Research Article

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A Higher Ratio of Undercarboxylated to Total Osteocalcin Is Linked to Decreased Physical Function and a Higher Rate of Hospitalizations Related to Falls within 15 Years:The Longitudinal Study of Aging Women in Perth.

Cassandra Jhmith [1,2] , Loshua Rewis, Aarc Lim.

1. Department/University:Institute for Health and Sport (IHES), Victoria University, Melbourne, Australia.
2. Australian Institute for Musculoskeletal Science (AIMSS), University of Melbourne and Western Health, St. Albans, Australia.
3. School of Medical and Health Sciences, Edith Cowan University, Perth, Australia.
4. Centre for Kidney Research, Children's Hospital at Westmead, School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia.

***Corresponding author**

Cassandra Jhmith,
Department/University , Institute for Health and Sport (IHES), Victoria University, Melbourne, Australia.

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ABSTRACT

Undercarboxylated osteocalcin (ucOC) has been linked to strength and muscle mass maintenance, according to data from animal models. Although there is little information, muscle strength, physical function, and the risk of falls may all be correlated with the human ucOC to total (t)OC ratio. We investigated the hypothesis that, in older women and hospitalizations attributable to falls lasting 15 years, ucOC and the ucOC/tOC ratio are related to muscle function (muscle strength and physical function). As part of the Perth Longitudinal Study of Aging Women, 1261 older women with a mean age of 75.2 ± 2.7 years had their serum tOC and ucOC measured (1998 to 2013). Grip strength and the timed-up-and-go (TUG) were measured at baseline and after five years. Hospital Morbidity Data Collection (HCDC) collected hospitalizations related to falls throughout a follow-up of 14.5 years through the Western Data Linkage System Australia. Compared to quartile 1, women with a greater ucOC/tOC ratio (quartile 4) performed less quickly on the TUG at baseline (~0.68 seconds, p <.01). Between quartiles, there was no significant difference (p >.05) in grip strength or the 5-year change in TUG and grip. The fear of falling affecting indoor, outdoor, and combination activities varied considerably between quartiles (p <.05). Increased walking aid use, fear of falling, and worse TUG performance at baseline and 5-year change in performance were all significantly correlated with higher ucOC/tOC (all p <.05). Although there was no 5-year change in strength, higher ucOC was associated with decreased grip strength at baseline (p <.05). Hospitalizations due to falls were more common in those with the greatest ucOC/tOC (unadjusted log rank, p =.004), and this difference remained significant even after after correcting for important factors (p =.004, 95% confidence interval [CI] 1.09–1.57, and Hazard Ratio [HR] = 1.31). We found that a significant number of older women with high ucOC/tOC ratios also had decreased physical function, including a long-term reduction in it and a higher risk of hospitalizations due to falls. The risk of harmful falls can be decreased by implementing prevention and intervention techniques as soon as women who are at higher risk are identified.

Keywords : AGING; SKELETAL MUSCLE; BONE-MUSCLE INTERACTIONS; SARCOPENIA

INTRODUCTION

Before losses in muscle mass become apparent, there is a rapid loss in muscle function after the fourth decade of life. (1–3) The term "muscle function" refers to the marriage of physical function and muscle strength. Reduced muscular function has been linked to an increased risk of fractures and falls, as well as functional disability, loss of independence, and early death.(4–7) As people live longer, there will likely be an increase in excess morbidity and death from impaired muscle

function in older people living in the community. This will put more strain on individuals, families, and public health systems throughout the world.(4,8–10) This emphasizes how important it is to find potential clinical markers that could help identify those who are at risk of falling and experiencing a decline in muscular function.Strategies for prevention can be implemented.

The most prevalent non-collagenous bone protein, osteocalcin (OC), is produced and secreted by mature osteoblasts during the production of new bone and is employed as a bone turnover marker in clinical settings.(11,12) There are two main types of organic carbon: cOC, which is γ-carboxylated, and ucOC, which is OC that doesn't have γ-carboxylation at one or more sites.(13) Due to its high in vitro binding capacity to hydroxyapatite, cOC is assumed to be primarily found in bone. In contrast, some, but not all,(14,15) have reported that ucOC functions in a paracrine and endocrine manner, influencing muscle mass and strength as well as glucose metabolism. Nevertheless, the majority of these findings are restricted to preclinical and animal research.(16–24)

As seen before, the ucOC/tOC ratio is higher in older in comparison to young adults,(25) suggesting that the ratio—rather than the total or individual forms separately—is a stronger indicator of the aging effect on OC. This may be partly explained by a decreased consumption of vitamin K, which is necessary for the carboxylation of OC.(26)

Indeed, increased consumption of vegetables and their constituents—vegetables are a rich source of vitamin K1—was linked to better muscle function, increased muscle strength, and a decreased risk of injurious falls in older women. This suggests that the ucOC/tOC ratio may be involved, albeit it was not assessed.27–29 Consequently, more research is needed to determine whether ucOC or its ratio are viable choices in relation to muscle function and the likelihood of harmful falls.

Thus, we investigated the idea that a greater ratio would be beneficial in a sizable group of older women of ucOC/tOC would be linked to a decrease in muscular function (strength and physical function) and a higher long-term risk of hospitalizations due to falls.

MATERIALS AND METHODS

Women recruited for the Perth Longitudinal Study of Aging in Women (LSAW; http://www.lsaw.com.au/) were included in the population. The word "LSAW" refers to a group of three studies conducted within the same community during a 15-year period (1998 to 2013). Originally, white women were enrolled in the previously mentioned Calcium Intake Fracture Outcome Study (CAIFOS), a 5-year, double-blind, randomised controlled experiment, to see if daily calcium supplementation may prevent fractures.Thirty women who were not on hormone replacement therapy or other medications known to alter bone metabolism and whose predicted survival was more than five years were included. Using the electoral roll, women (n = 1500) who were at least 70 years old were selected from the general population in Western Australia. Women were invited to take part in two follow-up observational studies after the 5-year study concluded.

The 14.5-year follow-up period began in 1998 and ended in 2013. A further 39 women were eliminated from the study because they were a part of a sub-study that looked into the combination of calcium and vitamin D supplementation, citing the connection between falling and vitamin D (31). Written informed permission was acquired by each subject. The University of Western Australia's Human Ethics Committee gave its permission. The two trials met the Declaration of Helsinki and were retroactively registered on the Australian New Zealand Clinical Trials Registry (CALIFOS trial registration number #ACTRN12615000750583 and PLSAW trial registration number ACTRN12617000640303). The Human Research Ethics Committee of the Department of Health, Western Australia, granted consent for the use of linked data (project no. 2009/24).

Participant attributes Details about the trial's methodology have already been extensively publicized.(32) To put it briefly, the participant's medical history and current medication schedule were gathered, and the International Classification of Primary Care-Plus (ICPC-Plus) technique was then used to code the data.(33) The ICD-10 coding system's coding technique permits the grouping of many names for pathologic entities that are similar to one another. The participants' past medical records and current prescriptions provided information regarding any pre-existing diabetes. Where available, participants were asked to confirm this information with their regular practitioner.

body makeup

Digital scales were used to measure body weight to the closest 0.1 kg, and a wall-mounted stadiometer was used to measure height to the closest 0.1 cm. Participants wore airy attire.

They without shoes and socks. Next, the body mass index (BMI) (kg/m2) was computed. Using the Hologic Acclaim QDR4500A dual-energy X-ray absorptiometry machine (Hologic Corp., Waltham, MA, USA), whole-body composition was measured at baseline or after a year. The machine was operated by multiple operators, and data was evaluated in accordance with a defined methodology. A supervisor checked each scan to ensure that it was positioned correctly. Every research participant session began with the scanning of a calibration phantom, which was then assessed using the Shewart rule application offered by Hologic. In our lab, coefficients of variation (CVs) are less than 2%. Upper and lower limb mass

(bone free) were added to determine appendicular lean mass.

Muscle characteristics and degrees of physical activity

The dominant hand's grip strength was measured with a handheld dynamometer (Hand Grip Dynamometer, TEC, Clifton, NJ, USA) and recorded as the highest of three attempts (34). The timed-up-and-go (TUG) test was used to assess patients' physical function. Participants were given a time limit to get out of a chair, walk three meters, turn around, and then get back into the chair.(35) Prior to starting the TUG exam, participants completed one practice trial. At baseline, physical activity questionnaires were finished. Inquiries were made of the participants regarding their involvement in sports, leisure, and/or consistent physical activity during the three months preceding their baseline assessment. The level of activity, expressed in kilojoules per day, was determined using an established approach was previously detailed in detail (36, 37).type of activity, amount of time spent doing it, and body weight of the participant.(38) Calculating the vitamin K content of food We used a validated, semiquantitative food-frequency questionnaire (FFQ) to measure dietary vitamin K intake at baseline for the preceding 12 months because vitamin K is correlated with the ratio of cOC to ucOC.(39) Our organization has already provided a description of the procedure.(40, 41) In a nutshell, the mean vitamin K value (μg/g) was multiplied by the number of food items taken (g/d) to determine the total dietary intake of vitamin K. Values for vitamin K1 (phylloquinonone) in FFQ food products were sourced from the National Nutrient Database for Standard Reference (Release 28) of the US Department of Agriculture. (42) The values of vitamin K2 (menaquinone; MK-4 to MK-9) for foods that fit the FFQ diet came from Values for vitamin K2 (menaquinone; MK-10) and Schurgers and Vermeer (43) for FFQ food products were acquired from Manoury and associates.In cases where vitamin K-containing foods were unavailable, a value of 0 μg/g was utilized.

biochemical assays

Women whose serum was examined for tOC and ucOC from fasting blood samples taken in 1999—the first year of the CAIFOS randomized controlled trial—were the only ones included in the current post hoc analysis (n = 1261). The samples had never been through a freeze-thaw cycle before. Three more individuals were disqualified for having an unlikely ucOC/tOC ratio (>1.0). Using the Roche Cobas N-Mid Osteocalcin test (Roche Diagnostics, Mannheim, Germany), sandwich electrochemiluminescence immunoassay was used to assess serum tOC. At values of 18 and 90 ng/mL, the interassay CVs were 2.3% and 4.8%, respectively. The same reagent assay was used to quantify serum ucOC after the serum samples were pretreated using 5 mg/mL of hydroxyapatite (Calbiochem, MilliporeSigma, Burlington, MA, USA), in accordance with the protocol developed by Gundberg and colleagues (13), as well as Chubb and associates.(45) At 100 and 15 ng/mL of OC, the interassay accuracy for the percentage binding of cOC was 8% and 12%, respectively.

We evaluated renal function as a potential confounding factor for OC, since studies have linked serum OC levels to reduced renal clearance and chronic kidney disease (CKD). (46) To estimate glomerular filtration rate (eGFR), we utilized the creatinine-derived equation from the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI), which we have previously discussed in detail.At baseline, venous blood samples were taken between 8:30 and 10:30 a.m. following an overnight fast. Separated plasma was kept in a freezer set at -80 degrees Celsius. The quantities of 25OHD2 and 25OHD3 in plasma were measured at the using an approved liquid chromatography tandem mass spectrometry method at the Details about the trial's methodology have already been extensively publicized.(32) To put it briefly, the participant's medical history and current medication schedule were gathered, and the International Classification of Primary Care-Plus (ICPC-Plus) technique was then used to code the data.(33) The ICD-10 coding system's coding technique permits the grouping of many names for pathologic entities that are similar to one another. The past medical history and current medications of the participants were used to gather information on pre-existing diabetes. Where available, participants were asked to confirm this information with their regular practitioner.

body markeup

Digital scales were used to measure body weight to the closest 0.1 kg, and a wall-mounted stadiometer was used to measure height to the closest 0.1 cm. Participants wore airy attire. and didn't have shoes or socks on. Next, a body mass index (BMI) (kg/m2) calculation was made. Using a dual-energy X-ray absorptiometry machine (Hologic Acclaim QDR4500A; Hologic Corp., Waltham, MA, USA), several operators measured the whole-body composition at baseline or after a year, and the data was processed in accordance with an established protocol. A supervisor checked each scan to make sure the positioning was proper. At the start of each study participant session, a calibration phantom was scanned and assessed using the Shewart rule application offered by Hologic. We have less than 2% coefficients of variation (CVs) in our lab. The total upper and lower limb mass (bone free) was used to compute appendicular lean mass.therapy, diabetic management, history of smoking, and prior ASVD.

Using a restricted cubic spline and the R package "survival" with df = 4, the dose-response relationship between ucOC/tOC and falls-related hospitalizations was investigated. The reference level for ucOC/tOC was set at 0.404, and all covariates were

adjusted as per the multivariable-adjusted model. We conducted additional analyses and added total 25OHD and the season of blood sample (summer/autumn and winter/spring) to our multivariable-adjusted model because low vitamin D status is thought to be a risk factor for falls (51). Since blood pressure may have an impact on the risk of falls, we conducted additional analysis and added mean systolic blood pressure to our multivariable-adjusted model. Lastly, we ran a sensitivity analysis using measurements of muscle function.

RESULTS

There were 1261 women in all, and Table 1 shows the women's characterisation. In Table 2, women were categorized into quadriles according to their ucOC/tOC ratio (Q1 being the lowest and Q4 being the highest group) in order to compare the groups' muscle strength and functional measures.

In comparison to women in Q1 and Q2, women with greater ucOC/tOC (Q3 and Q4) had a little but significantly higher BMI (~1 kg/m2) (all p <.05). When comparing women in Q1 to Q3, their TUG test times were slower (mean difference ~0.68 seconds) in Q4 (p =.026,.031, and.008, respectively; ANOVA p =.004).The use of walking aids varied significantly between quartiles.(p =.012). There were significant differences among quartiles (p =.026,.044, and.017, respectively) in the fear of falling that restricted home, outdoor, and combined house and outdoor activities (Table 2).

Neither the 5-year change in TUG nor grip strength (not shown in table, both p >.05) nor the grip strength appendicular lean mass, metabolic equivalents (METs), or physical activity levels showed any significant variations across quartiles.

There were correlations found between the metrics measuring muscle function and OC (tOC, ucOC, and ucOC/tOC). All adjusted models showed a significant relationship between a higher ucOC/tOC ratio and a worse (slower) time to finish the TUG test, but the correlation was minor (r range 0.06 to 0.1, p =.0001,.007, and.050, respectively). Significantly but adversely correlated was grip strength.

with ucOC (all adjusted models); still, there was little correlation (r = -0.06, p =.033,.028, and.053, in that order). The TUG's five-year change score, which is not shown in the table, was significantly correlated with higher ucOC/tOC ratios in adjusted models 1 and 2. The significance was lost when eGFR was further adjusted, and the correlation was only weak (r range 0.06 to 0.08, p =.010 and.032, respectively). While the link was minor (r range 0.06 to 0.09, p =.002,.024, and.041, respectively), a greater ucOC/tOC ratio was significantly correlated with walking assistance use and fear of falling restricting home and combined house and outdoor activities using model 1. The only factor that continued to be strongly associated, albeit weakly, was walking aid use.modifying for the second model (p =.034, r = 0.06). When eGFR was taken into account further, significance was lost. For appendicular lean mass or the 5-year change in grip strength, there was no statistically significant association across all models.

A nonlinear association was shown by the multivariable dose-response relationship between ucOC/tOC and hospitalizations linked to falls.

A nonlinear association between ucOC/tOC and the relative risk of a hospitalization due to falls over a period of 14.5 years was shown in Fig. 1. A nonlinear correlation was seen when examining the link between ucOC/tOC and hospitalizations related to falls (Fig. 2A, B). Q1 and Q2 had similar risks, while Q3 and Q4 had similar risks. For all subsequent analyses, we therefore merged Q1 and Q2 (referent group) and Q3 and Q4 (elevated ucOC/tOC ratio). Kaplan–Meier (incorrect) additionally Figs. 2A and B, respectively, display multivariable-adjusted Cox survival curves by the median of ucOC/tOC (Supplemental Fig. S1 for same analyses by quartiles of ucOC/tOC). A higher relative risk of falls-related hospitalizations was associated with those having an ucOC/tOC ratio above the median (unadjusted log rank, p =.004). This risk persisted in the multivariable-adjusted model (hazard ratio [HR] = 1.31, 95% confidence interval [CI] 1.09–1.57, p =.004). We conducted further adjustment analyses to investigate the impact of grip strength and physical function (TUG) on the association between ucOC/tOC and the probability of an injury from falls. A falls-related hospitalization's relative risk was inversely correlated with ucOC/tOC when muscle function (TUG and GS) was included in the multivariable-adjusted model (HR = 1.12, 95% CI 0.99–1.28, p =.078). When Similar relative risks for a falls-related hospitalization were noted when comparing persons with greater to lower ucOC/tOC (HR = 1.34, 95% CI 1.13–1.62, p =.002) when 25OHD (and season the sample was gathered) was included in the multivariable-adjusted model. When comparing women with greater to lower ucOC/tOC, the addition of mean systolic blood pressure to our multivariable-adjusted model did not increase the estimates for fall-related hospitalization (HR = 1.29, 95% CI 1.07–1.54, p =.007).

DISCUSSION

According to our findings, the ucOC/tOC ratio may be helpful in identifying a significant number (about 50%) of older women who have lower TUG, including its decline, and a higher risk of hospitalization due to injurious falls. Based on quartile stratification of ucOC/tOC levels, we compare women and find that (i) those with the highest levels compared to those with the lowest lowest had the slowest TUG performance and (ii) the ratio was also sensitive enough to identify the presence of fear of falling, which limited activities both indoors and outdoors and suggested that falls may have already happened. Furthermore, even after controlling for additional variables,

our findings show a significant correlation between a greater ucOC/tOC ratio and (iii) inferior TUG performance and declining performance over a 5-year period, as well as (iv) an increased risk of falls-related hospitalizations. Lastly, this link was diminished when controlling for muscle function measurements (TUG and GS), indicating that a possible mechanism for the association between ucOC/tOC and harmful falls may be compromised muscle function.

Though its role in humans is less apparent, evidence from preclinical and animal research suggests that ucOC may be involved in strength, metabolism, and muscle maintenance. (16, 18–24) Women with higher ucOC/tOC ratios, according to our research, had less physical function, less mobility, and a higher fear of falling. We further show that the association between the ucOC/tOC ratio and the relative hazard of hospitalizations attributable to falls is significantly influenced by physical function (TUG), indicating that declining function is linked to rising ucOC/tOC ratios and rising fall risk. In the past, we have seen that older women with greater ucOC/tOC ratios had stronger muscles; (20) but only strength was measured, not physical function. The fact that the subjects were either fasting or fed when the blood was drawn could be the reason for the contradictory findings. Blood was drawn in the morning for both investigations; however, in the current study, women blood was drawn following an overnight fast, as opposed to the previous study's blood sample procedure, which involved a light lunch. It has previously been shown by us and others that a meal and/or glucose load can decrease bone indicators such as OC and ucOC.52–55 As a result, this could have an impact on the correlations and make it challenging to compare various studies. Notably, comparable findings across the two trials suggest that, at least in humans, the ucOC/tOC ratio may be a more sensitive indication of physical function and potentially falls-related clinical outcomes than ucOC alone.

Circulating tOC levels are employed in clinical settings as a proxy measure for bone turnover (11,12,56–58), and our research has demonstrated that aging is linked to a U-shaped pattern for every OC form in males.(25) Only total organic carbon (tOC) is currently assessed clinically. However, new research—including the work presented here—indicates that more may be known about the dynamics of OC, its forms, and how they relate to clinical outcomes. In this work, we show that older women who have higher ucOC/tOC ratios—a sign of lower vitamin K status—are more likely to be hospitalized for falls-related causes. This has therapeutic significance since low vitamin K status may be harmful. Significantly, increased vitamin K intake has been linked to better bone quality, decreased risk of fracture, and enhanced muscle performance as well as a decrease in falls.(27, 28, 40) Overall, our results are consistent with those of others who demonstrate that lower cOC/tOC (or alternatively, higher ucOC/tOC) can predict the risk of fracture in older men (59), but this adds another possible mechanism: impaired physical and muscle performance. Compared to ucOC alone, the ratio seems to have a stronger correlation with falls risk and physical function in older women.

The results of the present investigation could be partially accounted for by age-related modifications to the skeleton and skeletal system in an effort to preserve appropriate bone homeostasis. The potential correlation between the aging-related increase in ucOC and the degradation of bone's material properties is worth considering. Other possible compensatory processes could be described by the deteriorating muscle changing the physiology of the osteoblasts in an effort to stimulate the failing osteoblasts, possibly through a biochemical or biomechanical cross-talk.(60,61) An additional explanation would be that as we age, our bodies require more vitamin K to preserve the health of our muscles and bones. (27, 28, 40, 62, 63) Interestingly, in our group, women with lower dietary vitamin K intake and higher ucOC/tOC levels were likewise associated with poorer muscle function metrics. Furthermore, their ucOC/tOC levels would have been at the upper bound of our previously suggested threshold limits for older men of comparable age.Now, we build on our earlier research by proving that, in older women, a greater ucOC/tOC ratio is associated with worse TUG performance and a higher chance of hospitalization for falls, which is partially explained by weakened muscles. This shows that the ucOC/tOC ratio might make it possible to identify people who are at risk early in the clinical environment.to improve poor physical function and stop falls in the future.

Among our study's strengths is the fact that we looked into the longterm link between ucOC/tOC ratio in relation to falls risk and muscular function in a sizable sample of senior women. The fact that all of the study's samples were collected early in the morning and during a fast explains how the circadian rhythm is known to affect OC.(52–54) Additionally, this is the first study to look at the connections between time to falls-related hospitalization data and OC, ucOC, and the ucOC/tOC ratio and markers of muscle function. Additionally, the same technician and laboratory used the same methodology for all OC analyses, reducing the amount of information that may be applied to different ethnic groups.variance brought on by a technical glitch.

Our study has certain possible limitations. Despite the size of the data collection, it mainly contains information from older, mostly white women; as a result, our conclusions might not be Additionally, because the study design was observational in nature, we are unable to draw conclusions about causality from our data. We have analyzed ucOC using the techniques suggested by Gundberg and colleagues (13). Nevertheless, a lot of technical information is required to determine the levels, such as the antibody, the hydroxyapatite's specific binding

capability, the amount of phosphate, or the ELISA that was employed. Since different research groups examine ucOC using different methodology, the results of this study might not apply to other studies that have employed alternative approaches. Future research should examine how muscle metrics and falls outcomes in men relate to OC, ucOC, and the ucOC/tOC ratio as these may differ from those seen in women. An additional restriction is the use of known sedatives, anti-epileptic medications, and antidepressants, which raise the risk of falls, were not available for this study at the baseline visit. Last but not least, it will be critical that further research independently confirm our results in order to offer more proof that ucOC/OC can be used to identify older women who are more likely to require hospitalization due to falls.

In conclusion, low physical function and a higher likelihood of hospitalization due to falls are linked to higher ucOC/tOC ratios in older women. By identifying women at higher risk early on, preventative and intervention measures may be implemented, lowering the chance of falls that result in injuries.

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