



## Review Article

# BAT's specific Micro-RNA or Novel approach for treatment of obesity: A hypothesis

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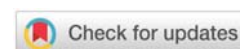
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## Abstract

**Background:** Type 2 Diabetes (T2D) is associated with coronary microvascular dysfunction, which is thought to contribute to compromised diastolic function, ultimately culminating in heart failure with preserved ejection fraction (HFpEF). The molecular mechanisms remain incompletely understood, and no early diagnostics are available. We sought to gain insight into biomarkers and potential mechanisms of microvascular dysfunction in obese mice (db/db) and lean rats (Goto-Kakizaki) pre-clinical models of T2D-associated diastolic dysfunction.

**Methods:** The microRNA (miRNA) content of circulating Extracellular Vesicles (EVs) was assessed in T2D models to identify biomarkers of coronary microvascular dysfunction/rarefaction. The potential source of circulating EV-encapsulated miRNAs was determined, and the mechanisms of induction and the function of candidate miRNAs were assessed in Endothelial Cells (ECs).

**Results:** We found an increase in miR-30d-5p and miR-30e-5p in circulating EVs that coincided with indices of coronary microvascular EC dysfunction (i.e., markers of oxidative stress, DNA damage/senescence) and rarefaction, and preceded echocardiographic evidence of diastolic dysfunction.

These miRNAs may serve as biomarkers of coronary microvascular dysfunction as they are upregulated in ECs of the left ventricle of the heart, but not other organs, in db/db mice. Furthermore, the miR-30 family is secreted in EVs from senescent ECs in culture, and ECs with senescent-like characteristics are present in the db/db heart.

Assessment of miR-30 target pathways revealed a network of genes involved in fatty acid biosynthesis and metabolism. Over-expression of miR-30e in cultured ECs increased fatty acid  $\beta$ -oxidation and the production of reactive oxygen species and lipid peroxidation while inhibiting the miR-30 family decreased fatty acid  $\beta$ -oxidation. Additionally, miR-30e over-expression synergized with fatty acid exposure to down-regulate the expression of eNOS, a key regulator of microvascular and cardiomyocyte function. Finally, the knock-down of the miR-30 family in db/db mice decreased markers of oxidative stress and DNA damage/senescence in the microvascular endothelium.

**Conclusion:** MiR-30d/e represents early biomarkers and potential therapeutic targets that are indicative of the development of diastolic dysfunction and may reflect altered EC fatty acid metabolism and microvascular dysfunction in the diabetic heart.

## Abbreviations

BAT: Brown Adipose Tissue; IR: Insulin Resistance; mRNA: messenger RNA; miRNA: micro-RNA; WAT: White Adipose Tissue

## Introduction

Obesity as a principal global health problem is the underlying cause of a variety of non-communicable diseases such as cancer, hypertension, and type 2 diabetes mellitus. Adipocyte disorders have affected 150 million people and one billion were overweight worldwide. Recently MicroRNA assembly has been used for miniature engineering of Brown Adipose Tissue (BAT) and leads to the development of new BAT biosynthesis and in turn, melts white fat tissues more properly. The suppression of BAT's specific miRNAs performs a critical role in molecular make-up and the modified new BAT display desirable metabolic affairs. Deletion of miR-22 leads to a reduction in fat accumulation and more beta-oxidation. The combinational effects of these two new metabolic functions may solve the problem of being overweight dilemma. The contribution of the developed results to human nature needs extra human trials and it should be assessed more meticulously. If pharmacological or molecular diet therapy would handle these epigenetic compartments, the developed results will produce new BAT to oxidize accumulated fat rapidly, thereby BAT activity will decrease adipocyte accumulation.

## Obesity

Obesity- a tremendous global health threat- is associated with early mortality and the underlying cause of a great number of non-communicable diseases such as cancer, hypertension, cardiovascular disease, and type 2 diabetes mellitus [1]. To the best of our knowledge, based on body mass index criteria, 39% of the global adult population (two billion) are reported to be overweight, while 12% (671 million) have obese [2]. Specifically, low and middle-income countries experience a sharp trend in the prevalence of obesity. It is projected that almost 20% of the general population (one billion adults) will be obese by 2025 [2]. Due to the limitations in the current therapeutic strategies for the management of obesity, including diet therapy, pharmacological treatments, and bariatric surgery, future research in the context of genetic modulator units such as micro-RNA (miRNA) seems necessary for the confidential treatment of obesity and aforementioned statistics highlight the need of an optimal approach targeting the treatment of obesity via detecting related pathways to find more specific molecular method [3-7].

## MicroRNA

Very tiny molecule explores the requirements of the deep consciousness of life, these molecules are originated from nuclei and spread through the organs and the developed products. miRNAs- a member of gene regulators- are commonly attached to the 3'-untranslated regions of messenger RNAs (mRNAs) of genes responsible for protein coding [8]. These specific RNAs, introduce the function of the biomolecules that manipulate

the most advanced achievements in the research of human health problems and challenges for a healthy life [7]. A high number of studies have been conducted to identify miRNAs and consequently target the responsibility of genes for obesity [8]. MiRNA makes this possible for direct weight loss and it would be feasible to reduce body weight by metabolic functions in experimental animal studies [5].

## Brown adipose tissue

Of note, animals spend winters in sleeping conditions or inactive manner and take the benefits of the physiological functions of brown adipose tissue (BAT). This fact also runs for newborns who take experience the positive features of BAT to generate body energy. The darkness of BAT's color is dependent on the contents of numerous small droplets and the much higher number of mitochondria that contain iron and make the brownness of this type of fat tissue [9,10].

BAT- a highly metabolic tissue - is considered a promising target for the management of metabolic disease [10-13]. By considering the role of BAT in burning extra energy through mitochondrial respiration, it is proposed that a treatment option for type 2 diabetes mellitus victims [14-16]. Although the majority of findings explain a negative link between obesity and BAT, future studies are needed to discover underlying molecular signaling pathways. Subsequently, the discovery of miRNA which is proposed to make a drastic hope for feature treatments regarding obesity, targeting BAT in experimental animal studies has received to the stage that may finalize this dilemma [17]. Collectively, BAT is offered for weight reduction and after that, a very wide perspective established experimental animal's trial had proved bright results for obesity treatment by miniature engineering of BAT [18-20].

In the milieu of this issue, the fundamental link between genetics and metabolic functions was first proposed by Victor Amboross, et al. [19,21]. Moreover, more than the presence of current strategies, patients with obesity should apply accessibility to other possibilities and results of research regarding cell nuclei and their management within the genetic sector [8,11]. It seems that following the experimental animal studies which recently have been conducted in this context, the probable positive findings could be attributed to human beings and cause brilliant results. Some undesirable results could cause unsuitable metabolic interactions such as liver disorders with more beta oxidations [22-24].

## Genetics, BAT and obesity treatment

Pioneer studies have documented that weight loss strategy could be similar to the miRNA modification approach, regarding insulin production in the pancreatic cells in a study on beta cell deficient rats. On the other hand, the commanding abilities of BAT for weight loss activate this biological tissue as an important tool to overcome obesity, we aimed to suggest an efficient approach for body fat mass melting procedure by reviewing the last findings related to BAT and genetic modification. Based on previous results [25-28], it is considered that:

Combination of two strategies including, (1) miRNA mediated metabolic function (particularly through the suppression of miR-22) and (2) the contribution of activated BAT in elevating energy expenditure and thereby losing body weight beside (3) the contribution of epigenetic factors that monitors this process, finally could be summarized as a possibility that miR-22 suppression in activated BAT may be reached to the state as an additional treatment strategy for obesity. The suppression of BAT's specific miRNAs (particularly miR-22) leads to a reduction in fat accumulation, increased beta-oxidation and thereby alleviating obesity

### Mechanism of action

White and brown adipose tissue production has been evoked for more energy generation. This process may cause more fat wasting by heat production similar to animals with weight reduction during winter. Hence, the presented theory may be possible in vitro by accelerating the biosynthesis of insulin by miRNA in the pancreatic cells in diabetic rats which is an advantage for a probable remedy for patients with youth diabetes mellitus that could be treated by new techniques for DNA transduction and *denovo* biosynthesis of insulin molecule similar to the secretion of insulin in type one diabetic mice [29,30]. If BATs' physiology accompanies by a well-programmed miRNA, this new procedure could achieve the details in fat adipose tissues and cause weight reduction by increasing beta-oxidation activity, triggering a definite weight reduction program by metabolic functions similar to animals, thereby the treatment of overweight/obesity become possible through melting white fat adipose tissue (WAT) similar to mammals in wild animals during cold winter dreaming season [9,31-33]. The release by Veitch, Shawn, et al. (2022) with the application of "MiR-30 that promotes fatty acid beta-oxidation and endothelial cell dysfunction as a circulating biomarker revealed the probability of our assumption [34].

### Strengths and limitations

The mentioned approach seems feasible and needs the cooperative function of other organs. The functional probability of the developed results would be retrieved in several in vivo and vitro studies, especially with close similarity to human nature. However, the safety of this approach in order to apply for human clinical trials needs high levels of sophistication. The revealed recent advantages made a new option for the possible abilities in the manipulation of other biomolecules and various types of BAT for facilitating body fat melting procedures that could take this responsibility with miniature programming of BAT.

### Conclusion

In conclusion, combining the two- aforementioned strategies as the suppression of BAT's specific miRNAs (particularly miR-22) leads to a reduction in fat accumulation and more beta-oxidation and thereby improves obesity. Applying this method to human needs further assessment in vivo and in vitro studies. This is considered as an additional approach that may produce ideal results, however, the feasibility of this

hypothesis is critical and tolerance of the human organism is extremely precise and needs more enlightenment but this is considered as an innovation that may produce ideal results and approach to this idea may provide ideal results and would be comprehensive for human life. Although the importance of the dysregulation of circRNAs in the onset of metabolic disorders discussed by different research [35] and the role of circular RNA in the pathogenesis of non-alcoholic fatty liver disease for proposed theory may resolve the big burden of obesity for world's population. Due to the consecutive investigations for different microRNAs their regulatory roles in different disorders have been declared [36] as Liu showed that the downregulated microRNA-130b-5p prevents accumulation of lipids and disorders for resistance in insulin physiologic functions would be treated in an experimental animal of nonalcoholic fatty liver disease [37].

### Ethics approval

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the Tabriz University of Medical Science.

### Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author at a reasonable request.

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### Authors' contributions

The authors' responsibilities were as follows: SRA and AFL contributed to data extraction and manuscript drafting. SA and HJ contributed to the conception of the article as well as to the final revision of the manuscript. All authors read and approved the final version of the manuscript.

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