

METABOLIC SYNDROME, MORBIDITY AND MORTALITY IN THE ERA OF COVID-19 PANDEMIC

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SUMMARY

The prevalence of obesity, diabetes, arterial hypertension and cardiovascular and cerebrovascular diseases is increasing worldwide. Nowadays we are witnessing a pandemic of metabolic syndrome and obesity and an epidemic of these diseases in Croatia as well. Moreover, every second Croatian citizen dies because of cardiovascular diseases. Visceral obesity, diabetes, dyslipidemia and arterial hypertension tend to cluster forming a syndrome that we call metabolic syndrome. The concept of metabolic syndrome was defined several decades ago as visceral type of obesity, hypertriglyceridemia, low HDL-cholesterol, arterial hypertension and diabetes mellitus (insulin resistance). Most widely used definition is the one by National Education Cholesterol Program, NCEP - Adult treatment Panel III - ATP III. Therefore, visceral obesity is considered as one of the greatest risks for mortality worldwide. COVID pandemic increased the risk of deaths especially among patients with metabolic syndrome. Pandemia perpetuated several other socio-economical risk factors (stress, depression, physical inactivity, deviant behaviour...) which also strongly influence cardiovascular health. Unfortunately, SARS-COV-2 virus enters the host (human) cell using signaling pathways (ANG II R_c) known very well from the metabolic syndrome research and connecting those two entities predisposing these patients for a much worse prognosis when infected with SARS-COV-2 virus. To conclude - chronic obesity pandemic goes hand by hand with novel COVID-19 pandemic dramatically increasing the risk of severe morbidity and mortality.

Key words: metabolic syndrome - COVID-19

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INTRODUCTION

The prevalence of obesity, diabetes, arterial hypertension, and therefore cardiovascular and cerebrovascular diseases as direct consequences of these risk factors is increasing worldwide.

Nowadays almost every second Croatian citizen dies because of cardiovascular diseases. Visceral obesity, diabetes, dyslipidemia and arterial hypertension tend to cluster forming a syndrome named metabolic syndrome. The concept of metabolic syndrome was defined several decades ago as visceral type of obesity, hypertriglyceridemia, low HDL-cholesterol, arterial hypertension and diabetes - insulin resistance (Reiner 2013, Aguiar 2015).

Most widely used definition of metabolic syndrome is a definition by the National Education Cholesterol Program, NCEP - Adult treatment Panel III- ATP III where three or more components together define this syndrome. Every single component of metabolic syndrome is independently a risk factor for atherosclerotic cardiovascular disease but when clustered together they are an even greater risk. COVID-19 pandemic is a serious additional risk for severe forms of morbidity and premature mortality among these patients.

The problem of obesity is a global chronic problem. Moreover, the World is facing already for some time the pandemic of obesity. To be honest, although we are aware of it for a number of years, we have not taken such rigorous measures as for acute pandemics like the COVID-19 pandemic. Experts estimate that until 2025 there will be around 2 billion people who will be

overweight or obese. Nowadays in the USA every third inhabitant has BMI greater than 30 kg/m². Although viscerally obese person can be metabolically healthy, obesity predisposes for metabolic disturbances (insulin resistance, arterial hypertension, dyslipidemia) that increase cardiovascular risk (De Bacquer 2010). Overweight, obesity and metabolic syndrome pandemic are a great problem in Croatia as well. We do not have available the exact data on the prevalence of metabolic syndrome in Croatia but we can extrapolate some numbers from the information on the prevalence of diabetes or hypertension. We will most probably not be wrong if we conclude that every third Croatian has metabolic syndrome. Available data are sparse. According to few Croatian authors the prevalence of metabolic syndrome in the continental part of Croatia is 40% (35% men; 42% women). Almost seven decades ago a big epidemiological study known as *Seven Countries Study* showed that Mediterranean lifestyle is beneficial and decreases cardiovascular risk. Nowadays these regional differences in cardiovascular morbidity and mortality are not present any more (Bergovec, 2008) due to migration of the Croatian population (especially after the war) and due to dramatic changes in the lifestyle (Kolcic 2006, Sahay 2013).

The concept of metabolic syndrome was introduced by an American endocrinologist Reaven in 1988 who was the first to describe the association between visceral obesity and cardiovascular risk in patients with arterial hypertension, hyperglycemia and atherogenic dyslipidaemia (Reaven 1988). Stressing

the concept of risk factor clustering with visceral adiposity as the milestone of the concept he has named this association Syndrome X. However, since the term syndrome X was already used in cardiology, in 1999 this clustering of symptoms was named metabolic syndrome. However other names were also used in the past such as – Deathly quartet, Plurimetabolic syndrome, Insulin resistency syndrome etc.

Nowadays we have several “user friendly” definitions that are used worldwide – the IDF definition and NCEP-ATPIII definition. Definitions of metabolic syndrome take into account waist circumference, hypertension, diabetes and dyslipidemia. European data show that every third adult inhabitant has a metabolic syndrome. Patients with metabolic syndrome have 2-4 times greater risk of cardiovascular morbidity and 5-7 times greater risk for the development of diabetes. Data from Japan showed that patients with metabolic syndrome have 10.5 times greater risk for myocardial infarction than healthy individuals (Nakamura 2001).

GENESIS OF METABOLIC SYNDROME

Genes are robust and hard to change in the process of evolution. So today we have genes that encode enzymes and rudiment and robust mechanisms that have not much changed in the last 10 000 years. These genetically determined mechanisms helped the humans to survive. Nevertheless, in the last hundred years humans have changed everything that surrounds us. We are programmed that when we have an excess of the energy we have to store it. That helped the humans to survive during periods of starvation which often occurred in the past. However, today most of the human kind has a plenty of energy available but still same old robust mechanisms are encoded by genes. As a result many humans are overweight and suffer from obesity accompanied with visceral adiposity.

Renin-angiotensin-aldosterone system (RAAS) is a part of this robust system that helped us to survive but nowadays this is the basis of metabolic disturbances. Moreover, SARS-COV-2 uses the same pathway (RAAS) in its pathogenic pathway.

RAAS AND SARS-COV-2

Aldosterone plays a pivotal role in the genesis of metabolic disturbances in patients that are viscerally obese. Adipocytes from visceral fat secrete adipokines. Among them are almost all components of renin-angiotensin-aldosterone system (RAAS). So viscerally obese patients are in metabolic state which is similar to the one in patients with primary aldosteronism. As a consequence of higher aldosterone levels they have insulin resistance, hypertension, dyslipidemia and endothelial dysfunction. Aldosterone interferes with inflammatory cytokines like IL-6 and TNF- α . Other adipo-

kines secreted by visceral fat are leptin, adiponectin, resistin, interleukin 6, PAI-1 and tumor necrosis factor alpha (TNF- α).

The responsible pathogen for COVID-19 is the new severe acute respiratory syndrome coronavirus (SARS-CoV) 2 belonging to the same family of viruses as SARS-CoV and Middle East respiratory syndrome coronavirus that originally are zoonotic and have been associated with severe illness during the outbreaks in 2003 and 2012, respectively. The virulence of coronavirus strains is mainly associated with variations in surface proteins mediating cellular entry of the virus. The focus of its pathogenicity is placed on “spike” protein (S-protein) and its potential cellular receptor, angiotensin-converting enzyme 2 (ACE2).

SARS-CoV-2 infects human cells via binding a “spike” protein on its surface to angiotensin-converting enzyme 2 (ACE2) within the host. ACE2 is crucial for maintaining tissue homeostasis and negatively regulates the renin-angiotensin-aldosterone system (RAAS) in humans. The RAAS is crucial for normal function of multiple organ systems including the lungs, heart, kidney, and vasculature. Given that SARS-CoV-2 internalizes via ACE2, the resultant disruption in ACE2 expression can lead to altered tissue function and exacerbation of chronic diseases. The widespread distribution and expression of ACE2 across multiple organs is critical for our understanding of different clinical pictures and outcomes of COVID-19.

It is quite clear that COVID-19 and metabolic syndrome share the same pathways perpetuating common deleterious effect on health. In a study performed in the U.S. during March 2020 on 1482 patients hospitalized with COVID-19 in fourteen states, 12% of them had history of comorbidities. Out of them 49.7% were hypertensive patients, 48.3% were obese, 34.6% were patients with chronic liver diseases, diabetic patients represented 28.3% and 27.8% were patients with cardiovascular diseases were 27.8% (Garg 2020). A study from Brazil on 347 398 confirmed cases of COVID-19 with 13 868 deaths found that most of them were associated with comorbidities. Heart disease was the most common comorbidity with total of 7318 deaths, followed by diabetes, kidney disease, neurological diseases, pneumopathy, obesity, immunosuppression and asthma.

Since obesity is a risk factor for several diseases, including infections, these data are even more alarming. Obese patients have a constant chronic inflammation due to the high concentrations of chemokines, adipokines and pro-inflammatory cytokines. This chronic inflammation causes a delayed and inferior immune response, with decreased activation of macrophages in the course of infection. In addition, the immune memory of obese individuals is also impaired, both humoral and cellular, weakening both adaptive response of immune system to infection and immunization of these patients.

Diabetes has been identified as the second most common comorbidity among patients with COVID-19. Hypotheses have been raised that this high incidence rate of COVID-19 in patients with diabetes is directly linked to the high gene expression of angiotensin-converting enzyme 2 (ACE2) in their cells, which are used by SARS-CoV-2 to enter human cells, due to treatment with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). This would not only increase the risk of these patients to infection but would also make it difficult to control comorbidity during treatment against COVID-19. This relationship is not yet fully understood and further studies are needed to confirm it, since the drug treatment protocols for diabetic patients remain the same for their metabolic dysfunction.

A meta-analysis involving more than 3000 patients with COVID-19 found that patients with cardiovascular disease are up to five times more likely to develop the critical stage disease (Zheng, 2020).

CONCLUSION

Metabolic syndrome is a risk factor that influences COVID-19 progression and prognosis. The prevalence of patients who are obese, have diabetes mellitus, arterial hypertension or liver damage among severe cases of COVID-19 all over the World supports the importance of prevention directed towards this risk group in prophylaxis, monitoring and treatment. The development of a vaccine for immunization and vaccination is still the best long-term solution for the prevention of serious complications of COVID-19 and fatal outcomes as well as future outbreaks of SARS-CoV-2 infections. In addition, people of any age who have pre-existing diseases, such as heart disease, diabetes, obesity and metabolic syndrome need to be more alert and try to avoid SARS-CoV-2 infection. We have to be aware that we are facing two pandemics. Maybe the acute one will help us to better understand and better deal with the chronic one that we are facing in the last decades.

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