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Lifestyle and severe SARS-CoV-2 infections: Does the individual metabolic burden determines the outcome?

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SARS-CoV-2 is widely spread around the world. Up to 2nd September 2020, more than 25 million cases of SARS-CoV-2 infections are confirmed, more than 850,000 people died from the consequences of COVID-19 disease. However, its virulence and mortality differ significantly between countries and populations. While a large number of infected patients only suffer from symptoms like fever and cough similar to a milder flu, especially patients with pre-existing comorbidities like diabetes, obesity, and hypertension present with more severe disease courses requiring the need for intensive care and prolonged invasive ventilation including ECMO support which subsequently results in an increased mortality.[1] While so far rather few SARS-CoV-2 infections confirmed in countries like Canada and Norway, a dramatic increase of new infections is reported from the United States (US) of America—actually among the highest worldwide. In this regard, it is remarkable that nearly 40 percent, that means almost every second US-citizen, suffer from diabetes or pre-diabetes.[2] In this context it is alarming, that already every fifth adolescent between 12 and 18 years in the US is affected from pre-diabetes, associated with an impaired insulin sensitivity, an elevated systolic blood pressure, and higher than normal blood cholesterol levels.[3] More interestingly, there is a dramatically increasing number of diabetic patients also in Asia, where SARS-CoV-2 originates. The WHO has recently released an individual body-mass-index for the Asian population.[4] Therefore we here aim to focus on the impact of the individual metabolic burden as a result of our western lifestyle predisposing to more severe SARS-CoV-2 infections

In brief, SARS-CoV-2 targets mucosal epithelial cells of primarily respiratory and intestinal tract due to the regulation of angiotensin-converting-enzyme 2 (ACE2). ACE2-dependent up-regulation of Angiotensin1-7 is associated with rather protective effects regarding its impact on endothelial function and vasodilatation as also its anti-fibrotic, anti-proliferative, and anti-inflammatory effects via binding to the MAS-receptor, an opponent of AT1 receptor. Down-regulation of ACE2 after SARS-CoV-2 penetration may lead to a controlled and most effective virus invasion resulting a high virus load while levels of ACE2 expression are decreasing.[5] In pneumonia and ARDS, an abrogated expression of ACE2 in mice is associated with a more severe form of disease due to an enhanced vascular permeability resulting in lung edema and worsened lung function.[6] Thus, ACE2 might protect lung function and prevent from lung failure. However, one question remains: May our individual metabolic burden that is diabetes, obesity and hypertension affect ACE2 levels and which consequences of that do we have to expect?

In diabetes, ACE2 deficiency is associated with a worsening of insulin resistance, body fat accumulation, and arterial hypertension. A latter, which is mediated by detrimental effects on insulin signaling, the activation and aggravation of inflammatory processes, and the upregulation of Angiotensin II.[7] In this regard, is worth mentioning that prescription habits of thiazide diuretics for the treatment of hypertension may contribute to this metabolic disorder, while pharmacotherapy varies significantly between Anglo-Americans and within continental European countries. Thiazide diuretics are known to further deteriorate preexisting pre-diabetic metabolism due to potassium-insulin dysregulation, an effect that

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could be put into perspective under regulation of the Angiotensin-Aldosterone axis again. In patients with diabetes, a higher cell affinity and penetration of SARS-CoV-2 on the one hand but on the other hand a reduced elimination of the virus and negative interference with the immune system and T-cell function resulting in hyper-inflammation and the occurrence of the most feared, so called "cytokine storm" were recently described.[8] ACE2 is also associated with inflammation in obesity, triggered in part by macrophage polarization, the subsequent release of cytokines like TNFα and IL-6, and direct stimulation of the adipokine signaling pathway.[9] Other relevant mechanisms in this context seem to be the down-regulation of glutamine metabolism in obesity or environmental factors, such as air pollution, which in turn is also associated with the development of diabetes, the dysregulation of cell immunity, systemic inflammation, oxidative stress, and multi organ dysfunction.[10,11] Thus, an already impaired innate and adaptive immunity which occurs in persistent chronic inflammation of (pre-) diabetic and obese patients is increasingly restricted, contributing to an unfavorable disease course in SARS-CoV-2 infection.

In contrast, the presence of ACE2 is known to exert an anti-obesity and anti-inflammatory effect due to its MAS receptor binding capacity.[12] Soluble ACE2 is described to even block SARS-CoV-2 infection.[13] In diabetes, an overexpression of ACE2 is associated with an improved insulin tolerance that is, due to an increased ß-cell proliferation.[13] However, a recently described increase of ACE2 levels in adipocytes and thus also in obesity may lead to a better virus invasion into the cells because of more receptor binding capacity. An additional increase of cytokine levels resulting in a chronic inflammatory condition as well as an impaired overall organ function due to a pre-existing metabolic syndrome and physical factors such as an increased abdominal pressure and limited chest expansion may explain the often more severe disease courses of SARS-CoV-2 infection especially in these patients.[14] On the other hand, potential anti-inflammatory effects of for example vitamins like vitamin D are not sufficient, in 40% to 80% of the obese population a vitamin D deficiency is reported.[15] Taken together, given the knowledge of individual metabolic burden in various populations around the globe will help to explain at least in part the dramatic mortality rates. Thus, it is tempting to speculate that our lifestyle contributes to the development of hot spots in the actual SARS-CoV-2 infection pandemic whereas the individual metabolic burden determines the mortality risk. Thereby, "lifestyle" is not only a simple word. It is rather driven by multiple interlocking environmental factors and their consequences. Only to name a few, an inadequate nutrition due to an excessive ingestion of unhealthy food, the so called stress-eating to compensate social isolation and anxiety is even more triggered by elevated blood cortisol levels. An increasing consumption of drugs, cigarettes and alcohol, the lack of physical activity, stress, psychological disorders and poor sleep in a performance-oriented population, aggravated during time of pandemic related quarantine, and negative social interactions have to be mentioned in this context.[16–19] Each of these factors, so called "anthropogens," is associated with the occurrence of smoldering processes of chronically inflammation ("metaflammation") and in turn with the emergence of diabetes, obesity, and hypertension.[18,19] Due to this, also a not inconsiderable risk of cardiovascular events and complications including severe arrhythmias, myocardial infarction, acute heart failure and cardiac arrest have to be mentioned.[20] In this regard, it remains to be investigated whether socio economic, epidemiologic and therapeutically interventions might reverse mortality rates in SARS-CoV2 infections. In consequence, we are convinced that we should critically revise our western life-style behavior since SARS-CoV2 will be part of our future environment.

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