

# Transcript

## Skeletal Muscle Molecular Alterations in Patients With Rheumatoid Arthritis

### FACULTY

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### INTRODUCTION

The following transcript was developed from a webcast featuring Kim Huffman, MD, PhD, and William Mencia, MD, that was filmed at the 2017 American College of Rheumatology annual meeting.

**DR. MENCIA:** Welcome to the Duke Clinical Practice Today series. My name is William Mencia, and I'm joined by Dr. Kim Huffman, associate professor of rheumatology and immunology at Duke. We are in San Diego for the American College of Rheumatology annual meeting. Dr. Huffman, welcome. Can you tell us a little bit more about your research?

**DR. HUFFMAN:** Sure. Since I've been at Duke, most of my research has focused on physical activity and how exercise can be beneficial for people with rheumatologic diseases, in particular, rheumatoid arthritis. Because skeletal muscle is really important in physical activity, a lot of that research is targeted at skeletal muscle, people with rheumatoid arthritis, how that muscle is different from that of people who don't have rheumatoid arthritis, and what we can do with exercise that may be helpful.

**DR. MENCIA:** Let's talk about your abstracts. Specifically, in one of your studies, you're looking at the role of cytokines and myostatin. What were your findings?

**DR. HUFFMAN:** We had previously noted that in people with rheumatoid arthritis, there are increased levels of inflammatory cytokines in the skeletal muscle, as compared with people who don't have rheumatoid arthritis but are age, gender, and body mass index, or size matched. What was interesting is that, even though there is an inflammatory process in the skeletal muscle, it is not completely reflective of the inflammatory process that is in the systemic circulation in rheumatoid arthritis. And what that implied to us is that process is a *local* process that's happening in the skeletal muscle of people with rheumatoid arthritis.

In addition, it is related to their disease activity, but it is also related to their physical inactivity, as well as disability. Those inflammatory cytokines and that inflammatory

process actually reflect a problem with skeletal muscle remodeling in people with rheumatoid arthritis. And so, the question that we were trying to address with this project is to figure out whether a physical activity intervention—in particular, a high-intensity interval training program—could reverse that inflammatory process in the skeletal muscle of people with rheumatoid arthritis.

Interestingly, we found that, for the group as a whole, the high-intensity interval training program did not globally reduce those cytokine levels. What we did find is that, in people who were able to improve body composition in that program, there were some reductions in those cytokine levels, indicating that inflammatory process is, indeed, somehow tied to their adiposity or their skeletal muscle tissue amounts and qualities. Myostatin is a really interesting molecule; it's involved in both the hypertrophy and the atrophy processes. And so, our thoughts were that if myostatin is elevated in rheumatoid arthritis, physical activity may actually cause it to be reduced, which would hopefully improve patients' ability to grow their skeletal muscle.

What we found was a little counterintuitive. When we examined people with rheumatoid arthritis, as compared with controls, they had much lower levels of myostatin. The people without rheumatoid arthritis, who were a bit more overweight but overall had similar body composition, had high levels of myostatin, which would then promote atrophy (one would expect). After the physical activity intervention, their myostatin levels were reduced, which one would think would be very beneficial. Unfortunately, the people with rheumatoid arthritis had much lower levels of myostatin in the beginning, and those levels were hardly impacted by the physical activity intervention. (Skeletal muscle concentrations of myostatin pre–high-intensity interval training program were 16.621 pg/mL/μg and post–high-intensity interval training program were 20.589 pg/mL/μg in rheumatoid arthritis patients; for prediabetes mellitus patients [control], myostatin levels were 73.976 pg/mL/μg pre-activity and 34.314 pg/mL/μg post-activity;  $P < .05$  for comparison between rheumatoid arthritis and prediabetes mellitus groups.) So what this is letting us believe is that myostatin seems to be dysregulated in people with rheumatoid arthritis. This is a very exciting finding for us, and we're going to follow up on it in the future.

**DR. MENCIA:** Interestingly, you also looked at similarities between the skeletal muscle and the myocardium. What did your research show?

**DR. HUFFMAN:** Yes, so we were really interested to know whether what we were seeing in the skeletal muscle or what we had hypothesized as a dysregulated remodeling process could also be occurring in the myocardial tissue within the heart and, perhaps, be responsible for some of the cardiovascular disease in rheumatoid arthritis. Interestingly, a molecule called galectin-3 is involved in the ventricular remodeling process and is also a marker of fibrosis. In this project, we were really interested in seeing whether galectin-3 was increased in people with rheumatoid arthritis, as

compared with those without rheumatoid arthritis, and whether that same exercise intervention could reduce galectin-3.

What we found, interestingly, was that, in the older persons with rheumatoid arthritis, the galectin was increased ( $8.8 \pm 3.5$  [SD] ng/mL), as compared with even the younger persons with rheumatoid arthritis ( $7.85 \pm 4.0$  [SD] ng/mL;  $P = .390$ ), but also as compared with the older controls who didn't have rheumatoid arthritis ( $6.89 \pm 1.9$ ;  $P = .042$ ). In those with rheumatoid arthritis, the galectin-3 concentrations were related to traditional cardiovascular risk factors, including their age (so older persons had higher levels of galectin-3;  $r = 0.39$ ), as well as increased levels of adiposity ( $r = 0.32$ ), and also some nontraditional cardiovascular risk factors such as interleukin-6 ( $r = 0.29$ ), which is a systemic inflammatory cytokine, and prednisone use. It's interesting to note that these people were using as little as 5 mg a day or less of prednisone.

With exercise training, galectin-3 was not reduced in the rheumatoid arthritis group as a whole. But in those people with rheumatoid arthritis whose galectin-3 was reduced, significant improvements were seen in their cardiovascular fitness, as measured by  $\text{VO}_2$  max ( $r = -0.57$ ;  $P = .05$ ). Therefore, what we're taking from these findings is that, number one, it seems like galectin-3 may be an interesting cardiovascular risk factor or biomarker in rheumatoid arthritis. Number two, that cardiovascular disease—in particular, cardiovascular fitness—can be modulated by exercise training in rheumatoid arthritis, which may be reflective of improved myocardial remodeling.

**DR. MENCIA:** Are these findings ready to be used in the community setting? Is there anything that our learners today could take from this?

**DR. HUFFMAN:** I don't know whether galectin-3 is commercially available; it certainly hasn't been validated in rheumatoid arthritis at this point (and a number of cardiovascular disease or cardiovascular risk markers are available). But, at this point, we need to study the galectin-3 a bit more and compare it with some other biomarkers of cardiovascular disease in rheumatoid arthritis, but I think it does have some promise and also some potential to inform the underlying pathogenesis of heart disease in rheumatoid arthritis.

**DR. MENCIA:** Let's talk about your third abstract. In this study, you and your colleagues were able to take stem cells and from that produce mature rheumatoid arthritis myobundles. Very interesting research. What were your findings there?

**DR. HUFFMAN:** Yes, this has been a fascinating area of research. I have to give credit to my collaborators and colleagues in the bioengineering department who have worked many years to develop these functioning skeletal muscle myobundles in healthy persons. What's interesting is that, when we try to study skeletal muscle with animal models, the animal models don't necessarily recapitulate humans. And if we try to study skeletal muscle in cell culture, you're basically looking at skeletal muscle in two

dimensions, and it doesn't allow you to really get at how well that skeletal muscle is functioning.

In this project, we isolated stem cells from rheumatoid arthritis skeletal muscle biopsies (those stem cells are also called myoblasts). The myoblasts are then grown onto a structure that the bioengineers have generated. They grow it into a fully functioning mature skeletal muscle, as you mentioned, and we can study how well it contracts. In the case of rheumatoid arthritis, when we compared it with healthy control skeletal muscle, number one, they noticed that the skeletal muscle was less pure, meaning that, for the same mass of skeletal muscle, there were many fewer myoblasts available in the isolate. Number two, even once we normalized the number of myoblasts in the isolate, once those myoblasts grew into functioning mature skeletal muscles, they didn't contract as well. Overall, their general function was poorer than that of the healthy controls.

**DR. MENCIA:** Alright, wonderful. Thank you, Dr. Huffman. Any final thoughts for our learners?

**DR. HUFFMAN:** My overarching goal is to get people to recognize that rheumatoid arthritis skeletal muscle is impacted certainly by the disease, as we may have known for some time. But also, in the days where we are doing a good job taking care of our patients and reducing their systemic inflammatory burden, there remains a problem with skeletal muscle that can be contributing to disability in rheumatoid arthritis. The bottom line is that skeletal muscle is important in rheumatoid arthritis, and it may be an important target for physical activity in rheumatoid arthritis.

**DR. MENCIA:** Wonderful. Thank you very much.

**DR. HUFFMAN:** Thank you.

## REFERENCES

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Developed in collaboration

