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CaMos
Canadian Multicentre Osteoporosis Study
Étude Canadienne multicentrique sur l'ostéoporose

BONE HEALTH *for life*

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Dr. David Goltzman

What have we learned from CaMos?

DR DAVID GOLTZMAN, *CO-PRINCIPAL INVESTIGATOR, MONTREAL*

Twenty years ago, close to 10,000 courageous and committed participants enrolled in CaMos, and in doing so, dedicated themselves to advancing our understanding of osteoporosis. Over this period, the CaMos participants have made outstanding contributions both to our ongoing study and to the field of osteoporosis research generally.

Here are some of the major findings based on the information that you have provided over the years:

We found, in contrast to other studies, that hip fracture risk is similar in men and women. While women are more prone to forearm and wrist fractures, men are more prone to rib fracture.

We were able to identify genes that appear to be implicated in the maintenance of bone mineral density (BMD), and the development of osteoporotic fracture.

We showed that the development of the shape of bone may influence susceptibility to osteoporotic fractures.

We identified a series of clinical factors which predict osteoporotic fractures and helped develop tools that allow the use of these risk factors by clinicians to aid in osteoporotic fracture risk prediction.

We found evidence that the presence of spine fractures on X-ray are very strong predictors of future fracture risk, even if they cause no pain.

We showed that some drugs, eg. those commonly used for treatment of depression (selective serotonin reuptake inhibitors), may further increase the risk of osteoporosis and fractures.

We showed that increased total calcium and vitamin D intake appeared to improve bone health. A higher total dairy intake, a major source of calcium and vitamin D, is associated with apparent better bone health in women and men, and reduced fracture risk in men aged 50 and over.

We found that low protein intake (below 15% of total energy intake) may lead to deleterious changes in indices of bone health and increased fracture risk in both women and men aged 50 and over.

These findings represent just a few examples of how, with your invaluable help, we have been able to advance the field both in Canada and internationally.

On behalf of the CaMos Research Group, I would like to very warmly thank our participants for their continued support and their commitment to making CaMos the world-class study it is. ◆

Question from the participants

My grand-daughter is pregnant and planning to breastfeed. Will a pregnancy or nursing the baby have any effects on her bones?

Answer by DR. CHRISTOPHER KOVACS
CO-DIRECTOR FOR THE ST. JOHN'S CENTRE

Dr. Christopher Kovacs

A brief answer is yes in the short term – especially when breastfeeding – but usually no in the long term. I need to give a fuller answer to explain this.

Starting in the third trimester and continuing after birth, every baby needs a lot of calcium for the developing skeleton. The mother provides that calcium during pregnancy and breastfeeding, but she also needs to meet her own body's needs.

During pregnancy the intestines double their efficiency of absorbing calcium, and this serves to meet the baby's and mom's needs. In fact for most women, more calcium is absorbed than required, with the excess excreted into urine. Because of this naturally occurring adaptation, the recommended daily intake of calcium for pregnant women is the same as for non-pregnant women. But if a woman has a

(see **Question**, page 2) ➤

➤ (**Question** from page 1)

very low intake of calcium, or very poor absorption because of an intestinal condition, then this adaptation won't help. Instead calcium will be borrowed from her skeleton to provide what the baby needs, and mom's bone density will decline. Rarely this drop in bone density can be enough to cause spine fractures late in pregnancy or soon after the baby is born. When fractures do occur they're usually in women with poor intake or absorption of calcium, or other conditions that made the bones weak before pregnancy.

Breastfeeding requires that a similar daily amount of calcium be provided to the baby through milk production, but the adaptation during this time frame is different. Several changes, including production of a hormone by the breasts, and low estrogen levels, combine to stimulate substantial borrowing of calcium from bone. In fact most of the calcium in milk appears to come from the mother's skeleton and not her diet. This leads to an average 8% drop in the bone density of the spine during six months of breastfeeding, with losses as great as 20% in some women. The more milk a woman produces, the more the bone density declines. Consuming extra calcium doesn't prevent the borrowing from bone. In most women this drop in bone density happens silently with no consequences. But occasionally the drop in bone density and strength is enough to provoke fractures, especially in the spine.

The most fascinating and reassuring aspect of these adaptations to pregnancy and breastfeeding is that the skeleton restores itself afterward. Bone density increases rapidly over the 6 to 12 months after the baby is weaned, including in the rare women who unfortunately suffered fractures. We don't know what stimulates the skeleton to recover. After most other causes of bone loss, recovery is slow and partial at best, whereas any losses caused by pregnancy and breastfeeding appear to be fully and rapidly restored. This effect is so pronounced that in dozens of studies of older women, a history of pregnancy or breastfeeding does not increase the risk for osteoporosis. In fact in about a dozen such studies, pregnancy and breastfeeding reduced the risk of osteoporosis.

And so in a healthy woman consuming adequate calcium – about 1,000 to 1,200 mg daily from all sources – her skeleton should be unaffected by pregnancy, but will have a silent decline in bone density while breastfeeding. In the long run her bones may be stronger for having gone through each interval of pregnancy, breastfeeding, and recovery. ◆

Further reading:

Kovacs CS. Maternal mineral and bone metabolism during pregnancy, lactation, and post-weaning recovery. Physiological Reviews 2016; 96: 449-547.

Kovacs CS and Ralston SH. Presentation and management of osteoporosis presenting in association with pregnancy or lactation. Osteoporosis International 2015; 26(9): 2223-2241.

The CaMos Bone Quality Study (BQS) Progress and Follow-up

DR JONATHAN D. ADACHI, *PRINCIPAL INVESTIGATOR AND DIRECTOR FOR THE HAMILTON CAMOS CENTRE*

DR ANDY KIN ON WONG, *DIRECTOR FOR THE BQS*

Dr. Jonathan Adachi

Thanks to the volunteerism of women between the ages of 60-85 at 6 of the 9 CaMos sites across Canada who were approached to participate in the CaMos Bone Quality Study, we were able to recruit over 800 participants. Scans on the high and low-resolution CT machines were completed on bones and muscles at baseline between 2011 and 2013. We are now in follow-up phase and just on our way to completing the third year of follow-up. We wish to continue our follow-up efforts up to at least 5 years so that we can measure associations between bone and muscle measurements and fractures, falls, and changes in frailty that are observed over time. The BQS will continue these follow-up activities either by collaborating with CaMos or independently. The messages drawn from our analyses of the baseline and follow-up data can have strong impact on how doctors can manage patients with osteoporosis in the future.

We recently demonstrated that bone information from the low-resolution CT is comparable to that achieved using its high-resolution counterpart. A single image slice from the low-resolution scanner was already able to associate with fractures in the past to a level that is just as strong as a deck of 110 images from the high-resolution scanner. Because of the lower cost associated with the low-resolution scanner versus that of the high-resolution scanner, this means that we could obtain detailed structural information about bone at a much-reduced cost. The high-resolution scanner, however, remains superior in measuring changes over time more sensitively than the low-resolution scanner.

We look forward to our continued interactions with CaMos BQS participants. ◆

Recent CaMos Publications

Characteristics of hyperparathyroid states in the Canadian Multicentre Osteoporosis Study (CaMos) and relationship to skeletal markers.

Clin Endocrinol (Oxf), 2015 March;82(3):359-368

by Claudie Berger

Parathyroid hormone (PTH) is a hormone produced by the parathyroid glands in the neck which is required for regulating normal calcium and phosphorus metabolism in the body. Excessively high concentrations of PTH in the blood can

(see **Publications**, page 3) ➤

➤ (**Publications** from page 2)

however produce bone destruction. Due to differences in the definition of high PTH, it is important to determine whether a given "normal" range (reference range) of PTH, as established in the laboratory, truly separates normal and abnormal function of the hormone. We therefore examined the relationship of serum PTH levels, defined as "within the normal range", to levels of bone mineral density. We found that even within the range of "normal", skeletal reductions could be identified in those with PTH levels in the higher regions of the normal range. Therefore, in addition to those with clearly elevated PTH levels, this study identified an increased number of participants having PTH-associated reduced bone mass which may lead to more participants at risk for skeletal abnormality. Long term assessment is now needed to further define whether maintenance of PTH in the lower part of the "normal" range would be optimal for preserving bone mass over the long term.

Comparison of fracture risk prediction among individuals with reduced and normal kidney function Clin J Am Soc Nephrol, 2015 April;10(4):646-53 ***by Kyla Naylor***

The World Health Organization's Fracture Risk Assessment Tool (FRAX) is widely used to predict future fractures using a procedure that includes age, sex and several clinical risk factors for fracture. Men and women with chronic kidney disease (CKD) have a higher fracture risk. The factors in the FRAX method that are associated with fracture risk in the general population may not accurately guess future fracture in individuals with reduced kidney function and therefore, the usefulness in CKD is unknown. Our study addresses these limitations, using data from CaMos to characterize the practicality of the FRAX method to predict fractures between patients with reduced and normal kidney function. We found that the ability of FRAX to make fine distinctions of major osteoporosis fractures was similar and independent of renal function. Therefore, FRAX may be a good tool to assess fracture risk in individuals with reduced kidney function. However, further studies are needed before FRAX can be used routinely in patients with reduced kidney function.

A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and its Relationship to FRAX J Bone Miner Res., 2016 May; 31(5):940-8 ***by Eugene McCloskey***

Trabecular bone score (TBS) is an index derived from lumbar spine dual-energy X-ray absorptiometry (DXA) images. TBS is a bone mineral density (BMD)-independent predictor of fracture risk. We used individual-level baseline and follow-up data from 14 prospective population-based cohorts (n=17,809 men and women). The results show that TBS is a consistent and significant predictor of fracture risk and provides information independently of FRAX in men and women from separate, international cohorts including multiple ethnicities.

Associations of protein intake and protein source with bone mineral density and fracture risk: A population-based cohort study. J Nutr Health Aging, 2015,19(8):861-8 ***by Lisa Langsetmo***

Fractures, especially those occurring from normal activities, are the main health threat of osteoporosis. High dietary protein has been assumed to cause lower bone mineral density and greater fracture risk. Previous studies are conflicting and few studies have assessed potential differences related to differing protein sources. We found that low protein intakes were associated with increased risk of bone brittleness and main osteoporotic fracture in post-menopausal women and men ages 50 and older compared to moderate intake. Higher protein intakes were associated with similar fracture risk when compared to moderate intake. Evidence suggests that adequate protein intake is an important risk factor that can be associated with reduced risk of fracture occurring as a result of normal activities.

Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature, 2015 Oct 1;526(7571):112-7 ***by Hou-Feng Zheng***

Recently, genetic discoveries have generally focused on common alleles identified through genome-wide association studies. The extent to which low-frequency and rare alleles contribute to complex traits and disease in the general population is mainly unknown. Bone mineral density (BMD) is highly heritable, and has been previously associated with common genetic variants. In this study we identify novel DNA component that do not translate into protein sequences with large effects on BMD and fracture in individuals of European ancestry from the general population. We identified a low-frequency DNA sequence that does not translate into a protein sequence near a novel locus, EN1, with an effect size fourfold larger than the mean of previously reported for lumbar spine BMD. This low-frequency sequence is also associated with a decreased fracture risk. These findings suggest that EN1 plays an important role in bone makeup and that low-frequency sequences that do not translate into protein sequences mapping near EN1 have large effects on BMD and risk of fracture, thereby providing the basis for whole-genome sequencing. ◆

Regional News

New Co-Director of the Vancouver Centre


Dr Shirin Kalyan

Dr. Shirin Kalyan is Assistant Professor in Endocrinology & Metabolism at the University of British Columbia (UBC). She received her PhD in Experimental Medicine from UBC and completed Post-doctoral Fellowships in Reproductive Endocrinology and Immunology. In 2010, Dr. Kalyan was awarded a fellowship from the Alexander von Humboldt Foundation of Germany to investigate the mechanism leading to the serious adverse drug effects of a common medication used for the treatment of osteoporosis and cancer-associated bone disease. Her research focus is to advance the knowledge of the complex immune-endocrine relationship that confers optimal bone health, metabolism and reproductive function to guide the safest and most effective therapies for diseases rooted in this dynamic intersection.

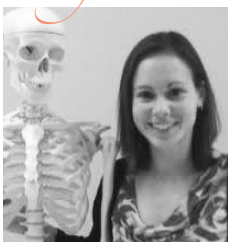
Co-Director of the Toronto Centre

Dr. Angela Cheung has been a member of the CaMos Research Group since 2013 and in November 2015 she was named Co-Director of the Toronto Centre. She is the Founding Director of University Health Network Osteoporosis Program, the Founding Director of Centre of Excellence in Skeletal Health Assessment (CESHA) and Professor of Medicine at the University of Toronto. Dr. Cheung was recently awarded the Tier 1 Canada Research Chair in Musculoskeletal and Postmenopausal Health for her outstanding work to improve the quality of life, health and healthcare of people with musculoskeletal conditions, especially postmenopausal women.

Director of the Calgary Centre

Dr. David Hanley, Centre Director of the CaMos Calgary Centre, was recently honored with having the Osteoporosis Centre named after him. The centre is known as the Dr. David Hanley Osteoporosis Centre. Dr Hanley's vision was to create a facility in Calgary, servicing Southern Alberta, staffed with health professionals, to treat people with osteoporosis. He was the founding director of the Osteoporosis Centre. Dr. Hanley is recognized both nationally and internationally for his contribution to the advancement of osteoporosis knowledge, awareness and research. ◆

Congratulations


Dr Lauren Burt

2015 Osteoporosis Canada – CaMos Fellowship Award

Dr. Lauren Burt is the recipient of the 2015 Osteoporosis Canada - CaMos Fellowship Award. Dr. Burt has a PhD in Exercise Science from the Australian Catholic University. Currently, she is a postdoctoral fellow within the Bone Imaging Laboratory at the University of Calgary where she works on the CaMos study under the supervision of Dr. Steven Boyd and Dr. David Hanley.

Dr. Burt's project is entitled "Transforming HR-pQCT for improved Clinical Diagnostic Applications: A Canadian Multicentre Osteoporosis Study". This work will produce a sex-and site-specific centile driven normative database for HR- pQCT parameters. Specific centile curves will be established at the radius and tibia for males and females. Being able to determine true age- and sex-related bone changes across the lifespan, with this high resolution imaging technology in a normal aging cohort may provide valuable information on bone quality, fracture risk and aging, not yet known.

2016 Osteoporosis Canada – CaMos Fellowship Award


Dr Olga Gajic-Veljanoski

Dr. Olga Gajic-Veljanoski is the recipient of the 2016 Osteoporosis Canada - CaMos Fellowship Award. She completed a medical degree and a specialization in epidemiology at the University of Belgrade. Dr. Gajic-Veljanoski also received a Master's degree in Clinical Epidemiology and a PhD degree in Health Administration from the University of Toronto. She is currently supervised by Dr. Alexandra Papaioannou and is a post-doctoral fellow at the Geriatric Education and Research in Aging Sciences (GERAS) Centre – St. Peter's Hospital and McMaster University.

Dr. Gajic-Veljanoski's project is entitled "What is the impact of osteoporotic fractures on trajectories of change in quality of life and healthcare resource use?" Together with Dr. Alexandra Papaioannou, Dr. Suzanne Morin and the CaMos investigators, she will examine the patterns of change over time in quality of life and healthcare costs after new or repeat osteoporostic fractures using data from the CaMos study. ◆

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