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EDITORIAL

ABDOMINAL OBESITY: THE TIP OF THE CARDIOMETABOLIC RISK ICEBERG!

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This issue of the **CMRe**Journal features 3 brief review papers that report on the key notions discussed during a symposium of the International Chair on Cardiometabolic Risk held in January 2009 at the XIXes Journées Européennes de la Société Française de Cardiologie annual meeting. In the first article, Dr. Paul Poirier describes how to identify the patients who have "at-risk" obesity and how to manage these patients in order to reduce the risk of future cardiovascular events. He also discusses the apparent "obesity paradox". The second short review, written by Dr. Éric Larose, deals with the patients who are at a more advanced stage of their "cardiometabolic disease", i.e., those who have developed coronary heart disease (CHD) and require percutaneous coronary intervention. The review article by Dr. Patrick Mathieu presents the important and multifaceted implications of cardiometabolic risk in the context of cardiac surgery. These brief, insightful reviews are followed by a "Special Article" written by Dr. Michael Jensen from the Mayo Clinic (Rochester, MN) that deals with what has been referred to as "normal weight obesity". Dr. Jensen makes the key point that assessment and management of patients should focus on their health, not only on their body mass index or percent body fat. Finally, we are grateful to another member of the Chair, Dr. Luis M. Ruilope from Hospital Octubre (Madrid, Spain), who generously wrote an "Original Article" on ambulatory pressure, which adds relevant information to the assessment/management of obese hypertensive patients.

Intra-abdominal (Visceral) Obesity: the "At-Risk" Obesity

Obese individuals are not all at equal risk of developing metabolic and life-threatening complications. There is a strong body of evidence supporting the concept that fat distribution and deposition in non-adipose tissues (liver, heart, muscle, pancreas) instead of subcutaneous adipose tissues is an important determinant of this inter-individual difference in the risk associated with obesity [1-3]. In the quest to identify the patients with "at-risk" obesity, several definitions and parameters have been proposed [4]: 1) Obesity defined as a body mass index $\geq$30 kg/m^2. This index is a crude marker of excess fat but does not account for the inter-individual variability in body fat distribution; 2) Ab-

dominal obesity, which refers to an increased waist circumference. The addition of this easily measurable parameter is an important step in the identification of "at-risk" obesity. However, the main limitation of this parameter is that it does not differentiate between intra- (i.e., visceral) vs. extra- (i.e., subcutaneous) abdominal fat; 3) Intra-abdominal obesity, which can be identified and quantified using imaging techniques such as computed tomography or magnetic resonance imaging and/or by the combination of increased waist circumference and specific blood metabolic abnormalities such as hypertriglyceridemia (hypertriglyceridemic waist). More recently, the term "ectopic fat" has been used in addition to intra-abdominal obesity. This term is more accurate than the latter in the sense that it refers to fat accumulation in non-adipose tissues, including viscera and muscles. Furthermore, it crystallizes the point that excess energy should normally be stored in the subcutaneous compartment and that this subcutaneous fat is rather protective. To this effect, it is important to remember that without this reserve of subcutaneous fat, human beings would probably have disappeared a long time ago. The excessive deposition of fat outside of the subcutaneous compartment is abnormal and leads to a cascade of metabolic and cardiovascular complications. Hence, subcutaneous fat constitutes a caloric reserve that may eventually be life-saving in some circumstances, whereas ectopic fat is associated with a dysmetabolism that may considerably shorten life expectancy.

The Multiple Target Organs of Intra-abdominal Obesity

Beyond the contribution of mere obesity, the crucial importance of pathophysiological processes associated with intra-abdominal adiposity/ectopic fat to the development of type 2 diabetes, atherosclerosis, and cardiovascular disease has been recognized in numerous studies and recently referred to as "cardiometabolic risk" [1-3] (Figure). Initially, most of the studies have focused on the link between abdominal or intra-abdominal obesity and the risk of CHD or stroke. When analyzed collectively, these studies suggest that the cluster of metabolic abnormalities linked to intra-abdominal obesity is associated with a 2-fold increase in the relative risk of CHD/stroke events [5]. However, the deeper the scientists dig on intra-abdominal obesity, the more metabolic abnormalities and target organs are identified (Figure). Recently, intra-abdominal obesity and associated dysmetabolism have been linked to increased risk of: 1) aortic valve disease; 2) degeneration of bioprosthetic heart valves; 3) operative mortality and atrial fibrillation following coronary artery bypass surgery; 4) adverse left ventricular remodelling and heart failure; 5) renal dysfunction; 6) sleep apnea; 7) cancer; 8) aging-related cognitive decline, etc. In summary, intra-abdominal adiposity/ectopic fat is associated with a cluster of diabetogenic and atherogenic abnormalities that, in turn, negatively affect several target organs including liver, heart, brain, kidneys, muscles, etc. (Figure). Ectopic fat deposition may also act directly on the target organs through the lipotoxicity phenomenon and/or the release of locally acting molecules. Another worrying aspect of intra-abdominal obesity is that this phenotype is not exclusively limited to the adult and elderly populations. It is also now frequently encountered in children and teenagers and is associated with early alterations of their metabolic profile. Hence, in coming decades, our healthcare system will have to face up to the catastrophic consequences of these millions of time-delayed, metabolic bombs.

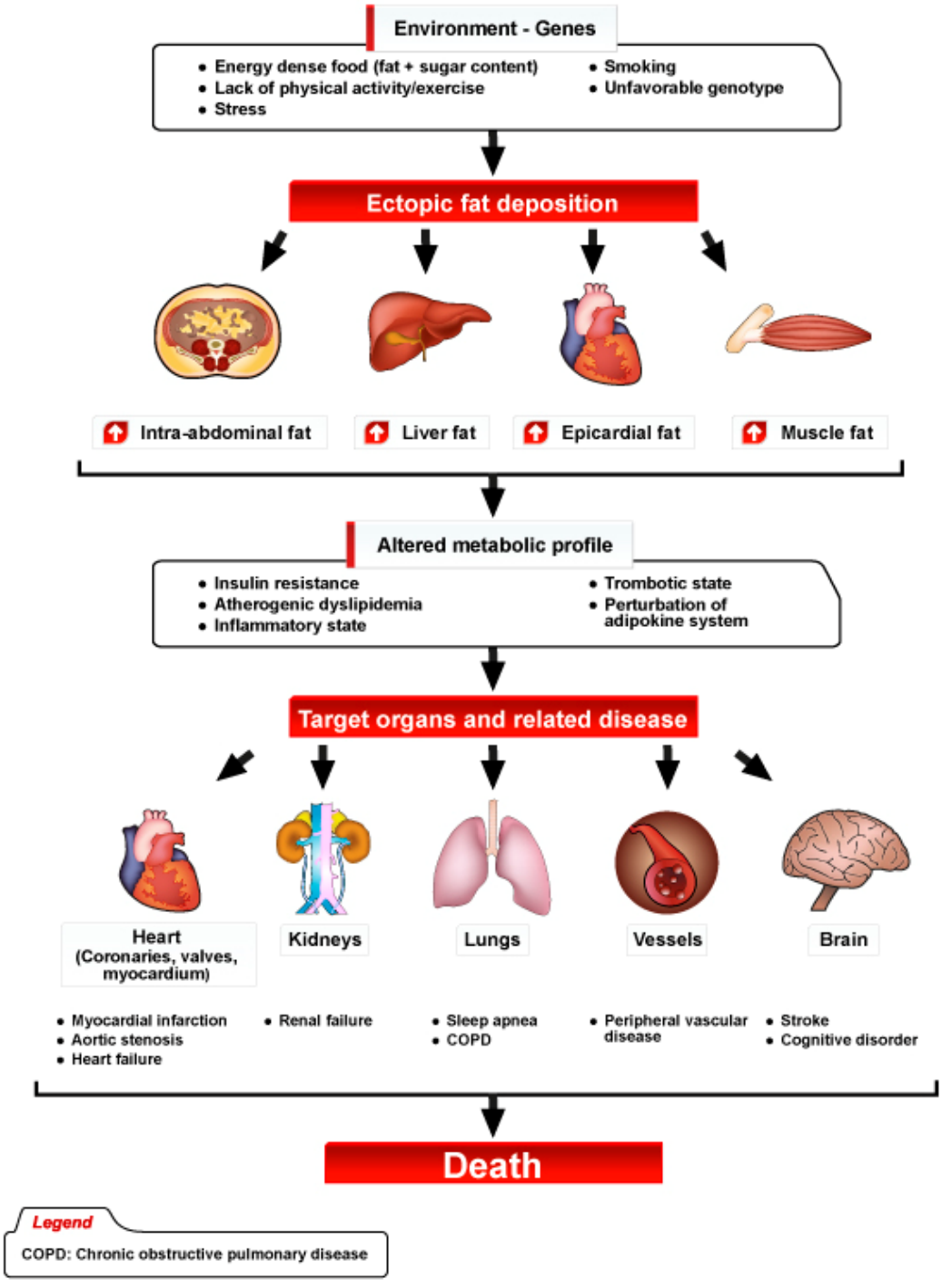

Figure: Determinants and consequences of intra-abdominal adiposity/ectopic fat.

Unanswered Questions

There are several unanswered questions that will need to be addressed in future studies:

1) What are the determinants of intra-abdominal adiposity/ectopic fat? Why, for the same positive energy balance, do some patients develop subcutaneous obesity with no or little alteration of their metabolic profile, whereas others develop the intra-abdominal obesity generally accompanied by an increased cardiometabolic risk?

2) Why do some (a few) patients with excessive intra-abdominal adiposity/ectopic fat accumulation nonetheless exhibit a normal metabolic profile? Are they genetically lucky individuals?

3) Is intra-abdominal adiposity/ectopic fat a factor actively contributing to the development of metabolic and life-threatening complications ***OR*** is it just a risk marker?

4) If we target and reduce intra-abdominal adiposity with the use of behavioural or pharmacological interventions, does this translate into significant reduction of metabolic and life-threatening complications? The presentation of such data would certainly help us to clarify the exact pathophysiological role of intra-abdominal adiposity/ectopic fat: i.e., is it a ***risk marker or a risk factor?***

Implications for Clinical Practice

Pending further studies to answer these important questions, it is urgent to implement strategies at the different levels of clinical practice to systematically identify the patients who have "at-risk" obesity, i.e., intra-abdominal adiposity/ectopic fat. This at-risk phenotype remains largely undiagnosed and untreated in current practice. One approach to detect and quantify ectopic fat would be to use computed tomography or magnetic resonance imaging, but this approach is expensive and does not apply to routine screening in general practice. As it is often the case in medicine, the simpler, the better, and in this regard waist circumference is a simple and cost-effective measure to identify abdominal obesity. The IDEA study provided convincing evidence that this measurement can successfully be used in general practice and that it provides important information for the patient's prognostication [6]. Hence, waist circumference should be systematically measured as part of the routine physical exam. The second step is to combine the measurement of waist circumference with the measurement of triglycerides to further track down the intra-abdominal (i.e., visceral) obesity phenotype. The hypertriglyceridemic waist phenotype is the clinical tool that likely offers the best compromise between accuracy, simplicity, and cost-effectiveness to identify "at-risk" obesity [7]. The algorithms of the National Cholesterol Education Program-Adult Treatment Panel III or the International Diabetes Federation can also be used but are more complex and require the measurement of more parameters [8].

Individuals with Intra-abdominal Adiposity/Ectopic Fat: Next Steps

The first line of treatment should logically focus on aggressive lifestyle changes, including improving eating habits and encouraging patients to be more active on a daily basis. In this regard, we clearly need more data on the applicability and long-term efficacy of lifestyle modification programs

in intra-abdominally obese individuals. Moreover, we can anticipate that a significant proportion of patients with intra-abdominal obesity will not respond to lifestyle modification programs and that pharmacological intervention may be required in these patients. However, to date, the pharmacotherapy targeting intra-abdominal obesity remains very limited and has significant side effects. More research and development are thus urgently needed to fill this gap in the arsenal that clinicians need to efficiently fight intra-abdominal obesity.

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References

1. Després JP and Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444: 881-7.
2. Mathieu P, Pibarot P, Larose E, et al. Visceral obesity and the heart. Int J Biochem Cell Biol 2008; 40: 821-36.
3. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006; 113: 898-918.
4. Poirier P. Adiposity and cardiovascular disease: are we using the right definition of obesity? Eur Heart J 2007; 28: 2047-8.
5. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007; 49: 403-14.
6. Balkau B, Deanfield JE, Després JP, et al. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. Circulation 2007; 116: 1942-51.
7. Lemieux I, Pascot A, Couillard C, et al. Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? Circulation 2000; 102: 179-84.
8. Grundy SM, Brewer HB, Jr., Cleeman JI, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109: 433-8.

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ABDOMINAL OBESITY: AN IMPORTANT RISK FACTOR IN CLINICAL AND INTERVENTIONAL CARDIOLOGY

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Introduction

Obesity is a complex multifactorial chronic disorder that develops from an interaction of genotype and the environment. The health hazards of obesity have been recognized for centuries. Populations in industrialized countries are becoming more overweight as a result of changes in lifestyle. Both overweight and obesity must be regarded as serious medical problems in our time since obesity is associated with reduced life expectancy. Indeed, obesity represents an independent predictor of cardiovascular disease (CVD) and this association is more pronounced in individuals under 50 years of age. This is why the American Heart Association stated ten years ago that obesity is a major modifiable risk factor for heart disease [1]. Nowadays, obesity has reached epidemic proportions in the United States as well as in much of the industrialized world and is increasing in prevalence in the developing world [2]. In the most widely used classification of body mass, body weight is expressed in terms of body mass index (BMI) [2]. In adults, obesity is defined as a BMI ≥30 kg/m^2, which is further subdivided into grades (Table 1).

Key Points

- The improvements in risk factor recognition and management that have occurred over the years in modern cardiology may be counteracted by the rising incidence of obesity.
- The presence of obesity may limit the accuracy of the physical exam. It also has the potential to affect the electrocardiogram. Moreover, transthoracic echocardiography can be technically difficult in obese patients, and obese individuals may have several limitations in the catheterization laboratory.
- The obesity paradox may reflect the failure of body mass index to adequately discriminate body fat distribution.
- From a clinical standpoint, both body mass index and waist circumference should probably be assessed and may be useful to better define "at risk" obesity.

The improvements in risk factor recognition and management that have occurred over the years in modern cardiology may be counteracted by the rising incidence of obesity [3]. Beyond an unfavourable risk factor profile, overweight/obesity also affects heart structure and function [2]. However, obesity is a remarkably heterogeneous condition, where the distribution of adipose tissue is of importance in determining the presence/absence of metabolic dysfunctions [4]. Obesity as defined by

BMI is undoubtedly associated with an increased rate of co-morbidities and cardiovascular mortality [5, 6], and obese individuals considered "at risk" are mostly characterized by features associated with abdominal obesity.

Physical Exam

The presence of obesity may limit the accuracy of the physical exam. Jugular venous pulse is often not seen, and heart sounds are usually distant. A common finding in massive obesity is pedal edema, which can occur in part as a consequence of elevated ventricular filling pressure, despite elevation in cardiac output. Obese individuals can also have increased demand for ventilation and breathing workload, especially in the supine position. Accurate blood pressure measurement is crucial since many obese patients are hypertensive. A small cuff size can cause considerable increases in blood pressure. This could incorrectly classify up to 35% of normotensive obese individuals as hypertensive. One should always evaluate the presence of cor pulmonale when examining an obese individual. In obese patients, the split S2, when either inaudible or very poorly defined in the second interspace, is often best heard at the first left interspace. Therefore, an increase in the intensity of P2, suggestive of pulmonary hypertension, may be missed at the bedside.

	BMI
Underweight	<18.5 kg/m²
Normal or acceptable weight	18.5-24.9 kg/m²
Overweight	25-29.9 kg/m²
Obese	≥30 kg/m²
Grade 1	30-34.9 kg/m²
Grade 2	35.0-39.9 kg/m²
Grade 3	≥40 kg/m² (severe, extreme or morbid obesity)
Grade 4	≥50 kg/m²
Grade 5	≥60 kg/m²
Abdominal obesity in Caucasians	Waist girth
Men	≥94 cm
Women	≥80 cm

Table 1: Classification of body weight according to body mass index (BMI) and waist circumference in adults.

Surface Electrocardiogram (ECG)

Obesity has the potential to affect the ECG in several ways: 1) displacement of the heart by elevating the diaphragm in the supine position, 2) increasing the cardiac workload and 3) increasing the distance between the heart and the recording electrodes. The voltage of the QRS complexes is attenuated by its passage through a fat-laden chest wall and is related to several factors, including the anatomy of the thorax, the degree of fatty infiltration of the heart, the degree of associated chronic lung disease, the increase in left ventricular muscle mass and, most importantly, the selection of the electrocardiographic leads for measuring voltage. Overall, the effect of weight loss in obese patients on the QRS voltage is a source of controversy in the literature; studies report a decrease, no change or an increase in the QRS amplitude after weight reduction. Heart rate, PR interval, QRS interval, QRS voltage and QTc interval all showed an increase with increasing obesity. An increased incidence of false-positive criteria for inferior myocardial infarction was reported in both obese indi-

viduals and in women in the final trimester of pregnancy, presumably because of diaphragmatic elevation (Table 2).

Echocardiography

Transthoracic echocardiography can be technically difficult in obese patients, and obtaining a good echocardiographic window is often difficult. This is of importance when evaluating the presence of left ventricular diastolic dysfunction. Pulmonary venous Doppler evaluation may be used but if it is not technically feasible, transmitral Doppler imaging with the use of the Valsalva maneuver may properly evaluate the presence of left ventricular diastolic dysfunction. Another feature of the echocardiographic assessment in obese patients is the differentiation between subepicardial adipose tissue and pericardial effusion, which can at times be difficult. Epicardial adipose tissue is known to be a common cause of pseudopericardial effusion, and this adipose tissue depot may cause an underestimation of the amount of pericardial fluid. Another issue is the presence of fat within the heart. Fat can accumulate in a variety of places, but the site of predilection tends to be the interatrial septum. Lipomatous hypertrophy of the interatrial septum should be suspected in the presence of a dumbbell-shaped appearance of the septum, with thick echogenic tissue surrounding a thin echo at the level of the fossa ovalis. Also, accumulation of fat may simulate a mass. Several heart functions can be unmasked with an echocardiogram (Table 3).

Clinically significant	
↑ Heart rate	↑ QT_c interval
↑ QRS interval	False positive criteria for inferior myocardial infarction
Less clinically signifiant	
↑ PR interval	ST depression
↑ or ↓ QRS voltage	Left axis deviation
↑ QT dispersion	Flattening of the T wave (inferolateral leads)
↑ Signal-averaged ECG (late potentials)	Left atrial abnormalities
ST-T abnormalities	

Table 2: Electrocardiogram (ECG) changes that may occur in obese individuals.

- Left ventricular diastolic dysfunction
- Left ventricular hypertrophy:
  - Eccentric, Concentric
- Right ventricular hypertrophy
- Altered left ventricular systolic function
- Altered right ventricular systolic function
- Pulmonary hypertension
- Adipositas cordis (cardiomyopathy of obesity)

Table 3: Functional and structural changes that may occur in obese individuals.

Cardiac Catheterization

Obese individuals may have several limitations in the catheterization laboratory. The catheterization laboratory table usually does not accommodate subjects weighing more than 160 kg. Moreover, vascular access to the femoral vein and artery may be difficult. The percutaneous radial approach has advantages in the very obese patient, for whom the percutaneous femoral technique may be technically difficult and bleeding hard to control after catheter removal. Indeed, the frequency of complications using the percutaneous radial technique is very low and should be contemplated when the evaluation of extremely obese individuals is necessary in the catheterization laboratory.

Assessment of Obesity by the Cardiologist

It appears that obesity as defined solely by BMI cannot always discriminate between the individuals at higher risk of developing CVD. Non-obese overweight patients with excess intra-abdominal (visceral) adiposity (i.e., patients therefore at higher risk) may not be detected on the basis of BMI alone [7]. For these reasons, measurement of waist circumference and a set of metabolic markers has been proposed to detect obese individuals at a higher CVD risk [5, 8]. Waist or waist-to-hip ratio (WHR) has been used as a proxy measure for body fat distribution. Abdominal obesity has been reported as a risk factor for CVD worldwide and is likely to better refine clinical assessment of obesity risk [7, 9, 10].

Coronary Artery Disease

Atherosclerosis begins in childhood (5-10 years) and is demonstrated predominantly as fatty streaks. Examination of arteries post-mortem from young individuals (15 to 34 years of age) in the Determinants of Atherosclerosis in Youth (PDAY) study who died from accidental injuries, homicides or suicides revealed that the extent of fatty streaks and even advanced lesions (fibrous plaques and plaques with calcification or ulceration) in the right coronary artery and abdominal aorta were associated with obesity and size of the abdominal panniculus [11]. In adults, it has been shown that 1) maximal density of macrophages/mm^2 in atherosclerotic lesions is associated with intra-abdominal obesity [12], 2) reduced coronary flow reserve is related to body fat distribution and insulin resistance [13], 3) the metabolic syndrome is associated with lipid-rich plaque [14], 4) coronary artery calcium and abdominal aortic calcium is associated with intra-abdominal adipose tissue [15]. Prospective evidence shows that abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men independently of overall obesity and other risk factors [16]. Also, the components of the insulin resistance syndrome have been reported, following coronary artery bypass graft, to be associated with angiographic progression of atherosclerosis in non-grafted coronary arteries [17].

The Obesity Paradox

Despite the fact that obesity has been shown to be an independent risk factor for CVD, many studies have reported that obese patients with established CVD have a better prognosis than do patients with ideal body weight: this is the so-called "obesity paradox". This paradox has been best described for patients with advanced systolic heart failure [2] and patients with coronary artery disease [18]. The

improved survival of obese individuals is paradoxical principally because of the assumption that excessive weight is always and invariably harmful. As a matter of fact, among patients with congestive heart failure, subjects with higher BMI are at decreased risk for death and hospitalization compared with patients with a "healthy" BMI [2]. Also, obesity was associated, in a prospective cohort study, with lower all-cause and cardiovascular mortality after unstable angina/non-ST-segment elevation myocardial infarction treated with early revascularization [19].

The obesity paradox may reflect the failure of BMI to adequately discriminate body fat distribution [7, 20, 21]. Since BMI measures total body mass, i.e., both fat and lean mass, it may better represent the protective effect of lean body mass on mortality. This negative confounding may have been underappreciated in prior studies that did not adjust for measures of abdominal obesity. It is possible that the favourable prognosis implications associated with mildly elevated BMI might actually reflect the intrinsic limitations of BMI in differentiating adipose tissue from lean mass. BMI's lack of specificity could dilute the adverse effects of excess fat with the beneficial effects of preserved or increased lean mass [22]. As an example, in patients with known CVD or following acute myocardial infarction, overall obesity as assessed by BMI was not associated with myocardial infarction, cardiovascular mortality and total mortality when abdominal obesity (WHR, waist circumference) was integrated into the analysis [9, 23, 24]. Another limitation in most studies reporting an obesity paradox in patients with CVD is that non-intentional weight loss, which would be associated with a poor prognosis, is not assessed, as BMI is measured only at the beginning of the study. Patients who have decompensated heart failure may lose weight because of extensive caloric demands associated with the increased work of breathing, and patients who show poor nutrients absorption by the edematous bowel may be at higher risk of recurrent CVD events.

Despite the high correlation between waist circumference and BMI, the combination of both indices may be very relevant in clinical practice because waist circumference for a given BMI is a strong predictor of all-cause mortality. Studies reporting negative results between all-cause mortality and waist circumference did not mutually adjust for waist circumference and BMI, a possible explanation for the inconsistent results [25, 26]. Another example is that the excess health risk associated with a higher BMI declines with increasing age. An explanation for the lack of a positive association between BMI and mortality at older ages is that, in older persons, higher BMI is a poor measure of body fat and may simply represent a measure of increased physical activity with preserved lean mass. Sarcopenic obesity, which is defined as excess fat with loss of lean body mass, is a highly prevalent problem in older individuals. In fact, the ideal BMI may be higher in older adults than in middle-aged adults. It was recently reported in ~4,000 persons aged ≥75 years that WHR rather than waist circumference predicted mortality in non-smoking men and women, mainly because of the association with cardiovascular deaths [27]. In the Health Professionals Study, in men aged 65 years, waist circumference and WHR were significantly related to CVD mortality [25]. It was found in the Cardiovascular Health Study in over 5,000 patients aged ≥65 years with a mean BMI of 26.3 kg/m^2 (42% overweight) that higher BMI values indicated a lower mortality risk once the risk attributable to waist circumference was accounted for, whereas waist circumference values indicated a higher mortality risk once the risk attributable to BMI was accounted for [28]. Death rates were highest in individuals with a high waist circumference within the overweight and obese BMI categories. Fi-

nally, in a large case-control study, WHR was found to be more strongly associated than BMI with myocardial infarction, whereas the association with BMI was weak and intermediate for waist circumference in older patients [29]. In order to discriminate low-risk vs. high-risk subjects, WHR could be more useful. Further studies are needed to clarify the concept of the obesity paradox in patients with known CVD.

Assessment of Adiposity in Clinical Practice

The introduction of waist circumference as a simple risk measure in public health settings has already begun, but debate regarding the simplification of the measure is ongoing. Thresholds for waist circumference to identify individuals with excess cardiovascular risk have been suggested, but the choice of waist circumference thresholds should be based on outcomes of importance, such as all-cause mortality or myocardial infarction. It seems from the data available that there is no basis for choosing thresholds because the mortality rate ratio increased steadily with waist circumference. Nevertheless, there may be a difference between different ethnic groups [29]. From a clinical standpoint, both indices should probably be assessed and may be useful to better define "at risk" obesity [11, 30, 31]. It was observed in the IDEA (International Day for the Evaluation of Abdominal obesity) study, which included 157,211 patients, that both waist circumference and BMI were independently associated with the presence of CVD in both men and women [32]. Nevertheless, with all the knowledge available in the literature regarding obesity and CVD, assessment and management of obesity following acute coronary syndrome is simply inadequate [33].

Conclusion

Without a doubt, obesity is a risk factor for CVD. There are numerous clinical indices to evaluate obesity (BMI, waist circumference, WHR). Accurate diagnosis of obesity may lead to more refined assessment of body fat composition/distribution. Over the years, studies have helped refine indices associated with CVD. For example, total cholesterol has been replaced by LDL and HDL cholesterol to better evaluate the patient's risk of CVD. Today, we are no longer using total weight to assess the presence of obesity. Although BMI has been useful in epidemiological studies in order to assess the presence of obesity, it fails to differentiate between differing body compositions. BMI does not characterize excess centrally distributed obesity, which is more consistently associated with adverse effects on metabolism, dyslipidemia and insulin resistance. BMI also can be falsely increased in the presence of increased lean body mass (such as in trained athletes), and low BMI values are associated with chronic conditions leading to loss of lean body mass. Thus, other clinical indices of adiposity such as waist circumference and WHR should be incorporated into the cardiologist's clinical approach in order to better target and manage "at risk" obesity.

References

1. Eckel RH and Krauss RM. American Heart Association call to action: obesity as a major risk factor for coronary heart disease. AHA Nutrition Committee. Circulation 1998; 97: 2099-100.
2. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006; 113: 898-918.

3. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med 2005; 352: 1138-45.
4. Després JP and Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444: 881-7.
5. Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415-28.
6. Poirier P and Després JP. Waist circumference, visceral obesity, and cardiovascular risk. J Cardiopulm Rehabil 2003; 23: 161-9.
7. Poirier P. Adiposity and cardiovascular disease: are we using the right definition of obesity? Eur Heart J 2007; 28: 2047-8.
8. Després JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008; 28: 1039-49.
9. Poirier P. Recurrent cardiovascular events in contemporary cardiology: obesity patients should not rest in PEACE. Eur Heart J 2006; 27: 1390-1.
10. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937-52.
11. Zieske AW, Malcom GT and Strong JP. Natural history and risk factors of atherosclerosis in children and youth: the PDAY study. Pediatr Pathol Mol Med 2002; 21: 213-37.
12. Kortelainen ML and Sarkioja T. Visceral fat and coronary pathology in male adolescents. Int J Obes Relat Metab Disord 2001; 25: 228-32.
13. Kondo I, Mizushige K, Hirao K, et al. Ultrasonographic assessment of coronary flow reserve and abdominal fat in obesity. Ultrasound Med Biol 2001; 27: 1199-205.
14. Amano T, Matsubara T, Uetani T, et al. Impact of metabolic syndrome on tissue characteristics of angiographically mild to moderate coronary lesions integrated backscatter intravascular ultrasound study. J Am Coll Cardiol 2007; 49: 1149-56.
15. Rosito GA, Massaro JM, Hoffmann U, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. Circulation 2008; 117: 605-13.
16. Lakka TA, Lakka HM, Salonen R, et al. Abdominal obesity is associated with accelerated progression of carotid atherosclerosis in men. Atherosclerosis 2001; 154: 497-504.
17. Korpilahti K, Syvanne M, Engblom E, et al. Components of the insulin resistance syndrome are associated with progression of atherosclerosis in non-grafted arteries 5 years after coronary artery bypass surgery. Eur Heart J 1998; 19: 711-9.
18. Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. Am J Med 2007; 120: 863-70.
19. Buettner HJ, Mueller C, Gick M, et al. The impact of obesity on mortality in UA/non-ST-segment elevation myocardial infarction. Eur Heart J 2007; 28: 1694-701.
20. Romero-Corral A, Lopez-Jimenez F, Sierra-Johnson J, et al. Differentiating between body fat and lean mass-how should we measure obesity? Nat Clin Pract Endocrinol Metab 2008; 4: 322-3.
21. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006; 368: 666-78.
22. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Diagnostic performance of body mass index to detect obesity in patients with coronary artery disease. Eur Heart J 2007; 28: 2087-93.
23. Dagenais GR, Yi Q, Mann JF, et al. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J 2005; 149: 54-60.
24. Kragelund C, Hassager C, Hildebrandt P, et al. Impact of obesity on long-term prognosis following acute myocardial infarction. Int J Cardiol 2005; 98: 123-31.
25. Baik I, Ascherio A, Rimm EB, et al. Adiposity and mortality in men. Am J Epidemiol 2000; 152: 264-71.

26. Visscher TL, Seidell JC, Molarius A, et al. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. Int J Obes Relat Metab Disord 2001; 25: 1730-5.
27. Price GM, Uauy R, Breeze E, et al. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. Am J Clin Nutr 2006; 84: 449-60.
28. Janssen I, Katzmarzyk PT and Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. J Am Geriatr Soc 2005; 53: 2112-8.
29. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005; 366: 1640-9.
30. Poirier P. Healthy lifestyle: even if you are doing everything right, extra weight carries an excess risk of acute coronary events. Circulation 2008; 117: 3057-9.
31. Poirier P. Targeting abdominal obesity in cardiology: can we be effective? Can J Cardiol 2008; 24 Suppl D: 13D-7D.
32. Balkau B, Deanfield JE, Després JP, et al. International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. Circulation 2007; 116: 1942-51.
33. Lopez-Jimenez F, Malinski M, Gutt M, et al. Recognition, diagnosis and management of obesity after myocardial infarction. Int J Obes (Lond) 2005; 29: 137-41.

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ABDOMINAL OBESITY: IMPLICATIONS FOR THE INTERVENTIONAL CARDIOLOGIST

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The Typical Catheterization Laboratory Patient is Changing

Traditionally, patients admitted to the catheterization laboratory have displayed typical risk factors for atherosclerosis, including advancing age, smoking, diabetes, dyslipidemia, hypertension or a family history of premature coronary artery disease. The contemporary interventionalist is confronted by a growing population of patients with only 1 or even no traditional risk factors, corresponding to a moderate or low probability of coronary artery disease based on traditional risk scores. Over two-thirds of younger adults presenting with acute myocardial infarction would not be considered high risk for coronary events if assessed using the National Cholesterol Education Program-Adult Treatment Panel III criteria [1]. In the recent EASY trial of over 1,000 all-comer patients undergoing coronary angioplasty, waist circumference was greatly increased to a mean 99 ± 5 cm despite a mean body mass index of 28 ± 5 kg/m^2, indicating overweight but not obesity. This "abdominally obese" population of a mean age of 60 years had relatively low incidences of traditional risk factors, including 30% smoking, 50% hypertension and 15% diabetes.

Key Points

- Traditional risk factors do not explain the full spectrum of risk in patients assessed in the catheterization laboratory.
- Atherosclerosis risk is related to underlying biology and not merely to luminal stenosis severity.
- Ectopic adipose tissue may partly explain the atherosclerosis risk observed in catheterization laboratory patients who do not have traditional risk factors.

Back To Basics: At-Risk Atherosclerosis

Atherosclerosis biology, more than stenosis severity, determines risk for coronary events, including unstable angina, myocardial infarction and sudden coronary death. While angioplasty in myocardial infarction reduces events, the interventionalist must face the harsh reality that angioplasty in stable coronary artery disease reduces angina symptoms but does not prevent acute coronary syndrome. The plaque at risk for thrombotic events has typical features, including a lipid-rich necrotic core, thin fibrous cap, active inflammation and at times an overhanging thrombus. Imaging methods based

on magnetic resonance imaging, ultrasound backscatter, optical coherence tomography, computed tomography and thermography have shown promise in better identifying at-risk biology and potentially broadening therapies based on atherosclerosis risk beyond atherosclerosis morphology (Figure) [2].

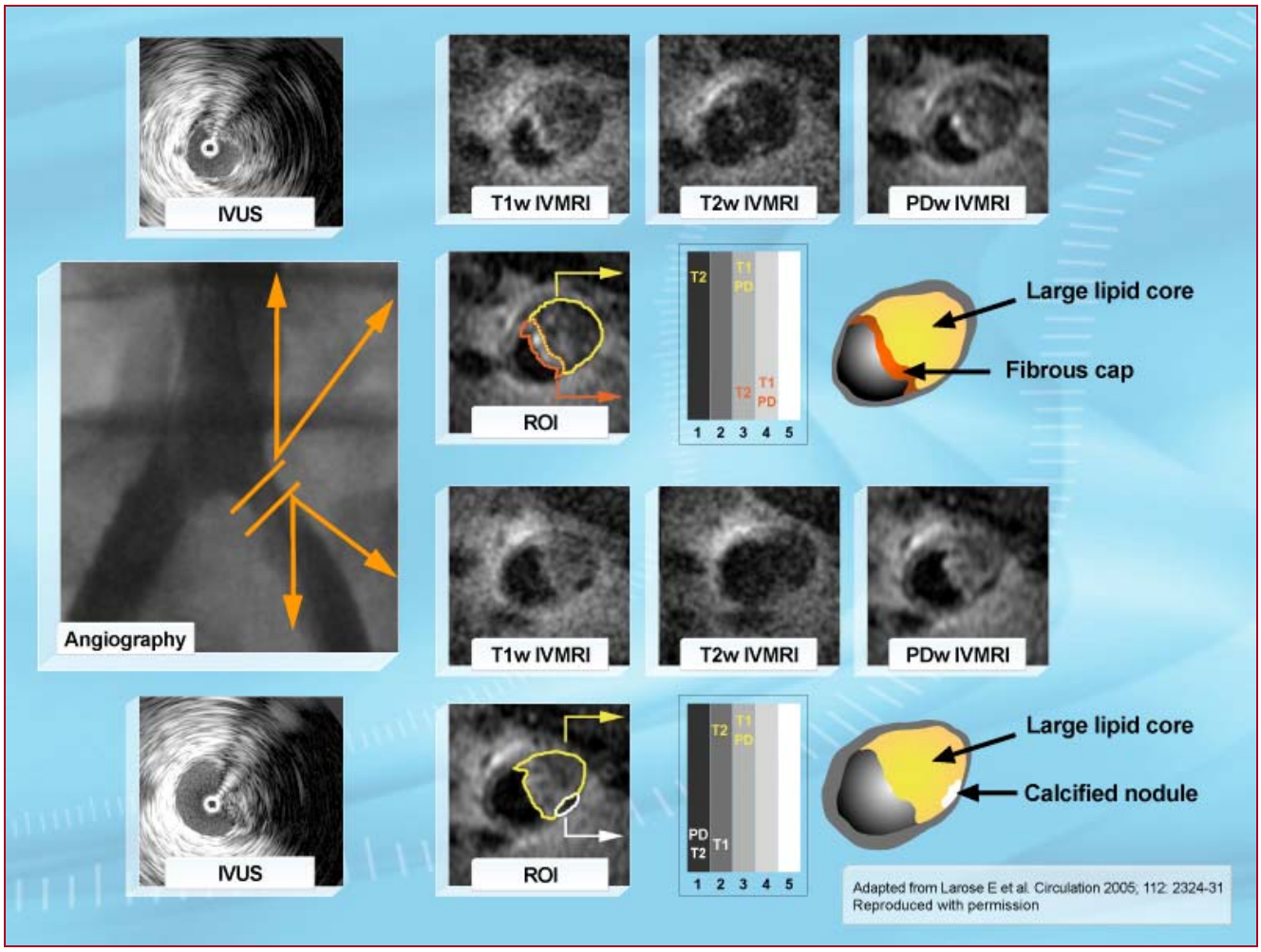

Figure: *Intravascular magnetic resonance imaging (IVMRI) of common iliac artery in vivo. Angiogram (left) of a common iliac artery and corresponding intravascular ultrasound (IVUS) and IVMRI images of the iliac artery at its origin (top half) and 6 mm distal to the bifurcation (bottom half). In both segments, the artery is characterized by angiographic narrowing and IVUS that images the outside edges of the artery and plaque incompletely, whereas the corresponding IVMRI depicts the entire plaque morphology. The validated approach to tissue characterization ex vivo applied to this in vivo study demonstrates a predominantly lipid core with overlying fibrous cap at the origin of the iliac artery (top half) and a large lipid core with a calcium nodule in the more distal segment (bottom half).*

Ectopic Adipose Tissue and Atherosclerosis

Increased intra-abdominal (visceral) adipose tissue is related to an increase in atherosclerosis risk factors. Coronary events also rise as intra-abdominal adipose tissue increases. A similar relationship to risk factors and atherosclerosis has been suggested with visceral adipose tissue on the surface of the heart. A lifestyle modification program that included increased physical activity/exercise and healthy eating habits (SYNERGIE trial) was found to generate significant reductions in ectopic intra-abdominal adipose tissue. The interventional cardiologist must remember that beyond traditional risk factor management, novel metabolic risk factors respond to lifestyle modifications. Patient motivation and adherence to a healthy lifestyle may be greatly improved by appropriate counselling from the interventional cardiologist when the patient is "all ears" following coronary angioplasty.

The typical patient treated in the interventional cardiology laboratory is changing. Focus is shifting towards therapy of atherosclerosis beyond mere stenosis, and the contribution of metabolic risk factors in addition to traditional risk factors is recognized. The role of the interventional cardiologist in targeting the appropriate patients for lifestyle modification cannot be overstated.

References

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.
2. Larose E, Yeghiazarians Y, Libby P, et al. Characterization of human atherosclerotic plaques by intravascular magnetic resonance imaging. Circulation 2005; 112: 2324-31.

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THE IMPACT OF INTRA-ABDOMINAL OBESITY IN CARDIAC SURGERY

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During the 17th century, in the midst of the Elizabethan Era, Sir Walter Raleigh brought tobacco from the New World to England. This marked the start of a new habit: smoking. Unfortunately, this new habit also proved to be a new health risk factor with devastating consequences. Quite later, during the second half of the 20th century, major social changes following the industrial revolution led to the introduction of commercially prepared, highly processed food in the New World, and this new way of life, now sometimes referred to as 'coca-colonization', spread at a startling speed throughout the world [1]. So, while smoking has decreased considerably in numerous developed countries, largely because of national health care policies, obesity has gained ground and is now considered by many authorities to be a major health care problem. As a result, obesity-associated conditions such as diabetes have reached gigantic proportions on a worldwide scale. In light of the research conducted during the last decade or so, it is important to stress from the outset that obesity is a very heterogeneous condition in which body fat distribution largely determines metabolic features [2]. In this regard, intra-abdominal (visceral) obesity has been consistently associated with glucose intolerance, low HDL, hypertriglyceridemia, and hypertension [3]. Intra-abdominal obesity, the most common form of the metabolic syndrome, has been linked to an atherogenic dyslipidemia and thereby to a high risk of coronary artery disease (CAD) [4]. Of special interest is the fact that the metabolic syndrome has recently been shown to be a composite modifiable cardiovascular

Key Points

- The metabolic syndrome is associated with aortic valve calcification and a faster aortic stenosis progression rate.
- Among the different features of the metabolic syndrome, a high proportion of small, dense LDL in blood plasma is associated with aortic valve inflammation along with a clinically faster progression rate.
- Following an aortic valve replacement, the metabolic syndrome increases the risk of bioprostheses structural degeneration.
- The metabolic syndrome is a risk factor in cardiac surgery increasing substantially the risk of postoperative death.
- In middle-aged patients, the metabolic syndrome increases the risk of postoperative atrial fibrillation, a common arrhythmia following coronary artery bypass surgery.

risk factor, which goes far beyond the so-called traditional risk factors [5]. As a matter of fact, it now appears that the metabolic syndrome is a strong risk factor for the development of aortic valve calcification and the progression rate of aortic stenosis (AS) [6]. AS, long thought of as a passive 'degenerative' disorder, is now considered a highly regulated process akin to atherosclerosis [7]. Studies in the last decade have conclusively shown that AS valves are infiltrated with oxidized-LDL and inflammatory cells, whereby the calcification is triggered and perpetuated. *In vitro* studies with aortic valvular interstitial cells have indicated that, when grown in appropriate conditions, interstitial cells may change their phenotype toward bone-like cells [8]. Since AS is an active and cellular process that shares some similarities with atherosclerosis, specifically the histological picture and risk factors, statins were seen as a way to treat AS in order to stop or lower the hemodynamic progression rate. However, this conception has been questioned recently with the publication of the first two randomized studies with statins in AS [9, 10]. In the two trials, despite a dramatic reduction of LDL cholesterol of at least 50%, aortic valve calcification as well as the hemodynamic progression rate remained unaffected by the lipid-lowering strategy. Recently, our group has demonstrated that among different clinical risk factors, the metabolic syndrome is a strong and independent risk factor for AS progression (Figure 1). More recently, a study has demonstrated that the small, dense LDL phenotype associated with intra-abdominal obesity is associated with aortic valve accumulation of oxidized-LDL and, perhaps more importantly, with the progression rate of AS [11]. This study has contributed, at least in part, to explain the inefficacy of statins in AS. It should be emphasized that the small, dense LDL phenotype is often associated with a near-normal or normal LDL level, and that statins have at best only a modest effect on the proportion of small, dense LDL in circulation.

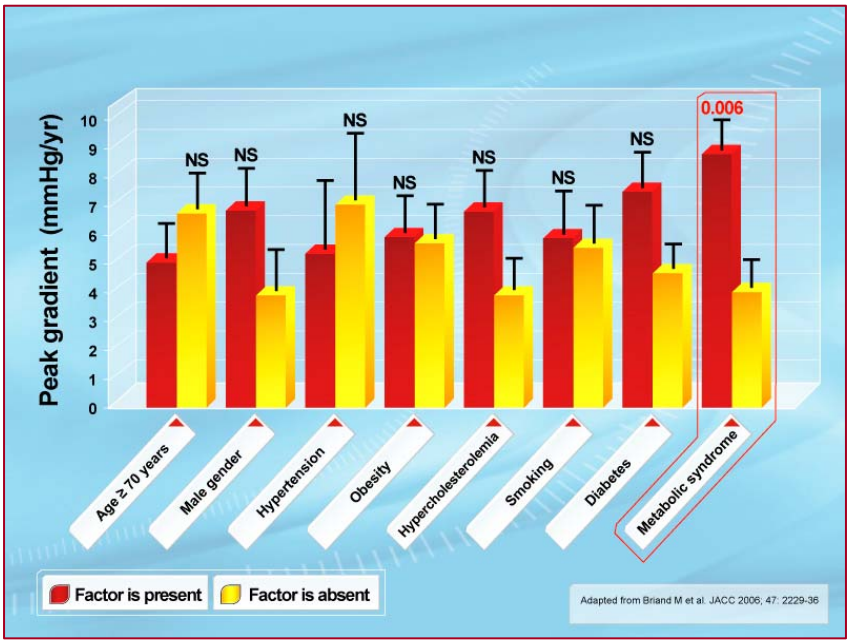

Figure 1: The metabolic syndrome is a risk factor for the progression rate of calcific aortic stenosis.

Thus, it is quite likely that the metabolic perturbations associated with intra-abdominal obesity, such as the high proportion of small, dense LDL, determine valve accumulation of oxidized lipids and thereby influence the mineralization process as well as the clinical activity of this disorder.

In the absence of effective medical treatments and possibly owing to the epidemic proportions obesity has reached, there has been a recent increase in the prevalence of severe AS and a considerable

influx of patients to surgery to replace these end-stage diseased valves. Globally, about half of these aortic valve replacements are done with bioprostheses, made either of porcine or bovine tissues. Although biosprosthetic valves have numerous advantages, their 'Achilles heel' is their propensity to calcify and become dysfunctional. While for many years this degenerative process was thought to be related to pre-implant fixation technique, recent investigations suggest that metabolic risk factors could also be involved. For instance, among different factors, the metabolic syndrome has been associated with early hemodynamic dysfunction of bioprostheses [12]. It is suspected that there are numerous mechanisms underpinning bioprosthesis dysfunction, including the possibility that some metabolic features of intra-abdominal obesity contribute to the inflammation of bioprostheses and matrix degradation.

Though medical treatment and percutaneous interventions have played a large role in the treatment of CAD, many patients still undergo coronary artery bypass grafting surgery (CABG). Considering the prevalence of CAD in our modern society and the changing mosaic of risk factors, it is of particular interest to document whether the metabolic syndrome may impact surgical outcomes. In this regard, we recently identified in a cohort of 5,304 men and women undergoing CABG that the metabolic syndrome was independently associated with a three-fold increased rate of perioperative mortality (Figure 2) [13]. Equally important, postoperative atrial fibrillation, a common complication after CABG and one suspected to have an inflammatory component as one of the triggers, has recently been linked to the metabolic syndrome [14]. The metabolic syndrome has also been identified as a risk factor for atrial fibrillation in the general population. Hence, although the mechanisms underlying the association of arrhythmic complications with intra-abdominal obesity have not yet been delineated, it is suspected that an exaggerated inflammatory response may partly explain this association. Thus, further studies in the years to come may hopefully shed some light on these issues.

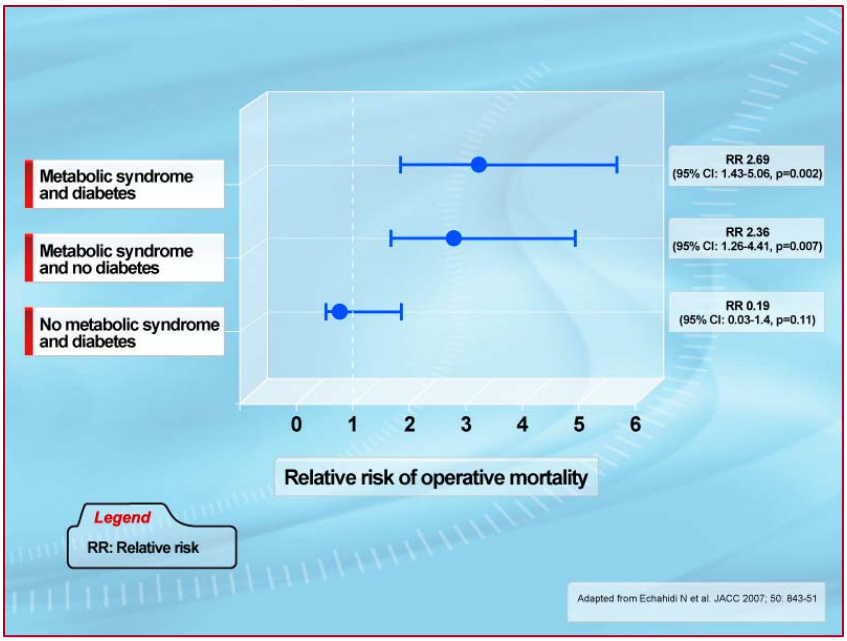

Figure 2: Interaction of the metabolic syndrome and diabetes with regard to operative mortality following coronary artery bypass grafting.

While considerable interest has been devoted to the mechanism by which excess intra-abdominal fat contributes to metabolic perturbations and increased cardiovascular risk, it is only recently that attention has been paid to the mechanisms controlling the distribution of excess energy in different fat

depots. It is now apparent that the biology of adipocytes is quite complex and that adipose tissue acts as an endocrine organ having intricate links with the metabolism, the brain, and the cardiovascular system. It has been elegantly shown that among other mechanisms, leptin, an adipokine with many functions, plays a crucial role in the partition of lipids and prevents ectopic fat accumulation [15]. According to the lipotoxic theory, accumulation of fat in organs, for which it is not the primary function, may contribute to cellular injury through the production of ceramides. New imaging technologies, such as magnetic resonance imaging, as well as direct surgical observation of excessive epicardial fat accumulation have resurrected an old observation in the realm of modern scientific inquiry. In the 18th century, physicians had already observed the 'fatty heart' at autopsy and had suspected a possible link between this condition and sudden death. More recently, magnetic resonance imaging studies have shown positive relationships between epicardial fat accumulation, intra-abdominal obesity, and a decreased regional systolic shortening of the myocardium [16]. Considering the common embryologic origin of epicardial and intra-abdominal fat, it is likely that epicardial fat is pro-inflammatory. It then follows that owing to the production of cytokines, epicardial fat may have an impact on the development of atherosclerosis. It should be pointed out that contrary to epicardial coronary arteries, intra-myocardial arteries are often in pristine condition without any sign of atherosclerosis. This latter observation may then lend weight to the role of epicardial fat, which is intimately related to epicardial arteries, as a potential contributor to atherosclerosis and/or plaque biological activity. Though the role of epicardial fat in cardiovascular pathologies is still ill-defined, it should be acknowledged that it deserves attention and further mechanistic studies, given its potential impact.

In light of the above discussion, excessive accumulation of ectopic/intra-abdominal fat appears to be a significant cardiovascular risk factor. Studies have therefore brought heart valve diseases, arrhythmia, and operative risk into the realm of cardiometabolic risk. With the identification of intra-abdominal obesity's huge impact on cardiovascular risk, and considering the epidemic proportions of obesity, a concerted effort from the scientific community and health care agencies is of paramount importance. Indeed, primary and secondary prevention, as well as identifying key molecular targets of the multi-faceted manifestations of intra-abdominal obesity on cardiovascular pathology, will be necessary to stave off the devastating consequences of our modern lifestyle.

References

1. Zimmet P. Globalization, coca-colonization and the chronic disease epidemic: can the Doomsday scenario be averted? J Intern Med 2000; 247: 301-10.
2. Mathieu P, Poirier P, Pibarot P, et al. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension 2009; 53: 577-84.
3. Després JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol 2008; 28: 1039-49.
4. Després JP, Lamarche B, Mauriège P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med 1996; 334: 952-7.
5. Mathieu P, Pibarot P, Larose E, et al. Visceral obesity and the heart. Int J Biochem Cell Biol 2008; 40: 821-36.
6. Briand M, Lemieux I, Dumesnil JG, et al. Metabolic syndrome negatively influences disease progression and prognosis in aortic stenosis. J Am Coll Cardiol 2006; 47: 2229-36.

7. Pibarot P, Dumesnil JG and Mathieu P. [New insight into the treatment of aortic stenosis]. Med Sci (Paris) 2007; 23: 81-7.
8. Mathieu P, Voisine P, Pépin A, et al. Calcification of human valve interstitial cells is dependent on alkaline phosphatase activity. J Heart Valve Dis 2005; 14: 353-7.
9. Cowell SJ, Newby DE, Prescott RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005; 352: 2389-97.
10. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008; 359: 1343-56.
11. Mohty D, Pibarot P, Després JP, et al. Association between plasma LDL particle size, valvular accumulation of oxidized LDL, and inflammation in patients with aortic stenosis. Arterioscler Thromb Vasc Biol 2008; 28: 187-93.
12. Briand M, Pibarot P, Després JP, et al. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. Circulation 2006; 114: I512-7.
13. Echahidi N, Pibarot P, Després JP, et al. Metabolic syndrome increases operative mortality in patients undergoing coronary artery bypass grafting surgery. J Am Coll Cardiol 2007; 50: 843-51.
14. Echahidi N, Mohty D, Pibarot P, et al. Obesity and metabolic syndrome are independent risk factors for atrial fibrillation after coronary artery bypass graft surgery. Circulation 2007; 116: I213-9.
15. Unger RH. Longevity, lipotoxicity and leptin: the adipocyte defense against feasting and famine. Biochimie 2005; 87: 57-64.
16. McGavock JM, Victor RG, Unger RH, et al. Adiposity of the heart, revisited. Ann Intern Med 2006; 144: 517-24.

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SPECIAL ARTICLE

NORMAL WEIGHT OBESITY

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Background

A recent publication on the topic of normal weight obesity [1] has received media attention. The investigators used the National Health and Nutrition Examination Survey database, containing information on body mass index (BMI), percent body fat and metabolic problems related to obesity from over 13,000 adults age 20-80. Using the traditional BMI cutoff values of ≤25 kg/m^2 for normal weight, 25-29.9 kg/m^2 for overweight and >30 kg/m^2 for obesity, they assessed the prevalence of "obesity" in each category. The World Health Organization (WHO)-recommended definition for obesity is 25% body fat in men and 35% body fat in women. The authors concluded that the current BMI criteria miss over half the people who would be categorized as "obese" using WHO criteria, especially in older adults.

Key Points

- There is a big difference between "metabolically obese, normal weight" as proposed by Ruderman et al. [2, 3] and "normal weight obesity". The former defines a group that may benefit from changes in eating (and activity) habits whereas the latter is an epidemiological construct with little physiological basis and limited clinical utility.
- Individuals with low amount of body fat may sometimes benefit from treatments traditionally provided to obese patients, and some patients who meet body mass index criteria for obesity will not see health benefits from weight loss.
- Clinicians should distinguish between the two and apply treatments as indicated by health, not by body mass index or percent body fat criteria.

I was surprised about the buzz surrounding "normal weight obesity". Many endocrinologists may have been asking "Where's the beef?" because almost 30 years ago an endocrinologist, Dr. Neil Ruderman, coined the term "metabolically obese normal weight" [2] to describe non-obese men and women with hypertriglyceridemia, type 2 diabetes or hypertension. He speculated on a number of possible explanations for this phenomenon [2], many of which have been confirmed in the following years. More recently, Dr. Ruderman and colleagues have published an update on this topic [3] providing more in-depth speculation regarding the potential mechanisms and explanations for the phenomenon of the normal weight, metabolically obese adult.

Adipose Tissue Functions

The WHO definition of obesity is based only upon percent body fat, which forces us to consider the role(s) of body fat and whether the amount that is unhealthy can be so specifically defined. Adipose tissue performs a surprising number of functions (Table 1), and although Americans tend to want to have as little body fat as possible, this is not always ideal for health. Most obviously, adipose tissue serves as a reservoir for energy. Adipose tissue is the primary means for storing circulating triglycerides during times of "feast" and making those triglycerides available to other tissues in the form of free fatty acids (FFA) at times of famine (Figure 1). Because the triglyceride fatty acids are stored in a relatively anhydrous fashion (as opposed to glucose and protein), relatively small amounts of adipose tissue store large amounts of energy. One kg of adipose stores ~7000 kcal, enough to provide the complete energy needs of an average woman for 3 days. Thus, a normal weight 60 kg woman with 30% body fat (18 kg) has the equivalent of 2 months of energy stored in adipose tissue! This is akin to carrying around 2 months' worth of groceries in a normal, healthy amount of body fat.

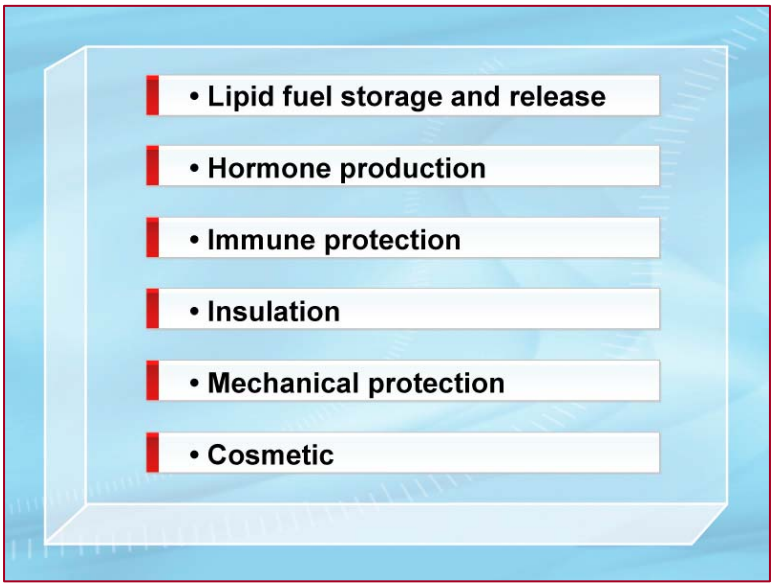

Table 1: Functions of adipose tissue.

Endocrinologists would likely argue that the endocrine functions of adipose tissue are of second-most importance—leptin and adiponectin being perhaps the two most well-known hormones produced almost solely by adipose tissue. Adipose tissue also produces a number of other cytokines/peptides (Table 2), but it is difficult to know the relative contributions

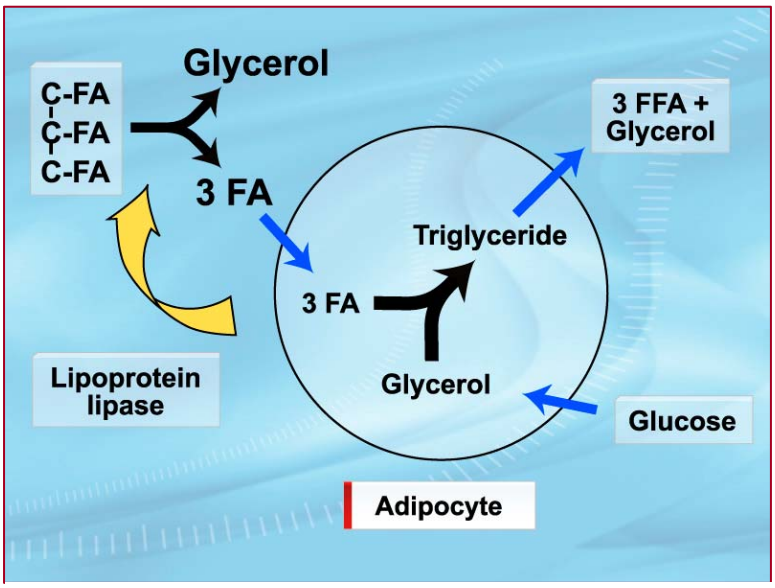

Figure 1: Lipid fuel management by adipocytes. Circulating triglycerides, which contain 3 fatty acids (FA) and glycerol, are hydrolyzed at the capillary endothelium by lipoprotein lipase. The FA are able to be taken up by adipocytes and re-stored as triglyceride. The process of lipolysis allows for the regulated release of free fatty acids (FFA) back into the circulation.

of adipose vs. non-adipose tissue to the circulating concentrations of these molecules. Another important function of adipose tissue is immune protection. Not only do preadipocytes and immune cells (macrophages) share a common lineage [4], the high local fatty acid concentrations in adipose tissue are highly toxic to bacteria and fungi, providing an excellent defence. It is speculated that subcutaneous fat plays a key role in protecting us from infections following skin wounds or superficial infections. Likewise, intra-abdominal (visceral) fat has long been recognized as a barrier, albeit imperfect, to peritoneal catastrophes such as a perforated viscus. The other functions, such as mechanical protection (think falls or sitting on a hard surface), insulation and cosmetic, are seldom considered until one encounters extremely wasted patients with almost no body fat.

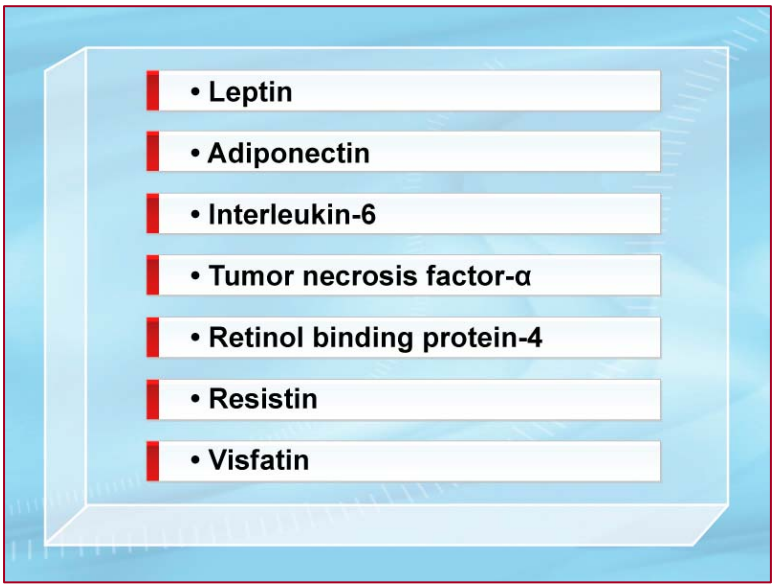

Table 2: Partial list of adipokines.

Use of BMI in Clinical Practice—Comparison with Body Fat Measures

The use of the term "normal weight obesity" also raises the question of how BMI was created for use in epidemiological studies and clinical practice and whether it was ever intended to predict percent body fat. BMI requires only the measurement of height and weight in the clinic and leads to reasonable characterization as to whether individuals are at lower or higher risk for weight-related complications [5]. Despite the availability of very sophisticated imaging techniques to measure percent fat, regional fat distribution, lean tissue, etc., it turns out that BMI, when combined with a simple measure of fat distribution such as waist circumference, provides as good or better predictive value for metabolic abnormalities than does percent body fat [6]. BMI has been compared with percent body fat as a way to define risk for metabolic abnormalities, and in general, BMI performs as well as percent fat [7]. Unfortunately, neither BMI nor percent body fat are exceptionally good predictors of the metabolic consequences of obesity for most adults in the BMI categories below ~ 30 kg/m^2 [8]. Thus, while BMI and percent body fat are correlated [7] and are both somewhat predictive of obesity-related health consequences, neither is perfect.

Definitions of Obesity

This brings us to the issue of finding an acceptable, medically useful definition of obesity. My contention is that obesity cannot reasonably be defined by some fixed percent body fat no matter how well measured. I propose the following two-part medical definition for obesity: 1) sufficient body fat to result in a dysmetabolic response and/or mechanical complications; AND 2) a long-term reduction in body fat leads to long-term improvements in health. Note that this definition may include normal weight individuals with hypertension, dyslipidemia, etc., provided that reductions in body fat alone (not increased exercise, which may have effects independent of body fat) improve or resolve the problem. By this definition, a woman with a BMI of 32 kg/m^2 with no metabolic (Table 3) or mechanical abnormalities related to obesity (Table 4) would not be considered obese. Because many of the metabolic abnormalities in obesity are linked to abnormal lipid fuel metabolism by adipose tissue, the normal regulation will be reviewed briefly.

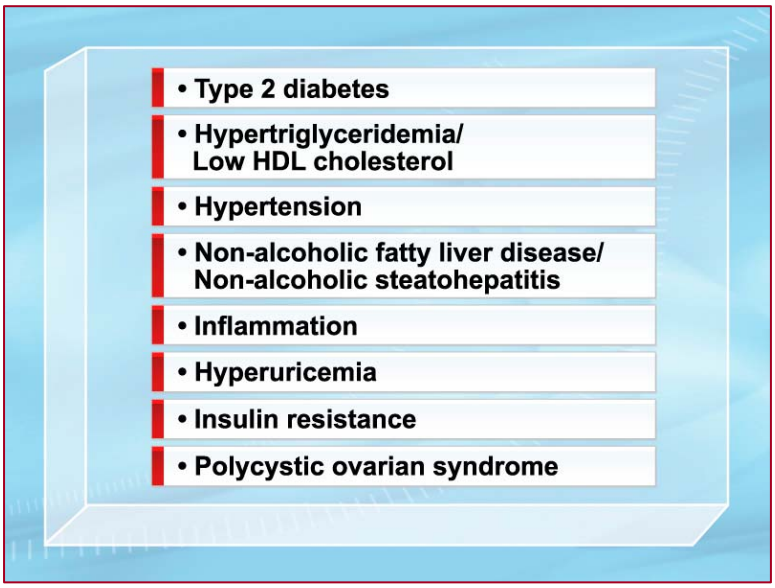

Table 3: Metabolic complications of obesity.

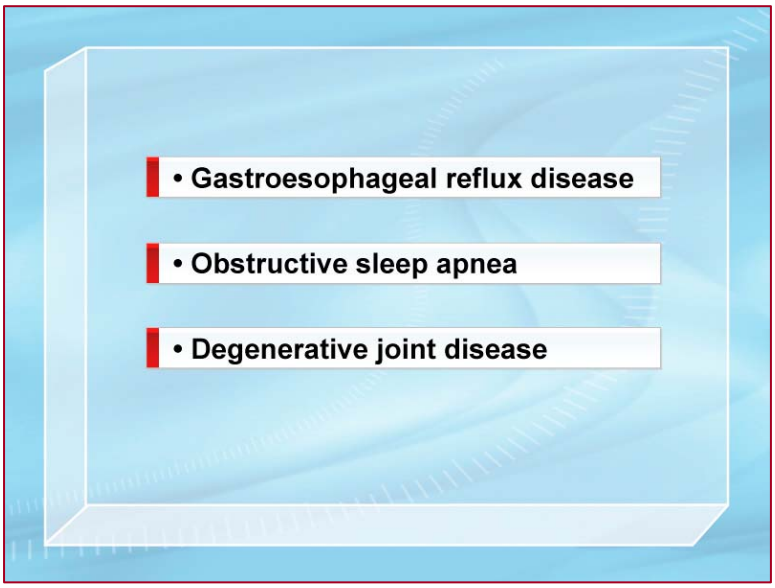

Table 4: Mechanical complications of obesity.

Regulation of Adipose Tissue Fuel Storage/Release

Adipose fatty acid storage

Adipocytes take up circulating fat via two pathways. The major and most well understood pathway of fatty acid uptake is dependent upon lipoprotein lipase (LPL), and the other, less well appreciated mechanism is direct uptake and storage of circulating FFA. LPL is responsible for the hydrolysis of meal-derived triglycerides in chylomicrons and VLDL triglyceride at the capillary endothelium. Given that dietary fat intake, and thus chylomicron triglyceride delivery to the circula-

tion, is commonly ≥100 g/day and VLDL triglyceride (largely derived from circulating FFA) secretion is ~15-25 g/day, it is easy to understand why variations in LPL activity would be seen as an important issue for fatty acid storage. In normal weight men and women, the storage of dietary fatty acids in upper and lower body subcutaneous fat is strongly correlated with postprandial, but not postabsorptive, adipose tissue LPL activity [9]. For unknown reasons, a similar relationship between adipose tissue LPL activity and meal fatty acid storage does not seem to hold true for overweight and obese women [10]. The implications of storage for obesity-related issues revolve around the limited clearance of triglycerides from the circulation. Low LPL activity will limit VLDL triglyceride clearance, and thus for any given degree of VLDL triglyceride production, plasma concentrations will be higher. In addition, triglyceride clearance is saturable, meaning that once a certain plasma concentration of triglycerides has been reached, all available LPL activity is being used. Any further inflow of triglycerides, including from chylomicrons, will have drastic effects on increasing plasma triglyceride concentrations.

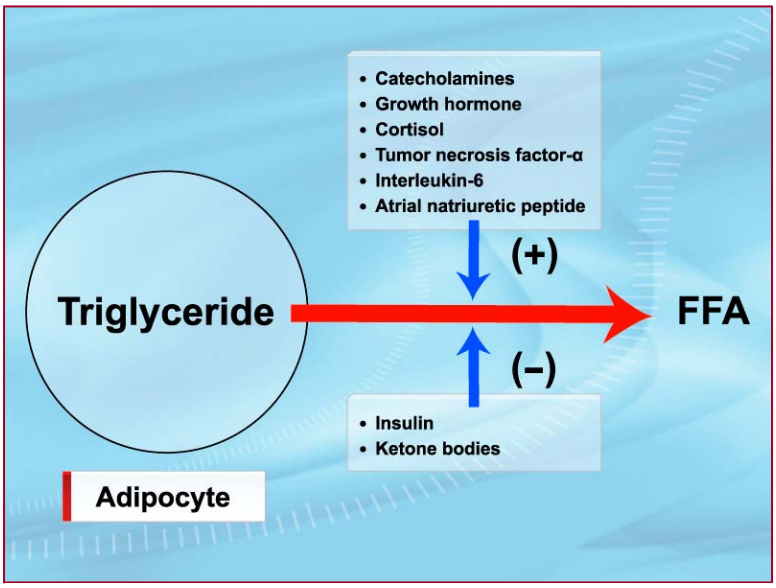

Figure 2: The known positive (pro-lipolytic) and negative (anti-lipolytic) hormones regulating free fatty acid (FFA) release from adipose tissue are listed.

Subcutaneous adipocytes also directly take up and store circulating FFA independent of the VLDL triglyceride pathway, accounting for a relatively small storage pathway after an overnight fast (~3% and ~9% in normal weight men and women, respectively) [11].

Adipose fatty acid release

The regulation of adipocyte FFA release has been very well studied and the modulators of lipolysis reasonably well defined (Figure 2). The factors that have been shown to have an important role in regulating FFA release in vivo in humans have been relatively well studied [12-17] (Table 5).

	Effect	Potency	Onset of action
• Insulin	Inhibition	Very high	Minutes
• Catecholamines	Stimulation	Very high	Minutes
• Growth hormone	Stimulation	Medium	Hours
• Cortisol	Stimulation	Low	Hours
• Atrial natriuretic peptide	Stimulation	Low	Minutes

Table 5: Regulators of lipolysis in humans – circulating factors.

Of particular interest, obese individuals with an upper body/intra-abdominal fat distribution have elevated FFA concentrations due to increased lipolysis under both postabsorptive and postprandial conditions [18, 19], whereas equally obese persons with a lower body fat distribution have normal FFA concentrations/metabolism. This likely contributes to the host of metabolic complications associated with abdominal obesity, which is now well-recognized as a very important predictor of adverse health consequences.

Etiology of Metabolic Complications of Obesity

There are a large number of metabolic complications that can be attributed to excess body fat (Table 3), as well as a number of mechanical complications directly linked to excess body fat (Table 4). While it is relatively easy to understand how mechanical complications can occur from excess body fat, understanding the etiology of metabolic complications of obesity is rather more complex. In order to understand how body fat might result in metabolic abnormalities, it is important to consider regulation of adipose tissue function with regards to fuel storage.

The effect of FFA on glucose metabolism in humans has been studied extensively; it is well established that obesity and increased plasma FFA concentrations are risk factors for the development of type 2 diabetes [20, 21]. The ability to manipulate FFA concentrations has shown that the FFA/metabolic function associations are not merely related abnormalities, but cause and effect. Studies using acipimox, an inhibitor of lipolysis, to lower FFA or lipid emulsion infusions to raise FFA have helped define the contribution of FFA to insulin action with respect to glucose, lipoprotein and vascular regulation. Elevated plasma FFA upregulate glucose production and impair muscle glucose uptake, oxidation and storage [22, 23], perhaps through generation of excess intracellular ceramides, diacylglycerol or other lipid signalling molecules. FFA also affect insulin secretion [21] as intracellular metabolites of fatty acids, such as long-chain acyl CoA and diacylglycerol, trigger insulin release [24, 25] as well as β cell dysfunction [26]. The perturbations in glucose metabolism and insulin secretion that reflect increased systemic FFA are implicated in the etiology of type 2 diabetes.

In addition to their effects on glucose metabolism and diabetes risk, elevated FFA concentrations have been shown to be risk markers for ischemic heart disease [27], perhaps indirectly through playing a part in the development of hypertension [28, 29] or directly via induction of vascular endothelial injury [30].

Examples of Body Fat/Health Outcome Exceptions

Patients with lipodystrophy are unable to store fatty acids as triglycerides in adipocytes, yet have extreme hunger due to low leptin (leptin is produced by adipocytes in increasing amounts with increasing fat). Thus, when lipodystrophic patients consume fat but cannot oxidize all of it, the triglyceride is stored in liver, muscle and other ectopic depots. Because there is no adipose tissue to store chylomicron triglycerides, severe postprandial hypertriglyceridemia is common. These patients develop non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), diabetes and ex-

treme hyperlipidemia despite negligible body fat. Fortunately, leptin replacement, which reduces hunger and lowers food intake by ~40%, also greatly improves the metabolic profile of these patients [31]. Similar beneficial effects have been seen with extreme exercise, which allows oxidation of dietary fat rather than storage in ectopic sites.

Many of our patients are now older and have BMIs that would be considered "higher risk" in the young and middle-aged. An enormous body of evidence indicates that the lowest mortality rates in the elderly (variably defined as >60 to >70 years) is at BMIs of 27-29 kg/m^2, with little appreciable increase at BMIs 30-35 kg/m^2 [32]. These patients are also likely to be the ones who are "over-fat" as characterized by body composition measures [1]. The paradox of lower mortality with greater body fat may relate to the ability to survive acute illnesses better thanks to greater reserves or some other factors relating to immune function. Thus, it would be a mistake to universally recommend weight loss for the elderly with BMIs above the normal weight range without taking into account whether there are urgent medical reasons to do so.

References

1. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond) 2008; 32: 959-66.
2. Ruderman NB, Schneider SH and Berchtold P. The "metabolically-obese," normal-weight individual. Am J Clin Nutr 1981; 34: 1617-21.
3. Ruderman N, Chisholm D, Pi-Sunyer X, et al. The metabolically obese, normal-weight individual revisited. Diabetes 1998; 47: 699-713.
4. Charriere G, Cousin B, Arnaud E, et al. Preadipocyte conversion to macrophage. Evidence of plasticity. J Biol Chem 2003; 278: 9850-5.
5. Bray GA. Overweight is risking fate. Definition, classification, prevalence, and risks. Ann N Y Acad Sci 1987; 499: 14-28.
6. Vega GL, Adams-Huet B, Peshock R, et al. Influence of body fat content and distribution on variation in metabolic risk. J Clin Endocrinol Metab 2006; 91: 4459-66.
7. Zhu S, Wang Z, Shen W, et al. Percentage body fat ranges associated with metabolic syndrome risk: results based on the third National Health and Nutrition Examination Survey (1988-1994). Am J Clin Nutr 2003; 78: 228-35.
8. Brooks Y, Black DR, Coster DC, et al. Body mass index and percentage body fat as health indicators for young adults. Am J Health Behav 2007; 31: 687-700.
9. Votruba SB and Jensen MD. Sex-specific differences in leg fat uptake are revealed with a high-fat meal. Am J Physiol Endocrinol Metab 2006; 291: E1115-23.
10. Votruba SB, Mattison RS, Dumesic DA, et al. Meal fatty acid uptake in visceral fat in women. Diabetes 2007; 56: 2589-97.
11. Shadid S, Koutsari C and Jensen MD. Direct free fatty acid uptake into human adipocytes in vivo: relation to body fat distribution. Diabetes 2007; 56: 1369-75.
12. Birkenfeld AL, Boschmann M, Moro C, et al. Lipid mobilization with physiological atrial natriuretic peptide concentrations in humans. J Clin Endocrinol Metab 2005; 90: 3622-8.
13. Cersosimo E, Danou F, Persson M, et al. Effects of pulsatile delivery of basal growth hormone on lipolysis in humans. Am J Physiol 1996; 271: E123-6.
14. Divertie GD, Jensen MD, Cryer PE, et al. Lipolytic responsiveness to epinephrine in nondiabetic and diabetic humans. Am J Physiol 1997; 272: E1130-5.

15. Divertie GD, Jensen MD and Miles JM. Stimulation of lipolysis in humans by physiological hypercortisolemia. Diabetes 1991; 40: 1228-32.
16. Jensen MD, Caruso M, Heiling V, et al. Insulin regulation of lipolysis in nondiabetic and IDDM subjects. Diabetes 1989; 38: 1595-601.
17. Meek SE, Nair KS and Jensen MD. Insulin regulation of regional free fatty acid metabolism. Diabetes 1999; 48: 10-4.
18. Jensen MD, Haymond MW, Rizza RA, et al. Influence of body fat distribution on free fatty acid metabolism in obesity. J Clin Invest 1989; 83: 1168-73.
19. Roust LR and Jensen MD. Postprandial free fatty acid kinetics are abnormal in upper body obesity. Diabetes 1993; 42: 1567-73.
20. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003; 289: 76-9.
21. Paolisso G, Tataranni PA, Foley JE, et al. A high concentration of fasting plasma non-esterified fatty acids is a risk factor for the development of NIDDM. Diabetologia 1995; 38: 1213-7.
22. Kelley DE, Mokan M, Simoneau JA, et al. Interaction between glucose and free fatty acid metabolism in human skeletal muscle. J Clin Invest 1993; 92: 91-8.
23. Randle PJ, Priestman DA, Mistry SC, et al. Glucose fatty acid interactions and the regulation of glucose disposal. J Cell Biochem 1994; 55 Suppl: 1-11.
24. Prentki M. New insights into pancreatic beta-cell metabolic signaling in insulin secretion. Eur J Endocrinol 1996; 134: 272-86.
25. Prentki M, Joly E, El-Assaad W, et al. Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in beta-cell adaptation and failure in the etiology of diabetes. Diabetes 2002; 51 Suppl 3: S405-13.
26. Prentki M and Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006; 116: 1802-12.
27. Pirro M, Mauriège P, Tchernof A, et al. Plasma free fatty acid levels and the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. Atherosclerosis 2002; 160: 377-84.
28. Steinberg HO, Tarshoby M, Monestel R, et al. Elevated circulating free fatty acid levels impair endothelium-dependent vasodilation. J Clin Invest 1997; 100: 1230-9.
29. Stojiljkovic MP, Zhang D, Lopes HF, et al. Hemodynamic effects of lipids in humans. Am J Physiol Regul Integr Comp Physiol 2001; 280: R1674-9.
30. Piro S, Spampinato D, Spadaro L, et al. Direct apoptotic effects of free fatty acids on human endothelial cells. Nutr Metab Cardiovasc Dis 2008; 18: 96-104.
31. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. N Engl J Med 2002; 346: 570-8.
32. Grabowski DC and Ellis JE. High body mass index does not predict mortality in older people: analysis of the Longitudinal Study of Aging. J Am Geriatr Soc 2001; 49: 968-79.

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ORIGINAL ARTICLE

AMBULATORY BLOOD PRESSURE IN OBESITY

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Introduction

It has been clearly established that hypertension prevalence is increased in overweight and obese subjects. Mechanisms leading to increased blood pressure in obesity include sympathetic overactivity, insulin resistance and sodium retention [1].

Differences in fat deposition and distribution seem to have a different impact on cardiovascular disease. Excess intra-abdominal (visceral) adiposity is detected by increased waist circumference and is often accompanied by disturbances in lipoprotein metabolism (increased VLDL and decreased HDL) [2] and other alterations in blood pressure and insulin sensitivity in the context of what is called the "metabolic syndrome" [3]. The latter's relationship with cardiovascular disease has proven to be closer than that observed with simple increases in body weight [4].

The evidence regarding the relationship of fat accumulation and distribution abnormalities with ambulatory blood pressure monitoring (ABPM) is scarce and has been limited to either children [5] or small cohorts [6]. In this preliminary analysis, we investigated both clinical and ABPM in a large cohort of hypertensives, divided into body mass index (BMI) and waist circumference categories.

Patients and Methods

Study design

The Spanish Society of Hypertension ABPM Registry was developed to promote the use of ABPM in clinical practice. As part of the ABPM Registry initiative, more than 900 Spacelabs 90207 ambulatory blood pressure (BP) monitors (Spacelabs Inc., Redmond, WA, USA) were distributed for routine use by physicians in primary care centres and specialized units. Details of physicians' recruitment and registry characteristics have been reported previously [7-11]. Briefly, physicians and nurses received specific training on the ABPM technique and used the web-based platform for

ABPM registries together with their corresponding medical records. Physicians then received a results report in real time, with registries being stored in a database hosted by an external clinical research organization. The protocol was approved by a series of institutional review boards in autonomous communities across Spain, and patients gave informed consent. The registry is growing continuously and receives data from approximately 1,500 patients per month, with the first patient recruited in June 2004. For the purpose of the present study, 68,045 hypertensive patients recruited by 1,126 physicians between June 2004 and December 2007 were selected.

BP measurements

BP was measured at the office with a calibrated mercury sphygmomanometer or a validated semiautomatic oscillometric device, after a 5-minute rest in a sitting position. BP values were estimated as the mean of two readings. Thereafter, 24-hour ABPM was performed using the Spacelabs 90207 automated non-invasive oscillometric device, programmed to register BP at 20-minute intervals for the 24-hour period. Valid registries had to meet a series of pre-established criteria, including ≥80% successful recordings of systolic BPs and diastolic BPs during the daytime and night-time periods, 24-hour duration and at least one BP measurement per hour. Daytime and night-time periods were defined individually according to patients' self-reported data regarding going-to-bed and getting-up times.

Study variables

Variables collected for each patient based on the interviews and physical examination at the time of visit and on data drawn from clinical records were defined and measured in accordance with national and international guidelines [12, 13]. These included age, gender, weight, height, BMI, waist circumference, duration of hypertension, known cardiovascular risk factors and clinical cardiovascular or renal disease (coronary heart disease, congestive heart failure, peripheral artery disease, cerebrovascular disease, chronic renal failure).

Statistical analysis

Data was presented as frequencies and percentages for qualitative variables and as mean ± standard deviation for quantitative variables. Differences in study variables among prespecified groups of BMI (<25, 25-29.9 or ≥30 kg/m^2) or among patients with and without abdominal obesity (waist circumference >102 cm in men and >88 cm in women) were assessed with the Pearson χ^2 for qualitative variables and one-way ANOVA or Student's *t* test for quantitative data.

Results

Differences in clinical and ABPM depending on BMI groups

From the total cohort of 68,045 patients, 12,932 (19%) exhibited BMI values <25 kg/m^2, 30,720 (45.1%) values between 25 and 29.9 kg/m^2 and 24,393 (35.8%) were considered obese (≥30 kg/m^2). As shown in Table 1, a progressive increase in clinical and ambulatory systolic BPs was observed with increased BMI values. In contrast, diastolic BP showed minimal or no changes. The magnitude

of BP increase with higher BMI values was clearly more pronounced in office, compared with ambulatory blood pressure (ABP), and the proportion of patients showing normal 24-hour and daytime BP values did not differ clearly among BMI categories, with the exception of nocturnal hypertension, which was higher in obese subjects. The prevalence of a normal dipping pattern was also reduced in obese hypertensives, compared with hypertensives with normal BMI.

Other differences observed in patients with increased BMI included older age, longer duration of hypertension and a higher prevalence of cardiovascular or renal disease (Table 1).

Variable	BMI <25 kg/m² n = 12,932	BMI 25-29.9 kg/m² n = 30,720	BMI ≥30 kg/m² n = 24,393
Age (years)	55.7 ± 16.0	59.1 ± 13.6	59.2 ± 13.0
Hypertension duration (years)	4.3 ± 6.4	5.6 ± 7.0	6.9 ± 7.6
Cardiovascular or renal disease (%)	10.1	12.3	12.8
Office systolic BP (mmHg)	146.3 ± 19.7	149.0 ± 19.1	151.1 ± 19.5
Office diastolic BP (mmHg)	86.2 ± 12.8	87.4 ± 12.5	88.1 ± 12.2
24-hour systolic BP (mmHg)	128.4 ± 14.7	129.9 ± 14.3	130.5 ± 14.8
24-hour diastolic BP (mmHg)	77.0 ± 10.4	77.1 ± 10.2	75.8 ± 10.4
Daytime systolic BP (mmHg)	131.7 ± 15.0	133.1 ± 14.6	133.3 ± 15.1
Daytime diastolic BP (mmHg)	80.0 ± 11.0	79.9 ± 10.8	78.5 ± 10.9
Night-time systolic BP (mmHg)	118.9 ± 16.7	121.0 ± 16.2	122.6 ± 16.8
Night-time diastolic BP (mmHg)	68.3 ± 10.4	68.9 ± 10.2	68.4 ± 10.7
Office BP <140/90 mmHg (%)	27.9	22.5	20.4
24-hour BP <130/80 mmHg (%)	45.9	42.5	44.5
Daytime BP <135/85 mmHg (%)	51.7	49.1	51.7
Night-time BP <120/70 mmHg (%)	44.7	40.6	39.7
Non-dipping pattern (%)	48.8	52.4	58.6

Legend
BP : Blood pressure

Table 1: Differences among patients with normal body mass index (BMI), overweight, or obesity.

Differences in clinical and ABPM depending on waist circumference

Abdominal obesity, defined using the aforementioned criteria, was present in 28,369 hypertensive subjects (41.7%). Table 2 shows the clinical and BP differences between patients with and without

abdominal obesity. As with BMI, clinical and ambulatory systolic BP were increased in patients with abdominal obesity, whereas diastolic BP was lower. Similarly, the magnitude of BP increase with higher values of waist circumference was clearly more pronounced in office, compared with ABP, and the proportion of patients showing normal 24-hour, daytime and night-time BP values did not differ clearly among those with and without abdominal obesity. Despite this, the prevalence of a normal dipping pattern was reduced in abdominally obese hypertensives.

Other differences observed in patients with increased waist circumference also included older age, longer duration of hypertension and a higher prevalence of cardiovascular or renal disease (Table 2).

Variable	Without abdominal obesity n = 39,676	With abdominal obesity n = 28,369
Age (years)	56.9 ± 14.4	60.7 ± 13.0
Hypertension duration (years)	5.1 ± 6.7	6.9 ± 7.7
Cardiovascular or renal disease (%)	11.3	13.2
Office systolic BP (mmHg)	147.9 ± 19.2	151.1 ± 19.7
Office diastolic BP (mmHg)	87.6 ± 12.9	87.2 ± 11.8
24-hour systolic BP (mmHg)	129.6 ± 14.4	130.2 ± 14.8
24-hour diastolic BP (mmHg)	77.5 ± 10.2	75.4 ± 10.3
Daytime systolic BP (mmHg)	132.7 ± 14.7	133.1 ± 15.1
Daytime diastolic BP (mmHg)	80.4 ± 10.8	78.1 ± 10.8
Night-time systolic BP (mmHg)	120.4 ± 16.3	122.2 ± 16.8
Night-time diastolic BP (mmHg)	69.1 ± 10.3	67.8 ± 10.5
Office BP <140/90 mmHg (%)	24.0	21.1
24-hour BP <130/80 mmHg (%)	43.1	44.9
Daytime BP <135/85 mmHg (%)	50.2	48.4
Night-time BP <120/70 mmHg (%)	41.3	40.7
Non-dipping pattern (%)	51.5	57.3

Legend
BP : Blood pressure

Table 2: Differences between patients with or without abdominal obesity.

Discussion

The present data shows that obesity, as measured by BMI, or abdominal obesity, as measured by waist circumference, has a definite impact on office or clinical BP measurements, with obese or abdominally obese subjects exhibiting significantly higher values of systolic BP when compared with their counterparts with normal BMI or waist circumference. This relationship is, however, minimized when ABPM is examined. In fact, the differences are half those observed with office BP. Moreover, the proportion of patients whose BP is controlled using the respective cut-offs for office, 24-hour, daytime and night-time BP differs if office or ABPM is used. For office BP, subjects with obesity or increased waist circumference show consistently lower rates of BP control. In contrast, with regard to ABPM, control rates for 24-hour and daytime are not different among groups, and for night-time values, only obese, but not abdominally obese hypertensives, show lower control rates than their counterparts. In patients with high BMI or waist circumference, there were no differences or even lower values for diastolic BP.

These results seem to indicate that a more pronounced whitecoat effect is present in obese hypertensive subjects, an hypothesis already postulated in a previous paper derived from the same cohort [8]. The reasons for obesity or abdominal obesity's minimal impact on ABPM are speculative but could be related to several factors, including a lack of physical activity, a limited therapeutical coverage of drugs administered once a day or an incorrect use of normal size cuffs in large arms. Other confounding factors, such as older age and female sex, also related to this enhanced whitecoat effect, may be partially responsible for the discrepancies between office and ABP.

Another important issue in obese or abdominally obese subjects is an increase in nocturnal BP and a greater frequency of a blunted nocturnal fall in BP (a non-dipping pattern), also suggested in a previous analysis [9]. This is even more important in terms of cardiovascular prognosis and also indicates that antihypertensive treatment, administered once a day in most of these patients, does not cover the therapeutical window of 24 hours. It has been previously demonstrated that both nocturnal hypertension and a blunted nocturnal BP fall are linked to a worse cardiovascular prognosis [14, 15].

In conclusion, ABPM seems to add important clinical information to the management of obese hypertensive patients. The detection of both an enhanced whitecoat phenomenon and the presence of nocturnal hypertension or a non-dipping pattern could be relevant in terms of choosing the best therapeutical options for optimal cardiovascular protection.

References

1. Mikhail N, Golub MS and Tuck ML. Obesity and hypertension. Prog Cardiovasc Dis 1999; 42: 39-58.
2. Després JP and Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006; 444: 881-7.
3. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005; 112: 2735-52.
4. Galassi A, Reynolds K and He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006; 119: 812-9.
5. Lurbe E, Torro I, Aguilar F, et al. Added impact of obesity and insulin resistance in nocturnal blood pressure elevation in children and adolescents. Hypertension 2008; 51: 635-41.

6. Helvaci MR, Kaya H, Yalcin A, et al. Prevalence of white coat hypertension in underweight and overweight subjects. Int Heart J 2007; 48: 605-13.
7. Banegas JR, Segura J, de la Sierra A, et al. Gender differences in office and ambulatory control of hypertension. Am J Med 2008; 121: 1078-84.
8. Banegas JR, Segura J, Sobrino J, et al. Effectiveness of blood pressure control outside the medical setting. Hypertension 2007; 49: 62-8.
9. de la Sierra A, Redon J, Banegas JR, et al. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension 2009; 53: 466-72.
10. Gorostidi M, Sobrino J, Segura J, et al. Ambulatory blood pressure monitoring in hypertensive patients with high cardiovascular risk: a cross-sectional analysis of a 20,000-patient database in Spain. J Hypertens 2007; 25: 977-84.
11. Vinyoles E, Felip A, Pujol E, et al. Clinical characteristics of isolated clinic hypertension. J Hypertens 2008; 26: 438-45.
12. de la Sierra A, Gorostidi M, Marin R, et al. [Evaluation and management of hypertension in Spain. A consensus guide]. Med Clin (Barc) 2008; 131: 104-16.
13. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105-87.
14. Dolan E, Stanton A, Thijs L, et al. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 2005; 46: 156-61.
15. Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens 2002; 20: 2183-9.