individuals with celiac disease may have reduced calbindin-D9k, directly causing diminished vitamin D levels and resulting in impaired calcium absorption.[125] Future studies may explore whether impaired calbindin synthesis resulting in decreased calcium transfer is a plausible explanation for our results.

The implications to the length of the disease should also be examined in future studies. Bone health deteriorates over decades, and this should be considered when studying the effects of celiac disease on bone health. Given the late average age of diagnosis, individuals with celiac disease have likely been experiencing nutrient malabsorption for years or even decades. A study examining treated and untreated celiac

disease patients diagnosed at different ages and lengths of celiac disease development could provide valuable insight on the implications of celiac disease duration.

APPENDIX A. ALL MULTIPLE LINEAR REGRESSION MODELS

Table 5. All multiple linear regression models for nutrient intake, status, and bone mineral density in serologically positive (EMA+) participants vs. control group

Variable	β-Coefficient	P-value	95% CI	
Energy Intake				
Kilocalories (kcal) (n=14,009)	Intercept = 2945			
Celiac disease status (ref=control)	344.2	0.046	6.6	681.8
Age, years	-10.3	0.000	-11.2	-9.3
Sex (ref=Male)	-695.2	0.000	-730.0	-660.5
Race (ref=Caucasian)	78.8	0.000	41.2	116.4
Poverty Income Ratio	5.8	0.334	-6.2	17.8
$R^2 = 0.1618$				
Carbohydrates (g) (n=14,009)	Intercept = 34.3			
Celiac disease status (ref=control)	3.1	0.763	-17.7	24.0
Age, years	-0.1	0.012	-0.2	0.0
Sex (ref=Male)	5.9	0.000	3.2	8.6
Race (ref=Caucasian)	-4.6	0.001	-7.3	-1.9
Poverty Income Ratio	-4.1	0.000	-4.9	-3.2
Energy intake (kcal)	0.1	0.000	0.1	0.1
$R^2 = 0.7591$				
Protein (g) (n=14,009)	Intercept = 16.7			
Celiac disease status (ref=control)	3.5	0.365	-4.1	11.1
Age, years	0.0	0.717	0.0	0.0
Sex (ref=Male)	-6.9	0.000	-8.1	-5.8
Race (ref=Caucasian)	-3.6	0.000	-5.2	-2.1
Poverty Income Ratio	1.3	0.000	0.9	1.6
Energy intake (kcal)	0.0	0.000	0.0	0.0
$R^2 = 0.6003$				
Fat (g) (n=14,009)	Intercept = -16.5			
Celiac disease status (ref=control)	-7.4	0.085	-15.9	1.1
Age, years	0.1	0.000	0.1	0.1

Sex (ref=Male)	3.3	0.000	2.3	4.3
Race (ref=Caucasian)	2.2	0.001	1.0	3.4
Poverty Income Ratio	0.5	0.011	0.1	1.0
Energy intake (kcal)	0.0	0.000	0.0	0.0
$R^2 = 0.7501$				
Calcium				
Dietary intake (mg) (n=14,009)	Intercept = 106.3			
Celiac disease status (ref=control)	213.3	0.007	62.3	364.3
Age, years	-0.9	0.002	-1.5	-0.4
Sex (ref=Male)	34.6	0.002	13.7	55.4
Race (ref=Caucasian)	107.9	0.000	84.5	131.3
Poverty Income Ratio	6.4	0.093	-1.1	13.9
Energy intake (kcal)	0.4	0.000	0.4	0.4
$R^2 = 0.3690$				
Total intake (mg) (n=14,009)	Intercept = -124.2			
Celiac disease status (ref=control)	281.7	0.008	75.9	487.6
Age, years	3.9	0.000	3.4	4.4
Sex (ref=Male)	155.6	0.000	129.2	182.0
Race (ref=Caucasian)	157.1	0.000	130.3	183.8
Poverty Income Ratio	20.9	0.000	12.3	29.6
Energy intake (kcal)	0.4	0.000	0.4	0.4
$R^2 = 0.2815$				
Nutrient Density (mcg/1,000 kcal) (n=14,008)	Intercept = 430.7			
Celiac disease status (ref=control)	112.1	0.011	27.4	196.7
Age, years	2.6	0.000	2.3	2.9
Sex (ref=Male)	100.5	0.000	87.4	113.6
Race (ref=Caucasian)	77.6	0.000	64.7	90.5
Poverty Income Ratio	9.5	0.000	4.9	14.1
Energy intake (kcal)	-0.1	0.000	0.1	0.0
$R^2 = 0.1137$				
Total serum calcium (mg/dL) (n=14,009)	Intercept = 9.5			
Celiac disease status (ref=control)	-0.1	0.064	-0.2	0.0
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-0.1	0.000	-0.1	0.0
Race (ref=Caucasian)	0.0	0.000	0.0	0.1
Poverty Income Ratio	0.0	0.311	0.0	0.0
Energy intake (kcal)	0.0	0.000	0.0	0.0

R^2 = 0.0119				
Vitamin D				
Dietary intake (mcg) (n=14,009)	Intercept = 0.2			
Celiac disease status (ref=control)	1.4	0.139	-0.5	3.2
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-0.2	0.126	-0.4	0.0
Race (ref=Caucasian)	0.4	0.003	0.1	0.6
Poverty Income Ratio	0.1	0.224	0.0	0.2
Energy intake (kcal)	0.0	0.000	0.0	0.0
R^2 = 0.0793				
Total intake (mcg) (n=14,009)	Intercept = -9.4			
Celiac disease status (ref=control)	4.0	0.237	-2.7	10.8
Age, years	0.3	0.000	0.3	0.4
Sex (ref=Male)	4.3	0.000	2.8	5.9
Race (ref=Caucasian)	3.1	0.000	1.9	4.3
Poverty Income Ratio	1.1	0.000	0.6	1.6
Energy intake (kcal)	0.0	0.001	0.0	0.0
R^2 = 0.0288				
Nutrient Density (mcg/1,000 kcal) (n=14,008)	Intercept = 0.3			
Celiac disease status (ref=control)	2.4	0.324	-2.5	7.4
Age, years	0.2	0.000	0.2	0.2
Sex (ref=Male)	2.7	0.000	1.6	3.7
Race (ref=Caucasian)	1.8	0.000	1.0	2.7
Poverty Income Ratio	0.5	0.013	0.1	0.9
Energy intake (kcal)	0.0	0.000	0.0	0.0
R^2 = 0.0337				
Serum 25(OH)D (nmol/L) (n=5,105)	Intercept = 39.9			
Celiac disease status (ref=control)	2.3	0.693	-10.0	14.7
Age, years	0.1	0.003	0.0	0.2
Sex (ref=Male)	4.4	0.002	1.9	6.8
Race (ref=Caucasian)	20.8	0.000	17.8	23.8
Poverty Income Ratio	1.4	0.000	0.9	2.0
Energy intake (kcal)	0.0	0.048	0.0	0.0
R^2 = 0.1810				
Serum 25(OH)D_2 (nmol/L) (n=5,106)	Intercept = -0.0			
Celiac disease status (ref=control)	0.3	0.811	-2.0	2.6
Age, years	0.1	0.000	0.0	0.1

Sex (ref=Male)	0.9	0.044	0.0	1.7
Race (ref=Caucasian)	0.2	0.645	0.7	0.1
Poverty Income Ratio	0.0	0.922	-0.3	0.3
Energy intake (kcal)	0.0	0.202	0.0	0.0
$R^2 = 0.0180$				
Serum 25(OH)D_3 (nmol/L) (n=5,106)	Intercept = 39.9			
Celiac disease status (ref=control)	2.1	0.737	-11.0	15.2
Age, years	0.0	0.169	0.0	0.1
Sex (ref=Male)	3.5	0.008	1.0	5.9
Race (ref=Caucasian)	20.6	0.000	17.9	23.3
Poverty Income Ratio	1.4	0.000	1.0	1.9
Energy intake (kcal)	0.0	0.027	0.0	0.0
$R^2 = 0.1658$				
Phosphorus				
Dietary intake (mg) (n=14,009)	Intercept = 105.6			
Celiac disease status (ref=control)	140.5	0.060	-5.9	286.9
Age, years	0.3	0.244	-0.2	0.7
Sex (ref=Male)	-40.6	0.000	-55.4	-25.8
Race (ref=Caucasian)	36.8	0.001	16.8	56.8
Poverty Income Ratio	16.8	0.000	10.4	23.1
Energy intake (kcal)	0.6	0.000	0.6	0.6
$R^2 = 0.6729$				
Total intake (mg) (n=14,009)	Intercept = 96.9			
Celiac disease status (ref=control)	135.8	0.070	-11.5	283.1
Age, years	0.5	0.041	0.0	0.9
Sex (ref=Male)	-40.3	0.000	-55.3	-25.4
Race (ref=Caucasian)	39.3	0.000	18.8	58.7
Poverty Income Ratio	17.5	0.000	11.0	23.9
Energy intake (kcal)	0.6	0.000	0.6	0.6
$R^2 = 0.6700$				
Nutrient Density (mg/1,000 kcal) (n=14,008)	Intercept = 691.3			
Celiac disease status (ref=control)	49.0	0.029	5.3	92.6
Age, years	0.4	0.001	0.2	0.7
Sex (ref=Male)	-11.9	0.000	-18.3	-5.5
Race (ref=Caucasian)	18.9	0.000	9.4	28.4
Poverty Income Ratio	7.7	0.000	4.9	10.5
Energy intake (kcal)	0.0	0.000	0.0	0.0

R^2 = 0.0410				
Serum alkaline phosphatase (U/L) (n=14,008)	Intercept = 66.0			
Celiac disease status (ref=control)	7.6	0.041	0.3	14.8
Age, years	0.2	0.000	0.1	0.2
Sex (ref=Male)	-1.0	0.041	-1.9	0.0
Race (ref=Caucasian)	-3.5	0.000	-4.7	-2.3
Poverty Income Ratio	-1.6	0.000	-2.0	-1.3
Energy intake (kcal)	0.0	0.771	0.0	0.0
R^2 = 0.0410				
Serum phosphorus (mg/dL) (n=14,005)	Intercept = 3.7			
Celiac disease status (ref=control)	0.2	0.009	0.0	0.3
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	0.2	0.000	0.2	0.2
Race (ref=Caucasian)	0.0	0.027	0.0	0.1
Poverty Income Ratio	0.0	0.168	0.0	0.0
Energy intake (kcal)	0.0	0.015	0.0	0.0
R^2 = 0.0271				
Femur				
BMC, g (n=7,035)	Intercept = 43.5			
Celiac disease status (ref=control)	-3.0	0.066	-6.2	0.2
Age, years	0.0	0.000	-0.1	0.0
Sex (ref=Male)	-13.4	0.000	-13.9	-12.9
Race (ref=Caucasian)	0.6	0.024	0.1	0.1
Poverty Income Ratio	0.4	0.000	0.2	0.5
Energy intake (kcal)	0.0	0.000	0.0	0.0
R^2 = 0.5235				
BMD, g/cm^2 (n=7,035)	Intercept = 1.1			
Celiac disease status (ref=control)	-0.1	0.014	-0.2	0.0
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-0.1	0.000	-0.1	-0.1
Race (ref=Caucasian)	0.0	0.000	0.0	0.0
Poverty Income Ratio	0.0	0.000	0.0	0.0
Energy intake (kcal)	0.0	0.015	0.0	0.0
R^2 = 0.2467				
Femoral Neck				
BMC, g (n=7,035)	Intercept = 5.5			
Celiac disease status (ref=control)	-0.4	0.012	-0.6	-0.1

Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-1.0	0.000	-1.0	-0.9
Race (ref=Caucasian)	0.0	0.216	-0.1	0.0
Poverty Income Ratio	0.0	0.004	0.0	0.0
Energy intake (kcal)	0.0	0.004	0.0	0.0
$R^2 = 0.3926$				
BMD, g/cm^2 (n=7,035)	Intercept = 1.1			
Celiac disease status (ref=control)	-0.1	0.005	-0.1	0.0
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	-0.1	0.000	-0.1	-0.1
Race (ref=Caucasian)	0.0	0.000	0.0	0.0
Poverty Income Ratio	0.0	0.024	0.0	0.0
Energy intake (kcal)	0.0	0.013	0.0	0.0
$R^2 = 0.2713$				
Total Spine				
BMC, g (n=5,151)	Intercept = 70.5			
Celiac disease status (ref=control)	-3.0	0.268	-8.4	2.4
Age, years	-0.1	0.000	-0.1	-0.1
Sex (ref=Male)	-13.0	0.000	-14.2	-11.9
Race (ref=Caucasian)	2.3	0.000	1.3	3.2
Poverty Income Ratio	0.6	0.000	0.4	0.8
Energy intake (kcal)	0.0	0.014	0.0	0.0
$R^2 = 0.2603$				
BMD, g/cm^2 (n=5,151)	Intercept = 1.1			
Celiac disease status (ref=control)	-0.1	0.127	-0.1	0.0
Age, years	0.0	0.000	0.0	0.0
Sex (ref=Male)	0.0	0.000	0.0	0.0
Race (ref=Caucasian)	0.0	0.521	0.0	0.0
Poverty Income Ratio	0.0	0.003	0.0	0.0
Energy intake (kcal)	0.0	0.221	0.0	0.0
$R^2 = 0.0569$				

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