BIOMARKERS OF OBESITY

Abstract

Obesity is one of the important epidemics of the world affecting both children and adults. It is a well-established risk factor for cardiovascular diseases, type 2 diabetes mellitus, stroke, hepatobiliary diseases, some types of cancer, etc. Thus, identification of obesity biomarkers is of growing interest. Leptin, adiponectin, plasminogen activator inhibitor (PAI-1), resistin, adipsin, fibronectin, circulating rennin-angiotensin system (RAS), kallikrein-kinin system (KKS), asprosin, visfatin, subfatin, 'omics' biomarkers, etc. are the potential obesity biomarkers. Biomarkers of obesity have a role in analyzing the molecular mechanism of obesity, describe their presence and also their potential mechanism of intervention. Adipocytes releases leptin and it can drastically reduce appepite. Serum levels of adiponectin, synthesized by adipocytes, is reduced in obesity. PAI-1, resistin, adipsin or fibronectin are elevated in obesity. Circulating RAS and KKS peptides are the potential obesity biomarkers of children and adolescents. Asprosin, visfatin and subfatin have relation with obesity. It appears that instead of using a single biomarker, combination of biomarkers may provide improved disease prediction and may give information about the condition and course of the disease.

Keywords: obesity, leptin, adiponectin, biomarkers.

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I. INTRODUCTION

Globally, obesity is one of the important epidemics affecting all sections of the society. It is a well-established risk factor for cardiovascular diseases, T_2DM, stroke, hepatobiliary diseases, some types of cancer, etc.[1] Although obesity is a risk factor for a wide variety of diseases, not all obese persons develop these diseases. An important role of biomarkers in obesity would therefore be identifying group of obese persons who are at greatest risk of developing the co-morbidities such as cardiovascular disease, T_2DM, cancer etc. Biomarkers of obesity have a role in analyzing the molecular mechanism of obesity, describe their presence and also their potential mechanism of intervention. Thus, identification of obesity biomarkers is of growing interest.

II. POTENTIAL OBESITY BIOMARKERS

Leptin, adiponectin, plasminogen activator inhibitor (PAI-1), resistin, adipsin, fibronectin, circulating rennin-angiotensin system (RAS), kallikrein-kinin system (KKS), asprosin, visfatin, subfatin, 'omics'biomarkers, etc. are the potential biomarkers for obesity.

Leptin was discovered in 1994 and its discovery was considered a cornerstone in the mechanism of obesity. Numerous studies have also been conducted regarding the relationship between leptin and obesity. It is probably the most well-studied obesity biomarker. It is released by adipocytes and it can drastically reduce appepite.[2] Mutation of leptin gene causes increased appetite and high insulin levels. Several studies showed association between leptin and cardiovascular diseases. Although not common in humans, leptin deficiency was shown to cause severe obesity due to increased food intake and hyperinsulinemia. Leptin deficient animals, on leptin administration, reduced food intake and thus has beneficial effect. However, its level were found to be increased with increasing body fat in most human subjects suggesting leptin resistance in such individuals. Thus, its role seems to be more complex. There are two forms of leptin- free and bound form. In the bound form, majority of leptin binds to a soluble leptin receptor. This soluble leptin receptor was thought to be one of the important mediators of association between obesity and colon cancer. But more studies are needed to come to conclusion.

Adiponectin is released exclusively by adipocytes. However, its serum levels is decreased in obesity and obesity-associated diseases.[3] Adiponectin has strong anti-inflammatory and anti-atherosclerotic actions. Higher levels of adiponectin seems to produce lesser complications of obesity. Role of adiponectin for the development of cardiovascular diseases and cancer is still controversial. Further studies are required to conclusively show the correlation between adiponectin activity and cardiovascular effects of obesity.

Plasminogen Activator Inhibitor (PAI-1), resistin, adipsin or fibronectin are found to be elevated in obesity.[2] They play a role in producing cardiovascular harm of obesity. Many studies have found association between increased resistin levels and development of insulin resistance, diabetes and cardiovascular diseases.

Obesity during childhood and adolescence is associated with higher cardiovascular mortality in adulthood.[4] Thus, it is a medical and public health concern requiring action to prevent the harmful effects of childhood and adolescent obesity into adulthood. Circulating

rennin-angiotensin system (RAS) and kallikrein-kinin system (KKS) peptides are the potential biomarkers of childhood and adolescent obesity. Fernandes et al[5] analysed the RAS and KKS and reported that Ang (1-7) was negatively and des-Arg^9-bradykinin was positively correlated with BMI. ACE2 is required for Ang (1-7) synthesis and des-Arg^9-bradykinin degradation. This findings suggest that ACE2 activity is decreased in obesity. More studies are needed to know the mechanism in detail.

Asprosin, visfatin and subfatin have relation with obesity and its complcations. Some studies have reported that asprosin levels in saliva was associated with an increase in BMI.[6] It was suggested to cause appetite stimulation and obesity. However, Wiecek at al[7] reported no correlation between them. Some authors revealed that serum visfatin was correlated with obesity. But some researchers argued that its level did not change or were lower in obesity when compare to healthy controls.[8] Subfatin levels in obesity and metabolic syndrome were controversial. Some studies showed increase level and others revealed no correlation between obesity and serum subfatin levels. Some researchers opined that measuring asprosin, visfatin and subfatin together can be more helpful to understand about the condition and course of the disease. More studies will help in confirming the findings.

The identification of novel 'omics' biomarkers could clarify the cause of obesity and its association with chronic diseases.[9] Many research in 'omics' have been conducted for the identification of genes (genomics), mRNA and miRNA (transcriptomics), proteins (proteomics), metabolites (metabolomics), DNA methylation (epigenomics) and gut microbiota (microbiomics) that are associated with obesity and its co-morbidities.

Genomic research has developed due to the advancement in technologies. DNA-microarray -based techniques and next generation sequencing allow mapping of generated sequences and analysis of population-specific genetic traits.[10] According to a recent genome-wide association studies (GWASs) based on 700000 individuals, 941 near-independent single-nucleotide polymorphisms were identified to be related with BMI.[11] The genes at different loci appear to work in interaction with each other leading to certain pathways reflecting biological activities which are associated with accumulation and distribution of fat. A number of studies have been conducted to develop genetic risk scores (GRS). GRS could be helpful in high-risk individuals to guide lifestyle intervention.

Transcriptomics may act as a bridge between GWAS and physiological studies by giving information present in genes. mRNA and non-coding RNAs (ncRNAs) serve as transcriptomic biomarkers. They can be measured by RNA sequencing and array-based gene expression methods. Some studies have shown correlation between whole-blood mRNA levels and BMI. miRNAs can have important regulatory roles in adipogenesis, adipocyte differentiation and insulin signalling.[12] Circulating miRNA (cmiRNA) are regarded as promising candidate biomarkers as blood sample can be easily collected. Disregulated cmiRNA expression was identified by some researchers in obese individuals when compared to lean controls. More studies are required on ncRNAs to have more clarity on the possibility of successful application in prevention and clinical management

Proteomics serve as an important tool in the identification and characterization of proteins associated with obesity and its complications. It has one advantage over genomics

and transcriptomics since it is capable of detecting protein post-translational modifications and protein interactions.

Metabolomics measures the totality of metabolites in a given biological system. Metabolites represents a diverse group of low-molecular weight structures such as lipids, amino acids, peptides, carbohydrates and organic acids. It has the potential to improve obesity through patient monitoring and might result in development of intervention strategies including drug discovery and testing.

Most epigenomic biomarkers are defined based on DNA methylation of cytosines in cytosine-guanine dinucleotides and are prone to changes in response to external factors. Improvement of the knowledge of the association between microbiome and host health might help in the identification of new targets for precision prevention and clinical care.

III. SUMMARY

Molecular and cellular events in biological system can be indicated by biomarkers. These can help epidemiologists and physicians better understand the relationship between obesity and its health effects. It appears that instead of using a single biomarker, combination of biomarkers may bring new opportunities for an improved disease prediction and may provide information about the condition and course of the disease.

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