Thursday, October 14, 2021

IDEAL RRTC Live Webinar

Make No Bones About it – There is More to Bone Health Than Density

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Once again, this webinar will be recorded, and the recording will be sent via e-mail. I will now introduce to you Dr. Michelle Meade who will moderate this webinar and assist the panelists with any questions or comments. Dr. Meade is a principal investigator and director of the Rehabilitation Research and Training Center on Investigating Disability Factors and promoting Environmental Access for Healthy Living, IDEAL RRTC, a full professor at the University of Michigan Departments of Physical Medicine and Rehabilitation and Family Medicine and co-director of the University of Michigan Center for Disability Health and Wellness.

Michelle, the floor is yours.

MICHELLE MEADE: Thank you very much and welcome, everyone, to this wonderful webinar, “Make no bones about it—There is more to skeletal health than bone density, and we have much to learn.”

This webinar is being sponsored by the IDEAL RRTC which stands for the Investigating Disability factors and promoting Environmental Access for healthy Living Rehabilitation Research Training Center, which is funded by the National Institute of Disability, Independent Living, and Rehabilitation Research.

The mission of the RRTC, and hopefully it will show that in a second, is to understand and enhance healthy aging of people with long-term physical disabilities, especially those at risk for poor outcomes because of a lack of resources, severity of disability, location, or other circumstances. And we do this through research and knowledge translation activities.

Our overall vision is that we want to recognize and address the social determinants that impact health and healthy aging for the individual with long-term physical disabilities. We conduct the research. We have five multipart research projects. We conducted case and training activities. We do knowledge translation and provide technical assistance. This webinar is part of the educational and knowledge translational activities. Please check out our website to learn more.

And, finally, I wanted to inform you about our two upcoming webinars and ask you to save the date. In January, we have a presentation on broadband Internet access and the implications for the health of individuals with disabilities. And in April Dr. Michael McKee will talk about reimagining primary healthcare for individuals with disabilities.

I will let Dr. Whitney share his screen but, in the meantime, please join me in welcoming Dr. Dan Whitney and Dr. Edward Hurvitz for their presentation.
Dr. Whitney is an Assistant Professor in the Department of Physical Medicine and Rehabilitation here at the University of Michigan. He received his Ph.D. in Applied Physiology studying musculoskeletal pathophysiology in people with cerebral palsy and has been conducting research about individuals with pediatric acquired disability across the life span.

Dr. Hurvitz is the James W. Rae Collegiate Professor and Chair of the Department of Physical Medicine and Rehabilitation as well as a pediatrician who has gradually developed expertise in seeing individuals with pediatric onset disabilities across their life span, so both are well aware of the health and healthcare disparities that this population experiences.

With that, I am going to turn the floor over to them and I will be monitoring the question and answer and chat boxes and will help facilitate questions at the end. Dr. Whitney.

DR. DANIEL G. WHITNEY: Thank you very much, and thank you very much for having us. We are very excited to be here. The title of our talk is “Make no bones about it—There is more to skeletal health than bone density, and we have much to learn.” This is being presented by myself, Dan Whitney, and Dr. Ed Hurvitz.

There are three aims to today's talk. We're going to first introduce bone fragility as a public health issue, but we'll talk beyond the excessive monetary cost and rather how bone fragility is implicated in loss of function, morbidity, and mortality.

The focus of today's talk is on abnormal bone development and how that impacts bone health across the life span and really in the context of disabilities.

In aim two, we'll introduce some basic fundamental principles of treating bone as a complex adaptive system. Once we better understand the different ways that bones can grow and are maintained across the life span, we'll then begin to talk about why the current clinical methods to assess bone fragility can really be insufficient for people with disabilities.

And aim three we'll wrap up and we'll present clinical scenarios of the different sort of pathways to structural bone fragility, we'll discuss pediatric conditions that have completely different reasons for abnormal bone development. The goal of aim three is to highlight how treating bone is a complex adaptive system and reveal new insights into the structural mechanisms underlying the bone fragility and we hope with these new insights it can motivate future research to develop better clinical monitoring, screening, and treatment strategies to really get at what the bone actually needs.

Now, we really hope we can deliver the take-home message that while bone density really is important to understand bone strength, there is more to bone than density alone. I tried to make that rhyme like a catch phrase. I hope that sticks.

Aim one, we'll first introduce some basic terminology. Bone strength and fragility are on opposite ends of the same spectrum. Bone strength refers to the ability to withstand forces to prevent fractures and therefore bone fragility is an arbitrary threshold in which bones are breaking under normal loading circumstances. Think about things like fracturing from a wheelchair transfer or

fracturing from a fall from seated or standing height.

Now, bone is composed of two major types of bone tissue, the ends of long bones we have trabecular bone. This is made up of individual trabecular structures that are interconnected, and they form a honeycomb like appearance. What encompasses the bone is cortical bone, a thick, dense tissue and it's predominant in the shaft of the bone or that's also referred to as the diaphysis. You're going to hear me refer to strength and fragility phenotypes throughout the talk. Phenotypes can be individualized but hopefully this gives some sort of idea of what I mean when I say strength and fragility.

The strength phenotype on the left is a thick, dense, cortical wall. It has a high concentration of trabecular bone and trabecular structures are thick and interconnected and the fragility phenotype on the right there's a thin cortical wall, not a lot of trabecular bone, the structures are thin, not connected. This person is more likely to fracture from a seated height.

The question is when -- one question and answer is when does bone fragility occur. It's studied in the elderly years and the menopause transition. The focus of this presentation is abnormal bone development which refers to when typical bone development goes awry or when something should be happening, but it doesn't or doesn't to the same extent.

Now, how the bones develop during growth sets the stage for life-long bone health. So, when bones develop abnormally bone strength may not be sufficiently achieved by the young adult years and additionally the bones can become weaker a lot quicker. Now, unfortunately, abnormal bone development in some form or

another is not uncommon for individuals with disabilities. So, we really need to be thinking about bone health well before the menopause transition and the elderly years for these populations.

Another question is how common is abnormal bone development? Are we talking less than 1% of the population?

It turns out there are several pediatric conditions with known or suspected abnormal bone development that can occur through a variety of direct and/or indirect pathways. Individually these pediatric conditions can be uncommon, and some are rare, collectively they account for a considerable portion of the pediatric population. To highlight this, we access nationwide data from the U.S. The sample here includes children who are 2 to 25 years of age that had continuous private health insurance health plan enrollment in the year 2017. And in order to identify conditions we require these children to have at least one healthcare service utilization in the year of 2017.

Well, of the 1.4 million children, 43% or two in five had at least one pediatric condition associated with abnormal bone development and this group accounted for nearly 80% of all the fractures that year. Studying fractures in the pediatric years is a really rare event so this is really compelling about the harmful effects of abnormal bone development in the pediatric years, but it gets worse across the adult life span.

Now, to provide a life span example, we're presenting a fracture risk across the adult life span from 26 years of age to over 70 years of age and we're using data from adults with cerebral palsy. The reason we're using this pediatric onset condition here is because we just published a study, so we were able to reuse some of these

figures.

What we're looking at is fracture risk by these narrow age bands, by about three- to four-year age bands from 26 to over 80 years of age, women on the left, men on the right. The top black lines are the cerebral palsy group, and the gray lines are the general population without CP.

So, we're looking at here, the fracture risk is elevated in the young adult years undoubtedly influenced to some extent by the abnormal bone development, but fracture risk continues to climb and at points exponentially climb, compared to the general population without cerebral palsy.

Now, what we're finding is that the sort of fracture risk profiles aren't present in other adult populations that have pediatric onset conditions, so it's not unique to cerebral palsy.

What's particularly concerning is that adults that have abnormal bone development they don't just have an increase in early risk of fracture, but they seem to have this excess post fracture health decline. So, the conceptual model I'll present here comes from our own evidence from adults with various neurodevelopmental disabilities and what we're finding is that when these adults sustain a fracture, they have substantially increased risk for cardiorespiratory diseases and mortality, even after accounting for a variety of confounders.

What we know is that when you get a fracture it can lead to loss of function. It can trigger a cascade of a series of events that lead to biological alteration, and this might be driving this sort of premature morbidity and mortality burden that we're seeing but these post-fracture health declines also increase risk for a new

subsequent fracture.

So really this could just accelerate the negative health spirals.

So, in summary of aim one, abnormal bone development affects a considerable portion of the population. It increases bone fragility across the life span which in turn increases premature risk for loss of function, morbidity, and mortality.

The question is, how do we prevent this?

Well, one way is to go back to the roots of the problem and to better understand how and when the bones are becoming fragile so we can develop interventions that have a lasting effect. In order to do that, we need to really better understand the different ways bones can be developed during growth and maintained across the adult life span. Once we understand that, we'll then tackle why our current clinical methods to assess bone fragility can really be insufficient and not positioned to detect bone fragility for individuals with disabilities.

Let's first introduce typical bone development. This is a complex, multifactorial process and informed by a gigantic network of genetic, biological, and environmental aspects. Bone development has unique priorities at different stages to form certain structural bone traits and collectively these processes harmonize to establish the permanent structural basis for the bone's framework. Some of the structural adaptations include increasing mass and size of the bone, defining the shape and defining and refining macro and micro architectural aspects of the bone.

Before we move forward, I wanted to quickly talk about how we're going to represent diaphysis phenotypes. This is a magnetic resonance image from a typically developing child. This is an axial view, that white outer ring is the

subcutaneous fat, the gray in the center is the muscle and what's in the red is the femur bone. Black is cortical bone. The circle is the bone marrow cavity. How we're going to represent the diaphysis phenotype is with a donut shape. We won't worry about the unique shapes of bone.

In this phenotype, gray is cortical bone. White is the bone marrow cavity, and the surface is matter. The outer bone surface is referred to as the periosteal. The inner bone surface, which separates the cortical bone from the bone marrow cavity is the endocortical surface.

How we might represent these phenotypes, this is an example image from a child with severe cerebral palsy. You can see the thigh is a lot smaller, really under-developed muscle and the red circle is the same size which shows the vast under-development of the femur bone. How we might represent is with a smaller donut shape.

This figure represents telescoping growth patterns of the diaphysis from eight years of age to 16 years of age all the way on the right. The space between these donuts or the diaphysis phenotypes represents what must have happened to go from one phenotype to the next with growth. And the color matters.

Black represents bone formation or bone that's being added which can occur on both surfaces. Red represents bone resorption where bone is being removed and blue represents this sort of balanced steady state.

So, let's dive into these growth patterns. So, this is an example of represents diaphyseal phenotype of a typically developing 8-year-old boy. As they grow the outer bone size increases primarily through bone formation but there's this

coordinated biological adjustment on the inner bone surface so as the outer bone size expands the marrow cavity expands accordingly. Around puberty there's a substantial increase in the outer bone size. Then the bone biology changes on the inner bone surface such that bone is now being added to the outer and inner bone surface.

Now, these coordinated processes aim to support the development of two very important structural traits. First, an increase in outer bone size. Well, outer bone size is a major determinant of fracture risk. Using basic biomechanical principles, bone strength is related to outer bone size rates to the fourth power. What this means is every increase in outer bone size there is a substantial increase in bone strength.

Second, bone development aims to increase the cortical thickness of the wall and here I'm showing in the -- a thicker cortical wall leads to a stiffer and stronger bone.

Here's an example of typically developing girls and just looking at the colors and the timing of the colors we can see that there's a slightly different biological strategy used but it still aims to accomplish similar sort of structural traits, that is, increasing outer bone size, and increased cortical thickness.

Well, it turns out that the complex nature of bone development is actually more complicated. So, we're starting to see that bone growth differs, completely differs based on the bone's phenotype. It's certainly up for debate on how you want to define a bone phenotype, but we work with Karl Jepsen in the department of orthopedic surgery who has been largely successful in studying different ways

bones can be constructed during growth and maintained across the adult life span from the context of bone robustness. Dr. Hurvitz and I were really excited. We feel like we finally have some sort of vantage point or anchor to study abnormal bone development and specifically how and when bones become fragile.

This is not purely an academic exercise. It has large clinical implications. Once we know how the bone should grow and when it's not and how it's not, that should really help tailor monitoring, screening, and treatment strategies in the future.

Now, bone robustness is a multi-trait measure. It describes the transverse expansion relative to linear bone growth. How we would capture that is outer bone size divided by bone length. Bone robustness is largely determined, is thought to be largely determined by genetics by about two years of age. When you are two and you have a certain bone robustness phenotype, you're probably going to carry you that for the rest of your life. The studies that help to form that conjecture were in typically developing children and we suspect that bone robustness and its determinants may be a little bit more complicated in the context of disability.

Now, in the general population, there is a substantial variation in bone robustness ranging from narrow to wide phenotypes. The femurs below represent what these bones might look like from a pharaoh, intermediate and wide phenotype and those below show how we represent these phenotypes.

What makes bone robustness so attractive is that it actually takes away the effect of certain sort of body composition profiles so we can study this in men and women and children and adults because outer bone size and bone length are both influenced by body mass and a height, but by taking the ratio we're actually

removing the effect by that. Studies have found that very large people have a range of narrow to wide phenotypes and small people also have a range of narrow to wide phenotypes.

Now, it turns out that there are completely different biological strategies used at different times to form a different set of structural traits, all of which is dependent upon that bone's adaptive needs which can be predicted by a bone's robustness. Now, when I first introduced bone development, I used this intermediate bone phenotype in the middle. Now, to keep things as simple as possible, what I'll do is I will contrast the narrow and the wide phenotypes and I will introduce the bone's basic adaptive needs and then I'll talk about the major compensatory strategies that it uses.

So, a narrow skeleton will sense that it is narrow and will realize it is automatically weaker because it has a smaller external frame. So, the adaptive needs of a narrow bone is to increase stiffness of that tissue. It does this by setting forth a unique set of biological strategies that leads to a higher degree of mineralization which I tried to reflect by the darker shade of gray and it also aims to develop a proportionally thicker cortex.

Now, on the other end, wide bones recognize that they're wide and they're automatically stronger because of their larger external frame. So, the adaptive needs of wide bones is to actually minimize the bulk and overall mass of it. So, it does this by setting forth unique set of biological strategies that compensates to develop a lower degree of mineralization and thinner cortex.

All of these sort of bone adaptations, this is what goes on in the general

population. And all of these are healthy adaptive mechanisms. That really optimizes the strength for that bone phenotype.

So, children with wide intermediate and narrow bones so long as they have these adaptive mechanisms, these bones are not going to fracture under normal loading circumstances, these children can play sports. As long as nothing is so high impact these bones are not going to fail.

One thing we're excited about, we feel like we have a template to study abnormal bone development and we can use this to better understand how and when bones become fragile. So as an example, let's say there's a child with a disability who has a narrow phenotype. We see at 8 years old they have -- their phenotype is on par with what we expect for narrow bone. Measure them at 12 years of age and the outer bone size is smaller than what we expect. This might tell us there was issues, there's not enough provisions to support bone formation prior to 12 years of age, not allowing for the outer bone size growth. So, we might think of some osteogenic stimuli to support what the bone is naturally trying to do.

The importance of this is some of these traits are really not adaptable after certain periods in the life span especially during growth. So, if you're 12 and you start with a small bone, you don't change, you can end with a small bone by 14 years of age and there may not be any sort of catch-up. Another way to put it is for some these traits, there's a deadline on intervention.

Now, in the other end of things for a wide bone let's say there's a child with epilepsy and they switch anti-seizure medications to maybe one associated with excess bone resorption. We monitor them at 14 years of age and measure it again

at 16 and we see the outer bone size doesn't change but there’s a thinner cortical wall. That might tell us there was too much bone resorption at the endocortical surface and we need to consider adjunct anti-resorption therapies so the child can retain the cortical thickness and carry it through with the rest of their life.

Now, I wanted to talk about just some very basic adult aging compensatory mechanisms. I'm going to keep this very simple. Adults with narrow bones actually see an increase in the outer bone size but it's small, 10 to 20% from 18 years of age to 70 years of age. But while it's not as drastic as what happens during developmental, these fundamental structural adaptations are important to maintain bone strength with aging. Just as a reminder, bone strength is related to outer bone size raised to the fourth power so minor increases in bone size yield a large increase in bone strength. It's probably a very unique mechanism that's important to narrow bones to maintain strength in aging.

Now, at the other end with wide bones, the outer bone size doesn't seem, according to a couple studies, doesn't seem to change across the adult life span but the path to fragility for wide bones is one of resorption. So excess resorption at the endocortical surface could lead to a cortical wall that thins from the inside out and that would create a weaker bone. There's also evidence of excess cortical porosity and cortical porosity refers to empty vacant spaces where bone could be, so a thinner, more porous bone leads to a weaker full bone.

Now, the first line pharmacological treatment for bone fragility is anti-resorption agents such as []. Theoretically speaking, not clinically because it hasn't been tested, people with wide bones may respond well to anti-resorption

therapy. It would allow for the cortical thickness to be retained and to mitigate the cortical porosity.

But these same therapies may not be very effective for people with narrow bones. That's because bone biology is really intimately tied. Bone resorption and formation cross-talk and they communicate with one another. So anti-resorption therapies will block or reduce the resorption but that might also reduce the bone formation.

The bone formation is what the outer bone size increase is really driven by that bone formation. So anti-resorption therapies may be blocking a necessary compensation of the outer bone size with narrow bone.

Now, I do want to say this is -- the reason I bring up these treatment things is really just to highlight how understanding these different bones how they grow and how they become fragile can really give us some insights on how they might be responsive with different therapies but this is an overly-simplified view and what's known about this already is -- there's still a lot left to discover so I really don't want anybody to stop taking their osteoporosis drug if they're taking one, just because all this theoretical stuff that I'm presenting here.

Dr. Hurvitz at the end will come in and talk about some of the clinical context so you can direct questions to that as far as that goes.

So, when taken together, bones can grow in completely different ways. And they can form a unique set of structural traits that optimize bone strength in that bone's phenotype. Some of the traits can be completely opposite of one another and some of these are shown on the table here. How can a single clinical method with

one range of values detect bone strength for everybody?

I don't know. What makes matters worse is that the current clinical assessment methods really just faux uses on one of these structural traits and it's the mineralization of bone matter. So, we end up missing out on a lot of important information that can tell us more about the structural composition of what makes that bone strong and what makes that bone fragile.

We can see here that a healthy narrow and sufficiently strong bone is going to naturally compensate with a higher mineralization in a healthy adapted sufficiently strong wide bone is going to compensate with a lower degree of mineralization. So, let's talk about this a little bit more.

The current clinical assessment methods to detect bone fragility really focuses on bone mass or that mineralization component. Measure bone mass commonly used with a scan to identify bone marrow strategy, the value gets converted to a standardized score and based on thresholds you're diagnosed.

The question is does BMD capture bone strength the answer is no it does not, yes it does, and maybe. I'm going to present a couple scenarios to highlight what BMD is measuring and the short shortcomings for people with disabilities and abnormal bone development.

So, in this first example, this is actually not what goes on, this is assuming no size mass integration. I'm trying to make a point which I'll get to in a second. What I mean by the no size mass integration, we talked about how narrow bones have higher degree of mineralize and wide bones have lower degree of medicine mineralization. Let. The report spits out three values, the bone area which is the

outer bone size here. Relates to the bone size. The BMC, the bone mass. And then the BMD value. The BMD value is a ratio of BMC divided by area.

So, if all of these bones have the same extent of mineralization, that means they have the same BMD value. You can see here, it's arbitrarily 0.92.

The problem with this is clinically it would be tempting to interpret as these three bones having equal bone strength. But we know that's not true because we know the wider bones are mechanically stronger than the narrower bones.

So, the take-home from this hypothetical situation is that BMD does not pick up on attributable fracture risk by bone size and the area measured there is just not interpreted.

What's more likely to happen in the general healthy adaptive state of bone is that pharaoh bones actually have a higher degree of mineralization so they can be stiffer which would reflect with a higher BMD of .98 here as an example and wider bones adapt by having a lower degree of mineralization which means a lower BMD.

The take-home here is that BMD for narrow bones would be clinically tempting to interpret as stronger than they actually are because of the higher BMD value. As I present and talk about in a little bit, individuals with pediatric onset disabilities are more like throw have under-developed bone size and so when it's poorly mineralized, like a double whammy to bone weakness and small external frame it's insufficiently stiff and why this becomes important is because a narrow bone that presents with maybe an average BMD value could really flag that, that's actually insufficiently mineralized for its narrowness. If it was appropriately mineralized it would have a higher BMD value. Patients that present would have a

narrow bone, with an average or slightly below average BMD likely have an insufficient degree for mineralization.

BMD for wider bones it would be tempting to interpret as weaker than they are because they present with lower BMD value despite potentially having a sufficiently strong skeletal framework.

As a third general scenario, individuals with disabilities are more likely to fracture a trabecular rich region so the ends of bones, around the knee, distal femur, and the hip. What I'm presenting here is in these boxes here is magnetic resonance imaging of trabecular bone architecture from typically developing children and those with cerebral palsy. The white represents the trabecular bone. You can see in the fragile box there's a low concentration of trabecular bone. The trabecular structures are disorganized, they're not connected. This might explain why distal femur, fractures of the distal femur are common in children with cerebral palsy. This does not pick up information about trabecular bone.

It does not pick up information on the cortical thickness or cortical porosity which are major determinants of fracture. So, for people with disabilities and abnormal bone development, the clinical consequence of BMD assessment alone is on one end under detection, leading to missed opportunities for early intervention. It's going to be primarily for people with narrow bones who have or are at risk for bone fragility. It might present with an average or slightly below average BMD but if the bone was sufficiently mineralized it should be much higher. This is a problem for people that have structural trait deficits that are not reflected in the BMD value. It can lead to false positive diagnosis for the fragility leading to inappropriate clinical

actions, predominant for those with wide bones who present with low BMD despite having sufficient sly strong skeletal frame.

Summary for aim two, there are completely different ways in which the bones can grow, and they form completely different structural trait sets that are -- could be completely different across the robustness spectrum. Unfortunately, current clinical assessment methods are really not positioned to pick up on these sorts of trait compensations and abnormal bone development but potentially explaining why bone fragility goes missed for so long for this population.

So, aim three we'll wrap up and we'll present some clinical scenarios of different pathways to structural bone fragility. We'll present pediatric conditions that have different reasons for abnormal bone development and the goal of this is to start to highlight how treating bone as a complex adaptive system can reveal new structural insights into the underlying bone fragility. We hope this can be used to motivate improvements in clinical monitoring, screening, and treatment for bone fragility based on what that bone actually means.

Some of the data we'll present in the pediatric populations unfortunately includes births that are like 5 to 17 years of age so we're not able to map out the longitudinal trajectories and we're presenting an average effect of that sample but I hope by doing this we can kind of inspire some creativity in thinking about how you might think about your own patient populations and their own health and what might be contributing to their structural weakness that goes missed or not looking at DEXA scans.

So, the two conditions, we had more, but the sake of time we'll talk about two.

Osteogenesis imperfecta, OI, this has a direct pathway to bone fragility.

We'll talk about cerebral palsy, CP, an indirect pathway to fragility. A commonality linking these two, they're labeled as low bone mass conditions and we rhetorically ask is this sufficient in the clinical setting.

Now, on one end, clinically it might be important to label these conditions as low bone mass so that the physician can have some sort of indication that this patient needs routine orthopedic care and assessment. But on the other end, is labeling a low bone mass falling short of motivating further tests to look at the structural mechanisms contributing.

So, this is going to be a building slide. We're going to build from left to right. This is the key or the figure, this is just an example of what a healthy adaptive typically developing narrow and intermediate and wide bone might look like and I tried to capture the major trait compensations so that narrow bone has a proportionally thick cortex and higher degree of mineralization, again reflected in the darker shade of gray.

Now, OI is an executive tissue disorder, abnormal collagen and bone material and it ranges in severity. A lot of studies have found that OI, bone in OI has low BMD, high cortical porosity, and impaired trabecular bone.

A recent study directly investigated bone robustness and found the cohort on average had a slightly narrower bone compared to the controls. But they actually had higher cortical -- proportional cortical thickness. So, in an overly simplified pathway to fragility for OI, the bone in OI is on average narrower. In and of itself a narrower bone doesn't mean bone weakness so long as it's employing sufficient

compensatory mechanisms. One is a higher degree or a thicker cortical wall and the bone in OI seems to be accomplishing that and the other is a higher degree of mineralization to make that bone stiffer but the bone in OI does not seem to have that.

How we might monitor and treat the bone in OI might be a little bit different than the general population. We might want to think about when that outer bone size starts to lag behind so we can apply osteogenic stimuli to help the outer bone size grow.

We might also want to focus on the mineralization and understand the interplay between bone formation buy you ology at certain times that leads to this under-mineralization.

Now, CP is a neuromuscular condition, ranges from independent ambulation to the use of a wheelchair. I'll represent two phenotypes, mild on the left, more severe on the right. What we know about the bone in children with CP, low BMD and impaired trabecular bone arc a texture. The cortical porosity I would suspect would be higher. Robustness has not been published in CP. We have preliminary data that helped support that -- I was able to go to the literature and pull data from tables and figures to provide indirect assessment for some of things we'll talk about here. What I find is that children with CP on average have a slightly narrower bone which is narrower with more severe CP. They seem to have thinner cortical walls which is not what you expect for a narrower bone. So, in an overly simplified pathway to fragility, the bone in CP seems to be on average narrower which again a narrow bone doesn't mean bone weakness so long as it has appropriate compensations. One of

the compensations is higher degree of mineralization which the bone in CP does not seem to be doing. And the other compensation is a proportionally thicker cortical wall which the bone in CP does not seem to be doing.

So similar to OI we might think about osteogenic stimuli to help build that outer bone size appropriate to that person's size and bone length but different than oh, I we might have to think about why that bone is thin from that inside out and that might be a sequential or multimodal formation resort strategy, increase the outer bone size and retain that cortical thickness.

So again, I just wanted to highlight these to show how we might monitor these bones and what we would look for to identify what makes these bones weak and how this could inform future research investigations about what might work to augment monitoring this population.

With that, we now move on to the clinical side of things. Treatment options and I will pass it off to Dr. Hurvitz.

DR. EDWARD A. HURVITZ: Thanks, Dr. Whitney. I'll take a few minutes just to make a few comments about that.

So, Dr. Whitney presented some of the work that we've done that has really shown that fractures are a significant problem that can lead throughout the life span to disease and actually early death. So, it's something that we have to be very aware about.

The problem is, is that the classic way of looking at treatment of bone fragility and fractures is to wait until somebody has a fracture and then treat them. That's the classic adult model for people that are aging.

The issue is, we know that individuals with cerebral palsy, osteogenesis imperfecta and many pediatric onset disabilities will have low bone density, so we want to think about treating them earlier. The question is how to do that. We can think about some of the things that any of us would just do naturally which is tell people to be more physically active, stand more, put more stress on the bone by being active. Certainly, if a person can do all those things, then that's a no-brainer, we should be doing that. What if those things are difficult or complicated?

A 16-year-old teenager who uses a wheelchair for all their mobility, standing is a difficult procedure which involves two physical therapists who put them into a standing frame, and it takes 20 minutes to put the teenager into the frame and 20 of minutes to get them out. And they stand there for half an hour. At the same time, that teenager is a straight A student, heading for law school. We pull them out of class. Is that the right thing to do? Is the half hour of standing going to help her?

We don't know yet. That's one of the things we need to find out with the research that we're doing.

So, at the same time, we're fortunate to live in a time where we can do things like DEXA scans and get this information. As Dr. Whitney pointed out, they're not so simple to interpret to us right now and that's where the direction of the research is going where we want to look at the full idea of what the DEXA scan is telling us. We're used to using one number, how much mineral, how much calcium is in the bone. That's not adequate for us to understand treatment. That's sees especially true for treatments like medications. You may ask, “Why don't we put all our patients on osteoporosis medications since we know there'll be a fracture risk?” The

medications have complications and, based on the work and what Dr. Whitney presented, we don't know which medications are right and some of the medications may cause damage so there's a lot of questions that we have about this but the important issue is, is that we need to help people to understand the problems of bone fragility, we need to think about better ways for treating them especially for patients who have difficulty with being active, maintaining proper nutrition and some of the simple things and we need to understand the royal of medications and the role of physical activity which is not so easy to bring about like I just explained and helping with bone fragility and how we treat it.

Dan, if you want to do a wrap-up, then we can take questions.

DR. DANIEL G. WHITNEY: Thank you. Okay. Take-home message. There's more to bone than density alone. And we have much to learn. We would like to acknowledge the team that helped us with this webinar, we really appreciate. It was very easy to work with everybody so thank you. There's a lot of people to thank on the scientific side of things but we listed some names here that have been involved directly with this work. One name I would like to highlight is Karl Jepsen who has really been the thought leader in driving these concepts that we presented in a typically developing population that we now get to use as a template to understand how and when bones become fragile for individuals with disabilities.

And here's our contact information. Thank you for your time.

MICHELLE MEADE: And thank you, doctors Whitney and Hurvitz for a very thorough explanation of a very complex issue. We have some issues in the chat. It starts with what are the early indicators that there are bone issues or problems that

may be observed?

DR. EDWARD A. HURVITZ: That's the problem. There are two things that come to mind. One is a fracture. That's the first thing that tells us usually that there's a bone fragility issue. The other early indicator that we know of is the diagnosis itself. As clinicians we know that people with cerebral palsy and spina bifida and with other pediatric onset disabilities and in the adult world people with spinal cord injury and so forth are going to have bone fragility issues, so we need to be aware of that and think about what's the proper time to start looking at this in our patients.

MICHELLE MEADE: Okay. There was a question, can you put the slides in the chat or provide the link where we may get them or if you would be comfortable putting these on the website?

I know that the recording of the film itself, of this webinar, will be available for individuals. Another question, what is the expected time course of bone density and growth change in response to osteogenic interventions.

DR. DANIEL G. WHITNEY: It's a good question. I think one of the take-homes from this is, is BMD a good marker to monitor change, because BMD is a ratio. So, you have a numerator, and you have a denominator and some of these different sorts of interventions might affect the mineralization, so the numerator of the BMD ratio, and some might affect the architectural size, that would be the denominator. If you see an increase in BMD, if that's a higher degree of mineralization then that's a great increase and the bone is probably getting stronger. You might see an increase in BMD because you might be blocking that bone size growth and so you're actually preventing that denominator from growing which is

itself an independent risk factor for fracture so a gain or loss in BMD could either be positive or negative. So, we don't know the time course but what we really need to do is figure out what do we need to be looking at.

MICHELLE MEADE: And I guess then -- I'm sorry. I was going to say are there then either existing norms or attempts to create norms for these different populations since you're now saying that there are different models that you're now using, and the normal metrics don't apply that we have to look at different relationships.

DR. EDWARD A. HURVITZ: Dr. Whitney and I joined with the group he put on the last slide to submit a large grant to the National Institute of Health to do just that, Dr. Meade, to try and look at creating norms, not only in the adult pediatric onset population but other populations based on some of the new findings, some of the information that Whitney presented. That is our goal to come up with new norms that will inform treatment.

MICHELLE MEADE: There was a question about could osteostimulation include post electromagnetic frequency therapy and the question from Carla. She is curious if the U.S. is starting to use this for bone growth and recovery as she sees units slowly being accepted by the public.

DR. EDWARD A. HURVITZ: It's a very interesting question. I'm not aware of the use of this technique for bone growth. I'm aware of electrical stimulation but not magnetic stimulation. Dr. Whitney, any awareness of this?

DR. DANIEL G. WHITNEY: No, I've heard of electromagnetic fields to help bone growth and I guess the question is, what is the bone naturally trying to do.

That's really what as far as developing the norms, first we have to see how the bone grows and then we can start to track what is that bone trying to do, at what time and what trait is it prioritizing and I don't know what the electromagnetic fields do, if it's a bone formation maybe it's effective at a time when a trait is being developed, primarily with bone formation. It's the interaction of timing and what the bone is naturally trying to do and what the bone naturally tries to do will differ based on the bone phenotype.

MICHELLE MEADE: A question from Lindsey: What are some of the other technologies or assessments coming down the pike to better assess this?

DR. DANIEL G. WHITNEY: I can take a first crack at that, Dr. Hurvitz, if you don't mind. It comes with area. They have to understand how the size and mass integrates across the size spectrum. We might be able to harness what we already have but there's better technologies that dive a lot deeper into some of these sorts of structural aspects, magnetic resonance imaging, computed tomography comes to mind. I don't know if these are necessarily new, but I think they are technologies that are being used in the research setting to eventually get to the clinical setting. Dr. Hurvitz, do you have any more comments there?

DR. EDWARD A. HURVITZ: What we don't have is the cheap, simple way to do this. We don't have the machine that I have in my clinic that I can do this quickly on and that's what we need.

MICHELLE MEADE: Okay. And how should we monitor children with cerebral palsy?

DR. EDWARD A. HURVITZ: So that's a great question that we don't have a

good answer to. Certainly, anyone who has a fracture should get a DEXA scan. If they don't have a fracture, at what point should they get a DEXA scan and that will depend somewhat on how mobile they are, if a child is more mobile, more -- has more walking function, spends more time on their feet, there's probably less risk of fracture. On the other hand, that child puts them self in more situations where they can get a fracture. So, if we get them involved in sports should we do a DEXA scan? What would we do with that information? We don't have this down yet. There's no clear consensus about this as of yet.

MICHELLE MEADE: To follow up on the question about the technologies, it was specific thoughts about to better assess the cortical thickness, porosity and organization of the bone as opposed to just what's provided by the DEXA.

DR. DANIEL G. WHITNEY: Oh, I see. I see that now. Still magnetic resonance imaging, that's how I was able to get some of this trabecular information that I presented, porosity, there are new and emerging technologies to do that. These are on the research side of things. Organization, computed tomography, high resolution, that's good for identifying detailed structural information. But MRI can do that as well to some extent. And so there are big push from radiologists, radiology research trying to get this into a clinically easily used sort of protocol. Hopefully we'll see that in the next decade or two.

MICHELLE MEADE: Great. Is there a correlation between nutrition, such as calcium intake and bone density and based on the current knowledge that you have suggested for an aging population, whether or not this is with pediatric onset conditions or not?

DR. EDWARD A. HURVITZ: There is. I recommend a healthy diet for everyone. If you want to talk about calcium supplementation or vitamin D supplementation, I think it's important to have a discussion with your physician as to your particular case but there certainly is a correlation with nutrition.

MICHELLE MEADE: Okay.

DR. DANIEL G. WHITNEY: If I may add on that. There is so many -- there's a myriad of factors that are affecting bone and so whenever we look at especially in cerebral palsy or other developmental disabilities where there are so many factors at once, isolating one and looking at the correlation with bone density, we're going to be really missing the bigger picture of things. So, nutrition matters definitely but it's just one of many, many factors.

MICHELLE MEADE: I think that is the message you've driven home that there are many factors and many of them we still have to understand, we have to study. But at least now we know that there are different models and different approaches that we need for these different populations and groups who are more at risk.

Thank you to both of you, doctors Whitney and Hurvitz, for this very thorough explanation. We are about at the end of the webinar. You will be sent the evaluation as well as the slides. Please complete that. You can ask any additional questions at that time and, once again, this information will be posted on the CDHW website. Finally, please join us for future webinars in January and in April.

Thank you very much for being here, for your attention and participation. Have a great day. [End of meeting]