



# GENERALIZED ATHEROSCLEROSIS, METABOLIC SYNDROME, AND RESISTANT HYPERTENSION - CAUSE AND CONSEQUENCES

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**SUMMARY** – The components of metabolic syndrome lead to generalized atherosclerotic changes and micro- and macrovascular complications with damage to systems and organs. Consequently, patients' treatment with the resulting changes in the target organs is costly, complicated, and unpredictable. We present a 65-year-old patient with diabetes diagnosed with hyperlipidemia, unregulated arterial hypertension in the presence of other metabolic syndrome components and who consequently developed complications of generalized atherosclerosis. Despite detailed, individually tailored therapy, in line with current recommendations, we suggest that treatment success is very closely related and dependent on dietary measures, healthy living habits, and patient cooperation.

**Key words:** *atherosclerosis; metabolic syndrome; renal failure*

## Introduction

Metabolic syndrome (MS) is a significant and growing cause of mortality and morbidity in most countries' general population, which is why cardiovascular risk assessment (CVR) models<sup>1,2,3</sup> have been developed. Metabolic syndrome is the medical term for a combination of diabetes, high blood pressure (hypertension), and obesity (add ref.-[www.nhs.uk](http://www.nhs.uk)). Hypertension alone, and especially within MS, is one of the main risk factors for developing atherosclerosis. The goal of treatment is to achieve the maximum reduction in overall cardiovascular risk and mortality. In addition to all preventive and non-pharmacological measures that can be implemented and adequate treatment of diabetes and dyslipidemia, pharmacological blockade of the sympathetic nervous system with indirect reduction of catecholamine levels and modification of baroreceptor sensitivity is desirable. The ASCOT

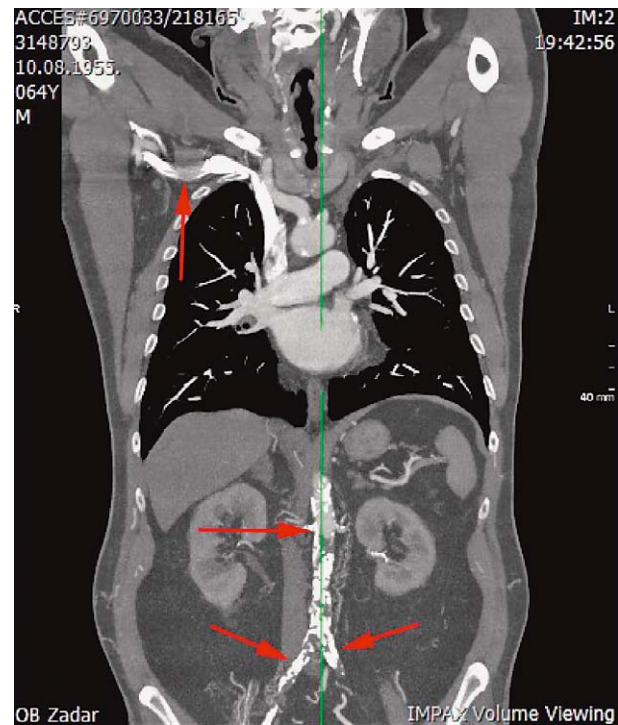
study showed a significant effect of a 1 mmHg increase in blood pressure as a 26% increase in CVR. Resistant hypertension, which we define when blood pressure is not controlled despite optimum doses of 3 first-line classes of antihypertensive drugs, including thiazide diuretic, isolated, represents a significant factor of CVR<sup>4</sup>. Elevated uric acid levels are an independent risk factor for hypertension.<sup>5</sup>

The renin-angiotensin-aldosterone system (RAAS) is one of the key pathophysiological determinant of hypertension<sup>6,7,8</sup>. Its contribution is particularly important in conditions of reduced glomerular filtration rate (GFR) when, in addition to increased activity of angiotensin II levels, there is also directly stimulated basally increased sympathetic tone with no decrease during the night (non-dipping). Present diabetes, as well as uncontrolled proteinuria, contribute to the further progression of kidney disease. We presented a patient with long-term unregulated arterial hypertension with other components of the metabolic syndrome and the consequent development of generalized atherosclerosis complications.

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## Case Report

A 65-year-old patient, long-standing nicotine use, obese, diabetic for over 15 years without signs of diabetic retinopathy, suffers from hyperlipidemia, unregulated arterial hypertension (for over 10 years), and generalized atherosclerosis. He was hospitalized for a planned kidney biopsy based on nephrotic proteinuria and azotemia. In physical examination: obesity (BMI 33.4 kg/m<sup>2</sup>), puffy peripheral edema, thin, pale skin of the lower extremities with hair loss, toenails on the remaining toes deformed. There was a significant difference in arterial pressure between the right (220/120 mmHg) and left arm (130/80 mmHg) with weakened distal arterial pulsations on lower extremities. He had an amputated toe on his left foot and the first three toes on his right foot. Subjectively, he complained of pain in his legs with a significant reduction in the walking distance of 100-200 meters and erectile dysfunction. Laboratory findings: glucose 16.6 mmol/L, HbA1C 8.7%, urea 19.9 mmol/L, creatinine 172 µmol/L, creatinine clearance 37.1 ml/min, 24-hour proteinuria 2.99 - 4.37 g/dU. Urine: proteins ++/+++, cholesterol 6.0 mmol/L, HDL-K 1.39 mmol/L, LDL - K 3.37 mmol/L, triglycerides 2.61 mmol/L, urate 504 µmol/L. Ambulatory blood pressure monitoring (ABPM) confirmed the absence of nocturnal drop (non-dipper). Before the hospitalization, he was taking ACE inhibitor in low dose, thiazide diuretic, CCB low dose, BB, and short-acting insulin 3 times a day. Aortic angiography describes severe atherosclerosis of the abdominal aorta, significant stenosis of the superior mesenteric artery, atherosclerotic altered major branches of the renal arteries (no significant stenoses) with significantly stenosed accessory renal arteries for the lower pole of both sides. From the L3 level, the infrarenal abdominal aorta was occluded, as was the iliac artery (AIC) bilaterally. Present occlusion of the left subclavian artery and vertebral artery (VA) in a section 2 cm long and significant stenosis of the ostium of the left vertebral artery. He had ischemic heart disease with a percutaneous coronary intervention (PCI) where coronary angiography revealed significantly stenosed and calcified left anterior descending (LAD) coronary artery, which is resolved in two acts (due to hemodynamic instability of the patient) by implantation of a 2 stents-DES ("drug-eluting stent"). According to cardiac ultrasound, he had mild concentric hypertrophy of the left ventricular



*Figure 1. Severe abdominal aortic atheromatosis. The main branches of the renal arteries are atherosclerotic changed, distal aorta is significantly stenosed as well as the proximal parts of the accessory renal arteries. Significant stenosis in the proximal part of the AMS. From the L3 level the infrarenal abdominal aorta is occluded as is the AIC bill. Left subclavian artery in the prevertebral part shows subocclusion and occlusion in a segment of 2 cm long; significant stenosis of the ostium of the left vertebral artery.*

wall, normal systolic function (EF about 60%) without clear regional outbursts of contractility. The left atrium was enlarged. The right ventricle was normal size, mild aortic valve atheromatosis with normal function. Color Doppler indicates mitral regurgitation (MI) of the first degree and tricuspid insufficiency (TI) of the first degree without indirect indicators of pulmonary hypertension. A kidney biopsy was performed. At the level of light and immunofluorescence microscopy indicate diabetic nephropathy class III with advanced nephroangiosclerosis and perihilar sclerosis that probably refers to a secondary form of focal segmental glomerulosclerosis. The X-ray of the right foot showed osteolysis of the distal part of the distal phalanx of the third toe. Ekg showed sinus rhythm, frequency 70/min, biphasic T wave in leads D1, aVL, and V5-V6.

We also investigated the possibility of OSA sy, but according to his results on the Epworth scale (3) and heteroanamnesis, we discarded it.

Considering all his comorbidities, we prescribed ACE inhibitor in therapy in a higher dose than he had before, CCB in maximum dose, thiazide as a diuretic for a better metabolic profile, and a low dose of MRA–spironolactone, checking kidney function (eGFR) regularly.

## Discussion

Long-term metabolic syndrome is a significant factor in cardiovascular risk with the presence of resistant hypertension, high-grade renal failure, and nephrotic proteinuria with its consequences (decreased GFR- 34-31 ml/min, nephrotic syndrome - 4.37 g/dU, elevated cholesterol 6.0 mmol/L, LDL 3.61 mmol/L, triglycerides 2.61 mmol/L and unregulated blood sugar -16.6mmol/L)<sup>1,2,4</sup>. Despite the modification of antihypertensive therapy, ABPM still shows unregulated blood pressure. Initial endothelial damage at the level of the intima of the blood vessel, increased sympathetic activity, hyperglycemia, dyslipidemia, and many other proatherosclerotic factors lead to severe micro and macrovascular complications<sup>9</sup>. Peripheral occlusive artery disease (PAD) develops gradually and is clinically manifested with moderate to severe Rutherford's grade IIa/IIb claudication. Subjective disturbances are expressed as dull pain during physical work, long walks, standing, and exposure to cold. They usually disappear while resting, but they can also appear as pronounced cramps at night at rest, indicating the existence of neuropathy. Occasionally, ulcerations and gangrene are present on the peripheral parts of the lower extremities. Symptoms are usually reciprocal to the degree of morphological changes in the blood vessels. This problem is significantly more common in males with diabetes, dyslipidemia, hypertension, increased blood urate values, long-term smoking, and most of them also present coronary heart disease. Atherosclerotic changes are generalized with severe stenoses of the aorta and many of its branches (Fig. 1). The consequences of these atherosclerotic changes are manifested in various organs and systems. In this case, it presents as ischemic heart disease with the need for PCI and valvular changes of MI, TI, chronic renal failure, cerebrovascular, and peripheral arterial occlusive disease. Given the complex interaction of the compo-

nents of metabolic syndrome and resistant hypertension as well as the high prevalence in the therapeutic approach, the emphasis, in addition to aggressive anti-hypertensive, antidiabetic and hypolipemic therapy, should be on dietary measures and healthy lifestyle habits to prevent fatal consequences.

## Conclusion

Given the complex interrelationship of all its comorbidities, male gender, and long-standing nicotine, the question is which of these factors is the initial and causal driver of all consequences. Significant morphological changes require a multidisciplinary approach with the necessary changes in lifestyle habits: smoking cessation, weight loss, restriction of salt and fat intake, moderate exercise, regulation of blood sugar, urate, and blood pressure, and the necessary invasive interventions.

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## Sažetak

GENERALIZIRANA ATEROSKLEROZA, METABOLIČKI SINDROM  
I REZISTENTNA HIPERTENZIJA – UZROCI I POSLJEDICE*D. Klarić, P. Grbić Pavlović i M. Klarić*

Komponente metaboličkog sindroma dovode do generaliziranih aterosklerotskih promjena te mikro i makrovaskularnih komplikacija s oštećenjem sustava i organa. Slijedom toga, liječenje bolesnika s posljedicama promjena na ciljnim organima vrlo je skupo, složeno i nepredvidljivo. Predstavljamo 65-godišnjeg pacijenta, dijabetičara, kojem je dijagnosticirana hiperlipidemija, neregulirana arterijska hipertenzija u prisutnosti drugih komponenata metaboličkog sindroma i posljedično razvijene komplikacije generalizirane ateroskleroze. Unatoč detaljnoj, individualno prilagođenoj terapiji, u skladu s trenutnim preporukama, smatramo da je uspjeh liječenja vrlo usko povezan i ovisi o prehranbenim mjerama, zdravim životnim navikama i suradnji pacijenta.

Ključne riječi: *ateroskleroza; metabolički sindrom; bubrežna insuficijencija*