



Articles:

Naga Yalla. *Bad Breaks*.

Piriyah Sinclair, et al. *Metabolic Effects of Bariatric Surgery*.

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Guests: **Dr. Naga Yalla** is Assistant Professor of Medicine in the division of Bone and Mineral Metabolism and Endocrinology, Metabolism, and Lipid Research and Director of the Fracture Liaison Service at Washington University, St. Louis. **Dr. Carel Le Roux** is an expert in Metabolic Medicine and is part of the Diabetes Complications Research Center at University College in Dublin.

Bob Barrett:

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

Although bariatric surgery techniques were originally developed to treat morbid obesity, the indications for their use have expanded as a consequence of the emerging evidence of their wider metabolic benefits. Now described as metabolic surgeries, these treatment methods derive as much benefit from their metabolic and cardiovascular effects as from the resulting weight reduction.

Though promising evidence is emerging, there is a need for further mechanistic studies to assess the true potential of metabolic surgery to treat the myriad other disorders of metabolism and to better understand their consequences in terms of cardiovascular disease and cancer risk reduction. Additionally, there may be unintended consequences of bariatric surgery that are related to long term adverse skeletal effects and nutritional deficiencies.

The January 2018 *Clinical Chemistry* special issue on obesity includes a review and a case report that highlight these contrasting and complex issues in treating severe obesity.

We are joined by the author of that case study, Dr. Naga Yalla, and by the senior author of a review article on the metabolic effects of bariatric surgery, Dr. Carel Le Roux.

Dr. Yalla is an Assistant Professor of Medicine in the division of Bone and Mineral Metabolism and Endocrinology, Metabolism, and Lipid Research. She also serves as Director of the Fracture Liaison Service at Washington University, St. Louis, Missouri.

Dr. Le Roux is an expert in Metabolic Medicine and is part of the Diabetes Complications Research Center at University College, Dublin. His research team is focused on

understanding how the gut talks to the brain and how these signals can be optimized to improve people's health.

And so, Dr. Le Roux, let's start with you. Is obesity really a disease or just a risk factor for other diseases?

Dr. Carel Le Roux: That's really an important question because if we want to treat obesity and it is a disease, our approach is very different to if we treat it as a risk factor. All the science is currently showing us that obesity is a disease. And part of the way that we understand whether or not it is a disease is what is causing it, but also what are the signs of obesity and what are the symptoms of obesity. Because for too long, we have only focused on the complications of obesity, we've been focusing on diabetes, on sleep apnea, on functional disabilities, and it's very important that we are able to make that better for patients, but the real question that we are asking ourselves now is, is obesity a disease? And the evidence is pointing that it is a disease in its own right.

Bob Barrett: So if obesity is a disease, then what are the pathognomonic symptoms of obesity?

Dr. Carel Le Roux: The symptoms and signs of any disease are critical to our understanding of the disease in its own right but also in our approach. Most diseases, what we aim to do is to attenuate the symptoms and reduce the signs. Now, the signs of obesity are really easy because it's the body mass index. It's how big a person is. It's how much fat mass they carry. And we are very good at measuring that. But what we have not been thinking about is, what are the symptoms that people with obesity suffer from?

And as I mentioned earlier, is we've been focusing on the complications, what are the symptoms of diabetes, or the symptoms of sleep apnea, or the symptoms of depression, et cetera? But, if we actually ask ourselves, "What are the symptoms of the disease itself, of obesity?" Then it becomes clear that there are two major symptoms that all patients who have obesity suffer from. The first is an excess hunger, and we hear that quite frequently when we treat children with obesity and the parents will come in and say, "My child is hungry all the time."

When we deal with adults who have obesity, we actually hear that most of them report that they may not be that hungry, but when they start eating, they don't feel satisfied. It takes them a large amount of calories before they feel satisfied. And of course, if those two symptoms, excessive hunger or lack of satiety are the pathognomonic symptoms of the disease, it helps us to focus on what we need to make better with our treatments.

Bob Barrett: Okay. Now, Dr. Yalla, let's go to you. We spoke about bariatric surgery as an effective treatment strategy for severe obesity in patients for whom other methods have been unsuccessful, or those who have significant obesity-related comorbidities. Your case report describes a woman with a history of Roux-en-Y gastric bypass surgery. How often are bariatric procedures, like this one, being performed in the United States?

Dr. Naga Yalla: So, that's a good question. I think you'd have to be living under a rock to not realize we're sort of in a midst of an obesity crisis, really worldwide. And while this has primarily had been seen as a problem in the developed world, increasingly, it's becoming a public health issue in developing nations as well.

Here in the United States, based on the latest figures from the CDC, more than one-third, about 36.5% of U.S. adults aged 20 years and older, are considered obese. And I think what's more concerning is that one in twenty American adults qualifies as being severely obese which is defined as a body mass index greater than 40.

Really in the last few decades, we've seen the development of both medical and bariatric surgical approaches to treating obesity. Not surprisingly concurrent with this obesity epidemic, the number of bariatric procedures has been steadily increasing as well, with the doubling in the number of procedures worldwide over the past decade.

Here in the United States in the last year, we estimate about a 196,000 procedures were performed. I think it's helpful for listeners to understand the indications for surgeries and the type of procedures that are available to our patients.

The main indications for bariatric surgery include a BMI of 40 or greater, or being at more than a 100 pounds overweight, or a BMI of 35 and greater and at least one or more obesity-related comorbidities such as type 2 diabetes, hypertension, sleep apnea, non-alcoholic liver disease, and the list goes on.

Another indication for surgery, and a softer one, is the inability to achieve healthy weight loss sustained for a period of time with prior weight loss efforts.

In terms of the types of procedures that our patients can avail, these procedures are largely divided into restrictive and malabsorptive procedures. And the case study that we presented in the journal this past month focuses on an individual who had a Roux-en-Y gastric bypass procedure which is considered a combination of the two.

In terms of restrictive procedures, these procedures involve reducing the stomach's size, so for example, laparoscopic adjustable gastric banding or gastric banding procedures in which a silicon band is placed around the proximal portion of the stomach. This creates a really small pouch that can only hold a very small amount of food. It's considered a wholly restrictive procedure, while those procedures that retard the mixing a food with bile salts and pancreatic juices are generally considered malabsorptive procedures. An example of this would be a vertical sleeve gastrectomy.

Getting back to the Roux-en-Y gastric bypass procedure that our patient had performed, the restrictive component is the result of a creation of a really small gastric pouch. It's only about 30cc which is then anastomose to the proximal portion of the jejunum. This reduces the intestinal surface area available for caloric absorption and can ultimately lead in addition to the weight loss, to profound malabsorption of minerals and critical fat-soluble vitamins.

In the United States, of that 196,000 procedures that are performed here, 23% are Roux-en-Y gastric bypass procedures. But worldwide, they're still the leading type of surgery that is performed in patients looking for weight loss.

Bob Barrett: Okay. So Dr. Le Roux, how do operations of the gut such as metabolic surgery attenuate the symptoms and complications of obesity?

Dr. Carel Le Roux: When patients come to me as internal medicine physician and after they've had an operation, very often they say, "Doctor, where did the surgeon operate? Did he operate in my tummy or did he operate in my head because all the effects after this operation are in my head. Now, for the first time in my life, I'm not feeling hungry" or "For the first time in my life, when I eat a small amount of food, I feel satisfied. It is like the surgeon has released me of being obsessed with food all the time. Not because of the operation and how stomach feels when I've eaten. It's actually the symptoms of the disease I suffered from have suddenly gone away."

But it's not only that the operations improved the symptoms and the signs of obesity. It also addresses the complications. Typically, it improves glycemic control and type 2 diabetes is improved because it reduces the effective glucose output. It improves insulin secretion from the pancreas, but it also reduces peripheral instant resistance.

So these effects of the operation, that's independent of weight loss, but that happens very early. But there's other complications also that's addressed -- we see the sleep

apnea improve dramatically because of the reduction of visceral adiposity and the way the diaphragm moves.

We also see improvements in blood pressure in randomized controlled trials because we see after certain operations an increase in urine sodium excretion. So the effect of the operation is not only related to the reduction in adipocyte mass, it also relates to the effects, the biology, between the gut and the kidney.

And as I think, what we are learning from these operations is although the operation is very difficult from a scalable option and that we can't operate on everybody and certainly not everybody wants to have an operation. But the mechanisms are teaching us what strategies work in the long-term and how we can actually use this in combination to improve patient's health.

Bob Barrett: We read there's promising evidence emerging to suggest metabolic surgery may be of benefit in metabolic disorders beyond obesity. So Dr. Yalla, I'll ask you. What are the metabolic implications of these surgeries?

Dr. Naga Yalla: Bariatric surgery really appears to be an effective intervention in patients who are overweight. We know it leads to significant and often durable weight loss and we see marked improvements in the associated comorbidities with obesity, such as diabetes, hypertension, obstructive sleep apnea. And increasingly, there is mounting data to suggest that it actually may contribute to decreased mortality in this very high-risk patient population.

However, over the last several years as these procedures have become more common, we're increasingly made aware that particular surgical modalities, namely, the Roux-en-Y gastric bypass procedure and biliopancreatic diversion procedures, may actually produce a negative impact on skeletal health. Multiple studies demonstrate changes in bone turnover markers, declines in bone density, and increasingly there's conflicting data regarding fracture risk following these procedures.

So in patients who've undergone bariatric procedures, we tend to see changes in the pattern of bone turnover markers that suggest a shift in bone remodeling that favors resorption or breakdown versus bone formation.

Examples of resorption markers include serum and urinary C-terminal telopeptide, or CTX, and the urinary and terminal telopeptide, or NTX. Markers of bone formation include osteocalcin, procollagen 1 Intact N-terminal, or P1NP, and bone specific alkaline phosphatase.

These markers begin to rise as early as three months post-operatively. And in some studies, it increases persist even beyond the first post-operative year even correcting for nutritional deficiencies and after stabilization of weight loss. The markers, it turns out, are predictive and mirror the ongoing declines that we've seen in multiple studies in bone mineral density. These declines appear to be more pronounced in the hip with some studies demonstrating some current declines in the lumbar spine bone density measurements as well.

So, do these changes in bone turnover markers and declines in bone mineral density actually translate to increased fracture risk for our patients? And thus far, the data has been conflicting. A retrospective study performed by the Rochester Epidemiology Project suggested a two-fold higher risk of fractures in the 258 patients that they had looked at who had undergone bariatric procedures when comparing them to community-based incidence rates. Interestingly enough, in this study, about 75% of patient who had undergone that Roux-en-Y gastric bypass surgeries as similar to the one that our patients had undergone in the case report.

However, a larger retrospective case controlled study from Quebec looking at over 12,000 patients only found that biliopancreatic diversion procedures were clearly associated with an increase fracture risk.

More recently, and this is after our article had been submitted for publication, Elaine Yu from Mass Gen published an article on the *Journal of Bone and Mineral Research* in June of 2017. And she looked back at commercial health data base claims for over 15,000 patients and was able to demonstrate a 43% increase risk of non-vertebral fractures in patients who had undergone a Roux-en-Y gastric bypass procedure compared to those who had adjustable gastric banding.

I think, increasingly, the data is suggesting that in relation to particular procedures, bariatric procedures, that there might be, in fact, a heightened risk of fracture. And that's certainly something we, as clinicians, who take care of these patients and patients need to be made aware of.

Bob Barrett: What mechanisms explain the effect of bariatric surgery on skeletal health?

Dr. Naga Yalla: So the etiology for the increased resorption that we see as evidenced by bone turnover marker measurements, the declines in bone mineral density, and the potential increase in fracture risk, I think are likely multifactorial. Some of the earliest explanations for bone loss really centered on

nutritional deficiencies that these surgeries can engender, namely, malabsorption of calcium and Vitamin D that in some cases can produce a condition known as osteomalacia.

More recently, people have looked at skeletal unloading from the weight loss itself as a potential explanation for bone loss.

But really, I think one of the most interesting things to emerge and this is basically been because of our colleagues, our bone biology colleagues, is people started to look at the complex crosstalk between the gut, the bone, and adipose tissue as a potentially etiology for this bone loss.

I'll start a little bit by talking first about the nutritional deficiencies. We know nutritional deficiencies are common in patients undergoing these procedures, particularly malabsorptive procedures like the Roux-en-Y gastric bypass. These results purposely in chronic malabsorption, but like we talked about, can create a situation where we're chronically malabsorbing calcium and Vitamin D.

Roux-en-Y gastric bypass procedures bypass the duodenum and proximal jejunum where it's estimated that about 80% of our calcium absorption occurs. These procedures as well as concurrent proton-pump inhibitor use which is very common in this patient population, may also limit gastric acid production and negatively impact calcium absorption. Additionally, it turns out the jejunum is a critical site for Vitamin D absorption which is facilitated by bile acids and pancreatic enzymes. And this can be compromised in these sorts of duodenal exclusion procedures.

Most studies to date have demonstrated an increase in parathyroid hormone concentrations, a decrease in urinary calcium, consistent with calcium malabsorption. Over time, this increase in PTH levels caused by the malabsorption from the gut, essentially, it creates a situation where the body is attempting to maintain normal calcium homeostasis at the expense of the skeleton.

We also know that patients who undergo these procedures are at risk for protein malnutrition and other vitamin and mineral deficiencies. Over time, untreated, this can lead to a condition known as osteomalacia, characterized by a decreased mineralization of the osteoid. Clinically, osteomalacia manifest as generalized bone pain, muscle weakness, bony tenderness, and can put our patients at risk for low trauma fractures and hypocalcemia. The biochemical manifestations of osteomalacia include a low 25-Hydroxy Vitamin D level, increased parathyroid hormone concentrations, and increased alkaline phosphatase activity.

Some patients, additionally, exhibit decreased serum calcium and phosphorus concentration and decreased 24-hour urine calcium excretion. We often make this diagnosis based on laboratory findings and radiographic findings that are pathognomonic of the disease. Rarely do we have to resort to a bone biopsy, but that offers the most definitive means of diagnosis.

The second etiology apart from nutritional issues that explains bone loss in this patient population may have to do with skeletal unloading itself, just by virtue of the significant amount of weight loss that these surgeries engender. Loss of mechanical loading results in bone loss by a complex changes may have to be mediated by a sclerostin. We know that the bone loss seems to be more pronounced in the hip and that maybe because the hip we know carries a load two to three times the body weight. And so, that may account for why it's preferentially affected by weight loss in this patient population.

And lastly, as I alluded to in this, much far too complex for a podcast to go into, we're increasingly made aware by the work of some very pioneer in bone biologists, that there is this complex crosstalk, as we had mentioned before, between the gut, the adipose tissue, and the skeleton. This is in area that we certainly need more research in, but we know from rodent models that adipokines, particularly leptin and adiponectin, seemed to play a very important role in bone metabolism. Recent data has also implicated serotonin, GLP-1 which is glucagon-like peptide, gherlin and GIP as potentially impacting skeletal health. So again, this remains an avenue for future research.

All in all, recognizing the potential for these surgeries to have a negative impact on the skeleton, the American Association of Clinical Endocrinologist, The Obesity Society, and The American Association of Metabolic and Bariatric Surgeons, have issued guidelines that really stress the importance of both preoperative and postoperative follow-up on these patients when it comes to skeletal parameters.

They recommend preoperative assessments of Vitamin D levels and aggressive replacement of calcium and Vitamin D prior to surgery. And postoperatively, the guidelines suggest that patients who have undergone, particularly these malabsorptive procedures, should have 25-Hydroxy Vitamin D levels, calcium, phosphorus, PTH, and alkaline phosphatase followed every six months, as well as a bone density test prior to and every one to two years, postoperatively until stable.

Bob Barrett:

Dr. Naga Yalla is an Assistant Professor of Medicine in the division of Bone and Mineral Metabolism and Endocrinology,

**Clinical Case Study: Bad Breaks and
Metabolic Effects of Bariatric Surgery**

Metabolism, and Lipid Research. She is also a Director of the Fracture Liaison Service at Washington University, St. Louis, Missouri.

Dr. Carel Le Roux is an expert in Metabolic Medicine and is part of the Diabetes Complications Research Center at University College in Dublin. They've both been our guests in this podcast about bariatric and metabolic surgery from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.