Clinical Chemistry

Targeting the Circulating MicroRNA Signature of Obesity

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Guest:
Dr. Francisco José Ortega from the Department of Diabetes, Endocrinology and Nutrition at the Biomedical Institute in Girona, Spain.

Bob Barrett: This is the podcast from *Clinical Chemistry*, I am Bob Barrett. Genomics has the potential to provide important insights into the pathogenesis of obesity. A paper in the May 2013 issue of *Clinical Chemistry* found that circulating microRNAs were deregulated in severe obesity.

The lead author of that study, Dr. Francisco José Ortega from the Department of Diabetes, Endocrinology and Nutrition at the Biomedical Institute in Girona, Spain, joins us today in this podcast.

Doctor, what exactly are microRNAs and how can they help us in the understanding of obesity and obesity-related diseases?

Dr. Francisco José Ortega: Yeah. Well, microRNAs are small non-coding and highly conserved RNAs. Since its discovery in 1993, microRNAs expression and functions are being studied in depth. This is because through modified protein synthesis, microRNAs regulate many cellular processes, such as proliferation, differentiation and cell death.

Moreover, since microRNAs are closely related to the cellular behavior and the correct development of tissues, change in these expressions is being analyzed in depth in physiological states in many diseases, looking for defining their specific function and their potential ability in medical care.

On the other hand, it should be noted that the clinical tools available for the detection and characterization of systemic disease such as obesity and obesity-related disturbances, do not allow an early and accurate diagnosis. Moreover, in most of the cases, these analysis are quite difficult to get and

expensive, in terms of sample, time, and clinical gadgets.

Whether there are new tools such as high-throughput technologies for genomic analysis may solve common problems in clinical practice allowing these yearly in accurate diagnostics of co-morbidities, and improving the detection and response to therapy. The utility of this technology is mostly tested in this field, and so we did.

Bob Barrett: How did you get the idea to look at microRNAs in circulation in association with obesity? Had you done some work in this general area before?

Dr. Francisco José Ortega: Yes, in 2010 we published one of the first studies that in the microRNA signature of human adipose tissue and in adipocytes. This study conclusively demonstrated that the pattern of microRNAs in human adipose is dependent on adiposity and closely related to the differentiation of these fat cells.

Our findings with human adipose tissue encouraged us to study these factors also in the circulation. Indeed, it should be noted that during the last eight years, several reports have suggested that microRNAs are not only regulated in tissues from tumors, another disease, but also in the circulation. So, we thought that these should be also the case in obesity and in obesity-related diseases.

Bob Barrett: What did you consider to be the big issue and the ultimate goal of this study?

Dr. Francisco José Ortega: Yeah. Well, our interest was to identify specific microRNA signature in the plasma from obese subjects. During the last decades, genomic studies using adipose tissue from obese subjects have yielded important insights into the pathogenesis of obesity. Indeed, new tools for genomic analysis might not only solve common problems in clinical practice, but also reveal new therapeutical targets.

However, the fat tissue is not only quite difficult to get, but also holds many clinical halts. Indeed, it is well-known that adipose tissue is very difficult to hunt, making the knowledge about this human adipose tissue and obesity particularly limited in patients.

So in our work, we present this careful comparative study which provides for the first time a set of circulating microRNAs, significantly that is regulated

in severe obesity. Moreover, the effects of surgery and diet-induced weight loss on this circulating concentration were also investigated and also validated in independent colleges.

Then the findings reported here could be a potential diagnostic and therapeutic value in this setting, with no need to have human biopsies.

Bob Barrett: It has been the hope that looking at microRNAs could help develop drugs or other treatments. How can looking at circulating microRNAs in obese subjects help these patients, and would it help physicians diagnose obesity-related disorders such as type 2 diabetes?

Dr. Francisco José Ortega: Well, in the future, on these circulating microRNAs that have been analyzed in detail, this investigation and other similar to us could reveal which microRNAs are over explicit in the plasma, could be also involved in triggering some metabolic inflammatory pathways associated with an increased risk for the development of obesity-related disorders, including cardiovascular diseases and type 2 diabetes.

Then the blocking of those increased microRNAs in circulation may constitute a target in developing a therapy to delay or even halt the appearance of those obesity-related pathologies.

On the other hand, taking into account that circulating microRNAs are not modified by other components of plasma which cannot interfere with conventional tools for diagnosis, the availability and stability of these microRNAs and the possibility of detecting, amplifying and analyzing, and the individual variations make them potential and very interesting new biomarkers for systemic disease such as obesity.

However, our study is just heading for a long and winding road, and a lot of work is needed to finally come across with a clinical application or medical set of recommendation to try to help obese people.

Bob Barrett: You say in the paper that this is the first microRNA study identifying differences in circulating microRNAs in subjects with severe obesity. Why do you think that no one had done this type of work before?

Dr. Francisco José Ortega: As far as we know, there are no publications about this topic. It is possible that although researchers

have the similar study to us, and it will appear published in the future.

On the other hand, we think that the main reason for this is that the scope is potentially interesting. An obvious question is whether there is a need for circulating biomarkers for obesity.

However, we think that this is only one-fifth step in the identification of how wide genomic profiling in plasma that could help in dealing with this complex and heterogeneous disease that obesity seems to be. Then we really believe that this topic needs further attention and that the data provided here is of importance.

Bob Barrett: Doctor, you found that some microRNAs were differentially expressed in the plasma of severely obese patients. What classes of microRNAs were up-regulated or down-regulated in these subjects?

Dr. Francisco José Ortega: Well, unfortunately the knowledge available regarding important aspects of microRNAs, basically those microRNAs in circulation, such as function and behavior is quite limited.

We just have some few clues about how they get into the plasma and the function that they may have. The main feeling is that the circulating microRNAs can be involved in proteins and communication as well as cytokines and hormones.

However, right now we can only speculate about this. The sure thing is that there exist important differences between control subjects and patients that microRNAs that are related in obesity might be a practice candidate in the study of the regulation of cell fate decisions and complex obesity-related complications as disclosed by the intersection for the target genes identified in silico.

We are working hard trying to identify, to explain the meaning of these differences and the causality of these associations.

Bob Barrett: The demonstration of significant changes after surgery-induced weight loss is quite impressive. Why did the weight loss induced by diet not show the same effect?

Dr. Francisco José Ortega: Okay, the growth in gastric bypass is the most commonly performed bariatric surgical procedure and

is an effective approach for achieving weight loss in obese patients.

The weight loss induced by the surgery improves or completely resolved almost completely related medical complications such as the insulin resistance and dyslipidemia, and leads to increase survival, whereas conventional diet-induced weight loss do not.

At this respect, it should be noted that the degree of weight loss induced by diet was far below that obtained from surgery. In any case, our findings report the possibility of modifying the circulating microRNA signature in obese individuals with surgical procedures.

Those signs, they are simultaneous coordination of a less number of target genes is potentially accomplished by a single microRNA. MicroRNAs that are weighted in obesity might not only be a useful tool for their prognosis but also attractive candidates for regulating cell fate decisions and revert complex obesity-related co-morbidities as demonstrated by this association.

Bob Barrett: What would you say were the most significant conclusions from this study?

Dr. Francisco José Ortega: Our study has demonstrated significant differences in the circulating microRNA profiles of obese subjects using this clean, noninvasive, fast, and reliable technology that is already available.

In our hands, 190 microRNAs are detectable in plasma and may explain how metabolically compromised a subject is. Of note, a discriminant function using only three microRNAs was specific for morbid obesity with an accuracy around 90%.

On the other hand, our study mainly shows that this profile could be modified. This means that the circulating percent of similar microRNAs may lead to novel biomarkers for risk estimation and classification of obese subjects, and could be also exploited for prognosis in the complications associated with the extreme accumulation of fat.

Bob Barrett: Were you surprised at these results?

Dr. Francisco José Ortega: I don't think so. Whether you get the results of how wide genomic profiling in biological flight, you do not have a predetermined idea of which RNA should

appear that are in these conditions you are comparing. I should say that you feel more surprised and anxious to start surfing the web to access the information about them.

Actually, microRNAs are a very hot topic. And the more you study about them, the more anxious you get because most of the times, you finally realize that these small factors you are writing about are real gold mine in clinical practice.

Bob Barrett: Well finally doctor, let's look ahead. Where is your research in this field going? Is there anything beyond circulating microRNAs that we should know about?

Dr. Francisco José Ortega: Yeah. Well, we are using our knowledge and expertise using this technology to design and make proper genomic analysis and comparing microRNA profiling in association with metabolic parameters in children and in patients with poorly controlled Type 2 diabetes.

We also sought to investigate the cellular and molecular mechanism behind our findings using different in vitro and in vivo models, and to assist in clinical implications following different strategies.

In addition, we are studying in more detail several of the identified microRNAs candidate and their potential as therapeutical targets, also going back from in vivo and in vitro models.

Bob Barrett: Dr. Francisco José Ortega from the Department of Diabetes, Endocrinology and Nutrition at the Biomedical Institute in Girona, Spain. He has been our guest in this podcast from *Clinical Chemistry.*

I am Bob Barrett. Thanks for listening!