Letter to the editor

Cardiovascular and thrombotic complications after COVID-19 vaccination

The Severe Acute Respiratory Syndrome Covid-19 (SARS-CoV-2) pandemic caused a disastrous global emergency with tremendous medical, financial and social consequences. Since December 2019 science has been fighting against a coronavirus with ~~a~~ high transmission and relatively low fatality rate [1]. The most severe clinical manifestation is a respiratory infection with ARDS (Acute Respiratory Distress Syndrome–with negative implications mainly among older people. Several other clinical scenari~~a~~os has been described worldwide in combination with the inflammatory and thrombogenic activation provoked by the virus. Pulmonary embolism, pericarditis, myocarditis, acute renal failure and degenerative neurological syndromes confirm an impressive range of diseases[2] accompanied by infection with up to- 6 million deaths globally.

The main reason which causes pathophysiologically the increased morbidity is the high binding affinity of the spike protein of the virus to the Angiotensin-Convertin Enzyme 2 (ACE2) of the endothelium [3]. The latter permits the entry of the virus in the cell and the modification of many molecular mechanisms. Postmortem cases of chronic endotheliitis after Covid-19 disease underlines the sustaining proinflammatory state in some of these patients.**Error! Bookmark not defined.** Furthermore, prothrombotic state as a result of hypercoagulability is the final clinical manifestation of a functionally impaired endothelium with a combination of thrombocytopenia and elevated von Willebrand factor(vWF).[5]

The vaccines developed against SARSCoV-2 provide in different ways the ultimate goal of production of neutralizing antibodies against spike- protein and activation of humoral and cellular immunity. According to the first randomized studies there is a wide range of observational ones as well, which underline the relatively preserved efficacy against death and severe disease but not transmission over months [6]. New strains reduce the capability of vaccines to control the pandemic.

Furthermore, a spread of adverse events disproportionately huge compared with the entire registration of all vaccines according to the main databases of VAERS and EudroVigilance. So, since endothelial ACE2- enzyme, consequently the vascular

one, is a key target-molecule of Covid-19 and relates to spike-protein (SP) antibodies of the vaccines, cardiovascular complications should be investigated under a possibly direct pathophysiological pathway. As Covid-19 disease tends to be endemic, registration of adverse events of the vaccines become more important.

Kounis N. et al. explained fatal cardiovascular events by activation of coagulation and allergic hypersensitivity caused by macrophages and mast cells [7]. The same mechanism provokes clinical identities in other vascular beds like coronary, mesenteric, pulmonary and cerebral vessels[8]. Such events have already recorded after Covid-19 vaccination [9]. Although myocardial infarction has not yet shown a clear hazard ratio after covid-19 vaccination, plethora of sudden deaths revealed an questionable coincidence. Elevated thrombogenicity of activated platelets could give an answer to the scenario. Pulmonary embolism and thromboses of extremities were registered as a result of thrombosis thrombocytopenia syndrome (TTS) with the prevailing mechanism of cross reactivity of antibodies against SP and Platelet Factor 4 (PF4). Moreover, cerebral venous thrombosis after vaccination confirms a unique cardiovascular complication severe and fatal with a preference in the younger population [11]. Not rare, a proportion of cerebral ischemic events are accompanied by bleeding findings.

There is a suspicion of exacerbation of heart failure, hypertension and arrhythmias due to the documented down-regulation of the endothelial ACE-2 enzyme by SP and vaccines in relation to the latter [12]. Although there is no strong verification in the current literature, a pivotal study after vaccination showed increased levels of inflammatory and thrombogenic factors in blood samples consisting of a cardiovascular negative prediction (PULS score)[13].

Myocarditis is more frequent among young males with an incidence from 1 to 37 after the second shot per 100000 vaccinations. Pericarditis has an incidence of 1.8 per 100000. The possible mechanism is immune- related, but the manifestation 5 days after shot remarks a direct idiopathic toxicity against myocardial mitochondria [14]. Specific groups like male adolescents[15] and military staff [16] present high incidence of myocarditis and pericarditis with mild to moderate severity.

On the whole, covid-19 vaccines need to be investigated as for cardiovascular complications, since SP-related pathophysiology and specific clinical syndromes are verified, documented and on official databases in large numbers registered. More observational studies accompanied by strict pharmacovigilance would contribute to

clear epidemiological conclusions. Possible mechanisms are focused on, which could be responsible for justification of relation between vaccine's toxicity and cardiovascular complications. Ultimate goal is the commitment on reliable safety of the COVID-19 vaccines in concordance with their inevitable efficacy on adverting severe disease. In addition, such findings could offer the appropriate literature for making decisions about mandatory vaccination.

Keywords: Complication; cardiovascular disease; COVID-19 vaccine; myocarditis; pulmonary embolism

References

1. J. Ioannidis Infection fatality rate of COVID-19 inferred from seroprevalence data. Bulletin W.H.O. 2021; 99: 19- 33F. PMID: 3371633, PMCID: PMC7947934, DOI: 10.2471/BLT.20.265892.
2. ZG. Dessie et al. Mortality-related risk factors of COVID-19: a systemic review and metanalysis of 42 studies and 429117 patients. BMC Inf. Diseases (2021) 21: 855.
3. Y.Suzuki. et al. SARS- CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascular Pharmacology 137 (2021) 106823.
4. Lopez Castro J. Post-COVID-19 Syndrome (PC19S): Chronic Reactive Endotheliitis and Disseminated Vascular Disease. Acta Med Port. 2020 Dec 2;33(12):859. doi: 10.20344/amp.14612.
5. Sieiro-Santos C, López-Castro J. Post-coronavirus disease syndrome and disseminated microthrombosis: the role of the von Willebrand factor and antiphospholipid antibodies. Clinics (Sao Paulo). 2021 Mar 24;76:e2784. doi: 10.6061/clinics/2021/e2784.
6. S. Thomas et al. Safety and efficacy of the BNT162b2 m-RNA Covid-19 Vaccine through 6 months. NEJM 2021; 385: 1761-73.
7. N. Kounis et al. Kounis syndrome: a new twist on an old disease. Future Medicine Vol. 7.6..3/11/2011.https://doi.org/10.2217/fca.11.63.
8. N. Kounis et al. Kounis Syndrome- not a single- organ arterial disorder but a multisystem and multidisciplinary disease. B. M. J. 2019; 34: 212-21.
9. N Kounis et al. Allergic reactions to current available Covid-19 vaccines: Pathophysiology, Causality and therapeutic Considerations: Vaccines 2021; 2021; 9.221.
10. P. Rzymski et al. Thrombotic thrombocytopenia after COVID-19 vaccination: In search of the underlying mechanism. Vaccines, 2021, 9, 559.
11. L. Palaiodimou et al. Cerebral venous sinus thrombosis and thrombotic events after vector- based COVID-19 vaccines. A systemic review and meta-analysis. Neurology November 23,2021; 97 (21).
12. Y. Lei et al. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE2. Research Leter. Circulation Research 2021; 128; 1323-1326.

13. S. Gundry. Observational findings of PULS cardiac findings for inflammatory markers in patients receiving mRNA vaccines. Circulation (08/11/2021); 144, Abstract 10721.
14. G. Witberg Myocarditis after COVID-19 vaccination in a large health care organization. NEJM 2021; 385: 2132-2139.
15. G. Chua et al. Epidemiology of acute myocarditis/pericarditis in Hong Kong adolescents following Comirnaty vaccination. Clinical infectious disease 2022; 10 (10) 1-9.
16. Montgomery J. et al., Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US army, JAMA Cardiol., 06/29/2021.