REVIEW

Ectopic fat deposition and global cardiometabolic risk : New paradigm in cardiovascular medicine

Michio Shimabukuro[1,2], Chisayo Kozuka[3], Shin-ichiro Taira[3], Koichi Yabiku[3], Munkhbaatar Dagvasumberel[5], Masayoshi Ishida[2], Sachiko Matsumoto[2], Shusuke Yagi[2], Daiju Fukuda[1,2], Ken Yamakawa[4], Moritake Higa[4], Takeshi Soeki[2], Hisashi Yoshida[5], Hiroaki Masuzaki[3], and Masataka Sata[2]

[1]*Department of Cardio-Diabetes Medicine,* [2]*Department of Cardiovascular Medicine, the University of Tokushima Graduate School of Health Biosciences, Tokushima, Japan ;* [3]*Division of Endocrinology, Diabetes and Metabolism, Hematology, Rheumatology, Second Department of Internal Medicine, University of the Ryukyus School of Medicine Graduate School of Medicine, Okinawa, Japan ;* [4]*Diabetes and Lifestyle-Related Disease Center, Tomishiro Central Hospital, Okinawa, Japan ;* [5]*Cardiovascular Division, Shonan Hospital, Okinawa, Japan*

Abstract : The obesity epidemic is a global public health concern that increases the likelihood of morbidity and mortality of metabolic and cardiovascular disease (CVD) and threatens to reduce life expectancy around the world. The concept of the metabolic syndrome (MetS) takes into account that visceral fat plays an essential role in the development of metabolic and cardiovascular diseases. However, MetS cannot be used to assess global CVD risk but is at best one more modifiable CVD risk factor. Thus, global cardiometabolic risk (the global risk of cardiovascular disease resulting from traditional risk factors combined with the additional contribution of the metabolic syndrome and/or insulin resistance) should be considered individually. There is solid evidence supporting the notion that excess abdominal fat is predictive of insulin resistance and the presence of related metabolic abnormalities currently referred to as MetS. Despite the fact that abdominal obesity is a highly prevalent feature of MetS, the mechanisms by which abdominal obesity is causally related to MetS are not fully elucidated. Besides visceral fat accumulation, ectopic lipid deposition, especially in liver and skeletal muscle, has been implicated in the pathophysiology of diabetes, insulin resistance and obesity-related disorders. Also, ectopic fat deposition could be deteriorated in the heart components such as (1) circulatory and locally recruited fat, (2) intra- and extra-myocellular fat, (3) perivascular fat, and (4) pericardial fat. In this review, the contribution of ectopic lipid deposition to global cardiometabolic risk is reviewed and also discussed are potential underlying mechanisms including adipocytokine, insulin resistance and lipotoxicity. J. Med. Invest. 60 : 1-14, February, 2013

Keywords **:** *obesity, insulin resistance, cardiovascular disease, diabetes mellitus*

Abbreviations : CVD : cardiovascular disease ; T2DM : type 2 diabetes mellitus ; BMI : body mass index ; AMI : acute myocardial infarction ; CHD : coronary heart diseases ; FFA : free fatty acids ; ROS : reactive oxygen species ; eNOS : endothelial nitric oxide synthase ; NO : nitric oxide ; TG : triglycerides ; lipoprotein-cholesterol ; HDL-C : high-density lipoprotein-cholesterol.

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Address correspondence and reprint requests to Michio Shimabukuro, MD, Departments of Cardio-Diabetes Medicine, the University of Tokushima Graduate School of Health Biosciences, 3-18-15 Kuramoto, Tokushima 770-8503, Japan and Fax : +81-88-633-7894.

INTRODUCTION

The obesity epidemic is a global public health concern that increases the likelihood of morbidity and mortality of metabolic and cardiovascular disease (CVD) and threatens to reduce life expectancy around the world (1-2). The concept of the metabolic syndrome (MetS) takes into account that visceral fat plays an essential role in the development of metabolic and cardiovascular diseases (3-5). MetS is merely a modifiable CVD risk factor as well as traditional risk factors such as LDL-cholesterol, diabetes, hypertension and smoking, but accounts for a great proportion of mechanisms under the obesity endemic era. Thus, global cardiometabolic risk (the global risk of cardiovascular disease resulting from traditional risk factors combined with the additional contribution of the metabolic syndrome and/or insulin resistance) should be considered individually (6-8). Despite the fact that abdominal obesity is a highly prevalent feature of MetS, ectopic fat deposition, especially in liver and skeletal muscle, has been implicated in the pathophysiology of diabetes, insulin resistance and obesity-related disorders (Fig. 1) (6-8). Also, ectopic fat deposition in the cardiovascular components is now recognized as a new cardiometabolic risk marker, as it is associated with increased insulin resistance, visceral fat and, in general, with the metabolic syndrome (6, 9-11). In this review, the contribution of ectopic fat deposition to global cardiometabolic risk and its potential underlying mechanisms are reviewed.

1. CONTRIBUTION OF ECTOPIC FAT DESPOSION TO CARDIOVASCULAR DISEASE

The amount of adipose tissue, as well as its distribution, is of special importance in the pathogenesis of insulin resistance and type 2 diabetes. Visceral adipose tissue is metabolically highly active (3-5) and its major role in the pathogenesis of insulin resistance is widely accepted. Simultaneously, lipids in ectopic (non-adipose) tissues such as liver and skeletal muscle are of increasing interest. Liver fat is elevated in insulin-resistant subjects (12, 13) and, furthermore, is strongly correlated with the amount of visceral fat in a prediabetic population (14). In addition, high intramyocellular fat is a marker of insulin resistance (15, 16). Thus, determination of fat in the visceral depot and in the ectopic tissues liver and muscle is thought to be a predictor for subjects who are insulin resistant and have a high risk of type 2 diabetes and cardiovascular dieases (Fig 2). Recenlty, we evaluated the relationship between hepatic and muscular lipid deposition and visceral fat accumulation in middle-aged Japanese men with MetS and found that visceral fat accumulation is accompanied by excess lipid deposition in skeletal muscle (iliopsoas muscle, back muscle, rectus

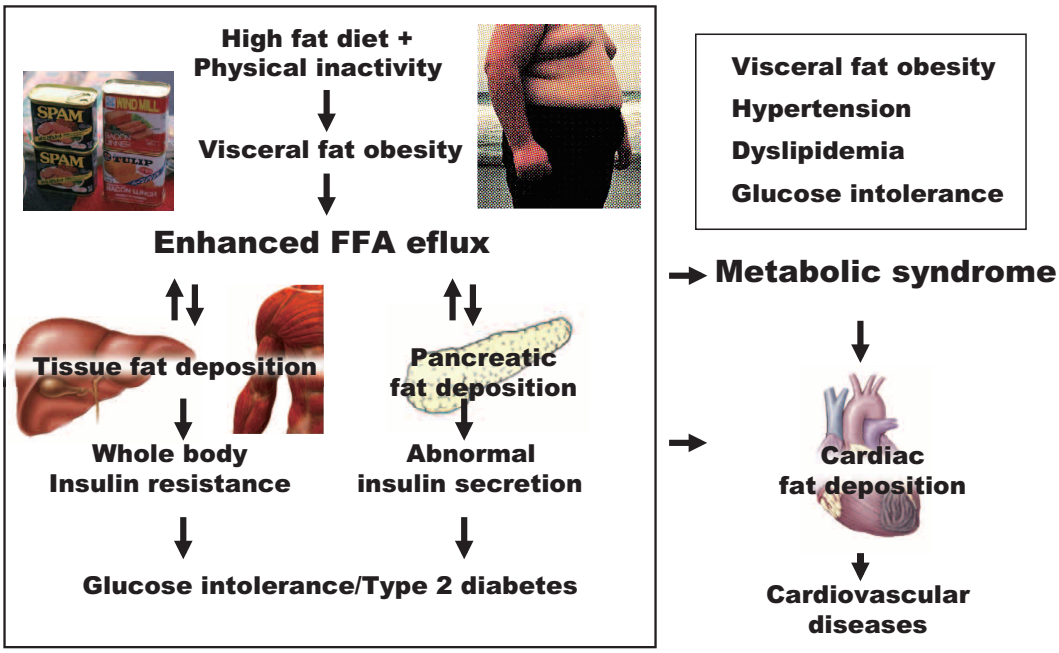

Fig. 1. Ectopic fat deposition rather the whole-body fat distribution causes insulin resistance and vascular failure.

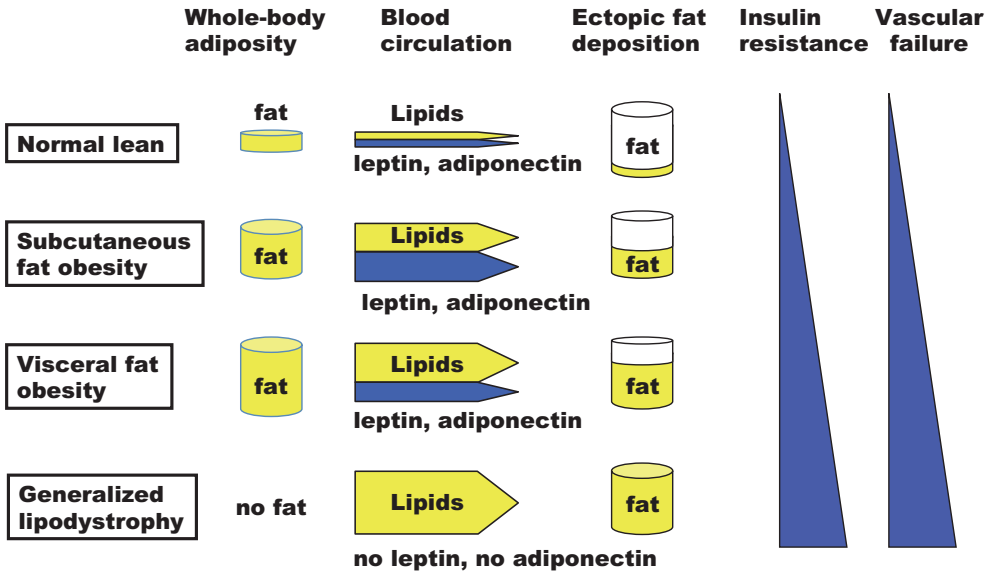

Fig 2. **Ectopic fat deposition causes metabolic derrangements and cardiovascular diseases**
Visceral fat obesity rather than subcutaneous fat obesity leads to lipid (free fatty acid) spreading to end-organs, causing ectopic fat deposition and resultant insulin resistance via lipotoxicity mechanism(s)). Vascular failure is a consequence of insulin resistance/glucose intolerance. Generalized lipodystrophy, genetic or acquired disorders without capacity to store fat in adipose tissue, shows lipotoxic damage such as severe insulin resistance and vascular failure.

abdominis muscle) and the liver (17). Interstingly, changes in lipid contents by atnti-diabetic medications were different in the tissues (visceral fat > liver fat > muscle fat), suggesting that ectopic fat desposion is regulated differently in these tissues. Contribution of ectopic fat desposion to cardiovascular disease are discussed below.

1.1. Coronary heart diseases

In the INTERHEART study (18), Yusuf *et al.* reported the effect of various measures of adiposity on rates of acute myocardial infarction (AMI) by comparing 12,461 AMI cases and 14,637 standardized-controls of variable ethnicity from 52 countries. BMI showed a modest association with AMI (unadjusted odds ratio [OR] 1.44 for the top quintile vs. the bottom quintile), but this association was lost after adjustment for other risk factors. Meanwhile, adjusted OR for quintile of waist-to-hip ratio was consecutively higher than that of the previous one (OR 1.15 ; 1.39 ; 1.90 ; and 2.52, respectively).

Targher *et al.* assessed prospectively whether Nonalcoholic fatty liver disease NAFLD, a typical phenotype of ectopic fat deposition, predicts future CVD events including nonfatal coronary heart disease (myocardial infarction and coronary revascularization procedures), ischemic stroke, or cardiovascular death, among type 2 diabetic individuals (19). After adjustment for age, sex, smoking history, diabetes duration, HbA1c, LDL cholesterol, liver enzymes, and use of medications, the presence of NAFLD was significantly associated with an increased CVD risk (odds ratio 1.84, $P<0.001$). Additional adjustment for the metabolic syndrome appreciably attenuated, but did not abolish, this association (1.53, $P=0.02$).

One form of ectopic fat deposition, epicardial adipose tissue (EAT), is correlated with various cardiovascular risk factors, independent of abdominal visceral adiposity, body mass index (BMI), hypertension, and diabetes mellitus (9-11). Two population-based studies, the Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study, showed that EATV is an independent risk predictor for cardiovascular disease (20, 21). EAT is shown to be metabolically active and the source of proatherogenic mediators and adipocytokines. We (22) and others (23) showed that proinflammatory cytokines and adipocytokines are expressed and secreted at a higher level in the adipose tissue of individuals with coronary artery disease (CAD) than in individuals without CAD. Abdominal fat distribution is dissimilar between men and women : Visceral fat obesity is the dominant form in men, while subcutaneous fat obesity is the dominant form in women (24, 25). We evaluated gender disparities in EATV and its impact on coronary atherosclerosis by using multi-detector computed tomography (MDCT) (Fig. 3). EATV/body surface area (BSA) was higher among men in the CAD group than in the non-CAD

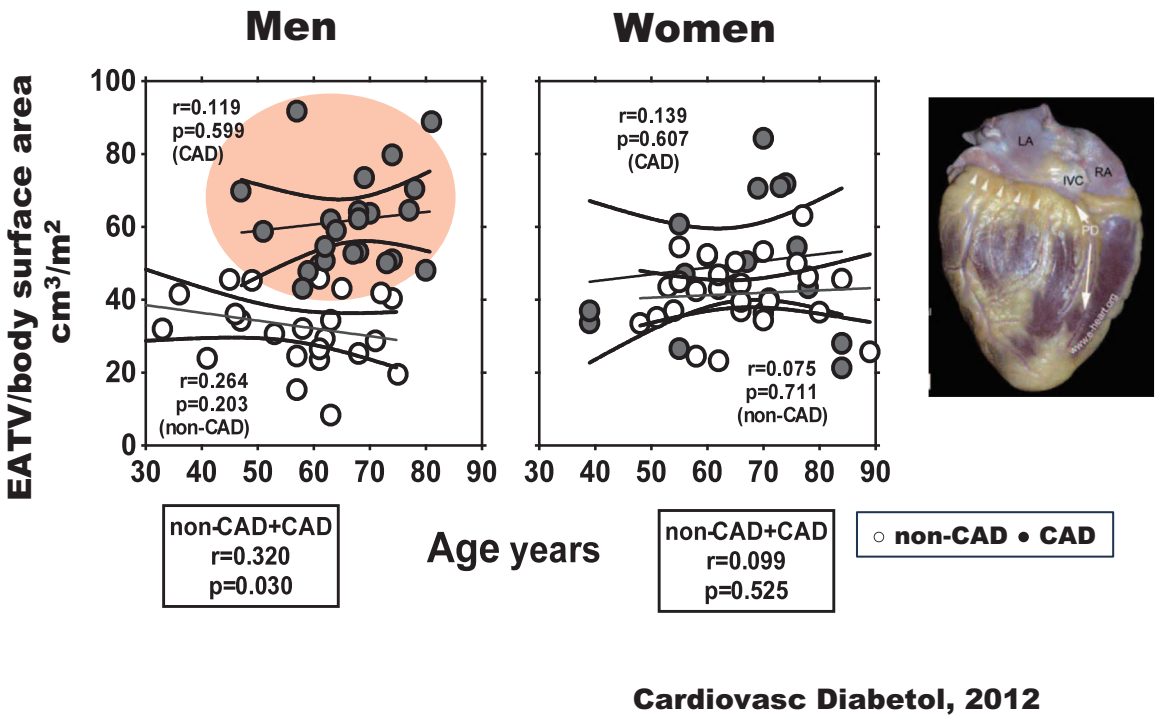

Fig 3. Men with coronary atherosclerotic disease (CAD) showed an increase in epicardial adipose tissue (EAT) volume

group (62 ± 13 vs. 33 ± 10 cm_3/m_2, $p < 0.0001$), but did not differ significantly among women in the 2 groups (49 ± 18 vs. 42 ± 9 cm_3/m_2, not significant) (26). Multivariate logistic analysis showed that EATV/BSA was the single predictor for > 50% coronary luminal narrowing in men ($p < 0.0001$). Thus, increased EATV might be strongly associated with coronary atherosclerosis only in men (26).

1.2. Cardiac dysfunction and heart failure

Echocardiographical measures of left ventricular (LV) structure and LV function were altered in metabolic syndrome (27). Patients with metabolic syndrome appeared more likely to show LV diastolic dysfunction, independently of LV mass (27). Thus, Veglobal, an index of global LV relaxation function, decreased progressively from absent group (0 of metabolic syndrome component), pre-metabolic syndrome group (1-2 component), to metabolic syndrome group (>=3 component), even after adjustment for LV mass (27). In patients hospitalized for CHF, 30%-40% present only with LV diastolic dysfunction but not with LV systolic dysfunction (28). The presence of metabolic syndrome provides important risk information beyond that of established risk factors also for congestive heart failure (CHF). In a community-based sample of middle-aged men, BMI and/or metabolic syndrome was a significant predictor of CHF, independent of established CHF risk factors (hypertension, T2DM, LV hypertrophy and smoking) (29). There is strong evidence for lipotoxic mechanisms in rodents showing that lipid accumulation in the heart leads to heart failure. 1H-MRS has been adapted to quantify lipid content in cardiac muscle of human subjects (30), showing that triglyceride (TG) was detectable in the myocardium of healthy human subjects even in those who are very lean. In overweight subjects myocardial TG content was elevated and was accompanied by increased left ventricular mass and a subtle reduction of septal wall thickening, which represents mild systolic dysfunction (30). Myocardial fat was found to be higher in obese than in lean subjects and myocardial fat correlated with FFA levels, epicardial fat, and waist-to-hip ratio (31). Epicardial fat was positively associated with peripheral vascular resistance and negatively with the cardiac index. Combined, the cardiac accumulation of TG is related to FFA exposure, generalized ectopic fat excess, and peripheral vascular resistance and that these changes precede left ventricular overload and hypertrophy (32).

1.3. Cerebrovascular diseases

In the Atherosclerosis Risk in Communities (ARIC) study, which included 14,448 men and

women, Ohira *et al.* determined contribution of risk factors on ischemic stroke subtype (33). In addition to traditional risk factors such as hypertension, current smoking and T2DM, waist-to-hip ratio was associated with increased risk for nonlacunar and cardioembolic stroke, but not with lacunar stroke. The population-attributable fraction for hypertension was approximately 35% for all ischemic stroke subtypes. The each population-attributable fraction for T2DM, current smoking, and waist-to-hip ratio were 26.3%, 22.0% and -5.6% for lacunar ; 11.3%, 11.4%, and 9.7% for nonlacunar stroke ; 16.4%, 20.7% and 2.9% for cardioembolic stroke. In Japanese population of the Hisayama Study, the multivariate-adjusted incidence of non-ischemic and ischemic stroke appeared higher in subjects with metabolic syndrome in men (hazard ration [HR] 1.68, p=0.06 and 2.54, p=0.02) and women (1.78, p=0.01 and 0.99, p=0.91), as compared with those without metabolic syndrome (34).

1.4. Atrial fibrilation, arrhythmic events and sudden death

In the Paris Prospective Study I, which investigated mortality of 6,678 middle-aged men, sagittal abdominal diameter, substituted for waist circumference, and the presence of metabolic syndrome were associated with an increase in <1 hour sudden death (multivariate adjusted HR, 2.26 and 2.02), so as with non-sudden death from AMI (HR 1.69 and 1.60) (35). Sudden death could be coming from arrhythmic events including lethal ventricular fibrillation, since patients with metabolic syndrome had significantly higher values of corrected QT interval (QTc) and QT dispersion (QTd) on electrocardiogram, which reflects myocardial refractoriness and electrical instability (36). In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) study (37), obesity (BMI >=30 kg/m2) was a risk factor for sustained ventricular tachyarrhythmia in patients after myocardial infarction with severe left ventricular dysfunction (LV ejection fraction< 30%).

In analysis of Japanese 592 hospitalized patients without obvious structural heart diseases (38), the metabolic syndrome was a significant risk factor for paroxysmal atrial fibrillation/flutter, independently of left atrial diameter (>44 mm) or age (>70 years) (OR 2.8, p<0.01). In a community-based cohort in Japan (>28,000 subjects), Watanabe *et al.* demonstrated an apparent correlation between the presence of metabolic syndrome and increased susceptibility to atrial fibrillation (39). Among the metabolic syndrome components, obesity (BMI >= 25) (age- and sex-adjusted HR, 1.64), as well as elevated blood pressure (systolic pressure >=130 mmHg and/or diastolic pressure >= 85 mmHg) (HR 1.69), low HDL-cholesterol (HR 1.52), and high fasting plasma glucose (>=110 mg/dL) (HR 1.44), showed an increased risk for atrial fibrillation (39). The association between the metabolic syndrome and atrial fibrillation remained significant in subjects without treated hypertension or T2DM (HR 1.78). Obesity and metabolic syndrome were also shown to be independent risk factors for atrial fibrillation after coronary artery bypass graft surgery (40). Whether the increased atrial fibrillation risk in metabolic syndrome is due to the syndrome as a whole or simply the sum of the risks of its individual components is currently equivocal. A recent report showed that EAT volume measured by MDCT was highly associated with AF, independent of traditional risk factors including left atrial (LA) enlargement (41). A large sample from the Framingham Heart Study (n=3,217) has shown that pericardial fat volume was associated with AF even after adjustment for risk factors, including body mass index (42). Nakanishi *et al.* also demonstrated that the peri-atrial EAT volume predicted future AF events more accurately than total EAT volume during follow-up of 3.3± 1.0 years (43). These results suggest the potential role of peri-atrial EAT in the development of AF such as local and direct effects on LA structures, generation of inflammatory cytokines, and modulation of the intrinsic autonomic nervous system.

1.5. Peripheral arterial disease

There are few studies examining the relationship between obesity and peripheral arterial disease (PAD). Whether obesity is a risk factor for development of PAD remains controversial (44, 45). The discrepancy may be due to the higher prevalence of PAD in elderly males and in smokers ; elderly males show a weaker relationship between obesity and CVD, and smokers tend to have lower BMI than non-smokers (46). A recent prospective cohort study revealed a positive relationship between waist-to-hip ratio, not BMI, and PAD prevalence (47). Mechanisms by which obesity causes PAD (if any), could be different to CHD, two do have different risk profiles ; e.g. cigarette smoking is more strongly associated with development of PAD than CHD (48). Studies should be done to clarify effects of

obesity on onset of PAD, complications such as rupture of aortic aneurysm and severity of limb ischemia.

1.6. Venous thromboembolism

Numerous studies have shown a clear relationship between obesity and the risk of idiopathic venous thromboembolism (deep vein thrombosis and pulmonary embolism), independent of other traditional risk factors (48, 49). In a study from Sweden, men with a waist circumference >=100 cm had a 4-fold higher risk of venous thromboembolism than with <100 cm (49). Obese patients have chronically raised intra-abdominal pressure and decreased blood velocity in the common femoral vein. Inactivity, poor gait, as well as other co-morbidity may collectively impair venous return from the lower limbs. Alternatively, obesity, in particular visceral obesity, may have prothrombotic propensity via mechanisms including : actions of adipocytokines, increased activity of the coagulation cascade and decreased activity of the fibrinolytic cascade, inflammation, oxidative stress, endothelial dysfunction, and disturbances in lipids and glucose homeostasis (50).

2. MECHANISTIC LINK BETWEEN ECTOPIC FAT DESPOSION AND CARDIOVASCULAR DISEASE

2.1. Adipocytokine and insulin resistance

There is solid evidence supporting the notion that excess abdominal fat is predictive of insulin resistance and of the presence of related metabolic abnormalities currently referred to as the metabolic syndrome (3-8). Despite the fact that abdominal obesity is a highly prevalent feature of the metabolic syndrome, the mechanisms by which abdominal obesity is causally related to the metabolic syndrome are not fully elucidated. When categorized by whole-body distribution of adiposity, insulin sensitivity is well explained by ectopic fat deposition in insulin-sensitive non-adipose tissue (Fig. 1, 3). Obese subjects constantly deliver more lipids and dysregulated adipocytokine than normal lean subjects ; visceral fat obese can produce more pro-atherogenic adipocytokine including free fatty acid (FFA) than subcutaneous fat obese. Adipose tissue is not only an energy storage tissue, but also a metabolically active organ secreting hormones, cytokines and growth factors, collectively called as adipocytokine (adipokine), that act in an autocrine, paracrine or endocrine manner (3-8). It is believed that anti-atherosclerotic adipocytokine such as leptin and adiponectin and pro-atherosclerotic cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNFα) cooperatively regulate metabolic and cardiovascular homeostasis at local and remote site (Table) (3-8, 51). Obesity and atherosclerotic process at least partly share an inflammatory etiology (52, 53), which hypothetically causes imbalance in the interaction between nitric oxide (NO) and reactive oxygen species (ROS) and result in a pro-atherogenic vascular bed (54).

Comorbidity of hypertension, glucose intolerance and dyslipidemia individually may cause cardiac dysfunction directly via impaired relaxation of LV and/or via vascular failure (endothelial dysfunction) (55). The excess production of ROS may elicit tissue damage in the heart, as shown in experimentally induced-heart failure model (56). ROS could be involved in the pathophysiology of human CHF (57). Systemic oxidative stress is enhanced in obese animals and in humans with visceral obesity (58) or the metabolic syndrome (59). ROS derived from visceral fat could affect LV geometry and LV function.

2.2. Lipotoxicity

Obesity is associated with lipid accumulation not only in adipose tissue, but also in non-adipose tissues (60). The latter is known as ectopic fat deposition and lipotoxicity, which is theorized to produce obesity comorbidities such as insulin resistance, T2DM and cardiovascular disease (Fig. 3). We first described this concept in pancreatic β cells (β cell-lipotoxicity) (61-63) and expand this to other tissues including the heart (64, 65). As obesity develops, insulin secretion increases parallel to insulin resistance in order to maintain normal glucose homeostasis. Patients predisposed to diabetes, however, fail to compensate for greater insulin requirements, and develop T2DM (60).

The remarkable hyperlipolytic activity of the visceral adipose tissue, over the subcutaneous adipose tissue, contributes to exposure the liver, skeletal muscle and even the cardiovascular system to excess FFA. This impairs insulin-dependent metabolic process, and leads to hyperinsulinemia, glucose intolerance (an increase in hepatic glucose production and decreases in skeletal and hepatic glucose uptake), hypertriglyceridemia (an increase in VLDL-apolipoprotein B secretion), low plasma HDL-cholesterol level, and cardiovascular disturbance (60).

2.3. Cardiac adiposity and epicardial fat : cardiac lipotoxicity

Mechanisms by which abdominal adiposity induces cardiac dysfunction remain unknown (27-32). From evidence described here, one of authors (MS) previously proposed an idea that ectopic fat deposition in the heart is causally related to cardiac performance and structural remodeling at multiple component by (A) circulatory and locally-recruited fat (66), (B) intra- and extra-myocellular fat (64, 65), (C) perivascular fat (67-69), and (D) pericardial fat (6-11), collectively to be called "cardiac lipotoxicity".

2.3.1. Circulatory and locally-recruited fat (Vascular lipotoxicity)

An oversupply of FFA to the bloodstream from visceral adipose tissues may disturb vascular homeostasis. We found a "vascular lipotoxicity" phenomenon that FFA does directly activate vascular ROS production and leads endothelial dysfunction in obese model (66). Circulating FFA can acutely increase vascular ROS signals and chronically enhance vascular expression of NADPH oxidase multisubunit complex, which is the major source of superoxide anion in the vasculature (70, 71). Two general mechanisms underlying activation of NADPH oxidase are either an acute increase in oxidase complex formation secondary to post-translational modification of regulatory subunits or mitochondrial uncoupling (72, 73), or a chronic increase in the expression and abundance of component subunits (70, 71). The locally produced ROS (66) and fat-derived ROS (58) simultaneously react with NO, generate peroxynitrite, and finally impair cGMP-dependent vasodilatation.

2.3.2. Intra- and extra-myocellular fat

Contents of intra- and extra-myocellular fat are shown to be closely related to visceral fat adiposity in animal model (64, 65) and in human (69). Fat accumulation of the myocardium is associated with LV hypertrophy and dysfunction that ultimately progresses to lipotoxic heart disease (64). Myocardial fat accumulation and lipotoxic cardiomyopathy in this model can be prevented by an insulin sensitizer treatment initiated at an early age (60). In human, Szczepaniak *et al.* showed that the contractile function of myocardium measured by MRS was negatively correlated with myocardial TG levels (69), and also found that elevated myocardial TG levels developed LV concentric hypertrophy. This observation suggests that high myocardial TG levels herald contractile dysfunction in humans.

2.3.3. Perivascular fat

Perivascular fat is another candidate of mediator for obesity-associated cardiovascular risk. It is defined as the accumulation of fat around vascular structures, mostly in the proximity of all blood vessels and around the coronaries and the aorta. Conventionally, perivascular fat was considered to act largely as a structural support for vasculature. Recent experimental data from ex-vivo epicardial adipose tissue and arteries suggest that periadventitial fat can modulate vascular responsiveness to vasoactive agents (55, 56) (68-70). Perivascular fat can secrete a variety of cytokines and chemokines and could contribute to the pathogenesis and/or progression of obesity-induced atherosclerosis.

2.3.4. Pericardial fat

Accumulation of excess pericardial fat, which shares the capacity to secrete cytokines with visceral fat might be related to cardiac remodeling (6-11). Its quantity is well correlated with the mass of visceral adipose tissue. Human pericardial adipose tissue has a considerable secretory activity ; epicardial adipose tissue from patients undergoing elective coronary aortic bypass grafting contained more mRNA and protein for IL-1β, IL-6, monocyte chemoattractant protein 1 (MCP-1) and TNFα compared to subcutaneous adipose tissue (22, 23). In pericardial tissue, the cytokine concentrations were correlated well with an accumulation of inflammatory cells, such as T-lymphocytes, macrophages and mast cells. Adiponectin might also play a role in pericardial adipose tissue, as patients with advanced coronary heart disease have lower level of epicardial adiponectin. A recent clinical study showed that pericardial adipose tissue represents a novel indicator of cardiovascular risk (20, 21).

3. MANAGEMENT STRATEGY FOR GLOBAL CARDIO-METABOLIC RISK

3.1. Individual risk factors and global cardio-metabolic risk

Although remarkable progress has been made in the management of traditional CVD risk factors such as hypertension, elevated LDL-cholesterol, smoking, and diabetes mellitus, approach to

abdominal obesity/metabolic syndrome have not been reached to a worldwide consunsus (7, 8, 74). The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as well as the International Chair on Cardiometabolic Risk have emphasized the critical importance of first using global risk calculators such as the Framingham risk score, the PROCAM algorithm or the European SCORE (74, 75). However, there is evidence to suggest that the risk assessment algorithms may not accurately estimate the global CVD risk in patients with visceral obesity/metabolic syndrome. Thus, it is essential to develop a risk assessment model of global CVD in the presence of traditional risk factors and emerging markers found in individuals with visceral obesity. Després *et al.* defined this model as global cardio-metabolic risk (76). Under this model, cardiometabolic risk is the global risk of CVD resulting from the presence of traditional risk factors combined with the possible additional contribution of the metabolic syndrome. Namely, the metabolic syndrome cannot be used to assess global CVD risk but is at best one more modifiable CVD risk factor. To modify this model for clinical setting, we propose cardiometabolic risk cascade causing cardiovasuclar disease (Fig. 4).

It is also claimed that the Framingham risk score does not properly assess lifetime risk particularly among young adults or adolescents with abdominal obesity (77), which are not considered at a risk of CVD by current algorithms because of young age. Surrogate markers to detect abnormalities in ROS and renin-angiotensin-aldosterone system (RAAS), vascular failure (endothelial dysfunction), neurohumoral stress and arrhythmogenicity could have additional powers in long-term assessment of global CVD risk.

3.2. Visceral fat management

Obesity management goals should encompass reduction in total cardiovascular morbidity and mortality. Losing 5% to 10% of body weight reduces the traditional CV risks (78). Increasing physical activity, in combination with a diet that emphasizes fresh fruits and vegetables, whole grains, and low-fat dairy products, can help patients reduce weight and obesity comorbidity.

Less is known about the long-term effect of weight loss on the development of T2DM and CVD outcomes in the form of death, myocardial infarction, and stroke. A trial to answer the most important

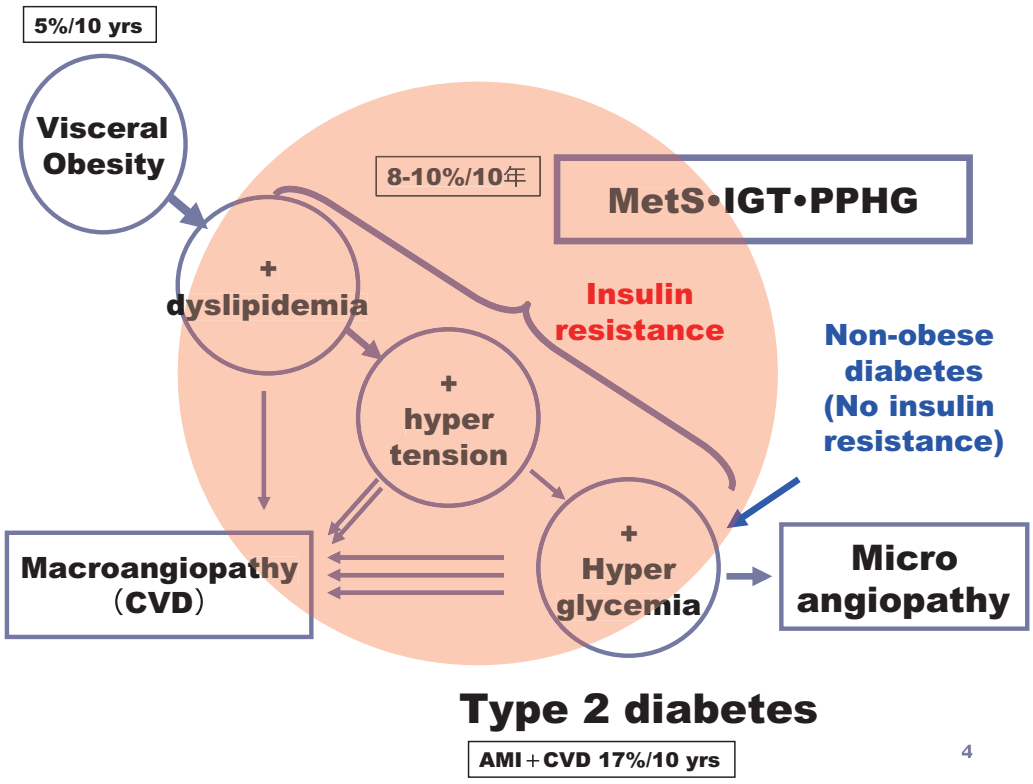

Fig 4. Cardiometabolic risk cascade causing cardiovascular disease
CVD, cardiovascular disease ; MetS, metabolic syndrome ; IGT, impaired glucose tolerance ; PPHG, postprandial hyperglycaemia

question whether the improvements in cardiovascular risk factors by managed weight loss will be associated with reduction in long-term cardiovascular events was investigated (The Look AHEAD (Action for Health in Diabetes) trial) (79). The study enrolled 5,145 people with type 2 diabetes and a BMI greater than 25, randomizing half to a lifestyle intervention and half to a general program of diabetes support and education (80). Although those in the intervention group kept off 5% of their initial body weight at 4 years, there was no difference between them and the standard care group in the rate of myocardial infarction, stroke, hospitalizations for angina, and cardiovascular death -- the primary outcome. Despite no reduction in cardiovascular events in those in the intense intervention arm, they did experience other health benefits. Patients in this group saw improvements in sleep apnea and mobility, as well as quality of life. In addition, their diabetes medications were reduced. In addition, at 1 and 4 years, both diabetes control (glucose, HbA1c) and most cardiovascular disease risk factors (blood pressure, HDL cholesterol, triglycerides) were more favorable in the lifestyle intervention than in the control group with the exception of LDL cholesterol, which was not different between groups at year 1. At year 4, those in the intensive lifestyle intervention group continued to have more favorable diabetes control and CVD risk factor reduction, with the exception of LDL-C in which there were slightly greater reductions in the standard care group. Participants in the lifestyle intervention group maintained greater improvements in fitness at both years 1 and 4.

According to AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease : 2011 Update : Intervention Recommendations With Class of Recommendation and Level of Evidence (Fig. 5) (81), weight management is recognized as

Weight management

Goals:

Body mass index: 18.5 to 24.9 kg/m^2

Waist circumference: women <35 inches (<89 cm), men <40 inches (<102 cm)

Class I

1. Body mass index and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance/reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m^2.[60–62,65–70] ***(Level of Evidence: B)***
2. If waist circumference (measured horizontally at the iliac crest) is ≥35 inches (≥89 cm) in women and ≥40 inches (≥102 cm) in men, therapeutic lifestyle interventions should be intensified and focused on weight management.[66–70] ***(Level of Evidence: B)***
3. The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated. ***(Level of Evidence: C)***

Table 2. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* COR III: No benefit — Procedure/Test: Not Helpful — Treatment: No Proven Benefit COR III: Harm — Procedure/Test: Excess Cost w/o Benefit or Harmful — Treatment: Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

Fig 5. Body weight management : AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease : 2011 Update : Intervention Recommendations With Class of Recommendation and Level of Evidence

Class I (Procedures/Treatment should be performed/administered), but estimated of certainty of treatment effect is named as Level B or Levels C. When indicated, exercise, caloric intake, and formal behavioral programs are recommended to maintain/achieve a body mass index between 18.5 and 24.9 kg/m2 (Level of Evidence : B), or to achieve waist circumference (< 89 cm) in women and (< 102 cm) in men or to reduce body weight by approximately 5% to 10% from baseline.

CONCLUSION

The concept of the metabolic syndrome takes into account the central role that visceral fat plays essential role in the development of metabolic and cardiovascular diseases, and indicates how waist circumference measurement is useful in aiding patient identification in a clinical setting. The metabolic syndrome cannot be used to assess global CVD risk but is at best one more modifiable CVD risk factor. Thus, global cardiometabolic risk should be considered individually. Increased visceral fat is associated with a shift in the normal balance of the adipocytokines resulting in pro-inflammatory and pro-atherosclerotic state. Although evidence for therapeutic efficacy in the treatment of abdominal adiposity and clustering of cardiometabolic risks are limited, this should be a promising challenge to reduce the highly contagious state around the world.

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