VIEWPOINTS

Side effect of mRNA-based COVID-19 vaccination in renal: pros- and cons- in pathophysiological view on renal function

Ari Baskoro, Pranawa

1Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Background: Several cases have been reported where mRNA-based COVID-19 vaccinations correlated with renal disease incidence in the form of minimal change disease (MCD) and immunoglobulin A nephropathy (IgAN) during renal biopsy investigation. However, this renal manifestation is not only detected in COVID-19 vaccination. Renal disease has been detected in other vaccinations such as influenza, pneumococcus, tetanus-diphtheria-polioomyelitis, and hepatitis B. However, the incidence was higher when the COVID-19 vaccination policy was carried out to minimalize the COVID-19's fatal effects and limit its spread. Objective: This viewpoint was written to describe the effect of mRNA COVID-19 vaccines on the renal area based on the scientific points of views in the nephrology field. Discussion: mRNA-based COVID-19 vaccination is carried out by lipid nanoparticles with the main target of activating T-cells as the adaptive immune response and inducing the innate immune system towards the virus via Toll-like receptors (TLR3 and TLR7). This leads to cellular activation and production of IFN type 1. mRNA-based COVID-19 vaccination in healthy adults produces an increment of IgA and IgG antigens. Further increments have been recorded after the second vaccination dose, and CD4+ T cells were stimulated towards Th1 to produce interferon-c (IFN-c), TNF-α, and IL-2. mRNA-based COVID-19 vaccination has been found to activate the immune function and trigger a flare of the disease, while others found that mRNA-based COVID-19 vaccines can re-activate autoantibody-mediated kidney disease. The pathophysiology of acute kidney injury (AKI) might be due to a secondary acute tubular necrosis because of the strong immune response. Conclusion: Although many kidney disease cases were reported during the mass COVID-19 vaccination policy, particularly in mRNA-based COVID-19 vaccination, this type of vaccine has been proven to be effective against COVID-19. There are more advantages to getting the vaccine than not. Moreover, the mechanism of renal disease after mRNA-based vaccination is unclear and debatable.


Corresponding Author: Pranawa, Internal Medicine Department, Faculty of Medicine, Universitas Airlangga/ RSUD Dr. Soetomo, Jl. Mayjen. Prof. Dr. Moestopo No. 6-8, Surabaya, Jawa Timur, Indonesia 60286. Tel.: +628123519787 Email: pranawa_nefro@yahoo.com
Highlights

1. Renal disease incidence post-mRNA-based COVID-19 vaccination has been reported.
2. The lipid nanoparticle vehicle of mRNA-based vaccines was suspected to be the causative agent due to it stimulating proinflammatory action through T-cells.
3. mRNA-based vaccines for combating COVID-19 are advantageous in reducing the mortality rate, disease severity, and outcomes, which means reducing the national burden in many aspects.

BACKGROUND

To combat coronavirus disease 2019 (COVID-19) and alleviate its symptoms, all nations have been enrolled in the COVID-19 vaccination policy. This strategy was employed due to COVID-19 causing severe symptoms on the respiratory, gastrointestinal, and renal tracts, which leads to higher mortality rate for patients (Ma and Xu, 2022). The Indonesian Ministry of Health has conducted this policy since January 2021 by using monovalent inactive COVID-19 viruses (Sinovac or Sinopharm) to prevent the spread of this disease (Nugraha et al., 2021). The COVID-19 mortality rate in Indonesia was higher (4.27%) than the world’s average mortality rate (2.68%) in October 2020 (Karnadi and Kusumahadi, 2021).

This virus had many variants due to its rapid mutation compared to DNA viruses (Park et al., 2021). The latest variant, omicron (December 2021), has made the previous COVID-19 vaccine (Sinovac) less effective (Konishi, 2022). As a result, continuous vaccination is needed to protect society from COVID-19’s negative effects. Two-dose vaccination has proven to relieve the delta variant symptoms and protect users from severe outcomes. The third dose had 61% effectiveness against omicron infection symptoms and 95% effectiveness against severe outcomes (Buchan et al., 2022).

COVID-19 vaccines have been developed in several forms: protein-based (Novavax), inactive virus-based (Sinovac), viral vector (Janssen), and mRNA-based (Pfizer/BioNTech, Moderna, CureVac) (Li et al., 2022). Inactive SARS-CoV-2 vaccines (Sinovac) were claimed to be more ineffective against COVID-19 infections compared to mRNA vaccines. Persons who received three doses of inactive SARS-CoV-2 had 1.13-fold higher risk of COVID-19 infection than those who received mRNA-based vaccines (Tan et al., 2022). Several studies have reported the effectiveness of mRNA-based against the latest COVID-19 variants, namely delta and omicron (Tang et al., 2021; Tseng et al., 2022). mRNA-based COVID-19 vaccines have been claimed to be effective for the delta variant, with lower hospitalization and mortality rates, but were less effective in combating the omicron variant (Tang et al., 2021). In children, its effectiveness against delta variant was 61.2%, rising to 66.8% in adolescents. However, its effectiveness declined during omicron outbreaks, dropping to only 37.6% effectiveness 15-30 days after vaccination. mRNA-based vaccines have been declared 66.9% effective in lowering the mortality rate during omicron outbreaks in children, with effectiveness rising to 97.6% in adolescents (Castelli et al., 2022).

However, mRNA-based COVID-19 vaccines were suspected to be the cause of several renal diseases (Klomjit et al., 2021). Kidney diseases have been the most frequent conditions reported after COVID-19 vaccination, particularly the mRNA-based vaccine (Li et al., 2021). Several kidney disorders have been reported after mRNA-based COVID-19 vaccinations (Luo et al., 2022).

OBJECTIVE

This view points was conducted to describe the effect of mRNA COVID-19 vaccines on the renal-based scientific viewpoints in the nephrology field.

mRNA-BASED COVID-19 VACCINE AND RENAL DISEASE INCIDENCE: IS THERE A CORRELATION?
SARS-CoV-2 is an enveloped single positive-sense RNA virus consisting of structural and non-structural proteins (Lim et al., 2022). SARS-CoV-2 has two polypeptides that are cleaved into 16 non-structural proteins (nsp1-6) with the following functions: 1. mediating the delivery of viral replication complexes to subcellular domains; 2. viral replication, transcription, and post-transcriptional processes (Park et al., 2021). Moderna Biotechnology released mRNA-1273 after the spike protein-coding sequence of SARS-CoV-2 was published, and the company claimed it to be effective and safe for COVID-19 prevention. This vaccine was a gene-based mRNA (Park et al., 2021). Other vaccine producers followed Moderna by launching other mRNA-based vaccines such as BNT162b2 (BioNTech and Pfizer) (Abbasi, 2020). This mRNA-based vaccine is delivered to the host cell via RNA vector to produce the corresponding antigens (Abbasi, 2020) by inducing T–cell (cytotoxic) and B-cell (humoral response) activation. Those vaccines use a lipid nanoparticle as the delivery vehicle. In the past, the use of mRNA vaccines was limited in several cases (preventing cancer, infectious disease and allergy treatment) because of its easily degradable property, the ubiquitous ribonucleases presence, and the lack of scalability (Park et al., 2021). The application of mRNA-based viruses for combating COVID-19 was advantageous in reducing mortality rate, disease severity, and outcomes, reducing the national burden in many aspects.

The kidney, one of the organs infected by COVID-19

SARS-CoV-2 can directly infect human kidney cells (Strzyz, 2021). Using different methods, COVID-19 infection in the kidney was found in 19% of subjects diagnosed with COVID-19 with immunohistochemistry, 49% with RT-PCR, 13% with in situ hybridization, and 77% with immunofluorescence (Hassler et al., 2021). Even when they recover from COVID-19, the infected people have a greater risk by 1.94-fold for developing kidney disease no matter how mild the infection was in the form of acute kidney injury (AKI). They also have 1.66-fold the risk of major adverse kidney events (a decline of estimated glomerular filtration rate/ e-GFR by at least 50%) (Torjesen, 2021). When the infection involves the kidney, growing evidence shows acute kidney injury (AKI) development increases the mortality and morbidity rate, as well as declining renal function in 6-to-12 months during the follow-up period without any signs of AKI (Copur et al., 2022). In the infected kidney transplantation recipients, AKI developed in 42.2% of patients, with 3.7% of those requiring renal replacement therapy (RRT). Meanwhile, 20% were admitted to the ICU, and 17.4% required mechanical ventilation. The mortality rate was 12.8% (Oto et al., 2021).

The kidney is one of organ attacked by SARS-CoV-2. It has been suggested that Protein S of the virus (“spike” proteins present at the virus’s surface) binds the angiotensin converting enzyme 2 (ACE2) receptors on the host’s cell surfaces (mainly in the lungs, heart, ileum, bladder, and kidney). Then, the virus incorporates into the cell via endocytosis. The virus is able to activate transmembrane serine protease type 2 (TMPRSS 2), and then start the replication intracellularly (Pacheco et al., 2022). When entering the host’s cells, SARS-CoV-2 will be attacked by the innate immune response. It then infects the new host by inhibiting (or eluding) the host’s innate immune signalling though this process remains unclear until now. When infecting the epithelial cells, the virus will damage them, which leads to cytopathic effects and ciliary dysfunction (Soliman, 2021). New viral particle production leads to cell disintegration, and the virus spreads to other cells. The immune system is designed to detect pathogens in the body (viral antigens). Antigen-presenting cells (APC) process these antigens, and natural killer and CD8+ cells act to diminish the virus. The cascade proinflammation response is activated, both innate and adaptive, to produce pro-inflammatory cytokines and chemokines in large amounts. In some people, this proinflammatory response is excessive, resulting in a “cytokine storm” or hyper-inflammation with deteriorative effects leading to multiple organ failure (Soliman, 2021; Soy et al., 2020).

Pathogen recognition receptors (PRRs), particularly Toll-like receptors (TLR) 3, 7, and 8 recognize the virus after the virus entering the cells (particularly in Monocyte) (Shah et al., 2020), leads to the activation of mitochondrial antiviral signaling protein (MAVS), and stimulates the activation of TANK-binding kinase 1 (TBK1). The activation TBK1 stimulates the phosphorylation and activation of IFN-regulatory factors 3 and 7 (IRF3, IRF7), and then those IRFs translocate to the nucleus to induce IFN type 1 production and secretion (IFNα, IFNβ, IFNε, IFNτ, IFNκ, IFNω, IFNδ, IFNγ). After IFN type 1 was secreted to the surrounding tissue, they will bind with the receptors (IFNAR) and leads to autocrine and paracrine actions. The binding between IFN type I with IFNAR activates
the receptor-associated protein tyrosine kinases Janus kinase 1 (JAK1), while tyrosine kinase 2 (TYK2) phosphorylate signal transducer and induce the activator of transcription 1 and 2 (STAT1 and STAT2) molecules, leading to their dimerization, nuclear translocation and binding to IRF9 to form the ISG factor 3 (ISGF3) complex until it reaches its peak with the transcription of hundreds of interferon stimulated genes (ISGs), that inhibit virus multiplication at distinct levels, potentiate the innate antiviral response and stimulate adaptive immune response. However, SARS-CoV-2 and MERSCoV diminished this mechanism to escape immune surveillance. They avoid PRR recognition so that IFN type I was not produced after the virus entering the cells (Palermo et al., 2021). RNA virus like hepatitis C virus also inhibit the TLR signalling complex and blocking the IFN type I production which acts as antiviral, so that the persistent infection is occurred (Pramod et al., 2021). This evidence was observed on the patients with severe COVID-19 disease, whom experiencing the reduction or even absence IFN type I activity compared to the patients with mild and moderate diseases. Several hypotheses have been advanced to explain this variability of response to SARS-CoV-2 infection, including comorbidities and genetic susceptibility (Tirelli et al., 2023).

Figure 1. The hypothesis of COVID-19 infection via the renin-aldosterone-angiotensin system (RAAS). Angiotensin converting (ACE2) has been suggested as the COVID-19 infection receptor, expressed in the epithelium (respiratory tract, intestine, central nervous system, heart and endothelial cells, kidney, and testicles). ACE2 plays an important role by degrading angiotensin (Ang) II into Ang (1-7 homolog) and transforming Ang I into Ang (1-7). This binds to the G protein-coupled Mas receptor and promotes vaso dilatation as well as limits inflammation, fibrosis, coagulation, and capillary leakage (Gressens et al., 2021).

Role of IFN type I is inhibiting virus replication and immune modulatory in several pathways such as upregulating MHC-I expression in various cells, as autocrine signaling on DC, promotes the activation and stimulatory T cell capacity. The more important thing is IFN type I promotes the production of antiviral adaptive immune response of non-infected cells (Teijaro, 2016).

Due to the suspected agent for COVID-19 being the ACE2 of the renin-aldosterone-angiotensin system (RAAS), hypertensive people are at risk of COVID-19 infection, particularly those who consume antihypertensive medicine targeting the RAAS; this finding is supported by clinical studies (Augustine et al., 2022). However, this hypothesis is attenuated. The medicine has no significant effect on the COVID-19 infection risk and disease severity (Bae et al., 2021; Coto et al., 2021); therefore, the American Heart Association recommended not to stop the ACE inhibitor or angiotensin receptor blocker medicine in COVID-19 patients with hypertension (Laurentius et al., 2021). Chronic renal disease patients are at risk for COVID-19 infection due to being immunocompromised. COVID-19 impacts renal disease due to hyper-inflammation.

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Renal disease incidence post-COVID-19 vaccination with mRNA-based vaccines

A global study noted 1,133 AKI incidents, and this incidence correlated with mRNA-based vaccines. Pfizer-BNT162b2 had a stronger correlation than Moderna and Janssen by 2.15-fold. However, this incidence was prevalent among the elderly (60-65 years old) and those with comorbidity (58.83%) (Luo et al., 2022). A systematic review recorded 130 renal disease cases, with 69% being new-onset kidney disease and 31% being relapse cases. The frequent cases reported with renal biopsy were minimal change disease (MCD) (52 cases), IgA nephropathy (IgAN) (48 cases), antineutrophil cytoplasmic autoantibody (ANCA)-vasculitis (16 cases), and acute interstitial nephritis (12 cases) (Zhang et al., 2022). Other findings have reported similar results with the main disorders being IgAN, MCD, and AKI (Lim et al., 2022).

Ten serial cases noted decreased renal function symptoms within two days after the second vaccination dose. These most frequently came in the form of macrohematuria (72.2%) and IgAN (45.7%) (Ritter et al., 2022). A small study noted eight new case of glomerulus nephritis after mRNA-based vaccination (Klomjit et al., 2021). One patient showed an IgA deposit before vaccination (Lim et al., 2022). Another report included 17 patients who were developing urinalysis (UA) and/or renal insufficiency within three months post-vaccination. They predominantly had MCD, acute tubulointerstitial nephritis (TIN), membranous nephropathy, IgAN, membranoproliferative glomerulonephritis, systemic lupus erythematosus (SLE), ANCA-associated vasculitis (AV), and tip-variant focal segmental glomerulosclerosis (Fenoglio et al., 2022).

mRNA-based COVID-19 vaccination on healthy people

mRNA-based COVID-19 vaccines were designed to stimulate innate, humoral, and cellular adaptive immune responses with safe and well-tolerated serological evidence and minimally adverse effects. It was designed to produce “spike” SARS-CoV-2 proteins, which stimulate the antigen and/or subunit peptide fragments in the circulation. This mRNA-based vaccine is carried out in lipid nanoparticles which most likely have a broad distribution in human tissue/organs by exerting proinflammatory actions through stimulating T-cells (Trougakos et al., 2022). Lipid nanoparticles in mRNA-based vaccines can deliver the mRNA to lymphatics and promote protein translation in lymph nodes. When lipid nanoparticles containing mRNA present in lymphoid nodes, they will be swallowed by dendritic cells (DCs), and trigger antigen production to activate T-cells as the adaptive immune response. Good vaccines must not induce excessive systemic inflammation (Teijaro and Farber, 2021). In mRNA-based vaccines, the mRNA serves as: (1) immunogens that act to encode the viral protein; (2) adjuvants due to intrinsic immunostimulatory properties (Teijaro and Farber, 2021).

After entering the cell, single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) on mRNA-based COVID-19 vaccine are recognised by various innate sensors, forming the innate immune response to viruses. Toll-like receptors (TLR3 and TLR7) bind to ssRNA in the endosome. Inflammasomes (MDA5, RIG-I, NOD2 and PKR) bind ssRNA and dsRNA in the cytosol. Those bindings on innate sensors lead to cellular activation and production of IFN type 1. mRNA contains in vitro modified ssmRNA to reduce binding with TLR and immune sensors. This new technology reduces excessive INF type 1 production and inhibits cellular translation (Teijaro and Farber, 2021).

mRNA-based COVID-19 vaccination in healthy adults produces increments of IgA and IgG antigens. Further increments have been recorded after the second vaccination dose. They stimulate CD4+ T cells towards Th1 dominance to produce interferon-γ (IFN-γ), TNF-α, and IL-2. The antibody titer also increases, leading to outbreaks of disease-like symptoms (Ma and Xu, 2022).

Effects of mRNA-based COVID-19 vaccination on the immune system

It has been noted that mRNA-based COVID-19 vaccination activates immune functions and triggered a flare of the disease (Klomjit et al., 2021). Others also state that mRNA-based COVID-19 vaccines can re-activate autoantibody-mediated kidney disease (Li et al., 2021). A nano lipid is used as the vehicle for transgenic mRNA-based COVID-19 vaccines, and is suspected to be the cause of
The suspected material on the incidence of renal disease post mRNA-based COVID-19 vaccination was polyethylene glycol (PEG) used as excipient of the vaccine as the conjugation form. PEGylation to increase the circulation time and reduce undesirable host response. In some people, PEG induced a pseudo-allergic reaction due to the presence of anti-PEG antibodies. Anti-PEG antibodies are able to activate the complement cascade and stimulate immunological adverse reaction (Padín-González et al., 2022).
al., 2022), or termed as complement activation-related pseudoallergy (CARPA), a non-mediated IgE reactions. Clinical symptoms including hypo- and hypertension (Klimek et al., 2021).

IgE-mediated allergic reaction due to PEGylated lipids on mRNA-based COVID-19 vaccine is caused by the activation of IgE leads to mast cells and basophilic granulocytes activation via IgE receptors and triggers the increment of CD63 and CD203c (surface markers) on basophils, resulting the anaphylactic reactions caused by mediators released from mast cells and basophilic granulocytes (histamine, prostaglandins, leukotrienes (LTB4, LTC4, and LTD4), tryptase, platelet-activating factor (PAF), heparin, proteases, serotonin, and cytokines) (Klimek et al., 2021).

Effects of mRNA-based COVID-19 vaccination on the renal function based on renal biopsy results

Glomerular diseases have been noted in several case reports in the form of MCD and IgA neuropathy IgAN (Fenoglio et al., 2022). The two minor forms of the most prevalent glomerular disease post-second-and-third mRNA-based vaccination are summarized below.

1. Minimal change disease (MCD). Several reported cases noted that this new onset of renal disorders was detected 6-8 weeks after the first Pfizer-BioNTech COVID-19 vaccination (Hanna et al., 2021). mRNA vaccines produced by Pfizer and Moderna use lipid nanoparticles as their vehicle, while AstraZeneca uses adenovirus. Lipid nanoparticles are designed to induce the synthesis of the SARS-CoV-2 “spike” protein in order to generate effective immune responses towards that protein. However, the T-cell induction produces proinflammatory responses by producing cytokines (interferon γ/IFNγ, TNFα, and IL2). This triggers podocytopathies and forces B-cells to increase immunoglobulin production (Hanna et al., 2021). Others have reported that this disease occurs between 2-14 days post-COVID-19 vaccination, in which three of four patients had new onsets, while the other one relapsed (Chandra et al., 2022). Another case was reported after receiving the AstraZeneca COVID-19 vaccine ChAdOx. MCD is a mild form of nephrotic syndrome due to mRNA vaccines, no matter the vehicle. It induces antigen-presenting cells (APC) and B-cells to produce cytokines, and then stimulates T-cells, causing podocyte injury (Krishna et al., 2022).

2. IgA nephropathy (IgAN). In IgA nephropathy (IgAN), the disease symptoms occur rapidly, showing a rapid immune mechanism to secrete galactose-deficient IgA1 antibodies (Zhang et al., 2022). IgAN incidence after mRNA-based COVID-19 vaccination might be because the vaccine stimulates excessive antigenic antibody production. This antiglycan antibody is cross-reactive with pre-existing Gd-IgA1 (Ma and Xu, 2022).

Vaccination side effects and renal disease incidence in the past

In the past, kidney disease (glomerular disease) incidence as a vaccination side effect has been reported after influenza, pneumococcus, tetanus-diphtheria-poliomyelitis, and hepatitis B vaccination in the form of MCD, a mild nephrotic syndrome (Fenoglio et al., 2022; Li et al., 2021), but the incidence is rare (Patel and Shah, 2019). This mild form of renal disease post-vaccination might be due to the alteration of T-cell subsets. This results in elevated IL2 R expression on the peripheral lymphocyte in MCD patients after hepatitis B vaccination (Fenoglio et al., 2022).

Similar with mRNA-based COVID-19 vaccination, there were few reported studies compared to the total amount of vaccinated subjects, with more than 4 billion doses (Li et al., 2021). Others state that 7 billion COVID-19 vaccines have been administered as a result of the global COVID-19 vaccination policy. They have also stated that this has been able to decrease the disease’s severity and alleviate national health pressure during the COVID-19 pandemic (Fenoglio et al., 2022). Moreover, the safety of COVID-19 vaccination has been evaluated among chronic kidney disease patients receiving dialysis as well as those going under renal replacement therapy. Although their seropositive and the host’s body ability to develop antibodies are low (Ma et al., 2022), this vaccine is still considered safe for them. Renal disease patients should be prioritized for COVID-19 vaccination due to lower vaccine response for them than normal people (Windpessl et al., 2021).

Moreover, the usage of mRNA vaccines has several advantages compared to other vaccines. They are 1. highly effective and safe; 2. efficient delivery to the host cells; 3. versatile; 4. protein translational machinery of the host; 5. easy to distribute (Park et al., 2021).
Limitations

Detailed and comprehensive research on the incidence of renal diseases post-COVID-19 vaccination is needed, along with more complete data from the nephrology and immunology site.

CONCLUSION

Although many kidney disease cases were reported during the mass COVID-19 vaccination policy, particularly after mRNA-based COVID-19 vaccination, this type of vaccine has been proven to be effective against COVID-19. There are more advantages to getting the vaccine than not. Moreover, the mechanism of renal disease after mRNA-based vaccination is unclear and debatable.

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Conflict of Interest

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REFERENCES


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