Μεταβολικό σύνδρομο: έχει ακόμη κλινική αξία στην υπέρταση;

Ass. Prof. Vasilios Kotsis, Chairman WG on Obesity, diabetes and the high risk patient ESH
Obesity: definition

- Measurement of the body mass index

$$\text{BMI} = \frac{\text{weight in kg}}{(\text{height in meters})^2} \text{ kg/m}^2$$

Adapted from the Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, National institute of health, USA
Measurement of waist circumference

- Measurement of waist circumference is a available tool for the assessment of the total cardiovascular risk.

- Men with waist circumference > 102 cm and women with waist circumference > 88 cm are in increased risk for diabetes, dyslipidemia and hypertension due to the increased abdominal fat.
Increased trends for obesity in USA between 1960 - 2004
Age-adjusted prevalence of risk factors in obese patients

Adapted from the Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, National Institute of Health, USA
Diagnosis of the metabolic syndrome (ATP III)

- Central obesity  
  (waist circumference):  
  - Men >102 cm (40 in)  
  - Women >88 cm (35 in)  
- Triglycerides: >150 mg/dL  
- HDL cholesterol:  
  - Men <40 mg/dL  
  - Women <50 mg/dL  
- Hypertension  
- Fasting Glucose: >110 mg/dL

* Diagnosis is based on at least 3 from the above factors
Obesity and hypertension
Obesity and hypertension prevalence confirmed with ABPM

V. Kotsis et al Hypertension 2005
Obesity and hypertension prevalence comparison to normal weight subjects

N=3216, normal weight patients=1057, obese=825

V. Kotsis et al Hypertension 2005: 45:602-607
High Fat Diet Increases Arterial Pressure

Mean Arterial Pressure (mmHg)

Body Weight (kg)

Time (weeks)

High Fat Diet

C 1 2 3 4 5

20 25 30 35 40

JE Hall, MW Brands, WN Dixon, MJ Smith
High Fat Diet Increases Heart Rate and Cardiac Output

Hall et al.
Circadian 24-hour systolic blood pressure profile in normal weight, overweight, and obese patients


Error Bars show 95% CI of Mean

Dot/Lines show Means
Circadian 24-hour heart rate profile in normal weight, overweight, and obese patients

Non-Dipping status in obesity

V. Kotsis et al Hypertension 2005
Obese adolescents exhibit higher 24h, daytime and nighttime SBP levels

Mechanisms of obesity-induced hypertension.

- **Hypertens Res. 2010 May;33(5):386-93.**
- **Kotsis V, Stabouli S, Papakatsika S, Rizos Z, Parati G.**

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**Abstract**

The relationship between obesity and hypertension is well established both in children and adults. The mechanisms through which obesity directly causes hypertension are still an area of research. Activation of the sympathetic nervous system has been considered to have an important function in the pathogenesis of obesity-related hypertension. The arterial-pressure control mechanism of diuresis and natriuresis, according to the principle of infinite feedback gain, seems to be shifted toward higher blood-pressure levels in obese individuals. During the early phases of obesity, primary sodium retention exists as a result of increase in renal tubular reabsorption. Extracellular-fluid volume is expanded and the kidney-fluid apparatus is resetted to a hypertensive level, consistent with a model of hypertension because of volume overload. Plasma renin activity, angiotensinogen, angiotensin II and aldosterone values display significant increase during obesity. Insulin resistance and inflammation may promote an altered profile of vascular function and consequently hypertension. Leptin and other neuropeptides are possible links between obesity and the development of hypertension. Obesity should be considered as a chronic medical condition, which is likely to require long-term treatment. Understanding of the mechanisms associated with obesity-related hypertension is essential for successful treatment strategies.
Kotsis et al. “Obesity, hypertension and dyslipidemia” In Endocrinology: Obesity. Pathogenesis, Diagnosis, and Treatment" , edited by  Paolo Sbraccia and Nicholas Finer. Springer
Why obesity is not always accompanied with hypertension

The mechanisms involved in obesity-induced hypertension are not yet clearly fully understood. Protecting factors may exist and it is important to understand why obesity is not always related to hypertension.
Animal models of obesity without hypertension
A spontaneous mutation of the leptin gene

Phenotypically, leptin deficiency leads to marked, early-onset obesity characterized by hyperphagia, reduced energy expenditure and hypothermia; further defects are hypercorticosteronemia, insulin resistance associated with hyperglycemia and hyperinsulinemia, hypothyroidism, growth hormone deficiency and infertility.

Obesity in Lep ob/ob mice can be effectively treated by the administration of exogenous leptin.

Leptin correlates positively with adiposity and increases SNS activity and BP when infused chronically into lean rodents. Models with the absence of intact leptin signaling pathways are expected to have low BP. Indeed the Lepob/ob mice (on the C57BL/6J background) are hypotensive.
Leptin deficiency has also been observed in rare cases of human obesity.

Increased leptin in obese subjects would be expected to reduce appetite, to increase thermogenesis and energy expenditure. However, obese individuals are resistant to the actions of leptin.
The Melanocortin 4 receptor (MC4-R) null mouse

- The Melanocortin 4 receptor (MC4-R) null mouse is another rodent model of obesity without hypertension.

- MC4-R is expressed in a number of nuclei in the rodent brain that are associated with autonomic and neuroendocrine pathways. The central melanocortin system is known to mediate many actions of the adipokine leptin and plays a crucial role in the central regulation of energy homeostasis.

- The MC4-R deficient mouse has a behavioral obesity syndrome characterized by hyperphagia, hyperglycemia, hyperinsulinemia, hypometabolism, increased lean mass and linear growth.

- Pair-feeding the MC4-R/mice to the same level as wild-type controls results in reduction of adiposity. However, MC4-R/ mice remain heavier than their wild-type counterparts, highlighting the role of the hypometabolism in this phenotype.

- Hyperinsulinemia in this model is partially independent of obesity, as young MC4-R-deficient mice have been shown to have elevated circulating insulin levels prior to the onset of obesity.

- Despite their profound obesity in adulthood, the MC4-R deficient mice are not hypertensive, but tend to be hypotensive.
MC4R gene mutations in human obesity

Alterations in the MC4R gene are the most common monogenic cause of obesity known in humans including recent genome-wide association studies.
Hypertension and MC4R deficiency in humans

**Figure 1. Prevalence of Hypertension and Blood-Pressure Measures.**

The graphs show the prevalence of hypertension (Panel A) and measures of systolic blood pressure (Panel B) and diastolic blood pressure (Panel C) in 46 subjects with MC4R deficiency, as compared with 30 overweight or obese control subjects. Four subjects with MC4R deficiency and seven control subjects were excluded from the analyses in Panels B and C because they were taking antihypertensive medications. The I bars represent the standard error.
Norepinephrine levels in MC4R deficient humans

**Figure 3. Twenty-four-Hour Levels of Urinary Norepinephrine, Epinephrine, and Dopamine.**

The graphs show levels of urinary norepinephrine (Panel A), epinephrine (Panel B), and dopamine (Panel C) in 10 subjects with MC4R deficiency and 19 control subjects. The I bars represent the standard error.
Figure 5. Differences in Mean Blood Pressure in Subjects Receiving Melanocortin Agonist LY2112688 or Placebo at 24 Hours, According to Dose.

The graphs show the differences from placebo in mean systolic blood pressure (Panel A) and diastolic blood pressure (Panel B) in 28 subjects receiving a melanocortin agonist, according to the dose of the melanocortin agonist. The I bars represent 90% confidence intervals.

Modulation of Blood Pressure by Central Melanocortinergic Pathways

Jerry R. Greenfield

New developments in the pathogenesis of obesity induced hypertension
New developments in the pathogenesis of obesity-induced hypertension.

Kotsis, Vasilios; Nilsson, Peter; Grassi, Guido; Mancia, Giuseppe; Redon, Josep; Luft, Frank; Schmieder, Roland; Engeli, Stefan; Stabouli, Stella; Antza, Christina; Pall, Denes; Schlaich, Markus; Jordan, Jens; on behalf of the WG on Obesity, Diabetes; the High Risk Patient, European Journal of Hypertension. 33(8):1499-1508, August 2015. DOI: 10.1097/HJH.0000000000000645
Weight loss in hypertension management

- Long term weight loss studies in hypertension management are needed
- Behavioral modifications, hypocaloric diets and physical exercise contribute to weight loss and BP reduction
- Most patients regain weight within months to a few years after intervention

Low dose topiramate/phentermine reduces body weight and BP in obese hypertensive patients.

Mild to modest BP reductions have been observed on treatment with liraglutide and lorcaserin.

But...

- Naltrexone/bupropion increased BP through monoamine uptake inhibition elicited by bupropion.
- Sibutramine reduced BP through weight loss, but drug-specific actions was attenuated these BP results.

Obesity and hypertension

Lifestyle modification
a. Exercise
b. Dietary intervention
c. Reduce salt intake

Pharmacological treatment for obesity
1. Topiraminate/phentermine
2. Liraglutide 3mg
3. Orlistat

Bariatric surgery

BMI≥30 or 27 with comorbidities

BMI<30
Lifestyle modification

BMI>40 or 35 with comorbidities

Stage 1 hypertension or low total cardiovascular risk

BP not at goal with lifestyle interventions or obesity drugs, Stage 2 hypertension or high total cardiovascular risk

Antihypertensive treatment
1. ACEi, ARBs, CCBs or low dose combinations of CCBs/ACEi
2. Combinations ACEi/ARB with CCB (full dose)
3. β-blockers (nebivolol, carvedilol) or low dose thiazide diuretics
4. Mineralocorticoid receptor antagonists (spironolactone, eplerenone)
5. Sacubitril/valsartan (+ LEFHF)

Obesity, hypertension and diabetes

If HbA1c goal is ≤1%
Add metformin or SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) or GLP1 analogues (exenatide, liraglutide, dulaglutide)

BMI<30
Lifestyle modification

BMI≥30 or 27 with comorbidities
Pharmacological treatment for obesity

BMI>40 or 35 with comorbidities
Bariatric surgery

To conjointly reduce BMI, glucose and BP

Conclusions

- Obesity pathophysiology is the key of understanding CV diseases.
- We should acknowledge the importance of lifestyle interventions in the prevention of CV disease.
- Anti-obesity drugs may reduce comorbidities.
- Drugs commonly used to treat comorbidities may increase or reduce body weight.


Obesity is a key factor for cardiovascular diseases and complications. Obesity is associated with hypertension, dyslipidemia and type 2 diabetes, which are the major predictors of cardiovascular diseases in the future. It predisposes for atheromatous heart failure, sudden cardiac death, renal disease, and ischemic stroke that are the main causes of cardiovascular hospitalization and mortality. As obesity and the cardiovascular effects on the vessels and the heart start early in life, even from childhood, it is important for health policies to prevent obesity very early before the disease manifestation emerges. Key roles in the prevention are strategies to increase physical exercise, reduce body weight, and to prevent or treat hypertension, lipids disorders and diabetes easier and efficiently to prevent cardiovascular complications. Epidemiology and mechanisms of obesity-induced hypertension, diabetes, and dyslipidemia will be reviewed and the role of lifestyle modification and treatment strategies in obesity will be updated and analyzed. The best treatment options for people with obesity, hypertension, diabetes, and dyslipidemia will be discussed.

Keywords: cardiovascular risk, diabetes, dyslipidemia, guidelines, hypertension, obesity

Abbreviations: β-blockers, beta blockers; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; CETP, cholesteryl ester transfer protein; CRF, cardiorespiratory fitness; CRP, C-reactive protein; DASH, dietary approach to stop hypertension diet; DPP4, dipeptidyl peptidase IV; FFA, free fatty acids; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MAP, mean arterial pressure; MCV, mean corpuscular volume; NCEP, National Cholesterol Education Program; NF-kB, nuclear factor-kappa-light-chain-enhancer of activated B cells; PPAR, peroxisome proliferator-activated receptor; RAS, renin-angiotensin system; SGLT2, sodium-glucose co-transporter 2; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; VLDL, very low-density lipoprotein