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COVID-19 vaccination followed by activation of glomerular diseases: does association equal causation?

Kidney International (2021) **100,** 959–965; https://doi.org/10.1016/j.kint.2021.09.002

KEYWORDS: COVID-19; glomerulonephritis; kidney biopsy

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To date, >4 billion doses of the various severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines have been administered worldwide in response to the coronavirus disease 2019 (COVID-19) pandemic. Even as widespread vaccination campaigns have contributed to declining case rates, adverse events are appearing beyond those originally reported in the clinical trials of vaccine efficacy and safety. Of particular relevance to the kidney is the increasing number of reports of *de novo* or reactivation of glomerular diseases (Table 1[1–25]). The occurrence of glomerular disease after immunization against influenza, pneumococcus, and hepatitis B has been reported in the past.[26–28] The reported patients developed acute onset nephrotic syndrome following vaccination, and kidney biopsies were consistent with a minimal change disease (MCD) pattern of injury. Although temporal association (median onset of 12 days) with vaccination and disease onset suggested a vaccine-related induction of immune injury, the pathophysiological mechanisms responsible have not been determined.

After vaccination against COVID-19, reports of exacerbation, and in some cases, new onset of glomerular diseases began arriving at *Kidney International* and other nephrology journals. Although the development of *de novo* glomerular disease is intriguing, increased patient awareness of symptoms after vaccination may have prompted medical attention, revealing a previously undiagnosed kidney disease as opposed to a *de novo* disease. Indeed, chronicity on the kidney biopsy may suggest the glomerular disease preceded COVID-19 vaccination. Although nearly all approved vaccine platforms have been implicated, cases have been far more common after the mRNA-based vaccines, Pfizer–BioNTech BNT162b2 and Moderna mRNA1273 (Table 1). Of course, this may simply reflect more widespread use of these mRNA vaccines. Another interesting feature of COVID-19 vaccine-associated glomerular disease (CVAGD) is that most cases appear to be either IgA nephropathy (IgAN) or MCD (Table 1). The timing of IgAN activation is generally within a day or two after receiving the second dose of BNT162b2 or mRNA1273, whereas MCD appears to occur at a median of 7 days after the first dose (Table 1). Although these associations do not prove causation, we suggest that the volume of cases of MCD and IgAN and the consistent time course of events indicate a direct role of the mRNA vaccines in these 2 glomerular diseases. Several other glomerular diseases have occurred in smaller numbers following vaccination, sometimes quickly (scleroderma renal crisis), but more often after about 2 weeks (e.g., membranous nephropathy, anti–neutrophil cytoplasmic antibody–associated vasculitis, anti–glomerular basement membrane disease, and IgG4 renal disease). Given the small number of cases of these immune-mediated glomerular diseases, and the longer time to their appearance, it is difficult to be certain that they were activated by the vaccines. Nonetheless, considering these cases in aggregate, it appears that the COVID-19 vaccines can (re)activate autoantibody-mediated kidney disease.

It is not clear how COVID-19 vaccines, and in particular the mRNA vaccines, induce MCD, IgAN, and other autoimmune kidney diseases. mRNA-based vaccine technology has been available for some time, although the SARS-CoV-2 vaccines were the first to be investigated in large-scale phase 3 randomized trials. It has been previously demonstrated that this vaccine technology promotes more potent immune responses than inactivated viral vaccines and even natural infection. A comparison of the immune responses to the COVID-19 vaccine platforms is given in Table 2[29–35]. This ability of the mRNA vaccines to enhance virus-specific responses over and above more traditional vaccines has likely contributed to the high efficacy in preventing disease from SARS-CoV-2, as well as the viral variants that have evolved during this pandemic. BNT162b2 or mRNA1273 deliver lipid nanoparticle

Table 1 | Summary of reported cases of glomerular disease activation with COVID-19 vaccination

Disease	Age, yr, median (range)	% Female (n)	Vaccine type	No. of cases	*De novo* or flare[a]	Maintenance immune therapy	Temporal association to vaccination, d	Treatment	Outcome	COVID-IgG response	References
IgAN	38 (13–52)	58 (7 of 12)	Pfizer–BioNTech, Moderna	12	5 *De novo*, 7 flare	No, or steroids, mycophenolic acid, calcineurin inhibitor in transplant patient	1–2	RASi, steroids, cyclophosphamide	Spontaneous resolution, renal response to immunotherapy	Positive	1–7
MCD	61 (22–"early 80s")	36 (4 of 11)	Pfizer–BioNTech, Moderna, Astra Zeneca	11	7 *De novo*, 4 flare	No, or steroids, calcineurin inhibitor, rituximab	1–13 (median, 7)	Steroids, calcineurin inhibitor	Renal response to immunotherapy in most cases	Positive	8–17
MN	68 (66–70)	50 (1 of 2)	Pfizer–BioNTech, Sinovac	2	1 *De novo* (anti-THSD7A^{+}), 1 flare (anti-PLA2R^{+})	No	7–14	RASi	NR	Positive	18,19
AAN	78 (52–81)	33 (1 of 3)	Moderna, Pfizer–BioNTech	3	*De novo*	No	14	Steroids, cyclophosphamide, plasma exchange	Renal response	Positive	3,20,21
Anti-GBM	60 (60–"older female")	100 (2 of 2)	Moderna	2	*De novo*	No	1–14	Steroids, cyclophosphamide, plasma exchange	No recovery	NR	6,22
IgG4-RD	66	0 (0 of 1)	Pfizer–BioNTech	1	Flare	Rituximab	14	Steroids, rituximab	Renal response	Positive	23
LN	42	100 (1 of 1)	Pfizer–BioNTech	1	Flare	Hydroxychloroquine	7	Steroids, mycophenolate mofetil	Partial response	Positive	24
Scleroderma renal crisis	34	100 (1 of 1)	Pfizer–BioNTech	1	*De novo*	No	1	RASi	Response	Positive	25

AAN, anti–neutrophil cytoplasmic antibody–associated nephritis; anti-GBM, anti–glomerular basement membrane antibody disease; COVID, coronavirus; COVID-19, coronavirus disease 2019; IgAN, IgA nephropathy; IgG4-RD, IgG4-related disease; LN, lupus nephritis; MCD, minimal change disease; MN, membranous nephropathy; NR, not reported; PLA2R, phospholipase A2 receptor; RASi, renin-angiotensin system inhibitor; THSD7a, thrombospondin type-1 domain-containing 7A.

[a]*De novo* indicates disease development in a patient not known to have a prior glomerular disease; flare indicates activation of a known, but controlled, glomerular disease.

Table 2 | Immune responses to SARS-CoV-2 vaccine platforms

Vaccine	Example manufacturer	T-cell responses	B-cell responses	Cytokine responses	References
LNP-mRNA	Pfizer–BioNTech, Moderna	Antigen-specific Th1-biased $CD4^+$ response, $CD8^+$ IFNɣ, IL-2	Prolonged S-specific germinal center B-cell responses	IFNɣ, IL-2, type I interferon via toll-like receptor-7	29–31
Adenovirus-DNA	AstraZeneca, Janssen/ Johnson & Johnson	Antigen-specific Th1-biased $CD4^+$ response, monofunctional and cytotoxic $CD8^+$ response	IgG1/IgG3 predominant, low IgG2/IgG4	IFNɣ, TNFα, IL-2, type 1 interferon via toll-like receptor-9	31,32
Inactivated whole virus	Sinovac Biotech	Th1-biased response with minimal Th2	RBD-specific binding antibody and neutralizing antibody production	IFNɣ, TNFα, IL-2	33,34
Recombinant protein subunit	Novavax	Th1-biased response with minimal Th2	S-binding antibody and neutralizing antibody production	IFNɣ, TNFα, IL-2	35

IFNγ, interferon gamma; IL-2, interleukin 2; LNP, lipid nanoparticle; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th1, T-helper cell 1; Th2, T-helper cell 2; TNFα, tumor necrosis factor alpha.

encapsulated mRNA encoding the full-length SARS-CoV-2 spike protein. These vaccines were found to be safe and efficacious in preventing severe COVID-19 in both clinical trial and real-world conditions, although patients with known autoimmune diseases were not included in the initial trials.[36] These lipid nanoparticle–mRNA vaccines stimulate robust antigen-specific T-cell responses, including T follicular helper (Tfh) cells, and potent germinal center B-cell responses, leading to durable neutralizing antibody production.[37]

In the cases of IgAN, disease symptoms occurred right after vaccination, suggesting a rapid immune mechanism, such as a memory recall response or mobilization of cells positioned to secrete galactose-deficient IgA1 antibodies. Although purely speculative, we wonder if the COVID-19 vaccines can robustly stimulate the gut-associated lymphoid tissue (Peyer patches) responsible for IgA1 production, as they do in other lymphoid tissues. IgA1 hyperresponsiveness has been observed in patients with IgAN following influenza vaccination.[38] In the case of COVID-19 vaccination, circulating IgA responses following administration have been observed to be similar in kinetics to IgG responses, with levels reaching a plateau 18 to 21 days after first mRNA dose, and further increases after a second dose peaking at 7 days after dose.[39] The temporal associations with hematuria onset following vaccination on the order of days argues against the contribution of spike protein-specific IgA molecules from participating in disease. However, it is known that patients with IgAN have increased circulating galactose-deficient IgA1, and perhaps bystander activation of the immune system with mRNA COVID-19 vaccination may act as a trigger for the formation of immune complexes and subsequent glomerular injury.

In contrast, the development of MCD following vaccination takes some time, suggesting a role for cellular immunity. Central to the pathogenesis of MCD is the development of podocyte injury due to dysregulated T-cell activation.[29] The COVID-19 mRNA vaccines trigger enhanced Tfh responses that peak 7 days after immunization. A potential contribution to the pathogenesis of MCD by Tfh cells has been suggested by observations that circulating subsets of Tfh cells are increased in patients with MCD, and the frequency of these populations is reduced in patients who are successfully treated with steroids.[40] Given these findings, and the reported onset of disease at a time point that correlates with Tfh response, perhaps mRNA vaccine-induced alterations in

the Tfh population and/or their associated cytokine profile in a susceptible individual could promote podocyte injury and the development of nephrotic syndrome and MCD.

The later appearing cases of autoantibody-mediated glomerular disease may be due to the induction of vaccine-associated autoimmunity. Vaccine-associated autoimmunity has been postulated to occur by antigen-specific and nonspecific mechanisms. Antigen-specific triggers for vaccine-mediated autoimmunity are thought to be secondary to molecular mimicry. That is, exposure to a non–self-antigen, such as SARS-CoV-2 spike protein, could elicit responses directed against host tissues if there was sufficient sequence homology to allow for cross-recognition. The SARS-CoV-2 spike protein shares homology with several human proteins, which may then be subject to off-target immune attack after vaccination.[41] Consistent with the mimicry hypothesis, it has been suggested that homologous sequences between human alveolar surfactant-related proteins and SARS-CoV-2 spike glycoproteins contribute to host immune attack and the subsequent pulmonary pathology seen with COVID-19 infection.[42] Similarly, mimicry of viral antigens with host proteins has been proposed to contribute to immune attack in the central nervous system, exacerbating neurologic complications in COVID-19.[43]

Antigen nonspecific mechanisms of autoimmunity with vaccination are thought to occur through bystander activation. In this model, the vaccine-stimulated immune response may trigger cellular damage and exposure of normally hidden self-antigens, which are then recognized by host immunity. Alternatively, by this model, innate immune responses may upregulate cytokine signaling and self-antigen presentation by antigen-presenting cells to potentially autoreactive T cells. Either of these mechanisms could conceivably contribute to the development of glomerular disease in response to vaccination, with perhaps different disease phenotypes resulting from each.

Interestingly, to date, there has been only one report of an exacerbation of lupus nephritis (LN) after COVID-19 vaccination, and this was with the BNT162b2 vaccine. This paucity of cases is somewhat unexpected. Tfh cells, robustly activated by mRNA-based COVID-19 vaccines, are important for autoantibody development in lupus.[44] Germinal center and peripheral leukocyte cytokine profiles after vaccination are reminiscent of cytokine profiles from lupus patients, with especially high levels of interferon-α, interleukin-6, and tumor necrosis factor-α.[45] In the reported case, a patient with known class V LN in remission developed nephrotic syndrome following the first vaccine injection, and kidney biopsy revealed International Society of Nephrology/Renal Pathology Society class II and V LN with an activity index of 0. Given the robust immune activation achieved with the mRNA vaccines, it is surprising that in this case immune complex deposits were limited to the subepithelial compartment and there was no development of proliferative LN. The absence of proliferative LN cases may arguably be because many patients who have lupus nephritis are maintained on long-term immunosuppression. Most patients who developed CVAGD were not on immunosuppression (Table 1). Perhaps a baseline level of immunosuppression is sufficient to blunt the immune response to mRNA vaccination and prevent autoimmune reactions. This is supported by the observation that solid organ transplant patients on various forms of immune suppression, including those typically used in lupus nephritis, such as glucocorticoids and mycophenolate mofetil, demonstrate a weaker response to 2 doses of BNT162b2 vaccination.[46] However, considering the few reports of patients on immunosuppression who still developed glomerular injury after vaccination, including one kidney transplant patient, being on immunosuppression is clearly not the only factor determining who will develop kidney disease with these vaccines. Ultimately, there are likely individual patient-specific factors involved that determine whether vaccination results in immune protection or autoimmune injury.

In the published cases of CVAGD, glomerulonephritis was often managed with the usual therapeutic options for these diseases, frequently leading to a clinical response (Table 1). Although evidence is limited, we support a management strategy of CVAGD that is consistent with the conventional therapy of glomerular diseases not associated with vaccination, including the use of immunosuppression if typical indications develop. It is not unreasonable to extrapolate from the management of glomerulonephritis in general, given the presumption in CVAGD that the same disease mechanisms and pathways of vaccine-independent glomerular disease are activated by COVID-19 vaccination. However, management decisions should be tailored to

individual cases given the rarity of these events.

As the worldwide COVID-19 vaccination campaign continues to accelerate, it is probable that we will continue to see CVAGD. Not all cases have been, or will be, reported, there is likely reporting bias, and the number of patients with known glomerular disease who have been vaccinated is not known, so the true incidence of CVAGD will be difficult to determine. As multiple doses of vaccines are now being offered, close observation to watch for an increase in CVAGD will be needed. However, in the context of the billions of doses of COVID-19 vaccine that have been administered, the relatively small number of cases thus far suggests a low incidence. Care providers should consider the possibility of glomerulonephritis in patients who develop gross hematuria or edema after vaccination to aid in the prompt diagnosis and management of these diseases. The possibility of CVAGD should not, however, prompt vaccine hesitancy. Most reported cases were easily managed and resolved on their own or responded to typical therapy. Also, COVID-19 infection itself has been linked to the development of immune-mediated kidney diseases.[47] The benefits of COVID-19 vaccination appear to greatly outweigh the risks of glomerular disease occurrence or recurrence, and vaccination remains the best method of preventing the morbidity and mortality associated with SARS-CoV-2 infection. Therefore, we are offering vaccination to all of our patients with glomerular diseases, with the following considerations.

Patients in remission and off all immunosuppression should be followed up closely after vaccination and be told to report hematuria or swelling immediately for early intervention. For patients undergoing active immunosuppressive treatment with anti-metabolites (e.g., mycophenolate mofetil or azathioprine), cytotoxic drugs (e.g., cyclophosphamide), anti–B-cell therapies (e.g., rituximab), and costimulation blockers (e.g., abatacept), antibody response to COVID-19 vaccines is likely to be poor.[48,49] It is probably reasonable to postpone vaccination until these intensive therapies have been tapered or completed. Timing is also important for anti-CD20 B-cell therapies as these have prolonged effects after dosing. For such patients, it is important to continue all preventative measures in place before vaccines were available, and all individuals within the patient's "bubble" should be vaccinated to provide an additional layer of protection. Finally, it is difficult to speculate on the management of patients who develop CVAGD after the first injection of an mRNA-based vaccine. Checking SARS-CoV-2 antibody response after the first dose may provide some confidence that the patient developed an immune response and may not need the second dose, but of course this does not equate with protection against COVID-19. A change in vaccine platform could also be considered for a second dose. Alternatively, if the CVAGD was mild and readily resolved, administration of the follow-up dose could be considered.

The Immunonephrology Working Group of the European Renal Association–European Dialysis and Transplant Association recently published recommendations on the use of COVID-19 vaccines in patients with autoimmune kidney diseases and supports the vaccination of all individuals without known contraindications.[50] However, these recommendations did not advise on whether vaccination with one vaccine platform was preferable to another. Despite the higher number of reports of glomerular disease activation or reactivation with mRNA COVID-19 vaccines compared with the traditional vaccines, it remains difficult to make a recommendation against the mRNA platform. As CVAGD has been seen with non-mRNA vaccines, avoiding Pfizer–BioNTech or Moderna vaccines does not completely eliminate autoimmune risk. Furthermore, the differences in efficacy between the various vaccines cannot be overlooked. Ultimately, as with all decisions in medicine, theoretical risks must be balanced against known benefits of interventions, and discussions between care providers and patients in this regard are important.

DISCLOSURE

All the authors declared no competing interests.

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