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Diabetes and Obesity International Journal
ISSN: 2574-7770

Circulating MicroRNAs in Overweight and Obese Patients

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Research Article

Volume 4 Issue 4

Received Date: November 25, 2019

Published Date: December 10, 2019

DOI: 10.23880/doij-16000215

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Abstract

MicroRNAs, short noncoding RNA sequences, regulate several biological processes and seem also regulate insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and food intake. miRNAs may have a role in molecular mechanisms linked to cellular pathways of some diseases, as viral infections, cancer, diabetes, obesity and cardiovascular disease. The recent discovery of circulating miRNAs (c-miRNAs) easily detectable and measurable in plasma and other body fluids, led to the hypothesis of their potential role as disease indicators. It has been shown that altered levels of several c-miRNAs are linked to overweight, obesity and their complications. Different levels of some c-miRNAs were found significantly associated with weight gain, but most of the data concern comorbidities and complications of obesity as insulin resistance, pre-diabetes, diabetes, dyslipidemia, adipogenesis dysregulation and inflammatory processes. Moreover, several evidences were obtained in obese children, in newborns and in maternal pre-gestational and gestational obesity. In particular the expression of some c-miRNAs differs in infants born to obese women compared with those born to lean women and these biomarkers might be useful in predicting future risk of obesity in children. At last, down-regulation of different c-miRNAs was observed in overweight/obese subjects after low or high glycemic index diet and after low-fat diet; c-miRNAs might also be potential novel biomarkers for the benefits of bariatric surgery and the effects of mild exercise. A potential role of c-miRNAs detection as diagnostic, prognostic and therapeutic biomarkers in overweight and obese patients is supported by scientific evidence but there are several limits: number, duration and sample size of clinical studies are small; source of c-miRNAs, extraction procedures, quantities of blood samples and methods of analysis were promiscuous and not well standardized; high costs required for c-miRNAs detection. Reproducible and well standardized methods as well as low-cost and wide availability assays to detect c-miRNAs with high sensitivity/specificity and large, long-term and randomized controlled clinical studies are need to determine whether c-miRNAs can play a role as biomarkers for management of overweight and obesity in daily clinical practice.

Keywords: Circulating microRNA; Overweight; Obesity

Introduction

MicroRNAs (miRNAs), a large family of short noncoding RNA sequences, synthesized in the cell nucleus through a complex multi-step biosynthetic process starting from RNA polymerase II, modulate post-transcriptional gene expression and regulate several biological cell processes, including cell growth, development, differentiation and proliferation, cell metabolism, stress response, cell-to-cell communication and apoptosis, tissue remodeling and organogenesis [1,2]. It has been estimated that the human genome contains more than 2500 mature miRNAs and these molecules seem also regulate insulin signaling, immune-mediated inflammation, adipokine expression, adipogenesis, lipid metabolism, and food intake [1,3].

There is evidence that miRNAs may have a role in molecular mechanisms linked to cellular pathways of some diseases, as viral infections, cancer, Alzheimer's, diabetes, obesity and cardiovascular disease [2,4-7].

The recent discovery of circulating miRNAs (c-miRNAs) easily detectable and measurable in plasma and other body fluids, led to the hypothesis of their potential role as disease indicators; concentrations of c-miRNAs could be used as potential indicators/biomarkers for the diagnosis of onset and progression of diseases, and/or prevention, prognosis, or follow-up [8].

Several techniques are available for quantifying circulating miRNAs; quantitative real-time Polimerase Chain Reaction (qRT-PCR) seems to be the gold standard because of its high sensitivity, specificity and reproducibility; moreover qRT-PCR requires less amount of RNA sample, usually more than 1 μg, though the number of miRNAs possible to analyze and RNA quantity may represent limitations for this assay [9]. Deep sequencing technology has recently emerged as an attractive approach for miRNA analysis; in some cases, this technique showed most specificity and sensitivity compared to qRT-PCR and Microarray [10,11]. Other techniques are Northern blotting and bead-based flow Cytometry [12,13].

Aims of the Study

We have investigated a possible role of circulating miRNAs as biomarkers in overweight and obese patients, also evaluating whether the detection of these nucleotides in the bloodstream can play a role in daily clinical practice.

Material and Methods

A review of literature has been carried out via PubMed database, matching this search term: circulating microRNA, overweight and obesity. Search was not limited by language or human subjects. All the found items, published in the last ten years were analysed. Additional articles were selected from the bibliographies of the quoted references.

Results

Looking for circulating microRNA and overweight and searching for circulating microRNA and obesity we have obtained 64 and 102 items, respectively. Altered expression and dysregulation of c-miRNAs are confirmed to correlate over all with obesity and a broad panel of c-miRNAs is involved (Table 1) [14-16]; weaker evidence was found in overweight.

miR-17-5p; miR-21; miR-34a; miR-126; miR-132; miR-146a; miR-150 (Obesity)
miR-15a; miR-125b; miR-130b; miR-140-5p; miR-142-3p; miR-221; miR-222; miR-532-5p; miR-423-5p; miR-520c-3p (Morbid Obesity)

Table 1: c-miRNAs more related to Obesity.

Different levels of some c-miRNAs were found significantly associated with weight gain and the expression of several c-miRNAs varies with body weight changes [17].

However, most of the data concern comorbidities and complications of obesity as insulin resistance, pre-diabetes, diabetes, dyslipidemia, adipogenesis dysregulation and inflammatory processes (Table 2) [15,16,18-20].

Several evidences were also obtained in obese children in whose were found deregulated, among others, miR-122 and miR-199a; levels of these c-miRNAs showed a statistically significant increase in children with obesity versus normal-weight controls [21]. Moreover, circulating

levels of some miRNA as miR-486, miR-146b and miR-15b, alone or in combination, seem to correlate with future risk prediction of Type 2 Diabetes in obese children [16,22,23].

High degree of variability in levels of c-miRNAs was identified among children from different countries, supporting the hypothesis that these molecules are likewise affected by environmental and lifestyle factors [22].

miR-122; miR-15b, miR-21; miR-138, miR-155; miR-376a; miR-503 (Obesity/Type 2 Diabetes)
miR-23a-3p, miR-27a, miR-130, miR-143-3p; miR-181a-5p; miR-195, miR-197, miR-320a, miR-509-5p (Obesity/Metabolic Syndrom)
miR-29a; miR-143, miR-221 (Obesity/Atherosclerosis/Cardiopathy)

Table 2: c-miRNAs related to Obesity and its Complications.

Some data were also obtained in newborns and in maternal pre-gestational and gestational obesity; in particular, the expression of some c-miRNAs, as miR-155, miR-181a and miR-221, differs in infants born to obese women compared with those born to lean women and these biomarkers might be useful both in predicting future risk of obesity and in epigenetic foetal programming of metabolic disorders in children born to obese women [24].

Several c-miRNAs were found up- and down-regulated in pregestational and gestational obesity; some are associated with pregnancy weight gain, others are closely associated with metabolic parameters during gestation and are independent predictors of pre- and post-natal growth [25]. Moreover, there is evidence that circulating levels of some miRNAs, in early- and mid-pregnancy, are associated with gestational diabetes, particularly in women who are overweight pre-pregnancy [26].

Some studies have also investigated as diet, exercise, weight loss and bariatric surgery can influence the expression of c-miRNAs in obese patients. In 6-month, parallel, randomized clinical trial, significant down-regulation of several and different c-miRNAs was observed in overweight/obese subjects after low or high glycemic index diet and after low-fat diet [27]; therefore c-miRNAs detection could be a useful tool to monitor low carbohydrate nutritional regimens. Others c-miRNAs, as miR-21, miR-126, miR-130b, miR-221, and miR-222, were found upregulated following acute aerobic exercise in obese and normal-weight subjects [28]. The results of a pilot study have shown that Roux-en-Y gastric bypass fundamentally changes microRNA expression in circulation with a time-dependent progressive departure in profile from the preoperative baseline and, in another study, the association of gastric bypass surgery with exercise also altered the pattern of several c-miRNAs suggesting their potential role as novel biomarkers for the benefits of bariatric surgery and the effects of mild exercise [29,30].

Conclusion

In conclusion, there are scientific evidences sustaining a potential role of c-miRNAs detection as diagnostic, prognostic and therapeutic biomarkers in obese and overweight patients. Promising prospects are the employment of c-miRNAs in medical nutrition therapy of obesity and their potential as new biomarkers for early identification of subjects at risk of overweight- and obesity-related metabolic diseases, over all Diabetes, but there are currently no circulating miRNAs validated as biomarkers of Overweight, Obesity and related diseases.

We have identified several limits: number, duration and sample size of clinical studies are small; source of c-miRNAs, extraction procedures, quantities of blood samples and methods of analysis were promiscuous and not well standardized; promiscuous nature of miRNAs targets and difficulties of obtaining tissue specificity; high costs required for c-miRNAs detection.

Further larger, long-term, observational and randomized controlled trials are needed to state whether circulating miRNAs detection may certainly represents a novel tool to predict susceptibility and progression of Overweight- and Obesity-related disorders as well as to provide information on therapeutic benefits. The uncertainty observed in Literature highlights the need for reproducible and well standardized methods, as well as low-cost and wide availability assays to detect c-miRNAs with high sensitivity/specificity, to make c-miRNAs detection applicable as biomarkers for Obesity and Overweight in daily clinical practice.

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