Curr Hypertens Rep (2013) 15:196–203
DOI 10.1007/s11906-013-0337-4

HYPERTENSION AND OBESITY (E REISIN, SECTION EDITOR)

Guidelines Updates in the Treatment of Obesity or Metabolic Syndrome and Hypertension

César Cerezo · Julian Segura · Manuel Praga · Luis M. Ruilope

Published online: 22 March 2013

Abstract Obesity and overweight are nowadays very prevalent worldwide. They are known to be linked with an increased risk of developing cardiovascular comorbidities and mortality. Abdominal obesity is frequently associated with a collection of metabolic disorders that include elevated blood pressure, characteristic lipid abnormalities (low high-density lipoprotein cholesterol and high triglycerides) and increased fasting glucose, with an underlying situation of insulin resistance, which has been defined as metabolic syndrome, conferring a high cardiovascular risk profile to these subjects. A multidisciplinary approach is required, including lifestyle changes and pharmacological and surgical approaches. Intensive management of all the risk factors of the metabolic syndrome is also needed to reduce body weight and waist circumference, lessen insulin resistance and avoid the development of new-onset diabetes and cardiovascular disease associated with this entity. This article will review the recently published literature and guideline updates on this topic, although it is not yet included in the highlights.

Keywords Obesity · Abdominal obesity · Overweight · Metabolic syndrome · Diabetes · Blood pressure · Dyslipidemia · Risk factors · Cardiovascular disease · Body mass index, BMI · Body fat distribution · Lifestyle changes · Bariatric surgery · Hypertension · Obesity paradox · Guidelines

C. Cerezo (✉) · J. Segura · M. Praga · L. M. Ruilope
Hypertension Unit, Nephrology Department,
Hospital 12 de Octubre Av. Córdoba s/n,
28041 Madrid, Spain
e-mail: ccerezo11@gmail.com

L. M. Ruilope
Departament of Public Health and Preventive Medicine,
Universidad Autónoma, Madrid, Spain

Introduction

In the last decades, unhealthy lifestyles characterized by sedentarism and high-calorie intake have driven an increase in the prevalence of both obesity and type 2 diabetes mellitus. Obesity is defined as a "condition of abnormal or excessive fat accumulation in adipose tissue" [1]. Body mass index (BMI) has been the classic tool to define different categories of body weight, considering overweight as a BMI from 25 to 29.9 kg/m^2 and obesity a BMI of 30 or more. Obesity has become an epidemic worldwide; increases in the prevalence of overweight and obesity among both adults and children have been observed in many countries throughout the world [2, 3•]. According to CDC/NCHS data, in 2009–2010 35.7 % of US adults were obese, and almost 6 % had a BMI higher than 40, with an added increase in childhood obesity. This relevant prevalence is more significant among males and in the subgroup of the population with lower incomes and educational levels [3•]. It is also well defined that a BMI >25 indicates an increased risk of developing cardiovascular (CV) comorbidities and mortality, such as coronary heart disease, heart failure, stroke, venous thromboembolism and atrial fibrillation [4].

However, the same amount of adipose tissue could confer a different CV risk profile depending on the body fat distribution. Thus, as was proven 2 decades ago, an excess of abdominal and visceral fat is related to a worse CV prognosis when compared with a non-visceral or subcutaneous distribution of adipose tissue [5]. Abdominal obesity is related to a clustering of metabolic abnormalities that includes high blood pressure (BP) levels, characteristic dyslipidemia [low high-density lipoprotein cholesterol (HDL-c) and high triglycerides] and especially glucose intolerance, with an underlying situation of insulin resistance, which has been defined as metabolic syndrome. Since the initial description by Reaven [6], different criteria have been used to identify this syndrome; the major difference relates

to the measure of central obesity as shown in Table 1. The definition proposed in 1998 by the World Health Organization (WHO) puts emphasis on insulin resistance as the main risk factor [7]. The National Cholesterol Educational Program Adult Treatment Panel III (ATP-III) in 2001 established the requirement of three of the following five factors to establish the diagnosis of cardiometabolic syndrome: elevated triglycerides, low HDL-c levels, elevated fasting glucose levels (impaired fasting glucose or type 2 diabetes mellitus), high BP and abdominal obesity [8]. Recently, both the International Diabetes Federation (IDF) [9] and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) [10] have reconciled their previous differences concerning the definition of this syndrome, agreeing that abdominal obesity should not be mandatory for the diagnosis but one of the five criteria, although insulin resistance and central obesity are recognized as the major causal factors [11••], and in fact, the cardiometabolic syndrome can be considered as a prediabetic state [12]. Remarkably, although previous guidelines of the European Society of Hypertension also considered subjects with metabolic syndrome as high CV risk individuals [13], the future edition of this guideline that will be published shortly will challenge the assumption of metabolic syndrome as an entity that adds to the prognostic strength of the different individual factors [14].

Cardiometabolic syndrome has also been related to a prothrombic and proinflammatory state and to an atherogenic dyslipidemia as a consequence of an increase in circulating free fatty acid together with low HDLc and high triglycerides, accompanied by other adipokines derived from the elevated amount of adipose tissue [15]. The presence of metabolic syndrome is not considered an independent indicator of absolute risk because it does not contemplate other risk factors such as smoking or low-density lipoprotein cholesterol (LDLc). However, it has been widely proven that patients with metabolic syndrome have twice the risk of developing CV disease [16] and a five-fold increase of risk of developing type 2 diabetes mellitus [17]. This risk of CV events increases with the number of metabolic syndrome components [18]. Moreover, those components have an elevated level of interaction; in particular, abdominal obesity and insulin resistance play a significant role in the worsening of blood pressure levels and in the development of arterial hypertension because of the progression of endothelial dysfunction and the stimulation of both sympathetic nervous and renin-angiotensin systems. This situation can lead to the demonstrated higher prevalence of subclinical organ damage in subjects with cardiometabolic syndrome, especially left ventricular hypertrophy, increased urinary protein excretion and arterial stiffness [19]. Finally, as there are differences between genders and ethnic groups, the final individual phenotype of metabolic syndrome will be the result of the interactions of demographic, lifestyle and genetic factors. This could be the explanation of why it is essential to reach worldwide consensus concerning the diagnostic criteria and the cutoff points for anthropometric measurements for different ethnicities in order to determine the best diagnosis and management of this syndrome and therefore reduce the overall elevated CV risk for these subjects.

Regional Body Fat Distribution

As previously described, BMI >25 is related to an increased risk of CV disease. Nevertheless, the regional distribution of total body fat has been proven to have a stronger relationship with CV events than body weight [20]. Since 1947, when Vague demonstrated that patients with an “android”

Table 1 Current accepted waist circumference goals for abdominal obesity by different organizations. *Adapted from* Alberti et al. [11••]

		Recommended waist circumference objectives for metabolic syndrome	
Population	Organization	Men	Women
Caucasian	WHO [7]	≥94 cm (increased high risk)	≥80 cm (increased high risk)
		≥102 cm (high risk)	≥88 cm (high risk)
Asian	WHO [7]	≥90 cm	≥80 cm
US	ATP-III [8]	≥102 cm	≥88 cm
Europid/sub-Saharan African	IDF [9]	≥94 cm	≥80 cm
Asian	IDF [9]	≥ 90 cm	≥80 cm
US	AHA/NHLBI [10]	≥94 cm (increased high risk)*	≥80 cm (increased high risk)*
		≥102 cm (high risk)	≥88 cm (high risk)
Caucasian	ESH [13]	≥102 cm	≥88 cm

*In subjects with increased insulin resistance

distribution of body fat were more likely to have diabetes or CV disease [21], several anthropometric measurements have appeared as indicators of central fat distribution, such as waist circumference or waist-to-hip ratio. Both are independently related with CV and all-cause mortality and are considered excellent markers of visceral adiposity [22]. Nowadays, BMI is recognized as a good index of adiposity that needs to be complemented with anthropometric measurements, mainly waist circumference, to differentiate those obese subjects with an increased risk of visceral fat distribution that is associated with a collection of metabolic disorders. However, these measurements have some limitations, such as the inability to distinguish between subcutaneous and visceral adiposity, showing the high heterogeneity that defines obesity as a very complex syndrome. More direct techniques for measuring fat mass (such as bioelectrical impedance) or for assessing the anatomical distribution of adipose tissue (such as computed tomography and especially MRI) are still not commonly used in clinical practice, although interesting data have been obtained in recent studies [23].

Several hypotheses have been proposed in the last 2 decades to explain how visceral fat relates to a high risk of CV events, such as an activated hypothalamic-pituitary adrenal axis [24], the role of gonadal steroids [25], stimulation of the endocannabinoid system [26] and different environmental factors (i.e., smoking habit) [27] and ethnicity (white adults and the Asiatic population are more likely to have an increase in visceral adipose tissue) [28]. The stronger hypothesis however is the so-called "lipid overflow-ectopic fat model" [29]; both increased caloric intake and sedentarism produce a high-energy balance. In situations of insulin-resistance or genetic susceptibility to visceral obesity, the dysfunctional subcutaneous adipose tissue will be unable to store the energy excess. The affected free fatty acid and the disrupted release of adipokines produce an excess of triglycerides that will be stored in non-expected organs, such as the liver, heart, pancreas, kidney, skeletal muscle and primarily visceral adipose tissue, a phenomenon described as ectopic fat deposition [30••]. This situation will produce all the changes that define the cardiometabolic syndrome, with the resulting increased CV risk profile previously described. Besides the visceral fat, ectopic liver fat is considered the most important ectopic organ where the fat can be deposited in an undesirable manner. This may reduce the hepatic extraction of insulin, producing an elevated hepatic glucose output, glucose intolerance and more atherogenic lipoproteins, leading by itself to a high cardiometabolic risk profile [31]. Recently, as all the ectopic fat deposits are related, it has been proposed that they can be divided into two different groups: those with predominantly systemic effects (visceral adipose tissue, liver fat and skeletal muscle intracellular lipids) and those with local effects (epi-/pericardial fat, perivascular fat and renal fat) [32]. This classification could partially explain why the first group has an increased metabolic risk. Further investigations in this area will facilitate a better understanding of how to improve the prevention and management of this regional body fat distribution.

Obesity and Overweight Management. New Approaches

The objective of treatment in obese patients is to reduce weight and body fat but also to decrease the risk of developing CV events in this group of subjects. The most accepted recommendation is to obtain an initial weight loss threshold of 10 % of the basal body weight in a period of 6 months, which can significantly reduce the severity of risk factors and decrease the prevalence of type 2 diabetes and organ damage related with obesity [33]. Many patients attain this goal, but it is ultimately not sustainable for most of them. A change of unhealthy lifestyle habits through a multidisciplinary approach is needed for effective and persistent weight loss, encouraging a reduction of excess food consumption and increase of physical activity.

A low-calorie diet (800–1,200 kcal/day) may reduce 8–10 % of total weight in 6 months and can help to diminish body fat. A more strict diet with very low calorie intake (250–800 kcal/day) will achieve higher initial weight reduction but similar long-term loss as the low-calorie diet, and it has a higher risk of complications such as electrolyte imbalances and nutrient deficiencies. Several recent trials have compared the efficacy of a low-fat diet or low-carbohydrate diet, showing similar weight loss [34]. Increasing concerns about the effects of the Atkins diet, the most popular low-carbohydrate diet, have been raised in the last few years, showing that it may be associated with increased harmful CV effects. Furthermore, the supposed optimal metabolic effects of this Atkins-type diet were not reliable in several studies [35]. Current guideline recommendations state that the overall calorie reduction should be related to the BMI (300–500 daily kcal reduction for subjects with BMI 27–35 and 500–1000 kcal/day for severely obese patients) instead of any specific calorie basis.

A decrease in sedentary activity with the goal of increasing energy consumption in association with reduced calorie intake is recommended for achieving weight loss. Current guidelines suggest a daily minimum of 30 min of moderate-intensity aerobic physical activity, leading to a reduction in coronary disease of 50 % with 60–90 min per week of walking, with walking time as opposed to speed being the best predictor of benefit [36]. The recent concept of "fat and fit subjects" has shown that obese and overweight individuals usually have a reduced level of cardiorespiratory fitness, which is related to higher levels of visceral adipose tissue,

partially explaining the increased CV risk profile these patients have [37]. Thus, improving cardiorespiratory fitness will predict a reduction in the development of CV disease.

Patients with BMI ≥30 or BMI ≥27 with important obesity-related risk factors meet the actual criteria for pharmacological therapy of obesity, recognizing the necessity of a complete and complementary lifestyle program that includes physical activity and reduced calorie intake as previously described. In the last decades, two different drugs (rimonabant and sibutramine) have failed to meet expectations because of a lack of efficacy and especially the poor safety profile, which caused them to be withdrawn. Orlistat, an inhibitor of lipase in the gastrointestinal tract, prevents the absorption of fatty acids, leading to a mild body weight reduction in combination with dietary modifications [38]. Recently, the FDA has approved two different drugs for chronic weight management. Lorcaserin, a selective agonist of 5-HTC2C (serotonin receptor), may produce a reduction of calorie intake by increasing satiety and reducing hunger, without affecting energy consumption. This leads to a a dose-dependent weight loss that was prolonged beyond 1 year of continuous use, but also to a reduction in inflammation marker levels and improvement in lipid levels and blood pressure [39]. An increased risk of valvulopathy is a major side effect, and it should be used carefully in patients previously diagnosed with stenotic or insufficient heart valves. The combination of phentermine and topiramate was also approved several months ago, showing effective weight loss results and favorable CV and metabolic risk factors [40]. A regular monitoring of the heart rate is needed because of the sympathomimetic action of phentermine, and it should be used with caution in subjects with unstable heart disease or stroke. Liraglutide, a glucagon-like peptide-1 (GLP-1) analog approved for the management of type 2 diabetes, could obtain a significant dose-dependent weight loss by decreasing appetite, added to the beneficial effects on insulin resistance and BP [41].

Bariatric surgery is currently considered the most effective treatment for severe obesity. Criteria for the surgical approach are: BMI ≥40 or ≥35 with comorbid conditions, failure of less aggressive procedures and high risk of obesity-related morbidity or mortality. Recent data have shown that bariatric surgery led to a 30 % reduction in the incidence of CV events in obese patients compared with those who received usual care and an almost 50 % reduction in CV deaths, with the remarkable finding that neither baseline BMI nor final amount of weight loss predicted the final CV benefit, but baseline insulin concentrations were strongly related with the future CV profile [42]. Furthermore, a significant improvement in metabolic control in type 2 diabetes (reduction of HA1c and insulin resistance) in individuals who received bariatric surgery was obtained when compared to medical therapy, both conventional and intensive, independently of the final weight loss [43]. Bariatric surgery seems to be a promising therapeutic technique for obese patients with associated morbidity, and guidelines may need to reconsider whether BMI should be the only criterion for defining the eligibility of obese patients that can obtain an improvement in their CV risk.

Obesity Paradox

Overall, overweight and obesity are linked with an increased risk of CV disease. However, recent findings have revealed epidemiological evidence showing that overweight and low-obesity categories may have a protective CV effect in the presence of chronic conditions (e.g., heart disease or diabetes) or older age when compared with normal weight or severe obesity. This concept is called the "obesity paradox." A current meta-analysis of 97 studies has included more than 2.88 million subjects and over 270,000 deaths with the aim of studying the relationship between BMI and all-cause mortality. If compared with normal weight, all grades of obesity were associated with significantly higher all-cause mortality, but obesity grade 1 was not related with the endpoint, suggesting that the excess of deaths in obese patients was mainly due to increased mortality at higher BMI levels. Overweight was, furthermore, associated with significantly lower all-cause mortality [44•]. A large study of patients with coronary heart disease showed that overweight and mild-obese individuals defined by BMI had a lower risk of death after percutaneous coronary intervention (PCI) than normal-weight or underweight 3 years after the procedure. This statement does not expand to the severely obese with BMI ≥35 [45]. A subanalysis of the ACCOMPLISH trial also revealed an unexpected higher risk of CV events in lean and overweight patients, especially those treated with diuretics, which partially could be explained by an increased stimulation of both the sympathetic and renin-angiotensin systems [46].

In conclusion, the relation between BMI and mortality shows that the lowest CV risk is found among overweight and mild-obese and the highest in underweight, normal-weight and severe-obese subjects, an assertion that is well defined essentially in patients with chronic CV diseases. The obesity paradox will probably require more attention and deserves to be recognized in the guidelines of different societies in the future.

Treating Metabolic Syndrome Factors. Prevention of Diabetes

It is widely proven that two of the main factors that define metabolic syndrome, high BP levels and elevated fasting

Table 2 Thresholds of risk factors in subjects with metabolic syndrome

Risk factor	Organization	Goals
Blood pressure	ESH [47]	<140/90 mmHg
Lipids	ATP-III [48]	LDL<100 mg/dl: high coronary heart disease (CHD) risk or CHD equivalent
		LDL<70 mg/dl: very high risk [established cardiovascular disease plus multiple major risk factors (especially diabetes) or severe and poorly controlled risk factors]
		HDL>41 mg/dl in males and >46 mg/dl in females
		TG≤150 mg/dl
Glycemia	ADA [49]	HbA1c <7 %

glucose, are often linked with enlarged waist circumference and insulin resistance, and this situation can lead to the development of hypertension and new-onset diabetes, with the resulting increased risk of organ damage or CV events [6]. Thus, it is reasonable to manage all CV risk factors aggressively in patients with metabolic syndrome using different drugs in addition to lifestyle interventions.

Goals of treatment include dyslipidemia, hypertension and prediabetes (Table 2) [47–49]. Although elevated triglyceride and decreased HDLc levels are the classical lipid abnormalities in metabolic syndrome, targeting atherogenic lipoproteins, especially LDLc, in clinical practice is crucial. ATP-III recommendations should be followed in all patients with dyslipidemia and metabolic syndrome [48]. Statins are the first-line drugs to achieve these thresholds and should be titrated up to the maximum tolerated dose. If goals are not achieved with the highest statin dose, use of combined therapy with other lipid-lowering drugs such as a bile acid sequestrant or ezetimibe can be considered, although this has not been evaluated in large studies from the standpoint of safety or CV event reduction. In fact, the recent HPS-2 THRIVE study showed no clinical benefit of adding extended-release niacin/laropiprant to statin therapy as this combination did not significantly reduce the risk of the composite of coronary deaths, nonfatal MI, strokes or coronary revascularizations compared with statin therapy, but it did significantly increase the risk of nonfatal but serious side effects [50].

The suggestion to initiate antihypertensive drugs in all patients with metabolic syndrome and BP levels ≥140/90 mmHg seems reasonable in order to maintain BP below these values [13]. More concerns appear when these individuals have BP in the high-normal range, whereas no clear CV benefit has yet been proved. Renin-angiotensin suppressors such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are considered elective drugs because of their favorable metabolic profile when compared with beta-blockers and diuretics. They improve or at least do not worsen insulin sensitivity, delaying the onset of diabetes by reducing the microcirculatory flow in muscle and decreasing the rate of intracellular glucose disposal. Calcium channel blockers can be considered as a second step when a combination schedule is needed. As hypokalemia is known to worsen glucose intolerance, the association with a potassium-sparing agent should be considered if thiazide diuretics are needed. Recent data confirming this hypothesis have proved the neutral effects of mineralocorticoid antagonists such as eplerenone on new-onset diabetes in patients with heart failure [51].

There is evidence that, among all components of the metabolic syndrome, patients with prediabetes are those at higher CV risk. Preventing the development of diabetes is crucial, especially reducing insulin resistance. First, lifestyle interventions including weight reduction and increased

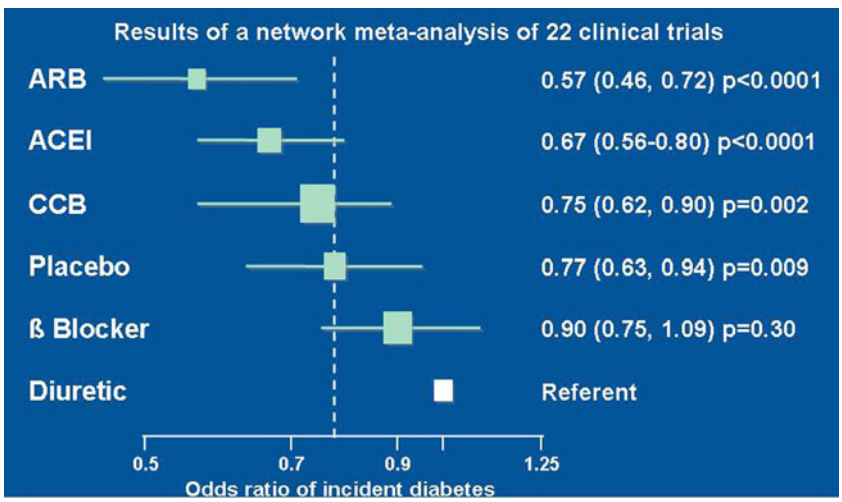

Fig. 1 Effect of different antihypertensive medications on incident diabetes. *Reprinted from The Lancet*, 369, Elliott WJ, Meyer PM [53], Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis, 201–207, 2007, with permission from Elsevier

physical activity should be encouraged in subjects with prediabetes. Therapy with metformin was recently recommended in patients with prediabetes and a high CV risk profile or other metabolic syndrome components to delay conversion to diabetes, since it is known that this approach is useful in 40 % of subjects with increased fasting glucose or impaired glucose tolerance [52]. Renin-angiotensin suppressors have proven their efficacy in preventing and delaying the development of new-onset diabetes (Fig. 1) [53, 54]. Nevertheless, controversial results were obtained in the DREAM study. Ramipril when compared with placebo did not match the primary endpoint of delaying conversion to diabetes in patients with impaired fasting glucose or impaired glucose tolerance, but regression to normoglycemia was significantly more frequent in the ramipril group [55]. The recently initiated Aleprevent and Alecardio trials, which will include patients with established CV disease and glycosylated hemoglobin >5.7 % (both prediabetes and diabetes), will provide more evidence about how to improve the prevention of CV events and CV mortality, but also to delay the development of new-onset diabetes [56, 57].

Conclusion

Obesity and metabolic syndrome are characterized by high cardiovascular risk and increased prevalence of new-onset diabetes. Lifestyle habit changes based on a multidisciplinary approach are required for effective and persistent weight loss and should include a meaningful reduction of calorie intake and increase in physical activity. However, control of body weight is difficult to achieve only with an adequate lifestyle. Thus, pharmacological treatment is helpful, and new drugs are welcomed to improve and maintain body weight. Bariatric surgery in patients with severe obesity and cardiovascular comorbidity is also a useful option. Aggressive management of all the components of metabolic syndrome is needed to reduce waist circumference, diminish insulin resistance and prevent the development of new-onset diabetes and cardiovascular disease.

Conflict of Interest C. Cerezo declares that he has no conflict of interest.

J. Segura declares that he has no conflict of interest.

M. Praga has received payment for consulting from Abbott, Alexion, Fresenius and Gambro; payment for lectures including service on speakers' bureaus from Novartis, Astellas, Abbott, Alexion and GlaxoSmithKline; payment for travel, accommodations and meeting expenses from Novartis, Astellas, Abbott and Alexion.

L.M. Ruilope has received payment for consulting from AstraZeneca, Novartis, Takeda and Daiichi-Sankyo; for expert testimony from Bayer; for lectures including service on speakers' bureaus from Roche, Novartis, Medtronic and Takeda.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. WHO Consultation on Obesity: Obesity: preventing and managing the global epidemic: report of a WHO consultation. WHO technical report series 894. Geneva, WHO, 1999.
2. Gutiérrez-Fisac JL, Guallar-Castillón P, León-Muñoz LM, Graciani A, Banegas JR, Rodríguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008–2010: the ENRICA study. Obes Rev. 2012;13(4):388–92.
3. • Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief. 2012;82:1–8. *Recent appraisal of the epidemiology of obesity and overweight in USA.*
4. Murphy NF, MacIntyre K, Stewart S, Hart CL, Hole D, McMurray JJV. Long-term cardiovascular consequences of obesity: 20-year follow-up of more than 15000 middle-aged men and women (the Renfrew–Paisley study). Eur Hear J. 2006;27:96–106.
5. Després JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis. 1990;10:497–511.
6. Reaven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr. 2006;83:1237–47.
7. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabetes Med. 1999;16:683–9.
8. 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.
9. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. Lancet. 2005;366:1059–62.
10. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, 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.
11. •• Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato K, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5. *Current agreement of different organizations concerning the most commonly accepted diagnosis criteria of metabolic syndrome, especially related to the measure of waist circumference.*
12. Grundy S. Pre-diabetes, metabolic syndrome, and cardiovascular risk. J Am Coll Cardiol. 2012;59:635–43.
13. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 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. 2013 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) (in press).
15. Deng Y, Scherer PE. Adipokines as novel biomarkers and regulators of the metabolic syndrome. Ann N Y Acad Sci. 2010;1212: E1–E19.
16. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56:1113–32.
17. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care. 2004;27:2676–81.
18. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation. 2005;112:666–73.
19. Mancia G, Bombelli M, Corrao G, Facchetti R, Madotto F, Giannattasio C, et al. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension. 2007;49:40–7.
20. Mathieu P, Poirier P, Pibarot P, Lemieux I, Després JP. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. Hypertension. 2009;53:577–84.
21. Vague J. Sexual differentiation, a factor affecting the forms of obesity. Presse Med. 1947;30:339–40.
22. Taylor AE, Ebrahim S, Ben-Shlomo Y, Martin RM, Whincup PH, Yarnell JW, et al. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. Am J Clin Nutr. 2010;91:547–56.
23. Sebo P, Beer-Borst S, Haller DM, Bovier PA. Reliability of doctors' anthropometric measurements to detect obesity. Prev Med. 2008;47:389–93.
24. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care. 1991;14:1132–43.
25. Eibers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, et al. Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. Clin Endocrinol (Oxf). 2003;58:562–71.
26. Coté M, Matias I, Lemieux I, Petrosino S, Alméras N, Després JP, et al. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. Int J Obes (Lond). 2007;31:692–9.
27. Barrett-Connor E, Khaw KT. Cigarette smoking and increased central adiposity. Ann Intern Med. 1989;111:783–7.
28. Katzmarzyk PT, Bray GA, Greenway FL, Johnson WD, Newton Jr RL, Ravussin E, et al. Racial differences in abdominal depot-specific adiposity in white and African American adults. Am J Clin Nutr. 2010;91:7–15.
29. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity (Silver Spring). 2006;14 suppl 1:16S–9S.
30. •• Després JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012;126:1301–13. *Updated review of the critical importance of the body fat distribution and its relationship with cardiovascular risk*.
31. Mehta SR, Godsland IF, Thomas EL, Pavitt DV, Morin SX, Bell JD, et al. Intrahepatic insulin exposure, intrahepatocellular lipid and regional body fat in nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2012;97:2151–9.
32. Britton KA, Fox CS. Ectopic fat depots and cardiovascular disease. Circulation. 2011;124:e837–41.
33. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults – The Evidence Report. National Institutes of Health. Obes Res 1998;6 (suppl 2):51S-209S.
34. Foster GD, Wyatt HR, Hill JO, Makris AP, Rosenbaum DL, Brill C, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. Ann Intern Med. 2010;153:147–57.
35. Lagiou P, Sandin S, Lof M, et al. Low carbohydrate – high protein diet and incidence of cardiovascular disease in Swedish women: prospective cohort study. BMJ. 2012. doi:10.1136/bmj.e4026.
36. Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity and coronary heart disease in women: Is "no pain, no Gain" passe? JAMA. 2001;285:1447–54.
37. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. Circulation. 2011;124:2483–90.
38. Lindgarde F. The effect of orlistat on body weight and coronary heart disease risk profile in obese patients: the Swedish Multimorbidity Study. J Intern Med. 2000;248:245–54.
39. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab. 2011;96:3067–77.
40. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity. 2012;20:330–42.
41. Astrup A, Rossner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009;374:1606–16.
42. Sjöström L, Peltonen M, Jacobs P, et al. Bariatric surgery and long-term cardiovascular events. JAMA. 2012;307:56–65.
43. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012. doi:10.1056/NEJMoa1200225.
44. • Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309:71–82. *Actual and promising hypothesis that explains the protective cardiovascular effects of overweight and mild obesity when associated with other comorbidities*.
45. Angerås O, Albertsson P, Karason K, et al. Evidence for obesity paradox in patients with ACS: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2012. doi:10.1093/eurheartj/ehs217.
46. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359:2417–28.
47. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27:000–000.
48. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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): Final Report. Circulation 2002;106:3143–421.
49. Standards of Medical Care in Diabetes – 2012. Position Statement. Diabetes Care. Vol 35, Supplement 1, January 2012.
50. Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial. In ClinicalTrials.gov. (cited 2012 Nov 19): Available from: http://www.clinicaltrials.gov/ct2/show/NCT00461630.
51. Preiss D, van Veldhuisen DJ, Sattar N, Krum H, Swedberg K, Shi H, et al. Eplerenone and new-onset diabetes in patients with mild

heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Eur J Heart Fail. 2012;14(8):909–15.
52. Nathan DM, Davidson MB, DeFronzo RA, for the American Diabetes Association, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care. 2007; 30:753–9.
53. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007; 369:201–7.
54. Kjeldsen SE, Julius S, Mancia G, McInnes GT, Hua T, Weber MA, et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertens. 2006;24:1405–12.
55. Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, et al. Effect of ramipril on the incidence of diabetes. N Engl J Med. 2006;355:1551–62.
56. Aleprevent. A Phase 3b Study to Evaluate the Potential of Aleglitazar to Reduce Cardiovascular Risk in Patients with Stable Cardiovascular Disease and Glucose Abnormalities. In ClinicalTrials.gov. (cited 2013 Jan 24): Available from: http://www.clinicaltrials.gov/ct2/show/NCT01715818. NLM.
57. Alecardio. A Safety and Efficacy Study to Evaluate the Potential of Aleglitazar to Reduce Cardiovascular Risk in Coronary Heart Disease (CHD) Patients With a Recent Acute Coronary Syndrome (ACS) Event and Type 2 Diabetes Melitus (T2D). In ClinicalTrials.gov. (cited 2013 Jan 24): Available from: http://www.clinicaltrials.gov/ct2/show/NCT01042769. NLM.