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Review

Obesity as a risk factor for cardiovascular diseases: one of the biggest problems in health care today

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Abstract

Obesity, especially central obesity *per se* is considered as a strong risk factor for cardiovascular diseases (CVD), and it is considered to be a chronic metabolic disorder, associated with chronic low-grade inflammation and results in marked alterations of adipokines and proinflammatory cytokines and other molecules that affect cardiovascular function. Obesity might cause endothelial and vascular dysfunction and therefore leads to CVD. Although, the associations of obesity and CVD have been unquestionably proven in more clinical trials, the exact mechanisms by which obesity eventually leads to CVD, is not completely elucidated and currently represent an area of intensive research. Understanding of the underlying mechanisms leading to the development of obesity as well as those linking obesity to CVD is of great importance for the design of therapeutic strategies targeting obesity in CVD. In this review article, we summarized the presently known data which focus on pathophysiology of obesity and its links to development of CVD.

Keywords:

Heart hypertrophy, metabolism, free fatty acids, dyslipidemia, adipokines, inflammation.

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List of Abbreviations

Apo	*apolipoprotein*
ATP	*adenosine-triphosphate*
BMI	*body mass index*
CVD	*cardiovascular diseases*
DMT2	*diabetes mellitus type 2*
ER	*endoplasmic reticulum*
FABP	*fatty acid-binding protein*
FAT/CD36	*fatty acid-transport protein*
FFAs	*free fatty acids*
HDL	*high density lipoprotein*
IKKβ	*IκB kinase β*
IL-1	*interleukin-1*
IL-6	*interleukin-6*
IR	*insulin resistance*
LV	*left ventricle*
MetS	*metabolic syndrome*
NF-κB	*nuclear transcription factor-κB*
NO	*nitric oxide*
PPARs	*peroxisome proliferator-activated receptors*
ROS	*reactive oxygen species*
SdLDL	*small dense low-density lipoprotein*
TG	*triglyceride*
TNF-α	*tumor necrosis factor alpha*
VLDL	*very low-density lipoprotein*

I. Introduction

Obesity and associated diseases are a major public health problem and expanding rapidly all around the world [1]. Obesity is a result of a complex interplay of genetic predispositions, over nutrition combined with sedentary lifestyle, infectious agents, environmental factors, behavior, and social structures.

Given its prevalence, obesity itself is a serious health problem given that entails an increased risk for the development of many diseases, including cardiovascular diseases (CVD) like heart disease, hypertension and atherosclerosis, diabetes mellitus type 2 (DMT2), and malignancy. Obesity, especially central obesity, *per se* is directly linked to cardiovascular risk and it is now considered as a strong independent risk factor for CVD and numerous studies have shown the link between enhanced mortality and morbidity of CVD and obesity [2-7]. Therefore, obesity should be considered as a serious disease requiring significant medical attention and prevention. Understanding of the underlying mechanisms leading to the development of obesity as well as those linking obesity to CVD is of great importance for the design of therapeutic strategies targeting obesity in CVD.

In this review article, we summarize the data from recent studies which focus on pathophysiology of obesity and its links to CVD.

II. Search Strategy

We searched using electronic databases [PUBMED/MEDLINE 1954 - October 2013]. Additionally, abstracts from national and international obesity and cardiovascular related meetings were searched. The main data search terms were obesity, CVD, heart hypertrophy, metabolism, free fatty acids (FFAs), dyslipidemia, adipokines, and inflammation.

III. Pathophysiology of obesity

Obesity and overweight have reached pandemic proportions, and it is not only the "prevalence" of industrialized countries but also affects developing countries. Obesity is defined as an excessive presence of fat in the body which can leads to many health complications that worsen the quality of life and shorten lifetime [8]. Obesity is a result of the physiological responses of the organism in a situation when caloric intake is greater than the actual energy needs of the body for a longer period of time without adequate energy consumption [8]. Thus, obesity occurs when there is an energy imbalance between calories consumed and calories expended [9], whereby the excess is stored in the body in the form of energy reserves (glycogen, fat) consumed in the case of increased energy needs of the organism or during fasting [8, 10]. According to the World Health Organization (WHO) latest statistics, obesity has been nearly doubled worldwide since 1980 and also overweight and obesity are in the fifth place in the palette of the leading causes of death globally [8].

In 1947, Jean Vague was the first to describe two sex-related forms of fat distribution and also argued that upper body fat is far more greater risk factor for DMT2 [11]. Central obesity (visceral or "apple" shape) is characterized by the accumulation of adipose tissue predominantly intraabdominally. A high incidence of metabolic syndrome (MetS) and CVD is associated with central obesity but independently of body mass index (BMI). On the other hand, gluteofemoral obesity (gynoid, obesity in the form of a "pear") represents accumulation of subcutaneous adipose tissue in the region of the hips and thighs and is considered to have partially protective role in MetS and related complications [12].

Obesity is characterized by disorders in lipid metabolism and dyslipidemia develops when there are increased levels of very low-density lipoprotein (VLDL) cholesterol, triglyceride (TG) and total cholesterol, an increase of small dense low-density lipoprotein (sdLDL) particles and lower high density lipoprotein (HDL) cholesterol levels [13-15]. In persons with visceral adiposity there are predictors for CVD endpoints such as apolipoprotein (Apo) B/A1 ratio [4], sdLDL particles, and low HDL cholesterol [13]. "Atherogenic lipid triad" is consisted of increased sdLDL and TG levels and decreased protective HDL cholesterol levels [16-19]. The other terms that describe a risk-conferring lipid/lipoprotein profile are "atherogenic dyslipidemia" or the "atherogenic lipoprotein phenotype" and they were defined for the first time by Austin et al [20, 21].

Obesity is primarily considered to be a

chronic metabolic disorder, but it has recently been suggested that some forms of obesity are associated with chronic low-grade inflammation [22, 23]. There is a question whether stresses initially causes the activation of inflammatory pathways? Also it is important to know, are these signaling pathways emerging from a common mechanistic platform and integrating with each other? Recently, it has been shown that endoplasmic reticulum (ER) stress is critical to the initiation and integration of inflammations' pathways and action of insulin in obesity and DMT2 [24]. In obesity, adipose tissue hypoxia seems to be a causal factor for inflammation, ER stress, oxidative stress, lipolysis and adipocyte death in adipose tissue [25-27].

Adipocytes produce large numbers of hormones, peptides, and other molecules that affect cardiovascular function, not only in an endocrine manner, but also by autocrine and paracrine mechanisms [23, 28]. Discovery of tumor necrosis factor alpha (TNF-α) in 1993 in adipose tissue, and leptin in 1994, as adipose tissue specific secreted protein, put a new light on this passive long-term energy storage organ [8, 29]. The secretory status of adipose tissue varies depending on the site of an adipose tissue depot. It is mainly found in subcutaneous and visceral depots, but adipose tissue accumulate in the heart, the kidneys and the adventitia of blood vessels as well. Also, expression of adipokines depot can be modified by changes in the cellular composition of the tissue, including alterations in the number, phenotype and localization of immune, vascular and structural cells [30]. Pro-inflammatory state in these depots is similar to that observed in subcutaneous and visceral adipose tissue. Adipose tissues in obese individuals as well as in animal models of obesity, are infiltrated by a large number of macrophages, and this recruitment is linked to systemic inflammation [30-32]. Abnormal levels of inflammation-related adipokines such as leptin, adiponectin, resistin, TNF-α, interleukin-1 (IL-1), interleukin-6 (IL-6), procoagulant substances such as PAI-1, vasoactive substances such as angiotensinogen and endothelin, and molecules that may act on immune cells leading to local and generalized inflammation, also may affect vascular (endothelial) function by modulating vascular nitric oxide (NO) and superoxide release and mediating obesity related vascular disorders including atherosclerosis and insulin resistance (IR) [1, 18, 22, 23, 33-35]. Local and systemic subclinical inflammation and IR may be caused by adipocyte dysfunction and by the infiltration of inflammatory cells in adipose tissue [27, 36]. These inflammations may cause development of obesity-related comorbidities [27] and also FFAs have the ability to cause inflammation and oxidative stress [37, 38]. The translocation of nuclear transcription factor-κB (NF-κB) to the nucleus, which is caused by FFA-mediated activation of IκB kinase β (IKKβ), results in increased production of pro-inflammatory cytokines such as IL-6 [39]. Also, in cultured adipocytes FFAs have been shown to activate NADPH oxidase and induce reactive oxygen species (ROS), which results in dysregulated pro-inflammatory cytokine production [40].

IV. Obesity and CVD

The presence of obesity has been associated with the presence of endothelial and vascular dysfunction, which provides partial explanation of how obesity may leads to CVD [1, 23, 41-44]. Numerous epidemiological studies show that obesity predisposes to CVD [9, 45-47]. In most cases, these clinical conditions result from atherosclerosis, which was once identified as a lipid-storage disease [22]. CVD, including heart disease, vascular disease, and atherosclerosis, is the most critical global health threat, contributing to more than one-third of the global morbidity. Albeit the associations of obesity and CVD have been unquestionably proven in more clinical trials, the exact mechanisms by which obesity eventually leads to CVD, and therefore prospects for therapies remain poorly understood [1, 23, 48].

Obesity has a number of negative effects on the morphology and physiology of the cardiovascular system [23, 48, 49]. In obese patients, excessive fatty tissue mechanically press the blood vessels, causing heart failure, while on the other hand, due to obesity itself, the size of the body increases and need a larger amount of blood for his perfusion [50, 51]. In order to meet its increased metabolic demands, the body with excessive adipose depots, increases the volume of circulating blood and cardiac output, causing a hyperdynamic circulation due to the obesity [51-53]. Elevated cardiac output in obese patients is mainly derived from the amount of blood that

is pumped out of the heart during contraction, although the heart rate is increased due to increased sympathetic activity [54]. Furthermore, in such patients, due to the increased blood volume, dilation and increased wall tension occurs in the myocardium of the left ventricle (LV), which then leads to its hypertrophy [53]. Heart hypertrophy characterized by cell hypertrophy and increased protein synthesis is associated with an increased risk of ventricular dysfunction, heart failure, and malignant arrhythmias in obese individuals [55, 56]. In obese patients, weight loss reduces heart size and improves cardiac function in the absence of any systemic hemodynamic alteration [57], proposing an independent role for hypertrophy in heart dysfunction in obesity [56]. Hypertension is three to five times more common in obese patients compared with those with a normal body weight [58], and obesity-related hypertension imposes an elevated afterload to LV, while obstructive sleep apnea disorders may also augment right ventricular afterload [52, 53]. The existence of a positive correlation between body and heart mass has been shown in several studies [51, 52, 59, 60]. In obesity, fat cells accumulate between muscle fibers and lead to the degeneration of cardiomyocytes, resulting in defected cell signaling in the heart [51]. Especially interesting are the fat cells originating from epicardial fat [51, 52, 61], which constitutes a visceral adipose depot and is a significant source of proinflammatory mediators [52, 62]. A strong correlation between epicardial fat mass and visceral adiposity has been shown [52, 62], too.

Vascular endothelium plays a key role in inflammation, blood flow, regulation of arterial tone and thrombosis [63-65]. Endothelial dysfunction presents a risk marker for CVD [66, 67]. Accumulation of adipocyte accelerates endothelial dysfunction, and endothelial dysfunction is regarded as an early stage of atherosclerosis, which is a chronic inflammatory disease [68] and also a condition for high prevalence of atherosclerotic CVD [15]. Development of more atherogenic metabolic profile is commonly associated with an increase in visceral adipose tissue and in most cases, the CVD risk profile has been additionally worsen with age [69, 70]. However, alterations in insulin sensitivity, plasma lipid and lipoprotein concentration are also developed in other age-related processes which are independent of variation of total adiposity and deposition of visceral adipose tissue [69, 70]. Variations in accumulation of visceral adipose tissue are a considerable factor of substantial proportion of age and sex differences in the metabolic risk profile as a prognostic marker of risk for DMT2 and CVD [71]. It is possible that alterations of immune function can connect obesity to vascular dysfunction and risk factors for atherosclerosis [1, 23, 72-74]. Reduction of available NO in the vasculature is a major contributor of endothelial dysfunction [66, 73, 75-77]. NO influences endothelial functional homeostasis [76], heart rate by modulating vascular smooth muscle and myocytes contractility, migration and proliferation, leukocyte adhesion and also inhibits platelet aggregation [66, 78]. Inflammation in obese patients with IR, visceral and ectopic fat presence and adipokine secretion, could be an explanation for development of endothelial dysfunction and early CVD [13].

Obese persons with high BMI have a doubling of the risk of heart failure compared with those with a normal BMI [79]. Patients with progressive obesity and heart failure, without LV dysfunction, are diagnosed as patients with cardiomyopathy associated with obesity [80]. Earlier it was believed that obesity may be a cause of heart failure only through intermediary mechanisms such as hypertension or coronary heart disease, but recent studies have shown that other factors may be the cause of cardiomyopathy associated with obesity [81], such as LV hypertrophy associated with obesity, which cannot be explained only by increased blood pressure [81].

Cardiovascular complications associated with obesity contribute to high rates of morbidity and mortality [82]. All components of the MetS are independent causes of cardiovascular events such as stroke, cardiomyopathy, coronary artery disease, myocardial infarction, heart failure and sudden cardiac death [83]. Obese person (BMI>30 kg/m^2) have two to three times higher risk of death compared to those with normal weight, while excessively obese (BMI>35 kg/m^2) have a shorter life span of five to twenty years in compared to people with normal body mass of the same sex and age [58, 84]. Nevertheless it is becoming more and more clear that mild obesity (BMI>25 kg/m^2) is also associated with impaired cardiac function [52]. However, in patients with

higher BMI and chronic diseases such as coronary heart disease, a greater chance of survival has been recorded than in patients with low BMI. This phenomenon is known in medicine as the "obesity paradox" [82]. Pathophysiology of "obesity paradox" is unknown and some authors believe that this paradox can be explained by the additional diseases that occur in patients with low BMI [85] like cachexia [52, 86].

Obesity and overweight are the most common cardiovascular risk factors in patients who have suffered a myocardial infarction [81]. More than two-thirds of patients with coronary artery disease have an increased body weight or obesity [87, 88]. Obesity in adolescents and adults is associated with the frequent occurrence of early atherosclerotic lesions [89]. The prothrombotic state in obese patients probably contributes to the development of acute coronary events (nonfatal myocardial infarction and unstable angina) [81, 90].

Results from the large prospective cohort study confirmed by principal component analysis of lipoprotein subfractions that atherogenic dyslipidemia is an important independent CVD risk factor [21]. Today, gene variants, is a great contribution in identifying atherogenic dyslipidemia and these genes may be potential therapeutic targets to decrease detrimental effects of dyslipidemia [21]. It is expected that the results from novel long-term clinical studies will give an answer whether genetic and/or dietary interventions with aim of alteration of dyslipidemia might lead to reduction of CVD risk [21].

Obesity is also associated with an increased FFA uptake and oxidation in the heart [91, 92], considering that the rate of FFA uptake by the heart is primarily determined by the concentration of non-esterified fatty acids in the plasma [93, 94]. Alterations in cardiac FFAs metabolism may play an important role in the development of obesity-related CVD [92]. In addition, not only plasma TG are increased in obesity but myocardial, intracellular TG and lipids are also increased progressively with BMI [92, 95] which promotes lipotoxicity and dysfunction of the heart [94]. Studies performed in different animal models [92, 96-100] and in humans [92, 101, 102] suggest that low fatty acid oxidation does not lead to accumulation of lipids in the heart, and that fatty acid oxidation rates in the heart are actually elevated in obesity, IR, and DMT2 [92, 97, 99, 103-107]. Because high rates of fatty acid oxidation are followed with inhibition of glucose oxidation [96-99] and with decrease in insulin stimulated glucose oxidation, it seems that high rates of fatty acid oxidation in obesity contributes also to the IR because of the direct inhibition of glucose metabolism [92]. Although the effects of obesity on substrate selection in the heart have not been extensively investigated [92], there are emerging evidence that alterations in myocardial substrate selection in obesity towards increased FFA oxidation and away from glucose metabolism, results in decreased contractile efficiency [94] associated with altered energetic in the heart, [108] which make ATP production and utilization less efficient [94]. Furthermore, in addition to the effects of increased FFA uptake and utilization on the production of the electrochemical gradient that powers ATP production, there is now evidence that there are intrinsic defects in the metabolic machinery of the electron transport chain in human and animal models of obesity, where electron transport chain function and efficiency were reduced [109-113].

FFAs are also endogenous ligands for peroxisome proliferator-activated receptors (PPARs) in the heart and PPARs regulate the expression of several genes encoding key proteins involved in myocardial FFA uptake and oxidation [92, 114-117], as fatty acid transport protein (FAT/CD36), fatty acid-binding protein (FABP), acyl-CoA synthetase; and on the other hand, PPARγ, increases storage of TG in adipose tissue [115]. The activation of PPARα or PPARγ leads to decrement of circulating FFA and TG levels [92, 118]. Downregulation of PPARα and/or an inhibition of PPARγ in obesity results in underexpression of FFA oxidative enzymes, accumulation of lipids in the cells, "cardiac lipotoxicity", and development of cardiomyopathy [92]. Experimental and clinical studies reported that inhibition of fatty acid oxidation and stimulation of glucose oxidation may improve recovery of cardiac function and efficiency having an antiischemic effect [92, 119, 120]. Increased fatty acid uptake and oxidation in obesity is directly linked to decreased cardiac efficiency [94]. Further studies should clarify the mechanisms that regulate cardiac fatty acid metabolism in obesity and also, to identify nutritional and pharmacological interventions to prevent the adverse effects of obesity on the heart.

Expansion of adipose tissue mass in obesity may result in disturbances in secretion of adipocytokines and increased macrophage infiltration. This dysfunction of adipose tissue may explain the link between obesity and metabolic and cardiovascular diseases [121]. There is accumulating evidence to suggest that obesity leads to the altered release of adipokines, such are leptin and adiponectin, and both have impact on regulation of cardiac energy metabolism and on insulin signaling [92]. Heart and vasculature are specifically impacted by increased leptin and decreased adiponectin [92, 122-125]. Three currently identified adiponectin receptors in the heart: AdipoR1, AdipoR2, and T-cadherin, leads to conclusion that there is a direct effect of adiponectin on the heart [92, 126, 127]. It is considered that adiponectin stimulates fatty acid metabolism [128, 129], but significantly decreased adiponectin [130] and increased fatty acid metabolism in obesity indicates that the complete action of adiponectin on cardiac metabolism in obesity is still unknown [94]. On the other hand, increased leptin level in obesity [131] leads to reduced glucose and elevated fatty acid metabolism in the heart, probably *via* regulation of FABP trafficking to the plasma membrane [132]. Leptin could prevent cardiac lipotoxicity, by restricting storage of excess lipids to adipocytes, and simultaneously decreasing the

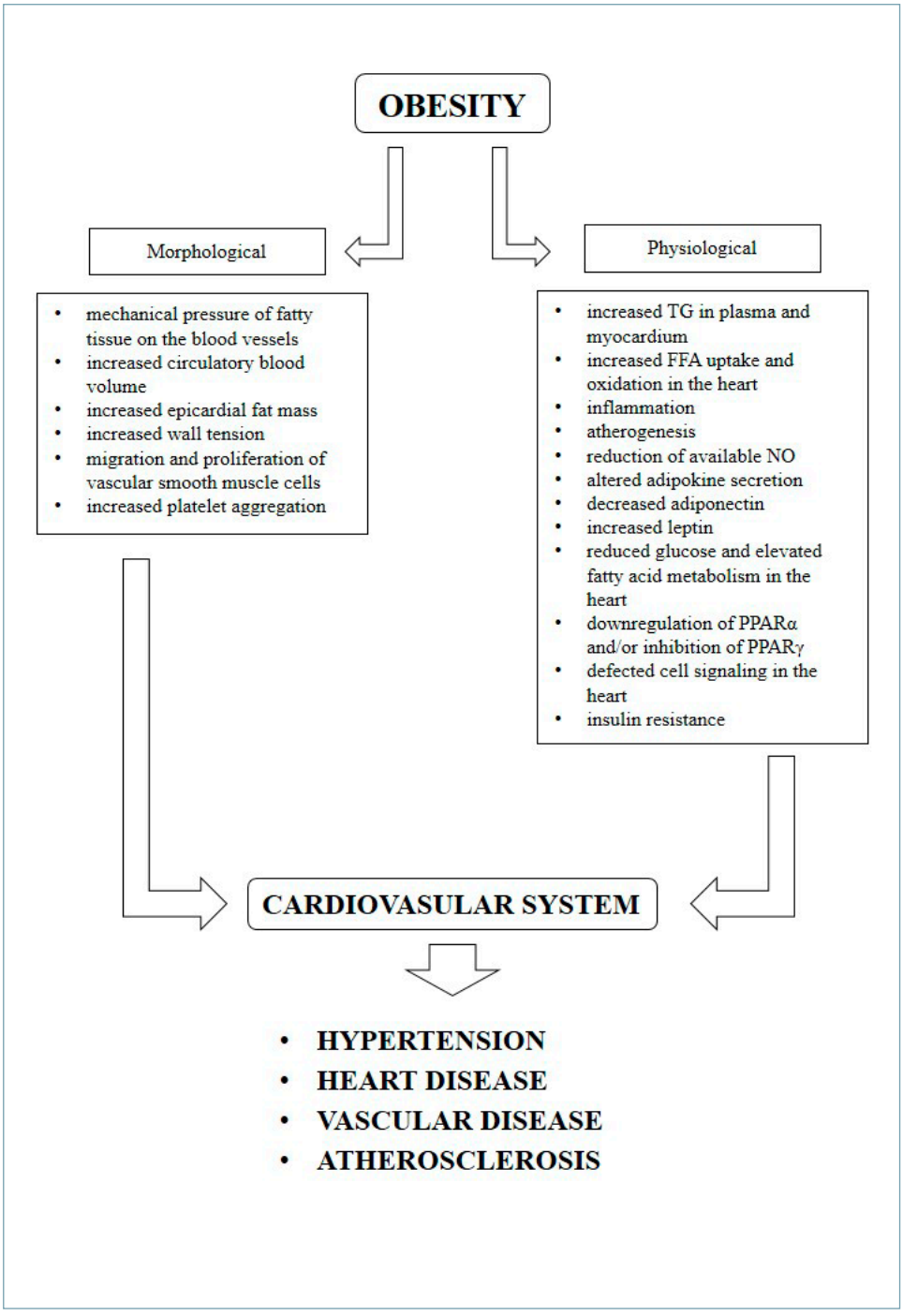

Figure 1.
Schematic overview of the effects of obesity on cardiovascular health and diseases. The morphological and physiological alterations in obesity that can lead to development of cardiovascular disease manifestations. FFAs- free fatty acids; NO- nitric oxide; PPARs peroxisome proliferator-activated receptors; TG triglyceride.

storage of lipids in myocardium [133]. Some of the morphological and physiological alterations in obesity that can lead to development of CVD are summarize in Figure 1.

V. Conclusions

The role of obesity in pathophysiology of CVD remains incompletely understood. Many studies in experimental models together with clinical trials and observational studies suggest that obesity is one of the most influential, independent risk factor for the development of cardiac dysfunction and CVD. This review supports the need for further translational investigation to elucidate molecular mechanism through which obesity is involved in CVD such are atherosclerosis and hypertension. Therefore the aim of future investigations should be directed to identify the potential influence of obesity as a cause of CVD. Also, in order to prevent the development of obesity, and thus diseases that occur as a result of this disorder, significant is the prevention and information given about the aspects that excessive accumulation of body fat may have on the normal functioning of the body.

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VII. References

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