

1 Extended abstract from IGM webinar May 6, 2021 Gender differences in COVID-19 pandemic around the world

COVID, sex, gender and cardiovascular disease

Vera Regitz-Zagrosek¹, Jasmin Berger²

¹Berlin Institute for Gender in Medicine, Charité, Germany, and University of Zürich, Zurich, Switzerland; ²Berlin Institute for Gender in Medicine, Charité, Germany

Introduction

Early in the pandemic we identified sex-disaggregated data for COVID-19 in several Countries, showing similar numbers of cases between the sexes, but more severe outcomes in men than women.¹ Case fatality was highest among middle aged men with pre-existing cardiovascular conditions. Since the course of the disease is modulated by potential sex-specific mechanisms, we discussed the hormone-regulated expression of genes encoding for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) entry receptors angiotensin converting enzyme (ACE)-2 receptor and transmembrane serine protease 2 (TMPRSS2), as well as the sex hormone-driven innate and adaptive immune responses. The impact on COVID-19 of gender-specific lifestyles, health behaviors, psychological stress and socio-economic conditions was also discussed, as well as the sex-specific aspects of the antiviral therapies.

Interaction between COVID and cardiovascular disease (CVD): epidemiological and observational data

The Nimgaonkar group used an innovative approach to analyze the interaction between CVD and COVID. They used large data sets from different European Countries (France, Germany, Italy, Spain and the Netherlands) and the US. Then they analyzed the mortality rates from cardiovascular disease, cancer and COVID. They found that the mortality rates from CVD and COVID share similar patterns across the adult life course whereas those from cancer are different.²

Similar mechanisms in COVID and cardiovascular disease could offer an explanation for this phenomenon, and the effect of sex hormones as a biological factor underlying both phenomena should be analyzed.

Yet another large study pointed out that age was the most significant risk factor for COVID in both sexes, and that hypertension or CVD alone was not significant, while diabetes was.³ In a large meta-analysis – which included 26 studies with 8,497 patients – sex had a relatively weak but significant effect, whereas CAD, hypertension, cerebrovascular diseases and diabetes mel-

litus had stronger effects.⁴ Thus, the interaction between age, cardiovascular disease and metabolic disorders, like diabetes, is particularly predictive of COVID. This led us to analyze the role of a physiological mechanisms that is predominant in all these inflammatory conditions.

Sex differences in myocarditis and cardiovascular inflammation

Inflammation plays a major role in cardiovascular aging and in metabolic disorders. Moreover, NAD⁺-dependent deacetylases, or sirtuins – a group of enzymes that regulate mitochondrial biogenesis and inflammation – are regulated by sex or sex hormones. In earlier studies we analyzed the age- and sex-related alterations of cardiac Sirt1 and Sirt3 along with mitochondrial biogenesis, anti-oxidative defense and inflammatory state in young (<40 years) and old (>51 years) human hearts.⁵ We found a significantly higher expression of Sirt1 and Sirt3 in the young female hearts versus male. The levels of sirtuins anti-oxidative proteins were higher in the young female hearts versus male, but were down-regulated in older females. Aging was associated with a significant increase in the number of cardiac macrophages and pro-inflammatory cytokines, as well as NF- κ B up-regulation in female hearts, indicating a pro-inflammatory shift in the aging female hearts. In conclusion, a higher expression of anti-inflammatory sirtuins in the young female heart could protect younger women from COVID-19, and the up-regulation of the inflammatory mechanisms in old age – together with a decline in the mitochondrial anti-oxidative defense – could contribute to an interaction between COVID and age, as well as to an interaction between CVD and age in both sexes.

Fairweather et al. have already proposed the pivotal role of sex hormones in the sex-related differences in cardiac inflammation.⁶ While in females estrogens have cardio-protective properties, characterized by reduced cardiomyocyte apoptosis, counteracting fibrosis and hypertrophy-inducing cellular pathways, testosterone increased cardiac inflammation in a myocarditis mice model, and promoted the M1 response of macrophages in males.⁷⁻¹²

In contrast with the protective effect of female sex or sex hormones, testosterone is responsible for adverse

cardiac inflammatory remodeling in males.^{13,14} The impact of testosterone replacement therapy on the cardiovascular risk has been analyzed by a number of studies, anticipating that it might be protective, however most studies showed that this was not the case. Testosterone enhanced the cumulative number of cardiovascular events in clinical trials. It also enhanced arteriosclerotic plaque formation, platelet aggregability, myocyte hypertrophy, and inflammation.¹⁵

Putting all these data together, we conclude that the differences in the cardiovascular immune system and its interaction with testosterone may lead to an increased susceptibility to COVID in men.

Non immunological mechanisms for sex- and age-dependent differences in COVID-19

The sex-, age- and disease-dependent regulation of ACE, AT1 and AT2 has been well described.^{16,17} We did a proteomic analysis to test the potential up-regulation of ACE2, the potential entry receptor for COVID-19 into cardiomyocytes in healthy and diseased human hearts in 41 patients with severe aortic stenosis (AS), in 17 patients with severe mitral valve regurgitation (MR) and in 17 controls.¹⁸ All patients had cardiac hypertrophy, but normal left ventricular ejection fraction. Myocardial samples were obtained from the left ventricular septum during valve surgery. Protein abundances were determined by label-free shot-gun mass spectrometry on a Thermo Orbitrap instrument and analyzed by MaxQuant with 1% false discovery rate (FDR). ACE2 protein abundance and mRNA expression in human hearts increased with pressure, but not with volume-overload. ACE2 abundance increased in the whole group in males and in females, but the fold change in males was twice that in females. Unfortunately, the ACE2 myocardial protein analysis was not powered to detect sex differences, and the difference between males and females did not reach statistical significance. However, based on this data, a contribution of greater myocardial RAAS activation in males to a greater cardiac damage in COVID cannot be excluded.

Gender-dependent mechanisms

In addition to biological sex, gender plays a major role in COVID. In general, men do have a more risk-related behavior than women, and frequently do not agree to wear a mask.¹⁹ Furthermore, women's working conditions are frequently poorer than men's; they frequently work more precarious jobs, or jobs with caring duties, and they take charge of unpaid caring duties within their family. Thus, they are more frequently in contact with other people and cannot just practice smart working. This was particularly evident from the numbers in Switzerland. Before the lockdown, equal numbers of wom-

en and men were diagnosed with COVID (49.5% vs 50.5%), but after the lockdown men were only 45% of the overall positive population.²⁰

Women are underrepresented also in cardiovascular prevention. Their cardiovascular risk factors – which are also the risk factors for COVID – are treated less intensively than men's.^{21,22} Gender-related under treatment of cardiovascular risk factors may also increase the risk of COVID in women.

Further similarities between COVID and CVD: the lack of sex-specific reporting

Cardiovascular studies frequently do not report outcomes in a sex-specific manner, even though this is clearly indicated by the SAGER (Sex And Gender Equity in Research) guidelines.

The low-dose colchicine (LoDoCo2) trial and the colchicine cardiovascular outcomes trial (COLCOT)²³ confirmed the efficiency and safety of low-dose colchicine after myocardial infarction, as well as in patients with chronic coronary artery disease. Both were limited by the low number of women enrolled, who accounted for only 15 or 19% of the study population. In both studies, hazard ratios for the primary efficacy endpoints were significant in the overall population and in men, but not in women. This was simply stated in the supplementary annex, without any further discussion. Adverse effects were not disaggregated for sex. This is a very recent example of under-recognition and under-reporting of sex-specific effects in the cardiovascular literature.²⁴ Moreover, adverse drug reactions to cardiovascular medicinal products are frequently not reported in a sex-specific manner. Less than 12% of the studies report the sex-specific adverse effects of heart failure drugs.²⁵

The same is true for COVID. In COVID studies, consideration for SAGER (Sex And Gender Equity in Research) guidelines is generally lacking. In a systematic meta-analysis, only 0 to 4% of the observational studies and 0 out of 17 interventional COVID-19 studies included sex-specific analysis in their introduction, methods and discussion section.²⁶ With regard to the inclusion of patients of both genders, vaccination studies did better: 80% of them included more than 45% of the smaller sex group, women or men. In the clinical treatment trials and in the observational studies this was not the case: 75% of the studies included over 55% of men. The fact that with COVID vaccination 90% of the allergic reactions occurred in women was not published in high-impact or large distribution journals.²⁷

In summary, sex-specific reporting is equally poor in CVD and COVID; differences in the cardiovascular immune system may lead to an increased susceptibility to COVID in men, and a greater myocardial RAAS activation in males may contribute to a larger cardiac damage

in men with COVID. In contrast, gender related exposure in women together with undertreatment of cardiovascular risk factors may increase the risk in women.

Keywords. COVID-19, sex, gender, cardiovascular disease.

References

1. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ*. 2020;11:29.
2. Nimgaonkar I, Valeri L, Susser E, Hussain S, Sunderram J, Aviv A. The age pattern of the male-to-female ratio in mortality from COVID-19 mirrors that of cardiovascular disease in the general population. *Aging (Albany NY)*. 2021;13:3190-201.
3. Silverio A, Di Maio M, Citro R, Esposito L, Iuliano G, Bellino M, et al. Cardiovascular risk factors and mortality in hospitalized patients with COVID-19: systematic review and meta-analysis of 45 studies and 18,300 patients. *BMC Cardiovasc Disord*. 2021;21:23.
4. Moola AI, Micali LR, Matteucci F, Luca F, Rao CM, Parise O, et al. Quantification of death risk in relation to sex, pre-existing cardiovascular diseases and risk factors in COVID-19 patients: let's take stock and see where we are. *J Clin Med*. 2020;9: 2685.
5. Barcena ML, Pozdniakova S, Haritonow N, Breiter P, Kuhl AA, Milting H, et al. Dilated cardiomyopathy impairs mitochondrial biogenesis and promotes inflammation in an age- and sex-dependent manner. *Aging*. 2020;12:24117-33.
6. Fairweather D, Petri MA, Coronado MJ, Cooper LT. Auto-immune heart disease: role of sex hormones and autoantibodies in disease pathogenesis. *Expert Rev Clin Immunol*. 2012;8:269-84.
7. Pedram A, Razandi M, Narayanan R, Levin ER. Estrogen receptor beta signals to inhibition of cardiac fibrosis. *Mol Cell Endocrinol*. 2016;434:57-68.
8. Dworzatzek E, Mahmoodzadeh S, Schriever C, Kusumoto K, Kramer L, Santos G, et al. Sex-specific regulation of collagen I and III expression by 17beta-estradiol in cardiac fibroblasts: role of estrogen receptors. *Cardiovasc Res*. 2019;115:315-27.
9. Jazbutyte V, Arias-Loza PA, Hu K, Widder J, Govindaraj V, von Poser-Klein C, et al. Ligand-dependent activation of ER{beta} lowers blood pressure and attenuates cardiac hypertrophy in ovariectomized spontaneously hypertensive rats. *Cardiovasc Res*. 2008;77:774-81.
10. Regitz-Zagrosek V, Oertelt-Prigione S, Seeland U, Hetzer R. Sex and gender differences in myocardial hypertrophy and heart failure. *Circ J*. 2010;74:1265-73.
11. Frisancho-Kiss S, Davis SE, Nyland JF, Frisancho JA, Cihakova D, Barrett MA, et al. Cutting edge: cross-regulation by TLR4 and T cell Ig mucin-3 determines sex differences in inflammatory heart disease. *J Immunol*. 2007;178:6710-4.
12. Coronado MJ, Brandt JE, Kim E, Bucek A, Bedja D, Abston ED, et al. Testosterone and interleukin-1beta increase cardiac remodeling during coxsackievirus B3 myocarditis via serpin A 3n. *Am J Physiol Heart Circ Physiol*. 2012;302:H1726-36.
13. CavaSin MA, Tao ZY, Yu AL, Yang XP. Testosterone enhances early cardiac remodeling after myocardial infarction, causing rupture and degrading cardiac function. *Am J Physiol Heart Circ Physiol*. 2006;290:H2043-50.
14. Fairweather D, Cooper LT Jr, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol*. 2013;38:7-46.
15. Gagliano-Juca T, Basaria S. Testosterone replacement therapy and cardiovascular risk. *Nat Rev Cardiol*. 2019;16:555-74.
16. Regitz-Zagrosek V. Sex and gender differences in pharmacology. Berlin Heidelberg: Springer-Verlag; 2012.
17. Regitz-Zagrosek V, Kararigas G. Mechanistic pathways of sex differences in cardiovascular disease. *Physiol Rev*. 2017;97:1-37.
18. Stegbauer J, Kraus M, Nordmeyer S, Kirchner M, Ziehm M, Dommisch H, et al. Proteomic analysis reveals upregulation of ACE2 (Angiotensin-Converting Enzyme 2), the putative SARS-CoV-2 receptor in pressure-but not volume-overloaded human hearts. *Hypertension*. 2020;76:e41-3.
19. Capraro V, Barcelo H. The effect of messaging and gender on intentions to wear a face covering to slow down COVID-19 transmission. <https://doi.org/10.31234/osf.io/tg7vz>
20. Bundesamt für Gesundheit. Grafische Darstellung der Daten: Verteilung nach Kanton, Alter und Geschlecht; 2020.
21. Peters SAE, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. *Circulation*. 2019;139:1025-35.
22. Lee CMY, Mnatzaganian G, Woodward M, Chow CK, Sitas F, Robinson S, et al. Sex disparities in the management of coronary heart disease in general practices in Australia. *Heart*. 2019;105:1898-1904.
23. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381:2497-505.
24. Gebhard C and Regitz-Zagrosek V. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2021;384:776-7.
25. Bots SH, Groepenhoff F, Eikendal ALM, Tannenbaum C, Rochon PA, Regitz-Zagrosek V, et al. Adverse drug reactions to guideline-recommended heart failure drugs in women: a systematic review of the literature. *JACC Heart Fail*. 2019;7:258-66.
26. Palmer-Ross A, Ovseiko PV, Heidari S. Inadequate reporting of COVID-19 clinical studies: a renewed rationale for the Sex and Gender Equity in Research (SAGER) guidelines. *BMJ Glob Health*. 2021;6:e004997.
27. Team CC-R, Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine - United States, December 21, 2020-January 10, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:125-129.

Authors contribution statement: both Authors have contributed equally to this work and to submit the manuscript

Conflict of interest: the Authors declare that they have no competing interests.

Correspondence to:

Vera Regitz-Zagrosek

Institute of Gender in Medicine (GiM)
Center for Cardiovascular Research (CCR)
Charité -Universitätsmedizin Berlin
Hessische Str. 3-4
D-10115 Berlin, Germany
e-mail: vera.regitz-zagrosek@charite.de