Guest Editorial

Negative Evidence: Renal Adverse Events Following COVID-19 mRNA Vaccination

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Introduction

This article continues an editorial series that examines controversial topics across science, politics, and heated ideological debates,[1–15] using the negative-evidence method (see https://jpands.org). This method seeks expected but absent information. Such omissions may indicate intentional exclusion of important but inconvenient facts, in order to shape misleading agenda-driven narratives.

The negative-evidence approach is well-suited for analyzing controversies in the current era of extreme ideological polarization. Hyperpartisan society now disagrees on issues that were once self-evident: such as differences between men and women, or negative consequences of opening the borders to masses of culturally incompatible strangers. Blinding political bias has led to the politicization of science that has blurred objective reality, turning scientific expertise into a tool for partisan interests. History shows that societies endure only when they are unified by a clear view of reality that is fact based, grounded in logic, and strengthened by the observance of divine law. Ideologies promoted by tyrants, oligarchs, and demagogues promise unity but offer no clarity, leading to inevitable collapse. Deeply divided societies not interested in unity face even quicker decline. In other words: unifying clarity ensures durability. Spurious unification by unsustainable lies results in a wretched and short existence.

The U.S used to be a country that prospered under the power of unifying clarity. Clear signs of departure from that successful model include deep partisan divides over the COVID-19 pandemic, such as disagreement on the mRNA vaccine's risks and benefits. Logic dictates that given substantial scientific advancements, the archetypically scientific dilemma of the vaccine safety should be promptly and persuasively clarified by trusted scientific experts, and their conclusions would be accepted by the public. Instead of such expected societal consensus we have two contradictory ideological narratives. Unifying clarity does not exist any more, because a large part of society does not believe that official experts are impartial and trustworthy. And this assessment is sadly accurate.

The official scientific position by the Left deems this novel vaccine to be the pinnacle of scientific achievement that is "exceptionally safe and effective." In contrast, those on the Right believe that the mRNA vaccine is a very dangerous and untested experimental therapy with no benefits, a calamity that has been recklessly unleashed upon the world due to the greed of its manufacturer and/or as a part of a sinister secret plot aimed at genocidal "population control."

Left-wing-dominated scientific officialdom blames this extreme divergence of opinions on the "scientific illiteracy" and "anti-science aggression" of the right-wing public that are fueled by unscrupulous "misinformation peddlers."[16–18] In response, right-wing public and scientific dissenters point out that their skepticism is well justified. Despite all the reassuring officialdom's proclamations, the serious adverse events of COVID-19 vaccination are continuously reported to the pharmacovigilance systems, described on social media, and published by the few brave researchers.[19] Moreover, "official experts" have lost their previously high public trust because they repeatedly lied to advance their political agenda—especially during COVID-19 pandemic.[20] During that horrible global disaster, the draconian policies endorsed by "the official experts" locked the right wingers in their homes, closed their private businesses, forced them to wear suffocating masks, denied access to medications of their choice, and finally tried to coerce them to take injections of the never previously used mRNA vaccine.[1,2,11] Those traumatic events have awakened many right wingers to the brutal reality of power asymmetry favoring the Left.[21]

For decades, the right-wing camp has been ignoring the incremental takeover of academic institutions by the Woke Left.[22,23] Ultimately, the Left took full control over universities and with it the immense power of official expertise. And they have destroyed any remnant of unifying clarity that still lingered. There were some right-wing thinkers who recognized the great importance of academic institutions for any civilized society. They postulated that academia should be taken back from the Woke Left. Unfortunately, for variety of reasons a majority of the modern right-wing community had very little appreciation of academia's significance. Consequently, they did not anticipate that "Woke academicians" whom they dismissed as ludicrous and weak could wreak havoc in their lives. COVID-19 tyranny was the first serious shock. The second jolt that roused right wingers from passivity toward Woke universities came soon. It was the elite academic medical centers' fervent endorsement of "pediatric transgender care"—a practice that all on the Right deemed abhorrent.

Finally, the arrogant behavior of the left-wing academicians created a significant backlash against them. Republican politicians started to listen to their voters' demands to rein in the despotic Woke academia. The second Trump Administration became the first Republican Administration that decided to go beyond rhetoric and take direct actions against the Left-dominated academia.[24] So far, those efforts have been primarily focused on opposing the supremacy of Woke ideology in academic life and assuring true civil rights compliance by universities. However, they also included substantial cutting of research funding. Initially, the explicit goal of cancelation of research grant money was to reduce wasting public funds on Woke ideology-driven projects. However, this action evolved into indiscriminate cuts of a variety of useful and nonpartisan research programs such as cancer studies. This resulted in the expected legal challenges from the left-wing-

dominated scientific community. However, even some right wingers expressed concerns about attempts to "reform" academia by destroying it with a wrecking ball—without any plans to rebuild it in the right way. After all, even under Woke supremacy American universities kept conducting cutting-edge scientific research. Furthermore, while many faculty members lied about COVID-19, they still provided state-of-the-art medical care for many other medical conditions.

While such criticism seems justified, it is too early to objectively assess the effectiveness of this well-intended and much-needed initiative. It is important to note that positive change from a long-lasting negative status quo takes time and patience, since it always involves complex processes and deeply rooted systemic challenges. Only time will tell whether this truly first Republican attempt to directly challenge Left-dominated academia will be successful. Therefore, in the meantime, the diligent efforts by scientific dissenters must keep moving forward at a vigorous pace.

The Intersection of Global Vaccination and Renal Health

The COVID-19 pandemic caused by the SARS-CoV-2 virus precipitated a global health crisis of historic proportions, according to the official narrative, although some researchers have expressed skepticism about such framing.[25,26] At any rate, in response to the emergence of SARS-CoV-2 virus the scientific community has been instructed to develop the new vaccines as the only approved method of dealing with the pandemic. Scientists responded with unprecedented speed, producing several types of vaccine. From the cluster of available options, the novel messenger RNA (mRNA) platform has been chosen. The global vaccination campaign that followed involved the administration of billions of doses of the type of the vaccine that has never been used before.[27] This massive-scale deployment of the de facto prototype of the experimental modality was hailed as "a triumph of public health" while its known and potential risks have been downplayed.

Despite the novelty of the mRNA methodology, the pharmacovigilance of its adverse effects has been based upon the very narrow method of adverse events of special interest (AESI) rather than on the much more appropriate and broader organ systems approach (OSA).[28] The utilization of this narrow tactic resulted in a reassuring conclusion. Yet, some researchers who were not based in the U.S. expressed concerns that due to frequently obscure initial symptoms of renal disorders many of those reactions could be undetected. The Chinese research group of Luo et al. have proven that indeed this is the case.[29] Those scientists postulated that vigilant post-market surveillance systems should be contiguously deployed as a cornerstone of vaccine renal safety.[29] As early as one year after the mRNA vaccine was rolled out, a number of case reports started to emerge describing various biopsy-confirmed renal pathologies that had a clear temporal association to the administration of COVID-19 mRNA vaccines.[30,31] Consequently, the perspective on the renal safety of the COVID-19 mRNA vaccine started to change. It became clear that promises of significant reduction in severe illness, hospitalization, and mortality from SARS-CoV-2 infection have not materialized. Instead, the terrifying side effects of the novel vaccine including renal problems became its shameful legacy.

Foundational Concepts in Nephrology

To fully appreciate the nature of potential vaccine-associated renal events, a fundamental understanding of kidney physiology and pathology is necessary. The kidneys are vital organs that perform numerous homeostatic functions. They maintain a stable extracellular environment by removing metabolic waste (like urea, creatinine, and uric acid) and regulating water and electrolyte excretion to balance intake and production. They adjust water, sodium, potassium, and hydrogen levels mainly through changes in tubular reabsorption or secretion.[32] Moreover, they secrete hormones that regulate blood flow (renin, prostaglandins, bradykinin), red blood cell production (erythropoietin), and mineral metabolism (calcitriol).[32]

The damage to the intricate structures of kidneys will manifest in specific and recognizable clinical syndromes. Some of those syndromes may be self-limiting, exhibiting favorable long-term outcomes, whereas others are irreversible, resulting in chronic morbidity and considerable mortality.

Renal Physiology

The primary role of the kidneys is to filter waste products from the blood and maintain fluid, electrolyte, and acid-base balance.[33] As depicted on Figure 1, each kidney contains more than a million microscopic functional units called nephrons, where the three-step process of urine formation occurs: glomerular filtration, tubular reabsorption, and tubular secretion.[34]

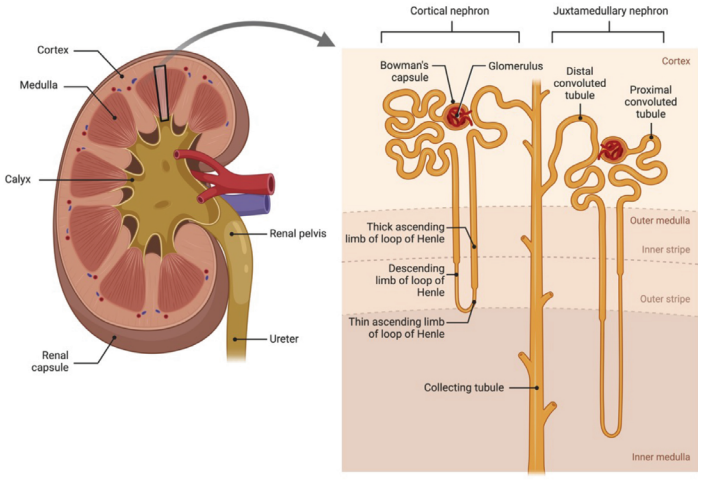

Figure 1. Kidney and nephron anatomy

Glomerular Filtration

As shown in Figure 2, urine formation begins at the glomerulus, a high-pressure network of capillaries nestled within Bowman's capsule.[34] Blood enters the glomerulus via the afferent arteriole and exits through the efferent arteriole. The pressure gradient drives water and small solutes from the blood across a sophisticated three-layered filtration membrane and into Bowman's capsule, forming the glomerular filtrate.[32]

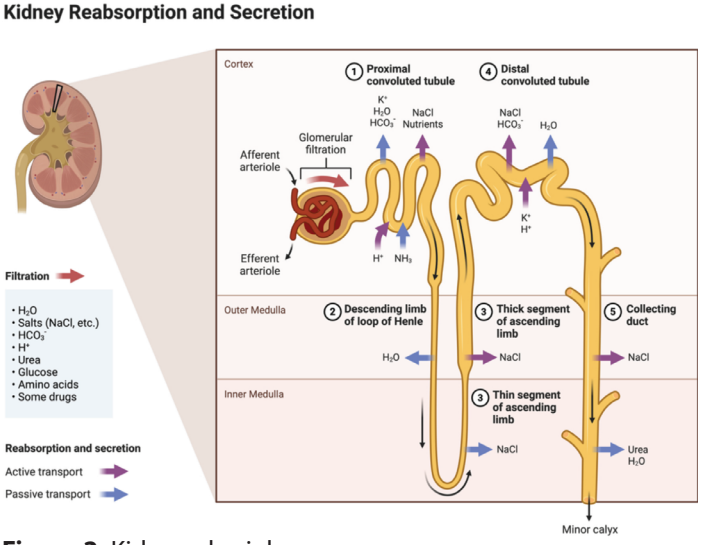

Figure 2. Kidney physiology

As depicted in more detail in Figure 3, the filtration membrane consists of three parts:[35] **fenestrated endothelium**, the inner layer of the capillary wall, which contains pores that allow plasma components to pass but block blood cells; **glomerular basement membrane (GBM)**, a middle layer that acts as a physical and charge-based barrier preventing the filtration of large proteins like albumin; and **podocytes**, specialized epithelial cells with interdigitating foot processes (pedicels) that wrap around the capillaries, creating narrow filtration slits between them. These slits form the final barrier to protein filtration.

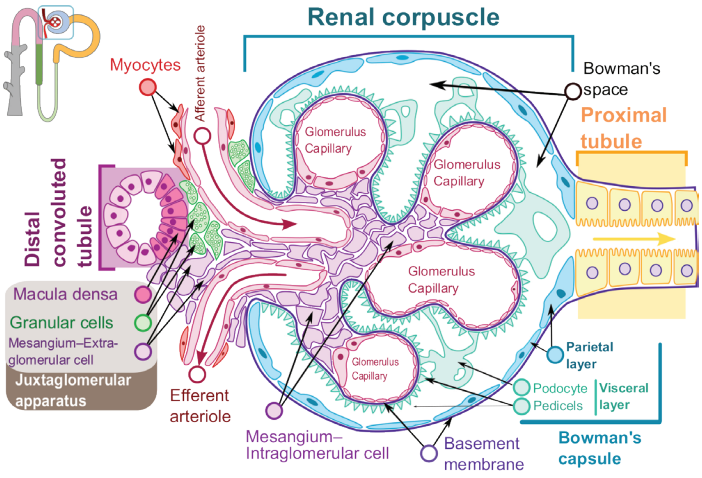

Figure 3. Detailed anatomy of glomerulus
Credit: Shypoetess and Komorniczak, licensed under the Creative Commons Attribution-Share Alike 4.0 International License (https://commons.wikimedia.org/w/index.php?curid=76356955)

The filtration process effectively separates the liquid plasma and small solutes from blood cells and large proteins, initiating the formation of what will become urine (see Figure 2).[32,35] The integrity of this filtration barrier is paramount; damage to any of its components can lead to the hallmark signs of glomerular disease: proteinuria and hematuria.

The **glomerular filtration rate (GFR)** is commonly used to assess kidney function. This is an important but confusing topic that requires elaboration. GFR is equal to the sum of the filtration rates in all the functioning nephrons. The glomeruli filter approximately 125 mL/min of plasma. The normal value for GFR depends upon age, sex, and body size, and is approximately 90 to 120 mL/min/1.73 m^2, with considerable individual variation.[32] In individuals diagnosed with kidney disease, a reduction in GFR may indicate either advancement of the underlying pathology or the emergence of an additional condition, such as diminished renal perfusion resulting from volume depletion.[32] GFR also serves as a prognostic marker in chronic kidney disease (see below).

While changes in GFR indicate pathology, it is important to understand that there is not a direct correlation between the reduction of kidney mass, such as nephron loss, and the decrease in GFR. The kidney compensates for the loss of nephrons through adaptive hyperfiltration in the remaining functional units. Consequently, loss of one-fourth of the total kidney mass does not necessarily result in a corresponding 25% reduction in GFR.[32] This fact has very relevant clinical implications. A stable GFR does not always mean stable disease, so other signs like urine sediment activity, increased protein excretion, or higher blood pressure should also be checked. An increased GFR might signal either kidney improvement or harmful hyperfiltration from hemodynamic changes. Finally, some patients with kidney disease may not be detected because their GFR can remain normal for a long time. Therefore, one must interpret GFR with caution, being aware of its limitations.

Tubular Reabsorption

The glomerular filtrate, while containing waste products, is also rich in substances the body needs to retain, such as water, glucose, amino acids, and essential ions (see Figure 2).[32] As the filtrate passes from Bowman's capsule into the renal tubule system—starting with the proximal convoluted tubule (PCT)—the crucial process of reabsorption begins. The cells lining the PCT are highly specialized for transport, actively and passively moving these vital substances out of the tubular fluid and back into the bloodstream via the surrounding peritubular capillaries.[36] In a healthy individual, nearly 100% of filtered glucose and amino acids, and about 67% of water and sodium, are reabsorbed in the PCT.[36] This process is so efficient that of the approximately 180 liters of fluid filtered by the glomeruli each day, over 99% is reabsorbed, leaving only 1-2 liters to be excreted as urine.[36]

Tubular Secretion

The final step in urine formation is secretion, which is essentially the reverse of reabsorption. This process actively transports additional waste products and excess ions from the blood in the peritubular capillaries directly into the tubular fluid.[36] Secretion is a critical mechanism for eliminating substances that were not efficiently filtered at the glomerulus, including metabolic wastes like urea and creatinine, drugs, and excess hydrogen and potassium ions.[36] This process primarily occurs in the PCT and the distal convoluted tubule (DCT), and it plays a key role in regulating blood pH and electrolyte concentrations. The final fluid, now called urine, passes into collecting ducts and is eventually excreted from the body.[36]

Pathology of Kidney Injury

Kidney disease arises from damage to any of the nephron's

components. The nature of the clinical presentation is directly linked to the primary site of injury.

Acute Kidney Injury (AKI)

AKI is a general clinical syndrome defined by a rapid decline in kidney function, occurring over hours to days, resulting in the accumulation of metabolic waste products and the dysregulation of fluid and electrolyte balance.[37] The term AKI is now commonly used instead of acute renal failure (ARF) because even minor declines in kidney function—which may not cause obvious organ failure—are still clinically important and linked to higher risks of illness and death.[37] To provide a uniform definition of AKI several consensus definitions and criteria for AKI diagnosis have been developed. Currently, the preferred definition follows the guidelines established by The Kidney Disease: Improving Global Outcomes (KDIGO) AKI Workgroup.[38] It defines AKI as follows:

- Increase in serum creatinine by ≥0.3 mg/dL within 48 hours, or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or
- Urine volume <0.5 mL/kg/hour for six hours (after exclusion of urinary tract obstruction or other easily reversible causes of reduced urine output).

Those criteria should be used in the context of the clinical presentation and following adequate fluid resuscitation.

According to the KDIGO criteria, AKI is classified into three clinical stages using serum creatinine, urine output, and estimated GFR. Stage 1 is the mildest, and stage 3 is the most severe one and associated with the worst prognosis.[38]

The KDIGO approach has been selected as the best one available; however, it still has some limitations. For instance, its AKI definition does not distinguish between the multiple etiologies that can cause AKI. Additional limitations involve relying exclusively on urine output as an AKI diagnostic criterion while its validity has not been definitively established. Furthermore, assessing baseline renal function can be challenging in patients without recent creatinine measurements.[37]

The etiologies of AKI are broadly categorized into three groups:[39,40]

- **Prerenal AKI:** This is the most common form and results from decreased blood flow (perfusion) to the kidneys.[40] Causes include dehydration, hemorrhage, severe heart failure, or sepsis. In this state, the kidney itself is not damaged, and function can be restored if blood flow is promptly reestablished.
- **Intrinsic AKI:** This category represents direct damage to the kidney parenchyma.[39,40] The injury can be localized to specific structures: the tubules (acute tubular necrosis), the interstitium (acute interstitial nephritis), the glomeruli (glomerulonephritis), or the renal blood vessel. This is the category of AKI most relevant to potential vaccine-associated adverse events.
- **Postrenal AKI:** This form is caused by an obstruction in the urinary tract that prevents urine from draining, such as an enlarged prostate or kidney stones. The blockage causes pressure to build up within the kidneys, impairing their function.[39,40]

Key Pathological Processes in Intrinsic AKI

Understanding the specific types of intrinsic renal injury is crucial, as they correspond to the pathologies reported in the literature following vaccination.

- **Acute Tubular Necrosis (ATN):** The most common cause of intrinsic AKI in hospitalized patients, ATN involves the death of renal tubular cells due to severe ischemia (prolonged lack of blood flow) or exposure to nephrotoxins (e.g., certain antibiotics, contrast dye).[41]
- **Acute Interstitial Nephritis (AIN):** This condition is characterized by inflammation and swelling of the interstitium, the space between the renal tubules. It is most often an allergic or hypersensitivity reaction to medications (e.g., NSAIDs, proton pump inhibitors) but can also be caused by infections or autoimmune diseases. The inflammatory infiltrate, often including eosinophils, directly impairs tubular function.[42]
- **Glomerulonephritis (GN):** This term encompasses a group of diseases characterized by inflammation of the glomeruli. Most forms are caused by an abnormal immune response that leads to the deposition of antibodies and complement proteins in the glomeruli, triggering an inflammatory cascade that damages the filtration barrier. This damage allows red blood cells and protein to leak into the urine, leading to hematuria and proteinuria, and can cause a rapid decline in the GFR.[43-45]

Common Clinical Syndromes

The distinct functions of the glomerulus as a protein barrier and the tubules as the engine of reabsorption and secretion mean that injury to these separate compartments produces different clinical pictures and consequently different syndromes, which are grouped into **glomerular** and **tubulointerstitial** clusters. This anatomical and functional distinction is used for classification of kidney disorders. It is fundamental to understanding the patterns of renal adverse events from COVID-19, but it can be very confusing to physicians who are not nephrologists, since the additional categories (like AKI) are used in various nephrological classification schemes. In general, however, **glomerular** damage, as seen in glomerulonephritis, classically presents with proteinuria and hematuria. In contrast, **tubulointerstitial** injury, as in acute interstitial nephritis (AIN), more directly impairs the kidney's core filtering and processing functions, leading to the rapid rise in waste products characteristic of AKI.[46]

Among the many clinical syndromes linked to renal disorders, chronic kidney disease (CKD) and nephrotic syndrome are the most relevant for the renal side effects of mRNA vaccines.

Chronic kidney disease (CKD) is a heterogeneous group of disorders characterized by alterations in kidney structure and function, which manifest in various ways depending upon the underlying cause or causes and the severity of disease.[47,48] Importantly, early-stage CKD is often asymptomatic and may go undiagnosed.[47] Those disorders are long-term conditions characterized by a gradual and progressive loss of kidney function over months or years. The term "end-stage kidney disease" (ESKD) refers to CKD treated with either dialysis or transplantation.[47] The most common causes are diabetes and high blood pressure, which slowly damage the small blood vessels within the kidneys.[49] The presence of underlying CKD is a significant risk factor for developing AKI and for having worse outcomes from an acute insult.[47] This concept of a preexisting, subclinical vulnerability is critical when interpreting reports of de novo kidney disease after an inflammatory stimulus like a vaccine, which may in fact be "unmasking" a previously silent condition.

Nephrotic syndrome is not a specific disease but a clinical syndrome defined by a quartet of findings: heavy proteinuria (>3.5 g/day), low blood albumin levels (hypoalbuminemia), generalized edema (swelling), and high blood cholesterol (hyperlipidemia).[46] It is the classic presentation of diseases that cause severe damage to the podocytes of the glomerular filtration barrier, such as minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS).[46]

Contextualizing Renal Injury: SARS-CoV-2 Infection and Side Effects of Other Vaccinations

To properly evaluate the significance of hard-to-diagnose renal adverse events following COVID-19 vaccination, it is imperative to place them in a broader context. This requires a dual comparison: first, against the well-documented and severe renal complications of SARS-CoV-2 infection itself, and second, against the historical backdrop of adverse renal events associated with other established vaccines.

For numerous reasons (including pervasive direct and subliminal advertisement by vaccine manufacturers), the method of preventing infectious diseases by vaccination has been regarded with great enthusiasm in the mainstream medical community. Medical officialdom views vaccination not just as a tool, but as a "cornerstone" of modern preventative medicine and even as "a moral imperative" for protecting both individual and public health.[50,51] From the detached and objective perspective such a strong emotional attachment to one preventive modality does not seem to reflect the rational principles of the evidence-based medicine that medical officialdom professes to follow.

The main concern about allowing emotions into clinical decision-making is that at certain point the "beloved" medical intervention will be reflexively recommended without regard to the objective assessment of the risk/benefit ratio. Therefore, contextualization is of pivotal importance. It removes the ballast of emotional attachment to vaccination and allows one to objectively assess the true risk/benefit ratio of the mRNA vaccine by synthesis of two perspectives. The first perspective looks at the existence or absence of the "risk-risk tradeoff" that is whether the risk of developing a renal disorder due vaccination is much smaller than the risk of kidney damage caused by the natural infection. The second perspective examines how the mRNA vaccine renal safety profile compares to that of other vaccines.

The Incidence and Outcomes of COVID-19-Associated Acute Kidney Injury (COVID-AKI)

From the perspective of basic virology, SARS-CoV-2 is a multi-organ pathogen, and the kidneys are one of its established targets.[52] The pathophysiology of COVID-AKI has been determined to be complex. The mechanisms driving COVID-AKI are multifactorial and reflect the systemic nature of the disease.[27] They include:

- **Direct Viral Invasion:** SARS-CoV-2 can directly infect kidney cells, particularly podocytes and proximal tubular cells, by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed at very high levels in renal tissue.[53]
- **Systemic Inflammation and Cytokine Storm:** A dysregulated, hyperinflammatory immune response to the virus can lead to a "cytokine storm," causing systemic endothelial damage, increased vascular permeability, and organ injury, including in the kidneys.[53]
- **Endothelial Dysfunction and Hypercoagulability:** COVID-19 is associated with a prothrombotic state, leading to the formation of microthrombi in small blood vessels throughout the body, including the glomerular capillaries, which can cause ischemic injury.[54]
- **Organ Crosstalk:** Severe respiratory failure (ARDS) and cardiac dysfunction, common in severe COVID-19, can lead to renal hypoperfusion and hypoxic injury.[27]

The spectrum of renal pathology caused by COVID-19 is very broad.[55] Kidney biopsies from patients with COVID-19 have revealed a wide range of severe pathologies, most commonly acute tubular injury.[55] Other significant findings include collapsing glomerulopathy (a particularly aggressive form of podocyte injury, strongly associated with high-risk APOL1 gene variants), thrombotic microangiopathy, and various forms of glomerulonephritis.[42]

These impressive scientific observations are frequently used by vaccination proponents as justification for the widespread use of mRNA COVID-19 vaccine to "protect patients from renal injury caused by COVID-19 infection." However, as always in medicine the most relevant question is how those basic science findings are translating into the clinical setting. From real-world anecdotal observations, we know that primary care physicians do not encounter large numbers of patients affected by COVID-AKI. However, anecdotal evidence, while useful, can be misleading. Therefore, it is necessary to review the best available epidemiological studies to determine true incidence and severity of COVID-AKI.

Available data indicates that renal complications in COVID-19 are strongly correlated with disease severity: they are uncommon and generally mild in mild cases, but become more frequent and severe in moderate, severe, and especially critical illness.[56-60] Specifically: In mild COVID-19, the incidence of AKI is typically around 1–1.3%.[56] Most patients do not develop significant renal dysfunction, and long-term sequelae are rare.[57] In moderate COVID-19, AKI incidence rises to approximately 2.8%.[56] Proteinuria and hematuria may occur but are usually transient and resolve as the infection improves.[58] Most renal abnormalities in this group are mild and reversible. In severe and critical COVID-19, renal complications are common (in 16–36%) and often severe, with the risk increasing dramatically in ICU patients—as much as 30 to 36 times higher than in non-severe cases.[56,59,60] Proteinuria and hematuria are seen in 50% and 30% of hospitalized patients, respectively.[59,60] Severe AKI may require renal replacement therapy (RRT) in 5–15% of severe/critical cases.[56]

This quantitative data confirms that the real-world experience indicating that severe COVID-19 induced renal injuries (COVID-AKI) are present very rarely in the vast majority of patients affected by COVID-19, that is, those with mild COVID-19 disease.

An Historical Perspective: Documented Renal Events Following Other Vaccines

A literature review shows that immune-mediated kidney disease occurring after vaccination is neither new nor unique to the COVID-19 vaccines.[30] For decades, case reports have described a temporal association between various vaccines and the onset or relapse of specific nephropathies.[61] Robust data on

this phenomenon is lacking, but selected reports provide many interesting clues.

Influenza vaccine, one of the most widely administered vaccines globally, has been associated in available case reports with the development of nephrotic syndrome (due to MCD, membranous nephropathy, or AIN) and pauci-immune glomerulonephritis, a form of vasculitis.[62] Hepatitis B vaccine has been temporally associated with sporadic cases of GN, including lupus-like nephritis and membranous nephropathy.[62] Similar but scarce reports exist for other common vaccines, including the pneumococcal vaccine (associated with anti-GBM disease), the polio-diphtheria-tetanus vaccine (associated with MCD), and the varicella vaccine (associated with nephrotic syndrome).[62]

Global pharmacovigilance data show that mRNA COVID-19 vaccines have the highest disproportionality signal for GN and AKI among all vaccine types studied.[61] For non-mRNA vaccines used for other conditions (e.g., hepatitis B, HPV), the severity of renal complications appears to be slightly less than those reported with mRNA COVID-19 vaccines.[61] However, the studies performed to assess this issue appear to be statistically underpowered. Therefore, it is likely that with additional studies the difference in severity may become much more than "slight." One can only wonder why more of such studies were not performed. There are certainly strong indications for performing them for both mRNA and non-mRNA vaccines. For instance, research demonstrated that hepatitis B vaccines show a disturbingly high disproportionality signal for GN, and even more concerningly that its signal is not as high as the one of mRNA COVID-19 vaccine.[61,63] Since a disproportionality signal merely indicates an association in reporting patterns and not necessarily a direct causal link, such findings should trigger performance of further observational and experimental studies to promptly clarify the implied danger. Yet not much is being done for that purpose.

This historical context suggests two hypotheses: (1) Since both novel mRNA and traditional non-mRNA vaccines are associated with similar renal side effects it is possible that both of them trigger the same pathomechanism responsible for kidney injury. Most likely, the harmful and unintended autoimmune response is inadvertently triggered by the vaccines' intended immune activation. (2) Since the mRNA vaccine causes more severe kidney injury than non-mRNA vaccines, it is plausible that, besides the autoimmune mechanisms shared by all vaccines, mRNA vaccines may damage kidneys through a process unique to their mRNA platform. These are hypotheses to be tested, not firm conclusions. Yet, those are very solid hypotheses that contradict the official reassurances about vaccine safety. It is illogical that they are not being vigorously tested.

Kidney Pathologies Temporally Associated with COVID-19 mRNA Vaccines

Since the rollout of the global COVID-19 vaccination program, a body of literature consisting primarily of case reports and small case series has described various renal pathologies occurring in temporal association with the administration of mRNA vaccines.[64-66] These disorders have been reported as both de novo and relapsing presentations, with most cases occurring within weeks of vaccination. A systematic review of 130 published cases found that 69% were new-onset diseases, while 31% were relapses of pre-existing conditions.[64] Table 1 synthesizes the key features of the most commonly reported renal pathologies related to COVID-19 vaccination that are relevant for the primary-care practice settings. Community physicians should be aware that some of their patients who present with "unusual renal issues" may be affected by the renal side effects of COVID-19 vaccine. Table 1 can help them in process of differential diagnosis.

Table 1. Selected Renal Pathologies Temporally Associated with COVID-19 mRNA Vaccination

Pathology	Typical Clinical Presentation	Commonly New Onset or Relapse?	Typical Latency Post-Vaccine	Predominant Vaccine Dose	General Prognosis & Management
Minimal Change Disease (MCD)	Acute nephrotic syndrome (edema, heavy proteinuria)	Primarily new onset (73.1%)	2–14 days	1st dose (53.8%)	Excellent; highly responsive to corticosteroids
IgA Nephropathy (IgAN)	Gross hematuria, often with flu-like symptoms	Primarily relapse/flare (39.6% relapse)	1–3 days	2nd dose (72.9%)	Generally favorable; often transient and resolves with conservative management
ANCA-Associated Vasculitis (AAV)	Acute Kidney injury (AKI) / rapidly progressive GN; systemic symptoms	Both new onset (62.5%) and relapse (37.5%)	7–21 days	2nd dose (68.8%)	Serious; requires aggressive immunosuppression. Remission is common, but risk of CKD.
Acute Interstitial Nephritis (AIN)	Acute Kidney injury (AKI) with bland urine sediment	Exclusively new onset (100.0%)	>7 days	2nd dose (66.7%)	Good; typically resolves with corticosteroids

Data for percentages derived from a systematic review of 128 cases.[64]

From the more theoretical standpoint, renal pathologies reported in temporal association with mRNA vaccine include the wide variety of etiological syndromes that are dangerous but frequently hard to diagnose and even harder to classify for physicians who are not nephrologists.[64-66] For the purpose of this editorial we will use following simplified approach that distinguishes the following categories of (sometimes overlapping) syndromes: the general syndrome of **acute kidney injury (AKI)** and anatomical **glomerular** and **tubulointerstitial** clusters. These clusters include **glomerulonephritis** (IgA nephropathy, podocytopathies including minimal change disease and focal segmental glomerulosclerosis, and autoimmune glomerulonephridities), **membranous nephropathy**, and **acute tubulointerstitial nephritis** (specifically acute interstitial nephritis).

Understanding the unique characteristics of these distinct syndromes is essential not only for clinical purposes but especially for risk assessment of the COVID-19 mRNA vaccine.

Acute Kidney Injury (AKI)

The term AKI is not related to anatomical cluster classification but indicates presence of serious renal pathology as discussed above. Forms of AKI associated with mRNA COVID-19 vaccination include crescentic glomerulonephritis, acute tubular injury, and IgA nephropathy.[65] AKI cluster is considered to be one of the most difficult to diagnose and manage group of renal disorders.[42] AKI is associated with substantial morbidity and mortality. It is the

most frequently encountered adverse effect of novel COVID-19 vaccine.[55]

Glomerulonephritis (GN)

The types of GN reported in temporal association with mRNA COVID-19 vaccination include podocytopathies (such as minimal change disease), IgA nephropathy, and autoimmune glomerulonephridities.

Minimal change disease (MCD) belongs to podocytopathies category, and it is the single most frequently reported de novo glomerular disease following COVID-19 vaccination, accounting for approximately 41% of cases in one large review.[67] The hallmark of MCD is the abrupt onset of full-blown nephrotic syndrome. Patients typically present with rapid weight gain, generalized edema (anasarca), and foamy urine, usually within 2 to 14 days following a vaccine dose.[68] Laboratory findings confirm severe proteinuria, hypoalbuminemia, and hyperlipidemia. Cases have been reported across a wide age spectrum, from adolescents to the elderly.[68] While most cases are new onset, relapses in patients with a known history of MCD have also been documented.[69] In compiled case series, new-onset MCD appeared more frequently after the first vaccine dose (54% of cases), whereas relapses were more evenly split between the first and second doses.[64] The diagnosis is confirmed by kidney biopsy. On light microscopy, the glomeruli appear normal or show only minor abnormalities, hence the name "minimal change." Immunofluorescence studies are negative for immune deposits. The definitive finding is seen on electron microscopy, which reveals diffuse effacement (flattening) of the podocyte foot processes, confirming severe podocyte injury.[68] The prognosis for vaccine-associated MCD is generally excellent. The condition is highly responsive to corticosteroid therapy, with most patients achieving complete remission of nephrotic syndrome, often rapidly.[68]

Another podocytopathy reported after COVID-19 vaccine is focal segmental glomerulosclerosis (FSGS). FSGS, less frequent than MCD, is characterized by scarring in parts of some glomeruli and has a higher risk of progression to CKD.[67]

IgA nephropathy (IgAN) is the second commonly reported glomerular disease in temporal association with COVID-19 vaccination, accounting for about 37.5% of cases in a major review.[64] The classic presentation is the sudden onset of visible, or gross, hematuria (cola-colored urine), often accompanied by flu-like symptoms such as fever and myalgia.[70] The key feature is the extremely short latency period: symptoms typically appear within 1 to 3 days of vaccination.[64] This rapid onset is highly characteristic of an anamnestic (memory) immune response, strongly suggesting the activation of a pre-existing disease process rather than the initiation of a new one. A crucial distinction in the literature is that a substantial proportion of IgAN cases (approximately 40% in one review) occur in patients with a known history of the disease, representing a clear relapse. Among the cases classified as "new onset," many patients were found to have had prior, undocumented microscopic hematuria or proteinuria, suggesting the vaccine merely "unmasked" a subclinical or undiagnosed condition.[70] Concerns about the IgAN forms that could be induced by the vaccine were so significant among clinicians that a dedicated "reassuring" paper has been published presenting claims that such this renal side effect of COVID-19 vaccine is "extremely rare."[71] This can be true. However, with time it was reported that secondary cases of IgAN became more commonly reported after the second dose (73% of cases), which aligns with the theory of a boosted memory immune response.[64] Kidney biopsies performed during an acute flare often show active features, such as endocapillary hypercellularity (an increase in cells within the glomerular capillaries) and in some cases, crescent formation, which indicates more severe injury.[70] Despite the often dramatic presentation, the prognosis for vaccine-associated IgAN flares is said to be generally favorable,[72] although robust data to validate that opinion is clearly missing. The gross hematuria and any associated acute rise in creatinine are typically transient. In many cases, renal function and proteinuria return to the patient's baseline over a period of weeks to months, often with only supportive care.[67] A short course of corticosteroids may be used in cases with more severe inflammation.[66]

A smaller but clinically significant number of cases involve the new onset or relapse of severe systemic autoimmune diseases that affect the kidneys known as autoimmune glomerulonephridities.[73] Those include **ANCA-associated vasculitis** (AAV) **and lupus nephritis**.

AAV is a serious life-threatening autoimmune disease characterized by inflammation of small blood vessels, frequently involving the kidneys.[73,74] The diagnosis is supported by the detection of anti-neutrophil cytoplasmic antibodies (ANCA) in the blood. In post-vaccination cases, the MPO-ANCA subtype is far more common than the PR3-ANCA subtype.[75] The definitive diagnosis is made by kidney biopsy. AAV is a serious condition that requires prompt diagnosis and aggressive immunosuppressive therapy, typically with high-dose corticosteroids combined with either cyclophosphamide or rituximab. The risk of permanent kidney damage and progression to CKD is considerably higher than with vaccine-induced MCD or IgAN flares.[75]

Finally, new-onset or flared lupus nephritis is a rare but reported side effect of COVID-19 vaccination.[76]

Membranous Nephropathy (MN)

Membranous nephropathy (MN) is an autoimmune glomerular disease, but it is not classified as GN because it lacks significant glomerular inflammation.[77,78] MN is characterized by subepithelial immune complex deposition and thickening of the glomerular basement membrane, with minimal or absent leukocyte infiltration and cellular proliferation.[77,78] Case reports described both new-onset and relapsed MN occurring within days to weeks after COVID-19 vaccination. Most patients presented after the second dose and with an acute kidney injury.[79]

Tubulointerstitial Nephritis

While the glomerular diseases discussed above have dominated the reports, pathologies affecting the tubules and interstitium have also been described. Acute interstitial nephritis (AIN) accounts for a smaller fraction of reported cases (around 9% in one review) but is a recognized cause of post-vaccination AKI.[64] Patients typically present with AKI—a rising serum creatinine—often with a non-specific or "bland" urine sediment (i.e., without significant blood or protein).The onset is occurring days to weeks after vaccination.[66] Kidney biopsy is essential for diagnosis and shows inflammatory cell infiltrates (including lymphocytes and often eosinophils) in the interstitium, along with inflammation of the tubules (tubulitis) similar to that seen in drug-induced AIN.[66]

The prognosis is generally good. Management involves avoiding subsequent doses of the same vaccine type and a course of corticosteroids.[66, 80]

Other Rare Manifestations

Isolated case reports have described other pathologies, including thrombotic microangiopathy (TMA) and C3 glomerulopathy, a disease driven by dysregulation of the complement system.[73,81]

Proposed Pathophysiological Mechanisms of Vaccine-Associated Renal Injury

While a definitive causal link between COVID-19 mRNA vaccines and rare renal events remains to be proven, the temporal clustering of these events has prompted significant scientific inquiry into the potential underlying biological mechanisms. The central theme emerging from this research is discussed above. In addition to the known mechanism of unintended autoimmune reaction, components and mechanisms associated with the novel mRNA platform may cause some new form of the undesired multifaceted autoimmune response.

The Role of Potent Immune Activation by mRNA Platforms

Unlike some traditional vaccines that use inactivated or attenuated pathogens, mRNA vaccines work by delivering a genetic template (mRNA encoding the SARS-CoV-2 spike protein) directly into host cells. This process is designed to be exceptionally immunogenic, eliciting a robust and coordinated immune response involving both the humoral (B-cell and antibody) and cellular (T-cell) arms of the immune system.[82] This powerful stimulation is fundamental to their efficacy in preventing severe COVID-19. However, this same potent activation can be an initiating factor for the undesired autoimmune reaction. This powerful stimulus may overwhelm regulatory controls, leading to a misdirected immune attack.[30,83]

Hypothesized Mechanisms of Immune Dysregulation

Several non-mutually exclusive immunological mechanisms have been proposed to explain the spectrum of renal pathologies observed. It is likely that different mechanisms predominate in different disease states, reflecting the complexity of the immune system:

- **Dysregulated T-Cell Response:** A strong, cell-mediated immune response, characterized by the activation of CD4+ helper T-cells and CD8+ cytotoxic T-cells and the production of pro-inflammatory cytokines like interferon-gamma (IFN–γ), is a key feature of the response to mRNA vaccines.[84] This T-cell activity is crucial for clearing virally infected cells. However, it is hypothesized that in certain individuals, this response could become dysregulated. An over-exuberant T-cell response could lead to the production of cytokines that increase glomerular permeability or directly cause podocyte injury, a leading theory for the pathogenesis of minimal change disease (MCD).[68] Similarly, a misdirected T-cell response against renal tubular antigens could precipitate acute interstitial nephritis (AIN), which is histologically a T-cell-mediated hypersensitivity reaction.[84]
- **Molecular Mimicry:** This is a classic mechanism for autoimmunity, wherein structural similarities exist between a foreign antigen (in this case, the viral spike protein) and a self-antigen (a protein within the host's own tissues). The immune system, in generating antibodies or T-cells against the foreign antigen, may produce clones that cross-react with the similar-looking self-antigen, leading to an autoimmune attack.[68,84] This mechanism is considered a plausible explanation for the onset of true autoimmune diseases like ANCA-associated vasculitis (AAV) or lupus nephritis, where the immune system targets specific self-proteins in neutrophils or other cellular components, respectively.[68,84]
- **Bystander Activation:** The intense inflammation generated at the site of vaccination and in the draining lymph nodes leads to the release of a wide array of danger signals and inflammatory mediators. This highly inflammatory microenvironment can lead to the nonspecific activation of nearby autoreactive T-cells and B-cells—cells that recognize self-antigens but are normally kept in a dormant or anergic state by regulatory mechanisms. Once activated by this "bystander" effect, these autoreactive cells can migrate and cause tissue damage.[68,84] This mechanism could contribute to the flare of a pre-existing, quiescent autoimmune condition.
- **Hyperresponsive Humoral (B-Cell) Response:** This mechanism is particularly relevant to IgA nephropathy (IgAN). The pathogenesis of IgAN involves the production of an abnormal, galactose-deficient form of IgA1 (Gd-IgA1) and the formation of immune complexes that deposit in the glomerular mesangium.[68,84] It is hypothesized that the potent B-cell stimulation provided by the vaccine could, in individuals predisposed to IgAN, lead to a surge in the production of pathogenic Gd-IgA1, triggering an acute inflammatory flare and the characteristic presentation of gross hematuria.[68,84] The convergence of these potential mechanisms with the observed clinical pathologies provides a logical framework for understanding these rare events. T-cell-mediated pathways align well with the presentation of MCD and AIN. Autoimmune phenomena like molecular mimicry and bystander activation are plausible triggers for AAV. Finally, a hyper-responsive B-cell response directly explains the rapid flares seen in patients with IgAN.[85,86]

Adjuvants and Autoimmune/Inflammatory Syndrome (ASIA)

Many traditional vaccines incorporate adjuvants, such as aluminum salts.[87] Over the years, a concept known as ASIA, or "autoimmune/inflammatory syndrome induced by adjuvants," has been proposed to describe a collection of rare autoimmune conditions that may be triggered by the chronic immune stimulation provided by adjuvants.[88]

COVID-19 mRNA vaccines do not contain traditional adjuvants like aluminum.[89] However, the lipid nanoparticle (LNP) delivery system that encapsulates the mRNA possesses its own intrinsic immunostimulatory properties that contribute to the vaccine's potency.[90] While the specific clinical entity of ASIA may not be directly applicable, the underlying principle is highly relevant: any powerful immunostimulatory component, whether a classic adjuvant or a novel delivery system, carries an inherent potential to perturb immune tolerance and trigger an autoimmune response.[80]

Synthesizing the Evidence and Future Imperatives

The comprehensive review presented here of the literature on renal adverse events following COVID-19 mRNA vaccination reveals a complex and concerning picture. This analysis highlights a surprising lack of robust research studies that should be done in response to real-world data. Even limited information available today suggests that COVID-19 vaccines may cause severe kidney damage, outweighing its purported benefits. Decision-makers must fund high-quality studies guided by available information. The results need impartial analysis of causality and risk-benefit ratio (including risk-risk tradeoffs) to reach objective conclusions regarding vaccine safety. Only in that way can unifying clarity leading to the societal consensus about safety of COVID-19 vaccine be achieved. The successful execution of the optimal plan outlined above will take a very long time, unfortunately.

Conclusions

A review of the spectrum of reported kidney pathologies associated with administration of the COVID-19 vaccine, and the purported pathophysiological mechanisms, gives a disturbing picture of its unrecognized serious nephrotoxicity. The unexpected paucity of the quality studies disallows a confident appraisal of the safety profile of COVID-19 vaccine. To bridge the existing knowledge gap, an efficient research program should be carefully designed and executed. Since such necessary process will be lengthy, it is prudent to suspend the administration of COVID-19 vaccine until its safety profile can be definitively evaluated.

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