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Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease

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Guest: Dr. Matt Greenblatt studies basic and translational osteoblast biology at a research lab at Weill Cornell Medical College and is the Assistant Director of the Core Clinical Laboratories at the Cornell Campus of New York Presbyterian Hospital.

Bob Barrett: This is a podcast form *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

Osteoporosis is the most common disorder of bone metabolism. It causes bones to become so weak and brittle that fractures occur due to minor falls and other stresses like coughing.

Approximately one in two women and one in five men are expected to experience an osteoporotic fracture during their lifetime, which incurs a high degree of morbidity and mortality. Therefore, the diagnosis, treatment, and monitoring of treatment for osteoporosis are of critical importance. A major challenge in this regard is that osteoporosis is asymptomatic until presenting with a fracture. Thus, clinical diagnosis and subsequent treatment relies on radiologic and laboratory testing in patients at risk based on clinical history and demographics.

Measurements of bone turnover markers aid in the diagnoses and therapeutic monitoring of bone metabolic disorders, but are associated with several challenges that must also be recognized for optimal use. The February 2017 issue of *Clinical Chemistry* features a review on this topic titled, "Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease."

For this podcast, we're joined by its first author, Dr. Matt Greenblatt. His research lab at Weill Cornell Medical College studies basic and the translational osteoblast biology and he is Assistant Director of the Core Clinical Laboratories at the Cornell Campus of the New York Presbyterian Hospital.

So, Dr. Greenblatt, tell us a little bit about why measuring bone turnover markers might be important.

Dr. Matt Greenblatt: So, it's sometimes something that's overlooked, but osteoporosis associated bone fractures are common and deadly. So, one in two women and one in five men will suffer an osteoporotic fracture during their lifetimes. And it turns out about as many women die from the complications

of these osteoporotic fractures each year as die from breast cancer.

From that perspective, I think it's very important that we have a health system identify and treat the patients that are at increased risk for osteoporotic fractures, but there's a big challenge in doing this. The fundamental nature of this challenge is that while the lifetime risk of a fracture is relatively high, the per patient/per year risk of fracture is actually relatively low, which means that we need to make special efforts to distinguish which patients are at high enough risk of fracture to benefit from treatment.

That's traditionally taken the form of assessing the patient's clinical history. But in addition to this, radiographic measures, especially something called DEXA scans, have been a mainstay in making that assessment. But it's well-established that radiographic approaches don't fully capture the determinants of fracture risk. So, people have been looking for many years for other factors that will capture that additional risk. So, in looking for these complementary approaches, one of the most obvious is biochemical markers of bone turnover.

Bob Barrett: So, how can bone turnover markers address this clinical challenge posed by osteoporosis?

Dr. Matt Greenblatt: So, related to what we were just discussing, one area where bone turnover markers have turned out to be potentially useful, is in addressing our ability to predict a given patient's risk of fracture, as levels of a catabolic bone turnover markers, which are the products of bone breakdown that reflect bone absorption, are linked to fracture risk.

However, it's still unclear who should have this sort of testing and when this testing should be performed. And because of this, to what degree bone turnover markers have a place in routine screening for osteoporosis is still not totally worked out. There's also a potential wall for bone turnover markers' monitoring therapy, especially as bone turnover marker levels observed in the early time after starting therapy correlate with treatment efficacy in terms of fracture outcomes.

However, similar to the issue with using bone turnover markers to assess fracture risk, it's still unclear how or if this sort of analysis should be universally applied to all patients. Additionally, in addition to these, the strong ability of some anti-absorptive drugs to suppress bone turnover marker levels, catabolic bone turnover marker levels also means that in some cases, measuring these can be useful tools for assessing patient compliance.

However, perhaps the clearest role for bone turnover markers lies in clinical trials for osteoporosis therapies. So, I mentioned that the per patient/per year rate of bone fracture is relatively low. And in addition to this posing a challenge for treating patients, it also poses a major challenge for clinical trials for new drugs to treat osteoporosis. It means that you need to follow a greater number of patients over a longer period of time in order to really be able to demonstrate benefit for a new therapy.

So, as with a lot of clinical areas that are trying to study difficult endpoints, this has led to adoption of surrogate endpoints that may be able to tell you more quickly if your drug is working or not. And so, bone turnover markers have arguably become the most important of these in the bone area. What this means for us as laboratory clinicians as well, is that it's increased the quality of data supporting bone turnover markers, as now many major trials for fracture and other bone indications provide a wealth of longitudinal bone turnover marker data, especially including how quickly bone turnover marker levels respond over time to treatment.

So ultimately, the use of bone turnover markers in many clinical trials has and will likely continue to feed into our ability to use them clinically by providing high-quality longitudinal data.

Bob Barrett: Doctor, you mentioned some of the challenges impeding routine systematic use of bone turnover markers. Can you talk a little bit more about the underlying reasons for this?

Dr. Matt Greenblatt: So, the biggest challenge in this area is the high level of pre-analytic biologic variability that's inherent in nearly all the bone turnover markers that have been studied today. And at least part of this is due to a number of now well-established patient factors, including circadian variation in levels of bone turnover markers, seasonal variation in this, effects of eating on levels of bone turnover markers, even variation throughout the course of the menstrual cycle.

So, some of these can by minimized by trying to be very consistent in how and when we draw samples for bone turnover markers, but that's been a major challenge across the board. So really, these variability issues are likely one of the major or maybe the major factor impeding wide scale routine application of bone turnover markers for screening fracture risk or therapeutic response, at least in routine clinical practice.

Sort of on the back end as well, sometimes communicating the limitations imposed by this variability is a challenge, in

particular when working with primary care clinicians who don't have a major focus on bone health. So, there's a potential for a great amount of confusion in terms of small changes in bone turnover marker levels being over-interpreted, when in fact these are really just within expected biologic variability.

In the literature, some people have tried to tackle this by defining and reporting alongside the reference interval to clinicians the smallest change in bone turnover marker levels that is statistically significant, the so-called least significant change, and that's something that may be helpful.

In addition to the variability of bone turnover marker levels, another contributing factor to the challenge in this area is that comorbid conditions like diabetes can alter the link between bone turnover marker levels and fracture risk. There's also a large and growing body of evidence suggesting that osteoporosis, due to less common causes other than the garden-variety postmenopausal osteoporosis, may display different patterns of bone turnover marker levels.

So probably as with a lot of areas in medicines, we may just need to get more sophisticated in how we subset patients prior to testing in order to get the most utility out of our assays.

Bob Barrett: Looking ahead, what's coming up? What's new in the realm of bone health?

Dr. Matt Greenblatt: One major advance is that new therapeutic agents are becoming available to treat low bone mass, including a couple of new or upcoming agents that increase bone formation. So because we have an increasing range of drugs to treat osteoporosis on the market, clinical studies are increasingly looking at defining optimal approaches to sequential or combination therapy.

The second major issue is that more and more data is showing that we are very much under-treating osteoporosis, even in patients who have declared themselves as high risk for fracture after being hospitalized after a prior hip fracture. This may be a combination of both poor patient compliance and underutilization of anti-osteoporosis treatment by some clinicians.

For patients, this may largely come down to the fact that osteoporosis is asymptomatic until at least until a fracture occurs and sometimes, it's hard to motivate people to engage in risk reduction if that doesn't change how they feel from day to day. So overall, we're in a somewhat

paradoxical position of having a broader array of treatment options than ever before, but increasing data that we, as a medical system, are not effectively delivering those therapies to eligible patients.

Bob Barrett: What role could clinical labs possibly play in these changes?

Dr. Matt Greenblatt: So, regarding the increasing number of therapeutic agents available to treat osteoporosis, as more and more drugs become available, the choice of how to use these many therapies becomes more and more complex. And I think that clinicians will increasingly be looking for some form of objective guidance in making those decisions. It's very possible that bone turnover marker measurement becomes increasingly important because of this increase in complexity in choosing the right drugs for the right patients.

In some cases, it may be that laboratory data like bone turnover marker levels can also play a role in building a case that one of the newer, more expensive treatment options, such as some of the therapeutic antibodies, are more appropriate for a patient than one of the older, cheaper options, such as a class of drugs called bisphosphonates.

Regarding the patient compliance issue we discussed, several studies have tried using bone turnover marker values as an educational tool to improve patient compliance. For instance, during a patient's visit with the caregiver showing them their numbers and using that as a motivational tool to get them to engage in this treatment and continue it. While studies of this have largely failed to show that this is effective as an educational intervention, it's probably worth saying that this is something that's highly dependent on a particular clinician's style in engaging with his or her patients, on a patient's cultural background, educational background and other factors.

So, there may still be a very important role for the lab in helping to improve patient compliance with therapies for osteoporosis, and there may be certain patients still who respond very well to seeing the number of various bone turnover markers and using that as a tool to motivate them to engage in this therapy.

Bob Barrett: Dr. Matt Greenblatt studies basic and translational osteoblast biology at a research lab at Weill Cornell Medical College and is the Assistant Director of the Core Clinical Laboratories at the Cornell Campus of New York Presbyterian Hospital. He's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett, thanks for listening.