Chapter 6

Biomarkers, Obesity, and Cardiovascular Diseases

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62555

Abstract

Obesity and overweight are among the major health problems in the world today. The excessive accumulation of fat in adipose tissue is accompanied by low-grade inflammation, adipokine secretion dysregulation, oxidative stress, and an alteration of the secretion of gut hormones and food intake related to peptides. This is related to the development of cardiovascular diseases, which have been increased worldwide during the last 15 years approximately. The biomarkers are tremendously important to predict, diagnose, and observe the therapeutic success of common complex multifactorial metabolic diseases, such as obesity and cardiovascular diseases. This chapter presents a review of the most common biomarkers that have been used in the prevention, treatment, prognosis, and diagnosis of obesity and cardiovascular diseases.

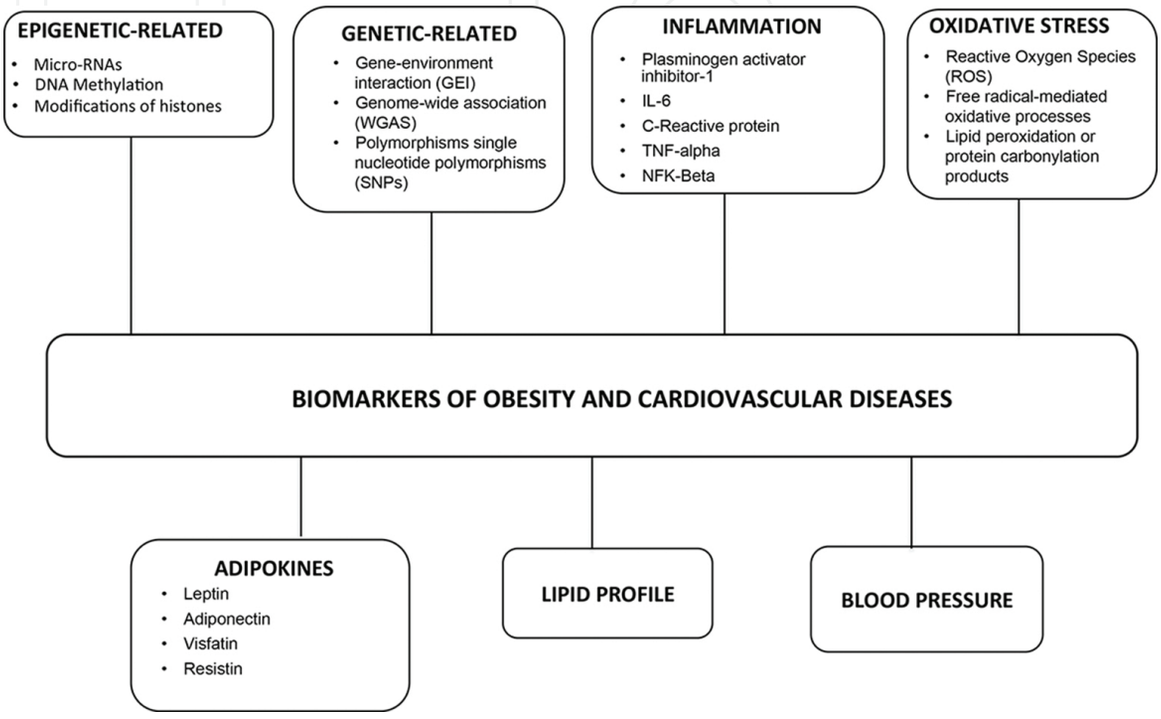
Keywords: biomarkers, cardiovascular disease, obesity, genetic markers, serum markers

1. Introduction

1.1. Overweight and obesity

Obesity and overweight have greatly become a stigma in most of the countries around the world since the middle of the past century, depending on the location, but it was not recognized as a disease until 2013 [1]. Its presence and the difficulty to eradicate it, it is mainly due to the multifactorial nature of this trait that depends on genetic and environmental factors as well as stimuli, learning, reward, and representation of food processing at high centers of the nervous system, which results in an increase of energy intake and subsequently body fat [2]. The most recent estimations (2014) by World Health Organization (WHO) have pointed out that

more than 1.9 billion adults who were 18 years old or more (39%) suffered overweight and more than 600 million were obese (13%). Predictions about this epidemic growth do not seem to be very promising with a theoretical increase of 33% in obesity prevalence and a 130% increase in severe obesity prevalence by 2030 [3].



The WHO defines overweight as an abnormal or excessive fat accumulation that represents a health risk [4]. This disproportionate fat in the adipose tissue includes a low grade of inflammation, adipokine secretion dysregulation, hypoxia, oxidative stress, and an alteration of the secretion of gut hormones and food intake-related peptides [5]. All of these disturbances are associated to a wide variety of disorders such as diabetes, cardiovascular diseases (CVDs), cancer, depression, conception and respiratory problems, and musculoskeletal disorders [6].

Body mass index (BMI) is a measure of weight adjusted to height and calculates weight as in kilograms divided by the square of height in meters (kg/m^2). Although BMI is often considered an indicator of body fatness, it is a surrogate measure of body fat because it measures excess weight rather than excess fat. Despite this fact, studies have shown that BMI is correlated with more direct measures of body fat, such as underwater weighing and dual-energy X-ray absorptiometry. The clinical limitations of BMI should be considered. Factors such as age, sex, ethnicity, and muscle mass can influence the relationship between BMI and body fat [7]. Considerable literature has grown up around the theme and suggests that other measures of body fat, such as skinfold thicknesses, bioelectrical impedance, and/or dual-

http://dx.doi.org/10.5772/62555

energy X-ray absorption may be more accurate than BMI, for example, waist circumference (sometimes divided by height) is a simple measure of fat distribution. The main problem of standardization is that the cost of it tends to be highly overpriced, intrusive, not widely available, or difficult to standardize across observers or devices. Therefore, the procedures previously mentioned are considered not suitable for a regular physician exercise purpose. In addition, most of the literature concerning obesity health risks is based on several BMI studies and their outcomes, yet there are not enough standardized frames to calculate body fatness which may compromising the measurement of the fat amount that an individual may preserve.

Nowadays, just one of the anti-obesity therapies was approved; bariatric surgery can effectively lead to considerable weight loss sustained over the long-term period [8]. However, it has largely been rendered impractical as a useful anti-obesity approach, mostly due to its cost and its mortality rate. In general, obesity alters the perfectly co-ordinated homeostatic system that regulates food intake, leading to an increase, decrease, or absence of change of the signals that are involved in this function such as adipokines, metabolites, gastrointestinal, central peptides, and other factors. There is awareness regarding those effects, but discovering the contribution of each one of those aspects and its relation to food intake is still obscure.

1.2. Cardiovascular diseases (CVDs)

Cardiovascular diseases refer to a disorder of the heart or blood vessels; there are three main types of CVDs depending on the grade of affectation and organ that is being disturb: heart could suffer acute coronary syndromes, angina, arrhythmia, cardiomyopathy, coronary heart disease, heart failure, inflammatory heart disease, ischemic heart disease, etc.

The brain could suffer cerebrovascular disease, hemorrhagic stroke, ischemic stroke, and/or the circulatory system, deep vein thrombosis, hypertensive heart disease, peripheral artery disease and pulmonary embolism [9].

The most recent data show that global death rate caused by CVDS increased by 41% from 1990 to 2013 (except 39% out of that 41% decreases at specific age death rates) [10] and it has become the first death cause of all noncommunicable diseases (NCDs) by 17.5 million people annually. Factors such as smoking, physical inactivity, alcohol ingest, and unhealthy diets increase the risk of suffering NCDs [11]. Heart attacks and strokes can be prevented if high-risk individuals are detected and treated early. For eligible subjects aged from 40 to 79 years, a prescription where aspirin and/or statin to lower blood pressure has been estimated to prevent about one-fifth of cardiovascular deaths. This instruction can be assigned to a prospect population with an increase tendency of suffering NCDs (including those with hypertension, diabetes, and other cardiovascular risk factors) where an integrated primary program care is implemented [12]. Several mechanisms have been proposed to be linked to CVDs with obesity, along with the state of inflammation, oxidative stress, and gut microbiome [13]. Thus, there is significant evidence of association with central obesity and coronary artery disease [14] and stroke [15]. Nevertheless, in the last decade, there is no consensus about the relation between obesity and mortality due to CVDs. In this decade, the hypothesis called "obesity paradox" has shown that

mild obese people have healthier cardiovascular profile than average weight individuals [16]. This chapter gathers the most significant information concerning validated or well-correlated biomarkers and its relation with obesity and CVDs.

2. Indicators and biomarkers

2.1. Definition and classification

The term biomarker was presented in 1989 as a Medical Subject Heading (MeSH) and defined in 2001 as "*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic treatment* [17]." The tern biomarker itself may refer to different concepts; for example, interleukin-6 (IL-6) could classified as a marker of inflammation, obesity, or CVDs.

It should be quite clear the difference between a biomarker and an endpoint. A biomarker, because of the nature of its definition, is objective and may not related to a patient's emotions and sense of well-being. Thus, an endpoint defines how a subject in a study or clinical trial "*feels*, *functions or survives.*" In some trials, they use biomarkers as surrogate endpoints, but it is mandatory to obtain solid, scientific evidence (eg epidemiological, therapeutic, and/or pathophysiological) [18]. Depending on the function of the biomarker, it can be classified into markers of exposure, effect, and/or susceptibility [19]. Other classifications are based on their biochemical or biological properties (e.g., metabolites, hormones, adipokines) or the disease of interest (e.g., CVDs, obesity) [20].

2.2. Relevance and validity

An important aspect of a biomarker is that it refers to its relevance, a term commonly used for Biomarkers, which have significant impact on public health Matters. Due to the use of them in research or risk Assessments, they can contribute to provide useful information that cannot be obtained accurately with the implementation of other approaches such as surveys, environmental measurements, or record revisions.

During the past decade, there has been noticed a rapid development of the study of the validity of biomarkers since then it is still being debated. To validate them, it is required either laboratory and epidemiological support, and even more specifically, a case of control and cohort studies with prospective studies as a key to its investigation to provide estimates of the risk of disease in individuals with and without a particular biomarker which the cost is the main problem [19]. Recently, in order to evaluate the adequacy of a biomarker, it is important to take into consideration three important matters: the analytical validity, clinical validity, and clinical utility [21]. A tool that is highly recommended and needed for evaluating a potential biomarker is the receiver-operating characteristics curve (ROC) analysis, which is well-explained in a study [22] and that can be summarized as a statistical tool that allows the determination of the threshold which can be considered as a "*positive*" or "*non-positive*" in relation to a specific biomarker and a particular disease; ROC is based on the concept of sensitivity that describes the portion of subjects with the trait that have been determined as

"*positive*" and specificity that tell us the portion of subjects without the trait that have been identified as "*negative.*" This tool is essential for biomarkers that are detected with metabolomics techniques.

A case of a scale used to classify the validity of biomarkers is the one proposed by the European Society of Cardiology (ESC) which establishes a range from I to III, considering the evidence and/or in agreement to the scientific literature as well as it considers the level of evidence depending on the type of the articles that were conducted [23, 24].

2.3. Biomarkers in obesity and CVDs

Biomarkers for obesity and CVDs can be used for three different purposes: study the tendency a prevalence, facilitating the identification of a target population that could require an approach to lower the risk of obesity development or future weight management, and improving the understanding of this complex trait which will help to find the adequate treatment [25].

When speaking about obesity, there are not enough validated biomarkers to be used as a diagnostic tool. That situation probably is mainly due to this trait has different levels of complexity and as we aforementioned, there are numerous traits associated with obesity which each one has its own characteristics that could also vary among the types of populations; such fact probably determines the specific alteration of the physiology and thus the biomarkers. As a matter of fact, there are some biomarkers that have shown strong correlation and signs of reliability related to BMI and/or body fat, which are going to be described hereafter.

In the case of CVDs, there are a wide variety of traits that can be caused and/or either by influenced common factors or specific ones. This chapter focuses on diseases such atherosclerosis, stroke, and heart attack as the most influence mortality traits and well-known biomarkers.

3. Genetics-related biomarkers

It has been proposed that genetic modifications could be involved in predisposition to obesity [26]; investigations of gene expression regulatory mechanisms during the evolution of obesity could be applied in prevention and early diagnosis, and treatment. This disease is associated with oxidative stress, insulin resistance, systemic inflammation, endothelial cell dysfunction [25]. The obesity and CVDs are the result from a complex interplay of many genetic and environmental factors [27]. Epidemiological and clinical studies have examined the roles of lifestyle, diet habits, and genetic factors in the development of this disease; studies related to the gene-environment interaction (GEI) have increased rapidly.

However, preliminary results regarding GEI on obesity are mostly inconclusive [28]. Obesity has become one of the most serious health problems, and its occurrence is attributed to the interplay between environmental and genetic factors. Over 40% of the variation in obesity-

related phenotypes is estimated to be Heritable. Genetic studies and knockout mouse models have uncovered new obesity-associated genes [29].

Epidemiological and clinical studies trials have examined roles of lifestyle and dietary factors in obesity prevention and weight control; it has been suggested that alterations in adipocyte growth, differentiation, and apoptosis could contribute to changes in fat mass involved in obesity. Recent studies indicate that the turnover rate of pre-adipocytes is low [2].

The increase in fat mass can develop adipocyte hypertrophy or hyperplasia; larger fat cells are closely linked to a greater fat mass rate and production of inflammatory cytokines [29]. This is because it proposed a possible approach, which aims to reduce fat mass and is by performing a therapeutically regulate adipocyte differentiation; however, cellular and molecular mechanisms that are involved are not completely understood in the adipogenesis. In the lasted years, this connection has been connected and concerned in the role of Micro-RNAs (miRNAs) and the fat cell development [30]. There is limited evidence of genetic involvement in the development of obesity.

Advanced studies of genome-wide association (WGAS) and obesity disorders stated that this field has a great potential to identify human genetics-related biomarkers and the contribution to elucidate the genetic mechanisms in the development of obesity. In this matter, it has been reported several genes involved in fat mass and obesity (FTO) such melanocortin-4 receptor (MC4R) which can be identified with GWA scans that have been convincingly associated with obesity risk in a variety of subjects population [31]. However, it has suggested and indicated that replication of genetic-related biomarkers may fail in small samples or in subjects exposed to other environmental factors; obesity is a multifactorial disorder that has a genetic basis but requires environmental influences in order to be able to manifest itself.

An estimation from 40 to 60% of the variation in obesity-related phenotypes BMI and sum of skinfold thickness, fat mass, and leptin levels are thought to be heritable [32]. Studies that show a sequel to discover the specific loci or genes involved in obesity, primarily through the combination of linkage scan and candidate gene-based association, have been performed to identify and examining the co-segregation of genetic markers distributed evenly in genome with the disease within families. It is highly important to mention that there are 253 quantitative-trait loci (QTLs) identified in 61 genome-wide scans, and 52 genomic regions contain QTLs, yet there are limitations in the linkage of the studies. The candidate-gene association analyses focus on identifying loci which are functional or positional; approximately 120 genes are different candidate that have been associated with obesity phenotypes [33]. Such candidate genes are categorized either to be knowledgeable or proposed to be a role that could be influence of adipogenesis, lipid turnover, insulin signaling, mitochondrion and energy expenditure, and adipokine secretion [34]. Some examples of genetic-related biomarkers prohormone convertase are (1/3) PCSK, PPARG (peroxisoma proliferadores-activados receptor gamma), UCP1 (disociación de proteínas 1), UCP2, UCP3, ADRB2 (receptor beta-adrenérgico 2), ADRB3 y PLIN (perilipina) [35–38].

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The majority of association studies of candidate genes in obesity focus on only a limited number of single-nucleotide polymorphisms (SNPs) [39]. The narrow topography of genome variation has impeded the candidate gene approach [2, 40].

There were found significant associations with SNP which is mapped in a biological candidate gene for monogenic obesity and fat mass and obesity risk [41]. Studies demonstrated that different shapes of genes variants might cause either monogenic or common form obesity that shares the same pathophysiological changes.

Recent findings have reemphasized the importance of *epistasis*, or gene–gene interactions as a contributing factor to the unexplained heritability of obesity; methods such as statistical epistasis networks (SEN) provide a reference that is likely to be used to address a computing challenge of studying pair-wise interactions among thousands of genetic variants. The outcomes have drawn a heritability rate estimated from 40 to 70% [42]. Still, genetic loci that have been found to be associated with BMI can partially explain its variation. Epistasis or gene–gene interactions are a possible contributing factors to this "*missing heritability*" [43]; meanwhile, some studies suggest to analyze pair-wise interactions that are associated with BMI among SNPs from twelve genes robustly associated with obesity [44]. The most prevalent leptin/leptin receptor genes (LEP/LEPR) and ghrelin/ghrelin receptor genes (GHRL/GHSR) SNP studied were LEP G-2548A, LEPR Q223R, and Leu72-Met [45, 46].

4. Epigenetic-related biomarkers

Previous literature has indicated that epigenetics heritable changes in concordance with the individual DNA sequence, while meta-analysis papers related with the genome have proposed a tool to assess the genetic variants of obesity and epigenetic modifications that can be influenced by environmental factors.

Some of the major genetic mechanisms that could be mentioned to help to regulate a gene expression are DNA methylation of guanine-followed cytokines, hypermethylation, modifications of histone, and RNA non-coding.

4.1. DNA methylation

The GWAs have identified 55 genetic loci that were associated with either obesity or BMI, but they only explain 1.18–1.45% of the variation observed in BMI. It has been validated the use of blood leukocytes method to categorize the epigenetic modifications that could be used as molecular markers to predict physiological changes linked with obesity and insulin resistance, which are closely associated with methylation and weight status [47].

Newest data have shown that alterations in global DNA methylation may significantly influence the risk incidence of cancer and CVDs [48]. The increased epigenetic variances may be reflected during the adaptation to the environmental risk factors. The obesity is the result of the interplay between external (environmental) and internal (genetic) factors [13]. The methylated CpG sites (DMCs) and differentially variable CpG sites (DVCs) may be related to

the development and growth of obesity as well as CVDs [49]. The recent epigenome-wide association studies (EWAS) have identified several DMCs related to obesity [50].

The literature focused on studies in epigenetic sites and proposed intron DNA methylation are able to indirectly prevent a transcription [51]. The DNA methylation is an epigenetic process that influences a wide variety of biological mechanisms including gene expression, chromosomal stability, imprinting, and cellular differentiation [52].

The abnormal DNA methylation patterns, including genome-wide hypomethylation, gene-specific hypo- and hypermethylation, have been shown to be associated with a range of health outcomes. In order to know the global levels of DNA, there are several methods available [total content of 5-methylcytosine (5-mC)] [53].

It has been suggested that obese individuals are likely to possess unique epigenetic patterns that tend to vary with weight. On the other hand, studies that have examined the methylation patterns in leukocytes showed a variation in individuals who lost enough weight from a certain level of obesity to normal weight [54]. The studies related to DNA methylation and obesity that had primarily focused on gene-specific methylation [55, 53] as well as recent global recent methylation levels studies in DNA from blood and BMI [55, 56].

The bioinformatics analysis of the search for the CpG islands promoter obesity-related genes sites has identified a high CpGs density that are implicated with adipogenesis such as human peroxisome proliferator-activated receptor gamma coactivator 1 (PPARGC1), the small heterodimer partner (NROB2), the glucocorticoid receptor (NR3C1), the peroxisome proliferator-activated receptor gamma (PPARG), the basic fibroblast growth factor (FGF2), the phosphatase and tensin homolog (PTEN), the cyclin-dependent kinase inhibitor 1A (CDKN1A), as well as at the estrogen receptor 1 (ESR1) [57–59].

It has been displayed that the same methylation frequency than subjects are likely to show in CpG sites located at 51 and 31 depending on the transcription of the starting site of the LEP gene [60]. Three CpG sites involved in BMI are 1. CpG7 (46801672, cg16672562) 2. CpG1, and 3. CpG5 [61].

The HIF3A regulates the transcriptional activity of some genes related to adipocytes [73]. The increased level of methylation in HIF3A relates to increasing BMI [62–64]; a BMI linked to DNA methylation might play a role in obesity [53].

4.2. Modifications of histones

Epidemiological studies that link epigenetic gene regulation and obesity outcomes are needed to understand the effects of the exposure development and identification of epigenetic biomarkers of latent onset of obesity [65].

Such modifications occur through various mechanisms, for instance, the post-translational histone modifications that can cause a transcriptional suppression.

Environmental stimuli where diet and exercise are meant to regulate these mechanisms might have inflammation as a probable contributory factor [66]. Recent literature in the field of

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epigenomics has led to the first epigenetic potential markers to detect obesity at birth which provides important foundations to determine the effects of exposure developmental to obesogenic [65]. During early stages, the relative expression of genes determines whether mesenchyme stem cells differentiate either osteocytes or adipocytes that potentially predispose the body to fat accumulation [67]. Furthermore, obesity-related chronic low-grade inflammation is implicated with an epigenetic level in the development of some forms of cancer [68].

4.3. RNA non-coding and obesity (Micro-RNAs)

Research focused on the gene expression regulatory mechanisms in obesity evolution, and CVDS will have crucial applications in prevention, early diagnosis, and treatment. The miRNAs are small molecular, non-coding, 21–23 nucleotide long RNAs that negatively regulate gene expression by pairing with the 3'-untranslated region (UTR) of their target miRNAs [69]. The miRNAs are involved in highly regulated processes such as proliferation, differentiation, apoptosis, and metabolic processes. The discovery of non-coding miRNAs which can post-transcriptionally regulate thousands of genes has generated enormous research interest [26]. Several studies have highlighted the significance of miRNAs in maintaining metabolic homeostasis [70, 71].

Furthermore, miRNAs have been found in tissues, in serum, in plasma, and other body fluids that have a stable form that is protected from an endogenous RNase activity. Because of these unique characteristics of circulating miRNAs, a possible useful biomarker for supplemental diagnosis can be inferred. The study of serum samples miRNAs can play the role of a potential biomarker as well as provide them since these have shown the ability to induce heritable modifications of several morphological, physiological, and behavioral phenotypes. Data concerning miRNAs imply that five types (miR-142-3p, miR-140-5p, miR-15a, miR-520c-3c, and miR-423-5p) may be primal biomarkers for risk estimation and classification in obese patients [72]. On the other hand, there have been studies in adipocyte-specific mRNAs that also have detected in isolated exosomes and microvesicles from rat serum. In recent researching, miRNA biomarkers have been found in many chronic diseases, for example, cancer, CVDs, and type 2 diabetes [82, 73]; probable future miRNA biomarkers may assist in the early diagnosis of chronic diseases and also provide new therapeutic targets [74]. Furthermore, the impact of extracellular factors such as inflammatory cytokines on adipocyte miRNAs might be considered [75].

The understanding of role miRNAs in proliferation and differentiation of adipocytes during fat cell development could provide new therapeutic targets for anti-obesity drugs [76–77]. The alterations in the number and size of adipocytes are typically accompanied by changes in the expression patterns for miRNAs subsets [78].

The expression of the majority of these miRNAs is known to be controlled by certain cytokines and adipokines that downgrade miR-103 and miRNAs-143 and upgrade miRNAs-221 and miRNAs-222 [79]. The levels of miRNAs-103, miRNAs-107, miRNAs-143, and miRNAs-185 were upgraded in the lean state but downgraded in the obese state [80]. Nevertheless, from

the miRNAs analyzed until now, just miRNAs-34a has been found to be positively correlated with the rate of adipocyte differentiation and development of the BMI [81].

Moreover, the miRNAs have also been recognized as regulators of adipocyte metabolic integration, energy homeostasis, and differentiation [83, 84]. Further studies have shown widespread regulation of protein levels caused by miRNAs in cellular and animal models [85].

Several miRNAs, such as miR-126, miR-132, miR-146, miR-155, and miR-221, have emerged as important transcriptional regulators of some inflammation-related mediators [86]. These non-coding RNAs are emerging as biomarkers with diagnosis value in prognosis protocols in personalized treatment of inflammation. The non-coding RNAs and the administration of exogenous miRNAs could be soon a promising therapeutic strategy in the treatment of inflammation-related diseases, for example, obesity [87]. There is also increasing evidence that non-coding miRNAs are critically involved in post-transcriptional regulation of cell functions, including oxidative stress, inflammation, regulation of cell proliferation, adipocyte differentiation, angiogenesis, and apoptosis [88].

5. Inflammatory biomarkers in obesity and CVDS

The inflammatory process is a very complex reaction since it is necessary to conduct further research for a better understanding of biological inflammatory biomarkers activity [89]. The obesity-induced chronic inflammation is a component during a pathogenesis of insulin resistance and metabolic syndrome. The pro-inflammatory cytokines can cause insulin resistance in adipose tissue, skeletal muscle, and liver by inhibiting the insulin signal transduction.

The initiating factors of this inflammatory response remain to be fully determined, and chronic inflammation in tissues that liver and fat could cause is localized in insulin resistance through an autocrine/paracrine cytokine signaling, and systemic insulin resistance through an endocrine cytokine signaling, which contribute to an abnormal metabolic phase. The role of inflammation in CVDs is to support the development of pharmacological strategies that aim to reduce inflammation [90]. The studies are mostly focused on the effectors of the inflammatory program, but not on the underlying causes, which initiates the pro-inflammatory stage; some candidates meant to be markers in the inflammatory response are cytokines/chemokines and C-reactive protein (CRP).

In addition, it has been proposed that pro-inflammatory cytokines formed increase the hepatic synthesis of an acute-phase protein. However, it is still unknown how the inflammation of low intensity contributes to increase the risk of suffering CVDs in overweight and obese individuals [91].

The identification of inflammatory markers improves insulin sensitivity and glucose control in insulin-resistant patients, and they are responsible of the reducing risk of CVDs and its complications [92]. It is known that obesity mechanisms, particularly visceral fat that are

http://dx.doi.org/10.5772/62555

related to morbi-mortality include increasing in and releasing of expression adipose tissue cytokines that are crucial in the phase proteins.

The resistin, leptin, and adiponectin adipokines, which are secreted by adipocytes, are capable to also affect the inflammation and insulin resistance. When is the case of a chronic and low-intensity inflammatory process, chemokines locally secreted attract pro-inflammatory macrophages to the adipose tissue and they will stimulate the cytokines release, which will activate the inflammatory way in adipocytes and adjacent tissues (autocrine and paracrine effect) that aggravate the inflammation and insulin resistance [87]. The result of an internal environment in adipose tissue is lipotoxic and pro-inflammatory; therefore, it is important to consider that local environmental cues that related the initial inflammatory response in obesity and insulin resistance mechanisms [93].

5.1. Plasminogen activator inhibitor-1

The PAI-1 is a protein that inhibits the residual plasminogen activator, which cleaves the plasmin to plasminogen; thus, it is the first physiological inhibitor of fibrinolysis in situ; this occurs while presenting the capacity to inhibit the plasmin forerunner that has as a function the rupture of fibrin network, thus avoiding a thrombus formation [94]. The PAI-1 is produced in several types of tissues, including liver and adipocytes. Many factors contribute to increase the expression and release of PAI-1 in adipose tissue (especially, visceral fat), among them the insulin, TGF-β, and IL-6, [95, 96]. These factors associated with the increase of body fat can explain theirs enhanced concentration in individuals obese and insulin resistant [97].

5.2. Interleukin-6 (IL-6)

Recent studies suggest that inflammation markers may reflect different aspects in the risk of developing CVDs and they may correlated with its grade of severity. Furthermore, it has been suggested that interleukin-6 (IL-6) might represent a major mediator of acute-phase protein response while it is a multifunctional cytokine produced by a variety of hematopoietic and non-hematopoietic cells [98, 99]. The IL-6 upgrades and regulates several acute-phase proteins such as CRP, fibrinogen, α1-antitrypsin, and serum amyloid [99]**.** This cytokine regulates lipid metabolism and C-reactive protein (CRP) production and the increase in obesity as well as it is related to insulin resistance [100, 102]. Additionally, it has been shown an association with BMI and fat [103].

5.3. C-reactive protein (CRP)

The C-reactive protein (CRP) has been extensively studied in individuals with CVDs, including those that apparently to be healthy. The features related to high CRP levels risk factors and CVDs are dyslipidemia, hypertension, diabetes mellitus, obesity, smoking, and sedentary lifestyle. The CRP used as an inflammatory marker detection of CVDs in plasma, the concentration is easy to determine, and it has the best clinical and epidemiological correlation until now. Another pro-inflammatory cytokines are IL-1-type cytokines that could be stimulated in

the liver production of CRP. High levels of certain inflammatory markers such as IL-6, tumor necrosis factor alpha (TNFa) and CRP are also associated with visceral fat [104].

5.4. Tumor necrosis factor alpha (TNF-alpha)

The TNF-a is a cytokine that mediates inflammatory responses and is implicated in pathogenesis such as cancer, diabetes, and obesity. The TNF-a is secreted by adipose tissue in obesity [106]; the major pathways activated by TNF-a include caspases, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and mitogen-activated protein kinases (MAP kinases) The TNF-a increases its expression in adipocytes associated with obesity and is related to increased visceral fat deposition and insulin resistance [107]; other studies was associated with glucose uptake and insulin resistance [105], partly through increased expression of cytokines in muscle [108, 109].

5.5. NFK-beta (nuclear factor kappa-light-chain-enhancer of activated B cells)

The NF-κB has an important role in regulation of immune response, and its dysregulation has been linked to cancer, inflammatory, and autoimmune diseases. Moreover, it was proposed that is an important cellular regulator in different mechanisms associated with cytokines and nutrients. Regarding nutrients that act via the mechanism, which is independent from NF-κB, demonstrate that obesity promotes the survival of inflammatory, possibly through NF-κB regulated macrophage mechanism [110, 111]. The activation of NF-κB creates a connection with a decrease of expression of proteins specific to β-cells, insulin, glucose transporter 2 (GLUT-2), pancreatic, and the increase in activity of iNOS [112].

The involvement of NF-κB in metabolic pathways comes from a complex network that involves a vast number of factors and post-transcriptional processes [113, 114]. This factor is related to obesity and CVDs mainly because its involvement in the promotion of the inflammatory factors expression (and could be anti-inflammatory as well) [106], insulin resistance, and adipokines such as visfatin takes place [115], and the microflora can have a role in the inflammation process [118].

6. Oxidative stress biomarkers in obesity

Oxidative stress is a major player CVDs and obesity [116, 117], the reactive oxygen species (ROS)-dependent signaling pathways, transcriptional and epigenetic deregulation, inducing chronic low-grade inflammation, platelet activation, and endothelial dysfunction. Because of this, several oxidative biomarkers proposed with the potential to improve current under standing of the mechanisms underlying CVDs [119].

Oxidative stress results from an imbalance between the production of ROS and biological systems ability to detoxify the reactive intermediates or to repair the resulting damages, which can impact all the cell components, including proteins, lipids, and DNA. High levels of ROS generated by hypertrophied adipocytes impact many metabolic signaling pathways as well as

http://dx.doi.org/10.5772/62555

neighboring environment for instance perivascular endothelium or immune residing [121]. Such impairment is further amplified by altered systemic metabolic parameters (hyperglycemia, hyperlipemia, hyperleptinemia, etc.) that also enhance ROS generation. Overall, systemic oxidative stress-associated obesity directly impacts insulin sensitivity of metabolic organs, promotes inflammation, and alters lipid metabolism or endothelial dysfunction. The increased levels of systemic oxidative stress that occur in obesity may contribute to the obesity-associated development of others diseases. Clinical evidences for obesity associated with oxidative stress have been provided by using a biomarker of free radical-mediated oxidative processes [122, 123].

Systemic oxidative stress is part of the numerous biological alterations reported during chronic obesity. Evidences regarding obesity-induced oxidative stress are derived from several clinical studies, which have established correlations with biomarkers, or end-products of free radicals-mediated oxidative stress (lipid peroxidation or protein carbonylation products) and BMI [124, 125]. There is also an inverse relationship between body fat, visceral fat, and antioxidant defense markers in obese individuals; the hypothesis is that oxidative stress is producing the development of metabolic disorders, especially insulin-resistant state, and it has been supported by different studies where treatments reducing ROS production improved insulin sensitivity, hyperlipidemia, and hepatic steatosis [59].

Hypertrophied adipocytes have been reported as a significant source of ROS that promote a significant dysfunction by altering the adipokine production. Furthermore, oxidative stress associated with obesity has also shown to alter the function of many cell types or tissues leading to consider oxidative stress as a contributor in obesity-related metabolic diseases [126]. Other examples of enzymes that have been proposed as biomarkers in oxidative stress, which may be an important contributor to ROS generation, are nitric oxide synthase (NOS) can react with vascular NO- and NAD-dependent deacetylases that will drive antioxidant and anti-inflammatory responses [127, 128].

7. Lipid profile

A factor that has more influence in these traits is lipoproteins and its related factors which among them is cholesterol, that is, also a sterol (or modified steroid), a molecule lipid that is biosynthesized by all animal cells, and it is required to maintain both membrane structural integrity and fluidity. This molecule is transported by a low-density lipoprotein with different types that depend on the density which are named as LDL, high-density lipoprotein, or HDL [129].

In case of cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides are the types that are the most studied, accepted, and recommended by *American and European Guidelines* as risk status of cardiovascular issues surrogate endpoints.

These biomarkers joint with others agents (age, smoking, etc.) are used in the *Framingham Score*, which is one of the most used, to estimate the risk of cardiovascular diseases (up to 10

or 30 years). However, there is a slight difference where age taken into consideration; levels of total cholesterol and blood pressure give us a risk of CVDs along with the recommendation of the analysis of the lipid profile. The total amount of cholesterol increased is a major cause of burden disease in both the developed countries and non-developing ones as a risk factor for ischemic heart disease and stroke [130]. When high levels of cholesterol are present, atherosclerotic plaque formation may take place, which can result in the narrowing of the coronary arteries and an increase of a heart attack and stroke due to the increased probability of a rupture. These references for total cholesterol are given by the *American Heart Association* (AHA) that recommends a desirable level of <200 mg/ml with a high risk (twice higher risk than lower levels) of heart attack and stroke if the levels are above 240 mg/ml [131]. LDL cholesterol (LDL-C) is the major cholesterol-carrying lipoprotein, and it makes up the majority of total cholesterol in blood. Moreover, LDL-C deposits in the arterial wall can lead to atherosclerotic plaque formation [132], which are recommended to be between 100 and 159 mg/ml, taking into consideration that a level above is a high risk to suffer cardiac disorders.

HDL cholesterol (HDL-C) is a significant predictor of CVDs risk, and its plasma levels have an inverse correlation with the risk of atherosclerosis and CVDs [132, 133]. It is reported that low levels of HDL are associated with cerebrovascular disorders in several populations (*Framingham Study, the Copenhagen Study, and the Israeli Heart Disease Study*) [134]; in any of the cases, it is not unanimously considered as a surrogate endpoint to CVDs risk due to the complexity of its physiology [126]. Organizations as the European Society of Cardiology recommend levels below 1.0 mmol/L (40 mg/dL) in men and 1.2 mmol/L (45 mg/dL) in women [23, 24].

Triglycerides are majority form of fats in vertebrates, and they consist of an ester of glycerol esterified with three fatty acids which have different physical properties depending on the type of the acid; its physiology, as it is pointed out in the extensive review performed by [135].

Triglycerides have an enormous complexity and are involved in many traits such as CVDs, obesity and diabetes. Although, by itself, it is not atherogenic, it is related to atherogenic factors as atherogenic cholesterol-enriched remnant lipoprotein particles (RLPs) and its relationship has been closer to metabolic syndrome and TD2M. Thus, its consideration as a surrogate endpoint for CVDs despite the fact categorized as general, it is becoming clearer as more studies are being conducted. Nevertheless, there is evidence that non-fasting triglycerides may predict CHD risk better in the post-prandial state [136, 137], but due to the lack of standardization, measuring non-fasting triglycerides is not recommended.

On the other hand, there are recommendations given by AHA (and ATP III) that have been changing as time passes by and based on the ethnic differences. There are not standard recommendations, yet this organization (and the ESC) recommends the following thresholds: Desirable <150 mg/dL, Borderline-high 150–199 mg/dL, High 200–499 mg/dL, and Very High ≥500 mg/dL [138].

http://dx.doi.org/10.5772/62555

8. Blood pressure

Elevated blood pressure can cause stress in the walls of the blood vessels, which can vanish the development of arteriosclerosis and increase the risk of myocardial infarction (MI) as well as stroke. Also, due to the increase of the pressure, it could led a coronary artery disease (CAD) and widening of the left ventricle [132].

High blood pressure is one of the leading risk factors for global mortality and is estimated to have caused 9.4 million deaths in 2010. A meta-analysis which includes 1 million individuals has indicated that death from both CHD and stroke increase progressively and linearly from BP levels as low as 115 mmHg systolic and 75 mmHg diastolic upwards [138].

The WHO pointed out that a "reduction in systolic blood pressure of 10 mmHg is associated with a 22% reduction in coronary heart disease, 41% reduction in stroke in randomized trials, and a 41–46% reduction in cardiometabolic mortality in epidemiological studies" [139]. Raised blood pressure is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg among adults (<60 years) [140]. Briefly, the reliability of blood pressure as a surrogate endpoint is supported by an extensive number clinical trials and observational studies [141].

9. Adipokines

9.1. Leptin

This peptide belongs to the adipokine family, it has a molecular weight of 16 KDa, and it consists of 146 amino acids. It was first discover in 1994 after the naming its gene as the *ob* because of the link between a mutation of it and the subsequent development of obesity. Thus, its receptor was subsequently named as the Ob-R and has several variants due to alternatives splicing that combined with the fact that they can act via different signaling pathways, (JAK/STAT, phosphoinositol-3-kinase, etc.), making possible the involvement of this peptide in a wide spectrum of functions in the body. Leptin is mostly secreted in adipose tissue with a correlation with the amount of it in the body. The leptin levels in human and rodent are the measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Serum immunoreactive-leptin concentrations are found in normal weight and obese humans but recent data show that it is also released by the placenta, skeletal muscle, and stomach [142].

Plasma concentrations vary mainly due to fat amount in the body by an average of 1300–1600 pg/ml in rats [143] and between 6000–10,000 pg/ml in humans [144]. These levels are altered in obesity (until now it is not clear if it is a cause or a consequence), and it seems that there is a state of leptin resistance [145] and the levels decreased with a mild weight lost [146].

It has an anorexigenic effect and the lack of it increase food intake [147]. This peptide is still not validate as a surrogate endpoint for any CVDs, but there are several studies that show an

involvement on CVDs with a pro-atherogenic effect due to its involvement in vascular proliferation and smooth muscle migration [148].

Although it is a useful tool, but it is not consider as a surrogate endpoint neither for the risk nor for the severity of obesity, but it is a good candidate for future studies. Thus, we suggest more precise studies to establish the exact role of this hormone in specific traits with detailed metabolic conditions.

9.2. Adiponectin

Adiponectin is an adipocyte-specific secretory protein that circulates in the blood in relatively high concentrations (2–30 μg/mL) in at least three forms: low molecular weight, middle molecular weight, and high molecular weight; being the latter considered as the active form of adiponectin [149, 150].

Adiponectin levels are reported to have a positive correlation with insulin sensitivity and lipid metabolism; therefore, they could be involved in metabolic syndrome, type 2 diabetes mellitus, obesity, and atherosclerosis [143].

Despite the beneficial role of adiponectin on vascular homeostasis, studies suggest that increased levels of circulating adiponectin are inversely related to myocardial infarction in men [151]. However, results from subsequent studies lack of unanimity about this correlation in similar conditions, while others show a decrease of this correlation when they were adjusted by other factors, for example, HDL cholesterol [152].

Referred to its role in obesity, it has been shown a decrease of the levels in the obese state and an inverse correlation with the amount of visceral fat [151]. Furthermore, there are several studies that show an increase of adiponectin levels after weight loss [153].

It is too prompt to say that adiponectin can be used as a biomarker or surrogate endpoint in CVDs and obesity. There is needed more research in order to understand the complexity of the metabolic network of this peptide. Lastly, it should be noted from several studies the utility of the leptin/adiponectin ratio and its possible role as a predictor of a cardiovascular events [152].

9.3. Resistin

Resistin is an adipokine secreted by white adipose tissue that has been proposed as a biomarker due to the accumulated clinical evidence Showed in very extensive reviews [154], which demonstrates its association with obesity and CVDs complications such as atherosclerotis. However, the validation of this peptide as a cardiovascular marker seems to be complicated due to its dual function as an inflammatory cytokine and a metabolic hormone. Therefore, additional studies are necessary to clearly define resistin as a new biomarker in atherosclerotic diseases.

http://dx.doi.org/10.5772/62555

9.4. Visfatin/Nampt

Visfatin/Nampt was discovered in 2005 and later became the newest adipokine unveiled until now [155]. Since then, it has been related to pathogenesis of diabetes, obesity, renal failure, and CVDs, although there are conflicting results about its relationship with atherosclerosis [156].

The complexity of the metabolism of this adipokine, the possible existence of isoforms, and the lack of unanimity about the assays to its measure, which complicates its study consequently research is needed to understand and validate it as a biomarker of obesity and/or CVDs.

10. Others

Furthermore, it has to be mentioned that actually B-type natriuretic peptide is used as a diagnostic biomarker for *Acute Decompensate Heart Failure* (ADHF) as well as myeloperoxidase (MPO) for a heart failure, and troponin T for cardiac injuries [157]. Regarding coronary artery disease, there are some emergent indicators such as lectin-like oxidized low-density lipoprotein receptor-1, nuclear factor-kappa B, osteoprotegerin, osteocalcin, osteopontin, CD40, pentraxin-3, amyloid A, fibrinogen, myeloperoxidase, myeloid-related protein 8/14, or PAPP-A that require further investigation [158].

11. Conclusion

During the past years, the field of biomarkers and surrogate endpoints has been constantly growing along with greater advances in genetic and physiology knowledge of obesity and associated traits as CVDs. All of these biomarkers are a heterogeneously group that is related mainly with the mechanisms relate to obesity as inflammation, oxidative stress, adipocyte physiology, and regulation of food intake ingest. These biomolecules represent a key role in the identification, treatment, and follow-up of these traits; however, the complexity of the networks that are involved hampers the validation of them as a biomarker of risk, diagnostic and/or prognostic. The genetic modifications could be involved in predisposition to obesity and CVDs; the investigations of genetic and epigenetic in regulatory mechanisms during the evolution of these diseases could have applications in the prevention, early diagnosis, and treatment. Finally, the understanding of development of oxidative stress and inflammation related to obesity and CVDs, their biological role as well as potential therapeutic implications would be transformed into consistent benefits for their effective prevention, intervention, and treatment.

12. Future perspectives

The present and future of this area is and will be based on the emergent "*omics*" strategies as metabolomics, transcriptomics, proteomics, etc. These data will enable a complete description

of the interactions between metabolites, proteins, transcripts, and genes toward a better understanding of the physiology of disease. The ability of metabolic profiling to provide non- or slight-invasive translational biomarkers provides it an important role in the move toward a better assessment of the risk, prognosis, as well as diagnosis.

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